Metamorphosis of Chronic Granulocytic Leukaemia, Lytic Bone Lesions and Hypercalcaemia

A Case Report

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SUMMARY

Chronic granulocytic leukaemia may undergo metamorphosis characterized by diffuse granulocytic sarcomas resulting in lytic bone lesions and hypercalcaemia. A patient with this rare complication is reported.

Hypercalcaemia is a frequent finding in non-endocrine neoplasms but is rarely encountered with leukaemia, especially chronic granulocytic leukaemia. Another rare complication of chronic granulocytic leukaemia is lytic bone lesions. Only isolated reports of both hypercalcaemia and lytic bone lesions associated with chronic granulocytic leukaemia have appeared in the literature. We report a further case.

CASE REPORT

A 28-year-old White woman was admitted to the National Hospital in Bloemfontein in January 1978 complaining of having had lower backache for the past 4 months. A diagnosis of Philadelphia chromosome-positive chronic granulocytic leukaemia had been made 5 years previously. The disease had been well controlled with intermittent courses of busulphan, the only side-effect of which had been amenorrhoea and hot flushes. The latter symptom was treated with conjugated oestrogens.

On examination the patient was generally well, and the only positive finding was the bone tenderness over the sternum and lumbar spine. The liver and spleen were not enlarged and lymph nodes were not palpable. There was no neurological deficit.

Results of relevant laboratory investigations were: haemoglobin 12,6 g/dl, leucocytes 43,7 x 10\(^9\)/l, with 3% promyelocytes, 17% myelocytes, 11% metamyelocytes, 6% staff cells, 61% neutrophils, 1% basophils and 1% lymphocytes; platelets 275 x 10\(^9\)/l, and ESR 28 mm/h (Westergren). The bone marrow aspirate was a dry tap. The serum calcium level was 3,8 mmol/l (normal 2,5 - 2,6 mmol/l), phosphate 1,13 mmol/l (normal 0,81 - 1,45 mmol/l), and alkaline phosphatase 221 IU/l (normal 25 - 100 IU/l). The serum urea level was 15,3 mmol/l (normal 2,5 - 6,7 mmol/l) on admission and remained elevated throughout her stay in hospital. Serum electrolytes were normal, the uric acid level was 0,3 mmol/l (normal 0,18 - 0,45 mmol/l), aspartate transaminase 26 IU/l (normal 25 - 100 IU/l), and alanine transaminase 26 IU/l (normal 8 - 30 IU/l). Total serum protein was 74,2 g/l (normal 65 - 80 g/l), albumin 39 g/l (normal 38 - 52 g/l) and protein electrophoresis showed a raised \(\alpha\)-globulin level of 9,4 g/l (normal 4 - 8 g/l), but otherwise was within normal limits. Serum IgG was 110 IU/ml (normal 100 - 240 IU/ml), IgA 45 IU/l (normal 70 - 280 IU/l) and IgM 290 IU/l (normal 80 - 330 IU/l). Bence-Jones protein was not detected in the urine.

Radiographs of the skull, ribs and lumbar spine revealed lytic lesions and a technetium polyphosphate bone scan confirmed multiple focal lesions in these areas (Fig. 1).

A biopsy specimen taken from a lytic lesion of a rib revealed a neoplasm composed of undifferentiated cells admixed with occasional neutrophilic and eosinophilic myelocytes. The appearance was interpreted as compatible with that of granulocytic sarcoma. Leder (naphthol AS-D chloro-acetate esterase) staining was negative, but as the tissue had been decalcified this finding was not considered to exclude the diagnosis. Unfortunately, no imprints of the tissue were obtained.

Active problems at this stage, therefore, were chronic granulocytic leukaemia with metamorphosis presenting as granulocytic sarcomas causing multiple bone lesions and hypercalcaemia.

Course in Hospital

The elevated serum calcium level, associated throughout with a normal albumin level, caused no symptoms and was treated with rehydration, furosemide, calcitonin, glucocorticoids and indomethacin. This therapy had no effect and the calcium level rose to 4,22 mmol/l after 2 weeks. Therapy with mithramycin, 30 \(\mu\)g/kg/d, daily for 3 days, was then instituted and the serum calcium level then decreased to 2,3 mmol/l (Fig. 2). Preterminally it became subnormal. No blast cells were detected on serial blood counts. The leucocyte count remained elevated above 30 x 10\(^9\)/l. The platelet count remained normal until just before death when it decreased to 136 x 10\(^9\)/l. On the 20th day after admission the patient was bleeding from the mouth and passed a melaena stool, and the haemoglobin value decreased to 8,1 g/dl. Haemostasis was evaluated: plasma partial thromboplastin time with kaolin was 51 s (control 33 s); plasma prothrombin time 24 s (control 13 s);
bleeding time (Ivy standardized) 15 min (normal 2.5-9.5 min), plasma thrombin time 25 s (control 9 s), reptilase time 26 s (control 12 s); fibrinogen 1.1 g/l, and platelets 136 x 10^9/l. The findings were interpreted as being compatible with disseminated intravascular coagulation. She died before any therapy could be commenced.

At autopsy there was macroscopic evidence of a diffuse haemorrhagic tendency: petechial haemorrhages and ecchymoses on the skin, a large pelvic haematoma, and haemorrhage into the visceral pleura, large bowel serosa and in the renal medullae. The skull had several lytic areas, none of which had a green colour. The spleen weighed 250 g (normal up to 195 g) and the liver was normal. Small bilateral renal cortical abscesses were present.

Microscopic examination of the infiltrates in the skull and lumbar vertebrae revealed a tumour histologically similar to the antemortem rib biopsy specimen. The marrow cavity showed marked fibrosis. Small groups of undifferentiated cells morphologically suggestive of blast cells were interspersed between the collagen bands. Several Gaucher-like cells were also evident. The liver and spleen were very autolytic, and although evidence of blast cell proliferation was sought in view of the high incidence of extramedullary transformation in these areas, it was not found. The presence of renal cortical abscesses was histologically confirmed. Some renal tubules showed metastatic calcification secondary to the hypercalcaemia. The ovaries were atrophic and fibrotic, a finding compatible with the previous busulphan therapy. Intravascular thrombosis could not be demonstrated histologically. The cause of death was ascribed to a combination of infection and haemorrhage.

**DISCUSSION**

Although the chronic phase of granulocytic leukaemia, which usually lasts 1-4 years, can be satisfactorily controlled with busulphan, the overall survival of patients with this disease has not changed during the last 50 years because the eventual metamorphosis cannot be treated with any degree of success.

Metamorphosis, which may occur at any time during the course of the disease, is a remarkably constant feature of this type of leukaemia. Various factors have been implicated in the pathogenesis of metamorphosis and it has been suggested that the Philadelphia chromosome is unstable and leads to the generation of more malignant clones. This final phase of the disease is characterized in 55% of patients by an acute leukaemia of varying severity and the others may develop a variety of changes including myelofibrosis; an accelerated form of the disease with increasing numbers of leucocytes, anaemia and thrombocytopenia; and granulocytic sarcomas. These, in turn, may later be followed by an acute leukaemia. Once the patient has developed metamorphosis the prognosis is poor, and death usually occurs within 3-6 months.

Granulocytic sarcoma is a neoplasm of undifferentiated cells of the myeloid series and comparable to metastatic nodules of other tumours. It may occur singly or as multiple tumours during the course of chronic granulocytic leukaemia. It is usually associated with blast cell meta-
morphosis. Recently it has been shown that granulocytic sarcoma may not uncommonly also precede metaplasia by several months.9,10 Similarly, granulocytic sarcoma is also associated with acute myeloblastic leukaemia and may precede this form of leukaemia by 2 years.9 The skull, bony orbit and subperiosteal bone are the most common sites of occurrence, but any organ may be involved.11 Our patient did not have overt clinical or laboratory evidence of blast cell metaplasia before she died, but the postmortem finding of blasts in the fibrotic bone marrow may be indicative of early transformation.

Bone lesions are far less commonly found in chronic than in acute leukaemia.12 In chronic granulocytic leukaemia an incidence of 3% has been reported, the lesions usually being lytic in nature. Only isolated cases of sclerotic bone lesions have been reported.13 The lytic lesions are most frequently associated with blast cell transformation1 and are then due to granulocytic sarcomas. Cases have been described where the histological findings in the bone marrow are those of a chronic granulocytic leukaemia with no evidence of excess blasts.13

Hypercalcaemia is often associated with malignant lesions, but is relatively infrequently encountered in leukaemia.14 Only isolated cases of hypercalcaemia in chronic granulocytic leukaemia, with and without bone lesions, have been reported.5,6,7 This finding is associated with a very poor prognosis.6 The aetiology of the hypercalcaemia is uncertain. It has been postulated that rapid bone destruction is caused by the malignant cells.8 Secretion of parathormone,9 a parathormone-like substance,10 prostaglandin E2,10 osteolytic sterol12 or osteoclast-stimulating factor16 by the malignant cells has also been suggested as a cause of the hypercalcaemia. Destruction of bone by granulocytic sarcomas was probably partly responsible in our patient. Tests for parathormone, prostaglandin E2 or osteoclast-stimulating factor activity were not done. The normal serum phosphate level was not interpreted as a significant finding because of the associated renal failure.

Mithramycin is well established in the treatment of hypercalcaemia associated with malignant tumours, whether bony lesions are present or not. The action of the drug is unknown. Dose-dependent side-effects of this drug are well known and encompass a wide spectrum of haemorrhagic features: direct injury to the terminal vascular bed resulting in erosive mucositis; quantitative and qualitative platelet abnormalities; reduction of plasma levels of many, if not all, the coagulation factors; and enhancement of fibrinolytic activity.24,25 The bleeding tendency in our patient could have been due to mithramycin, but the dosage and duration of therapy was less than that usually associated with this complication. The laboratory findings were also compatible with disseminated intravascular coagulation with fibrinolysis, a well-known complication of leukaemia.26

Gaucher-like cells may be present in chronic granulocytic leukaemia17,18 and are the result of the increased turnover of granulocytes and accumulation of membrane lipid in the histiocytes.

The various clinical manifestations of chronic granulocytic leukaemia undergoing metamorphosis are protean. Lytic bone lesions and hypercalcaemia are rarely encountered, indicate a poor prognosis and, as in this case, may present difficult diagnostic and therapeutic problems to the attending physician.

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REFERENCES