Letterer - Siwe Disease

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Introduction

The disease was first described by Letterer in 1924, who reported an infant having an eczematous haemorrhagic rash, hepatosplenomegaly, lymphadenopathy, fever and anaemia with a fatal outcome.

Seven additional cases were described by Siwe in 1933, and this clinical entity was then named as Letterer - Siwe Disease[1,2,3]

The disease is usually sporadic and occurs in children under 3 years old and more commonly in males[1].

Three clinical conditions have been described that have the common histologic features of an infiltrating histiocytosis but have widely varied clinical manisfestations:-

Letterer - Siwe Disease: It is a disseminated histiocytosis which primarily affects soft tissues particularly the skin, bone marrow, liver and lungs; localised disease carries a better prognosis while a disseminated one has a poor prognosis[1,2,3,4,5].

Hand Schuller Chritian Syndrome, characteristically seen in young children, is associated with bony lesions, but to a variable degree affects soft tissues as well exophthalmos, and diabetes insipidus forms part of the clinical triad of this syndrome.

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Eosinophilic Granuloma of bone usually presents as a solitary lesion in an older child.

Etiology and Pathogenesis: Hand suggested that the disease in his original patient resulted from an infectious agent.

Infectious has been suggested as the cause of histiocytosis but the evidence is tenuous; organisms have been grown from lesions in a few cases but most are sterile. The evidence given for infectious agent is the apparent response to antibiotics in a few cases, the response to glucocorticoids and the histologic features of the lesion.

Abnormality of immune function is present in many of these patients and similarity between histiocytosis and some of the immune deficiency syndromes suggested the possibility of its being an immunologic disorder.

Moreover, the heterogenous nature of cellular infilterate is consistent with the clonal proliferations of a single cell within the immune system, which is capabale of releasing lymphokinase or other chemotaxic factors to attract a varied cell population to the lesion.

The disease may be of a malignant nature, because of the fatal outcome especially in infants and the responsiveness of some patients to anti- cancer drugs.

A prenatal origin has been suspected because this syndrome has been reported in twins and also in a familial pattern consistent with autosomal recessive inheritance carrying a high mortality in patients under one year of age.

The disease can be suspected clinically but it is important to test a biopsy specimen for the confirmation of the diagnosis. The site of the biopsy being determined by the location of the lesions. Skin is the easiest tissue to obtain but sometime biopsy of the bone, lymph node, gums and liver may be necessary.

Pathology

The lesion consists of a proliferation of histiocytes in sheet like masses in lympho-reticular organs and bones. Liver, spleen and lymph

nodes are usually enlarged and anemia is frequent. There is a characteristic skin lesion and usually brown scaling papules which often ulcerate; destructive osteolytic lesions and miliary infilterations of lung are also seen. Lymph nodes are infilterated by well differentiated histiocytes with eosinophilic cytoplasm and ovoid or reniform nuclei with fine chromatin. The cytoplasm is vacoulated, less often foamy, may contain phagocytosed inclusions and hemosidrin. A few giant cells may be present. Total destruction of the node is seen only late in the disorder. Similar infiltrates are found in liver and spleen, characteristically in bones and skin. Infiltrates in the skin are characteristically found in the superficial part of the dermis. A curious ultra structural finding in Letterer-Siwe Disease is an elongated membrane bound inclusion, characteristically 42mm in external diameter with an electron dense core 11mm in diameters. This structure is similar to the Langerhan's granules of cutaneous Langherhan's cell.

The destruction of cells varies form lesion to lesion. In a series of 51 patients, two separate histo-pathologic types have been described, each with a different prognosis:-

Type 1 is characterized by a diffuse infiltration of the organs that compose the monocyte macrophage system, by individual histiocytes without giant cells, eosinophils or necrosis.

Type II is characterized by a variable focal involvement of the organs which contain the monocyte macrophage system, by syncetial sheets of histiocytes with eosinophils, giant cells, necrosis and fibrosis.

The course of the disease varies from an acute fulminating to a chronic relatively benign one with all variations in between.

Case Report

We report here an interesting case of Letterer-Siwe Disease in a 12 months old child who had all the clinical and pathological manifestations of this disease.

This patient was admitted with a 6 months history of abdominal distension, fever and diarrhoea off and on, body rash which started from the scalp and then spreading all over the body.

The pregnancy and delivery were uneventful and the mother was not exposed to any radiation nor had any medication during pregnancy.

There was nothing relevant in the family history.

Examination:

A pale ill looking, wasted baby who had a distended abdomen, anemia, fever (99Fo) and palpable cervical, axillary and inguinal lymph nodes.

There was a generalized pseudo-sebborheic rash on the body.

The liver and spleen were palpable.

Bilateral crepitations were present at the time of admission.

The following investigations were carried out:

Blood Complete Examination

Hb - 4.8gm.
TLC- 14,000/cum.
ESR- 75 m/lst hour.
DLC: N - 70%
L - 14%
E - 12%
M - 04%

Urine Examination

Albumin	- Traces.
Sugar	- Nil.
M/E	- Pus cells - 15-20/HPF.
R.B.Cs	- Rare.

Stool Examination

Colour	- Greenish.
Consistency	- Viscus.
Mucus	- Slight.
M/E	- Pus cells - 1-2
R.B.Cs	- Rare.

No ova and cyst were seen

Periphral Blood Smear

R.B.Cs showed mild hypochromia & a niso-poikilocytosis.
W.B.Cs were slightly increased in number.
Platelets appeared slightly reduced in number on the smears

Bone Marrow Examination

The marrow specimen was normocellular.

- Erythropoiesis was normoblastic.
- Leukopoiesis was within normal limits and had a normal maturation pattern.
- Quite a few histiocytic cells were noted.

Skin Biopsy

The dermis revealed infiltration by lymphocytes and histiocytes in focal areas around the skin appendages.

Lymph Node Biopsy

Sections revealed lymph nodes with effected architecture.

There were groups of histiocytes, having abundant light pink cytoplasm and small central nuclei. The groups of histiocytes were separated by polymorphs, lymphocytes, occasional multinucleated giant cells and ill defined granuloma like structures were also seen.

Morphological findings of the bone marrow and biopsy specimens were consistent with histiocytosis.

Discussion

The disease belongs to a group of rare disorders, ranging from systemic rapidly fatal neoplasia to solitary benigh focal granulomatous lesion.

They are the proliferative disorders of the macrophage mononuclear phagocyte/histiocyte.

The factors correlating with outcome are age of onset, extent of the disease and localization of the disease.

No patient over the age of 3 years at onset usually dies. The mortality rate for those under 3 years of age is reported to be approximately 50% and for those under 6 months as 80%.

Younger patients are more likely to have extensive disease and visceral involvement. Involvement of the liver, spleen, bone marrow, lungs or skin will lead to an unfavourable prognosis, while involvement of the skeleton or pituitary is not necessarily associated with a poor outcome[1,2,3]. Impaired organ function is the single most important prognostic factor; about 40% patients have organ dysfunction i.e. hematopoitic dysfunction (36%), hepatic dysfunction (10%) and pulmonary dysfunction (5%).

If a child survives for 3 years, the prognosis will be excellent.

Irradiation, glucocorticoids, antibiotics and a variety of cytotoxic agents and anti-metabolites have been used to treat Letterer-Siwe Disease.

Irradiation is effective in arresting the extenstion of the lesions and aids in their resolution, particularly in bone lesions.

In systemic disease irradiation can be used locally for specific problems such as chronically draining ears and proptosis and for bone lesions where a fracture might occur, particularly in the vertebral bodies[4,5,6,7,8].

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