

[CASE REPORT]

Primary Intramuscular Classic Hodgkin Lymphoma: A Rare Case Report

Yuya Kamura¹, Ikuyo Tsutsumi¹, Yukiko Miura¹, Masanori Seki¹, Takuya Komeno¹,
Haruo Ohtani², Yukinori Inadome³ and Chikashi Yoshida¹

Abstract:

Hodgkin lymphoma (HL) is a hematologic malignancy that typically presents with lymphadenopathy. We herein report a patient with HL who presented with an intramuscular mass that required differentiation from an inflammatory lesion. A 65-year-old Japanese woman was referred to our hospital with a chief complaint of chronic and expanding tumor in her left thigh. By surgical resection, she was diagnosed with primary intramuscular, Epstein-Barr virus-positive, mixed-cellularity classic HL. She received combined modality therapy, resulting in a complete response. Primary intramuscular classic HL is extremely rare. It should be listed as a differential diagnosis of intramuscular tumors.

Key words: classic Hodgkin lymphoma (CHL), muscle, primary intramuscular lymphoma

(Intern Med 60: 3789-3793, 2021)

(DOI: 10.2169/internalmedicine.7524-21)

Introduction

Hodgkin lymphoma (HL) is a hematologic malignancy that typically presents with lymphadenopathy, predominantly affecting the cervical, axillary, and mediastinal lymph nodes (1, 2). A biopsy is essential for the diagnosis of HL in order to confirm the pathological features, such as Reed-Sternberg cells derived from germinal center B-cells surrounded by inflammatory cells (3). HL is divided into two major types based on the immunophenotype and morphology of the tissue: nodular lymphocyte-predominant HL and classic HL (CHL). Furthermore, there are four subtypes of CHL: nodular sclerosis CHL, lymphocyte-rich CHL, mixed-cellularity CHL, and lymphocyte-depleted CHL (4).

Soft-tissue masses can generally be classified as mesenchymal tumors, skin appendage lesions, metastatic tumors, other tumors and tumorlike lesions, or inflammatory lesions (5). Primary intramuscular lymphoma is uncommon and rarely reported in HL.

We herein report a case of primary intramuscular CHL of the left thigh that responded to chemotherapy followed by radiotherapy.

Case Report

A 65-year-old Japanese woman was referred to our hospital with a chief complaint of swelling of her left thigh. She had noticed the mass 11 months earlier, and it gradually enlarged without pain. Subsequently, it was accompanied by enlargement of a left inguinal lymph node. Although a tissue biopsy was performed before her referral to our center, the histopathological diagnosis was inflammatory granuloma with necrosis debris and no evidence of malignancy. She had no B-symptoms, such as night sweats, a fever, or weight loss. Her medical history included type 2 diabetes mellitus and pulmonary fibrosis.

On a physical examination, she had a large (11×13 cm), firm, irregular and nontender mass in the left thigh with a solitary lymph node (1×1 cm) in the left inguinal region. No other lymphadenopathy or hepatosplenomegaly was identified. Laboratory investigations showed a normal white blood cell count (5,600 cells/ μ L: neutrophils, 50.0%; lymphocytes, 35.0%; and monocytes 9.0%) and a normal serum C-reactive protein level. Elevated serum lactate dehydrogenase (LDH) levels were observed (236 IU/L). The liver and kidney func-

¹Department of Hematology, National Hospital Organization Mito Medical Center, Japan, ²Department of Pathology, Mito Saiseikai General Hospital, Japan and ³Department of Pathology, National Hospital Organization Mito Medical Center, Japan

Received: March 10, 2021; Accepted: April 12, 2021; Advance Publication by J-STAGE: June 5, 2021

Correspondence to Dr. Chikashi Yoshida, c.yoshida@mitomedical.org

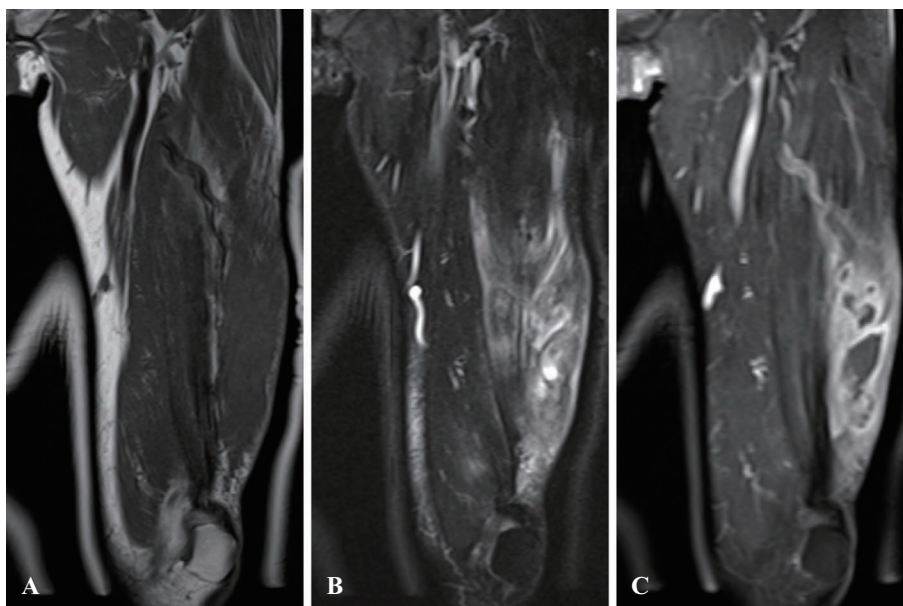


Figure 1. Coronal MR imaging of the left thigh. T1-weighted imaging reveals an intermediate signal intensity of the lesion compared with other normal muscle (A), while fat suppression T2-weighted imaging reveals increased signal intensity (B). Gadolinium-contrast enhancement demonstrates a series of cystic changes in the left vastus lateralis muscle (C).

tions were within the normal range. A serology test against hepatitis B, C, and anti-HIV were negative.

Contrast-enhanced computed tomography (CT) showed a low-density, irregularly shaped mass with rim enhancement in the left vastus lateralis muscle. Magnetic resonance imaging (MRI) was also performed to evaluate the nature of the lesion (Fig. 1). T1-weighted imaging revealed an intermediate signal intensity of the lesion compared with other normal muscle, while fat suppression T2-weighted imaging revealed an increased signal intensity of the lesion. Gadolinium-enhanced MRI demonstrated a series of cystic changes in the left vastus lateralis muscle, suggesting intramuscular abscess as a differential diagnosis at that time. We therefore performed soft tissue mass excision at the left thigh.

The histological examination of the surgical specimen showed that the central part of the tumor was mostly necrotic (Fig. 2A) with large, atypical cells, small lymphocytes, and macrophages infiltrating the periphery of the tumor (Fig. 2B). Some of the large, atypical cells were binuclear and pleomorphic and identified as Reed-Sternberg cells (Fig. 2C). An immunohistochemical examination revealed the large, atypical cells to be positive for CD30 (Fig. 2D), weakly positive for PAX5 (Fig. 2E), and completely negative for CD20 (Fig. 2F) and CD79a (Fig. 2G). They were also positive on Epstein-Barr virus-encoded small RNA *in situ* hybridization (EBER-ISH) (Fig. 2H). The disease was finally diagnosed as mixed-cellularity CHL. Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET)/CT from the head to upper thigh conducted after the surgery showed an abnormal accumulation of FDG only in the left inguinal lymph node (Fig. 3). A bone marrow bi-

opsy showed no evidence of tumor involvement. Based on these findings, we diagnosed her with Ann Arbor stage IIEA CHL of the primary left thigh muscle.

Although ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy was indicated for the initial treatment of this patient, the history of pulmonary fibrosis prompted us to refrain from using bleomycin because of possible pulmonary toxicity. Thus, she underwent 4 cycles of AVD chemotherapy that included doxorubicin 25 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on days 1 and 15 of a 28-day cycle. She did not experience any serious adverse events and tolerated the regimen well. Subsequently, involved-field radiation therapy (IFRT) was performed on the left thigh and left inguinal lymph node (total dose of 40 Gy in 20 fractions). After those series of treatments, the patient achieved a complete response and has been undergoing treatment-free follow-up for five years.

Discussion

HL characteristically presents with supradiaphragmatic lymphadenopathy. Extranodal involvement (including primary and secondary) of HL is less frequent, being noted in 15%-30% of HL cases (6). Among extranodal sites, the liver and lungs are the most common, followed by the bones (7). Muscle involvement was found in 0.32% of autopsy cases of CHL (8).

HL infrequently originates in extranodal organs. Indeed, there have only been two cases of primary intramuscular HL reported in the literature (9, 10), both of them involving gluteal tumors. Utkan et al. (9) described the first case of CHL in a 68-year-old man presenting with a history of pain-

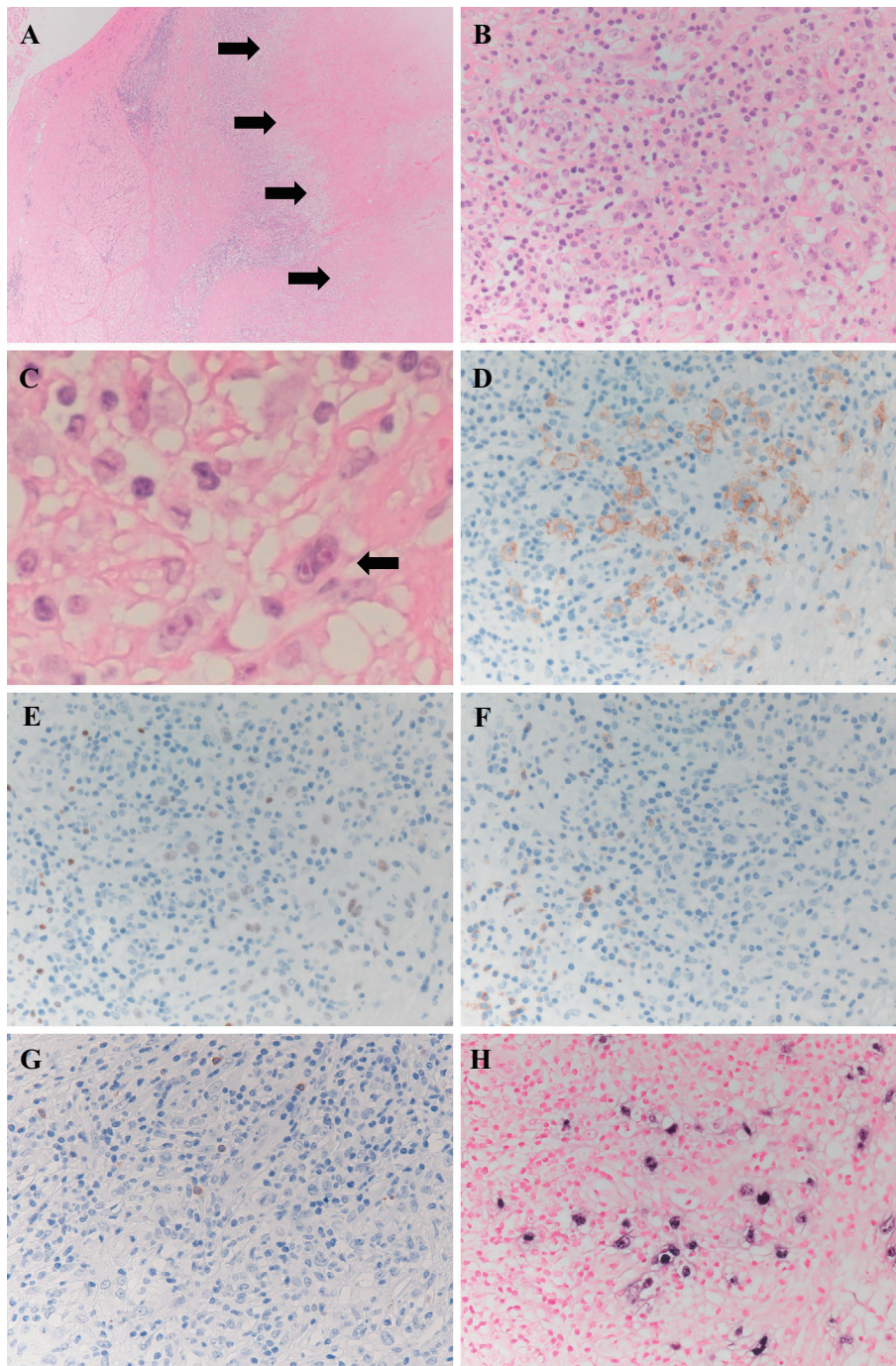


Figure 2. A histopathological examination of the left thigh mass. Hematoxylin and Eosin staining (A: $\times 40$, B: $\times 400$, C: $\times 600$) shows the central part of the tumor to be mostly necrotic (arrows in A), with large, atypical cells, small lymphocytes, and macrophages infiltrating the periphery of the tumor. Some of the large, atypical cells are binuclear and pleomorphic and are identified as Reed-Sternberg cells (arrow in C). An immunohistochemical examination reveals the atypical cells to be positive for CD30 (D: $\times 400$) and weakly positive for PAX5 (E: $\times 400$) but negative for CD20 (F: $\times 400$) and CD79a (G: $\times 400$). They are also positive for EBER-ISH (H: $\times 400$).

ful right gluteal swelling for 2 months with hypercalcemia, anemia, leukocytosis, and mild thrombocytosis. MRI revealed an approximately 15-cm mass infiltrating the gluteal and iliopsoas muscles. CT revealed no abnormalities except for a 2 \times 2.5-cm right inguinal lymph node. A histological examination of the gluteal mass demonstrated nodular sclerosis CHL. There was no description of the Epstein-Barr virus

(EBV) presence. The patient received six cycles of ABVD chemotherapy and achieved a complete response.

Jonjić et al. reported another case of primary intramuscular CHL in a 78-year-old man presenting with left gluteal lump (10). A laboratory examination showed an elevated erythrocyte sedimentation rate, anemia, and leukocytosis. 18 F-FDG-PET/CT revealed an over 10-cm-large FDG-avid

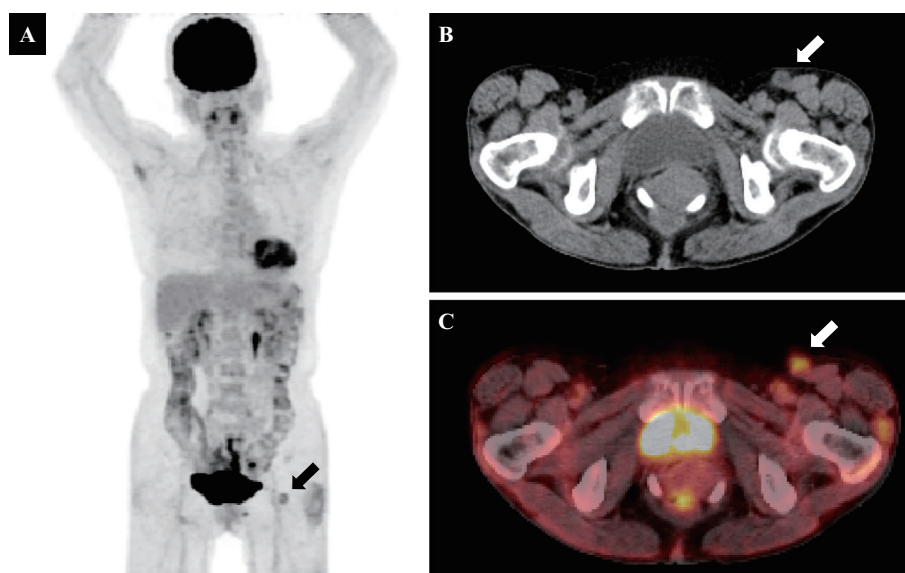


Figure 3. ^{18}F -FDG-PET maximum intensity projection image (A) of the head to the upper thigh taken after resection of the left thigh mass shows a single focal uptake (arrow in A), corresponding to the 10-mm-wide left inguinal lymph node indicated by the arrows on axial CT (B) and fused axial PET/CT (C).

Table. A Summary of the Reported Cases of Primary Intramuscular Classic Hodgkin Lymphoma.

Reference Number	Age	Sex	B-symptoms	Location	Stage	Subtype	EBV	Treatment	OS
9	68	Male	NR	Right gluteal muscle	II E	Nodular sclerosis	NR	ABVD	Alive at 15 mo (CR)
10	78	Male	+	Left gluteal muscle	II EB	Nodular sclerosis	-	IFRT 44 Gy	NR (achieved CR)
Present case	65	Female	-	Left vastus lateralis muscle	II EA	Mixed cellularity	+	AVD+IFRT 40 Gy	Alive at 60 mo (CR)

OS: Overall survival, NR: Not recorded, +: positive, -: negative, ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine, mo: month, IFRT: involved-field radiation therapy, CR: Complete response, AVD: Doxorubicin, vinblastine, dacarbazine

mass in the left gluteal region and no other lesions. An excisional biopsy of the mass demonstrated nodular sclerosis CHL. EBER-ISH was negative. IFRT was performed, resulting in a complete response.

In the present patient, the third reported case of primary intramuscular CHL, there was some suspicion that the left inguinal lymph node was the primary lesion. However, this is chronologically unlikely, as the patient initially presented with the thigh swelling, followed by left inguinal lymphadenopathy. In addition, the inguinal lymph node was only 1 cm in diameter, whereas the thigh mass was over 10 cm large. Considering the pre/post temporal relationship and the size of the lesion, we determined that left thigh muscle lesion to be the primary one. These three cases of primary intramuscular HL are summarized in Table.

The association between EBV infection and the development of HL has been widely investigated and has been found to vary by region, economic status, and age, suggesting that environmental factors may be involved in the development of HL. Endoplasmic reticulum stress associated with the viral infection has been shown to be involved in the

pathogenesis of HL (11). In addition, it has been reported that positivity of EBER-ISH is associated with a high frequency of extranodal involvement in patients with CHL (12). Reed-Sternberg cells and Hodgkin cells with a rich inflammatory background ensure their survival through the selective recruitment of cells in their microenvironment, constitutional activation of anti-apoptotic pathways, and elaborate evasion of the host immune system (13). As in the two previous cases (9, 10), the present case developed at an advanced age. Reed-Sternberg cells were positive for EBER-ISH, as shown in Fig. 2F. Taken together, these findings suggest that immunodeficiency along with aging and infection with EBV may contribute to the development of extranodal CHL. However, due to the extremely limited number of cases available, it is difficult to clarify the factors associated with the genesis of CHL primarily in muscle.

In conclusion, muscle involvement of HL is uncommon, and primary intramuscular CHL in particular is extremely rare. Nevertheless, it should be considered as a differential diagnosis in patients presenting with intramuscular tumors. Further studies are required to elucidate the clinical features

and pathogenesis of this rare form of disease.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We are grateful to Prof. Junia V. Melo (University of Adelaide, Australia) for the language editorial assistance.

References

1. Shimabukuro-Vornhagen A, Haverkamp H, Engert A, et al. Lymphocyte-rich classical Hodgkin's lymphoma: clinical presentation and treatment outcome in 100 patients treated within German Hodgkin's Study Group trials. *J Clin Oncol* **23**: 5739-5745, 2005.
2. Laurent C, Do C, Gourraud PA, de Paiva GR, Valmary S, Brousset P. Prevalence of common non-Hodgkin lymphomas and subtypes of hodgkin lymphoma by nodal site of involvement: a systematic retrospective review of 938 cases. *Medicine (Baltimore)* **94**: e987, 2015.
3. Marafioti T, Hummel M, Foss HD, et al. Hodgkin and reed-sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood* **95**: 1443-1450, 2000.
4. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* **127**: 2375-2390, 2016.
5. Beaman FD, Kransdorf MJ, Andrews TR, Murphey MD, Arcara LK, Keeling JH. Superficial soft-tissue masses: analysis, diagnosis, and differential considerations. *Radiographics* **27**: 509-523, 2007.
6. Guermazi A, Brice P, de Kerviler E E, et al. Extranodal Hodgkin disease: spectrum of disease. *Radiographics* **21**: 161-179, 2001.
7. Li ZM, Zhu YJ, Xia Y, Huang JJ, Jiang WQ. Clinical characteristics of the patients with Hodgkin's lymphoma involving extranodal sites. *Chin J Cancer* **31**: 342-347, 2012.
8. Komatsuda M, Nagao T, Arimori S. An autopsy case of malignant lymphoma associated with remarkable infiltration in skeletal muscles. *Rinsho Ketsueki (The Japanese Journal of Clinical Hematology)* **22**: 891-895, 1981 (in Japanese).
9. Utkan G, Buyukcelik A, Yalcin B, et al. Extranodal Hodgkin disease presenting with gluteal mass and hypercalcemia. *South Med J* **99**: 1149-1150, 2006.
10. Jonjić N, Valković T, Vujaklija DV, Ilijaš KM. Diagnostic challenge of soft tissue extranodal Hodgkin lymphoma in core-needle biopsy: case report. *Scott Med J* 36933020941262, 2020.
11. Piris MA, Medeiros LJ, Chang KC. Hodgkin lymphoma: a review of pathological features and recent advances in pathogenesis. *Pathology* **52**: 154-165, 2020.
12. Kiliçarslan A, Öztürk V, Yikilmaz AŞ, et al. Evaluation of the prognostic importance of c-Myc and Bcl-2 expressions and the presence of Epstein-Barr virus in classical Hodgkin lymphoma. *Turk Patoloji Derg* **34**: 199-206, 2018.
13. Bienz M, Ramdani S, Knecht H. Molecular pathogenesis of Hodgkin lymphoma: past, present, future. *Int J Mol Sci* **21**: 6623, 2020.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).