Pleural extramedullary haematopoiesis in myelosclerosis

H. C. ANTON
M.B., Ch.B., D.M.R.D., F.F.R.

J. B. P. FERGUSON
M.B., Ch.B.

G. P. LEWIS
M.D., B.Sc., M.R.C.P.(Ed.)

Stobhill General Hospital, Glasgow

DESPITE the extensive literature on myelosclerosis and extramedullary haematopoiesis (myeloid metaplasia), reference to the pleura as being the site of extramedullary haematopoiesis is not made in either the standard medical and pathology textbooks or in the radiological literature. We have recently encountered a case of myelosclerosis in which aspiration of what appeared on both clinical and radiological grounds to be a pleural effusion failed to reveal the presence of fluid. Subsequent pleural biopsy carried out at the same site showed tissue, at first regarded as tumour, but later shown to be a manifestation of extramedullary haematopoiesis. Because such a lesion when it occurs at this particular site is liable to be misinterpreted, we feel that a description of this case is justified.

Myelosclerosis may be regarded as a form of myelofibrosis with thickening of the bony trabeculae of the marrow on histological examination. The diagnosis of myelofibrosis is made when the presence of fibrosis on bone marrow biopsy is associated with a leuco-erythroblastic anaemia. A mild increase in bone trabeculation may cause an osteosclerosis visible on X-ray examination.

Myelofibrosis may be a complicating feature of many diseases including lymphoma, metastatic carcinoma, leukaemia and aplastic anaemia, under which conditions it is termed secondary myelofibrosis (Pitcock *et al.*, 1962). They emphasize that in secondary myelofibrosis, evidence of the underlying disorder may be found on examination of bone-marrow sections as well as the presence of fibrous tissue. Furthermore, in such cases, the blood picture may be distinctive. Myelofibrosis without an associated haematological, reticulo-endothelial or neoplastic disorder is classed as being idiopathic. The above authors, however, consider that myelofibrosis following polycythaemia vera should be included in the idiopathic

myelofibrosis group, because it cannot be differentiated pathologically once fibrosis has developed in the bone marrow. The case to be described belongs to the idiopathic myelofibrosis category.

Extramedullary haematopoiesis accompanies many types of bone marrow disease including idiopathic myelofibrosis, carcinomatosis, lymphoma, leukaemia, marble bone disease, erythroblastosis, haemolytic anaemia, pernicious anaemia, thalassaemia, Gaucher's disease, osteitis deformans, osteomalacia, osteitis fibrosa cystica, tuberculosis and exposure to toxic agents such as benzene, fluorine and irradiation. In a recent report, sickle-cell anaemia was found to be associated with extramedullary haematopoiesis (Seidler & Becker, 1964). Rarely, extramedullary haematopoietic tissue may occur in patients not suffering from diseases of the blood or bone marrow. Dodge & Evans (1956) describe a presacral retroperitoneal fatty tumour with haematopoietic foci, for which they suggest myelolipoma as a suitable descriptive term. It should be pointed out that extramedullary haematopoiesis does not necessarily occur in myelofibrosis: Korst, Clatanoff & Schilling (1956) found it in only eleven of their twenty-three cases.

Case report

The patient, a female aged 65, was admitted to hospital with a 6-month history of loss of weight and appetite, weakness and severe diarrhoea. A radium menopause had been carried out 20 years previously for menorrhagia.

On examination there was pigmentation of exposed areas of skin, pallor of mucous membranes and marked oedema of the legs and anterior abdominal wall, but no ascites. The spleen was palpable and firm and the liver grossly enlarged and tender with some nodularity. There were clinical signs of a left pleural effusion. This was confirmed by a chest X-ray which also showed a

marked sclerosis of bone (Fig. 1). Subsequently the left pleural reaction diminished on X-ray follow-up, but did not disappear, and later a right-sided

FIG. 1. Moderate pleural reaction at left lower zone. Patchy osteosclerosis.

pleural reaction developed. Although the first impression of one of us was that the bone sclerosis was probably due to osteoplastic metastases, films of the spine and pelvis were later reported as showing myelosclerosis. A pleural tap of the left lung base attempted 1 week after admission failed to reveal the presence of fluid. Because of this, pleural biopsy was carried out.

The pathology report described a cellular 'tumour' with giant cells, small cells with dark nuclei, and a few lymphocytes and eosinophils (Fig. 2). Subsequently a retrospective diagnosis of myeloid metaplasia was made. As it seemed likely that the 'tumour' was secondary, numerous investigations were carried out to locate a primary source, including IVP and barium studies, but no evidence of a primary focus was found. A sternal puncture was reported as follows: 'Sections show dense bone, no marrow, a few fat spaces and young fibrous tissue replacement. This is highly suggestive of myelofibrosis.' This diagnosis was confirmed by a trephine biopsy of sternum (Fig. 3).

Throughout most of her illness the haemoglobin ranged from 8.2 to 9.5 g/100 ml but terminally fell to 7.5 g/100 ml. The PCV averaged 29% and the MCHC varied from 29% to 33%. Reticulocytes, at first 2%, reached 5% in the late stages of

FIG. 2. Original pleural biopsy. High power. Marked anisocytosis and poikilocytosis of cells with hyperchromatic nuclei also varying in size and shape.

FIG. 3. Sternal marrow. Normal marrow replaced by young loose fibrous tissue with capillary spaces containing primitive red cells. Increased trabeculation of bone gives a mosaic appearance.

her illness. White cell counts ranged from 8400 to 15,800/mm³. The white cells showed immature forms, mostly myelocytes but with a few blast cells. Terminally the proportion of primitive cells rose considerably. Films showed the red cells to be well haemoglobinated but there was moderate anisocytosis and poikilocytosis. Nucleated red cells were present. Platelets were increased up to 820,000/mm³ and were unusually varied in size and shape, some being described as massive.

Other haematological tests showing abnormality included a serum vitamin B₁₂ level of 25 pg/ml and a serum iron of 6 µg/100 ml (TIBC 300 µg/100 ml).

During the course of her illness, the patient exhibited proteinuria of moderate degree. On the first admission the serum urea was 55 mg/100 ml but with deterioration in her condition gradually rose so that terminally it was 156. There was mild hyperchloraemia and hyperkalaemia. The total serum proteins showed a persistent moderate reduction; the albumin-globulin ratio was normal. Liver function tests were at all times normal apart from a raised alkaline phosphatase (35 KA U/100 ml).

Oedema and anaemia persisted in spite of therapy with diuretics, vitamin B₁₂, blood transfusion and oral and parenteral iron. In the summer of 1965 her poor general state was complicated by the development of haematemesis. At the time of her final admission in August 1965, ascites was manifest. She subsequently underwent gradual deterioration and died 18 months after her first admission.

Necropsy

There was clear amber fluid in both pleural cavities. Over the visceral pleural surfaces of both lower lobes and in the case of the right, especially the diaphragmatic surface, there were discrete flat white nodules with serrated edges, measuring from 1 to 2 cm in diameter. In places they had become confluent forming large plaques. The lungs were oedematous and congested and the heart showed slight brown atrophy.

Marked peritoneal adhesions and slight ascites were present. The spleen (1070 g) was greatly enlarged and cut section revealed a diffusely pale infiltrated surface. The liver (2450 g) was also greatly enlarged and on section there were large nodules of white 'tumour' tissue surrounding the porta hepatis. In the right lobe there were discrete white nodules surrounding the portal tracts, measuring from 1 to 5 cm in diameter. Enlarged glands were present along the line of the portal vein but there were no enlarged glands elsewhere. The kidneys were small, the capsules were removed

with difficulty and revealed a slightly granular surface. On section there was 'pouting' of vessels and narrowing of the cortices. There was pale marrow in the vertebrae but the sternal marrow was replaced by fibrous tissue. Other systems showed no abnormality.

Histologically, the marrow was replaced by loose fibrous tissue permeated by capillaries with small foci of erythropoiesis and some bizarre megakaryocytes, i.e. the typical findings of myelofibrosis. There was also an increased trabeculation of bone.

The spleen showed extramedullary haematopoiesis in the red pulp, fibrosis, bizarre giant cells probably megakaryocytes, a moderate degree of haemorrhage and slight subcapsular iron deposition. Liver sections showed that the nodules were formed of young fibrous tissue with small foci of primitive haematopoiesis and megakaryocytes. The normal liver architecture was not destroyed outside the nodules but groups of granulopoietic and erythropoietic cells were identified in and around dilated sinusoids. Similar histological appearances to that of the liver nodules were present in the lymph nodes and in the pleural nodules. The kidneys showed features of chronic pyelonephritis, diffuse membranous glomerulo-nephritis and moderate arterio and arteriolar sclerosis. Foci of myeloid metaplasia were present in the interstitial tissue.

Discussion

The clinical presentation and course of this patient's illness is consistent with the diagnosis of myelosclerosis with associated extramedullary haematopoiesis. The occurrence of intractable and persistent oedema is difficult to explain on the basis of hypoalbuminaemia alone. The subsequent demonstration at post-mortem of chronic pyelonephritis with diffuse membranous glomerulo-nephritis helps to clarify this puzzling feature. It is of interest that renal disease of slight to moderate degree, not characterized by calculi formation, was found in five of eight autopsies described by Pitcock *et al.* (1962). The bone sclerosis observed in this case could not, however, have resulted from renal disease because of the absence of both uncalcified osteoid seams and osteoclastic erosions, features normally found in uraemic osteodystrophy (Follis & Jackson, 1943; Craven, 1964). Furthermore X-ray of the lumbar vertebrae failed to reveal the 'Rugger Jersey' sign of renal osteodystrophy (band-like increases in the density of the upper and lower parts of the vertebral bodies) described by Dent (1955).

When first seen at the outpatient department the marked degree of cachexia exhibited by the patient led to a presumptive diagnosis of neoplastic

disease. This erroneous impression was later apparently confirmed by the demonstration of 'neoplastic tissue' in the specimen obtained by pleural biopsy. During the post-mortem examination the identification of enlarged glands in the region of the porta hepatis and obvious intra-hepatic nodules seemed again to support this diagnosis. That myelofibrosis can mimic carcinomatous metastases of osteoblastic type has been pointed out by Wyatt & Sommers (1950). These authors emphasize that the metastatic lesions can be distinguished by the presence of tumour masses in the liver and elsewhere. It therefore came as a surprise when detailed histological studies showed the tumour-like deposits affecting the glands of the porta hepatis and the liver to be solely foci of haematopoietic tissue with an unusual degree of fibrotic reaction.

The radiological signs in this case correspond to the description of twenty-five cases of myelofibrosis by Leigh *et al.* (1959). They emphasize the central distribution of the osteosclerosis with sparing of the peripheral bones and state that while the bone density is often diffusely increased, in more severe cases discrete sclerotic foci are present. As well as osteosclerosis they list splenomegaly and hepatomegaly as other radiological signs, but do not describe lesions in other sites due to extramedullary haematopoiesis. That unusual sites of extramedullary haematopoiesis may be mistaken for other pathological entities has been reported by many. Close, Taira & Cleveland (1958) describe a case of spinal cord compression demonstrated on myelography later shown to be due to extradural myeloid metaplasia associated with myelosclerosis. Similar cases have been reported by Lowman, Bloor & Newcomb (1963) and Appleby *et al.* (1964).

Intrathoracic extramedullary haematopoiesis showing on chest X-ray as fairly large, well-defined, lobulated masses located posteriorly in the paravertebral gutters can present a difficult diagnostic problem. Such a picture may occur in seminoma metastases and reticulosis (Shanks & Kerley, 1962) but a suspicion of such lesions being due to tumour-simulating extramedullary haematopoiesis may be raised by the blood findings, or by radiological evidence of bone marrow disease. Early reports of intrathoracic tumour-simulating extramedullary haematopoiesis were based on autopsy findings. The first diagnosis on clinico-radiological grounds, in a patient with acholuric jaundice, was presented by Ask-Upmark (1945). Another case was described by Knoblich (1960) in which an initial diagnosis of intrathoracic neurofibromata was made. In two cases of congenital haemolytic anaemia with paravertebral masses

demonstrated by chest X-ray, thoracotomy was considered mandatory to exclude neoplastic disease (Hanford, Schneider & MacCarthy, 1960). Two further cases associated with congenital haemolytic anaemia have been described in the paper by Lowman *et al.* (1963). Malamos, Papavasiliou & Avramis (1962) describe a case of Cooley's anaemia showing on chest X-ray characteristic rib thickening but with, in addition, tumour-like masses in the paravertebral gutters. Aspiration biopsy of these masses confirmed that they were due to extramedullary haematopoiesis.

Little mention has been made in the literature to the pleura as being the site of extramedullary haematopoietic deposits. Brannan (1927) merely states that myeloid activity may occur at this site but gives no further details. Knoblich (1960), using Brannan (1927) as his authority, includes the pleura in his comprehensive list of possible sites for extramedullary haematopoiesis. Pitcock *et al.* (1962) describing their autopsy series found diffuse thickening of the pleura and peritoneum in many. They make the interesting observation that extramedullary haematopoietic foci may present as tumours, which have many of the characteristics of intramedullary bone marrow tissue in that they contain, together with haematopoietic tissue, variable amounts of fibrous tissue.

More recently Lieberman, Rosvoll & Ley (1965) describe the clinical and autopsy findings in three cases showing extramedullary myeloid tumours out of twelve cases of myelofibrosis and myelosclerosis with myeloid metaplasia. In one case tumour nodules of myeloid tissue on the pleural surfaces, up to 1.5 cm in size, were found at post-mortem, with much larger nodules in the liver and spleen. In their third case a scalp tumour of myeloid tissue (at first interpreted as a reticulum cell sarcoma), was removed during life and later a 7.5 cm tumour mass in the wall of the small intestine was excised.

It is clear that pleural involvement has been previously noted at autopsy but we think that this case is the first in which it produced a diagnostic problem for the clinician, radiologist and pathologist during the life of the patient.

Summary

An account is given of a case of myelosclerosis with extramedullary haematopoiesis, involving the pleural surfaces. Previous reports of this phenomenon are quoted. Other presentations of extramedullary haematopoiesis are briefly discussed.

Acknowledgment

We wish to thank Mr T. P. S. Waldie for the illustrations.

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Neurofibromatosis with pancreatic duct obstruction and steatorrhoea

K. G. WORMSLEY
M.D., M.R.C.P.

V. F. SORRELL
M.B.(N.Z.), F.R.C.S.

W. F. W. E. LOGAN
M.B., M.R.C.P.

G. C. COLE
M.B., Ch.B.

Manchester Royal Infirmary

INVOLVEMENT of the alimentary tract is a well recognized and documented manifestation of neurofibromatosis, but there appears to be no record of steatorrhoea complicating this disorder. We have encountered two patients in whom steatorrhoea was due to obstruction of the pancreatic duct by neoplastic processes attributable to this disease.

Case 1

F.S., male, aged 40, was admitted to hospital for investigation of severe diarrhoea of 1 years duration associated with considerable weight loss. The faeces were typically fatty.

Examination revealed a cachectic anaemic man with oedema of the feet and the typical cutaneous stigmata of neurofibromatosis.

Investigation confirmed the presence of severe steatorrhoea (Table 1). Jejunal biopsy was normal but duodenal intubation with pancreatic stimulation (Burton *et al.*, 1960) showed no appreciable pancreatic secretion although the biliary fraction was normal. Radiological studies of the alimentary tract and gall bladder were normal. The anaemia (Hb 9.6 g/100 ml) was due to thalassemia minor (β chain type, Hb A₂ 4.1%, Hb F 1.5%).

Laparotomy revealed a nodule (7 mm diameter) on the medial wall of the second part of the duodenum at the orifice of the pancreatic duct, which was obstructed 1 cm from its entry into the duodenum. The pancreas was small and atrophic.

The bile duct opened into the duodenum 2 cm proximally to the pancreatic duct. The obstructing nodule was excised. Histological examination