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POLYCYTHAEMIA, LEUCO-ERYTHROBLASTOSIS, AND MYELOSCLEROSIS

BY

J. W. BEATTIE, M.D., M.R.C.P.

Department of Clinical Medicine, University of Leeds

AND

J. L. WITHEY, M.B., B.S.

Department of Pathology, Welsh National School of
Medicine

Reduction or obliteration of the bone marrow by connective-tissue proliferation or increased formation of bone occurs in the hereditary childhood condition of osteopetrosis, or marble bone disease of Albers-Schönberg, and also in a non-hereditary adult condition. This latter is probably best known as myelosclerosis, in which myelofibrosis or ossification of the marrow, sometimes called osteosclerosis, may be the predominant feature. The blood picture characteristically accompanying this condition shows leuco-erythroblastosis—defined by Vaughan (1936a) as “an anaemia characterized by the presence in the peripheral blood of unusually immature red cells and a few immature white cells of the myeloid series. The anaemia is not necessarily severe, nor is there usually a marked leucocytosis.” Previous polycythaemia in cases which eventually showed leuco-erythroblastosis and myelosclerosis has been described by Lehdorff and Zak (1907), Hirsch (1935), Vogel, Erf, and Rosenthal (1937), Stone and Woodman (1938), Rosenthal and Bassen (1938), Markoff (1939), Vaughan and Harrison (1939), Thompson and Illyne (1940), Jackson, Lemon, and Parker (1940), Rosenthal and Erf (1943), Stealy and Sumerlin (1944), Windholz and Foster (1947), Marson and Meynell (1949), Merskey (1949), Wyatt and Sommers (1950), and H. N. Robson (personal communication, 1952).

We are here reporting three further cases presenting as polycythaemia and terminating as leuco-erythroblastic anaemia and myelosclerosis.

Case 1

A 69-year-old woman, first seen in May, 1946, complained of pain in the lumbar region and in the hips and calves for one year and an aching mass in the left side of the abdomen for five months. Examination revealed a malar flush with slight cyanosis, a moderately enlarged heart, splenomegaly extending down to the symphysis pubis and across to the right side of the abdomen, and slight hepatomegaly. A blood count showed: red cells, 5,920,000 per c.mm.; Hb, 113%; white cells, 11,600 per c.mm. (premyelocytes 1%, myelocytes 8%, metamyelocytes 4%, neutrophils 68%, eosinophils 3%, basophils 2%, lymphocytes 11%, monocytes 3%); 2 nucleated red cells per 100 white cells; and some polychromasia. Achlorhydria was present, serum calcium was 9.6 mg. per 100 ml., and the Wassermann reaction was negative.

Nearly four years later, in February, 1950, readmission was necessary for pain and weakness of the left leg, frequency and urgency of micturition, and weakness, lassitude, and loss of weight. Ankle oedema with pigmentation and ecchymoses over both legs was present. All other physical signs were unchanged. Liver-function tests and radiographs of the long bones were normal. A blood count showed: red cells, 3,100,000; Hb, 66%; white cells 7,000 (myeloblasts 4.5%, premyelocytes 0.5%, myelocytes 6%, metamyelocytes 0.5%, neutrophils 56%, eosinophils 0.5%, basophils 5%, lymphocytes 16.5%, monocytes 8.5%, atypical monocytes 1.5%, mitotic figures 0.5%); 14 nucleated red cells per 100 white cells; and some macrocytosis. A biopsy of sternal marrow showed myelofibrosis; the haemopoietic tissue was almost entirely replaced by fibrous tissue; of the cellular elements megakaryocytes were present in increased numbers; polymorphonuclear cells with a small number of normoblasts could be seen scattered amongst the fibrous tissue; no haemosiderin could be detected by Perles's stain.

Case 2

A 48-year-old farmer's wife, when first seen in June, 1937, complained of morning hunger pains and three recent attacks of epigastric pain, backache, and vomiting. Examination showed a plethoric facies, slight sclerotic icterus, and splenomegaly extending 8 cm. below the costal margin. A blood count showed: red cells 8,500,000; Hb, 122%; white cells, 9,100 (neutrophils 92%, eosinophils 2.5%, basophils 1.5%, lymphocytes 2%, monocytes 2%); reticulocytes, 0.5–1%; some macrocytosis and moderate anisocytosis. Barium-meal examination showed only displacement of the stomach to the right. The presumptive diagnosis being polycythaemia vera, the spleen was irradiated, with considerable improvement.

Irradiation of the humeri and femora with reduction in the blood count—which had again risen to red cells, 7,500,000; Hb, 128%; white cells, 7,400—was carried out in February and March 1942. She remained fairly well for over three years, apart from several severe epistaxes in January, 1944, and on July 19, 1945. In January, 1946, treatment was necessary for the anaemia, then present—red cells, 3,200,000; Hb, 60%; white cells, 3,000; subsequently her condition remained stationary for over three years. Further treatment for the anaemia was necessary in August, 1949. The blood count showed red cells, 2,500,000; Hb, 48%; white cells, 4,200 (myelocytes 2%, metamyelocytes 6%, neutrophils 55%, eosinophils 4%, basophils 2%, lymphocytes 29%, monocytes 2%); 12 nucleated red cells per 100 white cells; and 3% reticulocytes. The spleen extended almost into the left iliac fossa and the liver to 9 cm. below the costal margin. Radiographs of the skull, pelvis, and long bones showed no abnormality. The red-cell fragility test showed commencing haemolysis in 0.5%

Sternal Marrow Counts

Cells	Case 1	Case 2	Case 3
Blasts	4.0	3.0	2.4
Premyelocytes	1.0	—	0.4
Myelocytes	22.0	15.0	10.0
Metamyelocytes	11.0	13.0	7.2
Neutrophils	41.0	34.0	39.6
Eosinophils	—	2.0	2.8
Basophils	—	—	2.4
Lymphocytes	1.0	21.0	23.6
Monocytes	4.0	—	—
Normoblasts	A	—	3.2
"	B	5.0	6.0
"	C	7.0	1.6
Mitoses	1.0	—	0.4
Megakaryocytes	—	—	0.4
Unclassified	3.0	—	—
Nucleated Cell Count per c.mm.	—	—	6,300
Leuco-Erythroid Ratio	—	—	1.6 : 1
Comment	—	A very poor cellular marrow.	Marrow easily obtained, bone not unduly resistant.

saline and completion in 0.35% solution. Sternal puncture revealed a very poor cellular marrow (see Table).

A biopsy was taken from the eighth rib. On section, the outer compact bone formed a thin layer no more than 2 mm. in thickness; the marrow cavity appeared greyish in the preserved specimen; transverse sections showed a notable fibrosis of the marrow spaces in the peripheral zones and a loose-constructed fibrosis, together with adipose tissue in the centre of the medullary cavity; there was no increase in the bony trabeculation of the rib, and, in fact, in many areas giant-cell osteoclasts was active; there was a marked reduction in haemopoietic tissue, which was mainly confined to one or two islets near the rib cortex; the predominant cells seemed to be eosinophil myelocytes; and there were also many eosinophil polymorphonuclears.

Subsequently she was admitted frequently in 1949, 1950, and 1951 for blood transfusion.

Case 3

A foreman engineer aged 51 was seen in March, 1944, complaining of occasional attacks of gout, recent slight loss of weight, and a left subcostal mass present for two years but only recently causing intermittent pain.

Examination showed only moderate enlargement of the spleen. A blood count showed: red cells, 5,600,000, Hb, 120%; white cells, 13,600 (myelocytes 9%, metamyelocytes 3%, neutrophils 45%, eosinophils 1%, lymphocytes 36%, monocytes 6%); 3 nucleated red cells per 100 white cells; and slight anisocytosis. Achlorhydria was present. Radiographs of the chest, lumbar spine, and pelvis revealed no bony abnormalities.

In September, 1945, the spleen extended into the left iliac fossa and the liver was slightly enlarged; few petechiae were scattered over the body. Irradiation of the spleen was carried out then, and in January, 1947, and in March, 1948, his general condition remaining fair. In March, 1949, he had severe perisplenic pain, general weakness, and acute gout. A blood count showed: red cells, 3,400,000; Hb, 64%; white cells, 9,200 (myelocytes 6%, metamyelocytes 15%, neutrophils 66%, lymphocytes 13%); 9 nucleated red cells per 100 white cells; reticulocytes, 3%; bleeding time, 3½ minutes; and clotting time, 5 minutes. The ribs showed an alteration in the bony texture radiologically, but no destructive process was visible. A sternal marrow biopsy showed myelofibrosis; the bony trabeculae were coarse and compactly arranged; the intervening marrow spaces were filled in some areas by adipose tissue, in others by vascular fibrous tissue; islets of haemopoietic cells were few, small, and widely scattered, and in most places were represented by the presence of a few megakaryocytes.

On his last admission, on September 27, 1949, five and a half years after his first appearance, examination showed

anaemia, gross splenomegaly, moderate hepatomegaly, ascites, basal pulmonary oedema, and gross oedema of the ankles. Death occurred on October 12, 1949.

Necropsy Findings

The lungs showed oedema with congestion of the lower lobes. The heart was dilated, with a pale greasy myocardium. The spleen weighed 2,330 g. Its capsule showed several large and small white opaque patches. On slicing, no Malpighian corpuscles could be seen. The surface showed a pale brick-red appearance with several irregular haemorrhagic zones of varying size. The liver weighed 4,020 g. Its capsule also showed opaque white patches. On slicing, the surface was paler and the consistency firmer than normal. There was an irregular fine whitish mottling, in parts simulating the nutmeg effect. Both kidneys on section were paler than normal. The gastric mucosa showed haemorrhagic patches. Some haemorrhages were also visible in the bladder.

Histology

Rib.—A section of rib showed pronounced osteosclerosis. Thick bony trabeculae were present. In some parts the trabeculae were very wide and the marrow space very small. The marrow was fatty towards the centre of the bone, but showed prominent fibrous areas with spindle-shaped cells, apparently fibroblasts, and groups of red- and white-cell precursors. The precursors were scanty and patchily distributed. Giant cells of the megakaryocytic type were prominent in some of the fibrous areas.

Vertebral Body.—The most striking changes were the presence of loose fibrous marrow and the sparseness of red- and white-cell precursors. Occasional multinucleated giant cells were visible. In some areas the bony trabeculae were wider than normal, but osteosclerosis was less pronounced than in the rib.

Spleen.—The normal splenic architecture was destroyed. Some increase in fibrosis was present. Malpighian bodies were absent. Numerous precursors of the red and white cells were present. Large cells with convoluted nuclei, some polychromatic and vesicular and others hyperchromic, were prominent in some parts, as many as eleven being in one high-power field. Numerous cells with indented nuclei and an eosinophilic slightly granular cytoplasm were also present.

Liver.—This showed scattered foci of leucopoiesis and erythropoiesis, situated mainly around the central vein. Amongst the cells of the granular and erythrocyte series there were large multinucleated cells similar to those found in the bone marrow and spleen.

Kidney.—Small foci of erythropoiesis and leucopoiesis were present.

Discussion

These cases presented the characteristic symptomatology, splenomegaly, and other physical signs and haematological features of polycythaemia vera, and resembled others described in that the polycythaemic blood-count figures were not very high.

The development of anaemia in the later stages of polycythaemia has often been noted. Minot and Buckman (1923) described a "secondary" anaemia, but the report of immature red and white cells in the blood suggests that this may have been leuco-erythroblastic anaemia. Several other authors have described the development of a typical leuco-erythroblastic anaemia. It is possible that the leuco-erythroblastic state has often been missed, for McMichael and Mc-Nee (1936) considered that repeated examination of the blood might be required to detect primitive red and white cells owing to the variations and fluctuations in the haematological features. In Case 2, unlike the others, immature red and white cells were not observed until the anaemic phase. As in the other cases mentioned above, myelofibrosis was found during the period of leuco-erythroblastosis. Recently, however, Hutt (1950) and Marson and Meynell (1952) in two cases discovered fibrosis of the sternal

marrow during actual polycythaemia. Cases of myelosclerosis with leuco-erythroblastic anaemia, but without previously recorded polycythaemia, have been reported by several authors, including Stephens and Bredeck (1933) and Rosenthal and Erf (1943).

A common feature of these cases, both with and without previous polycythaemia, has been the presence of myeloid metaplasia in the spleen. Numerous authors have commented on this—for example, Chapman (1933) found extramedullary hyperplasia of myeloid tissue described in 11 out of 14 reported cases. Askanazy (1904) apparently was among the first to indicate that reticulo-endothelial cells could become blood-forming cells in adults, while Hirschfeld (1905) recognized the importance of this myeloid metaplasia as a unifying feature of the cases. In the metaplasia Carpenter and Flory (1941) pointed out that, "in addition to leucoblastic cells, erythroblasts are constantly prominent and giant cells (megakaryocytes) are numerous." Most accounts, with the notable exception of that of Heller, Lewisohn, and Palin (1947), are in agreement with the view that all haemopoietic tissues are involved.

Vaughan (1936b) summarized 17 cases of myelosclerosis: in only one of the 14 cases in which necropsy or biopsy was performed was no myeloid metaplasia found in the spleen. Stephens and Bredeck (1933) collected 24 cases from the literature—19 of which were complete enough to be tabulated—and found that these latter showed splenomegaly, myelosclerosis, and myelaemia, and all but one showed normoblastaemia.

Despite the frequency of the occurrence together of myelosclerosis, leuco-erythroblastosis, myeloid metaplasia in the spleen, and megakaryocytic prominence in the spleen and marrow, which perusal of the literature reveals, the establishment of the syndrome comprising them has been rendered difficult by different authors emphasizing in their titles various characteristic features in these essentially similar cases.

The Syndrome

The morphological, haematological, and clinical features of this polymorphic leukaemia-like syndrome have been discussed by Heller *et al.* (1947). The condition, they say, is characterized clinically by a slowly progressive splenomegaly occurring in persons of either sex, usually within or beyond the fifth decade of life. There may be little impairment in the general health for many years, following which generalized weakness, anorexia, weight loss, ill-defined aches and pains, and discomfort occasioned by the greatly enlarged spleen frequently occur. The liver may enlarge. As a rule there is no significant involvement of the lymph nodes. The blood picture, according to Carpenter and Flory (1941), displays widely varying conditions from a rare initial polycythaemia to varying grades of anaemia, usually normochromic, but occasionally hypochromic; nucleated red cells have been prominent in all but a few cases. Immature red cells have not been seen in the peripheral blood in some cases—for example, Tudhope (1937) and Heller *et al.* (1947). Macrocytosis has occurred in the cases of Carpenter and Flory (1941), Heller *et al.* (1947), Robson (personal communication, 1952), and our Cases 1 and 2. Lindeboom (1938) thought that polychromasia, poikilocytosis, and anisocytosis were more pronounced in these cases than would be expected for the degree of anaemia.

The total white-cell count, according to Thompson and Illyne (1940), is rarely very high and is almost always well below the levels seen in untreated leukaemia. Myelocytes in the peripheral blood are rarely numerous. Occasionally, immature white cells have been absent from the blood as in the cases of Hewer (1937), Tudhope (1937), and Heller *et al.* (1947). Bleeding has occurred in several cases both with and without reported decreases in platelets (Hickling, 1937; Thompson and Illyne, 1940; Carpenter and Flory, 1941; and Heller *et al.*, 1947). Abnormal platelets, megakaryocytic fragments, and megakaryoblasts were observed by Hickling (1937), Carpenter and Flory (1941), Rosenthal and Erf (1943), and Heller *et al.* (1947). Other inconstant

features such as increased fragility of the red cells, slight reticulocytosis, positive indirect van den Bergh reaction, and high blood uric acid levels have been occasionally reported.

In several cases the liver as well as the spleen has been the seat of a myeloid change—for example, McMichael and McNee (1936), Hickling (1937), and Stone and Woodman (1938). This has been found commonly in the dilated sinusoids, but also in the periportal areas or peripherally between adjacent lobules. Less frequently the lymph nodes have been involved as well, as reported by Stone and Woodman (1938), Vaughan and Harrison (1939), and Rosenthal and Erf (1943). Fibrosis of the spleen has also been described by Stone and Woodman (1938) and Jackson *et al.* (1940). Our Case 3 showed some fibrosis in the myeloid metaplasia of the spleen; the liver showed the metaplastic reaction mainly around the central vein.

The bone marrow has not been reported as myelosclerotic in all cases showing leuco-erythroblastic anaemia, splenomegaly, myeloid metaplasia, and symptoms of long duration. How far this may have been due to incomplete examination of the bones cannot now be decided. In nine cases of this syndrome called by them "agnogenic myeloid metaplasia" Jackson *et al.* (1940) described the bone marrow as myelosclerotic in six and hyperplastic, aplastic, and normal in the others. Similar variation is found in the literature, but most frequently the marrow is hypoplastic. Sometimes "hyperplastic foci of haematopoiesis" have been scattered through the fibrotic elements; in a few cases hyperplastic myeloid tissue and fibrosis have been recognized together.

In regard to the sequence of events in the marrow, Wyatt and Sommers (1950), analysing 30 cases, regarded the fundamental lesion as necrosis of partly matured erythroid and myeloid cells with hyperplasia of surviving, usually more immature, cells and marrow reticulum cells. Subsequently, foci of atrophy appear. Eventually "the marrow is relatively acellular, made up of scattered reticulum cells, between which is a pink fibrillar or granular matrix and with numerous dilated empty vessels surrounded by small groups of bizarre megakaryocytes or nondescript haematopoietic cells." The end stage in certain cases involves a distinct type of new bone formation with "focal granular deposits of calcium in the eosinophilic matrix" and later deposition of bone in a layer about part or all of the old trabecular surfaces. The bony radiographic appearances of myelosclerosis have been described by Sussman (1947) as initially widening and increased density of the trabeculae followed by deposition of bone in an irregular fashion throughout the marrow cavity without thickening of the cortices or periosteal reaction.

Nature and Pathogenesis

Most authors, with the notable exception of Heller *et al.* (1947), believe this syndrome to be a separate entity and not merely a variant of leukaemia. Carpenter and Flory (1941) listed the principal features which have been held to differentiate this syndrome from leukaemic myelosis (myelogenous leukaemia) as (1) the diversity of cell types in metaplastic zones in organs and in the bone marrow; (2) the commonly low white-cell count with the low proportion of circulating primitive cells; (3) the almost constant presence of nucleated red cells; (4) the frequency with which osteosclerosis and myelofibrosis are encountered; and (5) the absence of characteristic leukaemic infiltrations. Further differentiation from leukaemia has been made by Erf and Herbut (1944), who pointed out that "extramedullary haematopoiesis is a focus of normal bone marrow situated elsewhere than within bone and attempting to produce normal circulating red and white cells," whereas "leukaemic infiltration is a focus of infiltrating immature white blood cells which because of their inherent reproducing capacities produce more immature white cells." They have also drawn attention to the large numbers of giant cells in the metaplastic myeloid tissue in the organs. In view of its asso-

ciation at times with tuberculosis of the spleen (Swirtschewskaja, 1926), generalized infections (Brannan, 1927), and malignant metastatic deposits in the bone marrow (Hickling, 1937), it would appear that extramedullary haematopoiesis cannot be regarded simply as compensatory to the marrow sclerosis. Indeed, as Heller *et al.* (1947) have pointed out, more severe and persistent anaemias of other types do not occasion the massive extramedullary haematopoiesis found in myelosclerosis.

The myelosclerosis has been thought to result from an unknown toxin (Donhauser, 1908), the irritative effect of hyperplastic myeloid tissue (Hewer, 1937), or atrophy of the marrow (Wolf, 1932); it has been found in association with haemolytic anaemia (Wyatt and Sommers, 1950), metastatic carcinomatous deposits (Thompson and Illyne, 1940; Erf and Herbut, 1944), and tuberculosis (Hewer, 1937; Stone and Woodman, 1938). Windholz and Foster (1947) suggested the importance of Rh factor serological studies.

We agree with Vaughan and Harrison (1939) that the sclerosis of the marrow follows the same stimulus as produces extramedullary haematopoiesis. In other words the myelosclerosis is a dynamic process resulting from a definite stimulus rather than a sequel to atrophy of haemopoietic elements. The stimulus might be a deficiency in some nutritional factor, either direct or conditioned by other disease, or an abnormal metabolite. As pointed out by Vaughan and Harrison (1939) all the cell types involved in the hyperplasia are derived from a common source—the primitive reticulum-cell of Maximow. A common stimulus might therefore affect in degrees, varying from patient to patient, the osteoblasts, fibroblasts, the several series of haemopoietic cells, and megakaryocytes.

From this basic pathological process with diverse morphological possibilities a complex clinical and haematological syndrome results, not every case of which, as might be expected, will show all the various features recognized as characteristic. In this respect, Robson's case (personal communication, 1952) is of interest. Initially a sternal trephine was obtained showing marked osteosclerosis and megakaryocytosis with fibrosis, the blood picture being leuco-erythroblastic anaemia, and the spleen and liver showing myeloid metaplasia. Subsequently the blood count reached polycythaemic levels. Finally, at necropsy, three years after the onset, the marrow was seen to have reverted to a hyperplastic state with megakaryocytes still numerous, and some fibrosis still remaining but with little sign of the previous osteosclerosis, while the spleen and liver still showed metaplasia. In another case subsequent polycythaemia was described by McMichael and McNee (1936) 17 months after splenectomy had been undertaken for splenomegaly, myeloid metaplasia, and leuco-erythroblastic anaemia.

An indication of this diagnosis may be obtained during the investigation of obscure anaemia by the finding of difficulty in obtaining marrow from a sternal puncture and the absence of the characteristic "give" which occurs normally when the needle has penetrated to the marrow cavity. Most important, however, is the performance of marrow biopsy in cases showing features suggestive of the syndrome, or where sternal puncture fails.

Summary

Three cases of polycythaemia in two women aged 69 and 48 and a man aged 51, are described. Leuco-erythroblastic anaemia and myelosclerosis subsequently developed after 4, 12, and 5 years respectively.

Previous reports of leuco-erythroblastosis with myeloid metaplasia and myelosclerosis following polycythaemia vera are reviewed.

The syndrome, comprising leuco-erythroblastosis, myeloid metaplasia, and myelosclerosis, as revealed in the literature, has a varied clinical picture. It is thought to be distinct from myeloid leukaemia.

Vaughan and Harrison's view of the concomitant development from a common source—the primitive reticulum-cell of Maximow—of extramedullary haematopoieses and of myelosclerosis following some, as yet unknown, stimulus offers a reasonable explanation of the events.

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New regulations enable penicillin and aureomycin (the latter in a restricted form) to be used in the food of pigs and poultry, subject to certain safeguards. Both these preparations are controlled under the Penicillin Act, 1947, so that their retail distribution is otherwise limited to supplies given by, or under the direction of, doctors, dentists, and veterinary surgeons, or dispensed on their authority by pharmacists. The regulations have been made after consultation with the Medical Research Council and Agricultural Research Council, and come into operation on September 1. The antibiotics may be used either in the form of a supplement to be added to existing food or ready mixed with the food by the manufacturers of pig and poultry food. Safeguards to health are provided for in that (a) only minute quantities are needed and a maximum concentration is specified for both the supplement and the feeding-stuffs, and (b) the appropriate Health Minister must approve the composition of the diluent of the supplement. It will not be practicable to extract the antibiotic for use as medicine. These arrangements will not affect medical supplies. There is plenty of penicillin, and aureomycin will be used in the form of the residue from the process of extraction or in any other approved dilute preparation. The regulations also require certain information relating to the supplement and the antibiotic included to be given on the labels of the containers in such manner as the appropriate Agriculture Minister may require; they also empower him to require additional information to be given about the storage and use of supplement. The regulations apply to England and Wales, Scotland, and Northern Ireland, and are entitled the Therapeutic Substances (Supply of Antibiotics for Agricultural Purposes) Regulations, 1953.