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Letterer-Siwe's Disease

A Report of Four Cases

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Letterer-Siwe's disease, which is regarded as one of the histiocytosis syndromes, involves, in most cases, clinical manifestations such as hepatomegaly, splenomegaly, and pulmonary infiltration. In addition to these findings, seborrheic dermatitis, papular or petechial skin lesions, bone marrow deficiency may also be observed in patients with this disesase.[1] In the majority of cases recurrent infections may occur.

Of the histocytosis syndromes, Letterer-Siwe's disease is the one most commonly seen during the first few years of life. In cases without pulmonary involvement and thrombocytopenia, prognosis is better and life expectancy is somewhat longer. In 1967 such a patient was reported to have lived more than two years.[2] In fact, this case was indicated to be the one with the longest life span, being alive at the age of 16 during the study. The aim of this study is to present four malnourished cases of Letterer-Siwe's disease together with the clinical and pathological findings and a review of the literature related to this disease. In reviewing the Turkish medical literature, we found only a few reports on Letterer-Siwe's disease; this, in our opinion, does not mean the absence of such cases in this country. Rather, the majority of patients with Letterer-Siwe's disease are extremely malnourished cases which die during early infancy as a result of malnutrition coupled with severe infections.

Previous Investigations

Until today, there have been several reports about individual cases in the medical literature. Shafer[3] reported three cases of Letterer-Siwe's disease in 1959. The three cases presented by Drs. Say, Sezer and Köksal[4] in 1961, were the first ones reported in Turkey. Schoeck,

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Peterson and Good[5] published two cases observed in the same family in 1963 and pointed out the possibility of a familial occurrence. An interesting case was reported by Cohen, Mitchell and Alexander[6] in 1966. In 1967 Doede and Rappaport[7] presented 96 cases of Letterer-Siwe's disease which were collected from various sources in the literature.[1] Of these 96 cases, 70 were reported to be dead and 26 living. Of the 26 alive, 17 had survived 24 months or more, after the onset of the disease. Of the 70 dead, none survived 30 months, from the onset of the disease. Our present study is aimed at discussing four cases observed at Hacettepe University Hospital between 1959 and 1970.

The cases reported in this study include two girls, one of 21 and the other 11 months of age and two boys, one 6 months old and the other 12 months old. The four patients were admitted to our clinic following complaints of high fever, skin lesions, itching and recurrent infections.

Case Reports

Case 1. A. I., a 12 month old boy, was brought to the Hospital by his parents with the statement that the child had suffered from a skin rash and fever for about 4 months. According to the parents the child was completely normal until he was eight months old (Figure 1).

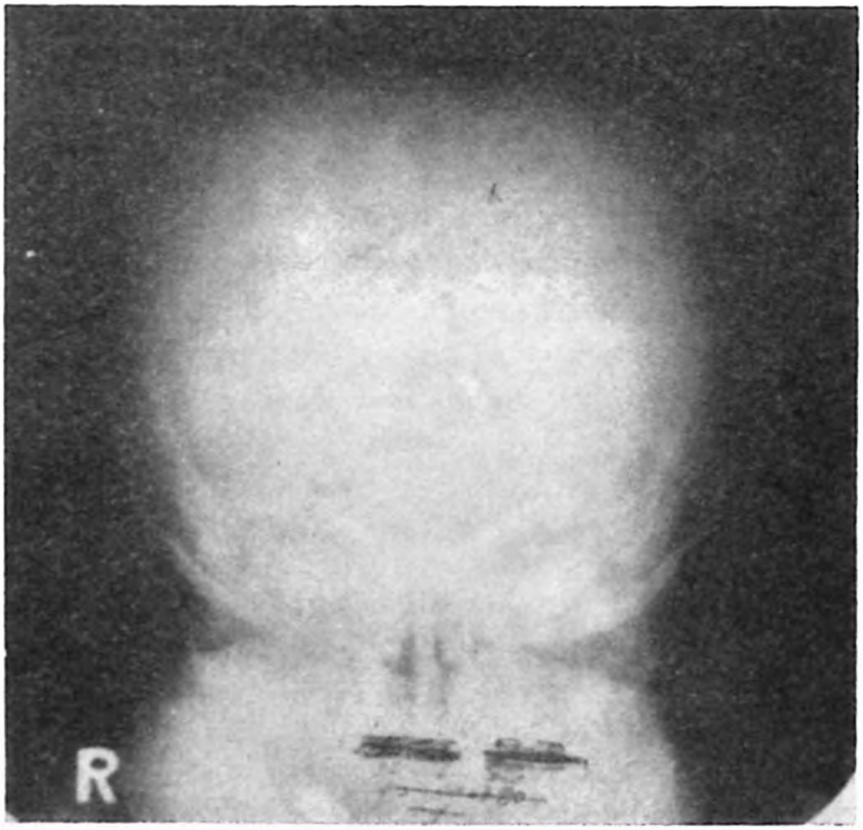

Figure 1

Physical Examination: The patient was found to be pale and irritated, malnourished. Wide-spread rash was observed on the abdomen and the back and a few rashes were spotted on the thorax. He was found to be suffering from suppurative otitis and gingivitis. The liver measured 4 cm. and the spleen 2 cm. below the costal margin. Lymph nodules of about 1 cm. in diameter were seen in the axillary region.

Laboratory Findings : Routine blood and urine tests were carried out. Hemoglobin was found to be 8.05 gr/100 cc. The differential indicated a left shift. Peripheral smear pointed to a hypochromic microcytic anemia. Urine test results were in normal ranges. The culture of the pus taken from the ear contained Staphylococcus albus.

Radiology: The skull graphy indicated a defect in size, in the parietal area about one and a half cm. in diameter. Bilateral infiltration was spotted in the lungs. The lymph biopsy taken from the axillary area showed histiocytic infiltration.

The patient was treated with antibiotics and deltacortryl was given in addition. Following treatment of seven days the child was taken out of the hospital by his parents despite the objection of the attending physician. They were supplied with a prescription containing the course of medicine decided previously, e.g. antibiotics and deltacortryl with the hope of having the child live a little longer.

Following correspondence with the parents we have learned that the child died 6 months after leaving the hospital. The parents stated that their son received deltacortryl until his death.

Case 2. G. N., a 21 month old girl, was admitted to our hospital with complaints of rash, itching and swelling of lymph nodules of the neck. The parents of the patient indicated that she was completely well five months prior to being brought for treatment, when the rash on the abdomen and thorax of the child had started developing.

Physical Examination: The infant was observed to be malnourished. Physical examination indicated disseminated petechial, papular and seborrheatic rash over the entire body. The patient's temperature was found to be around 38.8°C. The lymph nodules around the neck were swollen. A tumoral mass was located on the palate. Crepitant ralles were heard from both lungs. The liver was palpable 3 cm.

Laboratory Findings: Routine blood and urine tests indicated the hemoglobin rate to be 5 gr/100 cc., white blood cells around 5,600 and the differential as follows: Segmented cells 40 per cent, lymphocytes 58

per cent, stab cells 2 per cent. Platelets were found to be normal and reticulocytes in a range of 1.5 per cent.

Radiology: The X-rays of the skull and the extremities were normal. The lung X-rays showed bilateral nodular infiltration.

Diagnosis was made following consideration of the conditions of the lymph nodules and the results of the skin biopsy. Biopsy indicated a remarkable increase in the cellular infiltration. The patient was given corticosteroids, several blood transfusions and antibiotics. She was discharged following the request of her parents. The patient was followed up and the correspondence between the attending physician and her family informed us of the patient's death four weeks after leaving the hospital.

Case 3. G. S., an 11 month old girl was admitted to hospital with a high fever, severe coughing and rashes over the entire body. Her history also indicated a high fever, coughing and rashes over the entire body, and purulent discharge in both ears for a period of three months. Physical examination showed an unsatisfactory condition. The child suffered from malnutrition and from petechial, papular rashes on the scalp and the thorax. On the palate ulcerative papules were present. The liver was found palpable 3 cm. Axillary and inguinal lymph nodules could easily be felt (Figures 2, 3 and 4).

Laboratory Findings: Routine blood and urine tests indicated hemoglobin to be 9.20 gr/100, white blood cells 9,300, platelets 140,000 and urine within normal ranges. The throat culture showed Staphylococcus albus and Streptococcus hemolyticus.

Radiography: The lung X-ray indicated bilateral infiltration. The patient was prescribed a course of penicillin. Her general condition became poor, however, during the few days after the start of treatment and, despite all efforts by the hospital personnel, she died four days after admission into the hospital.

Skin biopsy: The biopsy taken from the skin definitely established the case to be one caused by Letterer-Siwe's disease. Since permission of the family could not be secured, autopsy was not carried out.

Case 4. B. A., a six month old boy, was admitted into hospital with high fever, skin rashes, diarrhea and purulent discharge from both ears. He showed an easily irritable nature and mild pallor. The awareness indicated a full-term baby who was fairly well developed until he was three months of age. The child developed a high fever and

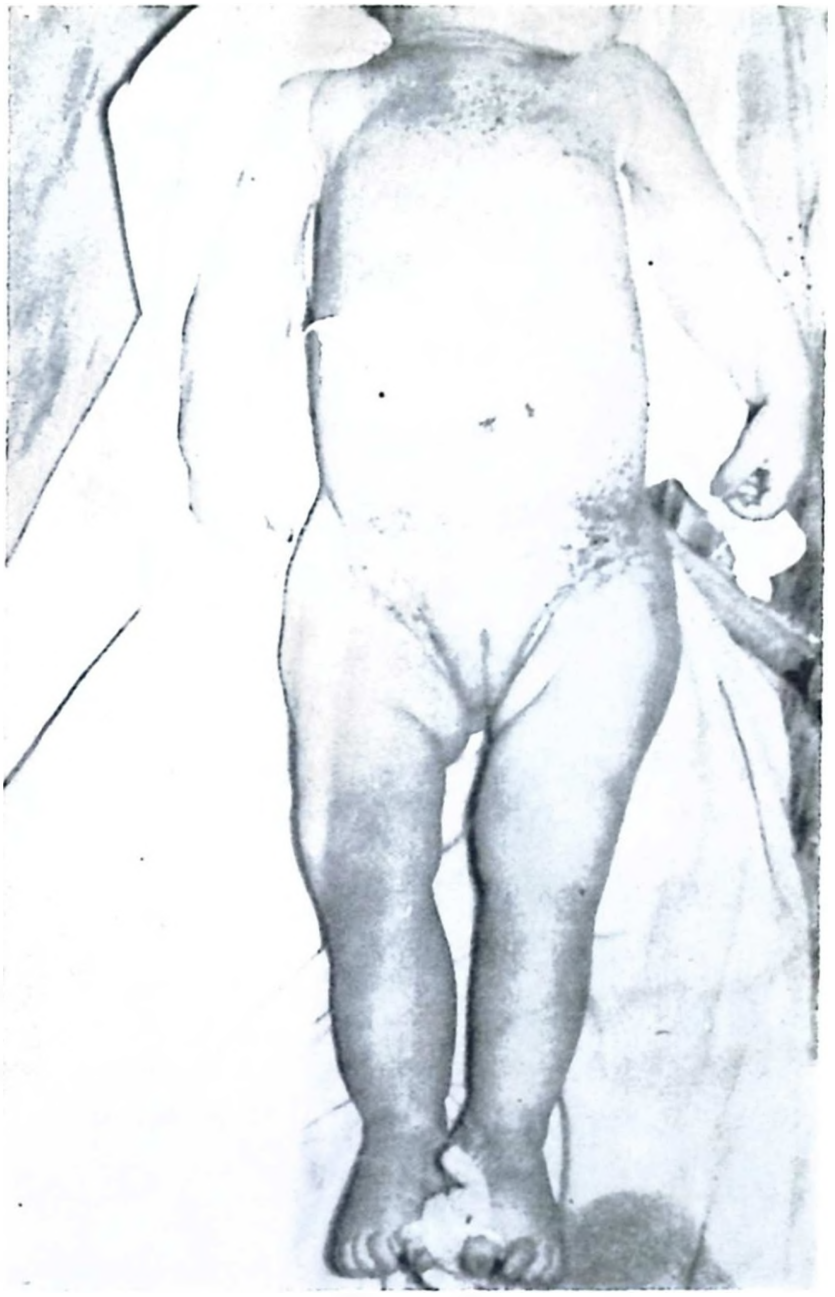

Figure 2

petechial skin lesions after this period. Two months prior to coming to hospital the rashes increased and the child lost his appetite. His abdomen became distended and the patient experience anorexia and felt irritiated. He became worse during the following weeks. Three days before being brought to our hospital he suffered from severe purulent discharge from both ears (Figures 5, 6, 7 and 8).

Physical Examination: The child looked somewhat underdeveloped for his age. He gave the impression of being severely ill and ran a very high fever. On the skin of the inguinal region, thorax and abdomen, papular, petechial and, in some areas crusted disseminated lesions were located. The patient showed a bilateral cervical lympha-

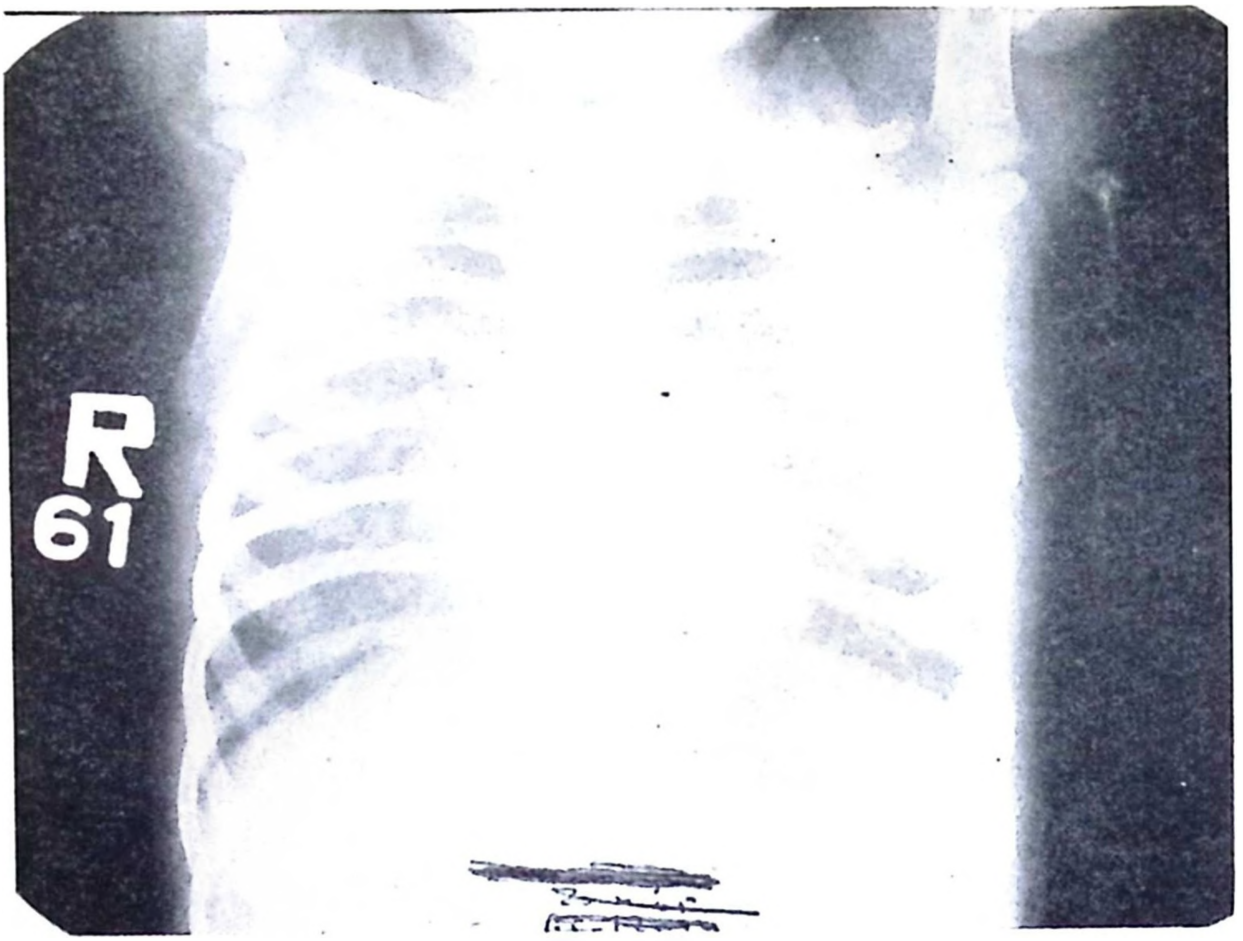

Figure 3

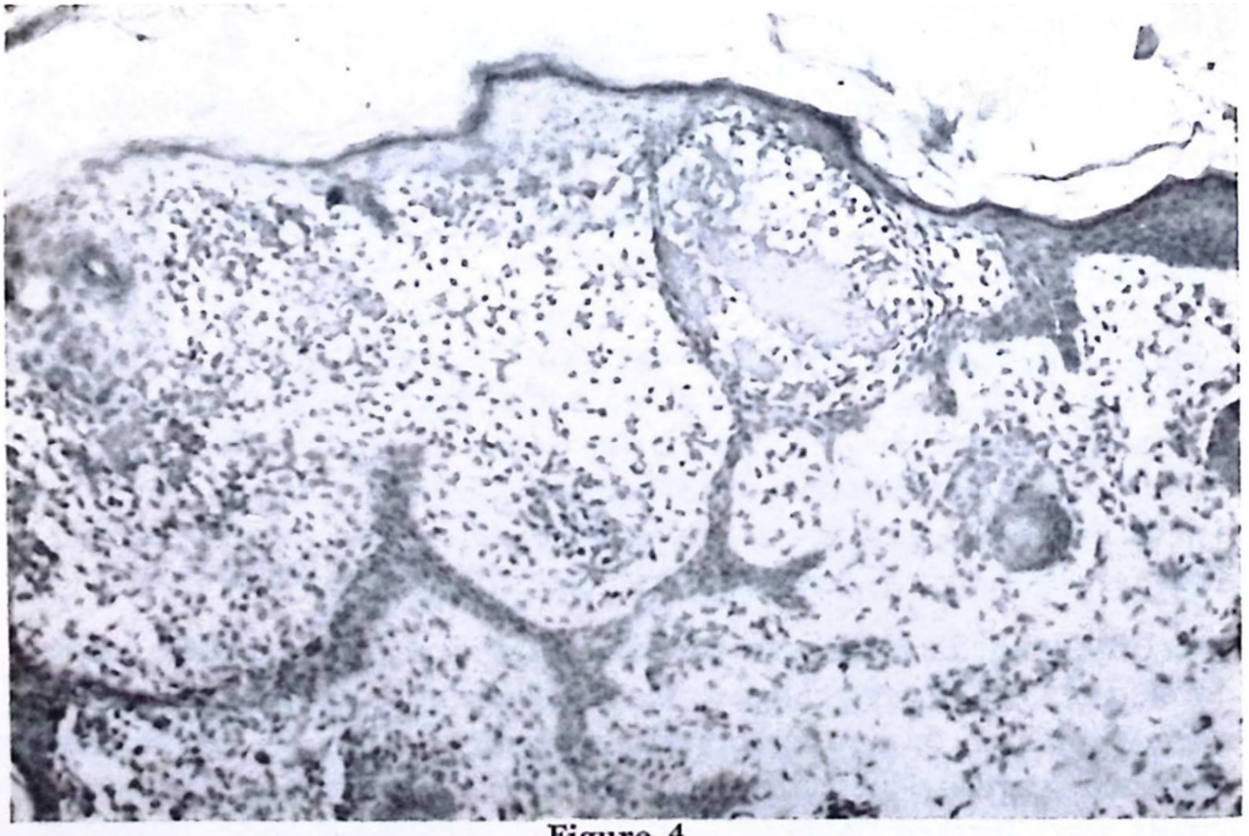

Figure 4

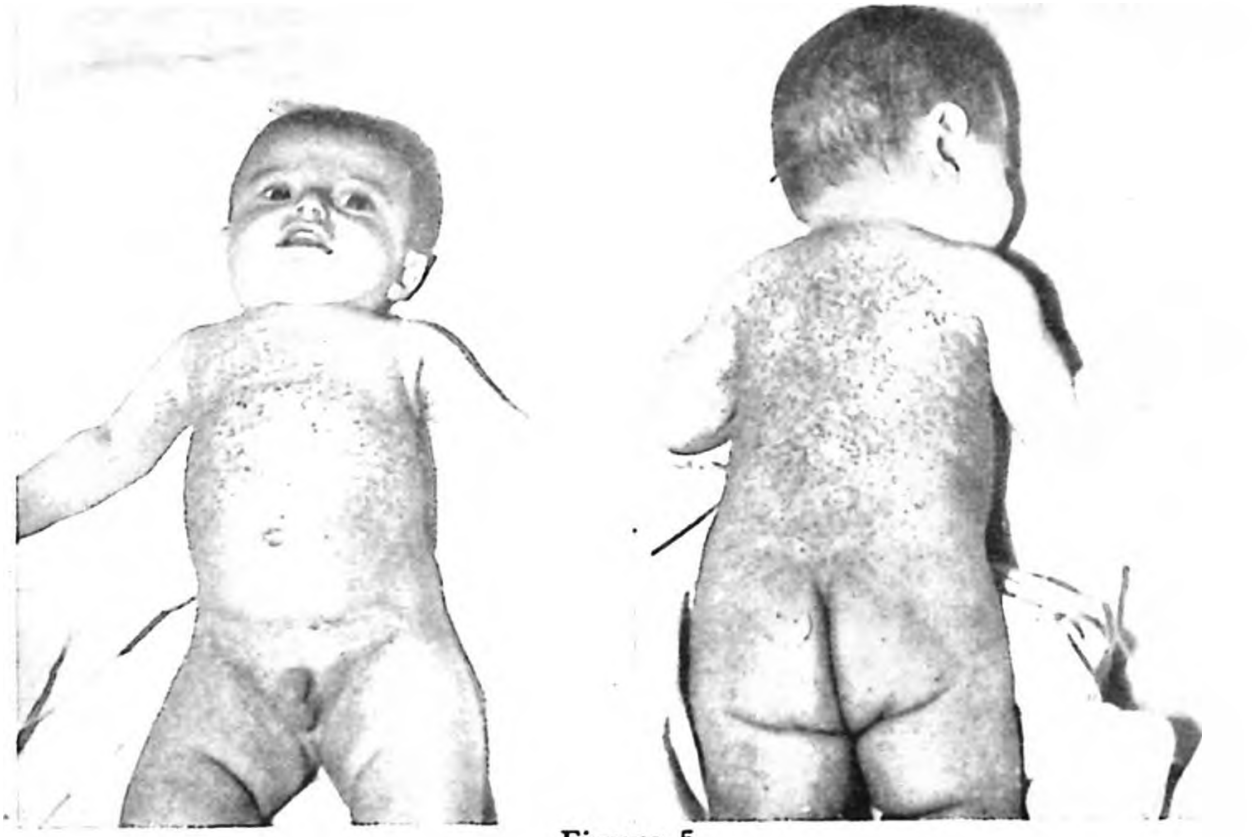

Figure 5

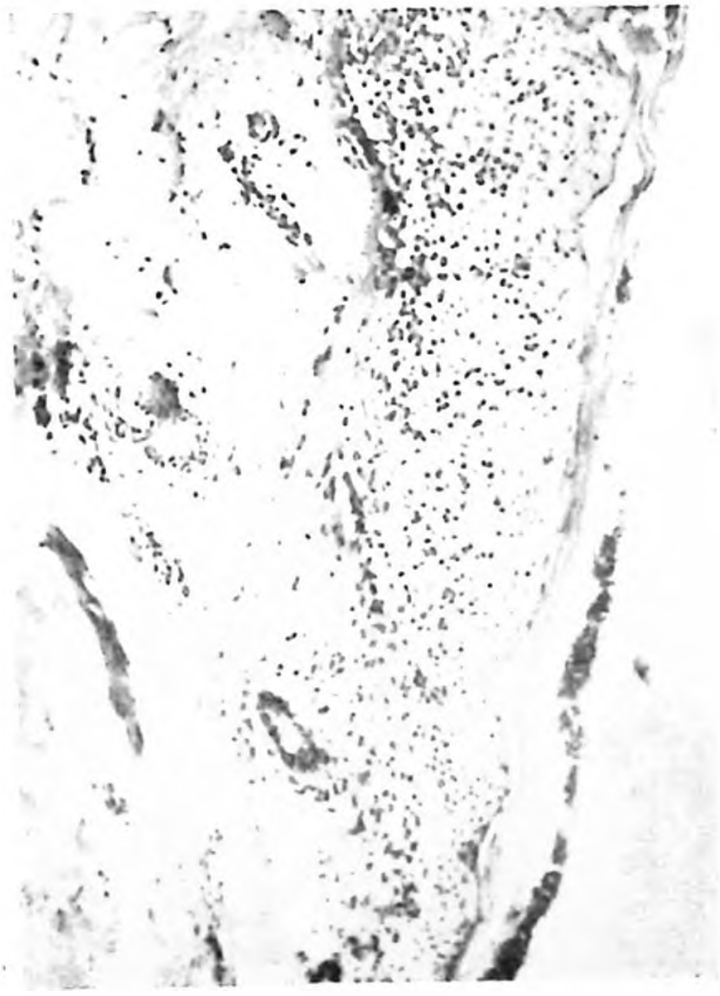

Figure 6

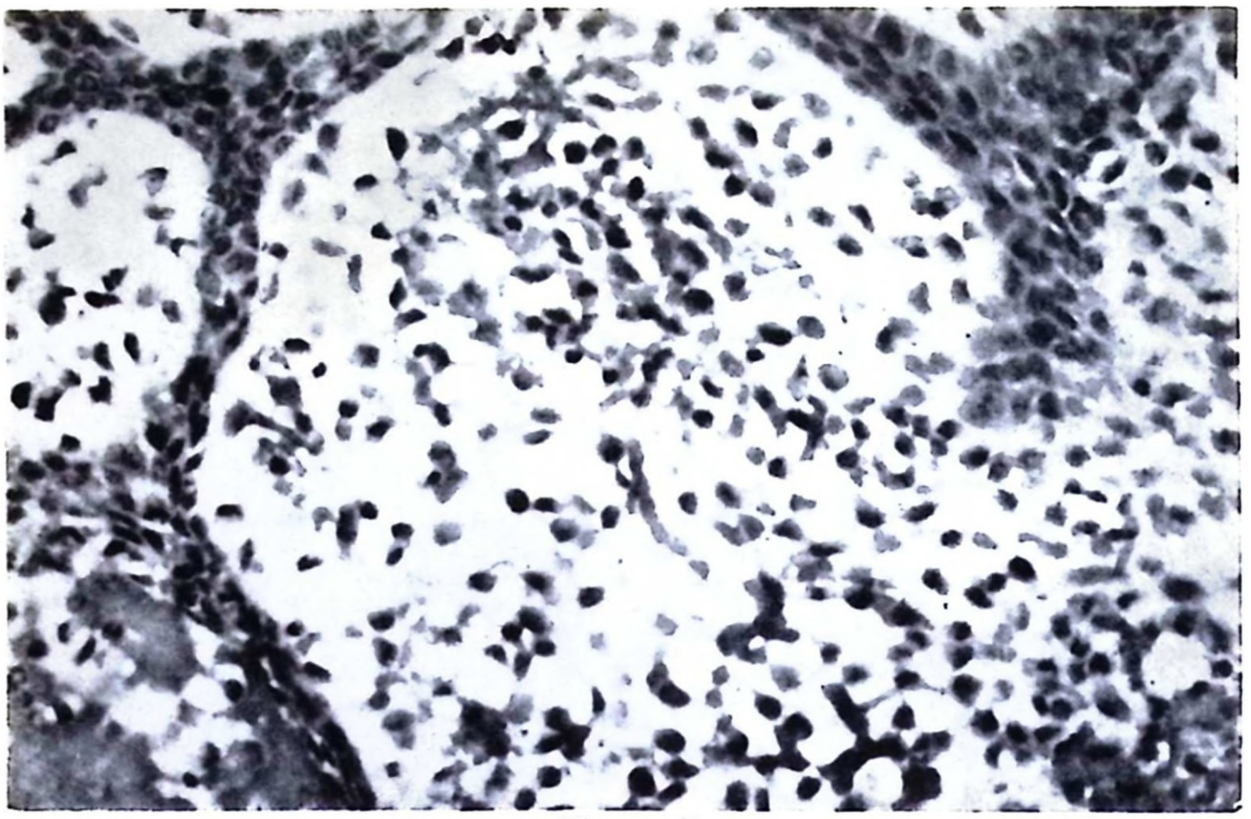

Figure 7

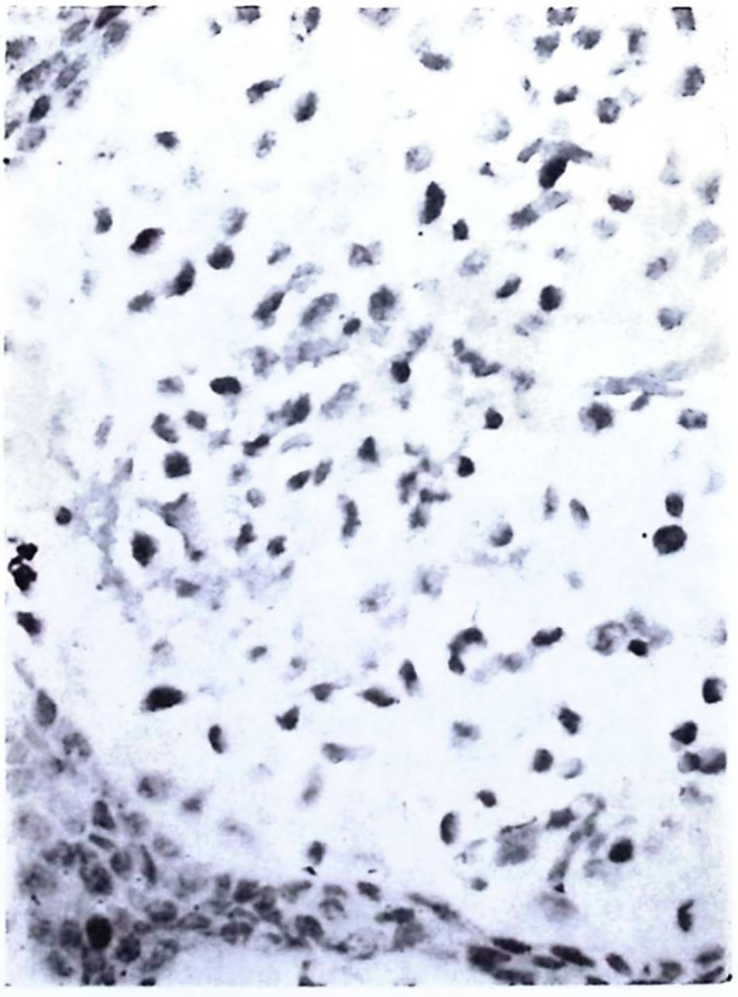

Figure 8

denopathy (2.5 cm. in diameter) one of which was inflammated. Purulent discharge from the ears seemed to be continuing. The tonsils were found to be hyperemic and an ulcerative lesion (0.5 - 3 cm. in diameter) was spotted on the palate. Rosary was positive, abdomen distended and the liver palpable 7 cm. below the right costal margin. The spleen was located 8 cm. below the left costal margin. The wrists of the child were observed to be extremely enlarged.

Laboratory Findings: At the time of admission, the hemoglobin was 6.4 gr/100 cc. The white blood cells were 12,500 per/mm. with a differential of 56 per cent segmented, 26 per cent lymphocytes, 2 per cent monoblasts, 8 per cent monocytes, 8.0 per cent band. Platelets were 160,000 per cubic mm., reticulocytes 8.2 per cent.

Bone marrow specimen was found hypercellular with erythroid series. Throat culture showed Staphylococcus aureus and E. coli. Ear culture indicated Staphylococus aureus.

Radiology: Rontgenograms of the lungs and the skeleton were normal. Skin biopsy showed abundant number of histiocytes, acute and chronic inflammatory cells and rare eosinophils and gave indications of Letterer-Siwe's disease. Subsequent laboratory testing pointed to a mild to severe anemia with a hemoglobin rate ranging from 6 to 4.7 gm. per 100 ml., leukopenia ranging from 4,800 to 4,000. A significant reduction in platelets to 42,000/cc. mm. was observed.

The patient was given multiple blood transfusions and was treated with antibiotics, Deltacortryl (2 mg./kg.) for 23 days and Vinblastine Sulfete (0.05 mg/kg.) for one week. Despite this therapy the child's general condition did not improve much and he died 26 days after admission.

Discussion

Histiocystosis syndromes are characterized by a wide variety of clinical manifestations in which histiocytic proliferation causes the development of granulomatous lesions.

These syndromes are not hereditary of familial and no consistent correlation between these syndromes and any specific organism has been noted.

Hepatomegaly, splenomegaly, generalized lymphadenopathy and high fever may occur in these syndromes and otitis media and other recurrent infections are not rare. Anemia is common and thrombocyto-

penia and leucocytosis may be seen. The bone marrow is usually normal until histiocytic proliferation becomes widespread.

The lesions are characterized by proliferated histiocytes. In the same lesions proliferative, destructive, xanthomatous and sclerosing manifestations may also occur. Most of the lesions are located in the liver, marrow, skin, lymph nodules, lungs and the meninges. The skin lesions are characteristically erythematous and papulous, causing ulcerated or scaly appearance. They give an impression somewhat similar to seborrhea (Table I).

TABLE I

CLINICAL MANIFESTATIONS OF OUR CASES WITH LETTERER-SIWE'S DISEASE

	Case 1	Case 2	Case 3	Case 4
Skin Rash	+	+	+	+
Fever	+	+	+	+
Hepatomegaly	+	+	+	+
Splenomegaly	+	+	-	+
Bone lesions	+	-	-	-
Pulmonary infiltrations	+	+	+	-
Anemia	+	+	+	+
Thrombocytopenia	+	-	+	+
Otitis media	+	-	+	+
Onset of disease/age of child (in months)	8/12	16/12	8/12	3/12

The most fatal prognosis occurs in infants showing major visceral involvement and the lesions are found to be disseminated in such patients. The ailment is highly progressive in younger patients and these children usually die of severe recurrent infections and bone marrow failure. The number of patients surviving this disease beyond 5 years is extremely rare, as indicated in the medical literature. Lakey[8] and Batson et al[9] accepted that a direct correlation exists between the age of onset and total duration of the disease. Prognosis was very poor in infants less than six months old. Young infants are susceptible to secondary infections whic accelerated the primary disease. The disease was considered to be fatal until the case which entered remission following treatment with streptomycin in 1951 was published by Aronson.[10] Beginning with this study, the cases which had a somewhat longer life span than excepted were reported. Holmland[2] followed one case for 15 years, Lightwood

and Tizard[11] for 6 years, Nezelof and Guibert[12] for 5 years and Langer and Leonhandi for 4 years pronty worked on case for a period of 3 months. Bass et a[13] followed a case for 42 months.

Beier et al[14] prescribed Vinblastine Sulfate in 3 cases. Lahey used Vinblastine Sulfate in 30 patients with histiocytosis and found improvement in 5 per cent of the cases.[8] Cohen et al reported a congenital type of Letterer-Siwe's Disease in a newborn following the autopsy.[6] Charles et al described a Letterer-Siwe's disease in a newborn who was treated with corticosteroids and vincristine sulfate. This case was reported to have been kept alive for more than two years.[7]

In a more recent study, Esterly[15] reported successful results with the employment of corticosteroids and antineoplastic agents, resulting in a nine-month remission.

In all of our four cases we located Staphylococcus infections and malnutrition in addition to other complications. The cases were observed to be vulnerable to recurrent infections due to a malnourished condition caused by inadequate protein, a characteristic of families with low income. One reason of the remission period being comparatively shorter could be these unfavourable conditions. We come to the conclusion that general supportive care is a must for keeping the patient alive for a somewhat longer period.

Summary

Four cases of Letterer-Siwe's diesase are presented and clinical and pathological results are discussed together with a brief review of the literature. The significance of the effects of malnutrition and secondary infections on the prognosis of this disease is emphasized.

Acknowledgement

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REFERENCES

1. Doede, K. G. and Rappaport, H.: Long-term Survival of Patients with Acute Differentiated Histiocytosis (Letterer-Siwe's disease), Cancer 20: 1782-1795, 1967.
2. Holmlund, D.: A case of nonlipoid granulomatosis (Letterer-Siwe's disease) observed for 15 years, Acta Peadiat. 51: 324-330, 1962.
3. Shafer, E. K.: Nonlipid Reticuloendotheliosis. Letterer-Siwe's Disease: A report of three cases, Am. J. Path. 25: 49-84, 1959.

4. Say, B., Köksal, M. and Sezer, V.: Acute non-lipid disseminated reticuloendotheliosis, Turkish J. Pediatrics 3: 163, 1961.
5. Schoeck, V. M., Peterson, R. D. A. and Good, R. A.: Familial occurrence of Letterer-Siwe's Disease, Pediatrics 32: 1055-1063, 1963.
6. Cohen, D. M., Mitchell, C. B. and Alexander, J. W.: Letterer-Siwe's Disease in a Newborn, Arch. Path. 81: 347-350, 1966.
7. Charles, G. H. and George, W. H.: Congenital Letterer-Siwe's Disease, Am. J. Dis. Child. 116: 1968.
8. Lahey, M. E.: Prognosis in Reticuloendotheliosis in Children, J. Pediat. 6: 664-667, 1962.
9. Batson, R. et al.: Acute Nonlipid Disseminated Reticuloendotheliosis, Am. J. Dis. Child. 90: 323-343, 1955.
10. Aronson, R. P.: Streptomycin in Letterer-Siwe's disease, Lancet 1: 889-890, 1951.
11. Lightwood, R. E. and Tizard, J. P. M.: Recovery from acute infantile nonlipoid reticuloendotheliosis (Letterer-Siwe's Disease), Acta Paediat. 43: 453-468, 1954.
12. Nezelof, C. and Guibert, C.: L'Histiocytose X, nosologie et prognostic-Etude fondee sur l'evolution controllee de 52 observations personnelles, Arch. Franc. Pediat. 20: 1063-1103, 1963.
13. Bass, M. H., Sapin, S. O. and Hodes, H. L.: Use of Cortisone and Corticotrophin (ACTH) in treatment of reticuloendotheliosis in children, Am. J. Dis. Child. 85: 393-403, 1953.
14. Beier, F. R., Thather, L. G. and Lahey, M. E.: Treatment of Reticuloendotheliosis with Vinblastine Sulfate, J. Pediat. 63: 1087-1092, 1963.
15. Esterly, N. B., Herbert, M. and Swich, M. D.: Cutaneous Letterer-Siwe's disease, Am. J. Dis. Child. 117: 2, 1969.