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Primary pulmonary histiocytosis X in two patients with Hodgkin's disease

SYED M SAJJAD, MARIO A LUNA

From the Department of Pathology, The University of Texas System Cancer Center, MD Anderson Hospital and Tumor Institute at Houston, Houston, Texas, USA

ABSTRACT The lungs may be involved in patients with histiocytosis X as part of the generalised disease, but histiocytosis X confined to the lungs without extrapulmonary involvement is rare. This report describes two cases of primary pulmonary histiocytosis arising in patients with Hodgkin's disease. It is impossible to state with certainty whether the pulmonary histiocytosis arose as a response to the defects of cell-mediated immunity, or as a consequence of immunosuppression by radiation and chemotherapy.

In 1953 Lichenstein proposed the generic designation "histiocytosis X" to encompass three major entities —eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease.[1] The ultrastructural demonstration of unique cytoplasmic pentalaminar structures referred to as Langerhans' or Birbeck's granules is highly characteristic of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease.[2 3] Histiocytosis X confined to the lungs, and this lesion's concurrence with Hodgkin's disease, seem to be exceptional, and we report two such cases with their characteristic histological appearance.

Case reports

CASE 1

A 20-year-old male was diagnosed as having nodular sclerosing Hodgkin's disease, stage 3A, in December 1976. He received radiotherapy of 4000 rads to the left cervical area, pelvis, mediastinum, both axillae, and the para-aortic chain of lymph nodes. The patient also received six courses of cytoxan, vincristine, procarbazine, and prednisone (COPP). In 1978, because of recurrent Hodgkin's disease in the lungs and pleura, he was treated with four cycles of adriamycin, bleomycin, vinblastine, and dimethyltrinzenoimidazole carboxamide (DTIC). A routine follow-up chest radiograph in November 1979 revealed a diffuse nodular reticular pattern. At that time the patient's blood count, skeletal survey, and bone scan were normal. Less invasive studies were unhelpful, so an open lung biopsy was performed.

A diagnosis of histiocytosis X was made, for which he received no treatment. In August 1980, he remained free of symptoms with almost complete radiological remission of his pulmonary infiltrates and had resumed his scholastic studies.

CASE 2

A 20-year-old white woman with nodular sclerosing Hodgkin's disease was initially diagnosed in 1973 as having stage 2 disease with mediastinal involvement. She received 4000 rads of radiotherapy to the left supraclavicular and mediastinal areas, and other nodal sites received a prophylactic dose of 3000 rads. After she was confirmed to have recurrent Hodgkin's disease of pleura and pericardial lymph nodes in August 1977, she received eight cycles of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP). After a recurrence of disease in the left lung, her chemotherapy was changed to 12 courses of adriamycin, bleomycin, and DTIC. In May 1979, a chest film revealed bilateral pulmonary infiltrates. Blood counts, liver scan, and bone scan were within normal limits. An open lung biopsy was performed to establish the diagnosis. In June 1979, the patient developed recurrent Hodgkin's disease in the mediastinum and died with septicemia. A necropsy was not performed.

Address for reprint requests: Dr SM Sajjad, Department of Pathology, The University of Texas System Cancer Center, MD Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, USA.

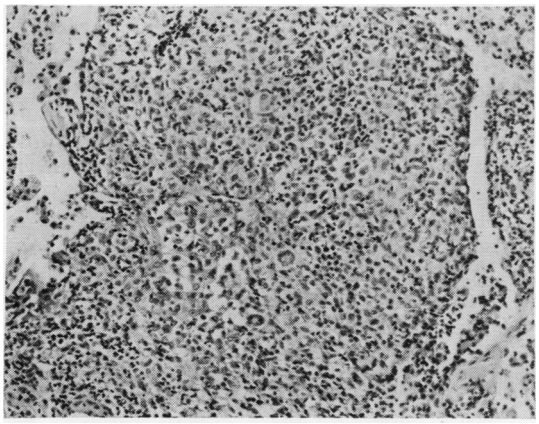

Fig 1 *Photomicrograph showing an interstitial nodule composed of histiocytes, lymphocytes, and eosinophils. (H and E × 110).*

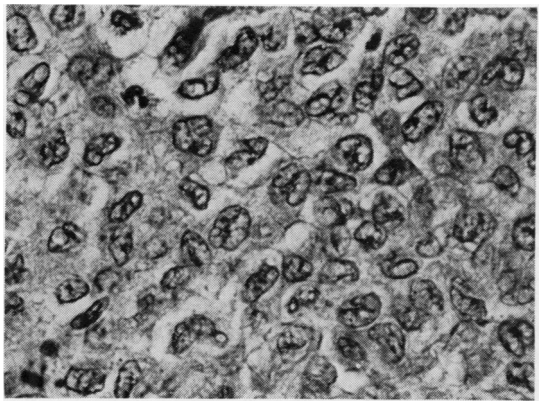

Fig 2 *Distinctive histiocytes with folded nuclear membranes, inconspicuous nuclei and abundant cytoplasm resulting in the characteristic "coffee bean" appearance. (H and E × 450).*

Pathological findings

In both patients histological findings were similar, with an interstitial pattern of involvement that was both diffuse and nodular. The diffuse areas showed widening of the alveolar septa caused by infiltrates of histiocytes, lymphocytes, and mature eosinophilic granulocytes (fig 1). The most common pattern of involvement was characterised by focal interstitial nodules. Some nodules surrounded bronchioles; others were adjacent to medium-sized and small blood vessels, and some were located just beneath the pleura. The more active nodules were composed principally of histocytes. These histiocytes had fairly abundant pale eosinophilic cytoplasm with the vesicular nuclei having idented nuclear membrane and inconspicuous nucleoli (fig 2). The adjacent lung contained haemosiderin macrophages. The older lesions showed varied degrees of fibroblastic proliferation.

ELECTRON MICROSCOPY

Tissue from both patients was examined with an electron microscope. Ultrastructurally, histiocytes with complex folded nuclear membranes, finely dispersed euchromatin, and inconspicuous nucleoli were evident. A few histiocytes contained distinct intracytoplasmic tubular inclusions identical to Langerhans' cell granules (fig 3). The cytoplasm of the histiocytes was ample and contained a number of free ribosomes, smooth and rough endoplasmic reticulum, and a considerable number of mitochondria.

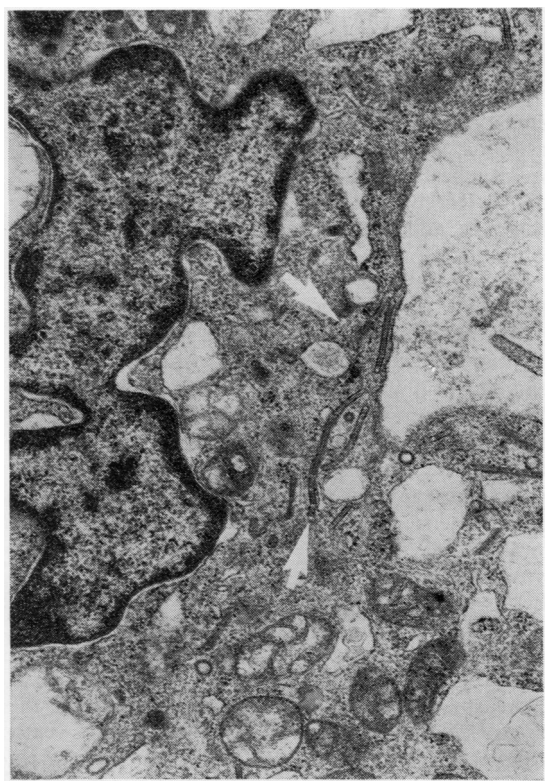

Fig 3 *Electron micrography shows characteristic tubular inclusions (arrowed) within the cytoplasm of a typical histiocyte. (Uranyl-acetate lead citrate × 31 800).*

Discussion

Histiocytosis X as a single or multiple lesion may appear not only in bones, but also in other sites, notably in the skin, oral cavity, anogenital region, stomach, liver, lymph nodes, brain, and lungs.[4-7] Although the existence of pulmonary involvement accompanying eosinophilic granuloma of bone has been reported by many investigators, it was Farinacci who in 1951 reported the first two cases of histologically confirmed eosinophilic granuloma of the lung.[8] Two clinical forms of lung involvement by histiocytosis X are seen: lung involvement as part of the generalised disease and as a separate entity known as primary pulmonary histiocytosis X. These two forms are indistinguishable pathologically.[9]

The lung biopsies of our patients showed granulomatous lesions with distinctive histiocytes, varying numbers of eosinophilic leucocytes. The ultrastructural demonstration of characteristic intracytoplasmic tubular inclusions allows a confident diagnosis of histiocytosis X. Both patients had histiocytosis X limited to the lungs with no other clinical or radiological findings of extrapulmonary disease. The usual age at which primary histiocytosis X occurs is 15-20 years, with a male to a female ratio of 5:1. The onset of disease is generally insidious, with few presenting symptoms, including cough, chest pain, shortness of breath, and weight loss.[10] Rarely, patients may present with severe dyspnoea and a chest radiograph showing honeycomb lung.

The clinical course of histiocytosis X confined to the lungs is unpredictable. In reported cases, the evolution of this type of lesion has varied from spontaneous improvement to progression of disease. leading to significant pulmonary disability or death. There is no agreed course of treatment. Corticosteroids have been advocated as treatment early in the disease, but spontaneous remission occurring without therapy has been reported, and there is no good evidence that corticosteroids alter the natural course of the disease. However, some patients with symptoms appear to benefit from corticosteroid therapy.

Although the clinical and pathological features of pulmonary histiocytosis X have been documented, the aetiology of the disease remains unknown. Lichenstein favoured infection as a cause, since the disease's clinical features include fever, night sweats, and weight loss. Auld believed that the lesions might represent a state of hypersensitivity, as eosinophilic infiltrate and arteriolitis often accompany the histiocytic proliferation.[11] Recently, Osband observed abnormal autoreactivity in patients with multiple-site histiocytosis and attributed it to a deficiency in thymic lymphocytes.[12]

Intracytoplasmic inclusions were first described ultrastructurally in the histiocytes of histiocytosis X by Basset *et al*[2]; initial suspicion of their viral nature was soon laid to rest and their structural identity with Langerhans' granules established.[13] The Langerhans' granules appear characteristic if not pathognomic of histiocytosis X and have been reported in patients with histiocytosis X at a variety of anatomical sites.[14] Langerhans' cells have been identified in stratified squamous epithelium and in other tissues including the cornea, cervix, lymph nodes, and thymus.[15,16] They are conspicuously absent from normal bone and lungs, common sites of involvement by histiocytosis X.[17] While the life cycle of Langerhans' cells remains obscure, the current consensus favours derivation from mesenchymal cells.[13]

It has been suggested that Langerhans' cells and interdigitating reticulum cells of lymphoid tissue are involved in cell-mediated immune reaction and that they bind antigen-antibody complexes at the cell membrane. Support for the concept that Langerhans' cells have an important role in immune reactions is provided by the demonstration of surface markers and receptors for C3 and FC.[18,19] Defects in cell-mediated immunity and greater frequency of leukaemia and other tumours have been described in patients with Hodgkin's disease. It has been proposed that intensive radiotherapy or chemotherapy or both might underlie this increase in risk.[10] The concurrence in the two cases reported here of Hodgkin's disease and pulmonary histiocytosis X underlines the concept that defects in immune mechanism as a result of iatrogenic immunosuppression caused by intensive radiotherapy and chemotherapy may be responsible for proliferation of Langerhans' cells in histiocytosis X.

In conclusion, pulmonary histiocytosis X has characteristic histological findings of which the pathologist should be aware when considering the differential diagnosis of interstitital lung disease in immunosuppressed patients.

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