Agnogenic Myeloid Metaplasia and Spinal Cord Compression

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SUMMARY

A 55-year-old White male with agnogenic myeloid metaplasia, proved on bone marrow trephine biopsy, underwent splenectomy for abdominal discomfort. Six months later he developed paraparesis and on myelography multiple extradural obstructions were seen. In the absence of other obvious diagnostic possibilities, these were attributed to areas of extramedullary haematopoiesis, and he was treated with local radiotherapy. However, the neurological deficit progressed and emergency laminectomy and decompression were undertaken. Tissue obtained at this time confirmed the diagnosis of agnogenic myeloid metaplasia. A repeat myelogram showed complete relief of the obstruction, but the patient developed fulminating septicaemia and died. These findings are reported in view of the great rarity of spinal cord compression due to multiple areas of extramedullary haematopoiesis.


Ectopic areas of blood formation or extramedullary haematopoiesis occur in association with many conditions including haemolysis and metastatic disease of the bone marrow. Of the many synonyms for this entity, the term agnogenic myeloid metaplasia is favoured for the idiopathic variant which is generally regarded as a member of the myeloproliferative syndrome. Whatever the mechanism causing the extramedullary haematopoiesis the symptoms reflect hyperplasia of marrow at sites of blood formation that existed in fetal life, and this distribution determines the protean manifestations of the disease in the adult. Thus, signs and symptoms may be related to collections of blood-forming tissue in the spleen, liver and lymph nodes and, on rare occasions, the lung, kidney, gastro-intestinal tract, and even further afield. However, haematopoiesis giving rise to symptoms in the central nervous system from compression of the spinal cord is exceedingly rare and we are able to report the details of one further case.

CASE REPORT

The patient was a 55-year-old male who was first seen by his private physician in 1962 because of a change in bowel habit. He underwent a right hemicolecotomy for stage I carcinoma of the colon, and in the ensuing 15 years he remained disease-free. Ten years later, at the time of herniorrhaphy, no organ enlargement was found and haematological investigations were normal. In August 1975, he presented with epigastric discomfort, easy bruising and sternal tenderness, but the remainder of the history was not contributory. Examination at this time showed the patient to be well preserved, and physical findings were restricted to a 10-cm hepatomegaly and a 12-cm splenomegaly.

Investigations showed a haemoglobin concentration of 13.1 g/dl; total white cell count varied between $10 \times 10^9/\text{l}$ and $30 \times 10^9/\text{l}$ with a well-marked leuco-erythroblastic blood picture; the red blood cells showed marked anisocytosis, poikilocytosis, and many tear-drop forms were present. Between 10 and 100 nucleated red blood cells were seen for every 100 white cells counted. The platelet count varied between $100 \times 10^9/\text{l}$ and $250 \times 10^9/\text{l}$ with many of the platelets being grossly abnormal and significantly right-shifted on platelet sizing. Tests of platelet function demonstrated a qualitative defect in response to the aggregating agents adrenaline and collagen. Bone marrow aspiration was unsuccessful but trephine biopsy demonstrated marked megakaryocytic dysplasia and myelofibrosis (Fig. 1). The biochemical profile was normal apart from a uric acid level of 0.7 mmol/l, and the patient was accordingly started on 300 mg allopurinol daily.

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Fig. 1. Low-power view of trephine biopsy specimen demonstrating increased reticulum.
Since the epigastric discomfort was clearly related to the patient's markedly enlarged spleen, and in view of the established diagnosis of myelofibrosis without evidence of leukaemic transformation, an elective splenectomy was carried out under cover of allogeneic platelet transfusions. The operation was uneventful and haematological values were not significantly changed.

The spleen, to which a 1.5-cm splenunculus was attached, measured 19 x 13 x 8 cm and weighed 925 g. The capsule and cut surfaces were unremarkable, but microscopy revealed sinusoidal congestion with extensive extramedullary haemopoiesis involving mainly the erythroid and myeloid series, although occasional megakaryocytes were present.

The patient was discharged from hospital and continued to attend the haematology outpatients department. In the middle of March 1976, 5 months after splenectomy, he complained of excruciating pain at the level of T7 and T8 which radiated in a characteristic root distribution. He volunteered that his legs felt weak, that he had been constipated for 10 days and had had urinary retention for 18 hours.

On examination he appeared generally well. Examination of the abdomen revealed a distended bladder and a liver palpable 10 cm below the costal margin. The anus was patulous on rectal examination. The legs were weak and graded 2/5 in all muscle groups, reflexes elicited at the knee and ankle were pathologically brisk, and both plantar reflexes were extensor. There was a clear sensory level on the trunk at T7 with loss or diminution of all modalities below this. Haematological and biochemical findings on admission were unchanged. A repeat trephine biopsy confirmed extensive fibrosis with left-shifted granulocytic series and numerous dysplastic megakaryocytes. No evidence of leukaemia or any infiltrative lesion was seen.

Radiological studies showed cervical spondylosis with disc narrowing at the level of D5 - 6 and a large paravertebral mass lying opposite the bodies of T7, 8 and 9 on the left. The lumbar spine was normal. A myelogram showed a partial obstruction caused by an extradural lesion extending from the lower border of L4 down to the sac (Fig. 2), a second epidural mass displaced the cord to the right at the level of T7 - 9 (Fig. 3), and a complete block to the flow of radio-opaque medium was present at T7 - 6.

In the context of the patient's established clinical diagnosis, these findings were interpreted as extramedullary haemopoiesis, and emergency radiotherapy was administered to the spinal cord with 600 rad fractions. Within 24 hours, however, the neurological lesion had progressed to paraplegia and emergency laminectomy and decompression were performed. At this operation an indurated brown mass of tissue was present in the epidural space extending from T6 to T8 on the left side and displacing the spinal cord to the right. At the level of T6 and T7 there was another large deposit lying behind the right side of the cord. As much of the abnormal tissue as was practical was evacuated. Histological examination of this material showed haematopoietic tissue with a predominance of granulocyte cells in all stages of maturation, occasional red cells and megakaryocytes (Figs 4 and 5).
Postoperatively the patient was treated with high-dose dexamethasone. There was initial improvement in the muscle power in the legs to grade 4/5, with return of bladder sensation. However, 3 weeks after the operation the patient relapsed, paraplegia returned, and following urinary tract infection and *Klebsiella aerogenes* septicaemia, he died.

Postmortem Examination

The positive gross features were the presence of anaemia, a moderate degree of atheroma with fatty degeneration of the myocardium and acute pyelonephritis with multiple abscesses and papillary necrosis in the kidneys.

In the haematopoietic system there was prominent extension of red marrow down the shafts of the long bones, the spleen was absent from the previous operation and the liver was enlarged to 1935 g. The spinal cord showed a mass of necrotic tissue in relation to the laminectomy sites measuring $10 \times 5 \times 5$ cm and this was intimately associated with the cord. There were no other masses, particularly at the level of L4 and L5.

Histological examination confirmed the presence of papillary necrosis and pyelonephritis in the kidneys and failed to show any evidence of extramedullary haematopoiesis in the liver. The bone marrow showed minimal myelofibrosis with general hypocellularity. The spinal mass was necrotic tissue only.

No evidence of residual colonic carcinoma was present either on macroscopical examination or in any of the histological preparations.

**DISCUSSION**

The pathogenesis of primary extramedullary haematopoiesis or agnogenic myeloid metaplasia remains enigmatic. On the one hand there is the suggestion that this entity reflects nothing more than an extension of bone marrow into anatomically related areas in response to enhanced haematopoietic drive, but a point against such a simplistic compensatory hypothesis is the fact that morphological characteristics of the marrow in the two sites are not necessarily the same. For example, in haemolytic anaemia due to the haemoglobinopathies the marrow should be characterized by erythroid hyperplasia, but extramedullary haematopoiesis contains megakaryocytes and myeloid cells. The alternative suggestion is that agnogenic myeloid metaplasia represents reactivation of the haematopoietic capacity of primitive mesenchymal cells reflecting fetal blood formation.

The most common association of agnogenic myeloid metaplasia is its appearance in the spleen, lymph nodes and liver. On occasions it may occur in more unusual sites such as the lung, kidneys and the gastro-intestinal tract, but cases of its presence in the central nervous system are exceedingly rare. It is not difficult to understand why this should be, since it reflects the site of primitive tissue laid down in a segmental pattern in association with the development of the spinal cord. An unexplained feature is the predilection for the mid- and lower thoracic regions of the spine. In general terms, the signs and symptoms resulting from such accumulations of marrow are of importance both in exploring the pathogenetic mechanisms of the syndrome and also because complications arising in this way are easily treatable, for example by local radiotherapy. In more specific terms the development of central nervous system signs and symptoms in the patient with myeloproliferative syndrome or in whom such an entity is suspected, should immediately focus attention on the possibility of this complication, since the tumour is radiosensitive, and local treatment provides an opportunity for rapid reversal of the complications. One possible explanation for the apparent rarity of the tumorous swelling in these sites is that, even in such patients, specific autopsy studies are not undertaken to examine this possibility. However, when studies are carried out in such patients, myeloid metaplasia, which has been clinically silent, is frequently found at autopsy. It therefore remains theoretically possible that such deposits may be present at a subclinical level more often than is generally appreciated.

The apparent discrepancy between two antemortem trephine biopsies in our patient, both showing advanced myelofibrosis, and the postmortem findings is not unusual. This disease is known to be patchy and it is quite possible to have areas of hypercellularity interspersed with fibrous tissue. Furthermore, there are examples of similar findings in the literature. We have interpreted our observations as being consistent with relatively early and rapidly progressive disease as gauged by the onset of clinical splenomegaly. We consider the diagnosis to be firmly based since the patient has unequivocal myeloproliferative syndrome with myelofibrosis, and haematopoietic tissue was demonstrated in the paravertebral mass obtained at operation.

Of interest is the possible association between splenectomy and the central nervous system tumours in our patient. The removal of the spleen is associated with hepatomegaly in some patients on the basis of myelofibrosis, and it is furthermore known that this may progress to liver failure. However, one study has demonstrated that splenectomy does not apparently produce any adverse effect upon the course of the disease, but in view of the
small number of patients studied and the great rarity of extramedullary haematopoiesis in the central nervous system, it might nevertheless be speculated that this was a contributing factor.

The failure of laminectomy and decompression, coupled with further radiotherapy, to completely relieve the symptoms in our patient may be related to oedema of the residual necrotic tissue that was demonstrated at the autopsy. It is noteworthy that in one report decompression did not alter neurological changes or muscle strength and a block revealed 2 months afterwards was treated with radiation. Even then these findings persisted. However, the fact that radiotherapy successfully removed the other obstructions in our patient is a cogent argument for its effectiveness in having been instrumental in reducing the symptoms. It may be speculated that the development of septicemia with constitutional changes was sufficient to retard recovery in our patient, who already had a compromised blood supply to the cord as a result of his previous therapy, possible arteritis from the radiotherapy and oedema from the residual tumour necrosis.

Finally, the role of splenectomy in possibly contributing to the pyelonephritis and the renal papillary necrosis was considered in the light of a recent study^{2} that removal of the spleen increases the risk of septicemia in patients in proportion to the severity of their underlying disease. While only marginal changes are found after splenectomy for traumatic rupture of the spleen, this complication assumes much more impressive proportions in the presence of haemolytic disease and other haematological disturbances. We conclude that the presence of myeloproliferative syndrome with agnogenic myeloid metaplasia in this patient was responsible for the development of extradural obstruction with spinal cord compression on the basis of extramedullary haematopoiesis. The possibility that prior splenectomy for splenomegaly may have contributed is unsubstantiated, although it is theoretically possible that removal of the spleen may have influenced the later development of infection and septicemia in this individual. The importance of considering this diagnosis is emphasized by the radiosensitivity of the masses of haematopoietic tissue and therefore the availability of a practical form of therapy by means of local irradiation. The progression of symptoms following treatment is believed to reflect oedema with further swelling from the radiotherapy which precipitated the need for decompressive surgery. The slow resolution of the neurological lesion may be associated with residual oedema, radiation-induced changes in the vessels and a compromised blood supply. Although this association is of great rarity, we believe it provides important information as regards the interrelationship between extramedullary haematopoiesis and either infiltration conditions of the bone marrow or those where there is a breakdown between cell division and regulation as exemplified by the myeloproliferative syndrome.

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