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Case Report

Langerhans Cell Histiocytosis in Bone: A Case Report

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease in which histiocytic infiltrations can be seen in bone, skin, lymph nodes, lungs, liver, spleen, bone marrow, central nervous system and endocrine glands. Pulmonary LCH has been closely associated with smoking while there is no data on genetic, viral or neoplastic etiology. In LCH with multiple system involvement, unifocal/multifocal infiltrations occur in two or more organs together with systemic symptoms such as weight loss and fever. In histology, Langerhans cells that do not contain phagocytic material in their cytoplasm, have a folded "coffee bean" appearance in their nucleus, express histiocyte markers CD1a, S100 and C207 and contain Birbeck granules under electron microscope. In treatment, if there is a risk of collapse in spinal or femoral bone lesions, surgery and radiotherapy can be applied for stabilization; if necessary, chemotherapy can be applied in multisystem disease. Here, we reported an LCH patient with a malignant shaped lytic lesion in the thoracic spine and adjacent bone.

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disease that can be seen as granulomatous histiocyte infiltrates in almost every tissue such as lymph nodes, lungs, liver, spleen, bone marrow, central nervous system, endocrine organs, mainly osteolytic bone lesions and/or skin lesions. Its incidence in adults has been reported as 1-2 per million. It is more prevelant in males, specifically in northern European Caucasians and between the ages of 1-3. Although pulmonary LCH is closely associated with smoking, extrapulmonary LCH is not associated with smoking.[1]

In the pathophysiology of LCH, the increase in regulatory T cells and various cytokines such as IL-17, IL-2 and growth factors was thought to be a reactive condition secondary to a defect in the immune regulatory system. In 2010, however, a BRAF-V600E mutation was reported in more than half of the LCH patient samples and ERK phosphorylation in all cases. After these developments, LCH is thought to be a clonal myeloid neoplasm. LCH is now defined as an inflammatory myeloid neoplasm in the revised 2016 Histiocyte Association Classification. Patients with BRAF-V600E mutation constitute the group with risky organ involvement multisystem disease, resistant to chemotherapy or high reactivation rate. Up-regulation of TGF-beta, BCL2, ICAM, CD14, CD2, osteopontin and vanin, which are genes that bring and activate T cells to the area of inflammation in LCH, have also been shown.[2,3]

In histology, granulomatous infiltration consisting of eosinophils, CD8 positive T cells and multinuclear giant cells is observed with heterogeneous collection of Langerhans cells in the tissue involved. Langerhans cells are myeloid dendritic cells with a slightly eosinophilic cytoplasm, few vacuoles, no phagocytic material, a "coffee bean" nucleus, expressing the histiocyte markers CD1a, S100 and CD207 (langerin), and containing Birbeck granules in electron microscopy. Birbeck granules are intracytoplasmic, rod-shaped organelles with enlargement at the tip, tennis racket-like organelles.[1,4]

The names: Hand Schüller-Christian disease, Letterer Siwe disease, Histiocytosis X, diffuse reticuloendotheliosis were used in the past for LCH. However, they are no longer used, instead the term "eosinophilic granuloma" continues to be used for the disease with isolated lytic appearance in the bone. Here, we wanted to report that we diagnosed LCH in a patient with a malignant lytic lesion in the thoracic vertebra and adjacent bone, since it is very rare in the practice of internal medicine.

Case Report

A 51-year-old male patient was admitted to our internal medicine outpatient clinic with the complaint of localized pain in the back that had been intensified for the last 3 months and had been bothering him for 1 year. The general condition of the patient, who had no known chronic disease, was good, his vital signs were stable, and system examinations were normal. LDH was 281 U/L (125-220). Other laboratory findings were unremarkable. In thoracic spinal CT-MR examinations, a lytic, destructive 66x37 mm mass lesion causing compression on the spinal cord and a nodular lesion area on the lateral of the 6th rib were observed in the costovertebral junction at the level of the 7th rib on the right, at the vertebral corpus-pedicle transverse process-articular facets *(Figure 1)*. In PET-CT, intensely increased FDG uptake was observed in the lesion with irregular borders (SUVmax: 10.5) and the lesion at the 6th rib (SUVmax: 8.0). Abdominal CT was normal. Total laminectomy at T6-T7 level, extradural total tumor resection, subtotal excision of the 6th-7th ribs was performed. Spinal stabilization was achieved, and the patient was discharged on the 7th postoperative day. No additional involvement was observed in bone scintigraphy. There was radiological regression in the postoperative 2nd month imaging of the patient *(Figure 2)*.

In the pathological examination, cells with oval vesicular nuclei, as well as ones with oval vesicular nuclei that have nicks and grooves in the nuclei were observed among the bone trabeculae, which had spread to the soft tissue, infiltrated the trabeculae and contained dense eosinophil leukocytes. Lastly it was rich in mixed type

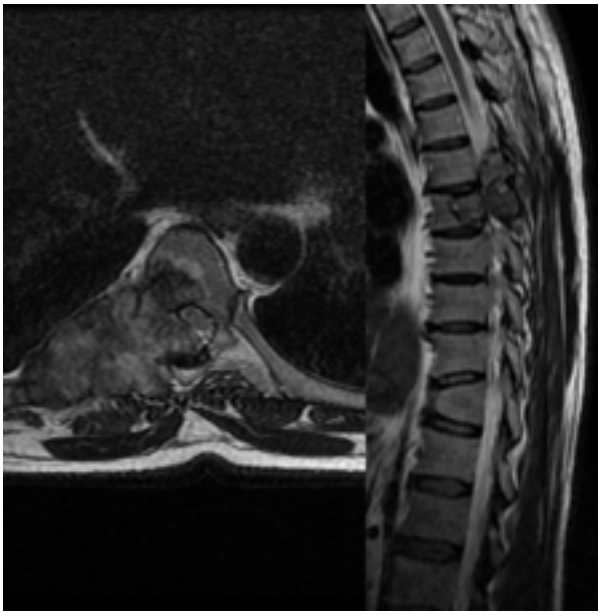

Figure 1. T2A axial and sagittal sections of preoperative MRI. A mass destructs the right costovertebral angle at the level of the T7 vertebra, showing infiltration in the right transverse process/intraarticular facets, and compressing the spinal cord.

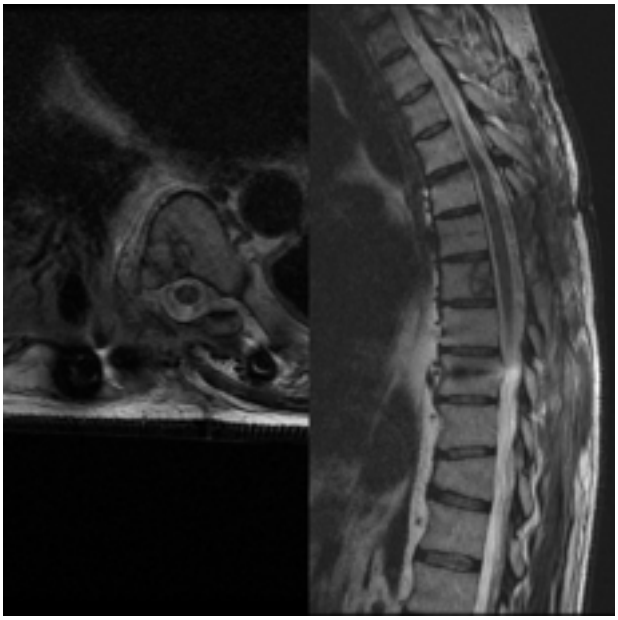

Figure 2. Aortic dissection images with multi-slice computerized tomographic angiography.

inflammatory cells *(Figure 3)*. CD1a (Thermo/Ab-5): positive, S100 (BioGenex/15E2E2): positive, CD68 (Biocare/KP1): positive were detected in cells with oval and vesicle nuclei. The findings were evaluated as compatible with Langerhans cell histiocytosis *(Figure 4)*. With the decision of the council, a total of 2000 cgy radiotherapy was administered to the patient in 10 sessions with the IMRT technique. The patient, who was in remission after treatment, was followed up.

Discussion

Patients with LCH may have unifocal or multifocal involvement in bone, skin, lymph nodes, lungs, CNS, thyroid and rarely the thymus. In LCH with single system involvement, systemic symptoms such as weight loss and fever are generally not seen. In multisystem LCH, there are two or more organ involvements that can be associated with risky organ involvement. The organs at risk are the hematopoietic system, liver and/or spleen, indicating a poor prognosis. While most patients wait 1-4 years for a correct diagnosis, some may be diagnosed 5-20 years after childhood-onset diabetes insipidus.[5]

Patients with bone involvement may be asymptomatic or complain of localized pain in the sensitive area. Huang *et al*.[6] reported that in 30 cases of eosinophilic granuloma diagnosed in their center, the cervical than thoracic regions were affected most frequently in the vertebral column. Radiographically, soft tissue mass is most commonly seen around the lytic lesion in the bone. The most commonly affected area of the vertebra is the corpus, and the lesion may compress the spinal cord, and collapse may occur with epidural invasion/pathological fracture.

Phillips *et al*.[7] evaluated the effectiveness of FDG-PET scans in identifying areas of active disease and evaluating response to therapy in patients with LCH. As a result of their studies, they showed that PET-CT is superior to other imaging studies such as X-ray, CT, and MRI in determining the extent of the disease and the response to treatment. In our patient, a multifocal disease with single system bone involvement was observed as a

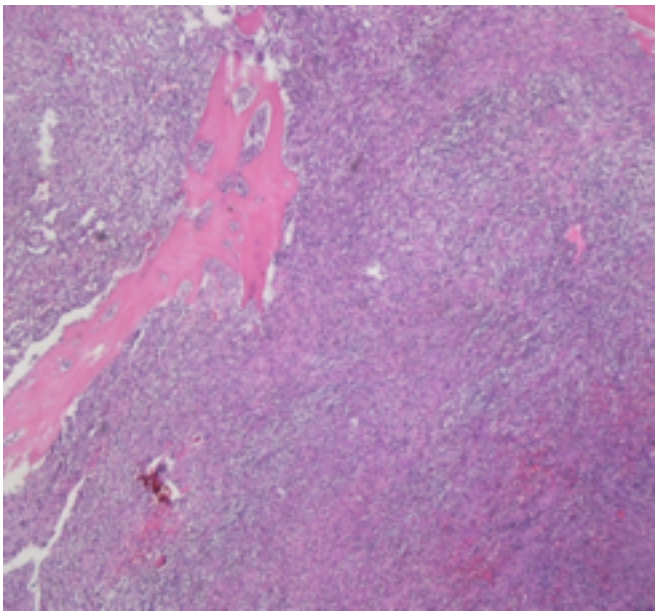

Figure 3. Cells infiltrating bone trabeculae, spreading to soft tissue with rich in mixed-type inflammatory are seen. HE x40 magnification.

result of PET-CT taken before the operation, and a treatment plan was made.

The BRAF–V600E mutation detected in more than half of LCH cases elucidated the pathogenesis of the disease. The BRAF protein is a component of the MAPK (RAS-RAFMEK-ERK) signaling pathway, which leads to the activation of transcription factors required for cell growth and proliferation. V600E is the most common mutation in BRAF and is the trigger for the development of malignancy.[8-10] Liquid biopsy, which allows detection of BRAF-V600E mutations in cell-free DNA extracted from peripheral blood plasma of LCH patients, using allele-specific real-time PCR or digital droplet PCR techniques, is promising as a potential biomarker for early detection in high-risk LCH.[11]

Since LCH is a very rare disease and different organs can be affected in the disease, its diagnosis is difficult. By histology and immunophenotyping, it should be differentiated from other histiocytic diseases, metastatic solid tumors, hematopoietic neoplasms such as lymphoma and myeloma, hemophagocytic lymphohistiocytosis, macrophage activation syndrome and lastly, Erdheim-Chester/Rosai-Dorfman disease.[12]

Although the treatment may vary according to the number of organs and lesions involved in a single organ system disease, curettage of the bone lesion, topical treatments for skin lesions can be combined with methotrexate (20 mg/m^2/week), mercaptopurine (50 mg/m^2/day), single agent prednisolone or vinblastine when necessary. If there is a risk of collapse in spinal or femoral bone lesions, surgery and/or intralesional corticosteroid and radiotherapy can be applied for stabilization. Since there was a risk of spinal cord compression in our patient, an operation was performed to eliminate the risk, and then radiotherapy was applied.

In multisystem disease, patients should be referred to clinical study groups. Since the discovery of the BRAF-V600E mutation, the pathophysiology of LCH has been largely resolved, making the feasibility of targeted therapies such as BRAF or MEK inhibitors possible. It has been possible to expand the treatment options with a BRAF inhibitor (vemurafenib, dabrafenib) and a MEK1/2 inhibitor (trametinib).[13-15] In the treatment of LCH, patients should be directed to centers where clinical trials of combined chemotherapy and targeted therapies are performed, and treatment results should be closely monitored.

Conflict of Interests

Authors declare that there are none.

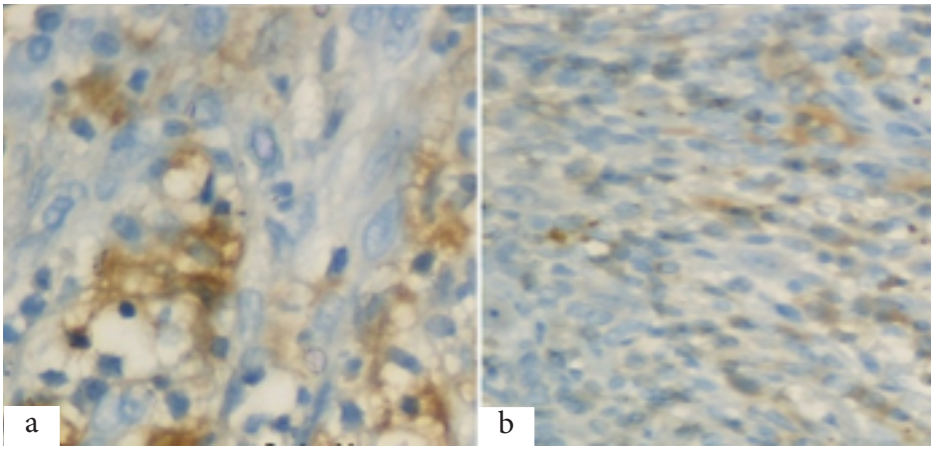

Figure 4. Positive staining is seen with immunohistochemical methods for CD1a (a) and S100 (b) which are specific for Langerhans cells. CD1a x400 magnification (a), S100 x400 magnification (b).

Authors' Contribution

Study Conception: OK, SEC; HE; Study Design: OB, AZK, DO; Supervision: OK, HE, SEC; Fundings: DO, HE, SEC; Materials: OK, OB, AZK; Data Collection and/or Processing: OO, MT, TDH, KA; Statistical Analysis: OK, GM; Data Interpretation: OB, AZK, DO; Literature Review: OK; TDH; Manuscript Preparation: AZK, OK, GM; Critical Review: OK, HE, GM.

References

1. De Young B, Egeler RM, Rollins BJ. Langerhans cell histiocytosis. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyons: International Agency for Research on Cancer; 2013:356.
2. Senechal B, Elain G, Jeziorski E, Grondin V, Patey-Mariaud de Serre N, Jaubert F, Beldjord K, Lellouch A, Glorion C, Zerah M, Mary P, Barkaoui M, Emile JF, Boccon-Gibod L, Josset P, Debré M, Fischer A, Donadieu J, Geissmann F. Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med. 2007 Aug;4(8):e253. doi: 10.1371/journal.pmed.0040253.
3. Berres ML, Lim KP, Peters T, Price J, Takizawa H, Salmon H, Idoyaga J, Ruzo A, Lupo PJ, Hicks MJ, Shih A, Simko SJ, Abhyankar H, Chakraborty R, Leboeuf M, Beltrão M, Lira SA, Heym KM, Bigley V, Collin M, Manz MG, McClain K, Merad M, Allen CE. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med. 2014 Apr 7;211(4):669-83. doi: 10.1084/jem.20130977.
4. Minkov M, Pötschger U, Grois N, Gadner H, Dworzak MN. Bone marrow assessment in Langerhans cell histiocytosis. Pediatr Blood Cancer. 2007 Oct 15;49(5):694-8. doi: 10.1002/pbc.21227.
5. Götz G, Fichter J. Langerhans'-cell histiocytosis in 58 adults. Eur J Med Res. 2004 Nov 29;9(11):510-4.
6. Huang W, Yang X, Cao D, Xiao J, Yang M, Feng D, Huang Q, Wu Z, Zheng W, Jia L, Wu S. Eosinophilic granuloma of spine in adults: a report of 30 cases and outcome. Acta Neurochir (Wien). 2010 Jul;152(7):1129-37. doi: 10.1007/s00701-010-0644-3.
7. Phillips M, Allen C, Gerson P, McClain K. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2009 Jan;52(1):97-101. doi: 10.1002/pbc.21782.
8. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, Kuo FC, Ligon AH, Stevenson KE, Kehoe SM, Garraway LA, Hahn WC, Meyerson M, Fleming MD, Rollins BJ. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010 Sep 16;116(11):1919-23. doi: 10.1182/blood-2010-04-279083.
9. Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. Cancer Sci. 2018 Dec;109(12):3707-13. doi: 10.1111/cas.13817.
10. Go H, Jeon YK, Huh J, Choi SJ, Choi YD, Cha HJ, Kim HJ, Park G, Min S, Kim JE. Frequent detection

of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology. 2014 Aug;65(2):261-72. doi: 10.1111/his.12416.

11. Héritier S, Hélias-Rodzewicz Z, Lapillonne H, Terrones N, Garrigou S, Normand C, Barkaoui MA, Miron J, Plat G, Aladjidi N, Pagnier A, Deville A, Gillibert-Yvert M, Moshous D, Lefèvre-Utile A, Lutun A, Paillard C, Thomas C, Jeziorski E, Nizard P, Taly V, Emile JF, Donadieu J. Circulating cell-free BRAFV600E as a biomarker in children with Langerhans cell histiocytosis. Br J Haematol. 2017 Aug;178(3):457-67. doi: 10.1111/bjh.14695.
12. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. Blood. 2015 Jul 2;126(1):26-35. doi: 10.1182/blood-2014-12-569301.
13. Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, Cluzel P, Drier A, Hervier B, Benameur N, Besnard S, Donadieu J, Amoura Z. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013 Feb 28;121(9):1495-500. doi: 10.1182/blood-2012-07-446286.
14. Diamond EL, Subbiah V, Lockhart AC, Blay JY, Puzanov I, Chau I, Raje NS, Wolf J, Erinjeri JP, Torrisi J, Lacouture M, Elez E, Martínez-Valle F, Durham B, Arcila ME, Ulaner G, Abdel-Wahab O, Pitcher B, Makrutzki M, Riehl T, Baselga J, Hyman DM. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol. 2018 Mar 1;4(3):384-8. doi: 10.1001/jamaoncol.2017.5029.
15. Papapanagiotou M, Griewank KG, Hillen U, Schimming TT, Moeller LC, Führer D, Zimmer L, Roesch A, Sucker A, Schadendorf D, Livingstone E, Schilling B. Trametinib-induced remission of an MEK1-mutated langerhans cell histiocytosis. JCO Precis Oncol. 2017 May 18;1:1-5. doi: 10.1200/PO.16.00070.