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Case report

Arthritis due to synovial involvement by extramedullary haematopoiesis in myelofibrosis with myeloid metaplasia

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SUMMARY A 60-year-old man presented with polyarthralgias, a psoriasiform rash, and severe elbow pain. Peripheral blood smear and bone marrow biopsy established a diagnosis of myelofibrosis with myeloid metaplasia. Biopsy of the skin lesions revealed a nonspecific dematitis. The clinical presentation was inconsistent with psoriatic arthritis, and there was no evidence for associated gout or collagen-vascular disease. Histological examination of tissue taken at the time of synovectomy indicated elbow arthritis to be due to myeloid metaplasia involving the synovial membrane.

Rheumatic complications of malignancy include direct synovial invasion by metastases of solid tumours or by leukaemic infiltrates, a variety of paraneoplastic syndromes, secondary gout, hypertrophic osteoarthropathy, and cancer polyarthritis.[1] To add yet another entity we report arthritis in a patient with myelofibrosis (agnogenic myeloid metaplasia) due to synovial infiltration by myelopoietic elements.

Case report

A 60-year-old white male presented in September 1975 with profound malaise of recent onset. He gave a 5-year history of intermittent arthralgias involving his elbows, shoulders, and neck; pain in the right elbow had become constant and increasingly severe over the past several months. Physical examination disclosed hepatomegaly and a psoriasiform rash on the shins, knees, and elbows. There were no nailbed abnormalities. The synovial membrane of the right elbow was thickened, and a 40° flexion contracture was present. Roentgenograms showed mild sclerotic changes in the right elbow (Fig.1) and calcification of the medial collateral ligament of the right knee.

Haematocrit (HCT) was 33%, white blood cell (WBC) count 12·1 × 10^9/l, (3% bands, 63% segmented polymorphs, 6% eosinophils, 1% basophil, 27% lymphocytes) and platelets 415 × 10^9/l. Peripheral smear showed tear drop poikilocytosis, fragmented red blood cells (RBC), occasional nucleated RBC, increased numbers of immature leucocytes (PMN), and giant platelets. A bone marrow aspirate yielded a dry tap; bone marrow biopsy showed 20–25% fibrosis with increased numbers of large megakaryocytes in clusters. Leucocyte alkaline phosphatase activity was normal. Skin biopsies of 2 psoriasiform skin lesions showed diffuse, mild, dermal lymphocytic and histiocytic infiltrates, with normal epidermis and cutaneous adnexa.

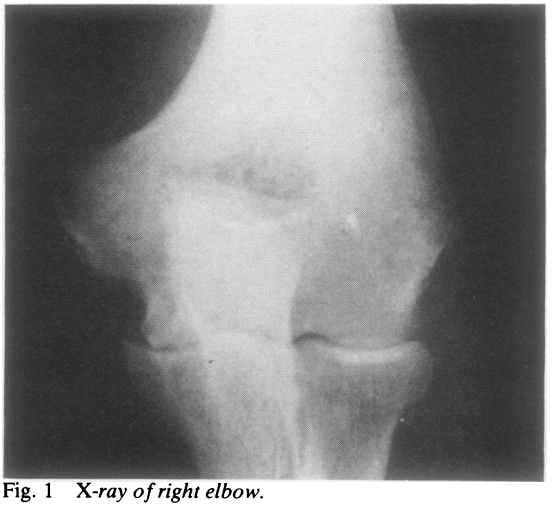

Fig. 1 *X-ray of right elbow.*

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Over the next year the patient continued to complain of migratory arthralgias, usually lasting several days, involving his shoulders, wrists, knees, and ankles, as well as nearly constant pain of the right elbow. Small warm effusions of the right elbow and left knee responded to intra-articular steroid injections, and he obtained modest benefit from 2600 mg of aspirin daily. The erythrocyte sedimentation rate ranged over 60–70 mm/h (Westegren).

In January 1978 he was readmitted to hospital complaining of malaise, anorexia, upper extremity weakness, and severe pain, tenderness, and swelling of the right elbow. There was marked muscle wasting of both shoulder girdles, more prominent on the right side, and massive splenomegaly. Serum aldolase was 3·5 times normal, 24-hour urinary creatine 1·5 times normal, and for the first time his serum alkaline phosphatase was elevated. Serum protein electrophoresis, uric acid level, rheumatoid factor, antinuclear antibody, immunoglobulin levels, and complement studies were normal, as was an electromyogram (EMG). A biopsy of the right deltoid muscle showed focal, acute, inflammatory infiltrates localised largely to the perimysium, with some extension between muscle fibres. There was no evidence of polymyositis or vasculitis, and no abnormalities were found on histochemical and immunofluorescence studies. An elective splenectomy was performed. The spleen weighed 3000 g and contained large amounts of myelopoietic tissue. After splenectomy the platelet count rose to 1490 $\times$ 10^9/l and WBC to 174 $\times$ 10^9/l (15% bands, 55% segmented polymorphs, 18% metamyelocytes and myelocytes, 3% eosinophils, 2% basophils, 7% lymphocytes). Chlorambucil and prophylactic allopurinol were started. Over the next few months the serum aldolase gradually returned towards normal levels.

In June 1978 he was admitted to hospital following the development of a large haematoma in the left flank. Repeat right deltoid muscle biopsy showed minimal round cell infiltrate in the perimysial fat. The EMG remained normal. A technetium-99m pyrophosphate bone scan showed increased uptake in the vertebral column and the ends of all long bones, with

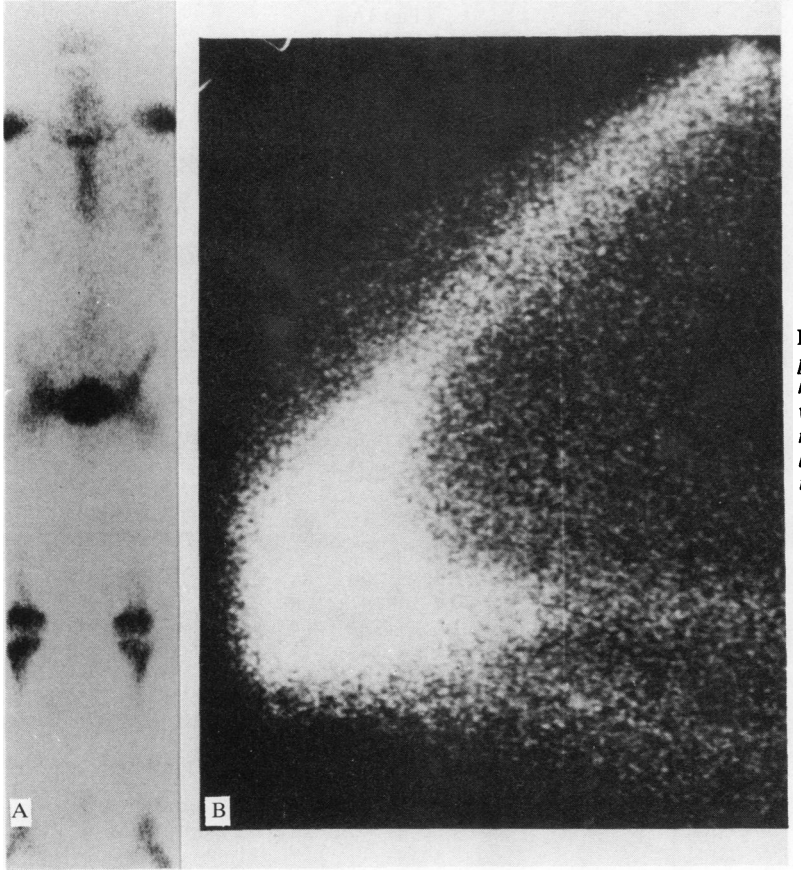


Fig. 2 A *Technetium-99m pyrophosphate scan showing hyperconcentration of isotope in vertebral column, shoulders, sternoclavicular joints, knees, and ankles.* B *Intense uptake of isotope in the right elbow.*

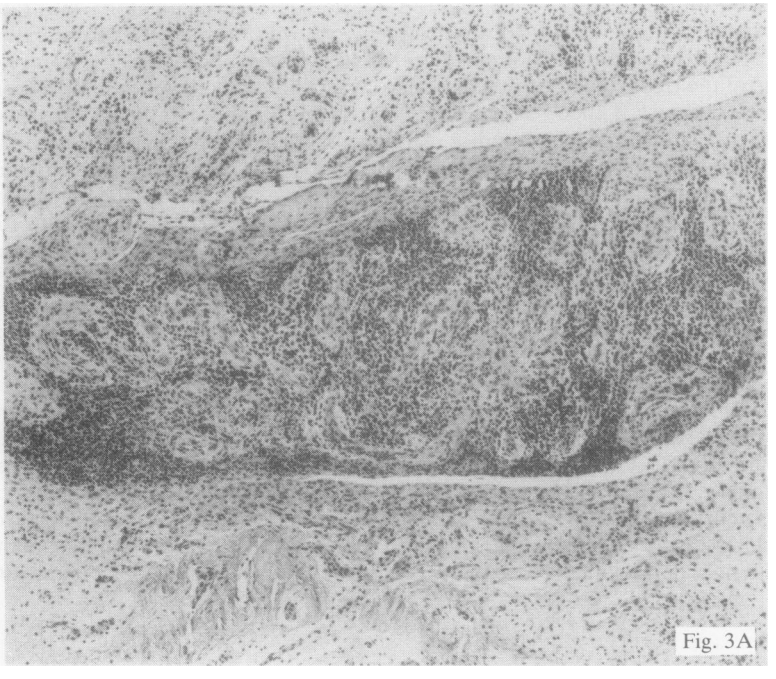
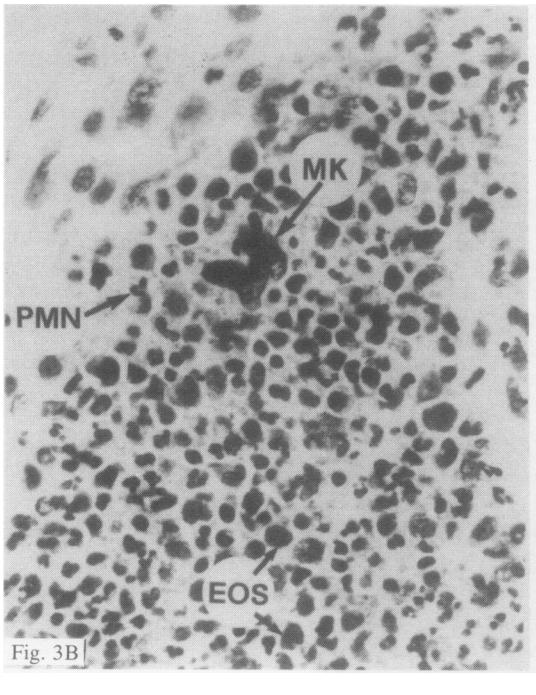
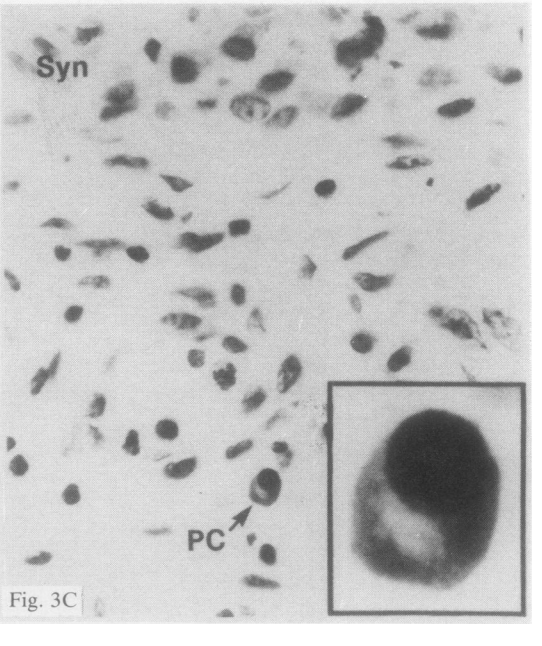


Fig. 3 A *Circumscribed myeloid in synovial frond. A low-grade diffuse inflammatory infiltrate and fibrovascular proliferation are present in the adjacent tissue. (Haematoxylin and eosin, ×144).* B *Higher magnification of nodule in Fig. 1 discloses polymorphous myeloid elements. MK = megakaryocyte. PMN = polymorphonuclear leucocyte. EOS = eosinophile. (Haematoxylin and eosin, ×460).* C *Greater magnification of margin of synovial frond discloses hyperplastic synovial lining cells (Syn) and a nonspecific chronic inflammatory infiltrate composed primarily of mononuclear and plasma cells (PC). (Haematoxylin and eosin, ×650). Inset shows PC with typically eccentric nucleus and vasculoar cytoplasm.*





the most intense uptake occurring in the right elbow (Fig. 2). Roentgenographic studies showed sclerosis of the thoracic and lumbar vertebrae and distal right humerus. The right elbow showed marked symmetrical narrowing of the joint space and small juxta-articular cortical lucencies. Arthrocentesis of the elbow yielded 4 ml of turbid yellow fluid. It contained 44 × 10^9/l WBC (83% polymorphs and 17% lymphocytes), glucose 68 mg/dl (3·8 mmol/l) (serum glucose 100 mg/dl (5·6 mmol/l)), and total protein 4·5 g/dl (45 g/l). No abnormal cells were seen in the centrifuged synovial fluid sediment either by light or electron microscopy, and no crystals were seen by polarising microscopy. Cultures for bacteria, mycobacteria, and fungi were negative.

Synovectomy of the right elbow was performed because of intractable pain and loss of motion. Grossly, the synovial membrane was hyperaemic and thickened. The cartilage had mild to moderate degenerative changes.

Microscopically the synovial membrane disclosed 2 types of cellular infiltration (Figs. 3A, B, C): a nonspecific, chronic inflammatory reaction involving principally the superficial portions of the specimen, and nodular infiltrates of myeloid cells, including many megakaryocytes and eosinophils, in the deeper areas.

Surgical operation gave 75% relief of the pain but no improvement of range of movement. The subsequent course was complicated by several more episodes of spontaneous soft-tissue haemorrhages. In January 1979 he was switched to hydroxyurea for better control of thrombocytosis. There were no further arthralgias, and the skin lesions remained inactive, with no development of nail pitting.

A final admission to hospital in July 1981 was precipitated by a one-week history of nausea, weakness, and fever to 101°C. HCT was now 49%, WBC 93·4 × 10^9/l (20% PMN, 9% bands, 36% blasts), platelets 9 × 10^9/l. Bone marrow biopsy showed myelofibrosis and changes consistent with acute granulocytic leukaemia. There followed rapid progression of bilateral bronchopneumonia, respiratory failure, and death. Post-mortem examination confirmed diffused osteosclerosis and extramedullary haematopoieisis involving the liver; peripheral joints were not examined.

Discussion

Infiltration of the synovial membrane by bone marrow elements has not so far been described as a complication of myelofibrosis with myeloid metaplasia. The usual course of this disorder is that of an indolent progression of bone marrow fibrosis, with metaplastic haematopoeisis occurring primarily in the liver, spleen, and lymph nodes. Occasionally locally aggressive tumefactions of metaplastic marrow elements occur. In most cases these 'tumours of haematopoeisis' are of modest clinical significance. They may occasionally cause abdominal masses, subcutaneous nodules, or other skin lesions, pleural effusions, or ascites without portal hypertension. Profoundly disabling or lethal complications include spinal cord compression, portal hypertension, and gastrointestinal haemorrhage, small bowel obstruction, hydronephrosis, and pulmonary infarction due to emboli of haematopoietic tissue. Evolution to acute granulocytic or myelomonocytic leukaemia is a common cause of death.[2]

Histological association of chronic synovitis with rests of ectopic marrow tissue in the specimen taken at synovectomy suggested to us that the latter may have contributed significantly to the chronic elbow pain in our patient. It may have been responsible for the elbow synovitis at least as far back as his clinical presentation 3 years prior to synovectomy. Hyperuricaemia has been found in 25–50% patients with myelofibrosis, with 6–13% developing symptomatic gouty arthritis.[2] Our patient was normouricaemic and careful study of synovial fluid and tissue by polarising and electron microscopy failed to reveal characteristic uric acid crystals. We also considered pauciarticular psoriatic arthritis as a possible diagnosis in view of the psoriasiform skin lesions. Against this possibility, however, was the lack of distal interphalangeal joint involvement, nailbed pitting, or ankylosing changes on *x*-ray.

The cause of polyarthralgias involving our patient's shoulders, wrists, knees, and ankles remains obscure. Myelofibrosis has been described as a complication of systemic lupus erythematosus in 10 cases[3] and in one patient with long-standing scleroderma treated with chlorambucil.[4] It has been suggested that the bone marrow may be a target organ for autoantibodies produced in the course of these disorders. In our patient, however, multiple serological studies done to investigate other rheumatic diseases were negative.

Similarly, although we confirmed an inflammatory myopathy by serum enzyme and histological studies, its pathogenesis in this setting remains obscure. Infiltration of muscle by myeloid elements has been described in one case report of myelofibrosis and particularly aggressive peripheral neuropathy.[5] This finding, however, was not seen in biopsy material obtained from our patient.

The *x*-ray findings reported here differ from those previously noted in patients with myelofibrosis. Osteosclerosis is found in about 40% of cases,[6] and there has been at least one case report of lytic lesions caused by exuberant marrow metaplasia.[7] The com-

bination of these findings in one patient, however, has not been recorded. Mason *et al.*[8] described 2 patients with myelofibrosis who developed fever and severe bone pains. In one case the elbow was involved. Radioscintigraphy showed increased uptake over involved bones in both patients. One of them subsequently developed *x*-ray evidence of periosteitis. This was confirmed at necropsy, with areas of hypercellular marrow being noted in adjacent tissue.[8] The existence of cortical defects in the distal humerus in our patient raises the possibility that the synovial infiltration may have come about through local extension of marrow elements through the eroded bone. It is also possible that they arose de novo from metaplasia of pluripotential mesenchymal cells in the synovium.

In retrospect is seems that the aetiology of chronic arthritis in our patient might have been suggested by the bone marrow biopsy and distinctive *x*-ray and bone scan findings. Synovial biopsy and synovectomy were required to establish the diagnosis and to treat this unusual complication of myelofibrosis.

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References

1 Caldwell D S. Musculoskeletal syndromes associated with malignancy. *Semin Arthritis Rheum* 1981; **10:** 198–223.
2 Silverstein M N. *Agnogenic Myeloid Metaplasia.* Mass, Publishing Sciences Group, 1975.
3 Rosen P J, Cramer A D, DuBois E L, Lukes R J. Systemic lupus erythematosus and myelofibrosis: a possible pathogenetic relationship (abstr). *Clin Res* 1973; **21:** 565.
4 Gisser S D, Chung B. Acute myelofibrosis in progressive systemic sclerosis. *Am J Med* 1979; **67:** 151–4.
5 Mussini J M, Poisson M, Leporrier M, Mashaly R. A case of myelofibrosis with aberrant myelogenesis in neuromuscular biopsy. *Muscle Nerve* 1979; **2:** 78–9.
6 Pettigrew J D, Ward H P. Correlation of radiologic, histologic and clinical findings in agnogenic myeloid metaplasia. *Radiology* 1969; **93:** 541–8.
7 Fayemi A O, Gerber M A, Cohen I, Davis S, Rubin A O. Myeloid sarcoma: review of the literature and report of a case. *Cancer* 1973; **43:** 253–8.
8 Mason B A, Kressel B R, Cashdollar M R, Bernath A M, Schecter G P. Periosteitis associated with myelofibrosis. *Cancer* 1979; **43:** 1568–71.