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MULTIPLE PRIMARY MALIGNANCY: A REPORT ON LANGERHANS CELL HISTIOCYTOSIS ASSOCIATED WITH HODGKIN'S DISEASE*

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Since multiple primary malignant tumors are rare in children, their presence can be a diagnostic and therapeutic problem. In this report, we present a six - year - old boy with Langerhans cell histiocytosis and Hodgkin's disease. On admission, the patient had lytic lesions and a periosteal reaction on the left trochanter major from which an open bone marrow biopsy was performed. The biopsy revealed Langerhans cell histiocytosis. Eight months later, the child presented with enlarged left cervical lymph nodes and the biopsy demonstrated Hodgkin's disease. Although there was an eight - month interval between the two histopathological diagnoses, the diffuse pulmonary parenchymal infiltration observed on the first admission, was later confirmed by an open - lung biopsy as Hodgkin's disease. The patient was said to have two concurrent lymphoreticular malignancies. To our knowledge, this is the youngest case reported with this association in the English language literature. *Key words: Langerhans cell histiocytosis, Hodgkin's disease, multiple primary malignancy, childhood tumors.*

Histiocytosis X denotes a poorly understood group of disorders affecting both children and young adults. Recently, The Writing Committee for the Histiocyte Society used the term, "Langerhans cell histiocytosis" (LCH) in order to identify this disorder among childhood histiocytoses[1].

Few cases have been reported of the association of Hodgkin's disease and Langerhans cell histiocytosis occurring in the same patient[2-4]. Most of the reported cases describe lesions involved in Langerhans cell histiocytosis as occurring in the lymph nodes of patients with malignant lymphoma.

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We recently had a patient with Langerhans cell histiocytosis who had been diagnosed eight months previously, and who had later developed cervical lymphadenopathy and progressive pulmonary infiltration. Histologically, the lesions in both sites proved to be typical of Hodgkin's disease.

Case Report

A six - year - old boy with an eight - month - history of left hip pain was seen in another hospital in July 1987. An open - bone biopsy was obtained from the left trochanter major and a pathological report showed LCH. The patient was referred to our hospital for further evaluation and therapy. Physical examination revealed normal findings except for a left trochanteric incision. A two-dimensional chest X - ray showed hilar lymphadenopathy and bilateral parenchymal infiltration. Roentgen studies of all bones did not disclose any abnormalities except for some lytic lesions and a periosteal reaction at the left trochanter major. Other laboratory studies including complete blood count, urinalyses, liver and renal function tests, and bone marrow aspiration were normal.

We did not perform pulmonary function tests because the patient had no respiratory symptoms. Thus the patient was assigned to stage IB LCH according to the classification devised by Raney et al[5]. He was put on chemotherapy which consisted of vinblastine (0.2 mg/kg, i.v. weekly) and prednisolone (2 mg/kg, p.o, daily).

After two months, there was no response to the therapy, as indicated by no changes in the pulmonary and skeletal lesions. The chemotherapy was changed to a regimen of methotrexate (30 mg/m^2, p.o. weekly) and 6 - mercaptopurine (75 mg/m^2, p.o. daily).

In December 1987, after five months of chemotherapy, there was progressive enlargement of the cervical lymph nodes. A lymph node biopsy was performed on March 4, 1988 and a diagnosis of Hodgkin's disease was established.

The routine staging procedure including complete blood count, liver and kidney function tests, two dimensional chest X - rays, abdominal ultrasonography and bone marrow biopsy was performed.

On the chest X - rays, hilar lymphadenopathies were visible and the entire lung parenchyma had a diffuse reticulo - granular appearance. Abdominal ultrasonography revealed multiple lymphadenopathies which were one cm in diameter in the paraaortic and parailiac regions. Since pulmonary involvement in Langerhans cell histiocytosis occurring without any parenchymal organ infiltration is rare in a six - year - old child, the pulmonary lesions observed were thought to be a manifestation of Hodgkin's disease. Moreover, the chemotherapy given to treat Langerhans cell disease had not been effective. The patient was assigned to stage IV Hodgkin's disease and chemotherapy with C - MOPP was initiated[6].

Following three courses of chemotherapy, there was no improvement seen in the patient's disease status. A bone survey showed multiple lytic lesions and periosteal reactions in different bones. The chest X - ray revealed a small area of consolidation in addition to apparent progression in the pulmonary lesions. An open left lung biopsy was performed to clarify the lung pathology (July 29, 1988). The histopathological examination again revealed Hodgkin's disease. Despite different types of combined therapeutic intervention (chemotherapy and radiotherapy), the patient died of progressive pulmonary disease two years after his first admission.

Histopathologic Findings:

First biopsy (July 23, 1987): The histopathological evaluation of the left trochanter major biopsy showed granulomas of various diameters which were composed of mixed inflammatory cells with large numbers of eosinophils and histiocytes. Some of the histiocytic cells had large cytoplasms and large lobulated nuclei. There were no Reed - Sternberg cells (Fig. 1).

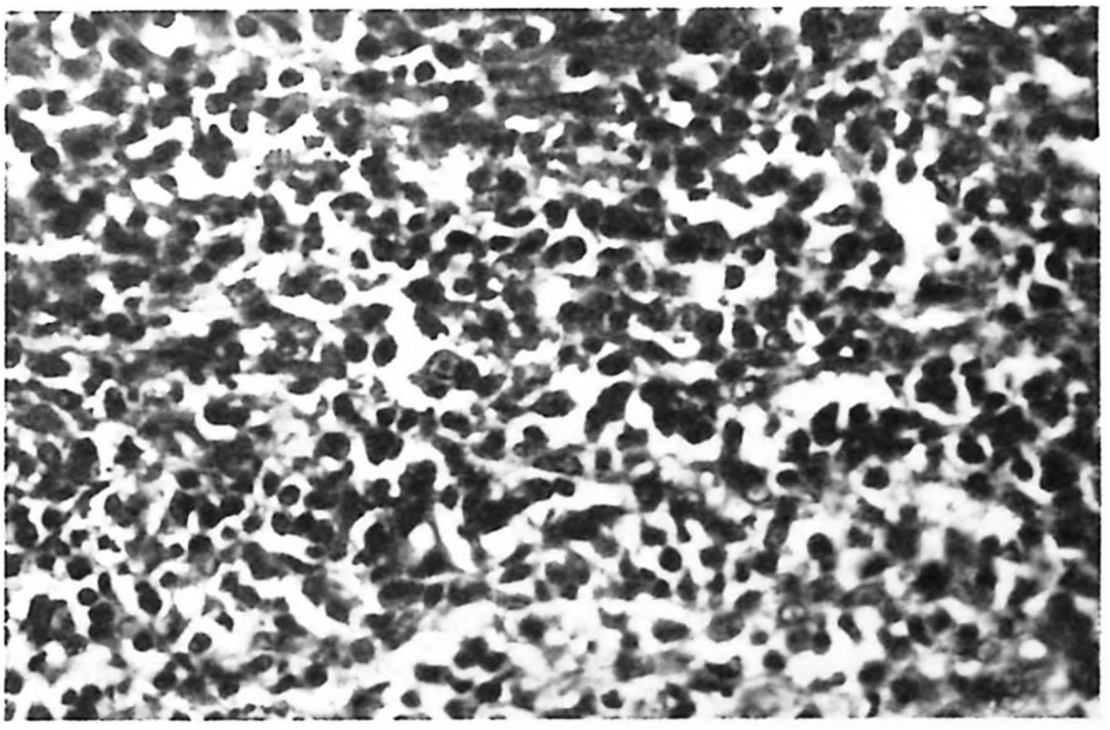

Fig. 1: Biopsy obtained from the left trochanter of the femur.
Dense infiltration of mixed inflammatory cells and some histiocytic cells. (HE x 400).

Second biopsy (March 4, 1988): The histopathological findings of the left cervical lymph node biopsy showed a cellular pattern consisting of lymphocytes, histiocytes, plasma cells and few eosinophils with some areas of nodularity and sclerosis. The typical Reed - Sternberg cells and variants were present (Fig. 2).

Third biopsy (July 29, 1988): The typical Reed - Sternberg cells and variants were

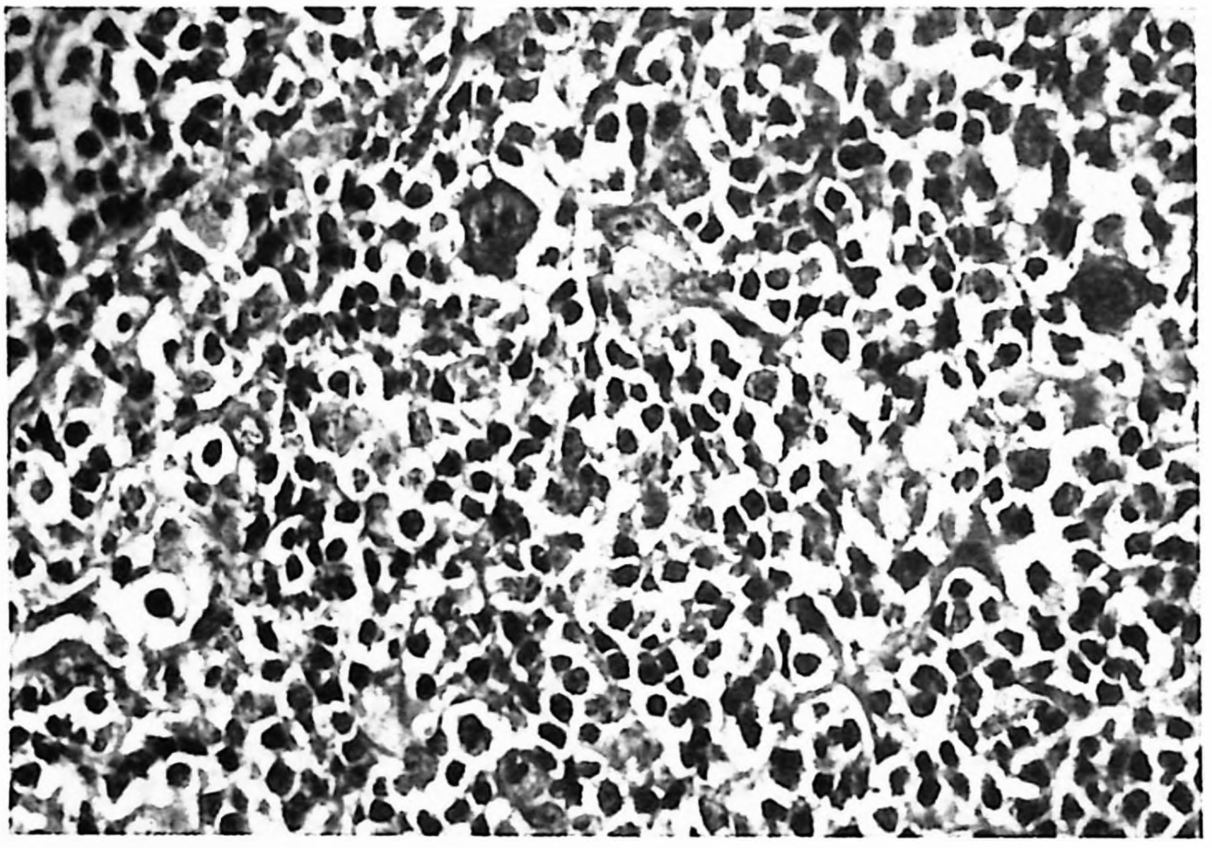

Fig. 2: Cervical lymph node biopsy showing mixed cellularity. Typical Reed - Sternberg cells and Hodgkin's cells (HE x 460).

seen in the open left lung biopsy. Hypocellularity and lymphocyte depletion were also noted.

Discussion

Generally, the pulmonary involvement of LCH is seen in the disseminated form in children[7]. Radiologic findings include micronodular and reticular opacities which may form large nodules with a honeycomb appearance, which may sometimes lead to pneumothorax[8]. In our case, the pulmonary findings on admittance was due to the original disease, LCH. However, the lung biopsy obtained during the progression of the disease clarified the etiology as Hodgkin's disease.

The most frequent intrathoracic findings in Hodgkin's disease are tracheobronchial and mediastinal lymph node involvement[9]. Pulmonary parenchymal involvement is found to be around 58 percent in necropsy series[9], and it is almost always associated with mediastinal lymph node involvement[10]. On the first admission, our patient presented with both mediastinal lymph node and pulmonary involvement. Primary skeletal involvement is rarely seen in Hodgkin's disease, but in our patient both the progression of the disease and the bone biopsy were typical of LCH[11]. According to reports in the literature, Hodgkin's disease is rarely associated with eosinophilic granulomas[2-4].

The etiologies of both Hodgkin's disease and LCH are unknown. Histologically they bear some similarities. In both diseases, especially mixed cell Hodgkin's disease, histiocytes and eosinophils are seen. In addition, infectious agents and immunologic factors have been suggested in their pathogenesis[12-14].

According to the literature, when these two diseases occur in association there is usually involvement of the same lymph node. In the six cases reported by Kjeldberg and Kim[2], eosinophilic granuloma and lymphoma were present in the same lymph node (three Hodgkin's disease cases and three non - Hodgkin's lymphoma cases). Transformation from benign to malignant lesions in the same lymph node has not been demonstrated. Kjeldberg and Kim[2] proposed that the histiocytic proliferation in eosinophilic granuloma could be a reaction to etiologic factors of malignant lymphoma or to malignant lymphoma itself or to an aberrant host response. Since the association of Hodgkin's disease with LCH is a rare occurrence, it is considered to be a coincidence. In a case reported by Frederiksen and Thommesen[3], LCH was diagnosed by biopsy of the gingival mucosa and mandibula. A year later, a cervical lymph node biopsy taken from the same patient revealed Hodgkin's disease. The patient died the following year.

In our case, biopsy of the femur showed LCH while the cervical lymph node biopsy taken eight months later revealed mixed cellular Hodgkin's disease. Frederiksen and Thommesen[3] suggested that a benign LCH lesion could have developed into Hodgkin's disease. However, the Birbek granules seen in the histiocytes of LCH have not been demonstrated in Hodgkin's disease. Since there are no histological similarities between Hodgkin's disease and aggressive histiocytosis, and the fact that LCH not only occurs in combination with Hodgkin's disease but also with non - Hodgkin's lymphoma, contradicts this proposal. Besides, Robert J. L'Hoste and colleagues[15] published a case with massive cervical lymphadenopathy in which an initial diagnosis of Hodgkin's disease was established and later histopathological sections also revealed LCH findings.

In conclusion, the rare association of LCH with Hodgkin's disease in the same patient suggests that it is most probably coincidental, as proposed by Kjeldberg and Kim[2], and that the occurrence of both diseases in the same patient may lead to difficulties in diagnosis and treatment. The diagnosis of Hodgkin's disease in a patient with LCH or LCH in a patient with Hodgkin's disease may therefore be missed.

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