Sinus Histiocytosis with Massive Lymphadenopathy

REPORT OF TWO ADDITIONAL CASES WITH ULTRASTRUCTURAL OBSERVATIONS

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SUMMARY

Two cases of a recently described entity, 'sinus histiocytosis with massive lymphadenopathy,' occurring in Black males, are reported. Prominent cervical adenopathy was the main presenting feature in both. Histologically, these nodes were characterised by pronounced proliferation of sinus histiocytes which showed phagocytosis of blood cells, predominantly lymphocytes. One of the patients has been followed up for 9 years and has remained clinically well despite persistence of the adenopathy. The importance of recognition of this condition is stressed in order to obviate unnecessarily radical therapy for a mistaken diagnosis of malignancy.

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Rosai and Dorfman[1] described 34 cases of a clinicopathological entity which they called sinus histiocytosis with massive lymphadenopathy (SHML). It was characterised by massive enlargement of predominantly cervical lymph nodes, a result of prominent proliferation of sinus histiocytes. More recently Lennert *et al.*[2] reported a case described as 'lymphadenitis with massive haemophagocytic sinus histiocytosis'. This emphasises two other typical histological features of the lesion, namely, a plasmacytic infiltrate and haemophagocytosis by the proliferating histiocytes. We document 2 such patients with SHML who were referred to this institution from East London. Ultrastructural examination of lymph node tissue from one of the patients confirmed the presence of haemophagocytosis by sinus histiocytes and demonstrated degradation of the phagocytosed cells.

CASE REPORTS

Case 1

A 10-year-old Black male was admitted to Red Cross War Memorial Children's Hospital with bilateral cervical lymphadenopathy, which had been present for 9 years (Fig. 1). At 5 years of age, he had received a prolonged course of antituberculous therapy but the adenopathy persisted. An enlarged cervical lymph node was then biopsied and the histological diagnoses considered were lipid storage disease, histiocytosis-X, and histiocytic medullary reticulosis. At the age of 6 years, an abdominal skin rash appeared and a biopsy was reported as showing a xanthomatous deposit. A chest X-ray film showed enlarged mediastinal lymph nodes. A small abdominal lymph node was biopsied and showed features similar to the cervical node. A liver biopsy showed no feature of note. At 9 years of age a course of vincristine (total dose 15,5 mg) was given because of an increase in size of the mediastinal glands, but they did not regress. Ten months before his present admission, a submandibular lymph node biopsy showed extension of the process into salivary gland tissue.

On clinical examination enlarged, firm mobile lymph nodes were palpated in the submandibular and supraclavicular regions. A chest X-ray film showed mediastinal lymphadenopathy, while a skeletal survey was normal. The haemoglobin was 11,4 g/100 ml, mean corpuscular haemoglobin concentration 32,9%, mean corpuscular volume 72% and the white cell count 6 300/mm^3, of which 60% were neutrophils, 17% lymphocytes, 3% monocytes and 20% eosinophils. The platelet count was 200 000/mm^3 and a bone marrow aspirate showed a normal cellular pattern. The serum albumin was 3,1 g/100 ml and serum globulin 4,2 g/100 ml. On electrophoresis the globulin concentrations were α_1 0,2 g/100 ml, α_2 0,7 g/100 ml, β 0,9 g/100 ml and γ 2,4 g/100 ml. Alkaline and acid phosphatase and transaminase levels were normal. Serum cholesterol was 171 mg/100 ml (normal 120 - 230), total triglycerides 54 mg/100 ml (normal 10 - 140), and phospholipids 169 mg/100 ml (normal 188 - 292). The Wassermann reaction, Tine and second-strength PPD tests were negative. Examination of the urine failed to demonstrate metachromatic substances. A specimen of an enlarged cervical lymph node was taken for histochemical and electron microscopical examination.

Case 2

A 30-year-old Black male presented with massive enlargement of the lymph nodes at the angle of the right jaw of 6 months' duration. There were no other symptoms or signs. The haemoglobin was 13,4 g/100 ml and a differential count was recorded as 61% neutrophils, 6%

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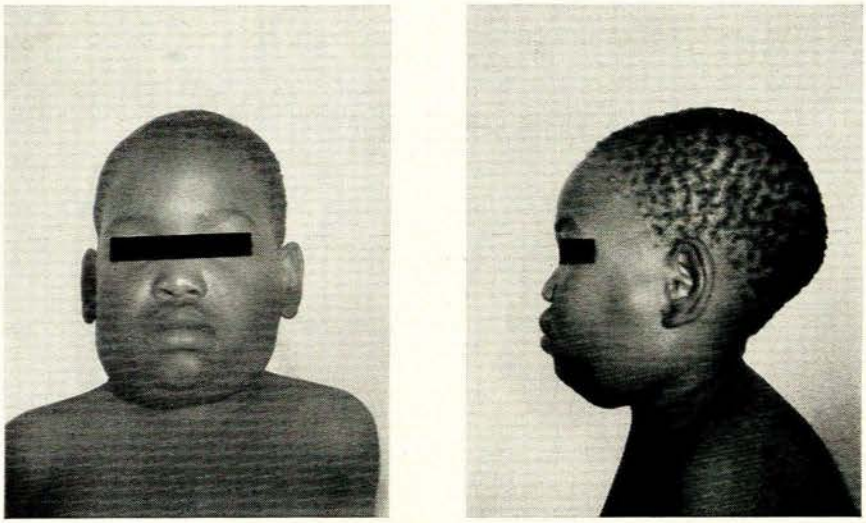

Fig. 1. Massive bilateral cervical adenopathy and left-sided pre-auricular swelling in a Black child (case 1).

eosinophils, 26% lymphocytes and 7% monocytes. Electrophoresis of the serum proteins was normal and there was no proteinuria. A skeletal survey and a bone marrow aspirate were normal. A nasal smear for leprosy was negative and macroglobulins were not detected in the urine. There was no response to 2 months of antituberculous therapy and a cervical lymph node was examined.

MATERIALS AND METHODS

Tissue was fixed in formaldehyde solution (10% formalin). Frozen sections were stained with Sudan IV, Baker's haematoxylin, PAS and perchloric acid-naphthoquinone stains, and paraffin sections with haematoxylin and eosin, PAS, Gram, Ziehl-Neelsen, Giemsa and methenamine silver stains. Tissue for electron microscopy was immediately fixed in phosphate-buffered glutaraldehyde, post-fixed in Palade's solution, dehydrated in graded acetone, and embedded in Spurr's epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope.

PATHOLOGICAL FINDINGS

The lymph nodes from both patients varied in size from 0,8 cm to 4 cm in diameter, and had an orange-brown colour. Microscopically the basic architecture of these nodes was preserved. There was fibrous thickening of the capsule and even extension of fibrous tissue into adjacent structures such as skin adnexa and salivary gland. Germinal centres were well preserved in case 1, but sparse in case 2. The architecture of the abdominal node from case 1 was somewhat distorted by fibroblastic proliferation. The most prominent feature was a proliferation of well-differentiated histiocytes within the sinuses (Fig. 2). This had caused severe sinusoidal distention. The cytoplasm of these cells was either abundant, pale-staining and

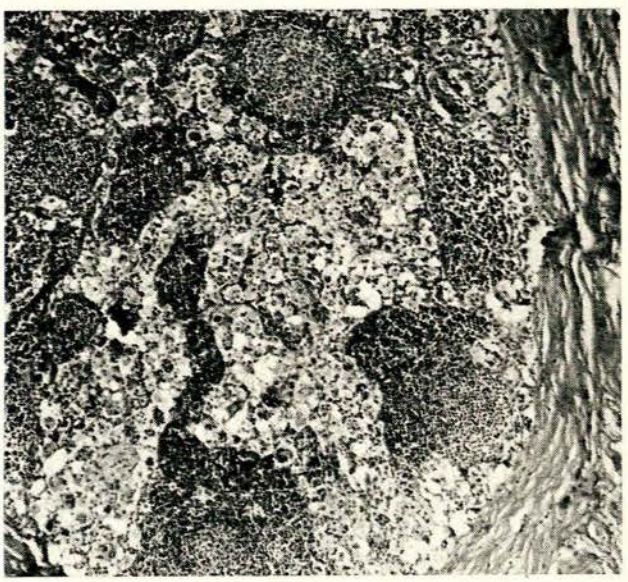

Fig. 2. Case 1. Photomicrograph of lymph node showing fibrous thickening of the capsule on the right and distension of sinuses by pale histiocytic cells (H. and E. × 160).

foamy, or more compact and eosinophilic. Within the cytoplasm of many of the cells there were lymphocytes, red cells, neutrophils, plasma cells and nuclear debris. The great majority of the phagocytosed cells were lymphocytes (Fig. 3). The histiocytes stained positively with the Sudan IV stain for neutral fat, Baker's haematoxylin for phospholipid, and perchloric acid-naphthoquinone for cholesterol. They were slightly PAS-positive and this staining was resistant to diastase. Gram, Ziehl-Neelsen, Giemsa and methenamine silver stains were all negative. Numerous mature plasma cells and Russell's bodies were present, predominantly within the medullary

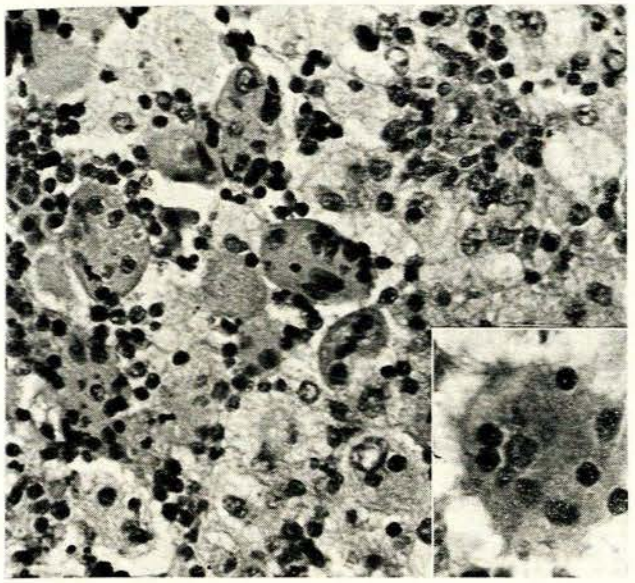

Fig. 3. Case 2. Detail of distended lymph node sinus showing numerous foamy histiocytes, several with phagocytosed lymphocytes in their cytoplasm. The inset shows greater detail of one of these cells (H. and E. × 350, inset × 700).

cords. The skin lesion in case 1 was composed of sheets of foamy histiocytes and fibrocytic-looking cells in the upper dermis.

Ultrastructurally the cytoplasm of the histiocytic cells contained numerous rod-shaped mitochondria and electron-dense lipid bodies, measuring up to 3,5 μm in diameter (Figs 4 and 5). In addition lymphocytes and smaller numbers of neutrophils, plasma cells and red blood cells in various stages of degradation were present within the cytoplasm of these histiocytes. Langerhans' granules were not seen (Figs 4 and 5). In addition, numerous mature-looking plasma cells were present (Fig. 5).

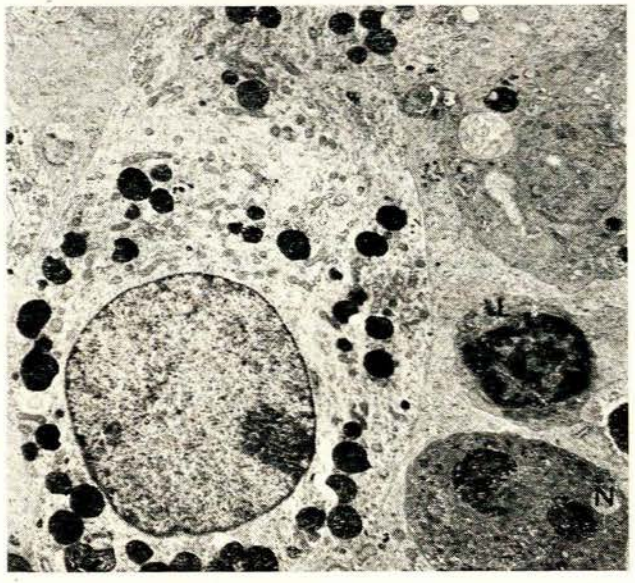

Fig. 4. Case 1. Electron photomicrograph showing histiocyte with numerous electron-dense lipid bodies and small rod-shaped mitochondria in its cytoplasm. A neutrophil (N) and a lymphocyte (L) are present within the cytoplasm of an adjacent cell (× 5 000).

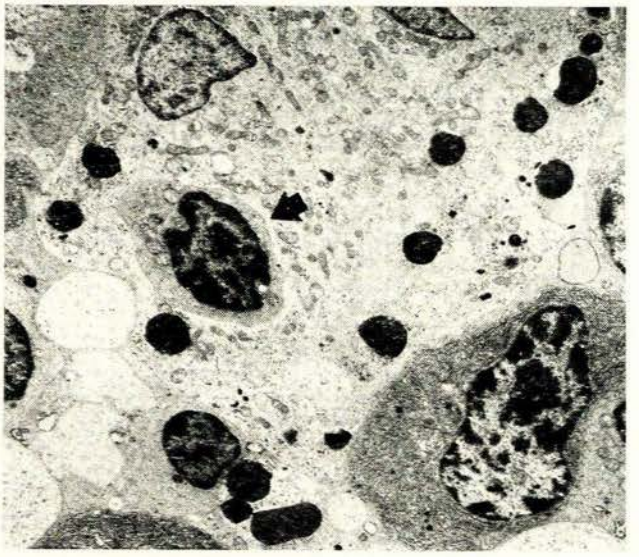

Fig. 5. Case 1. Electron photomicrograph showing histiocyte with numerous lipid bodies and mitochondria. A well-preserved lymphocyte is seen within the cell (arrow). **A mature plasma cell is present at the right lower corner of the photomicrograph (× 5 000).**

DISCUSSION

In 1969 Rosai and Dorfman[3] drew attention to an entity which they termed 'sinus histiocytosis with massive lymphadenopathy', and subsequently they analysed 34 cases.[1] The majority of patients were under 20 years of age. Usually they presented with massive, painless cervical lymphadenopathy, fever, leucocytosis, raised erythrocyte sedimentation rate and elevated gamma globulin. Other node groups, such as axillary, mediastinal, inguinal and mesenteric were occasionally enlarged but to a much lesser degree. Involvement of the tonsils, orbit, eyelid, skin or testes was also noted in a few cases. The course was prolonged, the lymphadenopathy persisting for months or even years, but complete resolution was noted in 15 out of 26 cases followed for periods ranging from 2 months to 14 years. In 3 cases, the adenopathy followed an intermittent course. The 2 deaths that occurred could not directly be attributed to the disease; one died of renal failure secondary to generalised amyloidosis, and the other from pseudomonas bronchopneumonia. Antibiotics, antituberculous drugs, radiotherapy and chemotherapeutic agents all failed to cause any significant reduction in the size of the lymph nodes. Histologically the lymph node sinuses were greatly widened by a proliferation of well-differentiated histiocytes showing prominent haemophagocytosis, predominantly of lymphocytes. Numerous plasma

cells were seen in the medullary cords and capsular fibrosis was present.

The clinical and pathological features of the 2 cases presented in this article are typical of SHML. One of these was submitted to Dr Rosai, who concurred with the diagnosis. Both our patients were Blacks. Nine other cases have been reported from Africa, 8 Blacks and 1 Indian.[4] The Indian and one of the Blacks were from South Africa.

The course of the disease in our first patient was typically prolonged and the cervical lymph node enlargement was intermittent. Additional features were the presence of a skin rash, and salivary gland and abdominal lymph node involvement. Lymphoid follicles with germinal centres were prominent in comparison to the described paucity of these structures in other cases of SHML. The fibrocytic-type cells noted in the salivary gland, skin and abdominal lymph node, probably represent facultative fibroblasts as they were intimately admixed with the histiocytes, and intermediate forms were noted.[5] Histochemical stains demonstrated the presence of neutral fat, phospholipid and cholesterol. Chemical analysis of lipids extracted from the lymph nodes of 2 patients with SHML by Marie *et al.*[6] demonstrated neutral fat, cholesterol and cholesterol esters.

Lennert *et al.*,[2] in a detailed ultrastructural study of a case of SHML, demonstrated degradation of phagocytosed blood cells by sinus histiocytes. Electron microscopic study of lymph node tissue in our first case confirmed the presence of numerous histiocytes containing phagocytosed lymphocytes in various stages of degradation. Numerous lipid bodies were seen but Langerhans' granules were not present.

These cases may cause considerable diagnostic difficulty. A correct diagnosis is important so as to avoid unnecessarily radical therapy. The lesions with which this disease is most likely to be confused are the differentiated histiocytoses (histiocytosis-X group), a lipid storage disease, familial haemophagocytic reticulosis, histiocytic medullary reticulosis and chronic lymphadenopathy simulating malignant lymphoma. Histiocytosis-X is characterised clinically by hepatosplenomegaly, bone involvement, skin eruptions; microscopically by the presence of eosinophils and the absence of lymphophagocytosis; and ultrastructurally by the presence of Langerhans' granules. The known storage diseases can be excluded on the basis of their distinctive clinical, histochemical and biochemical abnormalities. Familial haemophagocytic reticulosis of Farquhar and Claireaux[7] is a familial disorder occurring in infancy, and associated with hepatosplenomegaly. Erythrocytes rather than lymphocytes are phagocytosed. Histiocytic medullary reticulosis differs from SHML in its rapidly fatal course, pronounced splenomegaly, and the atypicality of the histiocytic cells.[8] Chronic lymphadenopathy simulating malignant lymphoma is characterised by hepatosplenomegaly and effacement of the nodal architecture by mature lymphocytes.[9]

The aetiology of SHML is unknown. An infective process is suggested by the fever, leucocytosis, hypergammaglobulinaemia and the increase of plasma cells in the node.[1,2] However, organisms have not been detected in the nodes by histological, bacteriological or virological examination. Antibodies to the Epstein-Barr virus were found in all 4 patients so tested in Rosai and Dorfman's series, but the significance of this finding requires more extensive investigation.[1]

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