HISTIOCYTIC MEDULLARY RETICULOSIS*

D. M. DE VILLIERS, M.MED. PATH., F.F. PATH., *Senior Lecturer, Department of Pathology, University of Pretoria*

Although Scott and Robb-Smith[1] were not the first to report the condition known as 'histiocytic medullary reticulosis', their publication drew the first general attention to it as an emergent entity. Previously reported cases, of which they quoted 6, had appeared under different designations. These reports, as quoted by them, originated from Tschistowitsch and Bykowa (1928), Bykowa (1929), Derischanoff (1931), Dameshek (1933), Nordenson (1934), and Beaver and Johnson (1934). Nevertheless the presentation of this condition by Scott and Robb-Smith gained little recognition outside England.[2]

In this publication a case of histiocytic medullary reticulosis is reported. This is believed to be the first case reported in South Africa and the youngest ever under this designation.

All the cases which Scott and Robb-Smith reported and quoted had a similar clinical presentation. Most of the patients had fever associated with wasting. Generalized lymphadenopathy appeared early and was associated with hepatosplenomegaly. In the final stages jaundice, purpura and anaemia with extreme leucopenia developed. Generally a rapid deterioration took place, with a fatal termination within weeks or months.

The characteristic pathological changes included discrete, soft, generalized lymph gland enlargement. On section these glands were pink, with haemorrhagic areas. Perisplenitis and a maroon-coloured cut surface were characteristic of the spleen. The liver was pale, with lighter zones in the periportal areas. Bony defects did not occur. Histological examination showed cellular proliferation throughout the lympho-reticular tissue, with occasional necrotic areas. Cellular proliferation in the medulla, as well as the sinusoidal lining cells of the lymph glands, was present. The proliferating cells were reticulum cells, large lymphocytes and histiocytes. Some were typical histiocytes, very much swollen with their contents of erythrocytes, other cells and nuclear debris. Others were regarded as prohistiocytes or their precursors and were of smaller size. Mitotic figures were often found and giant prohistiocytes were common, with twisted hyperchromatic nuclei. In addition, giant reticulum cells with pale chromatic nuclei of 'mirror-image' type resembling the Reed-Sternberg cell of Hodgkin's disease were scattered sparsely throughout the lymph glands. The presence of the latter cell had given rise to the designation of 'atypical Hodgkin's disease' in previously reported cases.

CASE REPORT

J. S., a male White child, was 1 year and 2 months old at the onset of the disease, which was marked by vague symptoms and the development of facial pallor noticed by the mother. A month after this vague onset a haematological examination (the details of which are not available) showed apparently normochromic anaemia, thrombocytopenia and relative lymphocytosis. A bone-marrow examination showed only hypoplasia.

About 6 weeks after the start of the illness, swelling of upper and lower jaws became apparent, with bilateral proptosis. A bone-marrow examination at this stage showed infiltration of lymphomatous cells which were considered to be morphologically compatible with lymphoblasts. One pint of blood was transfused and 6-mercaptopurine and Betnasol were administered. The tumorous enlargement of the jaws increased and hepatosplenomegaly became very marked. A few skin nodules were found in the peri-umbilical region. Endoxan was given and all other chemotherapy was discontinued. A month later the child was very much improved, and the swellings of the jaw and the proptosis had disappeared. The haemoglobin concentration had risen to 11·6 G/100 ml. Clinically the child appeared to be well.

A month later a swelling appeared on the forehead and the haemoglobin concentration was 9·9 G/100 ml. Methotrexate was administered, with good effect.

About 6 weeks later rapid deterioration set in, with enormous hepatosplenomegaly, and the bone marrow showed 61% abnormal cells of indeterminate type similar to those seen on the first occasion. Progressive thrombocytopenia developed. Treatment with BCNU* was started. Six days before death one pint of blood was transfused and a dose of cytosine arabinoside was given. Sudden death after left-sided hemiplegia terminated an illness of 5½ months.

Autopsy Findings

The body was that of a well-nourished male child. Sparsely distributed, bluish skin petechiae were seen. No proptosis or swelling of the jaws was present. Endocardial and epicardial petechial haemorrhages were found. Nodular haemorrhagic consolidations were present in both lungs. Petechial haemorrhagic necroses were present in the mucosa of the stomach, ileum and colon. The liver weighed 900 G and showed greyish portal infiltrations. The pancreas appeared normal. The spleen weighed 140 G and showed a muddy colour on the cut surface. Retroperitoneal glands were enlarged and had a light brown colour. A massive intracerebral haemorrhage of the right hemisphere was present and rupture had taken place into the ventricular system. Both kidneys showed diffuse greyish, nodular infiltrations. The bladder and testes were normal.

Histological Examination

The liver, spleen, lymph glands, lymphoid tissue and mucosa of the gut, as well as the lungs, kidneys, jaws, base of the skull and interstitial tissues, showed similar infiltrations, the appearance of which in a lymph gland (Fig. 1) can be taken as representative. The general architecture of the lymph glands was fairly well preserved. In parts, however, diffused infiltration obliterated lymphoid follicles and sinusoidal borders. The medullae of the lymph glands were massively infiltrated with phagocytic histiocytes. The contents of these cells were erythrocytes, cellular nuclei and debris. Some of these cells were very large and bulging with this cellular content. Many smaller histiocytes and prohistiocytes were also present. Cells simulating Reed-Sternberg cells were in evidence and some of the histio-

*Date received: 21 October 1968.

*Bis-chloro-ethyl-nitroso urea.

cytes showed mitotic activity. A few very sparsely scattered plasma cells and lymphocytes were noted, but these did not appear to be a constituent element of the pathological process. The sinusoidal lining cells were swollen and transformation into free histiocytes was apparent. The sinusoids very strikingly contained numerous phagocytic histiocytes. The capsules of the lymph glands were clearly being invaded. Small areas of necrosis were present. No liver necroses were seen and the infiltrate was present in portal tracts and sinusoids. Slight iron deposition was present in the spleen.

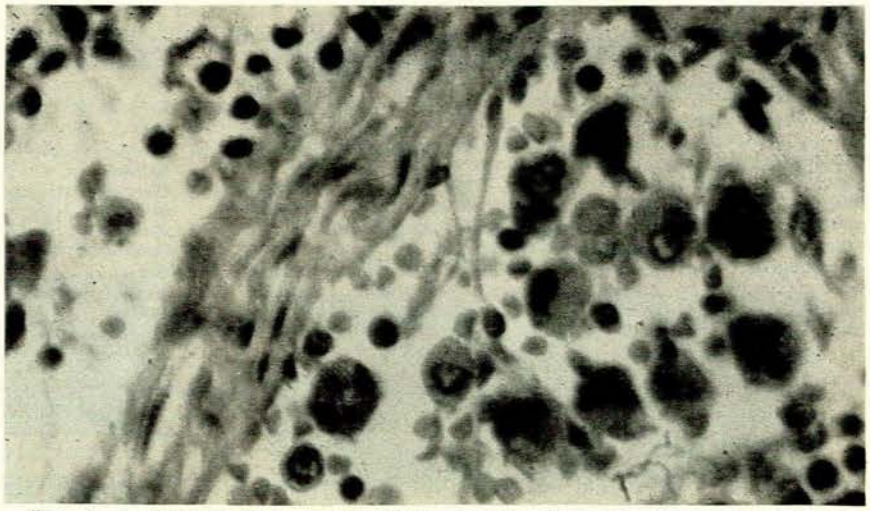

Fig. 1. A sinusoid in a lymph gland packed with large histiocytes, many of which show phagocytosis of erythrocytes and other cells.

DISCUSSION

The critical evaluator of the literature[1-10] on the subject of histiocytic medullary reticulosis cannot but come to the conclusion that in spite of views to the contrary an entity emerged with the report by Scott and Robb-Smith in 1939.[1] The earlier views that the condition was an infective process characterized by lympho-reticular hyperplasia cannot be substantiated by the nature of the disease, which eventually produces capsular invasion of lymph glands, progressive neoplastic enlargements and infiltration of multiple tissues with profound depression of haemopoiesis. Although having certain basic features in common with the malignant lymphomas, it nevertheless differs in many respects, the most important being that lymph nodal and splenic architecture is preserved till a late stage in the disease.

About 50 cases have now been reported. The age incidence is 18 - 78 years. Farquhar and Claireaux[7] reported 'familial haemophagocytic reticulosis' in 2 siblings who were both 9 weeks at the onset of the disease and who died within 21 and 94 days respectively. These cases correspond in all respects with other cases reported and designated as histiocytic medullary reticulosis. Because of this fact and the indefensible habit of pathologists of pinning new tags on an already superfluously adorned nomenclature, it is felt that the term 'familial haemophagocytic reticulosis' should be discarded. Moreover, the phagocytosis which is such a cardinal feature of the condition is not limited to phagocytosis of the formed elements of the blood. Furthermore, the fact that this condition occurred in siblings does not prove that the condition is familial.

The possibility that histiocytic medullary reticulosis could in fact be Letterer-Siwe disease can be discounted by first quoting Siwe[9] as presenting the disease (later to be known as Letterer-Siwe disease) as being neither hereditary nor familial. Reese and Levy[11] described a familial incidence in Letterer-Siwe disease. However, the presentation, course and pathology of the disease in siblings aged 1 month and 3 months, respectively, differ in no way from those of Farquhar and Claireaux as indeed they do not differ from any of the others reported in the literature. Letterer-Siwe disease characteristically occurs in the very young, has a rapidly fatal course and is hallmarked by widespread haemorrhagic skin infiltrations of non-lipid histiocytes and often bony defects. The histological appearance is that of a distinctly granulomatous lesion in which the histiocytes, although being phagocytic, are intermingled with plasma cells, lymphocytes and fibroblasts. Erythrophagocytosis is not a feature of Letterer-Siwe disease.[7] The cases reported by Farquhar and Claireaux had no skin lesions, excepting terminal petechiae. All other reported cases, apart from the siblings mentioned above, had an age incidence quite unlike that in Letterer-Siwe disease. One of the cases reported by Civin[5] had skin infiltrations. Anderson's case[10] had transient skin lesions which had disappeared at the time of death. Other cases had petechiae or purpura, usually terminally, which can readily be explained by almost inevitable thrombocytopenia. Clearly, the pathological features of histiocytic medullary reticulosis cannot be fitted into the pathological pattern of Letterer-Siwe disease.

The patient reported here exhibited no significant skin lesions. A few skin nodules were noted clinically in the umbilical region. At autopsy, only scattered petechiae were obvious. If a rapidly progressive course in Letterer-Siwe disease should influence the histological appearance to produce a monomorphic character (such as the histology of histiocytic medullary reticulosis), then it cannot be said to be operative in this particular patient whose life was prolonged by chemotherapy, thereby providing ample time for development of the granulomatous picture of Letterer-Siwe disease.

An interesting manifestation is the development of jaundice in some cases. It appears to have a haemolytic basis, but necrosis of liver cells or cholestasis were found in others. Cases associated with haemolytic anaemia as a prominent feature have occurred.[6,8] Iron-containing deposits are sometimes present in the reticulo-endothelial organs, and in the case reported here slight iron deposits occurred in the spleen. The terminal cause of death was cerebral haemorrhage resulting apparently from thrombocytopenia.

SUMMARY

Histiocytic medullary reticulosis was first reported by Scott and Robb-Smith in 1939. A review of the clinical and pathological features of this condition is given with reference to the cases reported by these and other authors. A case of this condition is reported in a child aged 1 year and 3 months. This is believed to be the first report of this condition specifically designated as 'histiocytic medullary reticulosis' in so young a child, and the first reported case in South Africa. A comparison is made between Letterer-Siwe disease, so-called haemophagocytic reticulosis and histiocytic medullary reticulosis. The last-mentioned condition is considered to be quite distinct from Letterer-Siwe disease and identical with haemophagocytic reticulosis. Furthermore, histiocytic medullary reticulosis should now be considered as an established entity, related to malignant lymphoma.

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