LETTERER-SIWE'S SYNDROME: REPORT OF A CASE WITH UNUSUAL PERIPHERAL BLOOD CHANGES

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In 1933 Siwe laid down the criteria of the syndrome now called Letterer-Siwe disease, and in the literature before and after that date the different features are discussed and related to the reported cases. The following case illustrates in particular the peripheral blood changes which may occur in this condition, and a table is appended summarizing the clinical and pathological features of 18 cases beginning with Letterer's (1924) case and bringing the series up to date (1950) with the present case.

Case Report

A boy aged 3½ years was admitted on March 11, 1948, with a history of soreness of the right ankle, anorexia, insomnia, and screaming in the night. The temperature was normal. The child was very pale and had puffy eyes. Firm and discrete nodes approximately 0·75 cm. in diameter were palpable in the neck, especially in the posterior triangle, the axillae, and the groins. The tip of the spleen was easily palpable but there was some doubt about the liver being palpable. The right ankle was swollen but there was no tenderness and the movements were neither limited nor painful.

A radiograph of the chest showed a doubtful hilar shadow; the skull, humeri, pelvis, femora, tibiae and fibulae were normal.

Blood Count:

Haemoglobin, 44% (Haldane).

R.B.C., 2,300,000 per c.mm. W.B.C., 7,000 per c.mm.

Differential white count: neutrophil polymorphs, 4% (280 per c.mm.), lymphocytes, 95% (6,650 per c.mm.), haemohistiocytes, 1% (70 per c.mm.).

A tentative diagnosis of aleukaemic lymphatic leukaemia was made. During the next fortnight the temperature ranged from 90°-100° F. and a mass became palpable in the left iliac fossa.

28.3.48. Sternal puncture was performed. In the marrow films haemohistiocytes dominated the picture. Very few mature lymphocytes, granulocytes, and normoblasts were to be seen.

29.3.48. Intramuscular penicillin (20,000 units four-hourly) was started.

Wassermann reaction + +; Kahn reaction, strong positive.

Volmer patch test negative after 48 hours.

Total serum protein	5·55 g. %.
Albumin	3·83 g. %.
Globulin	1·72 g. %.
Albumin/globulin ratio	2·2:1.

The father's and mother's Wassermann and Kahn reactions were negative.

Transfusion of 1 pint of packed cells.

6.4.48. Wassermann + +; Kahn, strong positive.

7.4.48. Penicillin dosage increased to 50,000 units four-hourly.

11.4.48. Wassermann and Kahn tests negative.

Paul Bunnell test negative.

22.4.48. Penicillin discontinued.

20.5.48. X-ray examination of the humeri, pelvis, femora, tibiae, and fibulae showed no abnormality.

26.5.48. Transfusion of 1 pint of blood. The spleen was easily palpable but not the liver, owing to guarding in the right hypochondrium. By percussion the liver was found to be enlarged two fingerbreadths below the costal margin.

17.6.48. Biopsy of a lymph node from the posterior triangle.

18.6.48. Liver palpable now.

19.6.48. Child vomited a few ounces of bright blood.

20.6.48. Occult blood in the stools. Transfusion of 1 pint of packed cells. Patient now running a hectic temperature.

24.6.48. Report on section of the lymph gland diagnosed reticulum cell medullary reticulosis.

30.6.48. Haemoglobin level falling rapidly.

4.7.48. Pallor now very marked, and ulcerative angina well established. The spleen and liver were larger than before.

9.7.48. Haemorrhagic gingivitis.

11.7.48. Patient died.

The clinical features of this and other reported cases are summarized in Table 1.

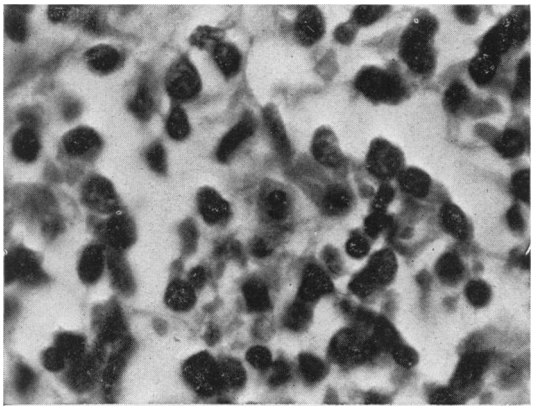

FIG. 1.—Bone marrow showing almost complete replacement by reticulum cells. Haematoxylin and eosin. × 675.

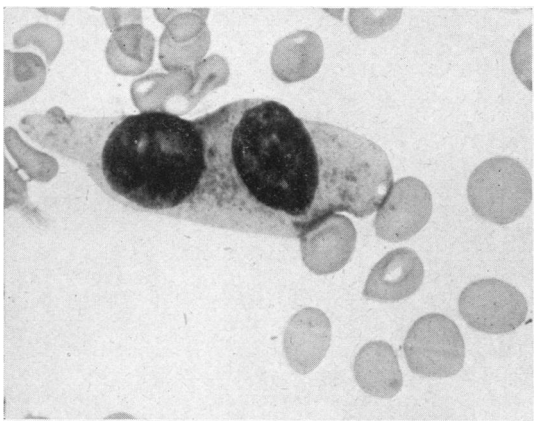

FIG. 2.—Peripheral blood smear showing binucleate form of haemohistiocyte which was present in appreciable numbers. Leishman. × 1200.

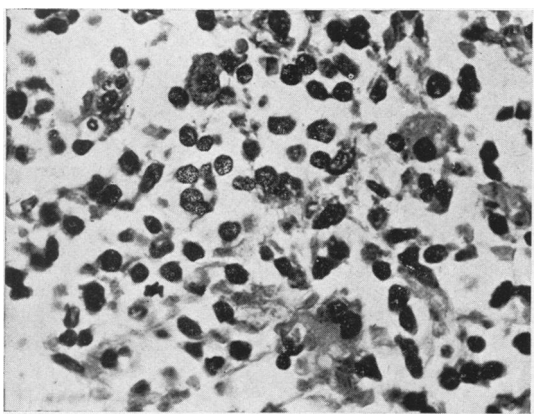

FIG. 3.—Lymph node: large numbers of reticulum cells are to be seen in the medulla. Haematoxylin and eosin. × 420.

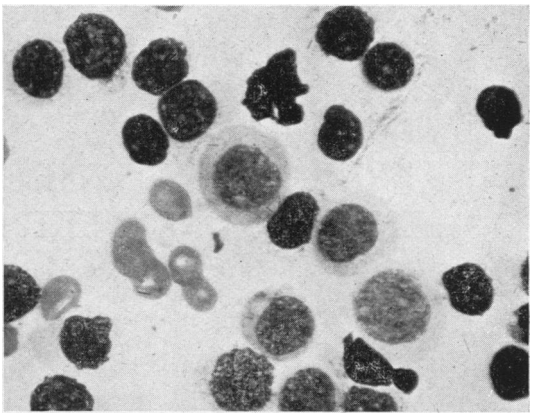

FIG. 4.—Smear of a lymph node showing large numbers of reticulum cells which are identical with the haemohistiocytes seen in Fig. 2. Leishman. × 675.

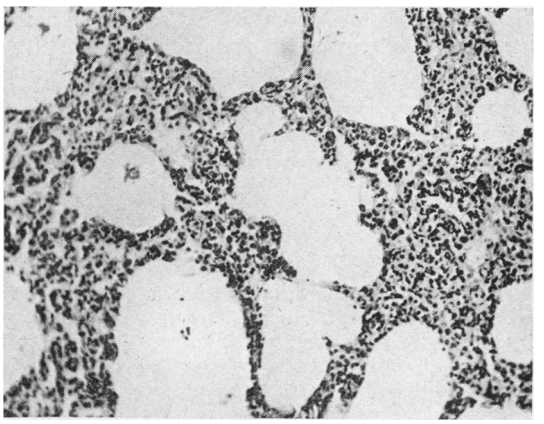

FIG. 5.—Lung showing alveolar septa markedly thickened and infiltrated by reticulum cells. Haematoxylin and eosin. × 100.

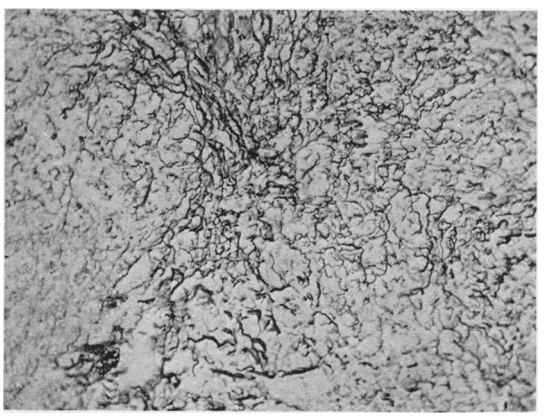

FIG. 6.—Lymph gland showing abundant formation of reticulin. Stained for reticulin. × 100.

TABLE 1

SUMMARY OF BLOOD FINDINGS IN PRESENT CASE

Date	R.B.C. (millions per c.mm.)	Hb. (Haldane) (%)	W.B.C. (millions per c.mm.)	Differential White Count					
				Neutrophil	Eosinophil	Basophil	Lymphocyte	Monocyte	Haemo-histiocyte *
March 11, 1948	2·3	44	7,000	280	—	—	6,650	—	70
,, 14, ,,	1·6	40	3,500	70	35	—	3,080	—	315
,, 21, ,,	1·6	38	3,900	195	—	—	3,042	—	663
,, 29, ,,	Transfusion of one pint of packed cells								
April 1, ,,	3·5	68	4,000	360	40	—	3,520	—	80
,, 11, ,,	3·5	68	5,400	864	—	—	4,104	—	432
,, 18, ,,	2·5	48	5,800	116	—	—	4,698	—	986
,, 28, ,,	3·0	64	4,200	84	—	—	3,528	84	504
May 16, ,,	2·3	50	6,500	130	65	—	4,875	65	1,365
,, 21, ,,	2·2	50	5,200	104	104	—	3,692	156	1,144
,, 26, ,,	Transfusion of one pint of blood								
June 9, ,,	3·2	62	6,300	252	—	—	4,158	—	1,890
,, 18, ,,	2·4	46	3,100	124	—	—	2,325	—	651
,, 20, ,,	Transfusion of one pint of packed cells								
,, 25, ,,	3·2	62	3,400	102	—	—	2,720	—	578

* The primitive cells in the peripheral blood were classed as haemohistiocytes. They were 15-25μ in diameter, having a large round reticular nucleus, a number containing nucleoli. The cytoplasm was abundant and of a pale dirty blue colour (Leishman stain). Some cells had cytoplasmic vacuoles and others fixed pseudopodia.

Post-mortem Report

External Appearance. A very pale and emaciated male child. The oral cavity showed ulcerative angina and gingivitis.

Chest. Oesophagus. Nil.

Thymus. Small and macroscopically normal.

Pleura. Left pleural sac contained one pint of yellow fluid.

Larynx. Nil.

Lung. Trachea and bronchi normal. Lungs pale: superficial area of collapse right lower lobe.

Pericardium. Nil.

Heart. Sub-pericardial haemorrhages near the apex and in the auricles.

Valves. Nil.

Vessels. Nil.

Abdomen. Peritoneum. Nil.

Stomach. Mucosa very pale.

Duodenum. Nil.

Bile ducts. Patent.

Intestines. Peyer's patches not enlarged; solitary lymph follicles of the colon were prominent.

Lymph Nodes. The cervical, axillary, pancreatico-splenic, external iliac and inguinal glands were red and varied in size from 0·75-1 cm. in diameter.

Spleen. Weight, 100 g. Cut surface dark red and firm.

Liver. Weight, 500 g. Dark terracotta colour. Structure appeared normal.

Pancreas. Nil.

Kidneys. Weight, 20 oz. Capsules stripped easily leaving a smooth surface. The cut surface was very pale.

Genito-Urinary Tract. Nil.

Brain. Very pale and macroscopically normal.

Spinal Cord. Not examined.

The sternal, vertebral, and femoral marrow was of a greyish pink colour.

Discussion

This is a case of reticulum cell medullary reticulosis with peripheral blood changes. The white blood count fluctuated between a low normal and frank leucopenia, with the lymphocyte as the predominant cell; a fair number of haemohistiocytes were invariably present. The reticulum cells showed unmistakable differentiation in two directions, namely, haemic and histiocytic. Without a doubt the haemohistiocytes in the peripheral blood and in the marrow were similar to the proliferating reticulum cells in the lymph glands, spleen, liver, lungs, and kidney. They were medullary reticulum cells with a tendency, as far as the nuclear structure was concerned, towards haemic differentiation. Definite evidence of differentiation towards histiocytes was to be seen in the liver, spleen, lungs, kidney, and, to a lesser extent, in the lymph nodes. Apart from a few departures from the accepted picture of the Letterer-Siwe syndrome (namely, the presence of haemohistiocytes in the peripheral blood, and the absence of purpura and osseous changes) the case reported satisfies the criteria laid down by Siwe. The Wassermann and Kahn reactions were strongly positive on two occasions but negative on the third. This no doubt was due to the change in the plasma globulin.

Summary

An unusual case of reticulum cell medullary reticulosis displaying the features of the Letterer-Siwe syndrome is described. A tabular review of the cases reported in the literature is presented in the Appendix.

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APPENDIX

ANALYSIS OF FEATURES OF REPORTED AND PRESENT CASES

Author	Age of Patient	Presenting Signs	Duration	Clinical Features									Reticulosis of Organs				
				Pyrexia	Agranulocytic angina	Haemorrhagic Diathesis	Anaemia	Change in Blood Picture	Generalized lymphadenopathy	Splenomegaly	Hepatomegaly	Osseous Changes	Lymph nodes	Bone marrow	Spleen	Liver	Lungs
Letterer (1924) ..	6 mths.	Purpura sepsis	11 wks.	+	−	+	−	+	+	++	+	None clinically	++	+	++	+	?
Akiba (1926) ..	10 mths.	Purpura sepsis	6 wks.	+	+	+	+	?	+	++	+	„ „	++	?	++	+	−
Krahn (1926) ..	5 years	Sepsis	6 mths.	+	−	+	+	S	+	++	−	„ „	++	++	++	++	?
Sherman (1929) ..	11 days	Jaundice erysipelas	4 days	+	−	−	+	−	−	+	+	„ „	?	+	+	+	++
Guizetti (1931) ..	3 mths.	Cough, fever, epistaxis	21 days	+	−	+	+	−	?	++	++	Cystic changes in the right humerus on x-ray examination	++	++	++	++	+
Podvinec and Terplan (1931)	1 year	Fever	14 days	+	+	+	−	−	+	++	++	None clinically	++	++	++	+	+
Uher (1933) ..	1¾ years	Sore throat, fever	17 days	+	+	+	−	S	+	+	+	„ „	++	+	++	+	++
Siwe (1933) ..	16 mths.	Swelling of the left leg	4 mths.	+	−	+	−	S	+	+	+	Cystic changes in the left fibula on x-ray examination	+	++	++	++	−
Gittins (1933) (*a*)	23 mths.	Anaemia	24 mths.	+	−	++	++	S	−	+	+	None clinically	++	++	++	+	?
(*b*)	21 mths.	Anaemia abscesses	3 wks.	+	−	+	++	+	+	+	−	„ „	++	++	++	+	?
(*c*)	1 year	Anaemia	11 days	?	−	−	++	+	+	++	++	Slight x-ray changes	+	−	++	+	?
(*d*)	17 wks.	Anaemia	4 mths.	−	−	S	++	+	+	++	+	None clinically	+	+	++	+	+
Klostermeyer (1934)	13 mths.	Swelling of the face	7 wks.	+	+	−	+	A	+	++	++	„ „	++	+	+	+	?
Foot and Olcott (1934)	2¾ years	Purpura, otitis media	1½ years	−	−	+	−	+	−	++	++	X-ray examination revealed rarefaction of the pelvis, upper end of the right femur. Osteoporosis of the spine at first suggested Pott's disease	++	++	+	+	+
Roussy and Oberling (1934)	8 mths.	Purpura	1 mth.	+	−	+	+	S	+	++	+	None clinically	++	+	++	++	++
van Creveld and Ter Poorten (1935)	4 mths.	Otitis media	8 wks.	+	−	−	−	S	+	+	+	Cystic changes in the skull, head of the right humerus and lower end of the right femur	+	++	+	+	++
Abt and Denenholz (1936)	2 years	Tumour of the skull	4½ mths.	+	−	+	+	+	+	++	++	Pulsating tumour of the skull. On x-ray examination a cystic area was apparent	++	++	++	++	++
Present case ..	3½ years	Swelling of right ankle, anorexia, insomnia	4 mths.	+	+	S	++	A	+	+	+	None clinically	+	++	++	++	++

?=Not mentioned. S=Slight. A=agranulocytosis.