Aims and scope
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Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL)

Jun-Ho Lee
Department of Plastic and Reconstructive Surgery, Y eungnam University College of Medicine, Daegu, Korea

Introduction

In August 2019, the Ministry of Food and Drug Safety of Korea (MFDS) ordered to stop using and selling Biocell textured breast implants (Allergan Inc., Irvine, CA, USA). This decision came after the first case of breast implant-associated anaplastic lymphoma (BIA-ALCL) in Korea was reported on August 14, 2019 [1]. As of now, three cases of BIA-ALCL have been reported in South Korea [2]. BIA-ALCL is an uncommon T-cell non-Hodgkin lymphoma characterized as CD30 positive and anaplastic lymphoma kinase (ALK) negative. Primary lymphoma of the breast is very rare, accounting for only 0.12% to 0.53% of all malignant breast tumors, approximately 2.2% of extranodal lymphomas, and less than 1% of all non-Hodgkin lymphomas. Over the past decades, there has been increasing doubt about an etiologic link between breast implants and the development of ALCL. In January 2011, the United States (US) Food and Drug Administration (FDA) stated the relationship between BIA-ALCL and breast implants for the first time as “Although ALCL is extremely rare, the FDA believes that women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant” [3]. In 2016, the World Health Organization declared BIA-ALCL as a new disease entity [4].

Epidemiology

The first case of BIA-ALCL was reported by Keech and Creech [5] in 1997, and by July 2019, the FDA updated a total of 573 US...
and global medical device reports of BIA-ALCL, including 33 deaths (Tables 1, 2) [6]. Because of its rare occurrence, it is difficult to determine the exact prevalence of BIA-ALCL. In 2008, de Jong et al. [7] published the first case-control study and reported that the risk of BIA-ALCL development in women with breast implants was 18.2-fold higher than in women who did not have implants (odds ratio, 18.2; 95% confidence interval [CI], 2.1–156.8). In 2018, the same group reported the relative risk of BIA-ALCL with breast implants as 421.8 (95% CI, 526.6–3,385.2) and absolute cumulative risks of 29 per million and 82 per million at 50 years and 70 years, respectively. The estimated prevalence of BIA-ALCL with breast implants in women aged 20 to 70 years was 3.3% [7]. In 2017, Doren et al. [8] published the first US population-based report demonstrating a significant association between

### Table 1. Summary of US and global deaths reported in MDRs received as of July 6, 2019 (n=33)

<table>
<thead>
<tr>
<th>ALCI deaths from MDRs and literature reported as MDRs (^a)</th>
<th>Deaths through 7/6/2019 (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at time of diagnosis (yr)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
</tr>
<tr>
<td>Range</td>
<td>37–83</td>
</tr>
<tr>
<td>Not specified (no. of reports)</td>
<td>13</td>
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<tr>
<td><strong>Time from the last implant to diagnosis (yr)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
</tr>
<tr>
<td>Range</td>
<td>1–20</td>
</tr>
<tr>
<td>Not specified (no. of reports)</td>
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</tr>
<tr>
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<td><strong>n</strong></td>
</tr>
<tr>
<td>Textured</td>
<td>15</td>
</tr>
<tr>
<td>Smooth (^a) with history of textured</td>
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</tr>
<tr>
<td>Not specified</td>
<td>17</td>
</tr>
<tr>
<td><strong>Implant fill</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Silicone</td>
<td>14</td>
</tr>
<tr>
<td>Saline</td>
<td>8</td>
</tr>
<tr>
<td>Not specified</td>
<td>11</td>
</tr>
<tr>
<td><strong>Reason for implant</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Reconstruction</td>
<td>5</td>
</tr>
<tr>
<td>Augmentation</td>
<td>17</td>
</tr>
<tr>
<td>Not specified</td>
<td>11</td>
</tr>
<tr>
<td><strong>Clinical presentation (breast) (^a)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Seroma</td>
<td>6</td>
</tr>
<tr>
<td>Breast swelling/pain</td>
<td>3</td>
</tr>
<tr>
<td>Capsular contracture</td>
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</tr>
<tr>
<td>Peri-implant mass/lump</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
</tr>
<tr>
<td>Not specified</td>
<td>7</td>
</tr>
<tr>
<td><strong>Anaplastic lymphoma kinase</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
</tr>
<tr>
<td>Not specified</td>
<td>21</td>
</tr>
<tr>
<td><strong>CD30 status (^d)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Not specified</td>
<td>21</td>
</tr>
<tr>
<td><strong>Implant manufacturer</strong></td>
<td><strong>n</strong></td>
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<tr>
<td>Allergan</td>
<td>12</td>
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<tr>
<td>Mentor</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
</tr>
<tr>
<td><strong>Reporter country: US or OUS (^e)</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>US</td>
<td>12</td>
</tr>
<tr>
<td>OUS</td>
<td>21</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
</tr>
</tbody>
</table>

US, the United States; MDR, medical device report; ALCI, associated anaplastic large-cell lymphoma; OUS, outside the US.

\(^a\)Includes one case of B-cell lymphoma. \(^b\)Percentage in terms of the total 33 deaths. There are no reports of deaths associated with tissue expanders. \(^c\)MDRs sometimes list more than one clinical presentation, e.g., seroma and peri-implant mass/lump, in which two presentations were counted. \(^d\)CD30 is a cell membrane protein associated with diagnosis of classic Hodgkin’s lymphoma and breast implant-ALCL. \(^e\)US/OUS is counted as the country reported in the narrative or the recorded reporter’s country in the MedWatch form.

Adapted from the materials of U.S. Food and Drug Administration [6].

Lee JH. Breast implant-associated anaplastic large-cell lymphoma

https://doi.org/10.12701/yujm.2020.00801
### Table 2. Summary of US and global data as of July 6, 2019 (n=573)

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases through 9/30/2018 (n = 457)</th>
<th>Cases through 7/6/2019 (n = 573)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Unique ALCL cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>a)</strong> Cases through 9/30/2018</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>b)</strong> Cases through 7/6/2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age at time of diagnosis (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td>Range</td>
<td>27–90</td>
<td>-</td>
</tr>
<tr>
<td>Not specified (no. of reports)</td>
<td>111</td>
<td>24</td>
</tr>
<tr>
<td><strong>Time from the last implant to diagnosis (yr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Range</td>
<td>0–34</td>
<td>-</td>
</tr>
<tr>
<td>Not specified (no. of reports)</td>
<td>110</td>
<td>24</td>
</tr>
<tr>
<td><strong>Implant surface</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Textured</td>
<td>310</td>
<td>68</td>
</tr>
<tr>
<td>Smooth</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Not specified (no. of reports)</td>
<td>123</td>
<td>27</td>
</tr>
<tr>
<td><strong>Implant fill</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>274</td>
<td>60</td>
</tr>
<tr>
<td>Saline</td>
<td>183</td>
<td>40</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Reason for implant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstruction</td>
<td>108</td>
<td>24</td>
</tr>
<tr>
<td>Augmentation</td>
<td>104</td>
<td>23</td>
</tr>
<tr>
<td>Not specified</td>
<td>245</td>
<td>54</td>
</tr>
<tr>
<td><strong>Clinical presentation (breast)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seroma</td>
<td>266</td>
<td>58</td>
</tr>
<tr>
<td>Breast swelling/pain</td>
<td>135</td>
<td>30</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>69</td>
<td>15</td>
</tr>
<tr>
<td>Peri-implant mass/lump</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>Others</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Not specified</td>
<td>105</td>
<td>23</td>
</tr>
<tr>
<td><strong>Anaplastic lymphoma kinase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>229</td>
<td>50</td>
</tr>
<tr>
<td>Not specified</td>
<td>228</td>
<td>50</td>
</tr>
<tr>
<td><strong>CD30 status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>215</td>
<td>47</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not specified</td>
<td>242</td>
<td>53</td>
</tr>
<tr>
<td><strong>Implant manufacturer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergan includes McGhan, Inamed</td>
<td>386</td>
<td>84</td>
</tr>
<tr>
<td>Mentor</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Sientra</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Other manufacturer</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Unknown manufacturer</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td><strong>Reporter country: US or OUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>276</td>
<td>48</td>
</tr>
<tr>
<td>OUS</td>
<td>181</td>
<td>32</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

US, the United States; MDR, medical device report; ALCL, associated anaplastic large-cell lymphoma; OUS, outside the US.

*Patients with bilateral breast implant (BIA)-ALCL are counted as two cases of BIA-ALCL.*

*Percentage in terms of the total 457 MDRs.*

*Percentage in terms of the total 573 MDRs.*

*In the 26 cases of smooth implants, 12 have unknown prior history of implants, seven have a history of textured implants, and seven have a history of prior implants with an unknown texture. There are no reports of cases associated with tissue expanders.*

*MDRs sometimes list more than one clinical presentation, e.g., seroma and peri-implant mass/lump, in which two presentations were counted.*

*CD30 is a cell membrane protein associated with diagnosis of classic Hodgkin's lymphoma and BIA-ALCL.*

*Other manufacturers include: Bristol Myers Squib, Nagor, Polytech Silimed, Silimed, and Sientra/Silimed.*

*US/OUS is counted as the recorded reporter's country in the MedWatch form, or if the event was noted to be from a foreign source in box G3 of the MedWatch form. Please note that the reporter country may not reflect the country where the event occurred or the country where the device is marketed.*

Adapted from the materials of U.S. Food and Drug Administration [6].
textured breast implants and BIA-ALCL. They reported that BIA-ALCL develops only with textured implants, with an incidence rate of 2.03 per million per year, which is 67.6 times higher than that of primary ALCL of the breast in the general population. Lifetime prevalence was estimated to be 33 per million (one per 30,000) women with textured breast implants [8]. In 2017, a study from Australia and New Zealand reported the highest incidence of BIA-ALCL. Fifty-six cases in total had been confirmed by 2017, including 26 new cases of BIA-ALCL diagnosed between January 2017 and April 2018, representing a 47% increase in the number of confirmed cases. The estimated incidence has subsequently been revised from one in 300,000 to one in 1,000–10,000 patients [9]. The number of cases is increasing with the growing interest and recognition among physicians.

**Implant texture and manufacturer**

All clinical case reports have demonstrated a strong relationship between BIA-ALCL and textured breast implants. In 2015, Brody et al. [10] reviewed all current BIA-ALCL literature, analyzing 173 cases of the disease, and found that all patients with a known clinical history had received at least one textured surface implant. Additionally, there were no cases before the introduction of textured surface implants. Of the 573 US and global medical device reports of BIA-ALCL, 385 cases had a history of textured implants, 162 were not specified, and 26 had smooth implants. However, these 26 smooth implant cases either had a history of prior exposure to textured implant before revision surgery to smooth implants or no clinical history to review (Table 2) [6].

Magnusson et al. [11] investigated the implant-specific risks of BIA-ALCL with 110 implants in 81 patients in 2019. They reported that the implant-specific risk is 23.4 times higher with Silimed polyurethane (Silimed, Rio De Janeiro, Brazil) and 16.52 times higher with Biocell implants, compared with Siltex implants (Mentor, Santa Barbara, CA, USA). A total of 484 cases of the 573 (84.5%) registered the US and global medical device reports had a history of Allergan implants. Of the 33 reported deaths, no information regarding the implant manufacturer was available for 20 of them; among the remaining 13, 12 had Allergan implants. This is the reason why MFDS ordered a ban on Biocell breast implants (Tables 1, 2). The FDA recalled Allergan textured breast implants and expanders because of the higher rate of BIA-ALCL associated with Biocell breast implants.

**Etiology**

The etiology and process of BIA-ALCL development are not well understood, but it is likely a complex process involving multiple factors. However, it is related to textured implants, and chronic inflammation has been proposed as a potential etiologic factor and precursor to tumorigenesis. Various pathogenic theories, including the immunologic hypothesis, tribology, and subclinical infection, have been proposed to explain the mechanism of chronic inflammation. The immunology hypothesis suggests that silicone particles released from the surface of textured implants generate foreign bodies, resulting in chronic inflammation [12]. According to the tribology hypothesis, aggressively textured implants cause delamination of the periprosthetic capsule and lead to the formation of a double capsule through mechanical tear stress [13], consequently causing unresolved inflammation, genetic instability, and activation of maladaptive homeostatic responses and dormant transcription factors [14]. The subclinical infection hypothesis was supported by studies carried out by Hu et al. [15] in 2015. He compared the microbiological colonization of implant capsules between BIA-ALCL patients and patients with capsular fibrosis. The BIA-ALCL groups had a higher bacterial burden and a significantly different distribution of bacteria, predominated by the gram-negative pathogen *Ralstonia pickettii*.

**Clinical presentation**

The first and most common symptom of BIA-ALCL is unilateral or bilateral peri-implant fluid collection following aesthetic or reconstructive implantation with textured surface breast implants. It can be accompanied by breast swelling, asymmetry, or pain. Skin symptoms (e.g., inflammation, papules) and unilateral regional lymphadenopathy have been described [16]. B-type symptoms such as fever, lymphadenopathy, night sweating, and fatigue can be accompanied [17]. Most cases of BIA-ALCL are detected on average 7 to 10 years after implantation. However, there was one reported within 2 years, and another reported as late as 32 years after implantation [18]. In addition, there was one occurrence 2 months after the exchange of an implant [17]. Most cases are unilateral, but four cases of bilateral involvement have been reported in patients with bilateral breast implants [19]. Approximately 60% of patients present with malignant effusion, 17% with a mass, and 20% of patients present with both seroma and mass [20].

**Diagnosis**

Standardized diagnosis and management guidelines for BIA-ALCL have been established by the National Comprehensive Cancer Network (NCCN) [21]. BIA-ALCL should be suspected and evaluated for patients who develop spontaneous peri-implant fluid
collection occurring more than 1 year after aesthetic or reconstructive implantation with a textured surface breast implant. Many patients with breast implants are likely to have a small amount of peri-implant fluid (5–10 mL) without symptoms. These are normal findings and do not require further evaluation. Ultrasonography is the best imaging method for detecting and defining any peri-implant fluid or mass. Suspicious fluid collections should be aspirated with a fine needle under ultrasonography guidance. A minimum of 10 mL (ideally > 50 mL) of fluid should be collected to diagnose BIA-ALCL. A suspected mass requires a tissue biopsy. Specimens should be sent for cell morphology by cytology, immunohistochemistry, and flow cytometry [22-25]. BIA-ALCL is CD30 positive, epithelial membrane antigen positive, and ALK negative (Fig. 1). After histologic confirmation of BIA-ALCL, further lymphoma workup and staging are recommended.

Each case should ideally be discussed at a multidisciplinary team conference consisting of oncologists, radiologists, pathologists, and plastic surgeons. Routine laboratory work should include complete blood cell count with differential, comprehensive metabolic panel, and lactate dehydrogenase levels. Positron emission tomographic (PET) and computed tomographic (CT) scans are beneficial for demonstrating associated capsular masses, chest wall involvement, regional lymphadenopathy, and/or distant organ metastasis [10].

Preoperative evaluation/staging

There are two main staging systems for BIA-ALCL, the Lugano modification of the Ann Arbor staging system and the BIA-ALCL tumor, node, and metastasis (TNM) staging system. The traditional staging system for non-Hodgkin lymphoma is the Lugano modification of the Ann Arbor staging system, which has been used in many previous reports. In this system, stage IE disease is limited to a single extranodal (E) site such as the breast or implant capsule, whereas stage IIE disease is defined as an extranodal disease with spread to or involvement of local lymph nodes [26]. Most patients with BIA-ALCL have an early-stage disease, either stage IE (83%–84%) or stage IIE (10%–16%), while a few of them (0%–7%) fall into stage IV disease with this system [21,27,28]. Because of the unique characteristics of BIA-ALCL that behaves like a solid tumor rather than a liquid tumor and that the Ann Arbor staging system does not consider capsular invasion, NCCN is now using the TNM staging system modeled after the American Joint Committee on Cancer TNM [27]. However, the TNM classification describes BIA-ALCL as a spectrum of disease from stage IA (35%–70%, effusion only), IB (3%–11%), IC (8%–13%), IIA (8%–25%) [7,14,21], IIB (3%–5%), and III (3%–9%) to IV (1%–2%) [7,27].

Treatment

The most important factors for the treatment of BIA-ALCL are timely diagnosis and complete surgical excision [27]. The goals of surgery are complete removal of the implant, including the surrounding fibrous capsule and any associated mass. Complete surgical excision prolongs overall survival and event-free survival compared with all other therapeutic interventions. In subpectoral implant placement, adherence to the rib cage can make complete resection difficult, while an injection of tumescent solution facilitates complete excision. In this case, care must be taken to avoid pneumothorax. The effect of local seeding of malignant seroma on capsulectomy is not yet clear. However, clinically, this has not been observed to influence the recurrence rate. In cases presenting with a mass, complete excision of the mass with a negative margin is es-

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Fig. 1. (A) Immunohistochemistry for CD30 highlights the membranes of neoplastic cells. (B) The neoplastic cells are negative for anaplastic lymphoma kinase (ALK) (immunohistochemical stain, x100 [A] and [B]).
sential. At present, there is no clear role for radical mastectomy or sentinel lymph node biopsy. Full axillary dissection has rarely been used for the gross involvement of multiple lymph nodes. According to the NCCN guidelines, an estimated 2% to 4% of patients develop bilateral disease, and therefore surgeons may consider the removal of the contralateral implant. The rate of disease events and recurrence is 2.6-fold higher for stage II disease and 2.7-fold higher for stage III disease than for stage I disease [26]. The recurrence rate following complete surgical excision is 14.3% for patients with T4 disease compared with 0% for patients with T1 to T3 disease [27].

**Adjuvant therapy**

There are no established treatment protocols for stage II or more advanced, disseminated, and recurrent cases after complete resection. Therefore, treatment protocols for primary cutaneous and systemic ALCL are generally used. Radiation therapy with 24 to 36 Gy is suggested for patients with local residual disease, positive margins, or unresectable disease with chest wall invasion like the cutaneous ALCL [29]. Systemic therapy combined with anthracycline-based chemotherapy or brentuximab vedotin is used for stage II or more advanced or disseminated state [30-35].

**Follow-up**

Patients showing complete response to treatment can be monitored with history and physical examination every 3 to 6 months for 2 years and then as clinically indicated. Monitoring may include CT or PET/CT scans every 6 months for 2 years and then only if clinically indicated.

**Conclusion**

As of 2020, three cases of BIA-ALCL have been reported in Korea. This means that Korea is no longer a safe country from BIA-ALCL, and more patients may be reported. Every symptomatic peri-implant fluid collection for more than 1 year after textured surface implantation with aesthetic or reconstructive surgery should be evaluated for BIA-ALCL.

**Notes**

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

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**References**

9. Loch-Wilkinson A, Beath KJ, Knight RJ, Wessels WL, Magnus-


Lactate: a multifunctional signaling molecule

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Since its discovery in 1780, lactate has long been misunderstood as a waste by-product of anaerobic glycolysis with multiple deleterious effects. Owing to the lactate shuttle concept introduced in the early 1980s, a paradigm shift began to occur. Increasing evidence indicates that lactate is a coordinator of whole-body metabolism. Lactate is not only a readily accessible fuel that is shuttled throughout the body but also a metabolic buffer that bridges glycolysis and oxidative phosphorylation between cells and intracellular compartments. Lactate also acts as a multifunctional signaling molecule through receptors expressed in various cells and tissues, resulting in diverse biological consequences including decreased lipolysis, immune regulation, anti-inflammation, wound healing, and enhanced exercise performance in association with the gut microbiome. Furthermore, lactate contributes to epigenetic gene regulation by lactylating lysine residues of histones, accounting for its key role in immune modulation and maintenance of homeostasis.

Keywords: Glycolysis; Homeostasis; Lactate; Lactate receptor; Lactate shuttle; Lactylation; Oxidative; Warburg effect

Introduction

Single-celled organisms, such as bacteria and fungi, are put under pressure to reproduce as soon as they encounter nutrient-rich environments. Their metabolism control systems have evolved to sense available nutrients and transfer the necessary carbon, nitrogen, and energy to generate building blocks for cell growth. When starved, the cells cease to produce biomass and begin adapting their metabolism to draw maximum energy from available resources to cope with nutrient depletion [1].

In multicellular organisms, uncontrolled proliferation is prevented as mammalian cells cease to take up nutrients from the environment unless otherwise stimulated by growth factors. Genetically mutated cancer cells, on the other hand, are non-dependent on such external stimuli and may show increased uptake and metabolism of nutrients, promoting cell survival and proliferation [1]. Oncogenic mutations often result in a high-rate uptake of nutrients, particularly glucose, which is required for cell growth and proliferation [2]. In 1923, Otto Warburg found that when glucose was added to cancer tissue slices in Ringer’s solution, they continuously produced lactate in the presence of oxygen [3,4]. His attempt was to understand why cancer cells preferred glucose fermentation over oxidative phosphorylation (OXPHOS), even in the presence of ample oxygen. This aerobic glycolysis occurs not only in cancer cells but also in exercising muscle cells, activated immune cells, and virally infected cells. A glycolytic increase in lactate concentration is found in local tissues under various disease conditions, such as sepsis, infections, inflammatory diseases, autoimmune diseases, and cancer.

Lactate has long been regarded as a by-product of anaerobic respiration. Increasing evidence, however, indicates that lactate is essential for energy and redox homeostasis. More recent data suggest that lactate is a multifunctional signaling molecule with its own receptor and plays an important role in communication between cells and tissues. The aim of this review was to provide knowledge on lactate, including its general physiology and historical paradigm.
changes, and to summarize the recent advances that highlight the regulatory role of lactate in diverse biological processes in both physiological and pathological conditions.

**Physiology of lactate**

Almost 99% of lactic acid is dissociated into lactate anions (La$^-$) and protons (H$^+$) within the physiological pH range. Therefore, in this review, La$^-$ will be referred to as lactate. Lactate is mainly composed of L (+) enantiomer (L-form) as detected in the sera of healthy humans [5]. Serum D-lactate concentration ranges from 0.013 to 0.2 mM, as opposed to that of L-lactate which may range from slightly above 1.14 mM at rest, 15 mM after an intense exercise, and 30 mM in some cancer tissues [6]. The daily production of lactate in resting humans is estimated to be approximately 20 mmol/kg/day [7]. In adults with an average body weight of 70 kg, approximately 1,400 mmol of lactate is produced daily from muscle (25%), skin (25%), brain (20%), red blood cells (20%), and intestines (10%) [8].

Lactate is produced by the reduction of pyruvate by lactate dehydrogenase (LDH) during glycolysis under anaerobic or aerobic conditions.

\[
\text{CH}_3\text{COCOO}^- + \text{NAD}^+ + \text{H}^+ \rightleftharpoons \text{CH}_3\text{CHOHCOO}^- + \text{NAD}^+ + \text{H}_2\text{O}
\]

LDH is a tetrameric enzyme that catalyzes the interconversion of pyruvate and lactate with the complementary interconversion of a reduced form of nicotinamide adenine dinucleotide (NADH) to NAD$^+$. The two most common subunits of LDH are the LDHM (or M subunit) and LDHH (or H subunit) proteins that are encoded by LDHA and LDHB genes, respectively. These subunits combine to form five isoenzymes: LDH-1 (4H), LDH-2 (3H1M), LDH-3 (2H2M), LDH-4 (1H3M), and LDH-5 (4M) [9]. LDH-1 is usually called LDHB since it is composed of four “H” LDHB subunits. LDHB preferentially converts lactate to pyruvate and is expressed mainly in the heart (H). In contrast, LDH-5 is usually called LDHA since it is composed of four “M” LDHA subunits. LDHA preferentially converts pyruvate to lactate and is expressed mainly in the skeletal muscle (M) [10]. Heterogenous LDHs (LHH-2 to LDH-4) exhibit subunit-dependent intermediate enzyme activity. The remaining two subunits, LDH-C and LDH-Bx, are specific to the testes and peroxisomes, respectively. In lactate-producing glycolysis, LDHA is the most important enzyme.

### Lactate paradigm changes

Lactate has long been considered a waste end product of anaerobic glycolysis [11-14]. The development of acidosis has traditionally been explained by lactate overproduction during high-intensity exercises or severe disease states such as sepsis and septic shock [15]. A high level of serum lactate has been regarded as a predictive factor of muscle fatigue, often associated with tissue hypoxia and poor clinical outcomes [16].

The early 1980s was marked by a drastic change in the lactate paradigm. The idea that lactate is not responsible for acidosis started gaining acceptance, as reviewed by Robergs et al. [17]. According to the theory, intermediate acids of glycolysis have a low pKa; hence they all exist in their base form. The first intermediate acid of glycolysis, 3-phosphoglyceric acid, is present as 3-phosphoglycerate. This signifies that the main form of glycolytic metabolites is not acid (pyruvic acid or lactic acid) but a base (pyruvate or lactate). For example, at physiological pH (∼6.4 to 7.1), lactic acid, due to its very low acid dissociation constant (pKa, ~3.86), dissociates immediately into lactate and hydrogen ion (H$^+$). This indicates that lactic acid does not exist in living organisms. In fact, lactate does not decrease metabolic acidosis, but rather removes H$^+$ from the cytosol and creates NAD$^+$ molecules, electron acceptors that are used for adenosine triphosphate (ATP) generation to maintain glycolysis [18,19].

How, then, is lactate removed? To maintain the serum concentration range of 1 to 2 mM, 60 to 120 mmol of lactate needs to be removed from the blood every hour [20]. Lactate is usually removed immediately from various tissues, for example, skeletal muscles, or it may be released and taken up by exercising muscle, heart, brain, kidney, and liver. Lactate may also be metabolized either by direct oxidation or transformation into glucose. Lactate transformation into glucose by the liver or kidney is known as the Cori cycle or gluconeogenesis [21]. Lactate can also be removed via its oxidation into pyruvate, which involves an entry into the tricarboxylic acid (TCA) cycle needed for ATP production [22,23].

### Lactate shuttles

As the product of glycolysis and the substrate for OXPHOS or gluconeogenesis, lactate can be regarded as the link between different metabolic pathways. In 1985, George Brooks [24] proposed the lactate shuttle hypothesis. Lactate shuttles and metabolic interplay are now recognized to mediate redox and energy homeostasis not only between cells, tissues, and at the whole organism level but also at an intracellular level between cell compartments, such as cytosol-mitochondria or cytosol-peroxisome shuttle. The early lactate
Lactate is a ligand for an orphan G-protein coupled receptor (GPR81), now termed hydroxycarboxylic acid receptor 1 (HCAR-1 or HCA1) [39]. HCA1 is predominantly expressed in the adipose tissue. Other tissues and organs also express HCA1, although to a lesser degree, in the skeletal muscle, liver, spleen, kidney, and brain. In addition to the plasma membrane, HCA1 is also detected in intracellular organelles, such as mitochondria. As expected from the broad presence of the lactate receptor HCA1 in various tissues, increasing evidence has shown that lactate plays diverse roles in various pathophysiological conditions, including inflammation and cancer. HCA1-mediated lactate signaling may affect lipid metabolism [43], neuronal excitability changes [44], cellular development and survival [45,46], and modulation of inflammatory responses [47,48]. Lactate generated by glycolytic cancer cells can also act on HCA1 expressed on non-cancer cells, including immune cells, endothelial cells, adipocytes, and fibroblasts in the tumor stroma. The final consequence of lactate-mediated activation of HCA1 on cells in the tumor mass is the facilitation of survival, growth, and metastasis of cancer cells via mechanisms that mediate increased angiogenesis, immune evasion, and chemoresistance [49].

Lactate signaling via HCA1 has been shown to work synergistically with insulin to decrease cellular concentration of cyclic adenosine monophosphate (cAMP) and lipolysis in the fed state, suggesting that HCA1 might be linked to obesity [29]. The mechanism of cAMP modulation includes attenuation of protein kinase A (PKA) signaling [50,51]. Lactate produced and released by inflammatory bone marrow neutrophils may induce mobilization via endothelial HCA1 signaling by inhibiting the expression of VE-cadherin in intercellular junctions of the vascular endothelium [52].

Lactate binding to HCA1 can also signal through a noncanonical, cAMP/PKA-independent pathway with arrestin beta 2 (ARRB2) as an adaptor protein, leading to the inhibition of toll-like receptor-4 (TLR-4)- and nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome-mediated induction of proinflammatory mediators such as interleukin (IL)-1β and IL-18 [47,48,53].

Warburg effect

Normal cells obtain ATP, an essential energy source for cell survival, from both glycolysis and mitochondrial OXPHOS. In 1923, Otto Warburg and Seigo Minami [3] found high rates of glycolysis in cultured tumor tissues, which were characterized by increased glucose uptake and excessive lactate production even in the presence of oxygen (aerobic glycolysis). They incubated slices of rat hepatoma in Ringer’s solution and found an increase in lactate concentration calculated from the increase in CO₂ during 30 minutes

**Lactate transporters**

Lactate is transported across cytoplasmic and intracellular compartments by several monocarboxylate transporters (MCTs) that perform proton-lactate symport. Among the 14 MCTs that have been identified to date, MCT1–4 are better characterized and have been shown to mediate the proton-linked transport of monocarboxylates such as lactate, pyruvate, acetoacetate, and β-hydroxybutyrate. MCT1 (also known as SLC16A1) is widely distributed and is usually involved in the import of lactate, whereas MCT4 (also known as SLC16A3) is expressed in highly glycolytic cells or tissues, such as white skeletal muscle, astrocytes, cancer cells, and white blood cells, and is mainly involved in lactate export [39,40]. In addition to MCTs, sodium-coupled lactate transport is carried out by the high-affinity transporter SLC5A8 or the low-affinity transporter SLC5A12 as was initially reported in the kidney [41]. The expression of SLC5A12 has also been reported in CD4⁺ T cells [42].

**Lactate receptor**

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of incubation. The rate of lactate production from the hepatoma slice was 70 times greater than that in the normal liver, kidney, and heart tissue [54]. Warburg [4] also showed, in a rat model, that the artery feeding the tumor had lower levels of lactate and higher levels of glucose than the draining vein from the tumor tissue. This glucose-avid, lactate-producing behavior of tumor cells regardless of oxygen availability was named the “Warburg effect” by Efraim Racker in 1972 [55].

**Why cancer cells prefer the Warburg phenotype?**

Mitochondrial function is not impaired in Warburg cells, as described in many types of cancers; the TCA cycle is activated in breast cancer, glioblastoma, and non-small cell lung cancer cells [56]. Therefore, the Warburg effect is a metabolic shift from (not a defect of) OXPHOS to glycolysis. Glycolysis generates only two molecules of ATP per glucose molecule, which is much less efficient than OXPHOS (36 ATPs per glucose). Nevertheless, most cancer cells obtain approximately 60% of the total required ATP from glycolysis. The activation of glycolysis has several advantages for rapidly proliferating cancer cells. In addition to the faster ATP synthesis than OXPHOS, the activation of the glycolytic pathway allows cells to feed several pathways that contribute to macromolecular synthesis. These include the pentose phosphate pathway, which produces ribose for nucleotides and NADPH for reductive biosynthesis, the hexosamine pathway, which is required for protein glycosylation, serine-glycine-one-carbon metabolism, which feeds glutathione, nucleotides, and methylation reactions; and glycerol synthesis for the production of complex lipids [57].

**The mechanism of the metabolic shift from OXPHOS to glycolysis**

One of the key components of glycolytic activation and OXPHOS suppression is hypoxia-inducible factor 1α (HIF-1α) [58], which was originally identified as a critical transcription factor for cellular adaptation to hypoxic conditions. HIF-1α induces most of the glycolytic enzymes, including hexokinase 2, pyruvate kinase M2 (PKM2), and LDHA. HIF-1α also activates the expression of glucose transporter (GLUT) 1 and GLUT3 and a lactate transporter MCT4. HIF-1α activates pyruvate dehydrogenase (PDH) kinase 1, which phosphorylates and inactivates PDH, the enzyme that converts pyruvate to acetyl coenzyme A (acetyl-CoA), which is essential for the TCA cycle.

Warburg and Minami [3] observed almost a century ago that Warburg-type cancer is characterized by the excessive production and accumulation of lactate. Tumors are a heterogeneous collection of normal cells, cancer cells, immune cells, and blood vessels. Even among cancer cells, some are glycolytic and others are oxidative in the context of vascularization and preferred metabolism. Extracellular lactate excreted from glycolytic stromal cells in the tumor tissue may be taken up by adjacent oxidative cancer cells, via MCTs, and be converted to pyruvate to enter the TCA cycle, which produces electron donors, such as NADH and reduced flavin adenine dinucleotide to support the electron transport chain (ETC) for ATP production. This type of two-compartment communication of tumor metabolism was termed the “reverse Warburg effect” as aerobic glycolysis takes place in tumor stromal fibroblasts rather than cancer cells [59]. The mitochondrial reactive oxygen species (ROS) produced by the ETC activity of reverse Warburg cells are released into the cytosol and inhibit prolyl hydroxylase (PHD) through the Fenton reaction and prevent the degradation of HIF-1α [60]. The stabilization of HIF-1α activates the transcription of glycolytic genes, thus converting the oxidative cells to glycolytic ones. Lactate can, in turn, promote HIF-1α stabilization by inhibiting PHD activity. Lactate-derived pyruvate competitively inhibits alpha-ketoglutarate, a PHD co-factor, from associating with PHD [61]. Recent findings indicate that lactate preconditioning also primes normal fibroblasts to switch from OXPHOS to glycolysis through mechanism(s) including ROS-mediated HIF-1α stabilization [62]. PKM2 is a rate-limiting enzyme that catalyzes the conversion of phosphoenolpyruvate to pyruvate. PKM2 enzyme activity is allosterically regulated by the oligomerization type. The PKM2 tetramer is enzymatically more active than the dimer form of PKM2. However, the PKM2 dimer acts as a transcriptional co-activator, which may translocate to the nucleus and promote the expression of HIF-1α-mediated pro-glycolytic genes such as lactate-producing LDHA [63]. Thus, lactate, the final product of normoxic glycolysis, further activates glycolysis through the activation of HIF-1α. In addition to hypoxia, the increase in several metabolic intermediates, such as succinate, fumarate, and lactate, facilitates the stabilization of HIF-1α. The oxygen-independent mechanism of HIF-1α activation is now termed pseudohypoxia [64].

**Lactate modulates immune cell functions**

Hypoxia and glycolysis have long been considered to activate the immune cells. For example, a metabolic shift from OXPHOS to aerobic glycolysis is regarded as a hallmark of T cell activation [65]. LDHA induced in activated T cells to support glycolysis promotes interferon (IFN)-γ expression and instead maintains high levels of acetyl-CoA to increase histone acetylation and transcription of ifng [66].
Recent studies have highlighted the counterbalancing regulatory function of the glycolysis metabolite lactate. In addition to its metabolic functions as an energy source and an intermediate metabolite for biosynthetic pathways, lactate also plays a modulatory role in inflammation and immunity. Recent reports suggest that lactate produced by aerobic glycolysis has an immunosuppressive effect in the local environment of various disease conditions including sepsis, cancer, chronic inflammation, and autoimmune diseases [67-69]. In sepsis, immunosuppression is a serious problem that causes life-threatening secondary infections and is now called immunoparalysis [70]. The immunosuppressive phase during sepsis is characterized by the depletion of effector cells and T cell exhaustion, and a concomitant increase in regulatory T cells (T_{reg}) and myeloid-derived suppressor cells [71]. Lactate has also been shown to suppress the proliferation and cytokine production in human cytotoxic T cells [72], thereby decreasing the cytotoxic effect. Effector T cells are more dependent on glycolysis for proliferation and cytokine production, while T_{reg} rely more on OXPHOS [73]. Lactate accumulation in the local tissue environment is a common feature of both inflammatory diseases and cancer. Lactate in the tumor microenvironment (TME) has been shown to help tumor escape from immune surveillance by reshaping T cells and macrophages to immunosuppressive phenotypes such as tumor-promoting T_{reg} and M2-like tumor-associated macrophages (TAMs) [72-76].

In contrast, increased lactate concentration observed in the local tissue of chronic inflammatory diseases contributes to the upregulation of the sodium-coupled lactate transporter SLCSA12 by human CD4+ T cells. In a mouse arthritis model, lactate was shown to promote IL-17 production by CD4+ T cells through phosphorylation of signal transducer and activator of transcription 3 (STAT3) by PKM2 and fatty acid synthesis (FAS). It also led to CD4+ T cell retention in the inflamed tissue by reducing the glycolysis rate and diverting metabolic fluxes into de novo FAS [68]. Lactate has been shown to inhibit antigen presentation and IL-12 synthesis by dendritic cells (DCs). The differentiation of DCs from monocytes is also affected by high concentrations of lactate, favoring less inflammatory DCs that are biased toward producing IL-10 [76,77].

Macrophages may undergo a switch in the metabolic pathways, which leads to differentiation into either a proinflammatory (M1) or a homeostatic and anti-inflammatory (M2) phenotype in response to various stimuli, including cytokines [78]. In general, IFNs promote M1-like inflammatory macrophage activation by suppressing homeostatic pathways. In the context of tumors, TAMs do not completely follow M1 and M2 subtypes. TAMs usually have an M2-like phenotype and facilitate tumor growth by immunosuppression. Signaling functions and polarization of M2 macrophages can be directly regulated by lactate in the TME via HIF-1α-dependent metabolic reprogramming [78]. The lactate produced by cancer cells further facilitates HIF-1α stabilization and induces an M2-like phenotype, such as vascular endothelial growth factor (VEGF). It has been shown that lactate promotes M2 polarization of macrophages by binding to the lactate receptor HCA1 [48].

**Lactate binds to and suppresses mitochondrial antiviral signaling for type I interferon activation**

Viral RNA can be detected by retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs), such as RIG-I and melanoma differentiation-associated gene 5 (MDA5), which subsequently activate the mitochondrial antiviral signaling (MAVS) protein and downstream axis for type I IFN production [79]. Cells infected by RNA viruses often show an increase in the rate of glycolysis and a decrease in OXPHOS activity, which is a favorable state for rapid viral replication [80]. Furthermore, lactate induced by glycolytic activation inhibits RLR-mediated IFN production [81,82]. Upon recognizing cytosolic double-stranded RNAs, RIG-I undergoes conformational changes, oligomerization, and exposure of the two N-terminal caspase activation and recruitment domains (CARDs) that are involved in a CARD-CARD interaction with MAVS. The transmembrane domain (TM) at the C-terminus of MAVS is required for its localization at the mitochondrial outer membrane. Upon activation, MAVS develops a functional prion-like structure, which serves as a platform for the MAVS signalosome for the activation of the type I IFN pathway. Intriguingly, a recent report showed that lactate inhibits this antiviral axis by directly binding to the TM domain of MAVS, disrupting the mitochondrial localization of MAVS, RIG-I-MAVS interaction and downstream signaling, and IFN-β activation [82] (Fig. 1).

**Epigenetic lactylation of histones**

Surprisingly, lactate can act as a precursor for the epigenetic lactylation of histone lysine residues, which stimulates gene transcription from chromatin. Histones are proteins that are critical in the packing of DNA into the cell and into chromatin and chromosomes. Histones may experience posttranslational modifications in their protruding N-terminal tails as well as within the C-terminal region. Various histone modifications, including acetylation, methylation, and ubiquitylation, were reported before the discovery of histone lactylation in 2019 [83]. These changes in the amino acids of histones...
tone proteins can affect gene expression as well as overall chromatin condensation. A total of 28 lysine lactylation sites have been identified on the core histones in human and mouse cells. For example, in macrophages stimulated to produce lactate by hypoxia, IFNγ plus lipopolysaccharide, or bacterial challenge, histone lactylation accumulated at their promoters is associated with the shift from the initial M1-like phenotype to induction of M2-like homeostatic genes at late time points (16–24 hours) after stimulation. Histone lactylation does not occur at the promoters of proinflammatory genes, such as Tnf or Il6. The induced M2-like genes include Arg1, which is involved in wound healing. Thus, it has been suggested that an endogenous “lactate clock” in M1 macrophages challenged by bacteria turns on the homeostatic genes at the end of the inflammatory phase. This is a new feedback mechanism that restrains macrophage activation [84]. Epigenetic regulation of metabolism and immunity by histone lactylation extends our understanding of the roles of lactate under diverse conditions.

Wound healing

In healing wounds, cells divide rapidly to activate the glycolytic pathway, resulting in lactate accumulation in the interstitial fluids up to a range of 5–15 mM [39,85]. Lactate has been shown to promote reparative angiogenesis through mechanisms including recruitment of endothelial progenitor cells, stimulation of endothelial cell migration, activation of procollagen factors, and enhancement of collagen deposition in the extracellular matrix. Lactate induces the release of mediators such as VEGF, IL-1, and transforming growth factor beta (TGF-β), all of which consequently stimulate angiogenesis and promote wound healing [86-88]. Exogenous lactate delivery is expected to be helpful in the management of non-healing wounds [88].
Microbiome, lactate, propionate, and exercise performance

The human gut microbiota is linked to various health and disease states. Many studies have indicated that the gut microbiota profile is related to the prevalence of chronic diseases such as diabetes mellitus and metabolic syndrome \[89\]. Iraporda et al. \[90\] showed that lactate downregulates proinflammatory responses in intestinal epithelial and myeloid cells. They suggested beneficial effects of lactate-containing foods, such as kefir, on gut microbiota in general and also showed their protective role against infection by pathogenic bacteria such as Salmonella sp. \[91,92\]. Lactate is an end product of bacterial fermentation in many lactic acid bacteria (i.e., Lactobacillus and Bifidobacterium), which are regarded as key members of the healthy gut microbiota. Lactate produced by Lactobacillus and Bifidobacterium in the colon is rapidly converted into short-chain fatty acids, such as propionate, butyrate, and succinate. Lactate produced in the gut may also be released into the systemic circulation via MCTs and removed or metabolized in distant organs \[93\]. On the other hand, lactate produced by exercising skeletal muscle may be released into circulation and can be transported into the gut lumen where lactate-utilizing microbiota strains are present. This type of novel communication of lactate between the gut and somatic organs was proposed as gut-soma lactate shuttle \[32,33\].

Many studies on the athlete’s gut microbiota have shown distinct microbial compositions, including elevated abundances of Veillonella, Bacteroides, Prevotella, Methanobrevibacter, and Akkermansia \[94,95\]. A bacterial strain belonging to Veillonella atypica was isolated by Scheiman et al. \[96\] from stool samples of elite marathon runners postmarathon who ran in the 2015 Boston Marathon. Intriguingly, inoculation of this strain into mice significantly increased the treadmill run time by 13%. They found that V. atypica, which utilizes lactate as its sole carbon source, metabolizes lactate into propionate and acetate, as detected by metagenomic analysis. The \[^{13}\text{C}\] -labeled lactate tracing experiment in mice showed that serum lactate crosses the epithelial barrier into the lumen of the gut \[96\]. This study revealed that lactate, a metabolic by-product of aerobic exercise, maybe shuttled into the gut lumen via circulation and provide a carbon source to V. atypica, a gut microbiota that can then convert it to a bioactive propionate that improves exercise performance.

Lactate in clinical settings

Lactate treatment can be helpful in several clinical conditions. For example, lactated Ringer’s (LR) solution is one of the most popular crystalloid fluids for patients with trauma, burns, and surgery. LR contains sodium lactate, which is known to be a metabolic fuel that improves cardiac function. In vivo, lactate is rapidly metabolized into bicarbonate by the liver \[97\]. In a recent study using a neonatal hypoxia-ischemia model, lactate administration reduced the extent of the brain lesion and facilitated behavioral recovery \[98\]. The usefulness of lactate administration has also been reported in wound healing \[88\] and muscle regeneration after injury \[99\].

Increased lactate levels may also be related to maladaptive pathological conditions. For example, lactate accumulation in the TME is associated with cancer progression and poor clinical outcomes, such as resistance to chemotherapy, increased metastasis, and immune evasion \[74,75\]. Lactate is often monitored as a prognostic indicator of severe disease conditions, such as sepsis. It should be noted that increased lactate production is due not only to hypoxia or tissue hypoperfusion but also multiple factors. In addition to hypoxia, serum lactate increases due to increased production during stress conditions (e.g., intense exercise, asthma, and sepsis) and decreased clearance of lactate by the liver and kidney. The lactate levels of patients with asthma or hypertension should be interpreted based on their medication information. Since \(\beta_2\)-adrenergic stimulators may induce upregulation of lactate production, serum lactate levels can be blunted in patients using \(\beta_2\)-adrenergic receptor blockers \[8\].

Conclusion

Since Warburg’s historical finding of aerobic glycolysis in cancer cells, lactate has long been regarded as a culprit of muscle fatigue and acidosis-induced tissue damage. However, it is now accepted that lactate is a useful metabolic fuel for skeletal muscles, heart, and brain. Lactate also functions as a metabolic buffer that links glycolysis and OXPHOS. The introduction of the lactate shuttle concept in the early 1980s vastly changed the lactate paradigm and revealed that lactate is a ubiquitous molecule that is metabolized and used almost everywhere in the body. Lactate shuttles were identified between astrocytes and neurons, contracting and resting skeletal muscles, glycolytic and oxidative cancer cells, and intracellular compartments such as the cytosol and mitochondria. The discovery of the lactate receptor GPR81/HCA1 further extended the landscape of lactate’s playing grounds, spanning adipose tissue, skeletal muscles, liver, kidney, heart, brain, immune cells, endothelium, and stromal fibroblasts in the tumor mass. The receptor-mediated nonmetabolic effects of lactate include immunosuppression, active participation in wound healing with increased angiogenesis, decreased adipocyte lipolysis, and neuroprotection.
through anti-inflammatory activities. Lactate overproduced during intense exercise has been shown to cross the epithelial barrier into the gut lumen, increasing the relative abundance of a strain of \textit{V. atypica}. Metabolic conversion of lactate into propionate by \textit{V. atypica} has been shown to increase exercise performance. Finally, lactate is involved in the epigenetic regulation of gene expression by lactylating histones, which contributes to immune modulation and maintenance of homeostasis.

Lactate, regarded for a long time as a metabolic waste product since its discovery, is now recognized as a fuel energy source, a precursor for gluconeogenesis, a signaling molecule, a regulator of gene expression, a precursor for exercise-enhancing propionate production by gut microbiota, and probably as more unknowns yet to be explored.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**References**

24. Brooks GA. Lactate: glycolytic end product and oxidative sub-
Hashimoto T, Hussien R, Brooks GA. Colocalization of MCT1, 
Brooks GA. Anaerobic threshold: review of the concept and di-

Brooks GA. Lactate production under fully aerobic conditions: 
the lactate shuttle during rest and exercise. Fed Proc 1986;45: 

Brooks GA. Lactate shuttles in nature. Biochem Soc Trans 
2002;30:258–64.


date during sustained exercise in mammals - the “lactate shut-
tle”. In: Gilles R, editor. Comparative physiology and biochem-


dent astrocyte-neuron lactate shuttle. Dev Neurosci 1998;20:

39. Sun S, Li H, Chen J, Qian Q. Lactic acid: no longer an inert and end-product of glycolysis. Physiology (Bethesda) 2017;32:


47. Harun-Or-Rashid M, Inman DM. Reduced AMPK activation and increased HCAR activation drive anti-inflammatory re-

48. Hoque R, Farooq A, Ghani A, Gorelick F, Mehal WZ. Lactate reduces liver and pancreatic injury in Toll-like receptor- and in-


50. Langin D. Adipose tissue lipolysis revisited (again!): lactate in-
volvement in insulin antilipolytic action. Cell Metab 2010;11: 

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Psychiatric understanding and treatment of patients with amputations

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Introduction

Amputation is an event that has a dramatic effect on an individual's life and is common in modern society. Although the frequency of amputation is expected to decrease because of the development of medical treatments and the decrease in the incidence of injuries, a certain number of cases are expected to remain owing to the aging population, diabetes, and peripheral vascular disease [1]. Furthermore, the number of amputated patients is expected to increase. In the United States, approximately 185,000 amputations are performed annually, and by 2050, the number of people with amputations is expected to reach 3.6 million, more than double the number in 2005 [2]. In Korea, there is still a lack of detailed and accurate statistics on the frequency of amputation. According to a 2017 survey of the disabled by the Ministry of Health and Welfare, physical disability (48.1%) accounted for the largest proportion of all types of disabilities as of 2018, with 14% of these people having amputations [3].

Amputation is both a physical disability and a psychological emergency. It leads to impairment of an individual's physical function, sensation, and body image, and causes intense and diverse emotional responses [4]. Patients may feel as if they have experienced death beyond the meaning of physical loss. In particular, those with trauma-related amputations may be greatly shocked by the unprepared loss and experience greater difficulties in adapting. Therefore, patients in these cases require a more delicate evaluation and treatment of psychiatric problems.

Patients with amputation have been found to experience anxiety, depression, and posttraumatic stress disorder [5]. These psychological problems can interfere with rehabilitation and cause additional psychosocial problems. Therefore, their early detection and treatment are important. A multidisciplinary team approach, including mental health professionals, is ideal for comprehensive and biopsychosocial management. Mental health professionals could help patients set realistic goals and use adaptive coping styles. Psychiatric approaches should consider the physical, cognitive, psychological, social, and spiritual functions and social support systems before and after amputation. The abilities and limitations of physical, cognitive, psychological, and social functions should also be considered. To improve the patient’s adaptation, psychological interventions such as short-term psychotherapy, cognitive behavioral therapy, mindfulness meditation, biofeedback, and group psychotherapy can be helpful.

Keywords: Amputation; Psychological intervention; Psychological stress; Psychosomatic medicine
depression, and posttraumatic stress disorder due to loss and self-stigmatization [5]. Depressive symptoms are common in the first 2 years after amputation, and depression and anxiety may increase again during adjustment to daily life after discharge [6,7]. In a previous study on patients with traumatic amputation, 35% experienced depression and 60% experienced anxiety in the first 6 months after amputation [8]. Of them, 83% received psychiatric treatment, but only 10% continued treatment 2 years later. As such, there is a need to care for psychiatric problems in amputated patients. However, there is still a lack of psychiatric understanding and effective treatment for them.

Ideally, the mental health of amputated patients should be properly managed throughout the entire process of returning to daily life, even before amputation. However, clinically, it is often difficult to see them in an outpatient consultation setting until the amputee complains of psychological problems. Sometimes, anxiety or depression after amputation is accepted as a normal reaction, which may not be well recognized by patients, families, or primary doctors. Early detection and treatment of psychological problems are important for enhancing the lives of patients and preventing derived psychosocial problems [9].

Mental health professionals can improve psychological adaptation by normalizing the patient’s emotions and experiences related to amputation and helping the patient use adaptive coping mechanisms. Mental health professionals also play a role in promoting communication and encouraging patients and therapists within a multidisciplinary team treatment. For mental health professionals to perform these roles, an in-depth understanding of the psychological characteristics of patients with amputation is essential. However, psychological characteristics and outcomes of patients with amputation are mainly being studied in the industrial field, and even within the department of psychiatric medicine, only a few are dealt with psychosomatic medicine and consultation-liaison psychiatry.

Despite many advances in the field of prosthesis, there are not many systematic studies on mental health or the effects of psychological interventions on amputated patients. Therefore, in this study, we aimed to understand the experience of amputated patients from deciding to perform an amputation in their daily lives and to determine the effect of amputation on a patient’s mental health. In addition, as psychiatrists, we intend to contribute to further research to improve mental health by identifying special considerations and applicable psychological treatments for patients with amputation.

Characteristics of amputation

1. Causes of amputation

The most common cause of amputation is peripheral vascular disease (75%), often seen in patients with diabetes and vasculitis. The second most common cause of amputation is trauma, followed by infection, tumors, nerve damage, and congenital malformations. Amputation of the upper limb is often caused by trauma, and amputation of the lower limb is often caused by peripheral vascular disease [1].

2. Sex

Amputation rates are higher in men than in women. Men who work with machines are at especially high risk of amputation; 87% of patients with trauma are male, of whom 80% are in their 40s [10]. While amputation rates in women are lower than in men, there are many amputations related to more serious medical conditions, which tend to lead to worse recovery than that for men [11]. Moreover, women are more susceptible to postamputation depression than men [12].

3. Age

Children may be sensitive to the acceptance and rejection of their peers, but they generally adapt relatively well [13]. Family cohesion and social support play important roles in positive adaptation after amputation in children [14]. However, adolescents tend to experience difficulties adapting to amputation. They may feel that amputation is a great threat to body image, sexual identity, peer relationships, and autonomy [15]. Adolescents feel sad and become dependent, but ultimately undergo a process of accepting the changes in their physical appearance and return to the social system [16]. There are reports that older adults experience more emotional difficulties, such as depression or adjustment problems, but the results are not consistent between studies [17,18]. In contrast, studies have shown that the risk of emotional difficulties is low because of reduced basic activities and better acceptance of physical limitations [19].

4. Site of amputation

Upper limb amputation is more frequently associated with posttraumatic stress disorder and depression than lower limb amputation [20]. This is because the upper limb plays a greater role in self-expression, self-care, and communication, resulting in more functional loss than lower extremity amputation. In the case of lower extremity amputation, above-the-knee amputation generally leads to poorer functional results than below-knee amputation [21].
5. Pain
Approximately 50%–95% of patients with amputation experience chronic pain [22]. Pain includes residual limb, non-amputated limb, and phantom limb pain. In amputated patients, phantom limb pain has a 50%–80% incidence and often does not respond well to treatment, which reduces the quality of life [23,24]. Chronic pain is associated with difficulties in psychosocial adaptation and unemployment [25].

6. Employment
Returning to work is affected by various factors such as age, vocational ability before amputation, level of amputation, social support, and the national disability system [5]. Patients who live with physical skills are more vulnerable to negative emotional reactions. It takes an average of 1 year to return to work, and more than half of patients with amputation tend to return to work within 2 years [26,27]. Among patients with traumatic amputations, more of them remain unemployed if diagnosed with depression [28].

**Psychological reactions and changes after amputation**

After amputation, psychological difficulties may occur because of altered perceptions and distorted body image of oneself. The belief that they will be considered incomplete is painful. When patients have difficulty accepting new body image and social stigma, their vulnerability is stimulated, and it is easy to use non-adaptive coping mechanisms [29,30]. In addition, amputation can cause problems of sexual function as well as changes in body image, and these factors can cause psychological difficulties, such as depression and anxiety, problems of adaptation, and lowered quality of life [31]. Factors affecting psychological reactions after amputation include age, personality traits, coping skills, flexibility, social support, comorbid physical illness, and the cause of amputation [32]. Also, psychological reactions can appear in various ways, depending on individual personality characteristics. For patients with narcissistic personality traits, amputation can be considered a great attack on self-worth and dignity. Conversely, those with dependent personality traits may welcome the patient role and may be relieved from preexisting responsibilities and pressures.

1. Grief
Grief and mourning reactions are common in the early stages of amputation [12,18]. Loss of limbs often entails psychological distress equal in intensity to that in reaction to a loved one's death. Patients with a tendency to suppress their emotions may need to be encouraged to express a grief response to aid rehabilitation and adaptation [32].

2. Depression
Approximately 21%–35% of patients with amputation experience depressive disorder, which is higher than the rate of 10%–15% in the general population [33]. Depression is influenced by the pre-morbid function and perceived helplessness of the individual. In addition, patients with a history of major depressive disorder may develop depressive symptoms following amputation [34]. Risk factors for major depressive disorder include young age, pain, neurotic personality, and maladaptive coping skills [35]. Depression interferes with rehabilitation and adaptation; therefore, mood and level of adaptation should be appropriately evaluated at each critical period. Normal mourning reactions and hypoactive delirium can cause depression; therefore, they need to be distinguished.

3. Anxiety
Mild to moderate levels of anxiety are normal after amputation and during hospitalization [36,37]. Anxiety reactions can occur when the patient starts recognizing the loss of a limb and evaluating the effects and consequences of amputation [38]. Unfamiliar hospital environments, frequent contact with medical staff, painful treatment processes, perception of loss of control, and uncertainty about the future can increase anxiety. Anxiety can also be caused by a reaction to concerns or fear of changed abilities when reorganizing roles in the family or preparing to return to work [32].

4. Posttraumatic stress disorder
Traumatic events can be accompanied by intense fear and helplessness. Posttraumatic stress disorder occurs in less than 5% of patients with surgical amputations due to chronic diseases [39], but more often in those who undergo amputation due to life-threatening situations, such as wars and accidents [40]. In stress-related disorders, reexperiences such as intrusive thoughts, recollections, and nightmares may continue, and trauma-related stimuli are actively avoided due to the intense psychological pain and increased autonomic arousal they induce [41]. These symptoms reduce the quality of life of the patient and interfere with adaptation; therefore, psychiatric intervention is needed [39].

**Considerations and psychological intervention by period**

Each stage of postamputation adaptation requires different aspects to be attended to and managed based on the needs and limitations of the patients. A multidisciplinary approach centered on patients and their caregivers is ideal for comprehensive rehabilitation and
biopsychosocial management [42]. Psychological interventions should be performed as early as possible to minimize psychological distress during amputation. The considerations for intervention include postamputation conditions, physical, cognitive, psychological, social, and spiritual function, current social support system, economic situation, access to community-based resources, and current capabilities and limits [32]. In this section, we discuss the applicable psychological interventions to address these considerations during the process of amputation and rehabilitation.

1. Preoperative stage
If patients have time to prepare before undergoing surgery or if the pain is severe, amputation may be perceived as the end of the pain; however, various concerns and anxiety reactions may appear along with acceptance. Factors that may concern patients include the loss of limbs, relationship between family and friends, loss of function and degree of recovery, vocational skills, and costs of surgery and rehabilitation. To minimize negative psychological effects, evaluation and screening of mental health are necessary before possible amputation. Physicians should pay attention to the psychological reactions of the amputee and be aware of situations in which mental treatment is needed, and should ask for advice and refer patients to the psychiatrist. Patient concerns should be addressed, and the consequences of amputation should be discussed.

2. Immediate postoperative stage
Twenty-three percent of patients with amputations report the most painful time from hours to days of amputation [43]. Rapid relief of pain has a positive effect on the patient's recovery. Therefore, it is important to actively control pain during this period. Psychological reactions to anxiety and fear may appear because of concerns about safety, pain, or complications. Some experience a certain degree of numbing, which may be the effect of anesthesia and may appear in part as dealing with the trauma of loss. Mental health professionals should validate the patient’s various emotional responses and support them in expressing their emotions and thoughts [44]. The patient’s family is also likely to experience significant shock and acute stress responses. Families often repress their psychological difficulties or concerns to protect the patient, so it is necessary to normalize or alleviate the emotional distress of the family.

3. In-hospital rehabilitation
Faced with the changes caused by amputation, this is the most challenging time of change for both patients and their families. New psychological adaptation and coping skills that were not required during the acute phase may be needed. During this period, anxiety may worsen due to stress, such as fear of negative evaluation of others, fitness of prosthetics, ongoing medical conditions, and rehabilitation treatment [45]. Initially, the patient is concerned about pain and damage of appearance, but afterward, the concern gets shifted to social returning and professional adaptation. The use of maladaptive coping styles during this period may result in overcompensation, surrender, and avoidance. Overcompensation can occur in the form of self-assertion, manipulation, and obsessiveness. In the case of surrender, they may refuse rehabilitation or be obsessed with their role as a patient, and avoidance can be seen in the form of psychological and social withdrawal [46].

In the early stages of rehabilitation, motivational enhancement therapy and solution-focused brief therapy are helpful. At the beginning of the first stage of postoperative recovery, the patient may be motivated, but also daunted by concerns regarding the changes. Therefore, it is necessary to evaluate and develop the patient’s motivation to understand their ambivalence and continue rehabilitation. Motivational enhancement therapy is a systematic intervention that supports a patient’s motivation for change [47]. The essential point of the therapy is to create a foundation for motivation for change and to encourage confidence and hope to set and accomplish achievable goals. The basic interview principles of motivational enhancement therapy include expressing empathy, dealing with resistance, and supporting self-efficacy. Solution-focused brief therapy refers to subjects who have the resources and ability to change themselves and apply therapy to solve problems [48]. It is a goal-oriented treatment that focuses on finding realistic and viable solutions as quickly as possible, rather than carefully identifying the problem [49]. The therapist identifies the patient’s positive qualities, strengths, and resources, and strengthens the patient’s confidence that patients can solve the problem on their own.

In the mid- to long-term aspects of rehabilitation, cognitive behavioral therapy, mindfulness meditation, and acceptance and commitment therapy (ACT) are applicable to modify maladaptive thinking and help emotional problems caused by adapting to change. Cognitive behavioral therapy (CBT) helps improve adaptation throughout the treatment and rehabilitation of patients who undergo amputation. CBT is well established as a treatment for mood disorders, and therapeutic approaches have been applied to various topics, such as body image and pain [50-52]. The goal is to help patients understand their emotions and thoughts related to their behavior and modify maladaptive cognitive patterns. Interventions such as psychoeducation, Socratic question-and-answer methods, and cognitive restructuring can expand perspectives and increase cognitive flexibility. Automatic thoughts often cause cognitive distortion, and typical cognitive distortions in patients with amputation are all-or-none thinking and catastrophizing [53].
Mindfulness meditation is used to reduce pain perception in chronic pain, increasing acceptance in patients with anxiety, depression, cancer, and enhancing life satisfaction [54-57]. It has the effect of reducing unpleasant sensations, thoughts, and emotions in patients through nonjudicial perception. In addition, through mindfulness meditation, objective self-observation is possible, and metacognitive insight is cultivated so that negative thoughts and feelings can be seen from a distance [58]. This improves the capacity to experience negative emotions completely as they are, reducing avoidance behavior [59].

ACT is applied to increase adaptation and psychological flexibility during the rehabilitation period after amputation. ACT emphasizes a mindfulness strategy that recognizes acceptance and presents experiences without judging them. In uncontrollable situations, acceptance increases adaptation, and commitment to new goals that contain individual values improves the purpose and meaning of actions [59]. Educating people to experience negative thoughts, emotions, and bodily sensations in a more open and flexible way can improve the quality of life and function in everyday life [60]. ACT can be applied to patients experiencing phantom limb pain or residual limb pain, as the therapeutic effect for chronic pain has been confirmed [61,62].

4. Return to daily life
This is when the change in life due to amputation becomes apparent. Since a well-fitted prosthesis will require time to prepare, most patients may experience difficulties with daily activities without wearing a prosthesis. The difficulty of adapting to and the function of the prosthesis may lead to unexpected feelings of disappointment and distress [63]. The dynamics of the family will change, and patients and their families must adapt to their new roles. During this period, concerns surrounding occupation, social acceptance, and sexual adaptation may grow, and various degrees of regression may occur. This can be exacerbated if the patient is responsible for the family’s main financial income [32]. Patients may show a tendency to rely on others or express anger when they are encouraged to live independently. Some patients perceive that they have failed to meet their economic and social responsibilities.

Interpersonal therapy can be helpful if both patients and family members are conflicted or have difficulties adapting to change. It is based on the perspective that an individual’s psychological conflict is closely related to social or interpersonal problems. Rather than the psychological and unconscious meaning hidden by symptoms, it is characterized by focusing on the content of symptoms and their emotional effects, and the relevance of the problems that arise from interpersonal relationships [64]. Some important topics covered in interpersonal therapy are grief, discord, role-transition, and interpersonal sensitivity [65]. After amputation, many patients experience major changes, such as changes in their way of life, degree of dependence, support system, or employment. Interpersonal therapy can also be applied at times of loss of body parts or role changes in the family.

Group psychotherapy can be applied to support patients and their families, such as peer support groups. It can help patients improve their symptoms and self-growth and offer education and support to patients and their families [66]. It is possible to expand coping skills and improve self-management to promote adaptation through group psychotherapy with therapeutic or supportive characteristics [67]. Group psychotherapy is possible across various methods, such as face-to-face, telephone, and e-mail, and can deal with psychoeducation, problem-solving, communication, and CBT approaches [19]. Peer groups provide information on problems that patients may encounter after amputation (use of prosthesis, change of relationship, job retraining, etc.). This promotes positive adaptation and emotional support for patients and their families [68].

Conclusion
Amputation is a life-altering event in the lives of patients and their families. The psychological responses to amputation range from complex grief to anxiety, depression, and posttraumatic stress disorder. Psychological responses are affected by age, sex, level of maturity, premorbid personality traits, self-efficacy, coping mechanisms, flexibility, social support, coexistent medical disease, pain tolerance, and the urgency of amputation decisions. Difficulty in adapting postamputation can lead to problems such as low self-esteem, distorted body image, increased dependence, and social isolation; therefore, early detection and treatment of psychological problems are crucial. A multidisciplinary approach, including mental health professionals, is ideal for rehabilitation in amputated patients, focusing on the needs of patients and their caregivers. The role of mental health professionals is to normalize patients’ emotions and experiences and promote psychological adaptation. Psychological intervention is recommended as the earliest opportunity to minimize psychological distress. Psychological and community-based interventions such as short-term psychotherapy, cognitive behavior therapy, mindfulness meditation, relaxation training, and group psychotherapy can be helpful. Research on the effectiveness of psychiatric interventions in patients with amputation is still limited, and additional evidence-based research with therapeutic interventions is warranted.
Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization: SHJ, SHK, WSS, BHK, SHY; Data curation: SHJ; Formal analysis: SHK; Methodology, Project administration, Investigation, Resources: SHJ, WSS, BHK, HGK, SHY; Supervision: SHK; Writing-original draft: SHJ; Writing - review & editing, SHJ, WSS, BHK, HGK, SHY.

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References

8. Melcer T, Walker GJ, Galameau M, Belnap B, Konoske P. Midterm health and personnel outcomes of recent combat ampu-
10. Pezzin LE, Dillingham TR, MacKenzie EJ. Rehabilitation and the long-term outcomes of persons with trauma-related ampu-
23. Richardson C, Glenn S, Nurmikko T, Horgan M. Incidence of phantom phenomena including phantom limb pain 6 months after major lower limb amputation in patients with peripheral

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257–62.
Introduction

Trigeminal neuralgia (TN) is an intermittent, severe, and electric shock-like facial pain [1,2]. This pain is not life-threatening, but it can seriously deteriorate the quality of life [2]. Various treatment modalities have been used to treat TN, including pharmacotherapy, stereotactic radiosurgery, suboccipital craniotomy with microvascular decompression (MVD) or partial sensory rhizotomy (PSR), and percutaneous procedures such as glycerol rhizotomy, balloon microcompression or radiofrequency rhizotomy [1,2].

The exact pathogenesis of TN remains unclear; however, it is well-known that vascular compression at the root entry zone (REZ) of the trigeminal nerve is one of the major causes of TN [3]. Thus, MVD has been widely applied to treat TN, and many positive results have been reported [4,5]. Since PSR was first described by Frazier [6], there have been various modifications in the surgical technique [7]. PSR is performed either alone or in combination with MVD,
and relatively good results have been reported [3,7].

In this study, we describe our experience with suboccipital craniotomy in patients with TN and present a thorough review of the literature.

Materials and methods

1. Patient population

We retrospectively reviewed the medical records and radiologic findings of patients with TN who underwent suboccipital craniotomy with MVD or PSR from 1994 to 2013. Surgeries were performed in patients with typical TN who did not respond to other treatments. All patients underwent preoperative magnetic resonance (MR) imaging using three-dimensional Fourier transformation constructive interference in steady state (3DFT-CISS). Eighty-eight patients underwent 89 surgeries because one patient underwent reoperation. The follow-up period ranged from 3 to 216 months, with an average of 43.2 months.

2. Surgical technique

All surgeries were performed by a senior neurosurgeon. Under general endotracheal anesthesia, patients were placed in the lateral decubitus position. Intraoperative monitoring was performed. After head fixation, a curvilinear skin incision of approximately 7 to 8 cm was made behind the hairline at the posterior of the mastoid process. Then, a retromastoid craniectomy of approximately 3 to 4 cm was performed. The craniectomy was extended to the border of the transverse sinus and sigmoid sinus. The exposed dura was incised in an inverted ‘T’ shape toward the junction of the transverse and sigmoid sinuses. Each incised dura was fixed superiorly (to the occipital bone) and laterally (to the mastoid process). After the cerebellum was gently retracted, the cerebrospinal fluid was drained. The arachnoid membrane was dissected sufficiently to expose the space between the tentorium of the cerebellum and the facial-auditory nerve complex. The trigeminal nerve and the REZ were then found. In case a compressive vessel was observed near the REZ, it was carefully detached from the latter, and horseshoe- or stick-shaped polytetrafluoroethylene sponges were inserted between the two. If there was no compressive vessel, PSR was performed. We cut the sensory root to be adjacent to the pons. The root was cut about 50% to 70% from the caudolateral side (Fig. 1).

3. Pain assessment

We evaluated the surgical outcomes in patients using the Barrow Neurological Institute (BNI) pain scale (Table 1) [8]. The categories of pain relief evaluated by this scale included cure (BNI pain

<table>
<thead>
<tr>
<th>Score</th>
<th>Pain description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>No pain no medications</td>
</tr>
<tr>
<td>II</td>
<td>Occasional pain no medications required</td>
</tr>
<tr>
<td>III</td>
<td>Some pain adequately controlled with medications</td>
</tr>
<tr>
<td>IV</td>
<td>Some pain not adequately controlled with medications</td>
</tr>
<tr>
<td>V</td>
<td>Severe pain or no pain relief</td>
</tr>
</tbody>
</table>

Table 1. Barrow Neurological Institute pain intensity score

Fig. 1. Intraoperative view of partial sensory rhizotomy in right-side approach. If there was no offending vessel in intraoperative findings (A), about half to two-thirds of trigeminal nerve sensory root (arrows) was cut off (B).
score I or II), improved (BNI score III), and poor (BNI score IV or V). The postoperative complications were also reviewed.

4. Radiographic and intraoperative finding analysis
We compared the MR findings with the intraoperative findings and analyzed the treatment results according to the intraoperative degree of compression of the causative vessel. The surgical techniques were either MVD, PSR, or MVD with PSR, and we examined the outcomes of each.

5. Statistical analysis
All statistical analyses were conducted using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). Categorical data were analyzed using the chi-square test or Fisher exact test. The p-values of less than 0.05 were considered statistically significant.

Results

1. Patient characteristics
The study population included 54 females and 34 males. The mean age of patients was 56.9 years (range, 29–82 years). The distribution and duration of the pain, and the previous treatment modalities are summarized in Table 2.

Table 2. Patient demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
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<tbody>
<tr>
<td>Symptom duration (yr)</td>
<td>3.6 ± 3.94</td>
</tr>
<tr>
<td>Pain side, right:left</td>
<td>54 (61.4):34 (38.6)</td>
</tr>
<tr>
<td>Pain distribution</td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>V2</td>
<td>25 (28.4)</td>
</tr>
<tr>
<td>V3</td>
<td>23 (26.1)</td>
</tr>
<tr>
<td>V1+V2</td>
<td>10 (11.4)</td>
</tr>
<tr>
<td>V2+V3</td>
<td>27 (30.7)</td>
</tr>
<tr>
<td>V1+V2+V3</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>55 (62.5)</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>13 (14.8)</td>
</tr>
<tr>
<td>Peripheral nerve block</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Peripheral neurectomy</td>
<td>9 (10.2)</td>
</tr>
<tr>
<td>Gangliolysis</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Gamma-knife radiosurgery</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Microvascular decompression</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Oriental medicine</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Total</td>
<td>88 (100)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation and number (%). V1, ophthalmic nerve; V2, maxillary nerve; V3, mandibular nerve.

2. Intraoperative findings
Of the 88 patients who underwent surgery, we could not find the offending vessel in five cases. In the rest of the patients, the superior cerebellar artery was the most common offending vessel. The offending vessels are summarized in Table 3. In most cases (79 cases), the suspected offending vessel in 3DFT-CISS images was consistent with the intraoperative findings. There were three cases in which there was no offending vessel in either 3DFT-CISS images or intraoperative findings. In two cases, vessels were suspected as causative in 3DFT-CISS images, but could not be found during surgery. Inversely, in four cases, no offending vessels were observed in 3DFT-CISS images, but we identified them intraoperatively.

We performed PSR in five patients with no offending vessel identified. The rest of the patients were divided into two groups according to the degree of nerve compression; the compression group and the contact group. The compression group (n = 59) consisted of patients with nerve deformation due to vascular compression. On the contrary, patients, in whom there was a mere neurovascular contact without any nerve deformation, were classified as the contact group (n = 24). Patients in the compression group underwent MVD. Patients in the contact group also underwent MVD; however, six patients, in whom the causative vessel was small and could not be identified as the definite cause, underwent MVD combined with PSR.

3. Relationship between outcomes and surgical modalities
The preoperative BNI scores of the patients who underwent MVD alone (n = 77) were IV in eight patients and V in 69 patients. The postoperative BNI scores of these patients were I in 33 patients and II in 20 patients. Therefore, the cure rate with MVD alone was 68.8%. The preoperative BNI scores of the patients who under-

Table 3. Intraoperative offending vessel at the root entry zone of 88 patients

<table>
<thead>
<tr>
<th>Offending vessel</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior cerebellar artery</td>
<td>49</td>
</tr>
<tr>
<td>Anterior inferior cerebellar artery</td>
<td>18</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>4</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>2</td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery</td>
<td>2</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>1</td>
</tr>
<tr>
<td>Superior petrosal vein</td>
<td>4</td>
</tr>
<tr>
<td>Multiple†</td>
<td>3</td>
</tr>
<tr>
<td>Absent</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
</tr>
</tbody>
</table>

†Multiple offending vessels are as follow: basilar artery+anterior inferior cerebellar artery, vertebral artery+posterior inferior cerebellar artery, and superior cerebellar artery+anterior inferior cerebellar artery.
went PSR with or without MVD (n = 11) were IV in three patients and V in eight patients, and their postoperative BNI scores were I in six patients. Thus, the cure rate with PSR with or without MVD was 54.5% (Table 4). When the outcomes of the MVD alone group and PSR with or without MVD group were analyzed statistically, there was no significant difference (p = 0.444). All patients with improved pain after surgery discontinued medication; however, patients who had sustained pain after surgery (postoperative BNI scores IV and V) continued medication for pain relief.

4. Complications and pain recurrence
We observed postoperative complications in 41 patients, and dizziness was the most common. Almost all complications were temporary, but permanent partial hearing disturbance was also observed in two cases. The complications are summarized in Table 5. There were three cases in which symptoms remained after the surgery and 10 cases in which pain recurred. Pain recurrence was observed in less than a month in two cases, within a year in five cases, and within 5 years in three cases. Among the patients with recurrence of pain, four patients underwent gamma-knife radiosurgery, and the rest resumed medication. Persistent symptoms were identified only in patients who underwent PSR. Among the patients with pain recurrence, eight belonged to the contact group and two belonged to the compression group. One patient who had recurrence underwent reoperation, and PSR was performed because there was no significant compression or adhesion in the operative field.

Discussion
Since Dandy [9] first introduced MVD for TN, it was thought to be the most reasonable method of treating TN [10]. The outcomes of MVD for TN have been quite good even in recent reports from the last 10 years [11-13]. In our series, the cure rate for MVD was 68.8%, and the efficacy rate (cure+improvement) was 87%. In this study, we observed pain recurrence in 13% of patients, and one patient underwent reoperation. The results of our series of MVD for TN are similar to those of previous studies.

Although MVD is an effective surgery for treating TN, the absence of neurovascular compression in TN is also well-known. Some authors have reported that an offending vessel is absent in nearly 20% of patients with TN [14,15]. In some cases, neurovascular compression is not confirmed by MR images. There are various methods to treat this type of TN, including stereotactic radiosurgery, radiofrequency thermal rhizotomy, balloon compression, and retrogasserian glycerol rhizotomy [16]. On the contrary, in some cases, preoperative MR images suggest that there is a causative vessel, but it is not present in the actual surgical field. In our series, there were two cases in which we suspected neurovascular compression in preoperative MR images, but did not find it intraoperatively. If no causative vessel is identified while performing suboccipital craniotomy for MVD, PSR is widely used.

PSR is performed instead of MVD in the absence of neurovascular compression, and it may be performed simultaneously with MVD [17]. A literature review of recent studies on PSR showed relatively good results [5,18,19]. Toda [17] reported that excellent results (pain-free without medication) of PSR ranged from 48% to 86%. In our series, the cure rate was 54.5%, and the efficacy rate was 72.7%. Pain recurred in one case. The results of our series for PSR are similar to those of previous studies.

In addition to PSR, ‘nerve combing’ has been introduced as another surgical option that can be performed if there is no causative vessel after suboccipital craniotomy [16]. This operation has been called as ‘neurocombing,’ ‘nerve brushing,’ and ‘internal neurolysis’

Table 4. Comparison of outcomes according to surgical modality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Postoperative BNI score</th>
<th>MVD alone</th>
<th>PSR with or without MVD</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>I and II</td>
<td>53 (68.8)</td>
<td>6 (54.5)</td>
<td>59 (67.0)</td>
</tr>
<tr>
<td>Improved</td>
<td>III</td>
<td>14 (18.2)</td>
<td>2 (18.2)</td>
<td>16 (18.2)</td>
</tr>
<tr>
<td>Poor</td>
<td>IV and V</td>
<td>10 (13.0)</td>
<td>3 (27.3)</td>
<td>13 (14.8)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>77 (100)</td>
<td>11 (100)</td>
<td>88 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
BNI, Barrow Neurological Institute; MVD, microvascular decompression; PSR, partial sensory rhizotomy.

Table 5. Postoperative complications with surgical treatment for trigeminal neuralgia

<table>
<thead>
<tr>
<th>Complication</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient</td>
<td></td>
</tr>
<tr>
<td>Hearing disturbance</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Hypesthesia</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20 (22.5)</td>
</tr>
<tr>
<td>Cerebrospinal fluid leakage</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Partial hearing disturbance</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Total</td>
<td>41/89 (46.1)</td>
</tr>
</tbody>
</table>
This procedure is performed as follows: after the same procedure as MVD, if there is no causative vessel, the sensory root of the TN is longitudinally split into two to six fascicles near the REZ [16,20]. The pain relief rates with nerve combing have been reported to be 72% to 82.1% [20]. However, the mechanism of pain relief is unclear, and there have been no comparative studies with other surgical techniques (MVD or PSR).

Generally, serious complications related to suboccipital craniotomy, such as facial palsy, cerebellar hemorrhage, and cerebellar edema, can be avoided by an experienced surgeon; however, mild complications are inevitable [22]. Mild complications include headache, nausea, dizziness, hearing change, and face paresthesia. Headache and dizziness are the most common [22,23]. In our series, dizziness was the most common complication, followed by facial paresthesia. Other complications included cerebrospinal fluid leakage and hearing loss. Most complications were transient, and only two patients experienced permanent partial hearing disturbance. There was no postoperative mortality. Complications in this study correspond with findings from previous literature [23]. Permanent complications mainly occurred in cases where surgeries were performed independently. These complications were presumed to be caused by excessive cerebellar traction due to a lack of experience of surgeons. Various surgical tips are needed to prevent these complications and improve surgical outcomes. For instance, sharp microdissection of the arachnoid membrane and slow suction of cerebrospinal fluid are needed rather than using retracting blades. In addition, it is better to use a narrow suction tip [10].

In a recent review article, pain recurrence after MVD for TN was reported to be 14.3% [24]. In this study, pain recurrence after MVD for TN was 12.8%, and it was more common in the contact group. The presence of vascular compression is known to be a major factor in the recurrence of pain, and the absence of compression has been shown to be associated with lower rates of recurrence [25,26]. These findings are consistent with our series. Contrasting ly, there was no pain recurrence after PSR with or without MVD in our series. However, no pain relief was seen in three cases (27.3%). Generally, the recurrence rate with PSR is reported to be higher than that with MVD [3,5,19]. There was no recurrence in our patients who underwent PSR; however, the short follow-up period and the small number of cases did not allow us to draw any definitive conclusions.

In this study, the clinical results for MVD were satisfactory; the cure rate was 68.8%. On the contrary, the cure rate with PSR was 54.5%. Although the outcomes of PSR were not as favorable as those of pure MVD in this study, PSR can be considered when there is no significant vascular compressive lesion, or the causative vessel is uncertain intraoperatively.

**Notes**

**Ethical statements**

This retrospective study was performed with approval from the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No: 1803-021-065).

**Conflicts of interest**

No potential conflicts of interest relevant to this article were reported.

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**Author contributions**

Conceptualization: CHC, JHL; Data curation: all authors; Formal analysis, Project administration, Supervision: CHC; Investigation: JHL; Writing-original draft: JML; Writing-review & editing: all authors.

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**References**


6. Frazier CH. Trigeminal neuralgia: fourteen years experience
with fractional section of the sensory root as the major operation. JAMA 1927;89:1742–4.
A retrospective analysis of etiology and outcomes of hemophagocytic lymphohistiocytosis in children and adults

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare but severe, life-threatening inflammatory condition if untreated. We aimed to investigate the etiologies, outcomes, and risk factors for death in children and adults with HLH.

Methods: The medical records of patients who met the HLH criteria of two regional university hospitals in Korea between January 2001 and December 2019 were retrospectively investigated.

Results: Sixty patients with HLH (35 children and 25 adults) were included. The median age at diagnosis was 7.0 years (range, 0.1–83 years), and the median follow-up duration was 8.5 months (range, 0–204 months). Four patients had primary HLH, 48 patients had secondary HLH (20 infection-associated, 18 neoplasm-associated, and 10 autoimmune-associated HLH), and eight patients had HLH of unknown cause. Infection was the most common cause in children (14/35, 40.0%), whereas neoplasia was the most common cause in adults (13/25, 52.0%). Twenty-eight patients were treated with HLH-2004/94 immunochemotherapy. The 5-year overall survival (OS) rate for all HLH patients was 59.9%. The 5-year OS rates for patients with primary, infection-associated, neoplasm-associated, and autoimmune-associated HLH were 25.0%, 85.0%, 26.7%, and 87.5%, respectively. Using multivariate analysis, neoplasm-induced HLH (p = 0.001) and a platelet count < 50 x 10⁹/L (p = 0.008) were identified as independent risk factors for poor prognosis in patients with HLH.

Conclusion: Infection was the most common cause of HLH in children, while it was neoplasia in adults. The 5-year OS rate for all HLH patients was 59.9%. HLH caused by an underlying neoplasm or a low platelet count at the time of diagnosis were risk factors for poor prognosis.

Keywords: Hemophagocytic lymphohistiocytosis; Human herpesvirus 4; Lymphoproliferative disorders; Neoplasms; Survival
Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, rapidly progressive, and life-threatening hematologic disorder with excessive immune activation [1]. HLH is a group of disorders characterized by accumulation of lymphocytes and macrophages leading to ‘hemophagocytosis’ (phagocytosis of hematologic cells by macrophages) [2]. If HLH is left untreated, most patients survive for only a few months with severe progressive multiple organ failure [1]. In 1983, the long-term survival in patients with HLH was reportedly only 4% [3]. HLH can be divided into two major categories; primary and secondary [4]. Primary HLH includes familial HLH (FHL), X-linked lymphoproliferative disease type 1 (XLP1), and other primary immunodeficiencies associated with HLH and partial albinism [5,6]. However, secondary HLH can develop because of various triggers, including infections, neoplasms, and autoimmune conditions [4]. HLH most frequently affects infants aged 0 to 18 months; however, the condition is also observed in children, adolescents, and adults of all ages [7].

In 1991, the Histioocyte Society first presented the diagnostic guidelines for HLH based on the common clinical, laboratory, and histopathological findings of HLH [8]. Subsequently, in 1994, the prospective international treatment protocol, HLH-94, based on etoposide, corticosteroids, and cyclosporine A (CSA), was introduced [9]. The HLH-94 protocol dramatically increased the survival rate of patients with HLH to 54% with a median 6-year follow-up [1,10]. Thereafter, a modified treatment protocol, HLH-2004, with revised diagnostic criteria, was introduced in 2004 [11]. In HLH-2004, CSA was incorporated into induction therapy; however, the survival outcomes of patients with HLH were not different between the two studies [11,12]. Although secondary HLH is more common, both HLH-94 and HLH-2004 protocols mainly focused on pediatric patients with primary HLH [1]. Therefore, implementing the same treatment regimen in all HLH subtypes has been questioned [13].

Although primary and secondary HLH exhibit common clinical features in the beginning, the distribution of each subtype and their respective prognoses vary globally [14,15]. According to a nationwide study on pediatric patients with HLH by the Korea Histioptysis Working Party from the Korean Society of Hematology, the most common genetic cause of primary HLH was FHL type 3 with UNC13D variants [13]. Moreover, secondary HLH induced by Epstein-Barr virus (EBV) infection had a relatively high incidence, and the 5-year overall survival (OS) rate was 68% in 251 Korean children with HLH [13]. According to the reports on HLH in adults, neoplasms as triggers are more common in adults than in children [16]. Additionally, secondary HLH is the most common HLH subtype in adults [17]. However, to date, there have been no data regarding HLH in adult patients or a comparison of HLH in pediatric and adult patients in Korea. Therefore, we aimed to retrospectively investigate the causes and characteristics of HLH in both pediatric and adult patients with different HLH subtypes in this study. We also investigated the survival rates of and risk factors for poor prognosis in children and adults with HLH.

Materials and methods

1. Subjects and ethical statement

In this study, patients diagnosed with HLH at Keimyung University Dongsan Hospital and Yeungnam University Medical Center in Daegu, Korea between January 2001 and December 2019 were investigated. The medical records of patients with HLH were retrospectively reviewed for age at diagnosis, sex, HLH etiology, treatment regimen, and death.

2. Definition and methods

HLH was diagnosed according to the diagnostic criteria presented by the Histioocyte Society in 1991 and updated in 2004 [8,11]. According to the HLH-2004 guideline, at least five of the eight listed items must be met for the diagnosis of HLH: (1) fever ≥ 38.5°C; (2) splenomegaly; (3) bicytopenia affecting ≥ 2 cell lines (hemoglobin < 90 g/L [hemoglobin < 100 g/L in infants < 4 weeks], platelet < 100 × 10^9/L, and neutrophil < 1.0 × 10^9/L); (4) hyperferritinemina (ferritin > 500 µg/L); (5) hypertriglyceridemia (fasting triglyceride > 3.0 mmol/L [265 mg/dL]) and/or hyperfibrinogenemia (fibrinogen, < 1.5 g/L); (6) hemophagocytosis in the bone marrow (BM), lymph node, spleen, or liver without evidence of malignancy; (7) elevated levels of soluble CD25 (also called interleukin-2 receptor) > 2,400 U/mL; and (8) low or absent natural killer (NK) cell activity [5,11]. In this study, NK cell activity could not be tested using flow cytometry; instead, interferon-γ was measured by enzyme-linked immunosorbent assay using the NK Vue kit (ATgen, Seongnam, Korea) through Seoul Clinical Laboratories (Yongin, Korea; http://www.scllab.co.kr) [18]. Since this external test method was not performed daily, the results of this test were available after several days. Therefore, it was not used directly as a diagnostic criterion but was referenced in previously diagnosed HLH patients. Additionally, mutations in the genes of typical FHL (PRF1, UNC13D, STX11, STXBP2), XLP1 (SH2D1A), and XLP2 (BIRC4) are sufficient to establish a diagnosis of HLH regardless of the number of fulfilled criteria of HLH-2004 [5,6,11].

3. Statistical analysis

The variables are described as median values and ranges. The
Mann-Whitney U-test was used to compare the variables between the two groups. The chi-square test was used to compare the ratio between the two groups. The 5-year OS rates between the two groups were compared using the Kaplan-Meier method with log-rank test and post hoc pairwise comparison. The 95% confidence intervals (CIs) were estimated using the means and standard errors. The Cox proportional hazards model was used for multivariate analysis. The p-values of < 0.05 were considered significant. For all statistical analyses, we used IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA).

Results

1. Baseline characteristics of patients with HLH

During the study period, 60 patients (35 males and 25 females) fulfilled the criteria for HLH. The median age at diagnosis of HLH was 7.0 years (range, 0.1–83 years). In the study population, 35 patients were children (aged < 18 years) and 25 patients were adults (aged ≥ 18 years). Although HLH occurred in all age groups, more than 50% of the patients (34/60, 56.7%) developed HLH under 10 years of age (Fig. 1A). The median follow-up duration was 8.5 years.

![Age distribution of patients with hemophagocytic lymphohistiocytosis (HLH).](https://doi.org/10.12701/yujm.2020.00591)

![Number of patients diagnosed with HLH per year.](https://doi.org/10.12701/yujm.2020.00591)
Table 1. Baseline characteristics of patients with HLH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>60</td>
</tr>
<tr>
<td>Age at diagnosis of HLH (yr)</td>
<td>7 (0.1–83)</td>
</tr>
<tr>
<td>Child, &lt; 18 yr</td>
<td>35 (58.3)</td>
</tr>
<tr>
<td>Adult, ≥ 18 yr</td>
<td>25 (41.7)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>35:25</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
</tr>
<tr>
<td>Primary HLH</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Familial HLH type 3 (UNC13D)</td>
<td>2</td>
</tr>
<tr>
<td>Familial HLH type 2 (PRF1)</td>
<td>1</td>
</tr>
<tr>
<td>X-linked lymphoproliferative disease 1 (SH2D1A)</td>
<td>1</td>
</tr>
<tr>
<td>Secondary HLH</td>
<td>48 (80.0)</td>
</tr>
<tr>
<td>Infection-associated</td>
<td>20</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
<td>6</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>3</td>
</tr>
<tr>
<td>SFTS virus</td>
<td>3</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Enterococcus (urinary tract infection)</td>
<td>2</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus agalactiae (meningitis)</td>
<td>1</td>
</tr>
<tr>
<td>Achromobacter xylosidans</td>
<td>1</td>
</tr>
<tr>
<td>Unknown organism (infectious colitis)</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasm-associated</td>
<td>18</td>
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<tr>
<td>Lymphoma</td>
<td>10</td>
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<td>Acute leukemia</td>
<td>3</td>
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<td>Castleman disease</td>
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<td>Myelodysplastic syndrome</td>
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<tr>
<td>Hepatocellular carcinoma</td>
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<tr>
<td>Pancreatic ductal adenocarcinoma</td>
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</tr>
<tr>
<td>Autoimmune-associated</td>
<td>10</td>
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<tr>
<td>Kawasaki disease</td>
<td>5</td>
</tr>
<tr>
<td>Kikuchi disease</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
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<td>Systemic lupus erythematosus</td>
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<tr>
<td>Steven-Johnson syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Uncertain cause</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td></td>
</tr>
<tr>
<td>HLH-2004</td>
<td>21 (35)</td>
</tr>
<tr>
<td>HLH-94</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>Others</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>7</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>5</td>
</tr>
<tr>
<td>Chemotherapy for underlying neoplasm</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroid+antibiotics</td>
<td>4</td>
</tr>
<tr>
<td>Corticosteroid+chemotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroid+IgG+antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>IgG+antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>Corticosteroid+IgG</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid+IgG+cyclosporin A</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid+IgG+cyclosporin A+antibiotics</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid+plasma exchange</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are presented as number (%), median (range), or number only.

HLH, hemophagocytic lymphohistiocytosis; SFTS, severe fever with thrombocytopenia syndrome; IgG, immunoglobulin G.

months (range, 0–204 months). On dividing the patients according to age, it was observed that the number of adult patients with HLH increased each year from 2001 to 2019 (Fig. 1B).

The baseline characteristics of the HLH patients are presented in Table 1. Among 60 patients, 15 underwent genetic testing for HLH, four of whom were confirmed as having primary HLH. Out of the four patients with primary HLH, three patients had FLH while one had XLP1. Forty-eight patients had secondary HLH; 20 patients with infection-associated HLH, 18 with neoplasm-associated HLH, and 10 with autoimmune-associated HLH. In the remaining eight patients, the cause of HLH was unknown. In secondary HLH, EBV was the most common cause of infection-associated HLH (6/20, 30.0%), lymphoma was the most common of the neoplasm-associated HLH (10/18, 55.6%), and Kawasaki disease was the most common cause of autoimmune-associated HLH (5/10, 50.0%). With respect to the treatment regimen, 28 patients were treated with HLH-2004- or HLH-94-based immunotherapy, and the remaining 32 patients were treated with other regimens; corticosteroid was the commonly used medication (20/32, 62.5%).

Each of the 60 HLH patients in this study underwent BM aspiration and biopsy. None of them underwent biopsy of organs (lymph node, spleen, or liver) other than BM. Among 60 patients, hemophagocytosis was found in the BM of 56 patients, but not in that of four patients. There were 26 patients who were included in the BM study, despite not meeting the five diagnostic criteria for HLH; the median hemoglobin level in these patients was 87 g/L (range, 51–157 g/L), the median neutrophil count was 1.95 × 10⁹/L (range, 0.18–14.09 × 10⁹/L), and the median platelet count was 70 × 10⁹/L (range, 15–108 × 10⁹/L). The blood test results of the remaining 34 patients were as follows: the median hemoglobin level was 96 g/L (range, 65–142 g/L), the median neutrophil count was 0.85 × 10⁹/L (range, 0.06–7.71 × 10⁹/L), and the median platelet count was 59 × 10⁹/L (range, 23–384 × 10⁹/L). There were no statistically significant differences in hemoglobin, neutrophil count, and platelet count between the two groups (p = 0.200, p = 0.051, and p = 0.617, respectively).

2. Comparison of the causes of HLH according to the age

The underlying pathophysiology of HLH according to the age group is shown in Fig. 2. In children with HLH, infection was the most common cause (14/35, 40.0%), followed by autoimmune diseases (6/35, 17.1%), uncertain causes (7/35, 20.0%), neoplasm (5/35, 14.3%), and primary HLH (3/35, 8.6%). In adults with HLH, neoplasm was the most common cause (13/25, 52.0%), followed by infection (6/25, 24.0%), autoimmune diseases (4/25, 16.0%), and primary HLH or uncertain cause (both, 1/25, 4.0%).
A higher proportion of children had infection as the cause of HLH (40.0%) than that of adults (24.0%) \((p = 0.029)\). Moreover, neoplasm-associated HLH was more common in adults (52.0%) than in children (14.3%) \((p = 0.004)\). Conversely, the difference in the prevalence of autoimmune diseases, uncertain causes, and primary HLH was not significant between children and adults \((p = 1.000, p = 0.123, \text{and} p = 0.634, \text{respectively})\).

3. Comparison of the variables between pediatric and adult patients with HLH
A comparison of the variables of clinical manifestations, laboratory tests, and treatment regimens between pediatric and adult patients with HLH is presented in Table 2. In the case of clinical manifestations, the prevalence of splenomegaly was higher in adults (24/25, 96.0%) than in children (24/35, 68.6%) \((p = 0.010)\). Conversely, the prevalence of hepatomegaly was higher in children (28/35, 80.0%) than in adults (10/25, 40.0%) \((p = 0.003)\). The levels of the liver enzyme alanine aminotransferase were also higher in children (median, 232 U/L; range, 14–1,230 U/L) than in adults (median, 120 U/L; range, 8–2,019 U/L) \((p = 0.024)\). With respect to the treatment regimen, the proportion of patients treated with HLH-2004/94 protocol was higher among children (28/35, 80.0%) than that in adults (0/25, 0%) \((p < 0.001)\). Differences in the variables for the rest of the clinical features and test findings between children and adults were not significant.

4. Comparison of the variables between survival and death groups of patients with HLH
A comparison of the variables between survival and death groups is presented in Table 3. The median age at diagnosis was lower in the survival group (median, 5.3 years; range, 0.1–76.5 years) than that in the death group (median, 39.3 years; range, 0.1–89 years) \((p = 0.007)\). The prevalence of neoplasm-induced HLHs in the survival group (5/37, 13.5%) was lower than that in the death group (13/23, 56.5%) \((p = 0.001)\). The hemoglobin levels were higher in the survival group (median, 99 g/L; range, 51–157 g/L) than in the death group (median, 86 g/L; range, 64–116 g/L) \((p = 0.006)\). The platelet levels were higher in the survival group (median, \(67 \times 10^9/L\); range, 25–384 \(\times 10^9/L\)) than in the death group (median, \(51 \times 10^9/L\); range, 15–117 \(\times 10^9/L\)) \((p = 0.030)\).

5. Survival of HLH patients
The 5-year OS rate of all patients with HLH \((n = 60)\) was 59.9% (95% CI, 46.6–73.2) \((Fig. 3A)\). The comparison of 5-year OS rates according to the variables by univariate analysis is shown in Table 4. According to age, the difference in 5-year OS between children (72.1%; 95% CI, 56.4–87.8) and adults (37.4%; 95% CI, 11.3–63.5) was significant \((p = 0.007)\). Based on the HLH classification, the 5-year OS rates in patients with primary, infection-associated, neoplasm-associated, autoimmune-associated, and uncertain cause of HLH were 25.0% (95% CI, 0–67.5), 85.0% (95% CI, 69.3–100), 26.7% (95% CI, 3.6–49.8), 87.5% (95% CI, 64.6–100), and 62.5% (95% CI, 29–96), respectively. Comparatively, the difference in the 5-year OS between the primary and infection-associated HLHs was significant \((p = 0.024)\). The difference in the 5-year OS between the neoplasm-associated and infection-associated HLHs was significant \((p = 0.001)\). Additionally, the difference in the 5-year OS between the neo-
plasm-associated and autoimmune-associated HLHs was significant \((p = 0.010)\). The 5-year OS rate, according to the HLH classification, is also shown as a graph in Fig. 3B. As per laboratory results, hemoglobin level of <90 g/L or platelet count of <50 × 10^9/L at initial diagnosis of HLH were risk factors for a low 5-year OS rate.

In terms of the treatment regimen, the 5-year OS rate in patients treated with HLH-2004 protocol was 74.5% (95% CI, 54.9–94.1), in those treated with HLH-94 protocol was 68.6% (95% CI, 32.1–100), and in patients who received other treatments was 45.8% (95% CI, 25.0–66.6). The difference in the 5-year OS rate between HLH-2004 and HLH-94 protocol groups was not significant \((p = 0.904)\). The difference in the 5-year OS rate between patients treated with HLH-2004/94 (73.1%; 95% CI, 55.9–90.3) and other treatments (45.8%; 95% CI, 25.0–66.6) was significant \((p = 0.017)\). By multivariate analysis using the Cox proportional hazards model, neoplasm-induced HLH (hazard ratio, 4.446; 95% CI, 1.876–10.538; \(p = 0.001\)) and platelet count of <50 × 10^9/L at initial diagnosis of HLH (hazard ratio, 3.298; 95% CI, 1.373–7.92; \(p = 0.008\)) were identified as independent risk factors of death in patients with HLH.

### Discussion

In this study, we retrospectively investigated the causes and survival rates in children and adults with different HLH subtypes. Moreover, we analyzed the differences in clinical characteristics between children and adults with HLH. Based on the statistical analyses of this study, HLH was observed primarily in children (median age, 7 years); however, during the period from 2001 to 2019, the number of adult patients diagnosed with HLH had increased. During the review of the medical data for this retrospective study, several patients suspected to have HLH and treated with corticosteroids or immunoglobulins were not included in this study because they had not undergone all tests corresponding to the diagnostic criteria of HLH. Therefore, the increase in the number of diagnoses...
Table 3. Comparison of the variables between the survival group and death group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival group (n = 37)</th>
<th>Death group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>20:17</td>
<td>15:8</td>
<td>0.432</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>5.3 (0.1–76.5)</td>
<td>39.3 (0.1–89)</td>
<td>0.007</td>
</tr>
<tr>
<td>Primary HLH</td>
<td>1 (2.7)</td>
<td>3 (13.0)</td>
<td>0.153</td>
</tr>
<tr>
<td>Infection-associated HLH</td>
<td>17 (45.9)</td>
<td>3 (13.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Neoplasm-associated HLH</td>
<td>5 (13.5)</td>
<td>13 (55.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Autoimmune-associated HLH</td>
<td>9 (24.3)</td>
<td>1 (4.3)</td>
<td>0.073</td>
</tr>
<tr>
<td>Uncertain cause HLH</td>
<td>5 (13.5)</td>
<td>3 (13.0)</td>
<td>&gt; 0.050</td>
</tr>
<tr>
<td>EBV</td>
<td>6/32 (18.8)</td>
<td>5/22 (22.7)</td>
<td>0.743</td>
</tr>
<tr>
<td>Fever</td>
<td>37 (100)</td>
<td>23 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>27 (73.0)</td>
<td>21 (91.3)</td>
<td>0.107</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>25 (67.6)</td>
<td>13 (56.5)</td>
<td>0.421</td>
</tr>
<tr>
<td>Neurologic symptom or sign</td>
<td>4 (10.8)</td>
<td>4 (17.4)</td>
<td>0.468</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (35.1)</td>
<td>5 (21.7)</td>
<td>0.387</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>99 (51–157)</td>
<td>86 (64–116)</td>
<td>0.006</td>
</tr>
<tr>
<td>Neutrophil count ( x 10^9/L)</td>
<td>0.9 (0.13–14.1)</td>
<td>1 (0.06–10.2)</td>
<td>0.638</td>
</tr>
<tr>
<td>Platelet count ( x 10^9/L)</td>
<td>67 (25–384)</td>
<td>51 (15–117)</td>
<td>0.030</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>228 (47–742)</td>
<td>206 (48–347)</td>
<td>0.335</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1.48 (0.70–5.00)</td>
<td>1.40 (0.45–6.18)</td>
<td>0.893</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>3,200 (528–204,887)</td>
<td>2,935 (185–57,186)</td>
<td>0.850</td>
</tr>
<tr>
<td>sCD25 (U/mL)</td>
<td>4,285 (825–10,013)</td>
<td>17,647 (1,139–27,060)</td>
<td>0.142</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td>33 (89.2)</td>
<td>23 (100)</td>
<td>0.288</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>307 (11–5,137)</td>
<td>285 (22–4,829)</td>
<td>0.238</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>178 (8–2,019)</td>
<td>120 (14–1,043)</td>
<td>0.110</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1,749 (262–5,861)</td>
<td>1,164 (437–15,062)</td>
<td>0.110</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.0 (0.3–11.8)</td>
<td>1.2 (0.1–8.2)</td>
<td>0.171</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>0.6 (0.1–8.8)</td>
<td>1.4 (0–6.2)</td>
<td>0.710</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>12.9 (11.0–22.3)</td>
<td>13.8 (12.9–16.5)</td>
<td>0.229</td>
</tr>
<tr>
<td>INR</td>
<td>1.17 (0.99–2.07)</td>
<td>1.27 (0.93–2.85)</td>
<td>0.368</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>40.1 (26.0–79.6)</td>
<td>38.6 (21.6–200.0)</td>
<td>0.681</td>
</tr>
<tr>
<td>HLH-2004/94 treatment</td>
<td>21 (56.8)</td>
<td>7 (30.4)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

Values are presented as number only, number (%), or median (range). HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein–Barr virus; sCD25, soluble CD25; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

Fig. 3. (A) In all patients with hemophagocytic lymphohistiocytosis (HLH) (N=60), the 5-year overall survival (OS) rate is 59.9% (95% CI, 46.6–73.2). (B) The 5-year OS according to the classification of HLH.
Table 4. Comparison of OS rate of patients with HLH according to the variables by univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>5-year OS rate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 18 (n = 25)</td>
<td>37.4</td>
<td>11.3–63.5</td>
<td>0.007</td>
</tr>
<tr>
<td>&lt; 18 (n = 35)</td>
<td>72.1</td>
<td>56.4–87.8</td>
<td></td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td></td>
<td></td>
<td>0.932</td>
</tr>
<tr>
<td>Primary HLH (n = 4)</td>
<td>25.0</td>
<td>0–67.5</td>
<td></td>
</tr>
<tr>
<td>Infection-associated HLH (n = 20)</td>
<td>85.0</td>
<td>69.3–100</td>
<td></td>
</tr>
<tr>
<td>Neoplasm-associated HLH (n = 18)</td>
<td>26.7</td>
<td>3.6–49.8</td>
<td></td>
</tr>
<tr>
<td>Autoimmune-associated HLH (n = 10)</td>
<td>87.5</td>
<td>64.6–100</td>
<td></td>
</tr>
<tr>
<td>Uncertain cause HLH (n = 8)</td>
<td>62.5</td>
<td>29.0–96.0</td>
<td></td>
</tr>
<tr>
<td><strong>EBV</strong></td>
<td></td>
<td></td>
<td>0.922</td>
</tr>
<tr>
<td>Positive (n = 11)</td>
<td>63.6</td>
<td>35.2–92</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 43)</td>
<td>55.7</td>
<td>39.2–72.2</td>
<td></td>
</tr>
<tr>
<td><strong>Splenomegaly</strong></td>
<td></td>
<td></td>
<td>0.164</td>
</tr>
<tr>
<td>Positive (n = 48)</td>
<td>54.8</td>
<td>39.5–70.1</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 12)</td>
<td>83.3</td>
<td>62.1–100</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatomegaly</strong></td>
<td></td>
<td></td>
<td>0.216</td>
</tr>
<tr>
<td>Positive (n = 38)</td>
<td>66.5</td>
<td>50.8–82.2</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 22)</td>
<td>46.0</td>
<td>21.3–70.7</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic symptom or sign</strong></td>
<td></td>
<td></td>
<td>0.619</td>
</tr>
<tr>
<td>Positive (n = 8)</td>
<td>30.0</td>
<td>0–75.3</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 52)</td>
<td>63.4</td>
<td>49.7–77.1</td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
<td></td>
<td>0.308</td>
</tr>
<tr>
<td>Positive (n = 18)</td>
<td>71.3</td>
<td>80.0–92.7</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 42)</td>
<td>55.4</td>
<td>38.9–1.9</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobin level (g/L)</strong></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>≥ 90 (n = 29)</td>
<td>41.4</td>
<td>22.8–60.0</td>
<td></td>
</tr>
<tr>
<td>&lt; 90 (n = 31)</td>
<td>80.1</td>
<td>64.0–96.2</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil count (× 10⁹/L)</strong></td>
<td></td>
<td></td>
<td>0.978</td>
</tr>
<tr>
<td>≥ 0.5 (n = 47)</td>
<td>60.9</td>
<td>45.8–76.0</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 (n = 12)</td>
<td>51.3</td>
<td>19.4–83.2</td>
<td></td>
</tr>
</tbody>
</table>

HLH, hemophagocytic lymphohistiocytosis; OS, overall survival; CI, confidence interval; EBV, Epstein–Barr virus; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; PT, prothrombin time; aPTT, activated partial thromboplastin time.

of adult patients with HLH during the study period is not exactly an increase in HLH cases, but the result of active examinations with increasing awareness among the medical staff. The awareness of the symptoms of HLH as well as the diagnostic criteria is crucial for physicians because early diagnosis and prompt therapy are crucial for the outcome given the life-threatening nature of HLH.

As with the previous Korean nationwide pediatric HLH data from the Korea Histiocytosis Working Party [13], EBV was the main cause of secondary HLH. This finding is an example of the higher rates of EBV-induced secondary HLH in the Asian population [19]. Apart from EBV, various other organisms may also cause HLH, as reported by previous studies [13,16]. In this study, infection was the main cause of HLH in children. However, neoplasm (mainly lymphoma) was the main cause of HLH in adults, which is consistent with other international data [16,19]. In terms of clinical manifestations and laboratory tests, hepatomegaly with increased aminotransferase was predominant in pediatric patients with HLH; conversely, splenomegaly was more apparent in adult patients with HLH in this study. This clinical aspect is also considered to be related to the difference in causative agents between children and adults.

In the case of pediatric HLH patients in this study, the 5-year OS rate was 72.1% (n = 35). In a previous nationwide data of pediatric
HLH in Korea, the 5-year OS rate was 68% [13]. Although it is difficult to directly compare these results because of the small number of subjects in this study, it can be said that the survival rates were relatively similar. The difference in the 5-year OS between the HLH-2004 and HLH-94 protocols was not significant \( (p = 0.904) \). These data are the same as previously published data [11,12]. However, we can consider the improvement of supportive and conservative therapy over time from HLH-94 to HLH-2004. In the case of adult HLH patients, specific therapeutic guidelines have not yet been confirmed worldwide. It seems that each institution decides the treatment direction according to the patient’s condition [16]. As in our study, most adult HLH patients were treated with corticosteroids, immunoglobulin G, or cyclosporin A [16]. Thus, there was no remarkable difference between the previous data and the present study. Recently, recommendations for adult HLH patients have been published that can be useful in determining treatment directions [20].

Although an accurate comparison is difficult considering the very small number of primary HLHs in this study, the most common cause of primary HLH was FHL type 3 with UNCI3D variants, similar to previous Korean data [13]. Interestingly, one patient with FHL type 2 (PRFI variant) in this study was a 28.3-year-old man. Initially, this patient was diagnosed with T-cell lymphoma that progressed aggressively, and he met the criteria of HLH with multiple organ failure. Because of this extraordinary disease course, the physician performed a genetic test and he was eventually diagnosed with adult FHL. Although primary HLH is commonly diagnosed in children, several examples of genetically confirmed HLH in adults have recently been reported [21-23]. Allogenic stem cell transplantation is a recommended therapy for adult primary HLH [23]. Furthermore, a 9.2-year-old pediatric patient with XLP1 (SH2D1A variant) was initially diagnosed with EBV-associated lymphoproliferative disease, which also demonstrated very aggressive features of HLH with multiple organ failure. As there was no pathogenic variant based on the conventional genetic tests for PRFI and UNCI3D, the pediatrician ordered next-generation sequencing, and finally, he was diagnosed with XLP1. These two patients with FHL would have been classified as neoplasm-associated secondary HLH unless additional genetic testing was performed. Therefore, physicians must not only perform all tests in the diagnostic criteria but also consider genetic testing for the accurate diagnosis of HLH. In this study, some patients with FHL may have been classified as patients with neoplasm-associated HLH or uncertain cause HLH because genetic testing had not been thoroughly conducted. Additionally, patients with uncertain cause HLH may include those who had not been thoroughly screened for underlying infective organisms.

In all patients with HLH, the 5-year OS rate was 59.9% in this study. Univariate analysis showed that the OS rate of HLH patients was affected by the age of diagnosis, type of HLH, treatment with HLH protocol, anemia, or thrombocytopenia. However, the underlying cause, neoplasm-associated HLH, was the only independent risk factor for death by multivariate analysis in this study. Therefore, optimal management for patients with neoplasm-associated HLH requires discussion. Treatment algorithms for HLH, such as HLH-94 and HLH-2004, are mainly based on pediatric protocols, which may result in unnecessary toxicity or overtreatment in adults [20]. Thus, an age-dependent modified therapeutic approach, such as individualized tailoring or reduction of treatment duration, must be considered [20].

This study has some limitations. First, this study was performed retrospectively; thus, there is a possibility of selection bias among the study populations. During the review of the chart, several children as well as adults had not undergone tests such as soluble CD25 or NK cell activity. Although several patients had the characteristics of HLH, they were not enrolled in this study because they did not undergo the tests and did not meet the diagnostic criteria. Therefore, HLH may have been underdiagnosed during the study period. Second, adult patients with HLH were enrolled according to the HLH-2004 criteria, which focused on pediatric patients to clarify the scope of the study subjects. The HLH-2004 criteria have not yet been formally validated for adults, and thus, it continues to be based on expert opinion [20]. Various case series have used modified HLH-2004 criteria [24].

In conclusion, this is the first Korean study that analyzed the underlying causes and patients’ survival in both children and adults with HLH. Additionally, we compared the clinical characteristics according to the age group and analyzed the survival rate according to the HLH subtypes. The most common cause of HLH in children was infection, while that in adults was neoplasm. The 5-year OS rate for all HLH patients was 59.9%. Neoplasm-induced HLH and platelet count of \(< 50 \times 10^9/\text{L}\) at the time of diagnosis were independent risk factors for poor prognosis in patients with HLH. Therefore, it is essential to accurately identify the cause in patients with HLH. In addition, the optimal treatment regimen for neoplasm-induced HLH requires further discussion to improve the outcome for adult patients.

Notes

Ethical statements

This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No: 2019-11-
006), and the requirement for informed consent was waived.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization: YJS, HSK, HJL, JML, MHH, YRD; Data curation: AK, HJL, MHH; Formal analysis: NJ, HSK, JML, YRD; Investigation: HJL, JML, MHH; Supervision: HSK, YRD; Writing-original draft: AK, YJS; Writing-review & editing: YJS.

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References


Clinical effectiveness of omental transposition in facilitating perineal wound healing after abdominoperineal resection: a systematic review

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Background: Omental transposition has been used to facilitate perineal wound healing in patients undergoing abdominoperineal resection (APR). However, there is no high-level evidence supporting the effectiveness of omental transposition in this regard. This study aimed to investigate the clinical efficacy of omental transposition in facilitating perineal wound healing after APR.

Methods: In this systematic review, we systematically searched the PubMed/MEDLINE, Embase, Scopus, Cochrane Library, and Web of Science databases for literature regarding the topic of our study. Studies published since the inception of each database were considered for review. The outcomes of interest were the perineal wound healing rate at 1 and 3 months postoperatively, perineal wound infection rate, and perineal wound healing period.

Results: Of the 1,923 studies identified, four articles representing 819 patients (omental transposition patients, n = 295) were included in the final analysis. The wound healing rates at 1 and 3 months postoperatively in the omental transposition group (68.5% and 79.7%, respectively) did not significantly differ from those in the control group (57.4% and 78.7%, respectively) (p = 0.759 and p = 0.731, respectively). Perineal wound infection and chronic wound complication rates, including sinus, dehiscence, and fistula rates, also did not significantly differ between the omental transposition (8% and 7%, respectively) and control (11% and 7%, respectively) groups (p = 0.221 and p = 0.790, respectively).

Conclusion: Our results suggest that omental transposition does not affect perineal wound healing in patients who undergo APR.

Keywords: Abdominoperineal resection; Omental transposition; Perineal wound; Wound healing

Introduction

Since abdominoperineal resection (APR) was first introduced by Miles [1] nearly a century ago, it has been an important surgical method for refractory anorectal diseases, including low rectal cancer, select anal cancer, and inflammatory bowel disease [2,3]. Although the number of patients requiring APR has decreased with the advancement of medical devices and surgical techniques, almost 20% of all patients with low rectal cancer require APR.

Delayed perineal wound healing and perineal wound complications are the most common post-APR complications. The rates of perineal wound complications following APR and delayed perineal wound healing over 6 months have been reported to be as high...
as 50% [4-7] and 25% [8], respectively. The high rate of perineal wound complications increases the length of hospital stay, readmission rates, and medical costs [9,10]. Several possible explanations include the formation of dead space in the presacral area after rectal resection and accumulation of fluids in the dead space, tension in the approximated perineum due to rigid side walls, and bacterial contamination originating from fecal material [8,11].

Surgeons have developed several techniques to reduce the rate of perineal wound complications, including the use of omental pedicles [2,11,12], local antibiotics [13], negative pressure wound management devices [14], and mucocutaneous flaps [11]. However, omental transposition is the easiest technique to perform and requires no additional cost. The omentum is considered the “policeman of the abdomen” because it consists of fatty tissue that plays a key role in resisting infection. Additionally, its fatty tissue and apron-like appearance allow for easy mobilization into the pelvis and filling of the presacral dead space [2,9] (Fig. 1).

However, there is no high-level evidence regarding the effectiveness of omental transposition in facilitating perineal wound healing because almost all related studies have been retrospective and have had small sample sizes. Therefore, this study aimed to investigate the clinical efficacy of omental transposition in facilitating perineal wound healing after APR.

Materials and methods

1. Study design and literature search
In this systematic review, we systematically searched the PubMed/MEDLINE, Embase, Scopus, Cochrane Library, and Web of Science databases for literature. Studies published between the inception of each database, the earliest date being January 1, 1970, and May 9, 2018, were considered for review. This systematic literature search was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15]. The keywords used for the literature search were as follows: “omental transposition,” “omental flap,” “omental flap transposition,” “omental pedicle flap,” “omentopexy,” “omentoplasty,” “abdominoperineal resection,” “APR,” “abdominoperineal excision,” “proctectomy,” “colo-proctectomy,” “Miles’ operation,” “wound infection,” “perineal wound infection,” “wound complication,” and “perineal wound complication.”

Two authors independently selected eligible studies from the databases by reviewing the titles and abstracts of the studies. If there was a disagreement between reviewers concerning study eligibility, they discussed it until reaching a consensus. If necessary, an independent third author was involved in the discussion.

2. Selection and exclusion criteria
Only original articles and clinical studies, including case-control, cross-sectional, and cohort studies that investigated the efficacy of omental transposition in facilitating perineal wound healing were included in this review. No language restriction was applied. Studies were excluded if perineal wound-related morbidities were not reported, and if they did not report on comparable groups with omental transposition. Studies that were published as complete academic papers in peer-reviewed journals, while only presenting an abstract were also excluded. If we identified duplicate studies or multiple studies that presented data from the same source, the study that was published first was considered for review.

3. Measured outcomes
The primary outcomes of this study were the perineal wound healing rates at 1 and 3 months postsurgery. Secondary outcomes were the perineal wound healing period, length of hospital stay, and perineal wound infection rate. Subgroup analyses were permitted if data for secondary outcomes could be extracted from more than two articles among the included studies.
Results

1. Study inclusion

Our literature search yielded 1,923 studies. Of these, 144 duplicate articles were excluded. After the remaining 1,757 articles were screened based on their titles and abstracts, only 22 articles were selected for a full-text review. After full-text review, 18 articles were excluded. Thus, four articles representing a total of 819 patients were included in the final analysis [8,16-18]. Fig. 2 provides a PRISMA flow chart that outlines the article selection process.

2. General characteristics of the included studies

Of the four included studies, three were from Europe (France, the Netherlands, and Switzerland) and one was from Taiwan. Additionally, three were retrospective studies, and one was a prospective, multicenter, non-randomized study. Of the 819 patients, 295 (36.0%) underwent omental transposition, and 549 (67.0%) were

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**Table 1. Summarization of the four including studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Type of study</th>
<th>Mean age (yr)</th>
<th>Sex (male: female)</th>
<th>Disease (n)</th>
<th>Omental transposition (n)</th>
<th>Control (n)</th>
<th>Major measured outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>John and Buchmann [8]</td>
<td>1991</td>
<td>Switzerland</td>
<td>Retrospective</td>
<td>63</td>
<td>44:30</td>
<td>Malignancy (71), benign (3)</td>
<td>38</td>
<td>36</td>
<td>Delayed wound healing, influence on perineal wound healing by grafted omentum</td>
</tr>
<tr>
<td>Wang et al. [16]</td>
<td>1994</td>
<td>Taiwan</td>
<td>Retrospective</td>
<td>56.7</td>
<td>49:33</td>
<td>Malignancy (83), benign (0)</td>
<td>21</td>
<td>82</td>
<td>Healing of the wound, postoperative complication</td>
</tr>
<tr>
<td>Hay et al. [17]</td>
<td>1997</td>
<td>France</td>
<td>Prospective</td>
<td>64</td>
<td>101:64</td>
<td>Malignancy (165), benign (0)</td>
<td>64</td>
<td>101</td>
<td>The number of healed perineums at 1 month, time to complete primary healing</td>
</tr>
<tr>
<td>Blok et al. [18]</td>
<td>2018</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>67</td>
<td>332:145</td>
<td>Malignancy (477), benign (0)</td>
<td>172</td>
<td>305</td>
<td>Non-healing rate of the perineal wound, 30-day mortality/complication/readmission</td>
</tr>
</tbody>
</table>

*Sum of the three control groups: suture of the pelvic perineum with open drainage (n=20), suture of the pelvic perineum and perineum with simple drainage (n=30), and suture of the pelvic peritoneum and perineum with suction drainage (n=32).
males. Most patients underwent surgery for malignancy, except for three patients who had inflammatory bowel disease. The characteristics of the included studies are summarized in Table 1.

3. Perineal wound healing rate

Table 2 shows the rate of perineal wound healing at 1 and 3 months postsurgery. All four studies revealed no significant differences in perineal wound healing rates between the omental transposition and control groups at 1 and 3 months postsurgery. The mean perineal wound healing rate at one month postsurgery was 58.6% in the omental transposition group and 57.4% in the control group ($p = 0.759$). The mean perineal wound healing rate at 3 months postsurgery was 79.7% in the omental group and 78.7% in the control group ($p = 0.731$).

4. Perineal wound healing period, perineal wound infection rate, and length of hospital stay

Of the four included studies, two presented data regarding the perineal wound healing period, three presented data regarding perineal wound infection rates, and three presented data regarding the length of hospital stay (Table 3). In one study, the omental transposition group required significantly fewer days to achieve perineal wound healing than the control group. However, another study reported no significant differences between the two groups in this regard. Additionally, two studies reported no significant differences in the perineal wound infection rates between the two groups. However, one study showed that perineal wound infection rates were lower in the omental transposition group than in the control group, but the sum of the infection rates was not significantly different between the two groups. Lastly, three studies reported that the mean hospital stay and mean length of hospital stay did not significantly differ between the two groups.

## Discussion

Perineal wound complications are one of the main causes of post-APR morbidity and discomfort. In the early period after the introduction of APR, perineal wounds were opened with packing after the operation, or the perineal skin was loosely approximated with the drain inserted [19]. This method was previously used for perineal wound management because it was believed that perineal wound healing via primary closure was impossible due to the large dead space formed after APR. However, this traditional method can cause considerable discomfort to patients and prolonged hospitalization periods. Therefore, many authors have proposed methods for the primary closure of perineal wounds in order to achieve favorable results [20,21]. However, despite these reports, the incidence of failed healing in closed perineal wounds remains high [21]. It is believed that fluid or blood clots may be collected in the postsurgical dead space, thereby causing pelvic and perineal sepsis, abscess formation, and delayed wound healing.

To prevent fluid collection in the presacral dead space, surgeons have attempted to fill the dead space with omental pedicle grafts [22]. Studies have shown that omental transposition reduces the
number of infectious post-APR complications, and recent systematic reviews have reported that it reduces perineal wound morbidity rates [8,17,23]. Additionally, omental transposition improves antibiotic delivery and local immunity by promoting angiogenesis, thereby preventing secondary infections [24]. Furthermore, omental pedicles are expected to prevent the small bowel from descending into the pelvic cavity, thereby reducing the risk of ileus.

However, contrary to previous reports and posited mechanisms for preventing failed/delayed wound healing, our systematic review showed that omental transposition did not improve perineal wound healing in APR patients. Omental transposition techniques have several limitations. For instance, mobilization of the great omentum requires additional abdominal incisions [25], and the operation time has been reported to be 15 to 20 minutes more [26]. Moreover, omental transposition-related morbidities, including omental necrosis caused by compromised perfusions [27], local discharge associated with partial necrosis [28], and obstruction due to adhesion or band [29], have also been reported. Additionally, if the size of the omentum is insufficient to fill the pelvic cavity, fluid collection and abscess formation can occur because of the presence of residual cavities.

In a recently published meta-analysis, it was found that omental transposition had no effect on wound healing [30]. Moreover, this meta-analysis reported omental transposition-related complications. However, unlike our study, the meta-analysis’ outcomes included wound healing and postomental transposition complications, such as perineal hernias, ileus, and omental flaps. They reported that the incidence of perineal hernias significantly increased due to omental transposition. Theoretically, omenta with long vascular pedicles descend further than small bowel loops, which are limited in their descent by the mesentery length. Therefore, fatty and non-fibrous omenta may cause hernias, as they apply constant pressure on the perineal skin while patients remain in the standing position.

This study had several limitations. First, the definitions of outcome variables in the included studies were inconsistent, and some outcomes, such as perineal wound healing and wound infection, were not consistently reported in each study. Second, since our outcomes were limited to wound healing and wound infection, our review only included four studies. Therefore, the number of patients included in the omental transposition and control groups was small. Third, since there was no control for certain variables, such as patient demographics and the American Society of Anesthesiologists status, correction for population heterogeneity was not performed. Fourth, of the four studies included in this review, three were conducted before the year 2000. The development of perioperative surgical and oncological practices was remarkable during this period, and it is likely that different surgical and oncological approaches were used. Lastly, the main limitation of our study was the possibility of allocation bias. Surgeons may have adapted omental transposition for patients with the potential for large presacral spaces in studies that did not involve randomized controlled trials. As such, it is possible that wound complications occurred more frequently in the omental transposition group.

In conclusion, this systematic review reveals that omental transposition does not have a beneficial effect on perineal wound healing in after APR.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization: Sungjin K, SIK, Sohyun K, JHK; Data curation: SIK, Sohyun K; Formal analysis: Sungjin K, SIK, JHK; Methodology: Sungjin K; Project administration, Software, Supervision: SIK; Visualization: Sohyun K; Investigation: Sungjin K, SIK, Sohyun K, JHK; Resources: Sungjin K; Validation: Sohyun K, JHK; Writing - original draft: Sungjin K; Writing - review & editing: Sungjin K, SIK, Sohyun K, JHK.

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References

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Significance of albumin to globulin ratio as a predictor of febrile urinary tract infection after ureteroscopic lithotripsy

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Background: We aimed to analyze the effectiveness of albumin to globulin ratio (AGR) in predicting postoperative febrile urinary tract infection (fUTI) after ureteroscopic lithotripsy (URS) and retrograde intrarenal surgery (RIRS).

Methods: From January 2013 to May 2018, 332 patients underwent URS and RIRS. The rate of postoperative fUTI and risk factors for postoperative fUTI were analyzed using logistic regression. Patients were divided into postoperative fUTI and non-postoperative fUTI (non-fUTI) groups. AGR with other demographic and perioperative data were compared between the two groups to predict the development of fUTI after URS.

Results: Of the 332 patients, postoperative fUTI occurred in 41 (12.3%). Preoperative pyuria, microscopic hematuria, diabetes mellitus, hypoalbuminemia, and hyperglobulinemia were more prevalent in the fUTI group. Patients in the fUTI group had larger stone size, lower preoperative AGR, longer operation time, and longer preoperative antibiotic coverage period. In a multivariable logistic analysis, preoperative pyuria, AGR, and stone size were independently correlated with postoperative fUTI (p<0.001, p=0.008, and p=0.041, respectively). Receiver operating curve analysis showed that the cutoff value of AGR that could predict a high risk of fUTI after URS was 1.437 (sensitivity, 77.3%; specificity, 76.9%), while the cutoff value of stone size was 8.5 mm (sensitivity, 55.3%; specificity, 44.7%).

Conclusion: This study demonstrated that preoperative pyuria, AGR, and stone size can serve as prognostic factors for predicting fUTI after URS.

Keywords: Albumin to globulin ratio; Biomarkers; Nephrolithiasis; Ureteroscopy; Urinary tract infections
of the most common postoperative complications after RIRS, and it has been reported that the rate varies widely between studies [2]. Postoperative UTI can be life-threatening because it can lead to sepsis and septic shock. If it advances to septic shock, higher postoperative mortality and longer hospital stays would be expected [3]. Attempts have been made to determine the risk factors to minimize postoperative febrile UTI. Some studies have suggested that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be effective biomarkers for predicting postoperative UTI after percutaneous nephrolithotomy [4,5].

Albumin and globulin are the main components of serum proteins, and these proteins play a pivotal role in acute inflammatory reactions and chronic inflammation. In this study, we validated the effectiveness of the albumin to globulin ratio (AGR) in predicting postoperative febrile UTI (fUTI). However, to date, few studies have evaluated AGR as a predictor of postoperative infection after URS and RIRS. AGR has already been studied in different types of cancer, and it has been found to be a possible prognostic marker for cancer [6]. However, so far, there have been limited studies investigating whether AGR can be used as a prognostic marker to predict postoperative fUTI in URS and RIRS.

Materials and methods

Patients who underwent URS and RIRS from January 2013 to May 2018 in a tertiary general hospital in South Korea were included in this study. Patients with bilateral stones and those without preoperative serum albumin and globulin data were excluded from this study. A total of 332 patients were included in the study. Patients were divided into the postoperative fUTI group (fUTI group) and non-postoperative fUTI group (non-fUTI group). Postoperative fUTI was diagnosed if the patient’s body temperature was above 38°C with pyuria and other fever foci that should have been excluded within a week after the surgery. Preoperative clinical data including age, sex, and underlying diseases such as hypertension, diabetes mellitus (DM), chronic renal failure (CRF) defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m², body mass index (BMI), presence of pyuria, presence of microscopic hematuria, presence of preoperative ureteral stent and percutaneous nephrostomy (PCN), and history of previous URS and RIRS were collected. Stone size prior to surgery was measured using noncontrast computed tomography, and the largest diameter was recorded. Preoperative pyuria was defined as more than five to 10 white blood cells (WBC) per high-power field (HPF), while preoperative microscopic hematuria was defined as more than three red blood cells per HPF on laboratory urinalysis. Blood samples were collected within 1 month prior to surgery, and AGR was calculated using the equation of AGR ratio = albumin/to-tal protein without albumin. WBC counts were collected to demonstrate their effectiveness as an inflammatory indicator. Sterile preoperative urine culture was performed before surgery.

The patients were admitted to the hospital a day before surgery. None of the patients had preoperative fever. Fluoroquinolone was administered from the day of admission to the day of surgery. Under spinal or general anesthesia, we used a semi-rigid ureteroscope and/or flexible ureteroscope for lithotripsy. A hydrophilic guidewire was used to engage the semi-rigid ureteroscope into the ureter. For renal stones, we used Amplatz Super Stiff guidewire (Cook Medical Inc., Bloomington, IN, USA) and Flexor Ureteral Access Sheath (Cook Medical Inc.) prior to the engagement of the flexible ureteroscope. A 200- or 365-micro holmium laser lithotripter was used to fragment the target stone into pieces, with a power of 20 joules and 0.5 frequency. We used a stone basket to remove the fragments larger than 2 mm., and six French ureteral stents were kept for 2 weeks after the surgery. Patients were discharged on postoperative day one, and antibiotics were prescribed for 5 days if there was no evidence of postoperative UTI.

Chi-square test for categorical variables and Student t-test for continuous variables were used to analyze the baseline characteristics. Multivariate logistic regression analysis was performed using the forward-likelihood ratio method, and p-values, odds ratios (ORs), and 95% confidence intervals (CIs) were collected. A receiver operating characteristic (ROC) curve was used to determine the optimal cutoff value and its sensitivity and specificity. Statistical significance was set at $p < 0.05$. IBM SPSS version 18.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the analysis.

Results

Table 1 shows the baseline characteristics of the patients and the chi-square test between the two groups. Of the 332 patients, 41 were included in the fUTI group and 291 were included in the non-fUTI group. Of all the patients, 135 had hypertension, 70 had DM, and nine had CRF. The mean age was 56.9 ± 13.3 years, mean stone size was 10.1 ± 4.2 mm, and mean preoperative AGR was 1.64 ± 0.43. Preoperative pyuria, microscopic hematuria, hyperalbuminemia, hyperglobulinemia, and DM were more prevalent in the fUTI group ($p = 0.001$, $p = 0.004$, $p = 0.001$, $p = 0.041$, and $p = 0.037$, respectively). Patients in the fUTI group had larger stone size, lower preoperative AGR, longer operation time, and longer preoperative antibiotic coverage period ($p = 0.004$, $p = 0.003$, $p = 0.028$, and $p = 0.003$, respectively). There were no statistically significant differences in hypertension, CRF, age, BMI, operation histo-
Table 1. Comparison of demographic, clinical, and postoperative data between postoperative fUTI group and non-fUTI group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Postoperative fUTI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>332 (100)</td>
<td>41 (12.3)</td>
<td>291 (87.7)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.9 ± 13.3</td>
<td>57.2 ± 12.0</td>
<td>56.9 ± 13.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.128</td>
</tr>
<tr>
<td>Male</td>
<td>227 (68.4)</td>
<td>32 (78.0)</td>
<td>195 (67.0)</td>
</tr>
<tr>
<td>Female</td>
<td>105 (31.6)</td>
<td>9 (22.0)</td>
<td>96 (33.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>135 (40.7)</td>
<td>17 (41.5)</td>
<td>118 (40.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70 (21.1)</td>
<td>14 (34.1)</td>
<td>56 (19.2)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>9 (2.7)</td>
<td>1 (2.4)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>History of stone operation</td>
<td>59 (17.8)</td>
<td>9 (22.0)</td>
<td>50 (17.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 ± 4.0</td>
<td>25.6 ± 5.1</td>
<td>25.3 ± 3.9</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td>0.445</td>
</tr>
<tr>
<td>URS</td>
<td>131 (39.5)</td>
<td>18 (43.9)</td>
<td>113 (38.8)</td>
</tr>
<tr>
<td>RIRS</td>
<td>180 (54.2)</td>
<td>22 (53.7)</td>
<td>158 (54.3)</td>
</tr>
<tr>
<td>URS+RIRS</td>
<td>21 (6.3)</td>
<td>1 (2.4)</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>Preoperative pyuria</td>
<td>54 (16.3)</td>
<td>9 (22.0)</td>
<td>45 (15.5)</td>
</tr>
<tr>
<td>Preoperative ureteral stent</td>
<td>6 (1.8)</td>
<td>2 (4.9)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Preoperative PCN</td>
<td>51 (15.4)</td>
<td>8 (19.5)</td>
<td>43 (14.8)</td>
</tr>
<tr>
<td>Stone size (mm)</td>
<td>10.1 ± 4.2</td>
<td>11.7 ± 3.9</td>
<td>9.9 ± 4.1</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>75.1 ± 31.6</td>
<td>83.3 ± 32.2</td>
<td>74.0 ± 31.3</td>
</tr>
<tr>
<td>Preoperative AGR</td>
<td>1.64 ± 0.43</td>
<td>1.46 ± 0.35</td>
<td>1.66 ± 0.44</td>
</tr>
<tr>
<td>Preoperative WBC count (10³/μL)</td>
<td>6,850 ± 2,240</td>
<td>6,874 ± 2,353</td>
<td>6,847 ± 2,228</td>
</tr>
<tr>
<td>Preoperative serum albumin (g/dL)</td>
<td>4.5 ± 0.4</td>
<td>4.2 ± 0.6</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>Preoperative serum globulin (g/dL)</td>
<td>2.9 ± 0.5</td>
<td>3.0 ± 0.6</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Preoperative microscopic hematuria</td>
<td>142 (42.8)</td>
<td>26 (63.4)</td>
<td>116 (39.9)</td>
</tr>
<tr>
<td>Preoperative hydronephrosis</td>
<td>111 (33.4)</td>
<td>19 (46.3)</td>
<td>92 (31.6)</td>
</tr>
<tr>
<td>Stone site</td>
<td></td>
<td></td>
<td>0.144</td>
</tr>
<tr>
<td>Renal</td>
<td>198 (59.6)</td>
<td>23 (56.1)</td>
<td>175 (60.1)</td>
</tr>
<tr>
<td>Upper</td>
<td>70 (21.1)</td>
<td>10 (24.4)</td>
<td>60 (20.3)</td>
</tr>
<tr>
<td>Mid</td>
<td>16 (4.8)</td>
<td>3 (7.3)</td>
<td>13 (4.5)</td>
</tr>
<tr>
<td>Low</td>
<td>48 (14.5)</td>
<td>5 (12.2)</td>
<td>43 (14.8)</td>
</tr>
<tr>
<td>Preoperative antibiotics cover (day)</td>
<td>1.5 ± 2.3</td>
<td>2.5 ± 4.3</td>
<td>1.4 ± 1.8</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.
AGR, albumin to globulin ratio; fUTI, febrile urinary tract infection; low, low ureter stone; mid, mid ureter stone; PCN, percutaneous nephrostomy; renal, renal stone; RIRS, retrograde intrarenal surgery; upper, upper ureter stone; URS, ureteroscopic lithotripsy; WBC, white blood cell.

Discussion

Advancements in laser technology and ureteroscopy have made lithotripsy less invasive and have yielded a higher stone-free rate with fewer complications. One of the most common postoperative complications is UTI, even when prophylactic antibiotics are adequately administered. Fan et al. [7] found that preoperative pyuria was the most important parameter for UTI, and similarly, our study showed that the presence of pyuria prior to surgery signifi-

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Table 2. Multivariate logistic regression analysis for predicting postoperative febrile urinary tract infection after ureteroscopic lithotripsy and/or retrograde intrarenal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis, $p$-value</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Preoperative pyuria</td>
<td>$&lt; 0.001$</td>
<td>5.8 (2.727–12.342)</td>
</tr>
<tr>
<td>Stone size</td>
<td>0.004</td>
<td>1.1 (1.003–1.186)</td>
</tr>
<tr>
<td>Preoperative AGR</td>
<td>0.003</td>
<td>0.4 (0.170–0.771)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.001</td>
<td>0.5 (0.215–1.064)</td>
</tr>
<tr>
<td>Operation time</td>
<td>0.041</td>
<td>1.0 (0.993–1.018)</td>
</tr>
<tr>
<td>Preoperative albumin</td>
<td>0.037</td>
<td>0.5 (0.198–1.434)</td>
</tr>
<tr>
<td>Preoperative globulin</td>
<td>0.028</td>
<td>0.7 (0.245–2.276)</td>
</tr>
<tr>
<td>Preoperative microscopic hematuria</td>
<td>0.004</td>
<td>2.1 (0.951–4.434)</td>
</tr>
<tr>
<td>Preoperative antibiotics cover</td>
<td>0.003</td>
<td>0.9 (0.890–1.134)</td>
</tr>
</tbody>
</table>

AGR, albumin to globulin ratio; CI, confidence interval; OR, odds ratio.

Table 3. Receiver operating characteristics curve analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>SD</th>
<th>$p$-value</th>
<th>95% CI</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGR</td>
<td>0.646</td>
<td>0.048</td>
<td>0.002</td>
<td>0.552–0.741</td>
<td>1.437</td>
<td>77.3</td>
<td>76.9</td>
</tr>
<tr>
<td>Stone size</td>
<td>0.640</td>
<td>0.039</td>
<td>0.004</td>
<td>0.563–0.717</td>
<td>8.5</td>
<td>55.3</td>
<td>44.7</td>
</tr>
</tbody>
</table>

AGR, albumin to globulin ratio; AUC, area under the curve; CI, confidence interval; SD, standard deviation.

cantly contributed to the rate of UTI. Lai and Assimos [8] found that preoperative hydrenephrosis was significantly associated with postoperative infection; however, our study showed that hydrenephrosis was not a contributing factor to fUTI. In our study, some patients with preoperative hydrenephrosis underwent PCN prior to the operation due to ongoing infection or acute renal failure, which may lower the risk of fUTI in patients with preoperative hydrenephrosis.

In our study, the stone size was found to be a risk factor for postoperative fUTI because larger stones may require a longer operation time. Moreover, larger stones might require excessive intrarenal and introuretal irrigation, which can lead to increased renal pelvic pressure, and the whole sequence would contribute to a higher risk of UTI, which is more likely to increase the absorption of bacteriotoxins and true pathogens [9].

Our results also showed that preoperative AGR is a significant factor that is highly associated with the incidence of postoperative fUTI. Patients with a lower AGR ($< 1.437$) were more susceptible to UTI after URS and RIRS. Previous studies have shown the effectiveness of AGR as a postoperative prognostic factor in patients with different cancers [10–12]. Moreover, Jian et al. [13] and Xun et al. [14] showed the validity of low AGR to predict postoperative fUTI in patients who underwent stone removal operation. Albumin and globulins are major serum proteins that reflect nutritional status and systemic inflammation. Low albumin levels usually reflect malnutrition, which makes one more vulnerable to systemic infections, including UTI. In addition, hypoalbuminemia has been found to lower target organ exposure to antibiotics, which decreases the effectiveness of antibiotics [15]. Non-albumin serum proteins are involved in various inflammatory reactions and consist of proteins such as globulin, C-reactive protein (CRP), and complements [16,17]. High globulin components are highly associated with worse prognosis in chronic inflammatory conditions, especially in patients with cancer [18]. High globulin levels reflect the inflammatory and active immune response of a host due to highly accumulated immunoglobulins and CRPs [19]. Hypoalbuminemia and hyperglobulinemia were more prevalent in the fUTI group, but each variable was not found to be a useful predictor of fUTI. Albumin can be influenced by various confounding factors such as stress, illness, hepatic insufficiency, and changes in the volume of body fluids, and this could affect the efficiency and accuracy of albumin as a prognostic marker [20]. Previous studies have proposed that AGR provides an assessment of albumin and globulin together, which could reflect the body’s nutritional status and inflammatory states comprehensively, and this increases its value as a novel biochemical index [20,21]. Thus, patients with a lower AGR could be more susceptible to acute inflammatory conditions (especially fUTI) after surgery.

Our study had some limitations. First, our study had the potential for selection bias due to the retrospective nature of the study design. Second, more inflammatory markers such as NLR, PLR, CRP, and erythrocyte sedimentation rate were not estimated in...
our study due to the retrospective nature of our study design. Finally, because our study population included patients from only one institution, ethnic and geographic variations in stone disease were not reflected in the study population.

Predicting postoperative fUTI after URS and RIRS is important because this complication can be life-threatening and can increase the cost of healthcare, mortality of patients, and hospital stay. Evaluation of preoperative AGR is cost-effective and reliable for predicting postoperative fUTI. According to our study, patients with preoperative pyuria, AGR below 1.437, or stone size greater than 8.5 mm should be monitored closely after surgery. Monitoring vital signs and giving careful attention to clinical symptoms would be necessary to manage postoperative fUTI. Further large-scale prospective studies are required to validate the efficacy of AGR in predicting postoperative fUTI.

Notes

Ethical statements
This was a retrospective study using personal medical records, and informed consent was waived. The study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: 2020-10-009-001).

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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References
Metachronous extranodal natural killer/T-cell lymphoma of nasal type and primary testicular lymphoma

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We report a rare case of metachronous lymphoma with two distinct cell lineages in a 75-year-old man. The patient complained about having nasal obstruction for 2 years and extranodal natural killer (NK)/T-cell lymphoma of the nasal type was diagnosed from a biopsy. The immunohistochemical staining for CD56 and in situ hybridization for Epstein-Barr virus (EBV)-encoded small RNA (EBER-ISH) were positive and the tumor cells were negative for CD20. After 13 months of concurrent chemoradiotherapy, the patient presented with swelling of the left testis. Positron emission tomography scan detected an abnormal uptake in the testis. A diffuse large B-cell lymphoma, not otherwise specified, was diagnosed from subsequent radical orchiectomy. The immunohistochemical staining revealed to be positive for CD20, BCL2, BCL6, and MYC and negative for CD10 and EBER-ISH.

Keywords: Diffuse large B-cell lymphoma; Extranodal NK/T-cell lymphoma; Lymphoma; Nasal type; Testicular cancer

Introduction

A metachronous lymphoma occurs when the second primary lymphoma is diagnosed more than 6 months after the diagnosis of the primary lymphoma. In this article, we report a metachronous extranodal natural killer (NK)/T-cell lymphoma of the nasal type, and a primary testicular lymphoma.

Extranodal NK/T-cell lymphoma, nasal type, is an extranodal lymphoma of the NK-cell or T-cell lineage, which is prevalent in Asians with a strong association with Epstein-Barr virus (EBV). On the other hand, primary testicular lymphoma is a rare form of extranodal non-Hodgkin lymphoma (NHL), accounting for 1% to 2% of NHL cases [1]. Most cases are diffuse large B-cell lymphoma (DLBCL) with extranodal tropism and frequent relapses. To the best of our knowledge, there is no previous report of metachronous lymphoma, including extranodal NK/T-cell lymphoma, nasal type, and primary testicular DLBCL.

Case

The patient presented with symptoms of nasal obstruction for 2 years with a previous medical history of operation for rectal cancer. The initial laboratory test results were white blood cells count, 8,800/µL; hemoglobin, 10.2 g/dL; hematocrit, 31.2%; and platelet, 180,000/µL. The initial computed tomography (CT) results showed both maxillary and ethmoidal sinusitis. The patient underwent an endoscopic biopsy for the necrosis area. Microscopic findings showed necrosis of the nasal mucosa with a diffuse infiltration of small-to-medium-sized lymphoid cells. The immunophenotype of the tumor cells was identified as CD56, CD30, cytoplasmic CD3 positive, and the in situ hybridization for EBV-encoded small RNA (EBER-ISH) was positive, but they were CD20 negative (Fig. 1). The T-cell receptor (TCR)-gamma gene rearrangement test detected no clonality. The cellularity of the bone marrow was 40%, presenting a normocellular marrow without any tumor cell. The EBV-DNA was elevated to 4.21 copies/µL. The positron emission tomography scan detected an abnormal uptake in the testis. A diffuse large B-cell lymphoma, not otherwise specified, was diagnosed from subsequent radical orchiectomy. The immunohistochemical staining revealed to be positive for CD20, BCL2, BCL6, and MYC and negative for CD10 and EBER-ISH.
emission tomography (PET) scan revealed no evidence of abnormal hypermetabolic lesions other than that in the nasal cavity. Taken together, a diagnosis of extranodal NK/T-cell lymphoma of the nasal type was made. The patient received concurrent cisplatin and radiotherapy, followed by two cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone).

Thirteen months after the diagnosis of extranodal NK/T-cell lymphoma of the nasal type, the patient presented with swelling of his left testis and a prominent paraaortic lymph node at the level of the renal hilum, during the follow-up abdominal CT. The regularly performed otolaryngologic examination and endoscopic findings showed no abnormality in the nasal cavity. The follow-up PET scan revealed a hypermetabolic mass in the left testis and a paraaortic lymph node, but there was no abnormal uptake in the nasal cavity and no significantly enlarged lymph node was identified in the neck. The patient underwent left radical orchiectomy. The microscopic findings of the testis showed a total architectural effacement based on the diffuse proliferation of large lymphoid cells. Immunohistochemical staining results of tumor cells showed that these were positive for CD20, MYC, BCL2, and BCL6, but negative for CD3, CD10, CD30, ALK, and EBER-ISH (Fig. 2). Ki-67 was positive in 90% of tumor cells. The serum EBV titer was lower than the detection limit. Clonality was also detected using a clonal immunoglobulin heavy chain gene rearrangement test, the BIOMED-2 clonality assay (InVivoScribe Technologies, San Diego, CA, USA). Therefore, the patient was diagnosed with DLBCL, not otherwise specified (NOS). The patient received seven cycles of chemotherapy using R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), combined with intrathecal methotrexate.

**Discussion**

Metachronous lymphoma is defined as the case in which the second primary lymphoma is diagnosed more than 6 months after the diagnosis of the primary lymphoma. In the present case, two types of lymphoma were diagnosed with an interval of 13 months. To the best of our knowledge, metachronous lymphoma, including extranodal NK/T-cell lymphoma of the nasal type, and primary testicular DLBCL have not been reported yet.

Extranodal NK/T-cell lymphoma of the nasal type, a highly aggressive tumor, is prevalent in Asia. It has a strong association with
EBV, suggesting that EBV might play a pathogenic role in this type of lymphoma [2]. Immunohistochemical phenotypes and pathological findings of EBV infections are compatible with those of extranodal NK/T-cell lymphoma of the nasal type. However, rare cases of CD56 or EBV positive peripheral T-cell lymphoma, NOS, have been described previously [3]. In the present case, a TCR-gamma gene rearrangement test confirmed the diagnosis of extranodal NK/T-cell lymphoma of the nasal type. The prognosis of this kind of lymphoma is poor, although a longer survival is expected with intensive chemotherapy and radiotherapy [2]. In the present case, the patient received concurrent cisplatin and radiotherapy, followed by two cycles of VIPD.

DLBCL, NOS is a neoplasm with a large B lymphoid cell with unknown etiology. DLBCL, NOS usually arises de novo. Secondary DLBCL is transformed from other less aggressive lymphomas. On the other hand, primary testicular lymphoma can arise from an immune-privileged site, traditionally described as an “immune sanctuary” site [4]. Although primary testicular lymphoma shares its biology with primary DLBCL of the central nervous system (CNS), it is currently classified as DLBCL, NOS. The majority of cases are DLBCL with a non-germinal center B-cell (GCB) subtype [5,6]. Immunohistochemical staining shows that both BCL2 and MYC proteins are expressed as a double expressor phenotype in 80% of cases [7]. The distinction between primary and secondary DLBCL, NOS in immune-privileged sites is essential. An evaluation of the systemic disease is needed for an unusual GCB subtype [6]. Immunophenotypes of the present case coincided with a typical primary testicular lymphoma. The characteristics of primary testicular lymphoma include a continuous pattern of relapse and an increased risk of CNS involvement [8]. The treatment and prognostic factors of primary testicular lymphoma remain controversial. However, the CHOP regimen is the mainstay of therapy with rituximab. The patient underwent radical orchiectomy and seven cycles of R-CHOP, accompanied by intrathecal methotrexate.

In conclusion, we present a rare case of primary testicular lymphoma of DLBCL, NOS, occurring 13 months after the treatment of extranodal NK/T-cell lymphoma of the nasal type. Results of microscopic findings, immunohistochemical staining, and clonality test revealed that the tumors of the patient were histologically different, originating from two different clones. The etiologies of these two metachronous lymphomas remain unknown. The standard therapy and characteristics of the tumor should be followed in
further study.

Notes

Ethical statements
This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB No: CR 20-136-L) and written informed consent from patient was waived by IRB.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization and Formal analysis: MYI, LSJ; Data curation and Investigation: MYI; Writing - original draft: MYI; Writing - review & editing: LSJ.

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Successful laparoscopic surgery of accessory cavitated uterine mass in young women with severe dysmenorrhea

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Accessory cavitated uterine mass (ACUM) is a rare and unique condition seen in young women. We report cases of ACUMs in two patients, a 14-year-old girl and a 25-year-old woman, both with complaints of severe dysmenorrhea that had started at menarche and had progressively worsened since. A large cystic lesion was localized in the anterolateral wall of the myometrium separate from the endometrium, which was difficult to distinguish from congenital uterine anomalies. Laparoscopic excision of the ACUMs was successful and completely resolved the dysmenorrhea. Early investigation of severe dysmenorrhea in young women can provide appropriate management and relieve symptoms.

Keywords: Adenomyoma; Adolescent; Dysmenorrhea; Laparoscopy; Uterus

Introduction

Severe dysmenorrhea in young women is usually primary dysmenorrhea, but cases with poor response to medical treatment may be due to endometriosis, adenomyosis, or Müllerian duct anomaly [1]. Juvenile cystic adenomyoma is a rare variant of adenomyosis characterized by the presence of a large hemorrhagic cyst resulting from extensive menstrual bleeding in ectopic endometrial glands [2]. Especially in young women, it can present as a focal cystic mass with severe dysmenorrhea, abdominal cramps, and pelvic pain resistant to medical treatment [3]. Currently, this unique entity has been renamed as accessory cavitated uterine mass (ACUM) [4]. ACUM is suggested to be a new variety of Müllerian anomaly that is usually located at the level of the insertion of the round ligament and is related to dysfunction of the female gubernaculum [4]. Therefore, ACUM closely mimics the unicorneate uterus with obstructed cavitated rudimentary horn, and differential diagnosis might not be easy even with the use of pelvic ultrasonography, hysterosalpingography, and magnetic resonance imaging (MRI) [5]. Confirmation of both ostia using hysteroscopy can be helpful in making an accurate diagnosis. Herein, we report two cases of successful laparoscopic mass excision in young women who complained of severe dysmenorrhea, diagnosed as ACUM, with a brief review of the literature.

Cases

1. Case 1

A 14-year-old girl complained of severe dysmenorrhea that had developed and progressively worsened since menarche at age 12 years. She experienced lower abdominal pain for more than 10 days around her menstrual period, along with nausea and vomiting. She had taken oral analgesics during these periods; however, they did not relieve the pain. She had to visit the emergency room and miss school several times. Her body weight was 47 kg, and her height was 157 cm. Physical examination revealed diffuse tender-
ness of the lower abdomen and bimanual pelvic examination was not performed because she was a virgin. Laboratory tests were all within normal limits.

Transrectal ultrasound revealed a 3-cm hyperechogenic mass on the right side of the uterus that was independent of the normal endometrium and ovaries. Pelvic MRI revealed a fluid collection in the right horn of the uterus. The preoperative MRI showed a bicornuate uterus with a noncommunicating horn (Fig. 1). After obtaining written consent, hysteroscopy was performed under general anesthesia, demonstrating a normal uterine cavity and bilateral ostia. Under general anesthesia with a muscle relaxant was used to avoid hymenal damage. Laparoscopy revealed a mass bulging out in the right anterior wall of the uterus. The myometrial wall over the cystic lesion was opened with monopolar scissors, and chocolate-like fluid was expelled from the cyst. The endometrial and myometrial tissue surrounding the cyst were completely resected using the monopolar hook. The myometrial defect was sutured by V-loc (Covidien, Mansfield, MA, USA) in two layers and reinforced interruptedly with 0-Polysorb Vicryl (Ethicon, Norderstedt, Germany) (Fig. 2). The abdominal cavity was thoroughly irrigated with saline, and the uterine wound was covered with Seperafilm (Genzyme Biosurgery, Framingham, MA, USA). The total operating time was 125 minutes, and the estimated blood loss was about 50 mL. Pathological examination showed a cyst wall lined with endometrial glandular epithelium and stromal cells surrounded by myometrium (Fig. 3). The postoperative period was uneventful. She was discharged 4 days after the operation. Her abdominal pain was completely resolved after surgery. She has had regular menstruation without complaints for 2 years after surgery.

2. Case 2

A 25-year-old nulligravida visited the emergency room with severe dysmenorrhea. Pelvic magnetic resonance imaging revealing a large cystic lesion (accessory cavitated uterine mass, asterisk) localized in the right side of the uterus, independent of the normal endometrium and ovaries. EM, endometrial cavity.

![Fig. 1. Pelvic magnetic resonance imaging revealing a large cystic lesion (accessory cavitated uterine mass, asterisk) localized in the right side of the uterus, independent of the normal endometrium and ovaries. EM, endometrial cavity.](https://doi.org/10.12701/yujm.2020.00696)

![Fig. 2. Laparoscopic mass excision. (A) After incision, chocolate-like fluid was expressed from the cystic cavity. (B) Cystic cavity seen after irrigation. (C) The surrounding endometrial and myometrial tissue of the cyst completely resected using the monopolar hook. (D) Myometrial defect sutured for two to three layers.](A B C D)
abdominal pain in the left lower quadrant. The urologist examined her first and ruled out the possibility of renal stones or other urological disorders. She had a history of erratic severe lower abdominal pain refractory to medical treatment. She showed a tender abdomen without rebound tenderness or costovertebral tenderness. Pelvic ultrasound revealed a 3-cm hypoechogenic mass on the left side of the uterus, which did not communicate with the endometrial cavity. The presumptive diagnosis of pelvic MRI was a unicor- nuate uterus with a rudimentary horn containing hemorrhage (Fig. 4). However, in the operative field, a smooth protruding mass was found on the left anterior wall of the uterus, with both ovaries and tubes grossly intact. We also ruled out unicornuate uterus by confirming that the uterine cavity and ostia were normal, using hysteroscopy. Laparoscopic mass excision was performed. On pathological examination, the cyst wall was lined with endometrial glandular epithelium and stromal cells. In the surrounding myometrium, no other adenomyotic lesion was found (Fig. 5). The postoperative period was uneventful. Until now, she has not complained of dysmenorrhea or abdominal pain after surgery.

**Discussion**

The typical feature of juvenile cystic adenomyoma or ACUM is early-onset severe dysmenorrhea, which usually starts soon after

**Fig. 3.** Histological section showing cyst wall lined with endometrial stromal cells, surrounded by myometrium (hematoxylin and eosin stain, ×200).

**Fig. 4.** Pelvic magnetic resonance imaging revealing a large cystic lesion (accessory cavitated uterine mass, asterisk) localized in the left side of the uterus, apart from the normal endometrium. Polycystic ovaries were also found. EM, endometrial cavity.

**Fig. 5.** (A) The excised specimens are irregularly shaped cystic structure with focal hemorrhage. (B) Histologic section showing the cyst wall lined with endometrial glandular epithelium and stromal cells, surrounded by myometrium. Adenomyotic lesions were not revealed in the surrounding myometrium (hematoxylin and eosin stain, ×100).

https://doi.org/10.12701/yujm.2020.00696
menarche and is refractory to medical treatments [6]. ACUM was first described by Acién et al. [4] in 2010 and was described as juvenile cystic adenomyosis [6,7]. The diagnostic criteria for ACUM are as follows: (1) an isolated accessory cavitated mass; (2) a normal uterus (endometrial lumen), fallopian tubes, and ovaries; (3) surgical evidence with an excised mass and pathological findings; (4) an accessory cavity lined with endometrial epithelium with glands and stroma; (5) chocolate-brown colored fluid content; and (6) no adenomyosis (if the uterus has been removed), although there could be small foci of adenomyosis in the myometrium adjacent to the accessory cavity [4].

Severe dysmenorrhea accompanied by a uterine mass usually suggests adenomyosis. Even though adenomyosis is usually a diffuse solid mass and develops in women in their forties, it can present as an adenomyoma, adenomyomatous polyps, and cystic adenomyomas [8]. Small cystic spaces, less than 0.5 cm in diameter, may be associated with adenomyosis. However, large adenomyotic cysts, referred to as cystic adenomyomas, are rare [9]. Juvenile cystic adenomyoma is defined as a solitary myometrial cyst measuring ≥1 cm, which is surrounded by hypertrophic endometrium, independent of the uterine lumen, and is present in women less than 30 years of age, in association with severe dysmenorrhea [10]. It is not common in late teenage. However, the youngest case known was a 13-year-old girl [11], and the case in the present study was 14 years old, only 2 years post menarche. To our knowledge, fewer than 40 cases, worldwide, have been reported in the literature [10,12,13]. We agree that most juvenile cystic adenomyomas might, in fact, be ACUMs because they present with similar clinical and histopathological characteristics [4]. When this lesion is considered a variant of adenomyosis, surgeons have to focus on en bloc resection with sufficient margins to reduce the risk of residual adenomyotic lesions in the surrounding myometrium. However, when it is considered a variant Mullerian anomaly, we can expect symptomatic relief only after the endometrial lesion of the cyst wall is eliminated. In our case, the surrounding myometrium did not contain adenomyotic lesions. The patients had complete symptomatic relief after resection of the endometrial lesion lining the cyst wall. However, the pathophysiology of this lesion still remains unclear and needs further study.

Cystic adenomyomas or ACUMs are mostly located in the lateral wall near the uterine round ligament attachment site. They mimic uterine anomalies such as a unicornuate uterus with a rudimentary horn, bicornuate uterus with a noncommunicating horn, and hematometra in uterine didelphys with a transvaginal septum. Additionally, the degenerated myoma and vesicouterine endometrioma are also considered as differential diagnoses [12]. ACUM is a cystic lesion that is independent of the normal endometrium, whereas hematomata and hematocolpos are present in the obstructing Mullerian anomaly [10]. Even with MRI, it can sometimes be difficult to differentiate it from a cavitated noncommunicating rudimentary uterine horn. In this situation, hysterosalpingography and hysteroscopy can be useful in distinguishing it from a uterine anomaly [5]. In our case, the patients were young and complained of unbearable severe dysmenorrhea that developed and progressively worsened from menarche. Therefore, obstructive Mullerian anomaly was first considered, and the interpretation of preoperative MRI was also a uterine anomaly with a noncommunicating horn. However, hysteroscopy showing a normal uterine cavity and ostia were helpful in making the differential diagnosis.

On pathological examination, ACUM is characterized by ectopic endometrial epithelium, glands, and/or stroma within the myometrium. A well-demarcated region of myometrial hyperplasia borders the endometrial tissue and appears as a thick-walled, well-circumscribed lesion within the uterine muscle [14,15].

Initial empirical treatment, including oral contraceptives and analgesia, can be attempted. However, ACUM is usually resistant to medical treatment, and surgical removal might be unavoidable. Laparoscopic excision has been attempted and has shown good postoperative results, comparable to those of exploratory laparotomy [10]. Other surgical approaches have been proposed, such as radiofrequency ablation under ultrasonography guidance [16], single incision with monopolar cautery [17], or the use of robotic surgery [18].

In the cases presented, ACUM was diagnosed in a 14-year-old adolescent girl and a 25-year-old young woman, both presenting with complaints of unbearable severe dysmenorrhea. Laparoscopic mass excision successfully resolved the dysmenorrhea. Early investigation of severe dysmenorrhea in young women can help with appropriate management and reduce the duration of symptoms.

Notes

Ethical statements
This study was approved by the Institutional Review Board (IRB) of the Keimyung University Dongsan Medical Center (IRB No: 2020-08-010). Written informed consent was obtained for publication of this case report and accompanying images.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Author contributions
Conceptualization, Formal analysis, Methodology, and Investigation.
tion: JCP, DJK; Data curation, Resources, and Software: JCP; Supervision and Validation: DJK; Writing-original draft: JCP; Writing-review & editing: DJK.

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The diagnosis of an imperforate anus in female fetuses

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Imperforate anus is an anomaly caused by a defect in the development of the hindgut during early pregnancy. It is a relatively common congenital malformation and is more common in males. Although there are cases of a solitary imperforate anus, the condition is more commonly found as a part of a wider spectrum of other congenital anomalies. Although urgent reconstructive anorectal surgery is not necessary, immediate evaluation is important and urgent decompressive surgery may be required. Moreover, as there are often other anomalies that can affect management, prenatal diagnosis can help in optimizing perinatal care and prepare parents through prenatal counseling. In the past, imperforate anus was diagnosed by prenatal ultrasonography based on indirect signs such as bowel dilatation or intraluminal calcified meconium. Currently, it is diagnosed by directly checking the perineum with prenatal ultrasonography. Despite advances in ultrasound technology, accurate prenatal diagnosis is impossible in most cases and imperforate anus is detected after birth. Here, we present two cases of imperforate anus in female fetuses that were not diagnosed prenatally.

Keywords: Fetus; Imperforate anus; Prenatal diagnosis; Ultrasonography

Introduction

Imperforate anus is a major form of anorectal malformation where-in the baby is born without a normal anal opening. The incidence of imperforate anus varies from 1:1,500 to 1:5,000 in neonates [1,2]. The anomaly is not life-threatening; however, it is likely related to VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, esophageal atresia, renal and radial anomalies, and limb defects) or to chromosomal anomalies [3-7]. Early reports of prenatal diagnosis have relied on indirect signs such as bowel dilatation or intraluminal calcified meconium detected with prenatal ultrasonography. Additionally, it is possible to diagnose imperforate anus directly by identifying the normal anus that appears as an external hypoechoic ring with an echoic genic center [8-18]. Currently, identifying the type of the imperforate anus was even attempted using ultrasonography prenatally [5]. However, prenatal diagnosis of imperforate anus in a female fetus is still difficult.

Cases

1. Case 1
A 33-year-old primigravida was referred to our tertiary center for fetal congenital heart disease at 21 weeks of gestation. She was healthy, had no medical or surgical history, and was taking folic acid and multivitamin supplements, including iron. She had undergone first and second integrated tests, with results showing a high risk for Down syndrome (1:29). Amniocentesis revealed a normal karyotype. At 20 weeks of gestation, a detailed fetal ultrasonography was performed that showed fetal heart disease, namely tetro-
gy of Fallot (TOF). In addition to TOF, a single umbilical artery and fetal toe anomaly (such as clinodactyly) were observed. At 30 weeks of gestation, the fetal anus was thought to be visible because the hypoechoic area indicating the anal sphincter and hypoechoic ring showed signs of anal mucosa (Fig. 1). However, the perineal body appeared to be shorter than that of a normal female fetus, which indicated to probability of imperforate anus diagnosis. At 38 weeks and 2 days of gestation, an elective cesarean section was performed and a female (2,320 g) neonate was born. She was in the 3rd percentile for weight and had an Apgar score of 8 at 1 minute and 9 at 5 minutes. After birth, the baby was diagnosed with TOF and imperforate anus, with clinodactyly in both the toes. Specifically, the imperforate anus was low-type and accompanied by a vestibular fistula, which was not diagnosed during the prenatal period (Fig. 2). The next day, a sigmoid colon colostomy was performed, and feeding began 2 days later.

2. Case 2
A 33-year-old multigravida visited our outpatient clinic for fetal heart anomaly at 23 weeks of gestation. She had undergone a cesarean section 3 years prior and had no medical history. During this pregnancy, she had routine obstetrical examinations and integrated tests, and the results were unremarkable. A detailed fetal ultrasonography was conducted again in our hospital, which suggested a double outlet right ventricle (DORV) with a large ventricular septal defect (VSD). No other anomalies were detected. Further, an ultrasonography of the fetal anus was performed, and the presence of an anal sphincter and anal mucosa was noted; therefore, a fetal imperforate anus was not suspected (Fig. 3). At 38 weeks and 3 days of gestation, an emergency cesarean section was performed due to labor pain, and a female (2,730 g) neonate was delivered. Operation findings revealed meconium-tinged amniotic fluid, but the baby cried well and was pink in color. She was in the 3rd percentile for weight and had an Apgar score of 7 at 1 minute and 9 at 5 minutes. The umbilical cord had a pH level of 7.24, indicating that fetal acidosis was absent. After birth, she was diagnosed with DORV with a large VSD and no pulmonary stenosis, as suspected on prenatal ultrasonography. In addition to multiple heart anomalies, she was diagnosed with imperforate anus after birth. The imperforate anus was a low-type with a vestibular fistula. The day after delivery, a sigmoid colon colostomy was performed. The baby

![Fig. 1. The images of fetal ultrasonography of case 1. (A) At 30 weeks of gestation, there is an echogenic ring (open arrow) in the hypoechoic area (solid arrow), suggesting an intact anus with a rather short perineal body (arrowhead). (B) At 35 weeks of gestation, a short perineal body (arrowhead) is revealed, and an echogenic ring (open arrow) indicating the anal mucosa in the hypoechoic area (solid arrow) is seen.](https://doi.org/10.12701/yujm.2020.00507)

![Fig. 2. Postnatal finding of case 1. No anal opening in the original location is present (arrow). A vestibular fistula is accompanied (arrowhead).](https://doi.org/10.12701/yujm.2020.00507)
The diagnosis of an imperforate anus in female fetuses

Fig. 3. The image of fetal ultrasonography of case 2. At 30 weeks of gestation, the perineum is seen, and an intact anus is suspected because of the hyperechogenic ring indicating anal mucosa (open arrow) in normal sphincter muscles (solid arrow), despite the short perineal body (arrowhead). After birth, the baby was diagnosed with a low-type imperforate anus with a vestibular fistula.

recovered well, and feeding began 2 days later.

Discussion

Imperforate anus is a common congenital anomaly with an incidence of 1:1,500 to 1:5,000 in neonates [1,2]. It may either be a solitary anomaly without any malformation or, in many cases, be associated with multiple congenital anomaly subsets, such as VACTERL association or trisomy 21 [3-7]. Imperforate anus, with other serious anomalies, can lead to significant morbidity and mortality.

Although imperforate anus is a relatively common malformation, it cannot be accurately diagnosed prenatally. Imperforate anus can occur as a solitary abnormality but is likely to have accompanying malformations. Hence, diagnosed with a fetal imperforate anus should be referred to a tertiary center that can provide accurate diagnosis and adequate management. Conversely, even if one malformation associated with VACTERL association is detected prenatally, more detailed ultrasonography examinations should be performed regarding the presence of imperforate anus. Even without considering other accompanying anomalies (except imperforate anus), the exact anatomical type of atresia and the existence of a fistula should be carefully examined. This is important because it determines the appropriate timing for corrective surgery as well as the surgical stages. Urgent reconstructive anorectal surgery is not necessary; however, immediate evaluation is important, and urgent decompressive surgery may be necessary. If a diagnosis is suspected prenatally, it is essential for the surgeon to provide appropriate guidance to the pregnant woman and to make a delivery plan to prepare for the possibility of neonatal operation [2]. Thus, detecting the presence of an imperforate anus via prenatal ultrasonography is important for obstetricians, pediatric surgeons, and pregnant women to plan for an early treatment.

There are three types of imperforate anus according to the distal rectal pouch and the puborectalis muscle [5]: (1) the high-type, in which the distal pouch ends above the puborectalis muscle; (2) the intermediate-type, in which the pouch ends at the puborectalis muscle; and (3) the low-type, in which the pouch ends through the puborectalis muscle [5]. Traditionally, imperforate anus is diagnosed by prenatal ultrasound on detecting the presence of a dilated distal bowel, or rectum or intraluminal meconium calcification, or enterolithiasis [8-17]; however, it is not always suspected with the presence of a fistula. After the 1990s, improvements in ultrasound resolution have helped in visualizing the fetal perineum and detecting the hyperechogenic ring indicating the perianal muscular complex (PAMC), namely the internal anal sphincter, puborectalis muscle, and external sphincter with an echogenic center, which indicates anal mucosa [18]. Nevertheless, care should be taken to distinguish the two components of the sonographic sign, anal mucosa and muscular components, to avoid misdiagnosis of a perineal fistula, which may be seen as the adequate development of the PAMC is expected in low imperforated anus [19]. A recent study suggested that a low-type imperforate anus is suspected if the size of the anus is small or the distance between the anus and the genitalia is short [5]. The high-type imperforate anus, however, is relatively well diagnosed during pregnancy and is more frequently found in male infants, with a higher mortality and morbidity compared to other types [5]. In contrast, low-type is more common in female fetuses, with a relatively good prognosis; however, it is difficult to recognize in the prenatal period.

In this study, the two neonates were diagnosed with congenital heart disease prenatally and were diagnosed with imperforate anus with vestibular fistula postnatally. Bowel dilatation was not observed; however, a decompressed obstructed bowel due to the presence of a fistula was noted [11]. Ultrasonographic findings revealed an anatomic structure in the PAMC, indicating the anal sphincter, anal mucosa, and a relatively short perineal body with other combined anomalies. These findings should have been regarded as a clue to diagnose an imperforate anus with or without fistula.

If any fetal anomaly is detected, the fetal anus should be examined since an imperforate anus is commonly associated with other anomalies. An imperforate anus is still difficult to diagnose in some cases, and as observed in these two female fetuses, a fistula makes the diagnosis difficult because it does not typically represent the
imperforate anus. Although it is possible to diagnose incomplete anus by directly visualizing the perineum of the fetus using ultrasonography, prenatal diagnosis of imperforate anus remains challenging, especially in female fetuses with a low-type imperforate anus. Even after birth, a close physical examination of the baby is necessary as the passage of meconium alone is not a sign of a correctly positioned anus because the presence of the fistula makes it possible to pass meconium.

Even if the structure of the anus appears normal, it is important to accurately identify the anus in female fetuses with other accompanying anomalies. Detailed prenatal ultrasonography and reasonable suspicion of imperforate anus based on images can increase the accuracy of the diagnosis. This can help counsel parents regarding the prognosis of the fetus by providing accurate information.

**Notes**

**Ethical statements**

This study was approved by the Institutional Review Board (IRB) of the Kyungpook National University Chilgok Hospital (IRB No: 2020-06-031). Written informed consent was obtained from the parent/guardian for publication of this case report and accompanying images.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Author contributions**

Conceptualization, Project administration: WJS; Data curation: MJK; Formal analysis: SHP; Methodology: MJK, SHP; Visualization: SHP, HHC; Investigation: HMK, HHC; Resources: WJS, JIK; Software: HMK; Supervision: JIK; Validation: HHC, JIK; Writing-original draft: MJK; Writing-review & editing: HMK.

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**References**

17. Shimo Take T, Higuchi K, Tsuda T, Aoi S, Iwai N. Infrared spec-


Introduction

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a self-limiting lymphadenitis. Its symptoms mainly include high fever, lymph node swelling, and leukopenia [1]. The etiology of KFD is unclear, and KFD is presumed to be preceded by infectious or autoimmune diseases, although this has not been confirmed [2]. Treatment is symptomatic with nonsteroidal anti-inflammatory drugs, and most symptoms improve within a few months [2]. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease with clinical symptoms similar to those of KFD, but it requires a significantly more aggressive treatment. A 19-year-old Korean male patient was hospitalized for fever and cervical lymphadenopathy. Variable-sized lymph node enlargements with slightly necrotic lesions were detected on computed tomography. Biopsy specimen from a cervical lymph node showed necrotizing lymphadenitis with HLH. Bone marrow aspiration showed hemophagocytic histiocytosis. The clinical symptoms and the results of the laboratory test and bone marrow aspiration met the diagnostic criteria for HLH. The patient was diagnosed with macrophage activation syndrome—HLH, a secondary HLH associated with KFD. He was treated with dexamethasone (10 mg/m²/day) without immunosuppressive therapy or etoposide-based chemotherapy. The fever disappeared within a day, and other symptoms such as lymphadenopathy, ascites, and pleural effusion improved. Dexamethasone was reduced from day 2 of hospitalization and was tapered over 8 weeks. The patient was discharged on day 6 with continuation of dexamethasone. The patient had no recurrence at the 18-month follow-up.

Keywords: Hemophagocytic lymphohistiocytosis; Kikuchi–Fujimoto disease; Necrotizing lymphadenitis
Case

A 19-year-old male patient presented with high fever and neck swelling for 5 weeks. The patient was treated with amoxicillin-clavulanate, ceftriaxone, and dexamethasone (5 mg/day) for 9 days at the local medical center (LMC), but his condition did not improve. The patient had experienced KFD 3 years earlier with symptoms such as fever, cervical lymphadenitis, and joint pain. In the laboratory tests, no specific findings, except elevation in the C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), were noted. Lymph node enlargement and slightly necrotic lesions were observed in the neck computed tomography (CT) scan. Analysis of the core needle biopsy specimen indicated histiocytic necrotizing lymphadenitis, which was observed in KFD. The patient had a steroid dependency and was treated with hydroxychloroquine [3].

Physical examination revealed painful cervical lymph node enlargement and tonsillar swelling on both sides. Variable-sized lymph node enlargements with slightly necrotic lesions were detected on CT (Fig. 1A). A small amount of bilateral pleural effusion and multiple infiltrative enlarged lymph nodes in the anterior mediastinum were observed (Fig. 1B). Mild hepatomegaly and segmental wall thickening of the gallbladder were also noted.

Laboratory findings were as follows: white blood cell count, 2,060/μL (54.9% neutrophils); absolute neutrophil count, 1,130/μL; hemoglobin level, 11.8 g/dL; platelet count, 145,000/μL; aspartate aminotransferase, 275 IU/L; alanine aminotransferase, 164 IU/L; and γ-glutamyl transferase, 916 IU/L. Other laboratory findings were as follows: elevated CRP level, 7.417 mg/dL (range, < 0.5 mg/dL); ESR, 32 mm/hr (range, 0–20 mm/hr); elevated procalcitonin level, 16.2 ng/mL (range, 0–0.5 ng/mL); elevated serum ferritin level, 19,640.61 ng/mL (range, 29–278 ng/mL); elevated fasting triglyceride level, 372 mg/dL (range, 35–160 mg/dL); fibrinogen level, 229 mg/dL (range, 200–400 mg/dL); elevated soluble CD25 (sIL-2 receptor) level, 2,817 U/mL (range, 158–623 U/mL); natural killer cell activity, > 2,000 pg/mL (range, > 500 pg/mL); C3 level, 99.6 mg/dL (range, 83–177 mg/dL); C4 level, 43.6 mg/dL (range, 15–45 mg/dL); CH50 level, 55 U/mL (range, 75–160 U/mL); antinuclear antibody, negative; cytomegalovirus immunoglobulin (Ig) M, negative; and Epstein-Barr virus IgM and polymerase chain reaction, negative. He was initially treated with vancomycin, meropenem, and metronidazole. However, he did not respond to antibiotic treatment, and the fever persisted. Core needle biopsy specimen from the cervical lymph node and bone marrow aspiration and biopsy were performed on hospitalization day 3. The cervical lymph node biopsy specimen showed necrotizing lymphadenitis with HLH (Fig. 2). Bone marrow aspiration and biopsy showed normocellular marrow with increased hemophagocytic histiocytosis (Fig. 3). The patient met the five diagnostic criteria for HLH. Thus, he was diagnosed with secondary HLH associated with KFD.

The patient initiated treatment with intravenous dexamethasone (10 mg/m²/day). The fever disappeared in a day, and other symptoms such as lymphadenopathy, ascites, and pleural effusion improved. Dexamethasone was reduced from day 2 and was tapered over 8 weeks. The patient was discharged on day 6 with continuation of dexamethasone. He was followed up at the outpatient clinic and had no recurrence at the 18-month follow-up. Next-generation sequencing was performed to determine any genetic abnormalities related to HLH, but no such abnormalities were found.

Fig. 1. (A) Neck computed tomography (CT) shows scattered, variable-sized lymph node enlargements (arrow) on both neck at levels I to IV. (B) Chest CT shows a small amount of bilateral pleural effusion (arrows).
**Discussion**

KFD is a benign disease mainly characterized by high fever, lymph node swelling, and leukopenia. It usually develops in young adults aged less than 30 years and is confirmed by biopsy with histological findings of histiocytic necrotizing lymphadenitis [1]. KFD usually requires no special treatment. However, when systemic symptoms are severe or accompanied by an autoimmune disease, steroid treatment should be considered [1].

HLH is a syndrome that manifests in patients with severe systemic hyperinflammation. The typical findings of HLH include fever, hepatosplenomegaly, and cytopenia. Other common findings include hypertriglyceridemia, coagulopathy with hypofibrinogenemia, liver dysfunction, and elevated levels of ferritin and serum transaminases. Other, less common, initial clinical findings include lymphadenopathy, skin rash, jaundice, and edema. Primary HLH occurs because of a genetic abnormality or is idiopathic, but secondary HLH is known to be caused by strong activation of the immune system, in most cases, because of severe infections and is mainly caused by immunosuppression. However, it can also occur in malignancy and rheumatologic conditions [4]. HLH has early symptoms similar to KFD but requires active treatment and has a poor prognosis.

We report a case of secondary HLH caused by recurrent KFD. Until now, fewer than 20 cases of HLH with KFD have been reported (Table 1) [5-18]. According to the literature review, the average age of patients was 17.5 ± 11.6 years, and this disease affected 12 male patients (63.2%) and seven female patients (36.8%). The incidence rates by country were as follows: Korea, 47.4% (n = 9); Japan, 15.8% (n = 3); Taiwan, 15.8% (n = 3); United Kingdom, 5.3% (n = 1); United States, 5.3% (n = 1); Qatar, 5.3% (n = 1); and Thailand, 5.3% (n = 1). In terms of race, 18 out of 19 patients were Asian, accounting for 94.7% of patients. The most common symptoms were fever (100%) and lymphadenopathy (89.5%), followed by seizure, fatigue, and erythema. The medications administered in the reports were steroid (68.4%), intravenous Ig (36.8%), etoposide (21.1%), and cyclosporine A (10.5%). In terms of outcomes, 17 of the patients (89.5%) had complete remission, whereas two patients (10.5%) died. HLH with KFD has a relatively good prognosis and response to treatment, but its diagnosis and standard treatment have not yet been established.

The manifestation of HLH symptoms in patients with rheumatic conditions is called macrophage activation syndrome (MAS). From the revised classification in 2016, the term MAS-HLH has been suggested. Among patients with secondary HLH, those with
Table 1. Clinical characteristics, treatment, and outcome of Kikuchi–Fujimoto disease-associated hemophagocytic lymphohistiocytosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Country</th>
<th>Race</th>
<th>Symptom</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Chen et al. [5]</td>
<td>2</td>
<td>14</td>
<td>M</td>
<td>Taiwan</td>
<td>Asian</td>
<td>Fever, fatigue, cervical lymph node swelling</td>
<td>IVIG</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td>10</td>
<td>F</td>
<td>Taiwan</td>
<td>Asian</td>
<td>Fever, cervical lymph node swelling</td>
<td>Steroid, IVIG</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2007</td>
<td>Lin et al. [8]</td>
<td>1</td>
<td>13</td>
<td>M</td>
<td>Japan</td>
<td>Asian</td>
<td>Fever, axillary and inguinal lymphadenopathy</td>
<td>Steroid</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2007</td>
<td>Khan et al. [9]</td>
<td>1</td>
<td>40</td>
<td>M</td>
<td>Qatar</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy</td>
<td>NSAIDs</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2008</td>
<td>Lim et al. [10]</td>
<td>5</td>
<td>12</td>
<td>M</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy</td>
<td>Steroid</td>
<td>CR</td>
<td>Recurred after 2 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>M</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, multiple lymphadenopathy</td>
<td>Steroid, IVIG, ACV, VP16</td>
<td>CR</td>
<td>EBV, recurred after 7 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>F</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, multiple lymphadenopathy</td>
<td>Steroid, VP16</td>
<td>NR, died</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>F</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy</td>
<td>Steroid, IVIG, VP16, CyA</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>M</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, multiple lymphadenopathy</td>
<td>Steroid</td>
<td>CR</td>
<td>EBV</td>
</tr>
<tr>
<td>2009</td>
<td>Byoun et al. [12]</td>
<td>1</td>
<td>21</td>
<td>F</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy</td>
<td>Steroid, ACV</td>
<td>CR</td>
<td>EBV</td>
</tr>
<tr>
<td>2010</td>
<td>Lee et al. [13]</td>
<td>1</td>
<td>16</td>
<td>M</td>
<td>Taiwan</td>
<td>Asian</td>
<td>Fever, cervical and axillary lymphadenopathy</td>
<td>Antibiotics</td>
<td>CR</td>
<td>EBV</td>
</tr>
<tr>
<td>2011</td>
<td>Kim et al. [15]</td>
<td>1</td>
<td>0.75</td>
<td>M</td>
<td>Korea</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy</td>
<td>Antibiotics</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2013</td>
<td>Koga et al. [16]</td>
<td>1</td>
<td>21</td>
<td>M</td>
<td>Japan</td>
<td>Asian</td>
<td>Fever, cervical lymphadenopathy, erythema</td>
<td>Steroid</td>
<td>CR</td>
<td>Sweet's disease</td>
</tr>
<tr>
<td>2016</td>
<td>Sykes et al. [17]</td>
<td>1</td>
<td>16</td>
<td>F</td>
<td>United States</td>
<td>NA</td>
<td>Fever, joint pain, fatigue</td>
<td>Antibiotics</td>
<td>CR</td>
<td>NA</td>
</tr>
<tr>
<td>2016</td>
<td>Nishiwaki et al. [18]</td>
<td>1</td>
<td>30</td>
<td>M</td>
<td>Japan</td>
<td>Asian</td>
<td>Fever, sore throat</td>
<td>Steroid</td>
<td>CR</td>
<td>NA</td>
</tr>
</tbody>
</table>

M, male; F, female; IVIG, intravenous immunoglobulin; CR, complete remission; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; ACV, acyclovir; VP16, etoposide; EBV, Epstein-Barr virus; NR, no response; CyA, cyclosporine A; SLE, systemic lupus erythematosus.

Associated rheumatic conditions are diagnosed with MAS-HLH [19]. In our case, the patient was diagnosed with HLH caused by KFD. As KFD is associated with rheumatic disease [2], HLH associated with KFD was regarded as MAS-HLH.

Currently, the standard therapy for HLH comprises dexamethasone and etoposide based on HLH-94 treatment protocol. The treatment of HLH should be accompanied by appropriate treatment of the identified underlying trigger [4]. Although the HLH-94 protocol is required in most HLH patients, steroids with or without intravenous Ig may be sufficient for patients with less severe HLH or those with MAS-HLH [20]. Cases of successful treatment by steroid alone have been reported [8,10,16,18]. Our patient did not appear seriously ill, and the dose of steroid therapy at the LMC was inadequate. Therefore, we decided to administer an appropriate dose of steroid alone. He was followed up at the outpatient clinic and presented with no recurrence at the 18-month follow-up. MAS-HLH is an autoimmune disease associated with rheumatic conditions. Therefore, steroid treatment was considered appropriate as the underlying triggers were eliminated with steroid administration. In this case, we confirmed the effectiveness of steroid treatment alone for MAS-HLH. Therefore, it would be appropriate to classify secondary HLH associated with KFD as MAS-HLH and to treat it accordingly.

In conclusion, recurrent KFD has the possibility of progressing...
to HLH. HLH requires a more aggressive treatment than KFD. However, in the case of MAS-HLH, specifically KFD-associated HLH, treatment with steroids alone should be provided without the administration of immunosuppressive drugs such as etoposide or cyclosporine A.

**Notes**

**Ethical statements**
This report was approved by the Institutional Review Board (IRB) of the Yeungnam University Hospital (IRB No: YUMC 2020-07-038). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

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**Author contributions**
Conceptualization: all authors; Data curation: SML, YTL, KMJ, MJG, JHL; Formal analysis and Supervision: JML; Funding acquisition and Validation: JML; Methodology: SML, YTL, KMJ, MJG, JHL; Investigation: SML; Resources: YTL, KMJ, MJG, JHL; Writing-original draft: all authors; Writing-review & editing: all authors.

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**References**

17. Sykes JA, Badizadegan K, Gordon P, Sokol D, Escoto M, Ten I,


Successful treatment with vedolizumab in an adolescent with Crohn disease who had developed active pulmonary tuberculosis while receiving infliximab

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Vedolizumab (VDZ) has been approved for the treatment of inflammatory bowel diseases (IBDs) in patients aged ≥ 18 years. We report a case of a pediatric patient with Crohn disease (CD) who was successfully treated with VDZ. A 16-year-old female developed severe active pulmonary tuberculosis (TB) during treatment with infliximab (IFX). IFX was stopped, and TB treatment was started. After a 6-month regimen of standard TB medication, her pulmonary TB was cured; however, gastrointestinal symptoms developed. Due to the concern of the patient and parents regarding TB reactivation on restarting treatment with IFX, VDZ was started off-label. After the second dose of VDZ, the patient was in clinical remission and her remission was continuously sustained. Ileocolonoscopy at 1-year after VDZ initiation revealed endoscopic healing. Therapeutic drug monitoring conducted during VDZ treatment showed negative antibodies to VDZ. No serious adverse events occurred during the VDZ treatment. This is the first case report in Korea demonstrating the safe and effective use of VDZ treatment in a pediatric CD patient. In cases that require recommencement of treatment with biologics after recovery of active pulmonary TB caused by anti-tumor necrosis factor agents, VDZ may be a good option even in pediatric IBD.

Keywords: Child; Inflammatory bowel diseases; Infliximab; Tuberculosis; Vedolizumab

Introduction

Crohn disease (CD) is an inflammatory bowel disease (IBD) characterized by ulcers and inflammation that develop anywhere throughout the gastrointestinal (GI) tract [1]. Approximately 25% of patients with CD are diagnosed at < 20 years of age, in whom a more aggressive disease course occurs compared with adult-onset disease. Hence, an earlier introduction of immunomodulators and/or anti-tumor necrosis factor (TNF) agents is required [1-3].

Vedolizumab (VDZ) is a humanized monoclonal antibody acting on α4β7 integrin that is present on the surface of lymphocytes and binds to MadCAM-1 on the intestinal endothelium. VDZ selectively inhibits the transmigration of lymphocytes into the inflamed intestinal tissue [4]. This gut-selective mechanism of action of VDZ is advantageous in terms of safety compared to other biologics. VDZ is currently approved for use only in adults with CD and ulcerative colitis (UC) [5,6]. Anti-TNF agents, such as infliximab (IFX) and adalimumab, are the only biological agents approved for use in pediatric IBD, whereas VDZ can be administered only off-label [7,8]. Herein, we report a rare case of a pediatric CD patient who successfully achieved and maintained remission with VDZ after developing severe active pulmonary tuberculosis (TB) during treatment with IFX.
Case

A 16-year-old female was admitted to Kyungpook National University Children’s Hospital with complaints of abdominal pain, diarrhea, and hematochezia for 2 months. The past medical history of the patient was unremarkable. She had completed Bacillus Calmette–Guérin (BCG) vaccination and had no past or family history of pulmonary TB. Initial laboratory tests showed a white blood cell count of 4,500/μL, hemoglobin level of 6.2 g/dL, platelet count of 532,000/μL, albumin level of 3.0 g/dL, erythrocyte sedimentation rate (ESR) of 110 mm/hr, and C-reactive protein (CRP) level of 8.0 mg/dL. The fecal immunochemical test (FIT) was positive, and fecal calprotectin (FC) was > 2,000 mg/kg. No pathogens were detected in the stool culture and stool polymerase chain reaction (PCR). Chest X-ray showed no abnormal findings in the lungs, and the interferon-gamma release assay (IGRA) was negative. Ileocolonoscopy showed multifocal ulcers throughout the terminal ileum and colon (Fig. 1). Cryptitis, crypt abscesses, and non-caseating granulomas were observed throughout the terminal ileum and colon on histology; however, the acid-fast bacillus smear and culture and PCR for TB were negative. Upper GI endoscopy revealed ulcers in the duodenum (Fig. 2A). Magnetic resonance enterography showed multisegmental wall thickening in the ileum (Fig. 2B). The patient was diagnosed with CD with a phenotype of A1b, L3+L4ab, B1, G0 according to the Paris classification. Her Pediatric Crohn’s Disease Activity Index (PCDAI)

Fig. 1. Images of ileocolonoscopy at the diagnosis of Crohn disease. Multifocal aphthous ulcers are observed in the (A) terminal ileum and (B) colon.

Fig. 2. Images at the diagnosis of Crohn disease. (A) Upper gastrointestinal endoscopy shows multiple ulcers in the duodenum. (B) Magnetic resonance enterography shows multisegmental wall thickening in the ileum.
score was 50, and the Simple Endoscopic Score for Crohn’s Disease (SES-CD) was 22.

Treatment began with exclusive enteral nutrition (EEN), mesalazine, and azathioprine, which were effective. One month after treatment, her PCDAI score had decreased to 10. However, 1 month after finishing her 8-week treatment with EEN, the disease relapsed and her PCDAI score elevated to 42.5; hence, prednisolone was started per oral at a dose of 50 mg/day. Despite corticosteroid treatment, symptoms persisted, and IFX was administered. Chest X-ray before the administration of IFX showed no abnormal findings in the lungs, and the IGRA was negative. Symptoms resolved after the second dose of IFX infusion, and her PCDAI score decreased to 7.5. However, during her visit for the third IFX infusion, she complained of fever, cough, and dyspnea on exertion for a week. Radiologic examination of the chest revealed a left pleural effusion with mild pleural thickening and nodularities indicating TB pleurisy on chest X-ray and computed tomography (Fig. 3). Thoracentesis was conducted, and pulmonary TB was confirmed by a positive TB PCR test of the pleural effusion specimen and a positive IGRA test. IFX treatment was discontinued and the standard TB treatment regimen consisting of isoniazid, ethambutol, rifampin, and pyrazinamide for 2 months, followed by isoniazid, ethambutol, and rifampin for 4 months, was started. EEN was restarted and maintained for 8 weeks. Subsequently, mesalazine was administered to treat CD.

Her pulmonary TB was completely cured after 6 months of TB treatment. However, symptoms such as hematochezia, diarrhea, and weight loss began by the end of TB treatment. Laboratory tests showed a white blood cell count of 7,010/μL, hemoglobin level of 6.8 g/dL, platelet count of 477,000/μL, albumin level of 3.1 g/dL, ESR of 45 mm/hr, and CRP of 2.2 mg/dL. FIT was positive, and FC was > 2,000 mg/kg. No pathogens were detected in the stool culture and stool PCR. Her PCDAI score was 47.5, and the exacerbation of CD was confirmed by ileocolonoscopy (Fig. 4A). Therefore, we planned to restart IFX. However, due to the fear of another severe disease course of active TB when IFX were to be restarted, the patient and parents preferred to start VDZ off-label instead of restarting IFX. Before starting VDZ, the patient’s weight was 57 kg. VDZ was administered according to the regular regimen approved in adults of 300 mg per dose at weeks 0, 2, and 6 for induction and 8-week intervals for maintenance treatment thereafter. The patient showed a fast response to VDZ treatment. At the week 6 visit for her third VDZ infusion, she was in clinical remission, and inflammatory markers were normalized (Table 1, Fig. 5). Ileocolonoscopy at the 1-year follow-up after VDZ treatment revealed endoscopic healing (Fig. 4B). Therapeutic drug monitoring (TDM) using commercialized enzyme-linked immunosorbent assay kits (Immundiagnostik AG, Bensheim, Germany) was conducted during VDZ treatment. An anti-drug antibody level of ≤ 10 AU/mL was defined as negative, according to the manufacturer’s manual. TDM results during VDZ treatment showed negative antibodies to VDZ (Table 1). The patient is currently in her second year of VDZ treatment and is maintaining clinical and biochemical remission. No serious adverse events, including TB reactivation, have occurred.

**Fig. 3.** Radiologic images at the diagnosis of active pulmonary tuberculosis during infliximab treatment. (A) Chest X-ray shows a marked amount of left pleural effusion. (B) Chest computed tomography shows left pleural effusion with mild pleural thickening and nodularities (arrow).
Fig. 4. Images of ileocolonoscopy before and after treatment with vedolizumab. (A) Multiple ulcers with mucosal friability are observed throughout the colon before treatment with vedolizumab. (B) Endoscopic healing is observed 1 year after treatment with vedolizumab.

Table 1. Crohn disease activity, laboratory results, and therapeutic drug monitoring during treatment with VDZ

<table>
<thead>
<tr>
<th>Week</th>
<th>VDZ</th>
<th>PCDAI</th>
<th>CRP (mg/dL)</th>
<th>ESR (mm/hr)</th>
<th>Albumin (g/dL)</th>
<th>VDZ TL (μg/mL)</th>
<th>ATV (AU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>#1</td>
<td>40.0</td>
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<td>45</td>
<td>3.1</td>
<td>25.25</td>
<td>1.91</td>
</tr>
<tr>
<td>2</td>
<td>#2</td>
<td>12.5</td>
<td>0.04</td>
<td>47</td>
<td>4.1</td>
<td>25.25</td>
<td>1.91</td>
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<tr>
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<td>#3</td>
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<td>0.12</td>
<td>19</td>
<td>4.1</td>
<td>14.35</td>
<td>4.56</td>
</tr>
<tr>
<td>14</td>
<td>#4</td>
<td>0</td>
<td>0.05</td>
<td>15</td>
<td>4.1</td>
<td>3.36</td>
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<tr>
<td>22</td>
<td>#5</td>
<td>2.5</td>
<td>0.08</td>
<td>24</td>
<td>4.0</td>
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</tr>
<tr>
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<td>16</td>
<td>4.2</td>
<td>3.59</td>
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<tr>
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<td>0.03</td>
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</tr>
<tr>
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<td>#9</td>
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<td>0.02</td>
<td>8</td>
<td>4.2</td>
<td>4.15</td>
<td>2.06</td>
</tr>
</tbody>
</table>

VDZ, vedolizumab; PCDAI, Pediatric Crohn’s Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TL, trough level; ATV, antibody to VDZ.

Fig. 5. Fecal immunochemical test (FIT) and fecal calprotectin (FC) results during vedolizumab treatment.
Discussion

With the introduction of anti-TNF agents in the treatment of CD, there is no doubt that treatment outcomes have improved. However, anti-TNF agents are known to increase the risk of serious infections, including TB [9]. It has been reported that anti-TNF agents are associated with a 2- to 8-fold increased risk of developing active TB [9]. Reactivation of latent TB infections (LTBI) rather than a new infection is considered to be the primary cause of active TB, as most of the active TB cases have been reported to occur within 3 to 4 months after starting anti-TNF treatment [9]. Therefore, screening for LTBI prior to anti-TNF treatment is strongly recommended worldwide, especially in Asia, where the prevalence of LTBI is higher than that of Western countries [9]. In this case report, the patient had completed TB vaccination, did not have any history or exposure to active TB, and TB screening was negative with both chest X-ray and IGRA at both times of diagnostic evaluation of CD and before the commencement of IFX. However, the patient, unfortunately, developed symptoms of active pulmonary TB 5 weeks after starting IFX treatment, indicating that the active TB was probably due to the reactivation of LTBI, which was missed on TB screening.

It is well known that when active TB is diagnosed during anti-TNF treatment, the anti-TNF agent should be withheld, and anti-TB therapy should be started [10]. Regarding when to restart anti-TNF treatment, it is considered safe to delay the resumption of anti-TNF therapy until the completion of anti-TB treatment [10]. However, if an early resumption of anti-TNF treatment is required, anti-TNF treatment may be restarted as early as 2 months after anti-TB treatment in patients who did not have an initially severe active TB, demonstrated a favorable response to anti-TB treatment, and when drug susceptibility was proven [10]. In this case report, the patient’s symptoms of CD were fortunately well controlled without IFX until the end of TB medication. According to the treatment guidelines, she could have restarted IFX when CD relapsed at the end of TB medication. However, because she had suffered a severe active TB and due to the fear of another severe disease course of active TB when IFX were to be restarted, the patient and parents preferred to start VDZ instead.

VDZ is effective for achieving both clinical remission and mucosal healing in adult patients with UC and CD [5,6,11]. Regarding safety, according to the integrated safety data from six trials, VDZ did not increase the risk of serious infections, progressive multifocal leukoencephalopathy, or malignancy [12]. Among 2,830 patients with 4,811 person-years (PYs) exposure to VDZ, TB was reported in only four patients (0.14%) with an estimated incidence of 0.1/100 PYs [12]. Meanwhile, the estimated incidence of TB during treatment with anti-TNF agents has been reported as 1.34/100 PYs and 0.79/100 PYs for IFX and adalimumab, respectively [13].

Compared with adults, there is limited experience with VDZ therapy in pediatric IBD. In children, VDZ is only available off-label and is used for patients who have already exhausted other treatment options, including anti-TNF agents. According to the ECCO/ESPGHAN (European Crohn’s and Colitis Organisation and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition) guideline, VDZ should be considered in chronically active or steroid-dependent pediatric UC patients as a second-line biologic therapy after anti-TNF failure, even though it has not yet been approved for use in children [7]. In addition, in pediatric CD patients who fail to maintain clinical remission on anti-TNF agents despite dose optimization and immunomodulator use, VDZ can be considered off-label [8]. A multicenter retrospective study showed that VDZ was safe and effective in pediatric IBD patients [14]. In this study, 64 children with IBD who had been previously treated with anti-TNF agents were included. During a median follow-up period of 24 months, corticosteroid-free remission was 37% in UC and 14% in CD at week 14, and 39% in UC and 24% in CD at the last follow-up [14]. Another retrospective study on 52 children with IBD showed clinical remission rates of 76% and 42% for UC and CD, respectively, at week 14 [15]. No serious adverse events were reported in either study [14,15].

In the GEMINI 3 trial, VDZ was not more effective than placebo in inducing clinical remission at week 6 among patients with CD who had failed previous treatment with anti-TNF agents [16]. The clinical benefits of VDZ in these patients were detectable later at week 10 [16]. This slow induction rate of VDZ was also observed in pediatric patients with CD [14]. Contrary to these findings, the patient in this case report showed a fast response to VDZ. Additionally, according to the clinical decision support tool developed for predicting the probability of response to VDZ in adult CD patients [17], the patient’s score in this case report was 16, which applies to an intermediate response probability. However, the patient continuously maintained clinical and biochemical remission, and endoscopic healing was observed at 1-year treatment with VDZ. One reason for this swift and favorable response to VDZ in this case report may be that the patient had not failed IFX due to poor response, but because discontinuation of IFX was inevitable due to active TB infection.

Data regarding TDM in VDZ are limited. An exposure-efficacy relationship does not seem as straightforward as they are for anti-TNF agents, and robust target VDZ trough levels are not well-defined [18]. However, according to data from a TDM study in adult IBD, VDZ trough levels of > 30 μg/mL at week 2, > 24
μg/mL at week 6, and > 14 μg/mL during maintenance therapy have been proposed for achieving clinical remission [19]. In another study in pediatric-onset IBD patients treated with VDZ, the mean VDZ trough level was 29.9 μg/mL at week 6 and 11.5 μg/mL during maintenance therapy [20]. In this case report, VDZ trough levels were lower than the proposed threshold targets; however, the patient responded well. This may be due to variability in the yet to be revealed association between individual pharmacokinetics and the degree of response to VDZ.

In conclusion, we report a case of a pediatric patient with CD who successfully achieved and maintained remission with VDZ after developing active pulmonary TB during treatment with IFX. In cases that require recommencement of treatment with biologics after recovery of active pulmonary TB caused by anti-TNF agents, VDZ may be a good option even in pediatric IBD.

**Notes**

**Ethical statements**

This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No: 2020-09-013). Informed consent was obtained from the patient and her parents.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**Author contributions**

Conceptualization, Formal analysis, Investigation: SC, BK; Data curation: All authors; Funding acquisition, Methodology, Resources, Software, Supervision, Validation: BK; Project administration, Visualization: SC; Writing-original draft: SC; Writing-review & editing: BSC, BHC, BK.

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**References**


Sciatic nerve neurolymphomatosis as the initial presentation of primary diffuse large B-cell lymphoma: a rare cause of leg weakness

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Neurolymphomatosis (NL) is defined as the involvement of the peripheral nervous system in lymphocytic invasion. It is a very rare form of lymphoma that may occur as an initial presentation or recurrence. It affects various peripheral nervous structures and can therefore mimic disc-related nerve root pathology or compressive mononeuropathy. NL often occurs in malignant B-cell non-Hodgkin lymphomas. Notwithstanding its aggressiveness or intractability, NL should be discriminated from other neurologic complications of lymphoma. Herein, we present a case of primary NL as the initial presentation of diffuse large B-cell lymphoma (DLBCL) of the sciatic nerve. The patient presented with weakness and pain in his left leg but had no obvious lesion explaining the neurologic deficit on initial lumbosacral and knee magnetic resonance imaging (MRI). NL of the left sciatic nerve at the greater sciatic foramen was diagnosed based on subsequent hip MRI, electrodagnostic test, positron emission tomography/computed tomography, and nerve biopsy findings. Leg weakness slightly improved after chemotherapy and radiotherapy. We report a case wherein NL, a rare cause of leg weakness, manifested as the initial presentation of primary DLBCL involving the sciatic nerve at the greater sciatic foramen.

Keywords: Diffuse large B-cell lymphoma; Neurolymphomatosis; Neuropathy; Sciatic nerve

Introduction

Neurolymphomatosis (NL), defined as lymphocytic invasion of the peripheral nervous system in a hematologic malignancy setting, is a rare form of lymphoma that may occur as an initial presentation or recurrence [1]. Involvement of the peripheral nerves, spinal nerve roots, nerve plexus, cranial nerves, and multiple sites has been reported [2]. Since its characteristic symptoms vary according to the site of involvement, physicians might fail to obtain an accurate diagnosis. NL should be discriminated from other neurological complications of lymphoma, such as compressive neuropathy due to tumor mass, paraneoplastic neuropathy, toxic neuropathy after chemotherapy, and neuropathy following radiotherapy [2]. Although NL often results from systemic dissemination of lymphoma or direct extension of a contiguous lesion into the nerve (secondary NL), it can also occur as isolated peripheral nervous system involvement with malignant lymphocytes at initial presentation (primary NL) [3,4]. As primary peripheral NL is extremely rare, only a few cases of primary lymphoma of the sciatic nerve...
nerve have been reported [3,5-7]. Here, we present a rare case of primary NL as the initial presentation of diffuse large B-cell lymphoma (DLBCL) of the sciatic nerve with a brief review of the literature.

Case

A 57-year-old male presented to the rehabilitation department with weakness and pain in his left leg for 2 months. The manual muscle test grades of his left lower extremity were as follows: knee flexion and ankle plantar flexion, grade 3 and ankle dorsiflexion and great toe extension, grade 0. Left ankle deep tendon reflex was absent. He had hypesthesia and allodynia in the left L5 and S1 dermatomes. Lumbosacral and knee magnetic resonance imaging (MRI) showed no neural compressive lesions that could induce neurologic deficits.

Electrodiagnostic tests performed to detect neurologic compromise revealed left lumbosacral plexopathy with denervation potentials in the left inferior gluteal nerve. Hip MRI with contrast showed a homogeneously enhancing, 6.3 × 2.9 × 2.8 cm-sized, fusiform, enlarged mass at the left greater sciatic foramen with diffuse hypertrophy from the left L5 and S1 nerve roots to the sciatic nerve (Fig. 1A), suggestive of lymphoma infiltration or neurogenic tumors such as perineurioma and neurofibroma.

Ultrasound-guided needle aspiration of the left sciatic nerve was performed for histopathologic confirmation. Considering the characteristics of the sciatic nerve, which is a major nerve that includes both motor and sensory components, needle aspiration was performed by targeting the soft tissue adjacent to the sciatic nerve to minimize nerve damage. Immunohistochemistry revealed tumor cells with infiltration of lymphocytes in the sciatic nerve (Fig. 2A). Lymphoma cells were strongly positive for CD20 (Fig. 2B). Consequently, the patient was diagnosed with a non-germinal center B-cell phenotype of DLBCL. Fluorodeoxyglucose (FDG) positron emission...
FDG PET/CT showed diffuse increased uptake of FDG in the left sciatic nerve and a few hypermetabolic foci in the left presacral area and pelvic cavity (Fig. 3A). The bone marrow biopsy showed positive expression of CD79, PAX-5, and CD3 and negative immunoreactivity for CD20 (data not shown). The patient was scheduled to undergo chemotherapy based on the biopsy results, and prednisolone was first administered to reduce inflammation and swelling of the lesion site. No symptom improvement was observed after daily administration of prednisolone (100 mg) for 5 days. Subsequently, the patient received six cycles of chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]).

On posttreatment hip MRI, the size of the enhancing mass at the sciatic foramen was markedly decreased (Fig. 1B). FDG PET/CT showed complete metabolic resolution of the mass at the left sacral foramen and partial metabolic resolution of the hypermetabolic foci in the left presacral area and pelvic cavity (Fig. 3B). Systemic involvement or recurrence was not observed. A follow-up electrodiagnostic study revealed left lumbosacral plexopathy with some axonal regeneration compared to the initial study. The patient showed slight motor improvement, equivalent to one grade on manual muscle testing, in all previously weakened muscles. The patient recently underwent adjuvant radiotherapy and is being followed up at our hospital’s departments of internal medicine and rehabilitation medicine. He is undergoing rehabilitation to maintain leg muscle mass and prevent tightness at the ankle joints.

**Discussion**

NL is an uncommon form of initial presentation or recurrence of lymphoma. It was described by Lhermitte and Trelles [8] in 1934 as a localized invasion of malignant lymphoid cells into peripheral nerves, roots, and cranial nerves. The nerve structures involved are peripheral nerves (60% of cases), spinal nerve roots (48% of cases), nerve plexus (40% of cases), cranial nerves (46% of cases), and multiple sites (58% of cases) [9]. NL often occurs in malignant B-cell non-Hodgkin lymphoma (NHL), which is aggressive, and systemic involvement is common [9]. DLBCL is the most common presentation of NHL, with approximately 40% of cases representing extranodal disease [5]. NL is a unique expression of extranodal NHL that accounts for 0.85% to 2.9% of newly diagnosed cases with neurological compromise [1].
Because of its rarity, the exact incidence of NL has not yet been clarified. A study conducted by the International Primary Central Nervous System Lymphoma Collaborative Group reported that 26% to 29.5% of all NL cases represented an initial presentation of systemic lymphoma, with a variable incidence of peripheral nerve involvement (20%–66%) [9]. Peripheral nerve involvement in NL is either due to systemic dissemination of lymphoma or direct extension of a contiguous lesion into the nerve [3]. Although less common, primary NL with isolated peripheral nerve involvement at initial presentation has also been reported.

Primary NL without systemic involvement is extremely rare and tends to have a predilection for the sciatic nerve [6,10,11]. The pathogenesis of this preferential involvement of the sciatic nerve has been debated. Baehring et al. [12] postulated that specific adhesion receptors on lymphoma cells that are analogous to normal lymphoid cells might lead to the involvement of specific tissues. Quiñones-Hinojosa et al. [13] suggested that the original lymphoma might be derived from B cells from or around the sciatic nerve.

NL presents with pure demyelinating or mixed axonal and demyelinating neuropathy, mononeuropathy, or symmetrical neuropathy [14]. Based on clinical features, NL has been classified into four types; (1) painful involvement of nerves or roots, (2) painless involvement of peripheral nerves, (3) painful or painless involvement of a single peripheral nerve, and (4) painful or painless cranial neuropathy [1]. Painful involvement of nerves or roots is the most common type. Consistent with this finding, our patient had pain in the L5 dermatome and ankle weakness corresponding to the L5 and S1 myotomes. As mentioned above, these symptoms are similar to those seen in L5 or S1 radiculopathy, lumbosacral plexopathy, and common peroneal neuropathy. Furthermore, dis-
tal lower limb weakness may be a clinical feature of motor neuron disease, distal myopathy, and polyneuropathy. These differential diagnoses must be considered in the clinical diagnostic approaches. Differentiating between NL and schwannoma on CT or MRI is sometimes challenging [6].

Histopathologic findings of peripheral nerve invasion by the tumor on nerve biopsy may be the most reliable method for a confirmed diagnosis of NL. However, it is not considered the diagnostic modality of choice for NL because of its invasive nature. There are several alternative imaging modalities, including MRI and FDG PET/CT, which can be used to diagnose NL. Previous studies have shown that FDG PET/CT is the most potent imaging tool for patients with suspected NL and has higher sensitivity than gadolinium-enhanced MRI [9,15]. Jeong et al. [4] reported that the sensitivities of FDG PET/CT and MRI for detecting NL were 100% and 78%, respectively. In this study, the patient underwent both MRI and FDG PET/CT before and after treatment. After treatment, the size of the enhanced mass was significantly decreased on MRI, and hypermetabolic foci showed partial remission on FDG PET/CT. Nevertheless, his neurologic weakness only improved slightly. This mismatch between the neurologic and metabolic responses could be due to a long time interval between symptom onset and treatment initiation, which could have led to irreversible axonal damage [4]. The absence of remarkable axonal regeneration on electrodiagnostic studies after treatment also supports this hypothesis.

The optimal treatment for primary NL is still under debate. Although various therapeutic approaches, including nerve resection, radiotherapy, and chemotherapy, have been attempted in previous studies, the outcomes have been poor [6,10]. Because of the aggressive nature of the non-germinal center B-cell type DLBCL, we administered R-CHOP with local radiotherapy to our patient. Consequently, satisfactory remission was achieved.

In summary, NL should be considered as a differential diagnosis in patients presenting with paresthesia, pain, and lower limb weakness to avoid misdiagnosis of peripheral neuropathy or lumbar disc pathology. FDG PET/CT is the most sensitive diagnostic tool for disease staging and monitoring treatment response. Electrodiagnostic studies provide additional information regarding the cause of neurological symptoms. If motor weakness persists even after appropriate treatment, rehabilitation should be performed to maintain the muscle bulk, prevent contracture, and aid self-regeneration. Considering its aggressive nature, early diagnosis and appropriate treatment with chemotherapy and radiation therapy should be performed in patients with NL.

**Notes**

**Ethical statements**

This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No: 2020-12-039). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Author contributions**

Conceptualization, Resources: YRD, HRJ, JHC; Data curation: YRD, HRJ; Formal analysis, Supervision: JHC; Methodology: KTK, SIK; Writing-original draft: KTK, SIK; Writing-review & editing: JHC.

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**References**

6. **Kahraman S, Sabuncuoglu H, Gunhan O, Gurses MA, Sirin S.** A rare reason of foot drop caused by primary diffuse large b-cell
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**Ethical considerations**

**Research ethics**

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports, state whether informed consents were obtained from the study participants. The editor of YUJM may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The YUJM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

**Instructions to authors**

Enactment December 30, 1984
First revision April 20, 2011
Second revision May 22, 2012
Third revision July 17, 2013
Fourth revision April 22, 2014
Fifth revised December 23, 2014
Recently revised April 30, 2018
Conflicts of interest
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Authorship
Each author is expected to have made substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author’s contribution to the study); AND to have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should preferentially indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgements. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

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- Formal analysis
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Redundant publication is defined as “reporting (publishing or attempting to publish) substantially the same work more than once, without attribution of the original source(s).” Characteristics of reports that are substantially similar include the following: (a) “at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication),” (b) “the subjects or study populations are the same or overlapped,” (c) “the methodology is typically identical or nearly so,” and (d) “the results and their interpretation generally vary little, if at all.”

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For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

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YUJM publishes editorials, review articles, original articles, case reports, and communications. Editorials are invited perspectives on an area of medical science, dealing with very active fields of research, current medical interests, fresh insights and debates. Review articles provide a concise review of a subject of importance to medical researchers written by an invited expert in medical science. Original articles are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers. Case reports deal with clinical cases of medical interest or innovation. Communications are interesting and instructive information for readers.

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Introduction

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Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer’s name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

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References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading “References,” and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed.” (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

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List all authors when six or less; when seven or more, list the first six and add et al.


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The Editorial Board of YUJM will discuss the suspected cases and reach a decision. YUJM will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

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All authors pledges that we follow the basic standards of research and publication ethics in the submission process to Yeungnam University Journal of Medicine

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