POLYCYTHAEMIA WITH LEUCOERYTHROBLASTOSIS

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Few cases of leucoerythroblastic anaemia following on polycythaemia have been described in this country (Stone and Woodman, 1938; Vaughan and Harrison, 1939). The term "leucoerythroblastic anaemia," or, better, leucoerythroblastosis (as there may be no anaemia), is used to describe a condition characterized by the presence of immature red and white cells in the peripheral blood, and is due to or associated with replacement of the bone marrow by some other tissue. It is usually classified as follows.

Primary.—(a) *Infantile:* osteosclerosis fragilis generalisata (marble bones). This is congenital and may be familial.

as well as decreased density of the cortex of long bones (Vaughan and Harrison, 1939). The interpretation of these radiographs requires some experience, and must be compared with controls of the same age and sex. The trephine biopsy will in many cases confirm the diagnosis.

The object of this paper is to record two further cases of leucoerythroblastosis, both of which presented with polycythaemia. The two patients are alive at the time of writing.

Case 1

A married woman with two children first attended hospital in May, 1936, at the age of 32, with a history of having noticed a lump in the left subcostal region one year previously. It had gradually increased in size and had been accompanied by pain on exertion during the previous five months. The only other illness was migraine for 20 years. Examination showed her to be of slim build, cyanosed, with the spleen enlarged to the umbilicus, and the liver enlarged two fingerbreadths below the costal margin. Blood pressure 120/90; van den Bergh indirect reaction faintly positive. A blood count confirmed polycythaemia (see Table I).

July, 1936.—Admitted to hospital; polycythaemia persisted; fractional test meal showed low-acid curve; red-cell fragility test revealed a commencing haemolysis in 0.55% saline, complete in 0.3%; occasional nucleated red cells seen. Course of deep x-ray therapy to spleen and lumbar spine.

TABLE I.—Case 1. Blood Counts

Date	R.B.C. (Thou- sands per c.mm.)	Hb %	W.B.C. (per c.mm.)	Varieties of Leucocytes %										Plate- lets (per c.mm.)	Remarks
				Myelo- blasts	Pre- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Unseg- mented polys.	Poly- morphs	Eosino- phils	Baso- phils	Lympho- cytes	Mono- cytes		
4/5/36	7,620	82	7,000	—	—	—	—	—	85.0	—	0.5	14.0	0.5	50 normoblasts per c.mm. Deep x rays Deep x rays	
18/7/36	7,405	116	30,000	—	—	—	—	1.5	81.0	1.5	0.5	13.0	2.5		
5/8/36	8,000	136													
11/8/36	7,565	124													
6/4/37	5,560	116												Few normoblasts Punctate basophilia 240 normoblasts per c.mm.	
25/10/37	5,345	108	3,700												
9/5/38	4,965	98	12,600												
17/5/39	3,795	84	9,400												
31/7/40	3,845	92	14,600	—	—	—	—	1.0	70.0	2.0	0.5	20.5	6.0	Some normoblasts 270 normoblasts per c.mm. Occasional normo- blasts. Reticulo- cytes 2.4%. 4 normoblasts per 100 w.b.c. 2 normoblasts per 100 w.b.c.	
16/10/42	3,775	78	12,000	8.5	—	4.5	—	4.0	68.5	1.5	—	13.0	—		
11/7/45	4,400	86	12,400	—	2.0	6.5	—	8.0	61.5	—	1.0	17.0	4.0		
25/4/46	4,040	80	9,100	—	—	2.0	—	12.0	67.0	—	—	15.0	4.0		
16/6/48	4,140	78	11,100	0.5	1.0	3.0	3.0	—	78.5	1.5	—	10.5	2.0	237,800	
29/6/48	3,860	74	12,100	1.5	2.0	3.5	9.5	21.5	50.0	—	0.5	9.5	2.0		
11/8/48	4,220	71	19,500	1.0	1.0	6.0	4.0	13.0	61.0	2.0	1.5	8.0	2.5	256,000	

(b) *Adult:* osteosclerosis; myelofibrosis; agnogenic myeloid metaplasia; and aleukaemic megakaryocytic myelosis. In all probability these last are different names for or different aspects of the same condition. If it were possible to examine a large enough sample of bone marrow during life it might be found that fibrosis and osteosclerosis, pronounced myeloid and erythroid activity, and megakaryocytic excess were all occurring coincidentally at different sites. Splenomegaly and, less often, lymphadenopathy may be present.

Secondary or Symptomatic.—Carcinomatosis of bone; multiple myelomatosis; Hodgkin's disease; and lipoidoses. The anaemia may be normocytic or macrocytic. The white cell count may be high or low. The immature cells, the presence of which is an essential part of the disease, are said to be derived from the heterotopic foci in the spleen, liver, kidney, etc. These tissues, it is stated, are incapable of retaining the cells until complete maturation results. Thrombocytopenia may be present. The splenomegaly is due to myeloid metaplasia, although infarcts may add to the enlargement.

Radiographic changes characteristic of the disease have been described—i.e., irregular increased density of the spongiosa of long bones and throughout the flat bones,

April, 1937.—No serious symptoms; spleen smaller; haemoglobin 116%.

October, 1937.—Better; haemoglobin 108%.

May, 1938.—No symptoms; haemoglobin 98%.

May, 1939.—Following deep x-ray therapy, had amenorrhoea for two years, since when menstruation has been heavy and irregular. Pale; haemoglobin 84%. Seen by Sir Beckwith Whitehouse, who thought x-ray therapy may have produced defective luteinization, and recommended progesterone therapy.

July, 1940.—Slight continual uterine haemorrhage for three months; haemoglobin 92%, with a few nucleated red cells present; referred to gynaecology department, where no pelvic cause of bleeding was found.

October, 1942.—Recent pain over splenic area, worse on exertion. On examination: spare, healthy-looking; spleen enlarged to left iliac fossa; liver and glands not enlarged; blood pressure 130/70; leucoerythroblastic anaemia present.

July, 1945.—Health fairly good since October, 1942, but has noticed progressive enlargement of the spleen.

April, 1946.—Admitted to hospital with further aching pain in left flank; amenorrhoea for three years. Spleen enlarged to left iliac fossa and tender on bimanual examination; blood

pressure 160/90. Radiographs of bones of forearms show osteoporosis; serum calcium 8.6 mg. per 100 ml.; serum phosphorus 3.6 mg. per 100 ml. Leucoerythroblastic anaemia present. Surgical belt supplied to support huge spleen.

June, 1948.—Admitted to hospital. Exacerbation of severe continual pain over spleen for one month, made worse by movement or deep breathing. Pale; spleen enlarged to both iliac fossae and very tender on palpation; leucoerythroblastic anaemia present. Platelets 238,000; reticulocytes 2.4%; radiograph of long bones showed osteoporotic appearance of upper half left humerus; sternal-marrow puncture gave a picture not unlike that present in the peripheral blood. A diagnosis of myelofibrosis was made clinically, and sternal biopsy was performed with a view to confirming this, since radiographs of long bones were indefinite. The biopsy was reported on as follows: "These small fragments of sternal tissue show diffuse fibrotic changes with occasional isolated megakaryocytes—very suggestive, if this is representative, of myelofibrosis."

Case 2

A married woman aged 64 first attended hospital in 1924, complaining of pain in the splenic region; a diagnosis of polycythaemia vera was made and x-ray therapy given. Attended regularly for eight years and was free from symptoms until 1942. No records available up to this date.

August, 1942.—Pain in splenic region for two months; spleen enlarged to umbilicus and tender; blood pressure 155/90. Red blood cells 4,700,000; normoblasts present (see Table II).

TABLE II.—Case 2. Blood Counts

Date	R.B.C. (Thou- sands per c.mm.)	Hb %	W.B.C. (per c.mm.)	Varieties of Leucocytes %										Plate- lets (per c.mm.)	Remarks
				Myelo- blasts	Pre- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Unseg- mented polys.	Poly- morphs	Eosino- phils	Baso- phils	Lympho- cytes	Mono- cytes		
17/8/42	4,700	92	7,100	—	—	—	—	10.0	56.5	1.0	2.0	21.5	9.0		1,000 normoblasts per c.mm.
14/4/44	4,465	118	6,600	—	—	—	—	10.0	66.0	1.0	2.0	15.0	6.0		Few normoblasts Deep x rays. Phenyl- hydrazine
15/9/44	7,970	110	10,900	—	—	—	—	7.5	74.0	—	—	14.0	4.5		
2/10/44	8,500	99	11,100	—	—	—	—	—	61.0	2.0	5.0	27.0	5.0		Deep x rays
5/3/46	6,120	112	9,200	—	—	—	—	—	—	—	—	—	—		
2/6/46	4,340	84	3,100	—	—	—	—	—	—	—	—	—	—		Petechial rash 1 normoblast 2 normoblasts per 100 w.b.c.
6/12/46	7,100	128	8,200	—	—	—	—	—	—	—	—	—	—		
2/1/47	8,030	118	4,600	—	—	—	—	—	—	—	—	—	—		
8/1/47	6,210	110	6,200	—	—	—	—	—	—	—	—	—	—		
27/1/47	6,330	98	70,000	—	—	—	—	—	—	—	—	—	—		
21/4/47	5,300	92	60,000	—	—	—	—	—	—	—	—	—	—		
31/10/47	5,610	106	5,600	—	—	—	—	16.5	30.0	2.5	3.5	30.0	17.5	270,000	
29/11/47	6,470	116	4,900	—	—	—	—	—	58.0	1.0	—	36.0	5.0		
5/3/48	5,400	100	5,600	—	—	—	—	—	63.0	—	5.0	26.0	6.0	165,000	
7/3/48	5,370	90	60,000	—	—	—	—	—	—	—	—	—	—		
20/5/48	4,370	76	4,100	2.5	2.0	5.0	12.0	16.0	34.5	1.5	5.0	17.0	4.5	54,000	
8/6/48	4,220	74	4,000	2.5	6.5	5.0	13.5	13.0	20.5	1.0	1.5	36.5	—	32,000	

April, 1944.—Slight ache over spleen for three weeks. Red blood cells 4,465,000.

September, 1944.—Patient noticed increasing size of left side of abdomen, but otherwise felt fairly fit; spleen enlarged as far as left iliac fossa; liver enlarged below umbilicus; red blood cells 7,970,000. Admitted to hospital and further course of deep x-ray therapy given to spleen, followed by phenylhydrazine therapy. Further x-ray therapy given in May, 1945.

June, 1946.—Blood count satisfactory, but in December, 1946, again markedly polycythaemic. Further deep x-ray and phenylhydrazine therapy given.

October, 1947.—Purpura on legs and arms; platelet count 270,000 per c.mm.; blood count satisfactory except for numerous unsegmented polymorphs.

May, 1948.—Admitted to hospital with eight weeks' history of lassitude, swelling of ankles, and noticeable enlargement of abdomen; rubicund facies; few petechiae of limbs; abdomen distended, with everted umbilicus and shifting dullness; spleen enlarged to right iliac fossa; blood pressure 145/95. Blood count showed mild hypochromic anaemia with numerous immature leucocytes, a few normoblasts, and 54,000 platelets per c.mm.

It was considered that this indicated the development of either myelosclerosis or aleukaemic leukaemia. Sternal puncture was twice performed and the picture was essentially that of the peripheral blood; the bone seemed soft and gritty on puncture. These findings are typical of myelofibrosis. Bleeding time 5½ minutes; clotting time 4½ minutes; prothrombin 55% of normal. Serum proteins 6.52 g.%; serum uric acid 5.6 g.%; serum alkaline phosphatase 7 units; blood urea 27 mg. per 100 ml. A barium swallow radiograph showed some irregularity of oesophageal wall consistent with varices; radiographs of sternum and femora were normal.

On June 17, 1948, the patient left hospital against advice. The diagnosis was considered to be myelofibrosis following polycythaemia vera, with cirrhosis of liver.

Comment on the Cases

Case 1 presented as a case of polycythaemia rubra vera and was treated with deep x rays. The blood count gradually fell, and once below normal never rose again. This suggests that the case was one of primary myelofibrosis presenting as polycythaemia (see Vaughan and Harrison, 1939). It is of course possible that the patient had previously had polycythaemia rubra vera and had already developed myelofibrosis when first seen. Certainly, in June, 1948, the sternal biopsy demonstrated myelofibrosis. The corpuscular fragility was increased (admittedly slight), which coincides with the findings of Vaughan and Harrison.

Case 2 was diagnosed as a case of polycythaemia rubra vera. From 1924 until 1947 this patient had a typical polycythaemic count. In May, 1948, she showed many of the features of leucoerythroblastosis associated with myelofibrosis—i.e., leucopenia, presence of immature red and white cells in the peripheral blood, gross splenomegaly, and a presumably non-functioning bone marrow. Myelofibrosis was suspected on the grounds that sternal puncture revealed a soft gritty bone, and the material, when examined, showed a picture not unlike that found in the peripheral blood. Such a terminal event in polycythaemia rubra vera has been recorded.

Discussion

The pathogenesis of the primary variety is obscure. Vaughan (1934) suggested that the undifferentiated mesenchyme develops predominantly along one line to produce fibroblasts or osteoblasts. There is no attempt to explain why this should happen. Myelofibrosis and osteosclerosis have followed benzol and phosphorus poisoning. The

picture of osteosclerosis with leucoerythroblastosis can occur in fluorosis. X rays have been known to produce fibrosis of the marrow; and Joan Ross (1932) describes the effects of gamma radiation over a period of three years. The marrow showed hyperactivity of the myeloid and erythroid cells with a marked increase in megakaryocytes. The nutrient vessels showed endothelial thickening and intravascular thrombi. It is not beyond possibility that repeated doses of deep x rays over many years may produce the picture of myelofibrosis in polycythaemia rubra vera.

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A CASE OF WEIL'S DISEASE, WITH TESTS FOR LIVER FUNCTION

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Familiarity with Weil's disease during the war has resulted in several publications in the English and American literature. Although jaundice is usually a marked feature of this disease, there is no record of liver-function tests. The following case is therefore described, together with the result of tests for liver dysfunction and for other biochemical disturbances. These were of great help in excluding the diagnosis of acute hepatic necrosis, which was made on admission. It is hoped that this will stimulate physicians who have greater opportunities for studying this disease to investigate its chemical pathology, and to deduce from their findings evidence concerning the site of tissue damage.

Case Report

The patient, a plumber aged 58, was admitted on April 13, 1949. Up to a week previously he had been working on a boiler in a meat-pie factory in which fat was rendered down. Seven days before admission he had a rigor; this was followed by another two hours afterwards. Four days later he noticed he was yellow, and he began to vomit incessantly. There was no abdominal pain.

On examination he was a very ill man, dehydrated, with subsultus tendinum, deep jaundice, and a generalized purpuric eruption. The mucosae were pale. He was afebrile; the pulse rate was 90, the blood pressure was 130/80, the heart sounds were faint, and there were basal crepitations. The liver was not palpable. There was some free fluid in his abdomen, and his stools were pale. Three days later he developed a swinging temperature up to 102° F. (38.9° C.), which was maintained for five weeks and subsided by lysis, and which did not respond to penicillin, 250,000 units six-hourly intramuscularly for 10 days.

He was given 5 pints (2.34 litres) of fluid by mouth, 3 pints (1.7 litres) of "casydrol" by intravenous drip transfusion, 6 ml. of "campolon" intramuscularly, 500 mg. of ascorbic acid, and 15 mg. of vitamin K daily. Later he developed a urinary infection with *Pseudomonas pyocyanea*, for which he was given 4 g. of streptomycin daily by injection for five days.

Subsequent Course.—His rash cleared up in three days; the jaundice had faded by the first week in July, but he was pyrexial

for a month. However, he remained mentally in a state of stupor, with considerable clouding of consciousness, marked loss of memory for recent events, and disorientation in time and place. Some measure of recovery occurred, but when his wife took him on May 31 he was able to sit out in a chair, though he showed a good deal of mental deterioration, with lack of all initiative and poor memory. A letter from his wife on July 27 stated that his general condition had improved, but his legs were weak and useless and his mental state poor.

Investigations

Agglutinations.—*L. icterohaemorrhagiae*: April 20, 1:1,000; April 29, 1:1,000; May 5, 1:3,000. *L. canicola*, nil. *Salm. typhi*, *Salm. paratyphi A*, *Salm. paratyphi B*, and *Br. abortus*, nil.

Blood Counts.—Haemoglobin: April 14, 59%; May 9, 59%; May 23, 72%. Red cells: April 14, 3,750,000; May 9, 3,020,000; May 23, 3,500,000. White cells: April 14, 25,000 (P. 77%, L. 21%, M. 1%); May 9, 25,000 (P. 89%, L. 10%, M. 1%); May 23, 18,000 (P. 75%, L. 25%, M. 4%).

Serum Proteins.—April 24: total, 5.75 g.% (albumin 4.2, globulin 1.5; A/G ratio 2.7:1). May 5: total, 5.5 g.% (albumin 3.7, globulin 1.8; A/G ratio 2.05:1).

Liver-function Tests.—Alkaline phosphatase: April 24, 10.7 units; May 5, 16.3 units; May 23, 12.8 units. Thymol turbidity: April 24, 1.5 units; May 5 and 23, 1 unit. The Takata-Ara and colloidal gold tests were negative.

Urine.—April 19 and 25: specific gravity, 1010; albumin, sugar, and bile salts, nil; bilirubin was in excess on April 19 and urobilin was present on April 25. On April 25 there were 10 cells per field and *Ps. pyocyanea* was found. On May 30 there were many pus cells and *Ps. pyocyanea* was still present. There were no spirochaetes.

Haemolysins.—On May 30 no cold agglutinins were present, and Coombs's direct and indirect tests were negative.

On April 14 the serum diastase amounted to 320 mg. per 100 ml. (normal, 70–150 mg.). On April 22 the blood urea was 27 mg. per 100 ml., the alkali reserve 49 volumes, and the serum calcium 8.6 mg. per 100 ml. On May 10 the blood urea was 35 mg. per 100 ml. and the alkali reserve 43.9 volumes. On April 22 the blood sugar totalled 148 mg. per 100 ml., and the serum cholesterol 177 mg. per 100 ml. (free, 80 mg.; ester, 97 mg.).

The diagnosis was based on the presence of jaundice, the rash, the patient's occupation, and the rising titre of agglutinins.

Comment

The morbid pathology of the liver in Weil's disease is described by Hutchinson *et al.* (1946). They say that the liver in their cases was usually of normal size, with masses of bile pigment in the biliary canaliculi of the centrilobar part of the liver lobules, and emphasize the absence of necrosis. On the other hand, Heringman and Phillips (1947) mention considerable disorganization of the liver pattern with moderate vacuolization and swelling of cells and the formation of continuous cords of liver cells instead of normal groups of two or three cells.

In the case described by Jackson and Oleesky (1946) there was no macroscopic hepatic necrosis; there were scattered areas of fatty degeneration and areas of regeneration, with enlarged binucleated liver cells. They mention that Walch-Sorgdrager (1939) refers to the frequent misdiagnosis of acute yellow atrophy, as happened in our case.

Our case on admission, being afebrile at the time and extremely ill and toxic, closely resembled the picture of acute hepatic necrosis. The finding of normal plasma proteins and Takata-Ara, thymol turbidity, and colloidal gold tests was therefore of distinct value in excluding this diagnosis, and would seem to rule out any overwhelming degree of parenchymal damage.