ACUTE NON-LIPID DISSEMINATED RETICULOENDOTHELIOSIS

Three Cases of Letterer-Siwe's Disease*

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Customarily, Hand-Schüller-Christian's disease, eosinophilic granuloma and acute non-lipid disseminated reticuloendotheliosis (Letterer-Siwe's disease) are grouped under the term non-lipid reticuloendotheliosis. Among these, Letterer-Siwe's disease is the rarest.

In 1955, Batson and his associates[1] reviewed medical literature and found forty-one cases of acute non-lipid disseminated reticuloendotheliosis seen up to that time. It is possible that there were many cases which were not published or were overlooked and that forty-one cases is too low a figure. However, there is no doubt that this disease is not common. In Turkish medical literature none appears, therefore we think it worthwhile to publish the cases of Letterer-Siwe's disease which we observed in our clinic last year.

Case 1: B.Y., an 18 month old male, was admitted to the hospital with a rash, swelling on the neck and axillary area, fever, cough and dyspnea. He died ten days later. According to the parents the child had had the rash intermittently for a year, the fever had been evident for five months and the cough for two months prior to admission.

Physical Examination: On admission, the temperature was found to be 38.1 C., the tonsils were hyperemic and there was a widespread hemorrhagic maculopapular rash over the body. On the neck, axillary and inguinal areas bilaterally, soft matted lymph nodules, many of them ulcerated, were present. These nodules ranged from the size of walnuts to that of oranges,(fig. 1). Tubular breathing was heard from the left lung area. Crepitant rales could be heard from both lungs. The liver was palpable 3 cm. below the right costal margin. The spleen initially was near the costal margin but later grew from 1 to 2 cm.

Laboratory: The urine was normal. Blood examinations revealed a hemoglobin level of 5.62 grams per 100 cc., red blood cells 2.28 million and white blood cells 11,300 per cubic millimeter, a sedimentation rate of 30. The differential showed 79

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per cent lymphocytes, 21 per cent polymorphonuclear leucocytes, and a normal platelet count. A skin test for tuberculosis with purified protein derivative, a serological test for syphilis, and blood cultures proved negative. Throat smears showed the presence of staphylococcus and ulcer smears showed staphylococcus and streptococcus. Bleeding time was one minute and coagulation time was six minutes. The tnorniquet test was negative and bone marrow normal.

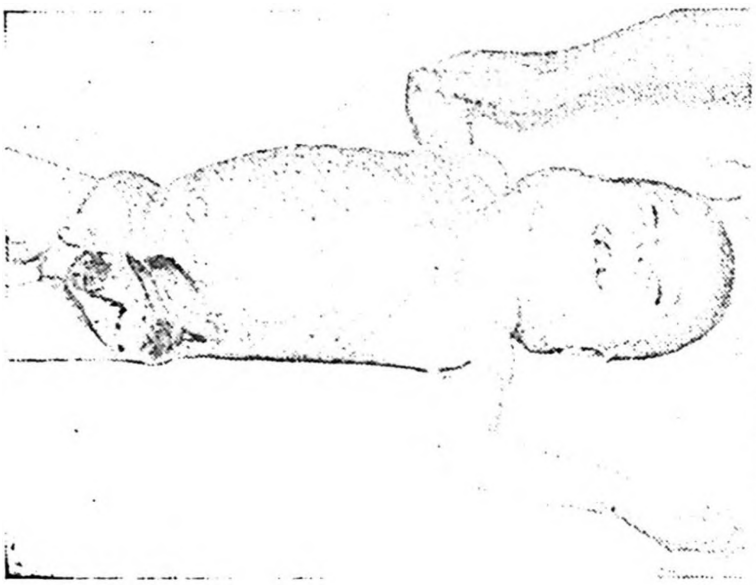

Figure 1.

Figure 2.

Radiology: The roentgen ray examination of the lungs showed a bilateral interstitial infiltration, (fig.2). The skull and extremity films showed normal development.

A diagnosis was made of Letterer-Siwe's disease, and the treatment consisted of antibiotics, several blood transfusions and steroids. The patient died ten days after admission.

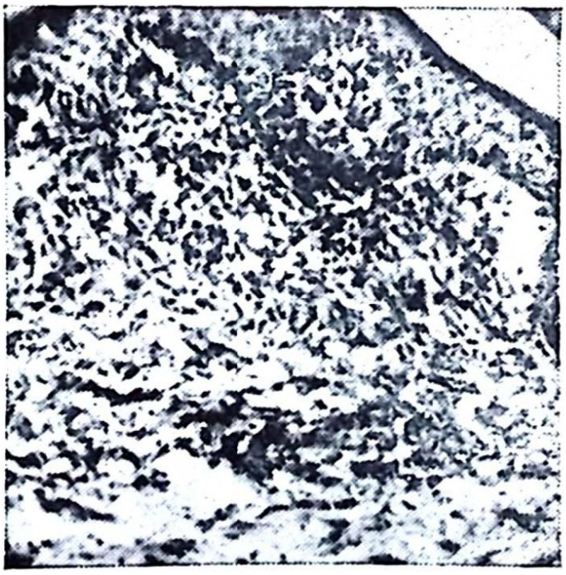

Figure 3.

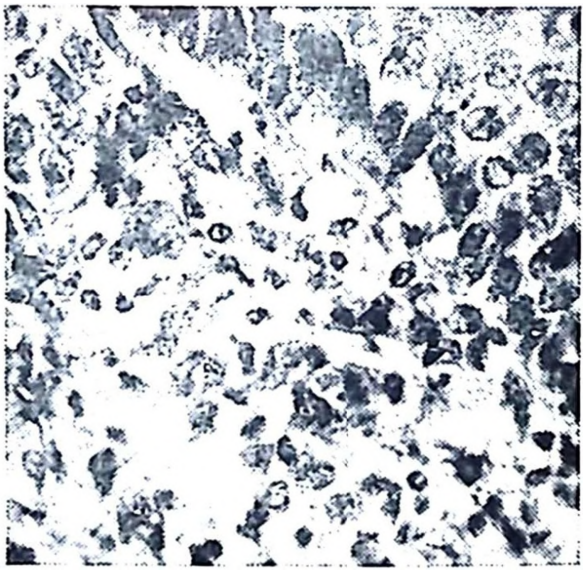

Figure 4.

Pathology: Macroscopic examination revealed inguinal, axillary, and cervical lymphadenopathy, and multiple ulcers on the skin of those areas. There were petech-

ial and ecchymotic spots on the abdomen and the back. Between the right upper lung lobe and the chest wall were multiple adhesions. Lungs were yellow and grey in color, granular in sections and with a mucopurulent exudate in the trachea and bronchi. The myocardium was anemic and the right ventricle was dilated. The liver had widespread fatty infiltration and the spleen was hyperemic. There were no significant findings in other organs.

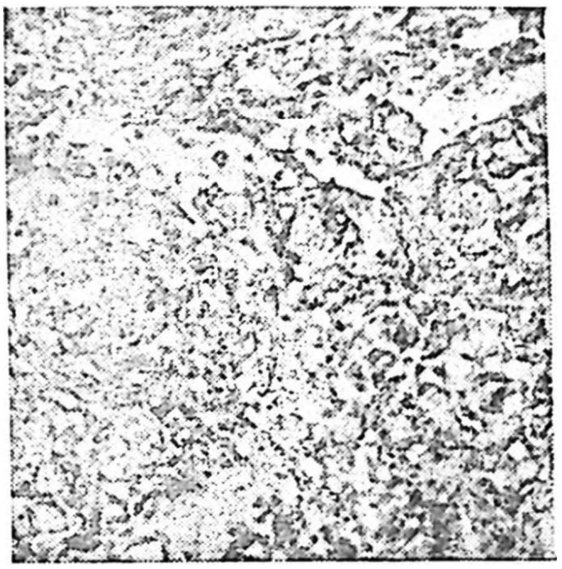

Figure 5.

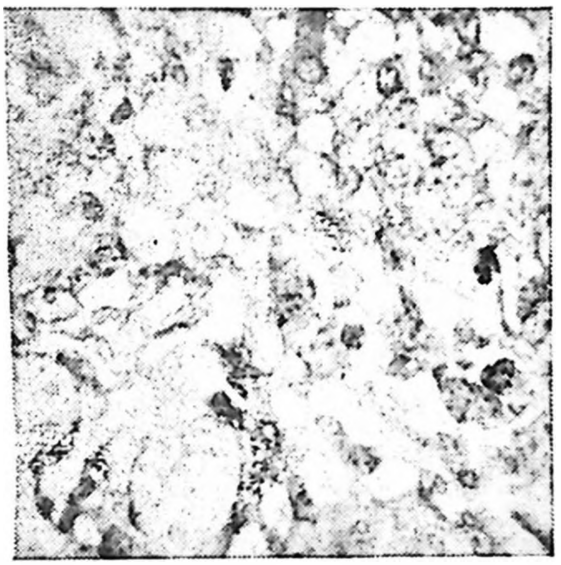

Figure 6.

Histologic examination showed marked atrophy of the epidermis, and there were nodules in the dermis formed by polygonal, round and fusiform cells (figs. 3, 4). There were architectural changes in the lymph nodes. The reticulum was made of cells of various sizes and shapes, including cells with small nuclei resembling histiocytes. In some areas, the picture resembled neoplasia. On the other hand

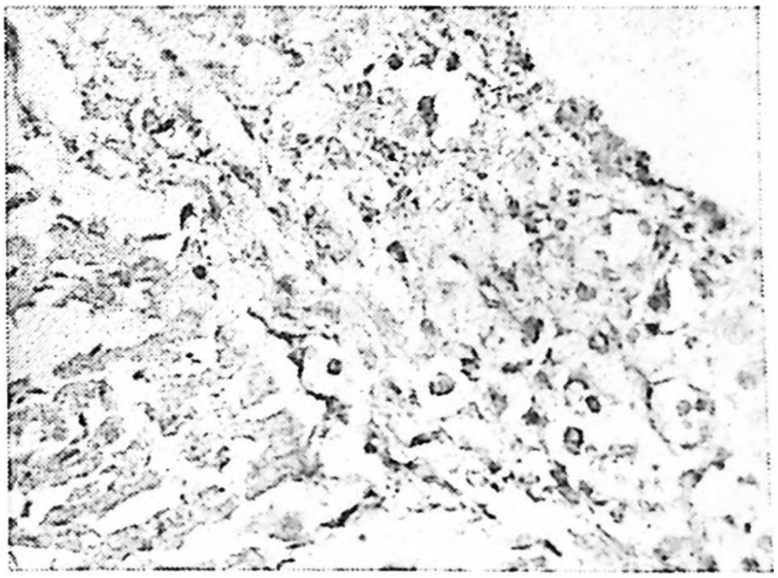

Figure 7.

there were areas where histiocytes predominated, somewhat like epithelioid cells. Intracellular and free brown pigment was rather abundant, and an interesting discovery was the presence of multinucleated giant cells like Langhans'. The lungs

were atelectatic and hyperemic and showed significant perivascular and peribronchial nodules formed by reticulum cells, (figs. 5, 6). In addition to these findings, which are characteristic of this disease, angiomatosis was present in several areas of the lungs. The liver disclosed no specific lesions. Diffused fatty infiltration was present and in the portal spaces there was an infiltration of round cells. The spleen was excessively hyperemic and reticuloendotheliol hyperplasia was present. As in the lymph nodes, the spleen showed an abundance of pigment. The only significant findings in the heart were groups of histiocytes in the subepicardial region, (fig. 7). The histologic changes in the other organs were non-specific.

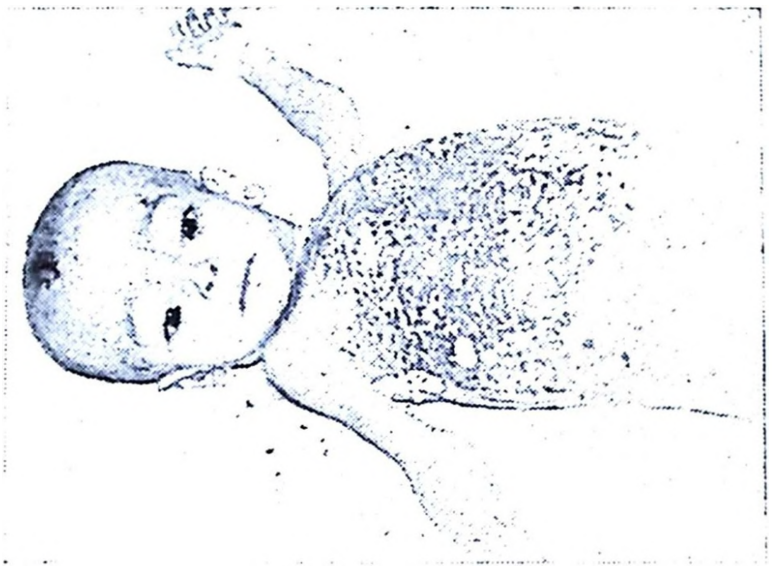

Figure 8.

Case 2 : N. S., a two and a half year old girl, was admitted to this hospital with an itching rash and swelling of the neck and lymph nodes. She died 8 days later. According to her parents, the rash had appeared over her entire body about three months before admission. She had been given antibiotics and vitamins by her physician and had been kept for twelve days in another hospital where she was given three blood transfusions. She was sent to our hospital for diagnosis and treatment.

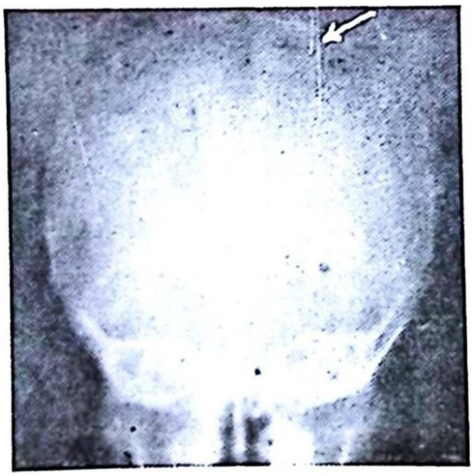

Figure 9.

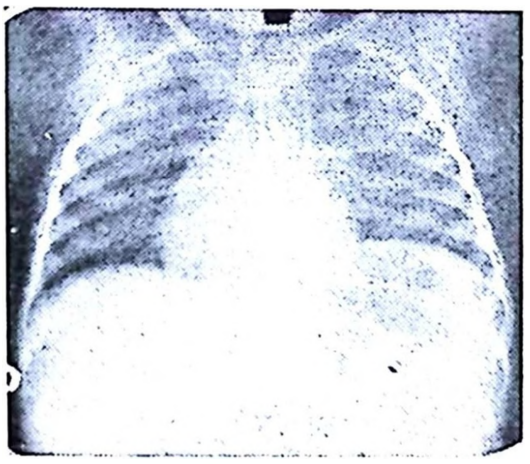

Figure 10.

Physical Examination: Examination revealed a pale malnourished infant. There were petechial and seborrheic lesions over the entire body, including the scalp, (fig.8).

Bleeding ensued when the crusts were removed. There were walnut sized nodules on the neck and hazel nut sized nodules in the axillary and inguinal areas. Both tympanic membranes were hyperemic. Crepitant rales were heard over both lung fields. The liver was palpable 4 cm. and the spleen was palpable 3.5 cm. below the costal margin. Both extremities showed pitting edema.

Laboratory: Laboratory tests showed the urine to be normal. Blood examination revealed hemoglobin 5.55 Gm. per 100 cc., red blood cells 1,900,000 and white blood cells, 5,600. The differential was as follows: stab cells 5 per cent; lymphocytes, 63 per cent and polys 32 per cent. Poikilocytosis, anisocytosis and polychromasia were present. Reticulocytes were 2 per cent. Platelets were normal. Non-protein nitrogen was 65 mg. per cent, total protein 3.4 Gm. per cent; albumin, 2.3 per cent; globulin 1.6 Gm. per cent; phosphorus, 4.5 mg. per cent, alcalen phosphates 26.5 B. U.; cholesterol 200 mg.; thymol 4.1 U; bilirubin 3.1 mg. (2mg. direct, 1.1 mg. indirect). The only significant finding in the bone marrow examination was a marked erythroid normoblastic hyperplasia.

Radiology: The skull films showed an oval defect in the parietal area, located 1.5 cm. left of the sagittal suture. It was the size of a bean with clear cut edges, and showed no sclerotic changes, (fig. 9). In the lungs, bilateral interstitial infiltration from apex to base was seen, (fig. 10).

The patient was given 50 mg. /Kg. Aureomycin, 20 mg. deltacortril daily and several blood transfusions. She died 8 days after admission.

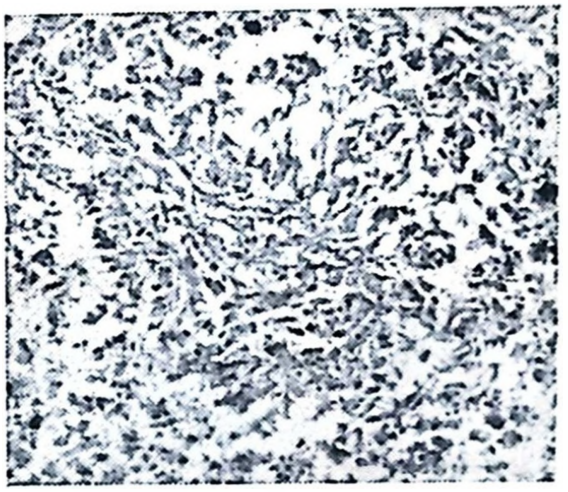

Figure 11.

Pathology: Macroscopic examination revealed petechiae and a seborrheic rash over the entire body, with the abdomen and back particularly affected. The gluteal and interscapular areas were ulcerated. Sections of the cervical, axillary and inguinal glands were a dark red color. The lungs revealed evidence of hypostasis. The liver was enlarged (500 Gm.) and was icteric and cirrhotic. A large white nodule about 1 cm. in diameter lay close to the hilar area. The spleen was enlarged (220 Gm.) and was excessively hyperemic, with a mottled appearence and brittle consistency. The peritracheal, periaortic and mesenteriac lymph nodes were enlarged and resembled the peripheral nodules. On the skull a soft yellow defect, 1 cm. in diameter, was discovered inside the left parietal bone near the sagittal suture. Subarachnoidal bleeding had occured on the right hemisphere covering the frontal and parietal lobes.

No significant observations were made in the other organs.

Histology: Beneath the epidermis, which showed signs of atrophy, papillae were found, and in the dermis, groups of cells resembling histiocytes were seen. The lymph nodes showed a decrease of the lymphatic follicles, but those follicles remaining were enlarged by reticulum cell hyperplasia. Some of these large follicles had an

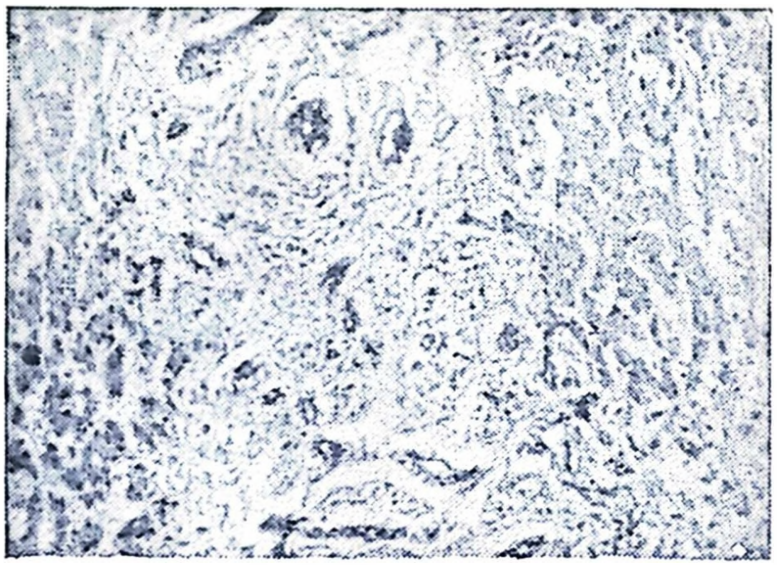

Figure 12.

epithelioid appearance and had formed a radial configuration so as to produce a pseudo-rosette formation. Other lymph nodes had an excessive reticuloendothelial proliferation. Besides the phagocytic cells which had eccentric nuclei there were other multinuclear cells, (fig. 11).The yellow-brown pigment in the phagocytic cells gave a positive reaction to Berlin blue, indicating the presence of hemosiderin. The reticulum group was impregnated with Laidlow silver and separated from the cells.

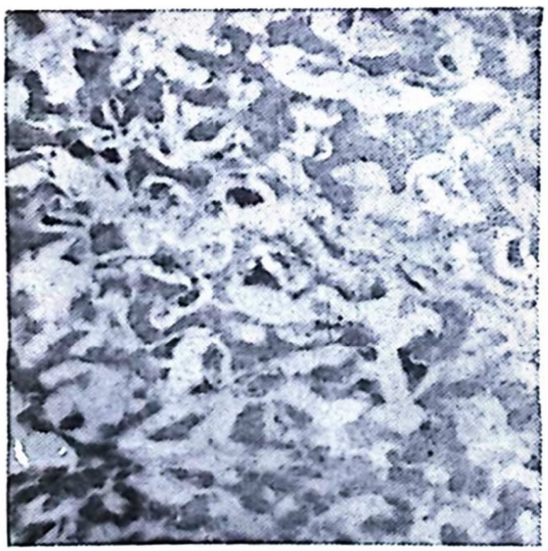

Figure 13.

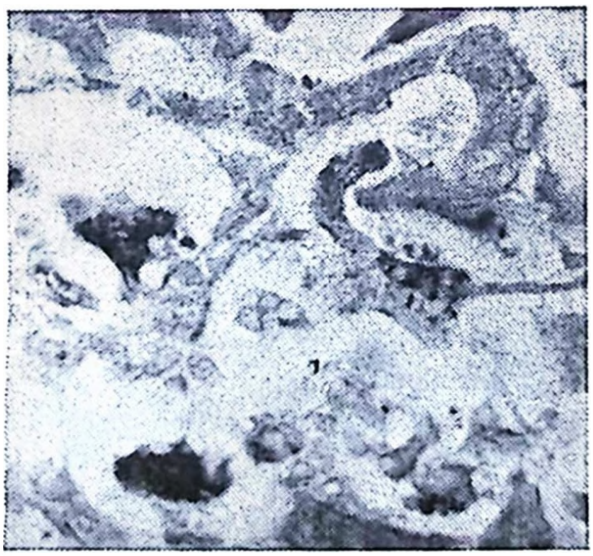

Figure 14.

The lungs were hyperemic and showed bronchopneumonial lesions. Subpleural, perivascular and peribronchial hystiocytic infiltration was also found. It is believed that this is one manifestation of this systemic disease.

The portal spaces in the liver were significantly enlarged and filled with a tissue of fusiform, triangular, oval and polygonal cells. There were also sections of bile canaliculi observed in the tissue, (fig. 12). There were areas in the portal spaces made up of reticulum cells. This condition in the portal spaces, that is, the proliferation of mesenchymal cells and the absence of inflammation, would not be consistent with a simple liver cirrhosis. The appearance was that of reticuloendotheliosis. Supporting this was the presence of nodules having the same histologic structure as those near the hilar area. The sinusoids had thickened and there was phagocytic activity with proliferation in the Kuppfer cells. The pigment, seen as rough granules in the cytoplasm of some of these cells, gave a positive hemosiderin reaction with Prussian blue, (figs. 13, 14). There were, however, some pigment granules which gave a negative reaction; these were believed to be bile pigments. Histologic changes in the spleen resembled those of lymph nodes plus necrotic areas (fig. 15).

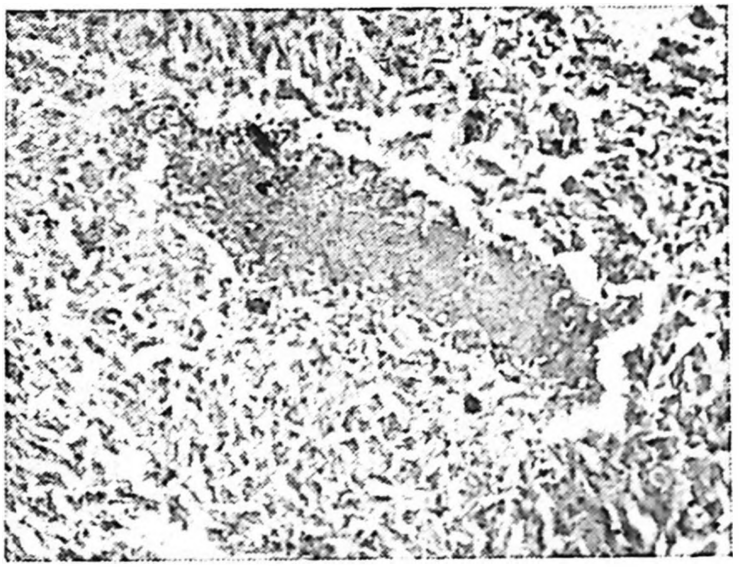

Figure 15.

Reticuloendothelial elements were rather immature, and phagocytic activity was less in the spleen. The soft tissue over the bony defect in the parietal area showed an abundance of hystiocytes as well as eosinophilic leucocytes; for this reason it was thought to be a lesion similar to eosinophilic granuloma. The brain bled in the subarachnoidal spaces, and there was petechial bleeding in the cortex. There were no significant findings in the other organs.

Case 3: M. A., a two and a half year old boy, was admitted to the hospital because of weakness, lack of appetite and swelling of the abdomen.

Physical Examination: On examination the child was found to have a temperature of 38 C., pulse 160, weight 8,300 Gm., length 80 cm. He was listless and there was evidence of micro-adenopathy. The lungs sounded normal and the liver was hard and palpable 7 cm. below the costal margin. The spleen was palpable 2 cm. below the costal margin. There was no mass palpable in the abdomen.

Laboratory: The urine, blood tests and liver function tests all were normal. The differential showed a left shift. PPD, Casoni and Weinberg tests were negative. Cultures and smears from gastric washings were negative for acid-fast organisms. The bone marrow was normal.

Radiology: The roentgenogram of the lungs revealed bilateral infiltration, especially in the right lung, which had interstitial characteristics (fig. 16). A flat plate of the abdomen showed a stone in the right kidney with no other abnormality. The skull and long bones were normal.

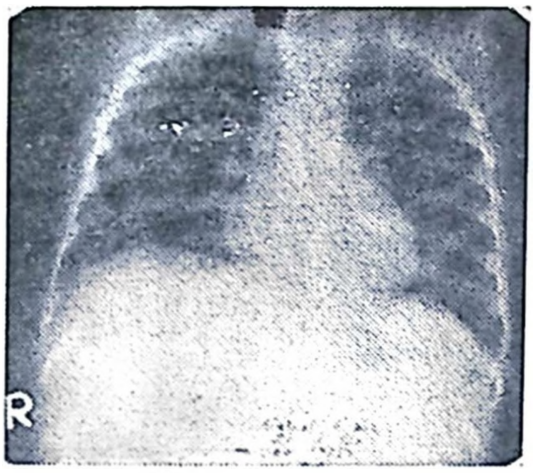

Figure 16.

Pathology: While the biopsy of the liver showed a cirrhotic condition, there was an absence of round cell infiltration and bile canaliculi proliferation in the portal spaces. This condition led to the belief that this was a systemic mesenchymal tissue proliferation rather than an inflammatory reaction. There was some Kuppfer cell proliferation in these areas. Indications pointed to reticuloendotheliosis (Letterer-Siwe's disease).

Eight days after admission, the patient's temperature rose and his general appearence deteriorated. The lips were cyanosed and his liver grew to the iliac crest.

On March 7, 1960, eleven days after admission, a maculopapular and hemorrhagic rash appeared on the abdomen and quickly spread over the entire body, (fig. 17).

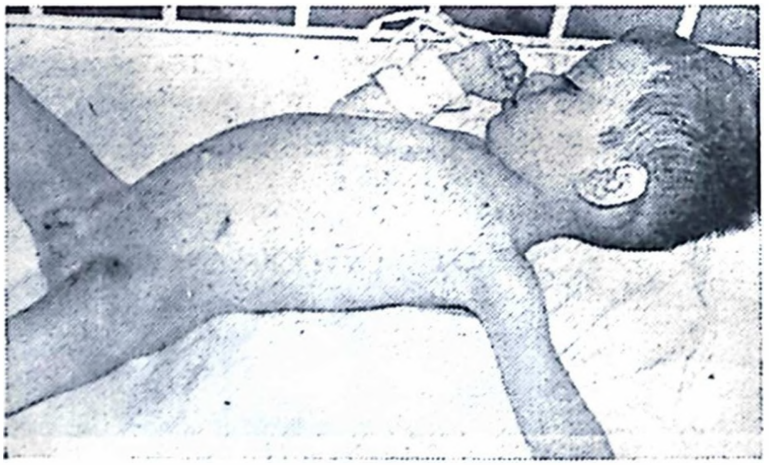

Figure 17.

Antibiotics were given to the patient. His family, however, insisted on removing him from the hospital. Prescriptions for deltacortril and antibiotics were given to the parents and the patient was discharged.

In order to compare the symptoms and development of the disease in our three patients, we have made the following table:

TABLE 1

SIGNIFICANT FINDINGS IN THREE CASES OF LETTERER-SIWE'S DISEASE

SYMPTOMS AND CONDITIONS	CASE 1	CASE 2	CASE 3
Sex	Male	Female	Male
Age at first appearance of disease	6 mo.	27 mo.	29 mo.
Duration of illness	1 year	3 months	1 month
High fever	+	+	+
Rash	+	+	+
Bone lesions	—	+	—
Pulmonary infiltration	+	+	+
Lymphadenopathy	+	+	+
Hepatomegaly	+	+	+
Splenomegaly	+	+	+
Hemoglobin, gm. %	5.62	5.55	12.80
Erythrocytes	2,280,000	1,900,000	4,000,000
Leucocytes	11,300	5,600	13,000
Hypoproteinemia	—	+	—
Otitis media	—	+	—

Discussion

Letterer-Siwe's disease, which is acute non-lipid disseminated reticuloendotheliosis, has the following symptoms: hepatosplenomegaly, anemia, bone and skin lesions and recurrent secondary infection, (table 2).

In 1831, Goldzieher and Hornick[2] defined this disease as reticulosis after studying twenty-two cases in the medical literature. Siwe,[3] in 1933 examined all pathological observations on eight similar cases and proved that the disease was neither hereditary nor familial in origin and that it involved a decrease in non-lipid macrophagocytes.

Galeotti and his associates,[4] in 1937, claimed that the Hand-Schüller-Christian syndrome and Letterer-Siwe's disease are variations of the same pathologic process. Wallgren,[5] who reviewed 23 cases in

the literature, thought the same. In his opinion, the absence of foam cells is due to the time factor, since foam cells do not develop until at least the third month after the onset. For this reason the absence of foam cells in Letterer-Siwe's disease could have little significance since the duration is usually too short for lipoids to collect in any quantity.

TABLE 2

ACUTE RETICULOENDOTHELIOSIS	HAND-SCHÜLLER-CHRISTIAN	EOSINOPHILIC GRANULOMA
0—1 $\frac{1}{2}$ years	2—6 years	over 6 years
	transition ←→	transition ←→
Histiocytes	Foam cells	
Rash	Bone lesions	
Bleeding	Exophthalmia	Eosinophilia
Anemia	Incipient diabetes	Solitary bone lesions
Hepatosplenomegaly		
Secondary infection		

However, there are authorities who do not agree. Siwe himself believes that Letterer-Siwe's disease and Hand-Schüller-Christian's disease are completely different. According to him, the presence of the histiocytic development in Letterer-Siwe's, with fibroblastic granulation and lipoids is characteristic of a chronic process. He also claims that eosinophilic granuloma is a totally different disease and suspects the presence of contagious forms among these three diseases.

However, in a typical eosinophilic granuloma case (typical as to bone lesions and histology), as the disease progressed the visceral symptoms of Letterer-Siwe's appeared.[6] In another case studied, all the symptoms of reticuloendothelial hyperplasia were present at the onset of illness but later examinations revealed bone defects.[7]

In another typical eosinophilic granuloma case, the disease progressed toward the Hand-Schüller-Christian syndrome.[8] Lipid cells have been found even in some cases diagnosed as Letterer-Siwe's disease, e.g. Steele[9] reports lipid cells in the lungs and thymus instead of the non-lipid macrophagocytes present in the o.her tissues. The opinion of some of those doing research in this field is that the Hand-Schüller-Christian disease frequently progresses rapidly and takes on the characteristics of Letterer-Siwe's disease, and that, in some typical eosinophilic granuloma patients, the eosinophilia are

present not only in the bone lesions but also in the lymph nodes.[10] They cite numerous cases to support this opinion. The etiology is not confirmed at the present time.

The course of Letterer-Siwe's disease can resemble an infection. In some patients, Salmonella coliform organisms and Brucella bacilli were found, as well as the growth of acidoresistant micro-organisms. Whether any of these is an etiological agent is not yet known.

Clinically, it is said, the younger the patient the shorter the course of the disease. In our own cases, the opposite has been observed. A two and a half year old child was admitted when the disease had reached the acute stage; we do not know when it began, but a study of the bone lesions showed it had been a chronic ailment for some time. Yet in case 3, a slightly older child, the disease progressed with great rapidity, (table 1).

As is shown in table 2, secondary infections occur more often in the infant age group, and it is possible that for this reason the real disease is apt to be overlooked. For example, more than half of the patients examined showed otitis media. In other papers published on this subject, patients were found to have pharyngitis, purulent rhinitis, gastroenteritis, impetigo, miliary abscesses, meningitis, pneumonia and moniliasis. All of these patients were treated as though the infections were primary until a diagnosis of Letterer-Siwe's was made. In these patients, the level of gamma globulin was normal, giving rise to the question of why they were not better able to resist disease. In older children, secondary infections appear less often. Every patient showed pathological pulmonary infiltration under roentgen rays.

The maculopapular rash may not be present. In the cases reported in the literature, in all patients the rash appeared first on the skin around the scalp. A minute examination of the rash showed that these lesions protruded above the surface of the skin, were yellow-grey and seborrheic. In one case, it was reported, the rash was present at birth. Approximately half of all patients reported, in the literature studied, had bleeding through these skin lesions, and in some places through the skin itself. Whether hemorrhagic or not, these skin lesions are so characteristic of Letterer-Siwe's disease that the diagnosis may be made by their appearance alone. As seen in our photographs, there was intradermal hemorrhage in our three patients.

It has been believed that the older the patient the more general is the adenopathy. We found in our patients that the opposite was true. Also we found that hepatosplenomegaly was present in our very young patients. As in our case 2, the bone lesions are found in late

infancy. When a series of consecutive roentgenograms was taken of the bone lesions, it was apparent that, as they healed, new osteotic lesions developed.

All the hematological findings were due either to the reticuloendothelial proliferation of the bone marrow or to the hypoplasia thereof. Observations on several cases, however, led us to believe that there was a hemolytic process. Blood protein was less than normal.

It is important, when examining this rash for diagnostic purposes, that eczema, seborrhea, exfoliative dermatitis and even meningococcemia be considered. When hepatosplenomegaly is encountered, care must also be taken in diagnosis not to overlook leukemia, miliary tuberculosis, Banti's syndrome, Cooley's anemia, Gaucher's disease, histoplasmosis and parasitic infestations. On histopathologic examination, Letterer-Siwe's disease is clearly identified. Each small lesion in disseminated reticuloendotheliosis is formed by large mononuclear cell groups; however, among these cells there are always plasma cells and lymphocytes, sometimes eosinophil and even neutrophil cells. This variety of types of cells gives the characteristic appearance to each lesion. This also explains why, in Letterer-Siwe's, among several patients there may be as many varieties of lesions. In order to recognize and diagnose a true Letterer-Siwe's disease, there must be a general proliferation of mononuclear cells, some resembling phagocytes and some resembling neoplastic cells. For example, the proliferation of mononuclear cells in some of the lymph nodes may be so great as to alter the normal structure so that it resembles sarcoma or reticuloma. As in our case 1, the neoplastic growth may take place in the lung tissue. However, examination of other lymph nodes showed thick masses of large immature mononuclear cells with a number of phagocytes present. The phagocytosis in these masses was high, and fragments of lipocytes and hemosiderin were scattered through the growths. Although these cells may damage the normal lymphocyte structure, the fact that cells are not present everywhere may lead us to the correct diagnosis. These cells infiltrate not only the lymphoid system but also the liver, pancreas, ureter, gall bladder, adrenal gland and gastro-intestinal tract. In some cases atypical mononuclear cells may be found in the bone marrow. In our cases, in the slides made from the bone marrow, so few cells of this kind were seen that we could not reach any diagnostic conclusion.

In every case reported, there was infiltration of this type of cell in lungs, liver and kidneys. In two of our cases, the autopsies showed this infiltration in the lungs and liver but not in the kidneys. The shadows

on the roentgenograms were caused by this. The infiltration in the liver is so widely spread that it has been known to develop a fibrosis which distorted the bile duct. Bearing this in mind, in the diagnosis of any case of infantile cirrhosis Letterer-Siwe's disease must not be disregarded. The liver in all cases deteriorates greatly from this disease. In our case 2, we could see reticulosis and histiocytosis in the affected areas of the portal spaces. It was suggested that this marked proliferation might be secondary to some infection, but there was no doubt that this was not a true cirrhosis when we compared it with usual cases. Also, the lesions in the liver are a manifestation of the disease itself, because only one type of cell (reticulum cells and histiocytes) dominated the whole picture and we did not see simple connective tissue nor a secondary inflammatory reaction.

The prognosis of this disease is grave; however, some cases have been reported as cured either by treatment or spontaneously.

Antibiotics, blood transfusions and vitamins have been used in treatment but ACTH and other adrenal cortex derivatives seem to be more specific. In some clinics, nitrogen mustard is given intravenously (0.4 mg. per kilo of weight) as a single dose followed by cortisone. Some physicians report good results with cortical hormones, others claim no benefit. However, one patient to whom cortisone was administered in the small dose of 5 mg. daily for some time, maintained a fair condition and died immediately after the drug was discontinued. Therefore, this drug may be a specific for Letterer-Siwe's disease.

Summary

Three cases of acute non-lipid disseminated reticuloendotheliosis are presented and the historical, clinical and pathological results are discussed.

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