

## *Sinus Histiocytosis with Massive Lymphadenopathy : Report of Five Cases*

JO THOMAS\* AND TA JUNAIID\*\*

### Summary

**Thomas JO and Junaid TA. Sinus Histiocytosis with Massive Lymphadenopathy: Report of five cases.** *Nigerian Journal of Paediatrics* 1987; 14:19. The clinicopathological features in five Nigerian children who presented with massive enlargement of cervical and other lymph nodes due to sinus histiocytosis with massive lymphadenopathy are reported. The pre-biopsy diagnosis in each case was malignant lymphoma or tuberculosis. None of the patients responded to antibiotics or antituberculous drugs. Attention is drawn to the remarkably good general condition of the patients inspite of the protracted course of the disease and the need to recognise its benign although frightful nature.

### Introduction

PRIOR to 1972 when Rosal and Dorfman<sup>1</sup> established the validity of sinus histiocytosis with massive lymphadenopathy (SHML) as a definite clinicopathological entity, similar changes within lymph nodes had been reported under various names<sup>2 3</sup>. Sinus histiocytosis with massive lymphadenopathy is a benign, often self-limiting disease that typically presents with large, painless cervical lymphadenopathy. It is thought to occur most frequently in black people and is considered by some workers to be a disease associated with low socio-economic status<sup>1</sup>. Diseases of the lymphoreticular organs are very

common in Ibadan<sup>4</sup> but inspite of this, there is no known documentation of SHML from the area. This, no doubt, contributes to the lack of familiarity with the entity.

The purpose of this preliminary report is, therefore, to highlight the clinicopathological features of a few cases of SHML that have been diagnosed at the University College Hospital (UCH), Ibadan. It is also to bring to the attention of physicians, the need to recognise this benign but frightening cause of massive lymph node enlargement.

### Materials and Methods

The cases included in this report were three in the file of one of us (TAJ) and two others that were recently diagnosed in the department of Pathology, UCH, Ibadan.

The histological slides were reviewed and where necessary, new sections were prepared.

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University College Hospital, Ibadan

Department of Pathology

\* Lecturer

\*\* Professor

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Correspondence : Professor TA Junaid

In addition to haematoxylin and eosin, periodic acid Schiff (PAS), acid fast stains, Gomori's methylamine silver (GMS), Brown and Hopps, Warthin-Starry and Giemsa stains were studied in all cases to exclude the presence of organisms. Similarly, the case-notes of the patients or the accompanying clinical notes were studied and relevant clinical information extracted.

### Case Reports

*Case 1 (EB).* This 9-year old boy first presented in September 1966, with proptosis of the left eye diagnosed as a retrobulbar tumour. Biopsy of the tumour was interpreted as Histiocytosis X. Enucleation of the eye was performed in October 1966 and pathological examination showed a collapsed destroyed eyeball surrounded by 'chronic inflammatory tissue with no evidence of malignancy'. A repeat biopsy of the orbital mass in January 1967, was diagnosed as a 'pseudotumour'. In October 1969, he presented with fever and cervical lymphadenopathy in addition to the persistent orbital mass. Burkitt's lymphoma was diagnosed but lymph node biopsy showed reactive changes with 'fatty contents' in the sinuses. His total white blood count varied between 9 and  $29.4 \times 10^3/\text{cmm}$  ( $9-29.4 \times 10^9/\text{L}$ ) with neutrophils 50-84%, eosinophils 25-35% and lymphocytes 3-30%. His blood group was 0 positive and haemoglobin genotype A. He was lost to follow-up in February 1980. There was no record of cervical lymphadenopathy when he was last seen.

*Case 2 (AK).* The lymph nodes resected from this 11-year old girl were sent to the department of Pathology, UCH, for histological diagnosis; the provisional clinical diagnosis was Hodgkin's disease. Following the diagnosis of SHML, the patient was seen at the Haematology clinic, UCH, where her general health was noted to be good although she had massive cervical lymphadenopathy. She was thereafter, lost to follow-up but was reported alive and well in June, 1986.

*Case 3 (NA).* This 15-month old girl presented in March 1976, with submandibular, submental and cervical lymphadenopathy which, unlike the accompanying cough and fever, had not responded to antibiotics. She weighed 8.8kg and had a grade I Heaf test reaction but was otherwise well. No lesion was found on chest X-ray. Her white blood count was 12, 100/cmm ( $12.1 \times 10^9/\text{L}$ ) with a differential of 49% lymphocytes, 29% neutrophils, 18% eosinophils and 4% monocytes. Her haemoglobin electrophoresis was A. A diagnosis of tuberculous lymphadenitis was made and although a lymph node biopsy in July, 1976, was reported as showing reactive hyperplasia, she was placed on antituberculous drugs for more than 1 year without any change in the nodal enlargement. For the next 6 years, she remained well and repeat nodal biopsies in February 1983 and April 1984, showed SHML. She is still attending follow-up clinic.

*Case 4 (BO).* In November 1985, this 13-month old boy presented in UCH with a 7-month history of bilateral cervical, supraclavicular, axillary and inguinal lymphadenopathy which had been accompanied by cough and fever. He weighed 7.9kg and appeared malnourished and irritable. The cervical nodes measured up to 6cm. A diagnosis of tuberculosis with a differential of Burkitt's lymphoma was made. He had a haematocrit of 42%, haemoglobin genotype A and blood group 0 positive. Biopsies of the cervical and supraclavicular lymph nodes were done in December, 1985 and May, 1986, and were diagnosed as SHML. He is still attending follow-up clinic.

*Case 5 (JE).* This 8-year old boy was referred to UCH from Abuja in August 1985, because of fever and painless swelling of the jaw region noticed in March 1985. He was well, with submandibular, submental, left cervical and axillary lymphadenopathy. His white blood count was 6,800/cmm ( $6.8 \times 10^9/\text{L}$ ) with normal differentials; the haemoglobin electrophoresis was

A, haematocrit 37% and the blood group, O positive. Biopsies of the cervical and submental swellings were performed on 30 August 1985. The lymph node biopsy was initially diagnosed as reactive but consistent with toxoplasmosis. He was treated with sulphonamides and pyrimethamine. A review of the biopsy later showed SHML. The child weighed 17.6kg when last seen in November 1985 and was well.

### Pathology

#### Gross

The excised lymph nodes measured between 1cm and 6cm in their widest diameters and 1gm and 20gm in weight. The nodes were firm and varied from tan to grey in colour. In three cases, the cut surfaces were nodular.

#### Microscopic

The lymph nodes showed marked capsular and pericapsular fibrosis (Fig 1) with division

of the parenchyma into irregular nodules (Fig 2). There was conspicuous dilatation of the sinuses with partial to complete effacement of the nodal architecture (Fig 3). The sinuses were filled with histiocytes with abundant granular, eosinophilic or foamy cytoplasm. In several foci, the histiocytes contained in their cytoplasm, lymphocytes or less often, plasma cells, polymorphs or erythrocytes. These ingested cells frequently appeared to be in a vacuole (Fig 4). In other foci, multinucleated giant cells filled the sinuses. Plasma cells with Russell bodies were prominent in the medullary cords. Segment of lymph nodes showed diffuse fibrosis. Stains for organisms were consistently negative.

In the first biopsy from Case 4, two foci of abscess formation with surrounding foamy histiocytes were noted (Fig 5). The orbital mass from Case 1 showed prominent histiocytes with plasma cells and lymphocytes.

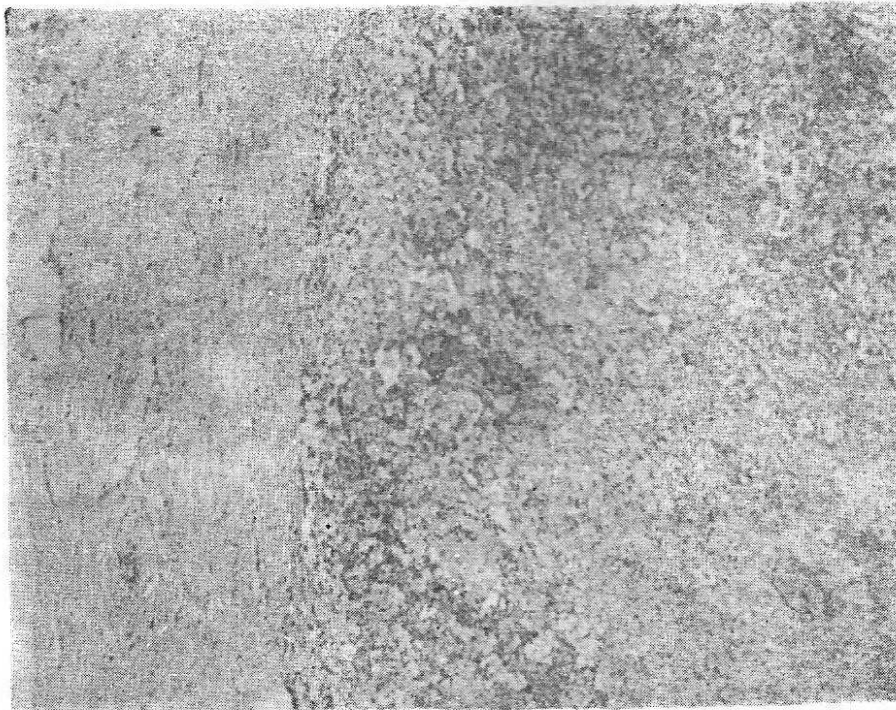


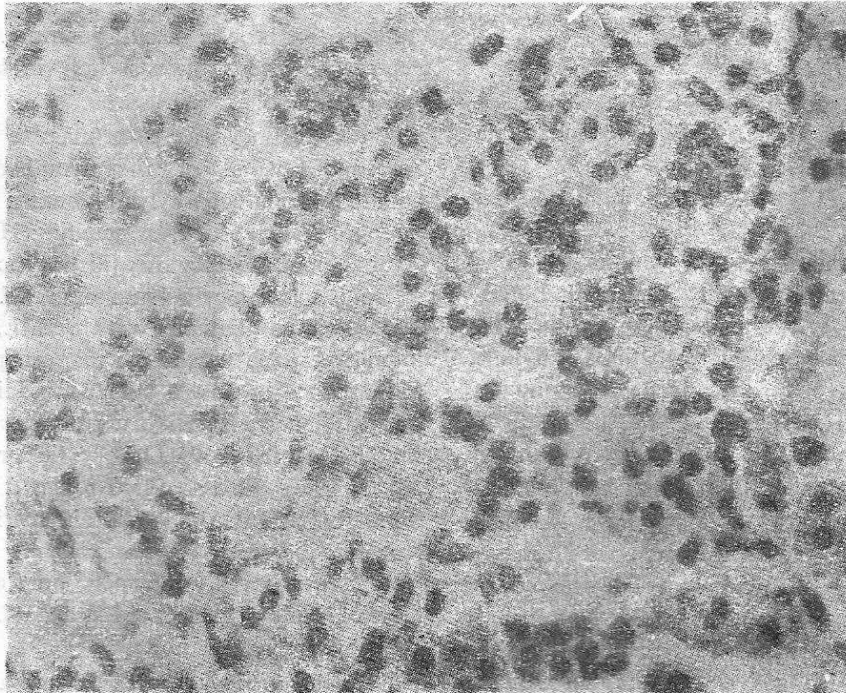
Fig 1. SHML (Case 4). Marked capsular fibrosis of lymph node (HE  $\times$  85).



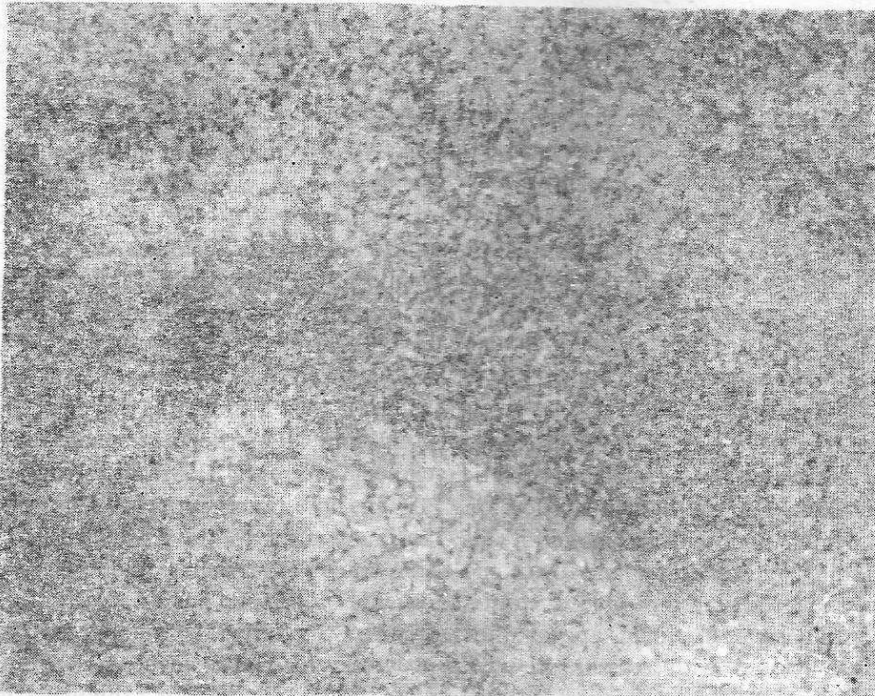
**Fig 2.** SHML (Case 4). Marked pericapsular fibrosis with resultant multinodularity of lymph node (HE  $\times$  85).



**Fig 3.** SHML (Case 3). Gross dilatation of sinuses with compression atrophy of lymphoid tissue (HE  $\times$  85).



**Fig 4.** SHML (Case 3). Sinus histiocytes with ingested lymphocytes (lymphophagocytosis). Note the vacuoles around the ingested cells. (HE  $\times$  400).



**Fig 5.** SHML (Case 4). One of two foci of necrosis with rim of foamy histiocytes (HE  $\times$  100).

### Discussion

In a review of 176 cases of peripheral lymphadenopathy in Ibadan, Attah<sup>5</sup> found non-diagnostic reactive changes in 59 (33%), tuberculosis in 53 (30%) and Hodgkin's lymphoma in 28 (16%). Reactive changes in lymph nodes may involve the lymphoid follicles, the paracortical areas, the sinuses and mononuclear phagocytic system and the medullary cords. Sinus histiocytosis with massive lymphadenopathy involves the sinuses and mononuclear phagocytic system and simulates malignant lymphoma both in its clinical presentation and its microscopic alteration of the lymph nodes<sup>6</sup>.

Sinus histiocytosis with massive lymphadenopathy classically presents with massive bilateral painless enlargement of the cervical lymph nodes. It may affect other lymph nodes or extranodal sites such as the orbit, eyelid<sup>3</sup>, respiratory tract, salivary glands, skin, bones, testes, kidneys and retroperitoneum<sup>7-10</sup>. One patient in this series initially presented with an orbital mass. Alone or taken together with the often accompanying episodes of fever, leucocytosis, anaemia, elevated ESR and hypergammaglobulinaemia<sup>1</sup>, the cervical lymphadenopathy almost always leads the clinician to a diagnosis of a malignant lymphoma or tuberculosis. The general well being of the patients observed in this and other series, however, argues against a debilitating disease such as cancer or tuberculosis. Besides, the most frequent form of lymphoma in the paediatric age group in this environment, Burkitt's lymphoma, rarely presents with peripheral lymphadenopathy.

At present, there is no satisfactory treatment for SHML. As shown by our cases, antibiotic and antituberculous therapy had little effect on the enlarged lymph nodes. Other modalities of therapy including radiotherapy and cytotoxic chemotherapy have similarly produced consistently poor responses<sup>1</sup>. It would appear that SHML is best treated with reassurance and masterly inactivity since spontaneous regression

appears to be the usual outcome. A recent report, however, suggests that vinblastine may be useful<sup>11</sup>.

Sinus histiocytosis with massive lymphadenopathy is one of the lymphadenopathies simulating malignant lymphomas and other lymphoreticular diseases including Histiocytosis X, malignant histiocytosis (histiocytic medullary reticulosis), histiocytic lymphoma and Hodgkin's disease. Non-familiarity with SHML, may lead to misinterpretation of the microscopic features as was done in Case 1 which was initially read as Histiocytosis X. The features which differentiate SHML from other histiocytic proliferations are extensively discussed by Rosai and Dorfman<sup>1</sup>. Similarly, SHML should be differentiated from lepromatous leprosy, rhinoscleroma and BCG-histiocytosis, lesions which not only share histological similarities with SHML but may also involve lymph nodes<sup>12</sup>.

The preponderance of SHML in black children in the third world, raises the possibility of both genetic and environmental factors playing a part in its causation. Of the possible environmental factors, malnutrition and infection appear most likely. Two of our patients had fever and were malnourished. Malnutrition is associated with altered immunological responses<sup>13</sup> and this on its own, may lead to an abnormal response to a common infective agent resulting in the morphological alterations recognised as SHML. Support for immunological impairment in SHML is provided by the finding of impaired PHA transformation<sup>4</sup>, varying degrees of lymphopenia<sup>2 4 5</sup> and phagocytosis of normal lymphocyte *in vitro* by histiocytes of patients with the condition<sup>16</sup>. On the other hand, many of the clinical features of SHML are strongly suggestive of an infectious process. The elevation of antibody titres to the Epstein-Barr virus<sup>17</sup> and the rare *Klebsiella rhinoscleromatis* and ozaenae<sup>15</sup> suggest possible roles for them in SHML. Similarly, the finding of lymphophagocytosis in nodes involved by salmonellosis raise the possibility of a salmonella infection<sup>18</sup>.

Both impaired immunological responses and infectious agents may have roles to play in the aetiology of SHML but their exact contributions to the aetiopathogenesis of this unusual reactive lymphadenitis is at present, uncertain.

The finding of foci of necrosis in one of our cases would appear to be the first time such an observation has been made. Absence of necrosis was a notable negative observation recorded by Rosai and Dorfman<sup>1</sup>. The possibility that the lymph node in this case might represent another form of reactive lymphadenitis such as eosinophilic lymphadenitis was considered but the characteristic histiocytic lymphophagocytosis demonstrable in both biopsies from Case 4 argue against such a differential diagnosis. Furthermore, the second biopsy obtained 4 months after the first, was devoid of any necrotic focus. We conclude that focal necrosis may occasionally be present in SHML.

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