

## Case Report

# Simultaneous Occurrence of Hodgkin's Lymphoma and Langerhans Cell Histiocytosis of the Spine : A Rare Combination

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Hodgkin's disease presenting with spinal cord compression owing to extradural and bone involvement is extremely unusual. A 48-year-old man presented with progressive lower extremity weakness resulting from spinal cord compression attributable to an epidural mass in the thoracic vertebrae. The patient underwent decompressive surgery, and was then treated with chemotherapy for Langerhans cell histiocytosis. However, the disease progressed, and we performed second decompressive surgery with stabilization. Subsequent histopathological investigations revealed Hodgkin's lymphoma of the bone. Here, we describe an unusual case of spinal Hodgkin's lymphoma and Langerhans cell histiocytosis to draw attention to this combination as a possible diagnosis in patients with mixed inflammatory cell infiltrate lesions in the spine.

**KEY WORDS :** Hodgkin's disease · Lymphoma · Langerhans cell histiocytosis · Spinal cord compression.

## INTRODUCTION

Non-Hodgkin's lymphoma arises in the lymph nodes in approximately 60% of patients and at extranodal sites in about 40% of patients. In 90% of patients with Hodgkin's lymphoma, the disease is thought to arise in the lymph nodes, whereas in 10% of patients the disease arises at other sites<sup>1,4</sup>. Although non-Hodgkin's lymphoma can affect the central nervous system (CNS), such involvement is less common with Hodgkin's disease<sup>4,10</sup>. Presentation with spinal cord compression arising from extradural and bone involvement in Hodgkin's disease, without associated systemic lymphoma, is extremely rare. In the literature, there had been approximately 30 reports of patients with the coexistence of Langerhans cell histiocytosis (LCH) and Hodgkin's disease<sup>3,8</sup>. We describe an unusual case of Hodgkin's

lymphoma and LCH of the thoracic spine.

## CASE REPORT

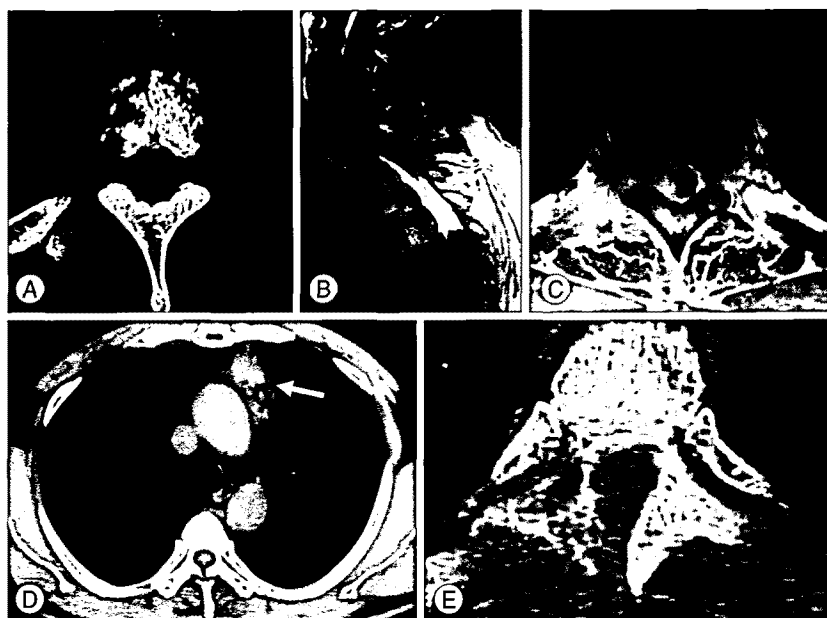
### History and examination

A 47-year-old man presented with a 6-month history of progressive motor weakness in the lower extremities, numbness below the midthoracic area, and spastic gait disturbance. His medical history indicated no abnormalities. Neurological examination revealed spasticity in the lower limbs with brisk deep tendon reflexes and grade 4/5 power in lower extremities that was worst in the hip flexors but did not preclude walking. There was a subjective decrease in pinprick sensation below the 4th thoracic dermatome. Computed tomographic (CT) scans of the thoracic spine showed a bone-destructive lesion in the second, third, and fourth thoracic vertebrae (Fig. 1A). A magnetic resonance imaging (MRI) scan demonstrated that the destroyed thoracic vertebral bodies had been replaced by an osteolytic mass and that the thoracic spinal cord was compressed by this mass (Fig. 1B and C). Routine blood analysis was normal. Skin tests using antigens to *Candida*, *Trichomonas*, and tuberculosis were negative. In a plain chest X-ray, no pro-

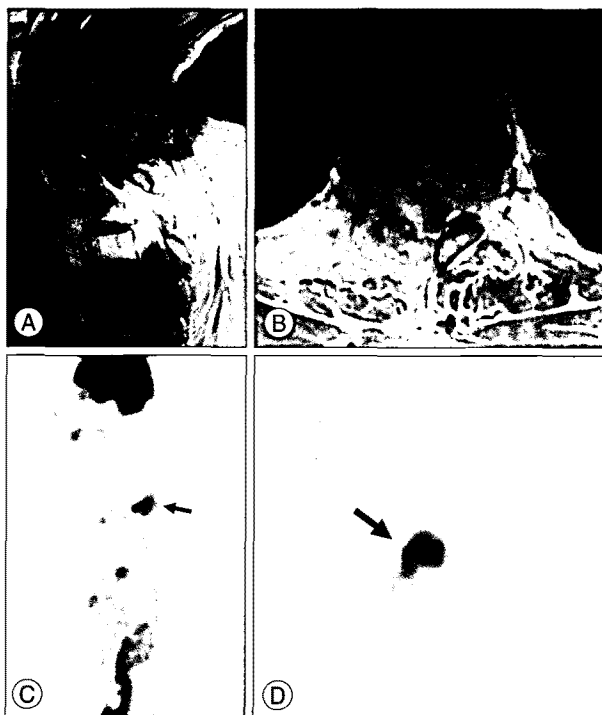
• Received : July 23, 2009 • Revised : September 15, 2009

• Accepted : March 17, 2010

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**Fig. 1.** Preoperative images (A-D). (A) Axial computed tomographic (CT) scan showing a bone-destructive lesion. Gadolinium-enhanced T1-weighted MR sagittal (B) and axial (C) images showing thoracic spinal cord compression. (D) The CT scan of the thorax shows a mediastinal mass (arrow). (E) A postoperative axial CT scan following the first surgery demonstrates a T3 laminotomy.



**Fig. 2.** Magnetic resonance images (A and B) and whole-body positron emission tomographic scan (C and D) images obtained 1 year after surgery, demonstrating progression of the thoracic spine lesion with spinal cord compression.

minent alteration of heart configuration or lung perfusion was seen. In a CT scan of the thorax, a large mass was detected in the chest wall with infiltration of the sternum and anterior mediastinum (Fig. 1D). The patient underwent

CT-guided needle biopsy of the anterior mediastinum and showed chronic inflammatory infiltrates with fibrosis. Bacterial, fungal, and tuberculosis cultures were negative. Analysis of a second percutaneous needle biopsy specimen yielded similar results.

### First operation and postoperative course

The patient underwent surgery to obtain a diagnosis and to decompress the spinal cord. A fibrotic, compressive epidural mass that resembled fibrous and granulation tissue was partially removed by T3 laminotomy (Fig. 1E). Postoperatively, the patient made an uneventful recovery, he experienced strength improvement up to normal power in lower extremities. The tissue that was removed during surgery showed lymphoreticular cell proliferation,

with lymphocytes, histiocytes, neutrophils, eosinophils, and Langerhans cells, consistent with Langerhans cell histiocytosis. Immunohistochemical staining for S-100 protein and CD1a was positive. Bacterial, fungal, and tuberculous cultures remained negative. Subsequently, the patient underwent chemotherapy with two cycles of cladribine. A combination of vinblastine and prednisone was administered weekly for 2 months. As maintenance therapy, seven cycles of vinblastine, 6-mercaptopurine, and prednisone were administered. After 6 months, a chest CT scan and a whole-body positron emission tomographic (PET) CT scan showed a decrease in tumor mass in the anterior mediastinum and no new lesions. One year after surgery, however, the patient developed recurrent progressive lower extremity weakness. MRI and a whole-body PET-CT scan demonstrated that the thoracic spine lesion had progressed with kyphosis but the mediastinal lesion had not changed (Fig. 2). There was abnormal enhancement of the 2nd to 4th thoracic vertebrae; these were expanded by a soft tissue mass that extended along the relevant portion of the thoracic spine. There was recurrent spinal cord compression and a more extensive prevertebral mass.

### Second operation and postoperative course

The patient underwent a second surgical procedure to obtain a diagnosis, decompress the spinal cord, and stabilize the spine. The patient underwent decompressive laminectomies from T2 to T4 with partial removal of the tumor, and



**Fig. 3.** (A) Scanning power view shows irregular osteolytic fibrous lesion with extensive inflammation (original magnification,  $\times 20$ , H&E stain). (B) High power view shows cellular lesion composed of a mixture of histiocyte, Langerhans cells, eosinophils, and fibroblasts in the densely sclerotic background (original magnification,  $\times 400$ , H&E stain). Insets : The Langerhans cells stain positively with S100 and CD1a. (C) Adjacent area shows numerous Reed-Stemberg cells, with their characteristic bi-lobed mirror image nuclei containing owl-eyed nucleoli among small lymphocytes, and plasma cells (original magnification,  $\times 400$ , H&E stain). Inset : Immunostain for CD30 (Ki-1 antigen).

posterior instrumentation from T1 to T5 using a pedicle screw and rod system. Analysis of the biopsy showed a lymphoid infiltrate with atypical nuclei that were larger and more pleomorphic than those of inflammatory cells (Fig. 3A). Examination of histological material from the second operation revealed that, in addition to the inflammatory infiltrate that comprised the bulk of the lesion, large, malignant lymphoma cells with prominent eosinophilic nucleoli and a few multinucleated giant cells with prominent nucleoli were present. The lymphoma cells were immunoreactive for S-100, CD1a, and CD30, but not for leukocyte common antigen, CD3, CD15, CD20, CD45, CD68, CD79A, CD138, CD4, CD5, CD8, CD10, CD163, CD138, CD56, CD117, CD34, activin receptor-like kinase-1, myeloperoxidase, B-cell lymphoma 6, or cytokeratin (Fig. 3B and C). Epstein-Barr virus was not detected within the tumor cells. The cells showed a germ-line immunoglobulin H gene rearrangement by polymerase chain reaction (PCR) and a weakly positive T-cell receptor- $\gamma$  gene rearrangement by PCR-heteroduplex analysis. The morphological and immunological phenotypes were consistent with Hodgkin's disease. The tissue from the first operation was re-examined immunohistochemically for the presence of Hodgkin's disease. However, the previous tissues were immunoreactive for S-100, CD1a, but not CD15, CD30.

Analysis of cerebrospinal fluid drawn via lumbar puncture, a whole-body gallium scan, a bone marrow biopsy, and CT scanning of the neck, abdomen, and pelvis showed no evidence of Hodgkin's disease other than at the primary site in the sternum, anterior mediastinum, and spine. The patient was treated with oral dexamethasone and adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. Lower extremity strength improved, and the patient was able to walk independently at the last follow-up visit. Final cultures from specimens obtained during the two operations grew neither *Mycobacterium tuberculosis* nor any other organism.

## DISCUSSION

Wood and Coltman<sup>15</sup> estimated that primary extranodal presentation of Hodgkin's disease occurs in no more than 0.25% of patients. Most patients with Hodgkin's disease with CNS involvement present with concurrent neurological and nodal disease or develop neurological disease after diagnosis of Hodgkin's disease<sup>5</sup>. Spinal cord compression secondary to lymphoma is not rare, although in most patients this occurs when the disease is well established<sup>12</sup>. Fifty (5%) of 1,039 patients with non-Hodgkin's lymphoma in one series developed CNS involvement<sup>6</sup>. Only 5 (0.5%) of the 50 patients had CNS involvement at the time of initial presentation. Compared with non-Hodgkin's lymphoma, spinal cord compression occurs much less often in Hodgkin's disease<sup>4,6,10</sup>. Sapozink and Kaplan<sup>13</sup> reported that none of 2,185 patients with Hodgkin's disease presented with spinal cord compression. In summary, spinal cord compression due to Hodgkin's disease is very rare and usually develops in the setting of diffuse, undiagnosed disease or at some time after initial diagnosis. To our knowledge, our case is the first report of a patient with both Hodgkin's disease and LCH who presented with spinal cord compression arising from epidural and spinal disease.

The isolated presentation in our case contributed to difficulty in diagnosis. Our initial diagnosis was LCH. The clinical presentation of spinal cord compression arising from extradural mass lesions is more likely related to metastatic tumors than to hematological disorders. However, Hodgkin's disease, or disease of the non-Hodgkin's variety, rarely presents with extradural spinal cord compression. Our patient seemed to have extranodal Hodgkin's disease. Several mechanisms of pathogenesis have been suggested. Hodgkin's disease may arise outside the lymph nodes after hematogenous dissemination from mediastinal nodal sites<sup>1,11,12</sup>. It is possible that lesions originate primarily in bony structures<sup>5,11</sup>. Direct spread from lymph nodes and lymphatics

into the epidural space, or perhaps into bone, may also occur. In the patient described here, the disease may have arisen from mediastinal lymphatic tissue and subsequently spread to the contiguous spine. Several authors have suggested that small lymphatic elements in the epidural space may give rise to lymphoma<sup>2,11</sup>.

It seems that an association of LCH with malignant lymphomas occurs more often than might be expected by chance, and Hodgkin's disease is the lymphoma most frequently associated with LCH<sup>3</sup>. To the year 2000, there had been approximately 30 reports of patients with co-diagnoses of LCH and Hodgkin's disease<sup>3,8</sup>. Most often, Hodgkin's disease either preceded LCH (11 cases) or was diagnosed at the same time (17 cases)<sup>3,7</sup>. Infiltration by Langerhans' cells took the form of localized foci and/or extensive multifocal involvement within dilated cortical and medullary sinuses, with no evidence of posterior systemic spread<sup>3,9</sup>. It seems that nodal LCH represents a process with a benign clinical course, as demonstrated in the literature<sup>3</sup>. This is, however, curious, if we consider the old hypothesis of a malignant change in cells of the monocyte-histiocyte system as the origin of "classic" Hodgkin's disease. In our patient, as in previously reported cases, there was no histological evidence for conversion of one form of lesion into the other. To summarize, we report the unusual coexistence of two hematological disorders, but the significance of this association remains unknown.

It should be mentioned that the role for extensive tumor resection via attempted gross total resection and vertebrectomy. This patient underwent initial surgery to obtain a diagnosis and to decompress the spinal cord. It is possible that due to a relatively conservative surgery, representative tissue showing Hodgkin's lymphoma might have been missed during first surgery.

## CONCLUSION

LCH may show a complex association with Hodgkin's lymphoma. LCH may precede, occur with, or follow Hodg-

kin's lymphoma. This is the first time that the coexistence of these two hematological disorders in the spine has been reported. Here, we describe an unusual case of mixed spinal Hodgkin's lymphoma and LCH to draw attention to this combination as a possible diagnosis in patients with diverse inflammatory cell infiltrate lesions in the spine.

## References

1. Bender BL, Mayernik DG : Hodgkin's disease presenting with isolated craniospinal involvement. *Cancer* 58 : 1745-1748, 1986
2. Drake RL : Lymphosarcoma involving the epidural space. *J Kans Med Soc* 42 : 212-222, 1941
3. Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME : Association of Langerhans cell histiocytosis with malignant neoplasm. *Cancer* 71 : 865-873, 1993
4. Freeman C, Berg JW, Cutler SJ : Occurrence and prognosis of extranodal lymphomas. *Cancer* 29 : 252-260, 1972
5. Fried G, Ben Arie Y, Haim N, Dale J, Stein M : Primary Hodgkin's disease of the bone. *Med Pediatr Oncol* 24 : 204-207, 1995
6. Herman TS, Hammond N, Jones SE, Butler JJ, Byrne GE Jr, McKelvey EM : Involvement of the central nervous system by non-Hodgkin's lymphoma : The Southwest Oncology Group experience. *Cancer* 43 : 390-397, 1979
7. Karadeniz C, Sarialioglu F, Göğüş S, Akytüz C, Küçükali T, Kutluk T, et al. : Multiple primary malignancy : a report on Langerhans cell histiocytosis associated with Hodgkin's disease. *Turk J Pediatr* 33 : 185-190, 1991
8. Michetti G, Cottini M, Scelsi L, Pugliese C, Minio A, Arnone P, et al. : Langerhans' cell granulomatosis and Hodgkin's lymphoma. Report of a case. *Minerva Med* 87 : 243-247, 1996
9. Neumann MP, Frizzera G : The coexistence of Langerhans' cell granulomatosis and malignant lymphoma may take different forms : report of seven cases with a review of the literature. *Hum Pathol* 17 : 1060-1065, 1986
10. Levitt LJ, Dawson DM, Rosenthal DS, Moloney WC : CNS involvement in the non-Hodgkin's lymphomas. *Cancer* 45 : 545-552, 1980
11. Love JG, Miller RH, Kernohan JW : Lymphomas of spinal epidural space. *AMA Arch Surg* 69 : 66-76, 1954
12. Perry JR, Deodhare SS, Bilbao JM, Murray D, Muller P : The significance of spinal cord compression as the initial manifestation of lymphoma. *Neurosurgery* 32 : 157-162, 1993
13. Sapozink MD, Kaplan HS : Intracranial Hodgkin's disease. A report of 12 cases and review of the literature. *Cancer* 52 : 1301-1307, 1983
14. Ultmann JE, DeVita VT Jr : Hodgkin's disease and other lymphomas. In : *Harrison's Principles of Internal Medicine*, 10th eds. New York : McGraw-Hill, 1983, pp140-149
15. Wood NL, Colman CA : Localized primary extranodal Hodgkin's disease. *Ann Intern Med* 78 : 113-118, 1973