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Giant cell granulomatosis of lymph nodes with a fatal course

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Summary. We report two examples of an unusual expression of fatal granulomatosis with primary lymph node location, characterized histologically by numerous giant cells of the Langhans' type, effacement of the nodal structure, mixed lymphohistiocytic infiltrate, and marked histiocyte cell maturity, all features which initially did not exclude the possibility of a granulomatous process of infectious origin.

The clinical features of these cases include cellular or combined immunodeficiency, a possible family history and a rapidly fatal course. The present article emphasizes the great similarity which can exist between histiocytic and granulomatous disorders, the great variability of histiocytic diseases from the pathological view-point, the presence of borderline examples, and the several overlapping features of different entities.

Specifically, the most remarkable finding of these two cases is the existence of numerous mature giant cells of the Langhans' type within a massive obliteration of the nodal structure. Furtherly, these giant cells are characterized by a strikingly orderly disposition of peripheral nuclei in a wreath-like pattern, frequently suggesting the structure of Touton's giant cells.

Key words: Reticuloendothelial system, pathology – Reticuloendotheliosis, pathology – Histiocytosis X – Malignant histiocytosis – Lymph node, pathology – Granuloma – Granuloma, giant cell

Introduction

Benign and malignant granulomatous and histiocytic diseases of lymph nodes include several entities which may represent the source of conspicuous diagnostic problems. We present two cases of a primary lymph node granu-

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lomatosis characterized by the following findings: 1) nodal structural effacement; 2) a very large number of giant cells of the Langhans' type; 3) a mixed lymphohistiocytic infiltrate with mature histiocytes, erythrophagocytosis and very rare eosinophils; 4) a diffuse or nodular pattern of growth; 5) an initial massive lymph node involvement and subsequent systemic diffusion; 6) a rapidly fatal course; 7) negative results of exhaustive attempts to detect bacteria, fungi and viruses.

This lesion is both granulomatous and aggressive at the same time. We were unable to find any previously reported instance of this process.

Case 1

A 6-week old male child was seen in December 1976 with a 2 week history of marked lymphadenopathy localized bilaterally to the laterocervical, axillary and inguinal regions (Fig. 1).

The infant was a 33-week gestation premature product of a gravida 1 para 1 young female. Clinical findings included a remarkable hepatosplenomegaly of 10 cm below the costal margins respectively. Cutaneous lesions of the Abt-Letterer-Siwe type were never observed.

Evaluation of the immune system included normal serum immunoglobulins for the age (IgG: 240 mg/dl; IgM: 54 mg/dl; IgA: 27 mg/dl), a moderately reduced proportion of T cells (50%) and a deficiency of the cellular immune system as demonstrated by extremely low in-vitro lymphocyte transformation with PHA, Con A, and PWM (about 5% of the normal value). No response was noted to the cutaneous tuberculin test and Kveim test.

Two lymph node biopsies were performed at two week interval. Cultures for bacteria, fungi, tubercular and atypical mycobacteria were repeatedly negative. The administration of antibiotic and antitubercular chemotherapy proved ineffective. The general conditions rapidly deteriorated and the infant expired after 3 weeks as a result of bilateral bronchopneumonia characterized by small confluent foci extending throughout the parenchyma.

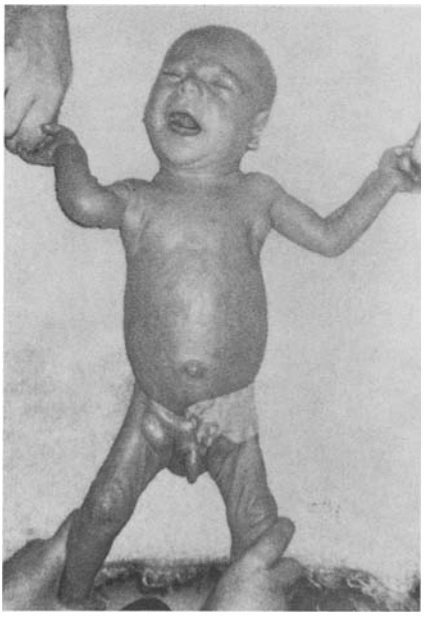

Fig. 1. Case 1. The picture of the infant shows huge multiple lymph node masses in inguinal, axillary and cervical location. Note the absence of a cutaneous rash of the Abt-Letterer-Siwe type on the thoracic and abdominal wall

At autopsy, external inspection revealed a debilitated infant with generalized lymph node enlargement and the presence of a very mild local dermatitis of the head. The lungs showed an advanced dense bilateral pneumonia with confluent acinar foci and pus formation. The very congested liver and spleen were twice the normal weight. The thymus remnants were extremely scanty. Mediastinal, lumboaortic and mesenteric nodes were not conspicuous and the bone marrow was hypocellular and cyanotic. No focal or diffuse alterations were seen in the oedematous brain.

Pathological findings

The two lymph nodes obtained at biopsy revealed identical general findings. One of the dominant features was the complete loss of the follicular and sinusoidal structure. The structural effacement was caused by intense proliferation of differentiated slightly atypical histiocytes intermingled with mature lymphocytes. The latter had cleaved or twisted nuclei. A coexisting lymphocyte depletion was an additional remarkable finding. The proliferation was prevalently of the diffuse type but in some areas a distinctly nodular configuration was noted (Fig. 2). The nodular pattern was underlined by the reticular stain, which demonstrated a peripheral circular arrangement of the reticular fibrils. A scanty amount of fibrils was present inside the nodules (Fig. 3). Moreover, the lymphohistiocytic tissue often assumed a fascicular pattern (Fig. 4). The moderately atypical histiocytes had abundant and vacuolated cytoplasm with both distinct or merging borders. Karyorrhexis and scattered cellular and nuclear debris were noted.

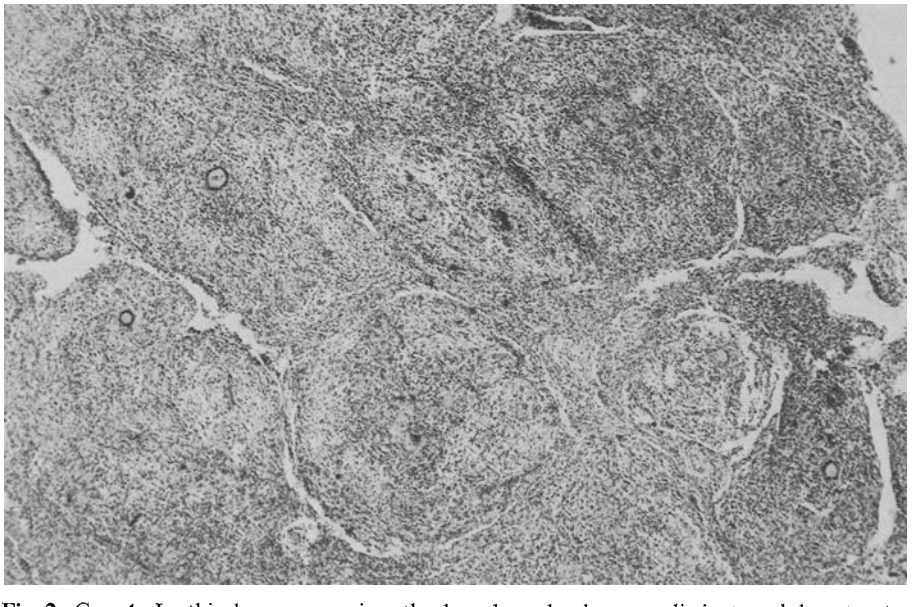

Fig. 2. Case 1. In this low-power view the lymph node shows a distinct nodular structure and numerous giant cells inside the nodules (Haematoxylin and Eosin Stain, Original Magnification $\times 40$)

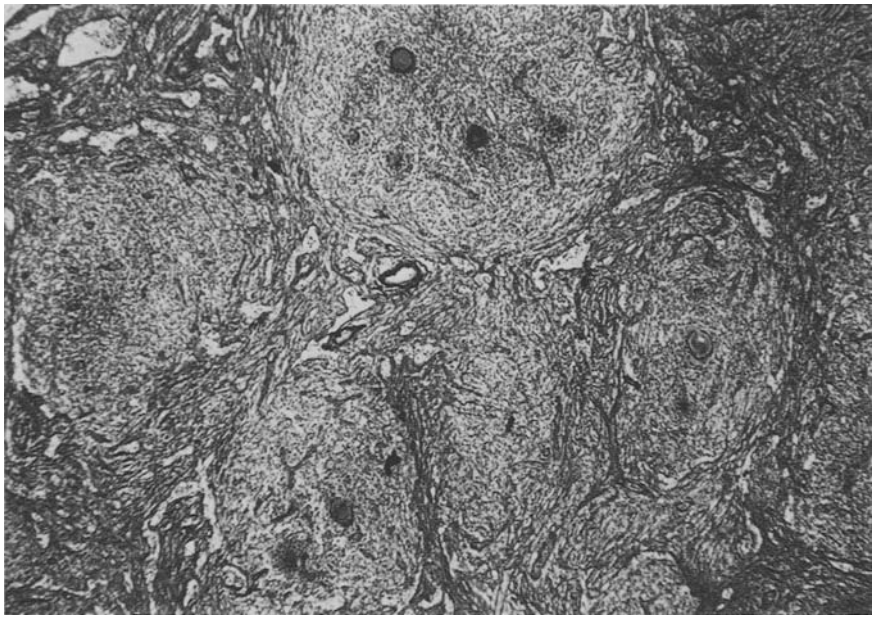

Fig. 3. Case 1. The Gomori reticulin stain underlines the nodular growth process in the lymph node (× 40)

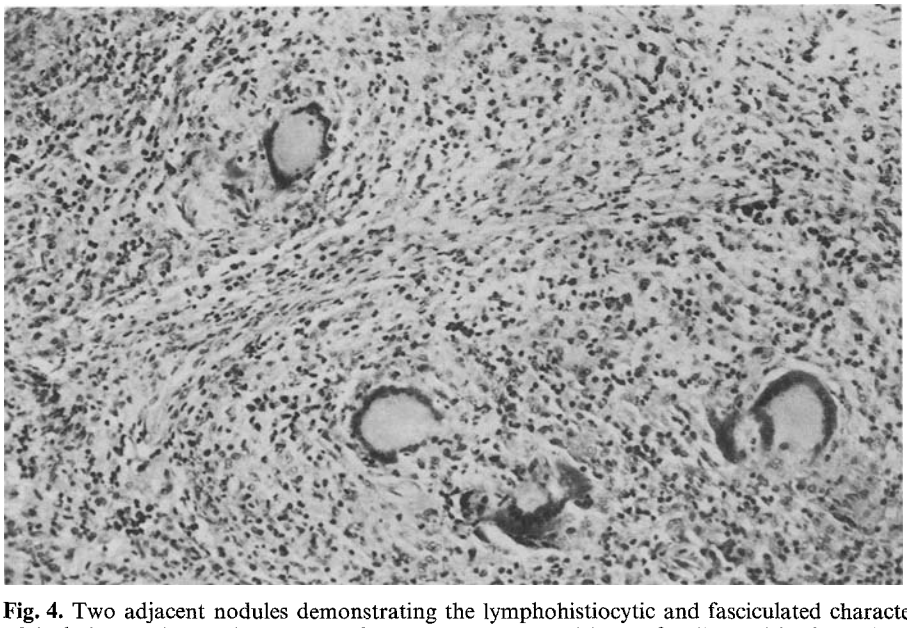

Fig. 4. Two adjacent nodules demonstrating the lymphohistiocytic and fasciculated character of the lesion, and several giant cells of the Langhans' type with a perfect "wreath" of peripheral nuclei (Haematoxylin and Eosin Stain, Original Magnification × 150)

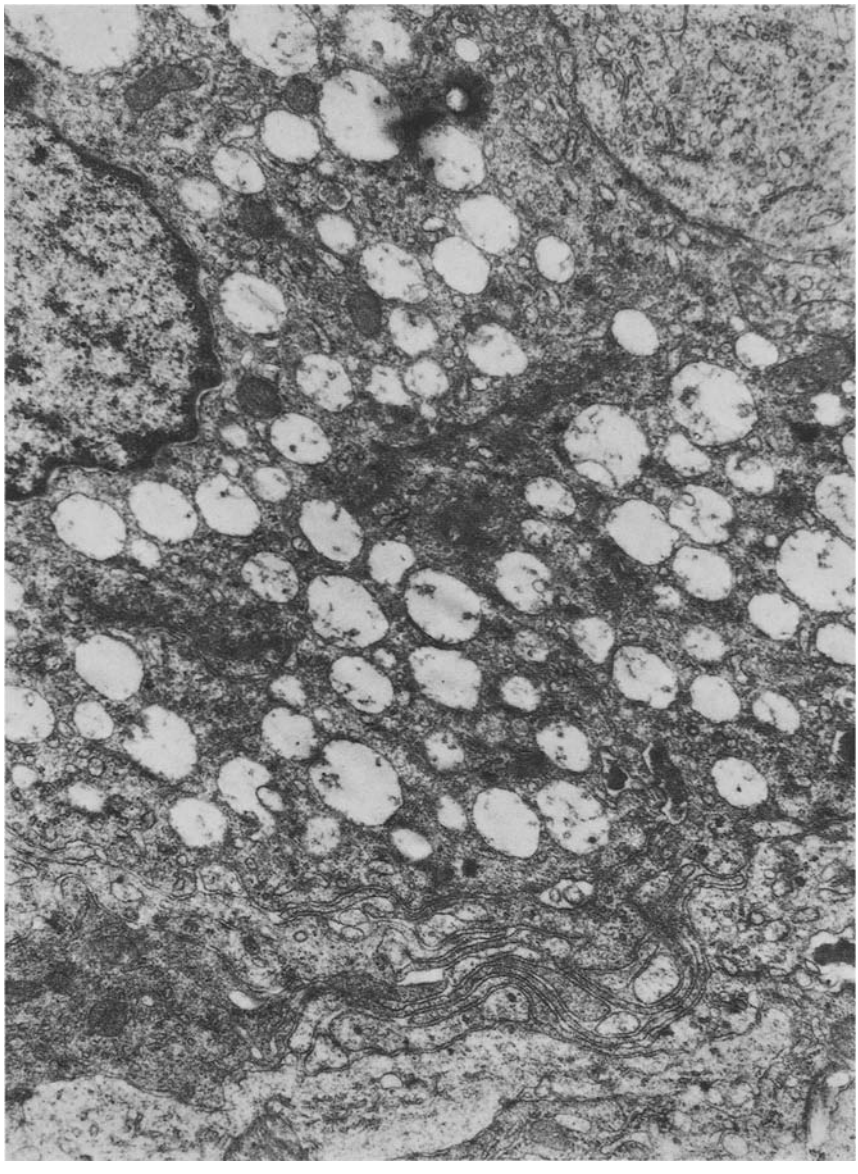

Fig. 5. Case 1. A histiocyte-like cell with several cytoplasmic vacuoles and convoluted membrane processes on the left side of the picture (×7,000)

A second important finding was represented by an abundant number of giant cells of the Langhans' type widely scattered throughout the lymphohistiocytic tissue (Figs. 2–4). These cells were characterized by a perfect "wreath" of peripheral nuclei and often by a peripheral rim of cytoplasm (Figs. 2–4). Inflammatory cells of other type were few. Rare eosinophils were randomly scattered. Erythrophagocytosis was present. Intensive search with special stains failed to reveal fungi and acid-resistant bacilli. The histological examination of autopsy specimens revealed numerous small nodules

of the same granulomatous tissue in the spleen and less scattered in the lungs, bone marrow, and portal tracts. Giant cells similar to those seen in the lymph nodes were always present in these nodules. Specifically, the spleen showed extensive loss of the follicular structure which was replaced by numerous scattered granulomatous nodules of lymphohistiocytic composition. These nodules included mature giant cells characterized by an extremely perfect disposition of peripheral nuclei.

The ultrastructural study of the lymph node specimen revealed an admixture of fibroblast-like and histiocyte-like cells and intermediate forms.

The most significant finding was represented by an extremely convoluted intermingling of cytoplasmatic processes from adjacent cells (Fig. 5). Extensive search failed to reveal Birbeck's granules. No viral particles or mycobacteria were found.

Case 2

A 6-year-old female was admitted in 1980 after a 3-year clinical history of persistent relapsing fever, marked hepatosplenomegaly, bilateral cervical nodes, anaemia, thrombocytopenia, therapy with steroids and repeated transfusions. A male sibling had died several years previously soon after an emergency admission to the local hospital with a clinical picture of hepatosplenomegaly, laterocervical lymphadenopathy and abdominal pain, but an autopsy was not performed. On admission the patient had basal nodules of the left lung evidenced by standard X-ray films, negative tuberculin skin test, absence of IgA globulins, normal IgM and IgG globulins, markedly reduced peripheral B lymphocytes (3%) and absence of T lymphocyte response to PHA, Con A and PWM. The father of the patient was found to be affected by a consistent reduction of IgA globulins. Antibody titres to Epstein-Barr virus, herpes simplex virus, adenovirus, cytomegalovirus, and varicella-zoster virus were within normal values; cultures for adenovirus and Epstein-Barr virus were negative; Paul-Bunnell, Widal-Wright, monotest and dye test were all negative; the serological tests for brucella and histoplasmosis were normal; phagocyte function test of this patient are not available.

A lymph node biopsy was performed; the biopsy material cultures did not reveal aerobic, anaerobic, mycobacterial or fungal organisms. Several weeks later a splenectomy was performed. The huge spleen weighed 1,700 g and had a congested and mottled cut surface with yellow streaks and nodules. Subsequently, during the hospital course a bilateral mediastinal lymph node mass was radiologically noticed. The patient underwent a course of chemotherapy and survived for less than one year in poor clinical conditions and ultimately died with severe pancytopenia and thrombocytopenia unresponsive to cortisone.

Pathological findings

The lymph node showed a massive and almost complete structural effacement with isolated and compressed lymphocyte cords (Fig. 6). There was an intense proliferation of mature histiocytes with abundant eosinophilic and sharply outlined cytoplasm, resulting in coalescing cellular masses with some rare necrotic foci (Fig. 6). The proliferating histiocytes were interspersed with mature lymphocytes. Erythrophagocytosis was not remarkable. Foam cells were not found. The prominent finding was represented by numerous giant cells of the Langhans' type which had a perfect wreath of peripheral nuclei and a thin rim of external peripheral cytoplasm (Fig. 7). Intensive search for fungi and acid-resistant bacilli was negative. No Sternberg or Sternberg-like cells were found in very numerous serial sections.

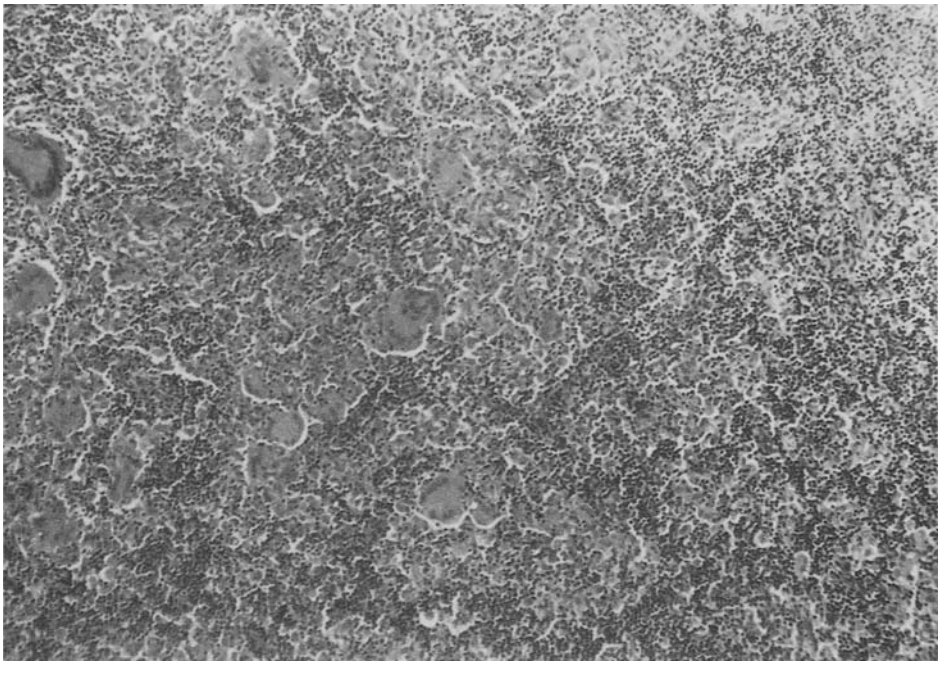

Fig. 6. Case 2. Laterocervical lymph node. Note the intense obliterating histiocyte infiltration studded with numerous giant cells (Haematoxylin and Eosin Stain, Original Magnification $\times 40$)

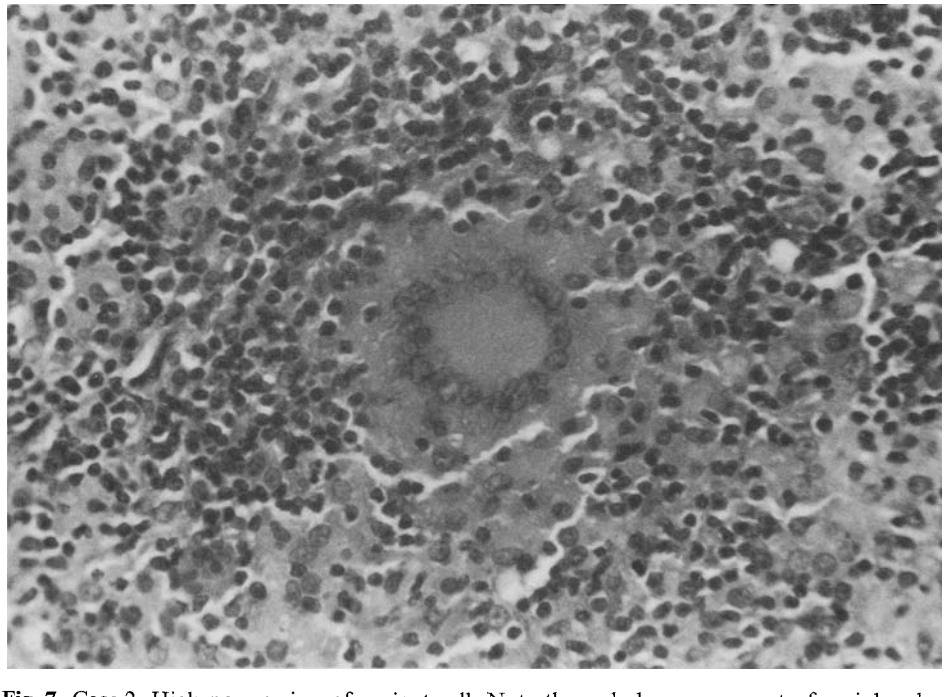

Fig. 7. Case 2. High power view of a giant cell. Note the orderly arrangement of peripheral nuclei and the outer rim of cytoplasm. The mixed lymphohistiocytic character of the infiltrate can also be noted (Haematoxylin and Eosin Stain, Original Magnification $\times 400$)

Reticulin fibrils were scattered in variable but generally scanty amounts, leaving empty areas which corresponded to the more active cellular proliferation foci. The spleen showed a marked obliteration of the follicular malpighian structure due to a distinctly nodular infiltration of a lymphohistiocytic tissue composed of mature lymphocytes and slightly atypical histiocytes with a more active erythrophagocytosis. The red pulp sinuses were patent and permeated by histiocytes with some atypical forms. A striking megakaryocyte hyperplasia with bizarre forms was present inside the nodules and sinuses. The liver demonstrated a lymphohistiocytic infiltration of the portal tracts without megakaryocytes. The iliac crest trephine biopsy revealed a marked depletion of bone marrow and replacement by a mixed lymphohistiocytic tissue consisting of numerous mature and bland histiocytes.

The ultrastructural investigation of lymph node specimens revealed numerous histiocyte-like cells. Langerhans' granules (Birbeck's granules), viral particles or bacteria were not identified after an extensive investigation.

Discussion

The lesion type described herein is essentially a granulomatous process characterized by a large number of Langhans' type giant cells, marked effacement of the nodal structure, histiocyte cell maturity and a fatal clinical course. We would like to discuss the differentiating features between this process and several other well known entities of granulomatous or histiocytic nature, supplying at the same time a brief general review of this complex and intriguing topic.

1) Tuberculosis. This diagnosis is most unlikely for several clinical and pathological features: the negative reaction to tuberculin skin test; the failure to culture M. tuberculosis in appropriate growth media and in guinea pig inoculations and the absence of tuberculous granulomas and caseous necrosis. Similarly, any type of productive non-caseating tuberculosis (which is usually referred to as Schuppel's lymphoma) can be eliminated from consideration for the same reasons (Kaufmann 1961).

2) Sarcoidosis can be excluded for its rare occurrence in infancy, the negative Kveim test, the absence of asteroid and Schaumann bodies.

3) The absence or scarcity of suppurative and necrotic foci and the failure to detect any aetiological infectious agent either by means of histochemical cultural or ultrastructural procedures exclude the possibility of a granulomatous lymphadenitis caused by *mycobacteria or fungi* (Reid 1969; van der Hoeven et al. 1958; Bindford and Connor 1976; Bültman et al. 1982). This differential diagnosis is of importance because fatal disseminated granulomatous diseases caused by mycobacteria have been reported (van der Hoeven et al. 1958; Bültman et al. 1982). These fatal infections are generally limited to immunologically compromised hosts. In histoplasmosis a striking

histiocyte sinusoidal hyperplasia simulating a histiocytosis can be observed (Rosai 1981).

4) Virus-associated haemophagocytic syndrome (Risdall et al. 1979). The histiocytic proliferation is mild with preservation of the nodal architecture. Active haemophagocytosis and lymphocyte depletion are additional important findings; immunoblasts and plasma cells may be present.

The bone marrow is preferentially involved, showing a histiocyte hyperplasia of moderate to marked degree and active phagocytosis of erythroid cells, platelets and granulocytes.

5) Histiocytosis X. Primary lymph node involvement by histiocytosis X in the absence of bone location is rare (Marshall 1956; Williams and Dorfman 1979; Reid et al. 1977); the affected lymph node shows a sinusoidal infiltration of mature well differentiated histiocytes interspersed by a variable amount of eosinophils; giant cells of the foreign body type and much less frequently of the Langhans' type may be present (Rappaport 1966). Cellular lipidization, foam cells, Touton giant cells and eosinophil abscesses are additional important findings. The nodal structural effacement may be marked but is usually incomplete. The compositive element is a peculiar type of histiocyte or reticular cell which is usually referred to as "Langerhans' cell" characterized by reniform nuclei with grooves and infoldings and by the ultrastructural finding of the so-called Birbeck's granule, a cytoplasmatic zipper-like structure (Nezelof et al. 1973).

6) Hodgkin's disease with tubercle-like and histiocyte reaction. In our experience the mixed subtype of Hodgkin's disease in children is frequently characterized by an abundant histiocyte component and difficulty to detect diagnostic Reed-Sternberg cells; in such cases the presence of eosinophils and non-diagnostic Sternberg cells is an important diagnostic guide.

7) Malignant histiocytosis. The nodal infiltration is sinusoidal and cellular pleomorphism is usually marked. The infiltrate is not lymphohistiocytic, and inflammatory cells are represented mostly by plasma cells. Giant cells are pleomorphic and bizarre, of the Reed-Sternberg or foreign body type (Byrne and Rappaport 1973; Rappaport 1966; Robb-Smith 1938; Robb-Smith and Taylor 1981; Warnke and Kim 1975).

8) Familial lymphohistiocytosis. This heterogeneous group encompasses several reported cases characterized by the following findings: mixed, mature and moderate lymphohistiocytic infiltration, erythrophagocytosis, familiarity, combined immunodeficiency, lymphocyte depletion of lymphatic organs, eosinophil infiltrative component (Barth et al. 1972; Berard et al. 1966; Bergholz et al. 1978; Cederbaum et al. 1974; Dehner 1975; Farquhar and Claireaux 1952; Janka et al. 1981; Koto et al. 1976; Ladisch et al. 1978; Marrian and Sanerkin 1963; Nelson et al. 1962; Omen 1965; Perry et al. 1976).

The clinical picture of lymphohistiocytosis as in malignant histiocytosis comprises fever, hepatosplenomegaly and pancytopaenia (Janka et al. 1981). Other symptoms as rash, icterus and neurologic signs appear later in the course of the disease. Additional important clinical findings are hyperlipidemia and coagulative disorders. Our two cases have in common with lymphohistiocytosis the mixed lymphohistiocytic infiltrate, the immunological impairment, and the possible familiarity for Case 2; but they are strikingly different from other viewpoints, for instance the marked superficial lymph node involvement which is unusual in familial lymphohistiocytosis, the nodal structural effacement and the plentiful giant cells.

9) Sinus histiocytosis with massive lymphadenopathy (SHML) characteristically presents as cervical lymphadenopathy, fever and leucocytosis (Dehner 1975). The lymph node histology reveals a striking sinusoidal pattern, Touton and foam cells, bland cytological appearance, and the distinctive feature of lymphophagocytosis (Dehner 1975).

10) Allergic granulomatosis. This is a very rare disorder characterized by nodular infiltration of the lymph node sustained by mature histiocytes and eosinophils with multiple necrotic foci frequently arising in eosinophil abscesses (Butler 1969). Several variants of allergic granulomatosis are recorded (Symmers 1978). In our two cases the eosinophil component and necrosis were absent or scanty.

11) Familial hepatosplenolymphatic reticuloendotheliosis with a chronic course in children (Polonowski et al. 1968; Verger et al. 1973; Nezelof 1979). This is a chronic disease affecting liver, spleen and lymph nodes, characterized by marked reticulum cell hyperplasia, a relevant plasma cell component and a slight attempt to granuloma formation. Hypergammaglobulinemia involving IgG and IgA, hypolipidemia, hyposideremy, hyperhemolysis of extracorpuscular type are additional important clinical findings. A chronic reactive nature has been postulated.

12) Pure giant celled lymphadenitis of unknown causation (Symmers 1978). This is a very rare lymphadenopathy described by Symmers. The lymphoid tissue is studded with giant cells some of which may contain asteroid bodies. The nodal structure is not disturbed and mononuclear histiocytes are scanty. The clinical picture is that of a moderate and generalized nodal enlargement.

13) Histiocytic necrotizing lymphadenitis with or without granulocytic infiltration (Fujimori et al. 1981; Pileri et al. 1982) frequently affects the laterocervical nodes of young women and bears an excellent prognosis. This lesion is characterized by intense histiocytic proliferation in the cortex and paracortex with partial structural effacement and necrosis of lymphoid tissue. In our two cases necrotic foci were absent or very scanty.

The common and overlapping features among all the aforementioned entities are so intriguing that it is difficult to claim a clear-cut distinction from each other.

The two cases reported herein reveal features suggestive of a granulomatous process (Langhans' giant cells, histiocyte cell maturity) coexisting with others indicative of a malignant disease (destructive loss of the nodal structure, a rapidly fatal clinical course). Such coexistence is very unusual.

Our two cases demonstrate how complex and unpredictable can be the appearance of histiocytic and granulomatous disorders and further suggest that the concepts of histiocytosis and granulomatosis should be regarded as unified.

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