JAUNDICE IN LEUCO-ERYTHROBLASTIC ANAEMIA

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The occurrence of leuco-erythroblastic anaemia in carcinomatosis of the bone marrow is well recognized. The characteristics of the blood picture are the presence of nucleated red cells even when the anaemia is slight, and a variable leucocytosis in which immature myeloid cells are found. The metabolism of bile pigment has not been extensively studied in this condition, and Vaughan (1936) points out that the interpretation of the van den Bergh reaction has usually been obscured by the presence of hepatic metastases or of carcinomatous glands in the portal fissure producing obstructive jaundice. We record two cases of leuco-erythroblastic anaemia complicated by jaundice. Both were cases of cancer of the stomach with widespread metastatic dissemination. In the first case many metastases were formed in the bone marrow. In the second an incomplete examination of the skeleton was made, but the clinical and haematological features so closely resembled those of the first case as to suggest the presence of metastases in the marrow. The jaundice was of the "haemolytic" or "retention" type (Rich, 1930), and both cases were at first thought to be examples of haemolytic anaemia of the type described by Lederer (1925, 1930). This author described a syndrome in which were associated rapidly progressive anaemia with signs of active blood regeneration, jaundice, pyrexia, and a leucocytosis with immature white cells. The patient usually complained of backache, and a characteristic feature was said to be the rapid and usually permanent improvement following blood transfusion.

Case I

A married woman aged 49 was first seen by one of us (J. MacD. H.) in consultation with Dr. E. G. Sherwood on January 3, 1939. Illness had begun five weeks previously with aching pains in the back and thighs, which the patient had attributed to rheumatism. When seen by Dr. Sherwood a fortnight later there was no evident anaemia. The pains in the limbs and back became worse, and a week before consultation pyrexia appeared and remained constant at about 100° F. Pallor and jaundice also became apparent. There was nothing relevant in her previous history.

Examination.—The findings were as follows: Severe pallor and slight jaundice. Liver palpable 1½ in. below costal margin, and tender. Spleen just palpable. Tenderness on pressure of dorsal and lumbar spine. Urine dark in colour and contained a small amount of albumin; urobilin and urobilinogen present in large amounts; bilirubin and bile salts absent. Bence-Jones protein absent. A blood count gave the following figures: haemoglobin, 37% (14.5 grammes = 100%); red cells, 1,900,000; colour index, 0.97; Wintrobe's volume index, 0.97; white cells, 8,400—polymorphs 58%, lymphocytes 35%, monocytes 4%, eosinophils 0.5%, myelocytes 2.5%; icterus index, 15 units; direct van den Bergh reaction, faint biphasic; quantitative indirect reaction, 3 units; reticulocytes, 6%. Red cells showed much anisocytosis and some were hypochromic. There was polychromasia. Six normoblasts were seen in counting 200 white cells. Red cell fragility was normal; haemolysis began at 0.44% and was complete in 0.25% saline. Agglutination tests were negative to organisms of the enteric group, composite *Salmonella* suspension, *B. enteritidis* (Gaertner), and *Brucella abortus*.

A diagnosis of acute haemolytic anaemia was made and a blood transfusion of 250 c.cm. was given. The progress of the patient during the next few days suggested that the anaemia was of Lederer's type. The pains in the limbs and back improved, the pyrexia began to subside, and there was an increased feeling of well-being. On January 6 a second transfusion of 500 c.cm. was given. After this the pyrexia subsided completely. On the 9th the haemoglobin had risen to 60%. A few days later the patient left the nursing home, no further pyrexia having occurred. In the next three weeks her condition slowly deteriorated.

On February 3 she was admitted to the Staffordshire General Infirmary, and it was found that the anaemia was almost as severe as before: red cells 2,590,000 per c.mm., haemoglobin 49%, colour index 0.98. Radiographs of the long bones showed appearances suggestive of secondary malignant deposits. She was again jaundiced, and urobilin was present in the urine. A fractional test meal showed that a normal amount of free hydrochloric acid was present, but blood was found in all the specimens and the emptying time was slow. The significance of these observations was not recognized at the time, as there were a few purpuric haemorrhages under the skin in various places, and it was assumed that the blood was due to purpuric haemorrhage from the gastric mucosa. On February 8 and during the next two days a drip transfusion of three litres was given, the haemoglobin being raised to 74%. The blood picture slowly deteriorated after this, and although another transfusion of 500 c.cm. was given on February 23 the patient died on March 3, 1939. Blood culture was sterile on three occasions.

A feature of this case was the occurrence of crises in which the pyrexia appeared together with increased anaemia and jaundice. These findings were thought to be consistent with a diagnosis of haemolytic anaemia, and the similarity to Lederer's syndrome was emphasized by the response to the earlier transfusions.

Post-mortem Findings (Four Hours after Death).—The essential features were as follows: Multiple secondary malignant deposits in heart muscle and pericardium; an ulcer with an indurated base and nodular edge, carcinomatous in appearance and about one inch in diameter, near the pylorus; a gland from the lesser omentum invaded by growth. Spleen slightly enlarged. Both ovaries replaced by large masses of tumour. Skeletal secondary deposits present in femora, humeri, lumbar vertebrae, and sternum.

Histological Examination.—Sections from the ulcer revealed a spheroidal-celled carcinoma. Lymphatics several inches from the ulcer were permeated by growth and an omental gland examined contained secondary deposits. The heart showed diffuse invasion by malignant cells, and, in the lung, many lymphatic channels contained tumour cells. The normal structure of the ovaries was entirely obliterated by tumour cells. Marrow from the femur, humerus, and lumbar vertebrae had a similar appearance. Many of the canals between the bony trabeculae were occupied only by loose fibrillary tissue, but others were plugged with tumour cells. Islands of haemopoiesis occupied some of the spaces. The haemopoietic areas consisted largely of normoblasts and groups of haemocyto blasts. In some areas, however, there was a definite shift of haemopoiesis to the left, haemoglobinized cells with immature nuclei being seen. Proliferating white cells of the granular series were present, but were much less numerous than the erythropoietic cells. In the liver large numbers of immature red and white cells lay free within the sinusoids. Clumps of haemocyto blasts were a conspicuous feature. In many of the sinusoids cells indistinguishable from normal megakaryocytes were seen. Many Kupffer cells contained free iron, and phagocytosis of erythrocytes by Kupffer cells was frequently observed. There was a moderate degree of fatty change, of patchy distribution. No malignant deposits were present in the liver proper, but a haemangioma found in the liver was of interest in that clumps of malignant cells were seen in several of the cavernous spaces, although a careful search failed to reveal any in the surrounding liver tissue. It would seem that slowing of the blood stream had caused tumour cells to accumulate in this site. In the spleen active haemopoiesis was present throughout and occasional megakaryocytes were seen. The Malpighian bodies were greatly reduced in size. There

was some erythrophagocytosis, but this was not conspicuous. There was a good deal of free iron, usually lying in the histiocytes.

Case II

This patient, a man aged 26, was admitted to hospital on June 17, 1936. There was a history of a gastrectomy performed in another hospital fourteen months previously, but details of this were not available. When first seen by one of us (A. J. McC.) he complained of weakness and malaise. His throat was sore, and he had pains in the loins, chest, and groins. There were no other symptoms.

Examination.—He did not seem very ill and was not thought to be anaemic. There were no petechiae and no jaundice. Temperature 99.4° F., pulse rate 120. The supraclavicular and cervical glands on both sides were palpable and tender. Dental sepsis was present. The spleen and liver were not palpable. The cardiovascular and respiratory systems were normal. Spinal movements were painful. The central nervous system was normal. On June 18 bleeding from the gums and slight jaundice were noticed. Urobilin was found in the urine, but no bile pigment. On the 19th ecchymoses appeared on the legs, and on the 22nd there was definite jaundice. The patient became severely ill and was obviously anaemic. The temperature since admission had varied between 99° and 102°. A blood count gave the following results: Red cells, 1,216,000; haemoglobin, 10% approx. (14.5 grammes = 100%); colour index, 0.43 approx.; Wintrobe's volume index, 0.7; halometer reading, 7.17; reticulocytes, 30%; white cells, 32,000—neutrophils 70%, eosinophils 2%, myelocytes 2%, myeloblasts 2%, lymphocytes 21%, monocytes 3%. Eighteen normoblasts per 100 white cells were counted. Red cells showed marked anisocytosis and hypochromia. Some cells had polychromasia and basophil stippling. Fragility was normal, haemolysis beginning at 0.45% and being complete at 0.3%. The icterus index was 25 units. The direct van den Bergh reaction was negative and the blood culture sterile. Agglutination reactions against organisms of the enteric group, composite *Salmonella* suspension, *B. enteritidis* (Gaertner), and *Brucella abortus* were negative. Urine contained a moderate amount of albumin and urobilin in excess.

On the same day a blood transfusion of 500 c.cm. was given, without improvement, and on June 24, 1936, the patient died.

Post-mortem Findings.—Essential findings as follows: A partial gastrectomy had been performed and the stoma appeared healthy. The head and body of the pancreas were indurated, the appearance resembling chronic pancreatitis. There was no demonstrable narrowing of the common bile duct. The spleen was twice its normal size, and was firm and congested. The mediastinal glands were enlarged, but the heart was normal except for subpericardial haemorrhages. The liver was pale and slightly enlarged, and the kidneys showed subcapsular haemorrhages. With regard to the bone marrow, unfortunately only the humerus was examined, and no malignant deposits were found.

Histological Examination.—The pancreas showed invasion by spheroidal-celled carcinoma, and a mediastinal gland also revealed spheroidal-celled deposits. In the liver the cells for some distance round the central vein were poorly stained, and in some areas there was definite pericentral necrosis. Occasional nucleated red cells were seen in the sinusoids, but no definite areas of haemopoiesis were observed. There was no erythrophagocytosis by the Kupffer cells, and no free iron was demonstrable. Examination of the spleen revealed that many of the sinusoids were empty, but the pulp contained large numbers of red cells. Normoblasts were present, but no recognizable haemocytoblasts. It is difficult to be certain whether or not haemopoiesis had occurred in the spleen. A fair amount of free iron was lying in the histiocytes. No tumour cells were present in the portion of bone marrow examined.

The metastases in this case clearly originated from a cancer of the stomach for which gastrectomy had been performed. The extremely rapid development of the anaemia, together with jaundice and pyrexia, seemed to indicate that a haemolytic process was responsible.

Discussion

It appears to us that not enough evidence is available to justify the assumption that the anaemia in these cases was definitely due to excessive blood destruction. Quantitative investigations on the excretion of faecal bile pigment were unfortunately not undertaken. It also seems likely that spectroscopic examination of the blood for methaemalbumin may prove important in this type of case, since the pigment was found by Fairley (1937) to accompany the intravascular haemolysis in blackwater fever.

It has been pointed out by Whipple (1922a, 1922b), Witts (1932), and many others that the findings often considered to be evidence of excessive haemolysis—such as an increased serum bilirubin, an augmented urinary and faecal excretion of bile pigments and their derivatives, and haemosiderosis of the organs at necropsy—may indicate an inability of the erythron to utilize these products rather than an excessive destruction of blood.

Rich (1930), in his excellent discussion on the pathogenesis of jaundice, has stressed the importance of impaired liver function in producing the type of jaundice commonly referred to as "haemolytic," but which he prefers to call "retention" jaundice. He emphasizes the fact that a normal liver can excrete any quantity of bile pigment likely to result from haemolysis, and that jaundice occurs only when hepatic function is impaired as a result of the anaemia. The liver necrosis observed in our second case must certainly have been a factor in producing jaundice. A number of cases similar to ours are, however, recorded in the literature, perhaps on insufficient evidence, as examples of haemolytic anaemia in carcinomatosis of the marrow. It is of interest that in some of these cases the fragility of the red cells to saline was increased.

Seemann and Krasnopolski (1926) reported a case of cancer of the stomach with extensive bone metastases in which the features of leuco-erythroblastic and haemolytic anaemia were combined. Waugh (1936) described two similar cases. The first did not come to necropsy, but radiological examination of the spine suggested vertebral metastases: the red cell fragility was increased. Waugh's second case was one of primary carcinoma of the breast with marrow secondaries. In the case recorded by Kiser and Rosenak (1936) the marrow was not examined. A case described by Caroli and Lavergne (1937) was very similar to ours. Eight months before the onset of the anaemia a gastrectomy had been performed for cancer of the stomach. Fever, jaundice, and urobilinuria were present. The red cell fragility was increased. More recently Lucey (1939) has recorded a case of bronchogenic carcinoma with leuco-erythroblastic anaemia and increased red cell fragility.

It is evident that a syndrome may occur in association with skeletal carcinomatosis which resembles clinically the "acute haemolytic anaemia" of Lederer. The wider recognition of this syndrome is desirable.

Whether or not the anaemia in these cases can be attributed to excessive haemolysis seems uncertain. In none of them does it appear that sufficient evidence, based on modern criteria, has been presented to support this view definitely. The finding of increased saline fragility of the red cells in some of the cases lends colour to the suggestion that a haemolytic process is responsible. It does appear quite certain that carcinomatous deposits in the marrow may cause increased fragility of the red cells. In this connexion two cases of leuco-erythroblastic anaemia occurring in myelosclerosis recently described by Vaughan and Harrison (1939) are of interest. In both

cases the red cell fragility was increased but the serum bilirubin was within normal limits.

In our cases a quantitative method of estimating the fragility (for example, Simmel, 1923) was not employed, but it is unlikely that there was any notable increase. Fragility to saline is, however, rather an artificial measure of the red cells' destructibility in the body. It is conceivable that the presence of metastases in the marrow may so upset the metabolism of the haemopoietic tissue as to render the cells abnormally susceptible to phagocytosis by the reticulo-endothelial system. This change might not necessarily be reflected in any increased fragility with *in vitro* tests. Erythrophagocytosis was in fact a conspicuous feature in our first case, but was not observed in the second.

In those cases in which the primary growth was in the stomach the importance of the loss of intrinsic factor is of interest. It is noteworthy, therefore, that these cases have not been examples of megalocytic anaemia, and of the two here described the first was normocytic and the second microcytic and hypochromic.

"Haemolytic Anaemia" in Other Infiltrative Conditions of Bone.—It appeared of interest to consider the frequency of the occurrence of a similar syndrome in infiltrative conditions of bone other than carcinoma. A number of cases of Hodgkin's disease presenting features resembling those of the cases noted above are on record. Singer (1936) reviews eleven cases with one of his own. These eleven cases were reported by Holler and Paschkis (1927), two cases; Davidson (1932), three cases; Heilmeyer (1932), one case; Gripwall (1932) and Bergqvist and Gripwall (1935), one case; Dalous and Fabre (1933), one case; Bensis and Gouttas (1934), one case; Parkes Weber and Schwarz (1934), one case; and Horak (1934), one case. Von Braitenburg (1938) recorded a case which was remarkable in that, although lymphadenomatous deposits were confined to the mesenteric and mediastinal glands, a severe haemolytic type of anaemia developed. Only in four of the thirteen cases quoted were osseous deposits of lymphadenoma found, but the examination of the skeleton was not always complete. The red cell fragility was not estimated in every case, but in four it was found to be slightly increased. We have been unable to find any record of "haemolytic anaemia" occurring in myelomatosis, Hand-Schuller-Christian's disease, Gaucher's disease, or Niemann-Pick's disease. In leukaemia, however, cases complicated by the type of jaundice in question are occasionally seen. This again is a condition in which there is widespread infiltration of the marrow.

Extramedullary Megakaryocytosis.—In Case I haemopoietic tissue was observed in the liver and spleen; this is, of course, not uncommon with widespread marrow destruction. The occurrence of extramedullary megakaryocytosis in carcinomatosis is, however, infrequent. Vaughan and Harrison (1939) give an exhaustive bibliography on megakaryocytic myelosis and related conditions.

Summary

Two cases of leuco-erythroblastic anaemia complicated by jaundice are described. The jaundice was of the "haemolytic" or "retention" type, and the clinical picture corresponded in many respects with Lederer's syndrome. The first case had extensive carcinomatous deposits in the skeleton, and it seems likely that bone metastases were present in the second case. The primary growth had its origin in the stomach in both cases. In both the fragility of the red cells was normal.

Records of similar cases, in some of which the fragility was increased, are reviewed, and the occurrence of a similar syndrome in other forms of generalized bone disease is discussed.

Cases of skeletal carcinomatosis in which leuco-erythroblastic anaemia is complicated by "retention" jaundice are likely to be diagnosed as "Lederer's anaemia." Radiographs of the skeleton should be taken in cases presenting the features of haemolytic anaemia of doubtful origin, and a careful search should be made for any focus of malignant disease.

There is not enough evidence definitely to attribute the anaemia and jaundice in these cases to a haemolytic process, but it is possible that such a process is responsible.

Our thanks are due to Dr. E. G. Sherwood for supplying the early history of the first case and to Dr. H. H. Mac-William of Walton Hospital, Liverpool, for access to the records of the second case and for permission to publish it. We are indebted to Professors J. H. Dible and T. F. Hewer for advice, and to Dr. J. Menton for help and laboratory facilities.

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PENETRATING BAYONET WOUND OF THE PERINEUM

A CASE WITH INTERESTING COMPLICATIONS

BY

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The following case may be considered of interest owing to its stormy history due to complications.

History of Case

The patient, a corporal in the R.A.F., aged 23, was admitted at 4.30 a.m. on July 5, 1940, having jumped off a barrage-balloon winch in the darkness and landed on the point of a bayonet, which was fixed to a rifle standing beside the winch. He experienced immediate severe abdominal pain, vomited once, and complained of a desire to pass urine but inability to do so.

On examination he was very shocked. The pulse was 120 and thready; there was generalized abdominal rigidity; and a wound an inch long was present on the medial aspect of the left thigh, passing up over the adductor longus. No blood could be milked from the external urinary meatus, and rectal examination revealed nothing abnormal. A pint of whole blood was given intravenously, and an hour later his abdomen was opened under gas-and-oxygen anaesthesia by an infra-umbilical mid-line incision.

There was a considerable amount of free blood in the peritoneal cavity and a rent about an inch in length was found in the fundus of the bladder. This rent was closed with catgut sutures and the suture line then oversewn. The peritoneum on the anterior surface of the rectum was gashed, but the muscular coat was intact. The point of the bayonet had entered the mesentery of a loop of ileum about three feet from the caecum and had ripped up the mesentery as far as the gut, the mesenteric aspect of which had been perforated. Bleeding-points in the torn mesentery were secured and the gap was sutured. The perforation in the ileum was closed and the affected segment of intestine wrapped in a