

Agnogenic Myeloid Metaplasia with Cutaneous Granulocytic Sarcomas

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A case of agnogenic myeloid metaplasia that transformed to acute myeloblastic leukaemia terminally, is described. The acute phase was heralded by the development of cutaneous tumours, which are rarely seen in this condition.

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Agnogenic myeloid metaplasia (AMM), also known as primary or idiopathic myelofibrosis, is a clonal haematopoietic stem-cell disorder characterized by marrow fibrosis and extramedullary haematopoiesis. AMM is incurable, has a median survival of 3 to 7 years, and the causes of death are mostly due to complications such as infection, haemorrhage, cardiac, hepatic or renal failure and thrombosis^{1,2}. Conversion to acute leukaemia occurs in less than 10% of cases^{1,3}. Skin manifestations are rare⁴.

We report a case of AMM that transformed to acute myeloblastic leukaemia with multiple skin tumours in the terminal phase. The case is presented in view of the rarity of the clinical presentation and the constellation of pathological findings.

THE CASE

A.H., a 43 years old man, presented in March 1998 with bone pains, slowly-growing abdominal distension, weight loss and decreasing appetite. Physical examination revealed moderate pallor, marked splenomegaly with the spleen extending below the umbilicus, and hepatomegaly 8cm below the costal margin. There was no lymphadenopathy.

A blood-count showed: haemoglobin 8.6 g/dl, platelets $382 \times 10^9/l$, and WBC $103 \times 10^9/l$. Peripheral blood smear showed: blasts and promyelocytes 10%, myelocytes 20%, metamyelocytes 10%, polymorphs 23% and basophils 6%. There was moderate anisopoikilocytosis, macrocytes, teardrop cells and fragmented erythrocytes. The neutrophil alkaline phosphatase score (NAP score) was normal.

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Bone marrow aspiration smears showed hypercellular marrow fragments with granulocytic hyperplasia and myeloid/erythroid ratio of 20:1. Normoblastic erythroid cells and many micromegakaryocytes were seen. Differential count of marrow cells showed : blasts 6%, promyelocytes 25%, myelocytes 28%, metamyelocytes 17%, neutrophilic polymorphonuclears 25%, basophils 4% lymphocytes 12%, plasma cells 2% and normoblasts 4%.

The trephine biopsy however, showed markedly thickened bone trabeculae with constricted marrow spaces showing marked fibroblastic proliferation (Fig. 1). Marrow reticulin was markedly increased. Liver biopsy showed extensive intrasinusoidal haematopoiesis. Biochemical tests showed mild hypoalbuminemia (32 g/l), hyperglobulinemia (40 g/l) and hyperuricemia (526 μ M).

Figure 1. Trephine biopsy showing myelofibrosis and thickened trabecular bone (osteosclerosis). Haematoxylin and eosin, x 100

Cytogenetic study of unstimulated marrow aspirate showed normal chromosome complement and banding pattern in 25 metaphases. In situ hybridisation with probes for the BCR and ABL loci showed these were spatially separated with no fusion, confirming Ph¹-negative status.

The patient was started on hydroxyurea 1.5 g daily. Over the next few months, WBC counts were controlled at a dose of 2 g daily. Eight months later, the patient was splenectomised in view of repeated blood transfusion requirement and pressure symptoms due to the massive spleen. The specimen of spleen was bulky and weighed 3.3 Kg. The cut surface showed markedly thickened capsule. Histologically, the entire organ was extensively infiltrated by myeloid cells at different stages of development and dysplastic megakaryocytes that were present in clusters (Fig.2). Erythroid precursors were less prominent and were usually present in sinusoids. Extensive fibrosis, deposition of hemosiderin pigment and a few atrophic lymphoid follicles were also seen.

Figure 2. Histology of spleen: clusters of dysplastic megakaryocytes

(arrows) and myeloid cells in areas showing extramedullary haematopoiesis. Haematoxylin and eosin, x 400

In October 1999, α -interferon was started but had to be stopped two months later because of troublesome flu-like symptoms. In December 1999, multiple skin nodules developed all over his body measuring 1-2 cm. in diameter. Fine-needle aspiration of these nodules showed evidence of extramedullary hematopoiesis with immature myeloid cells, megakaryocytes and normoblasts (Fig.3). These nodules increased in size and some became painful. The largest of these (Fig.4), over the right scapular region had to be treated with radiotherapy (300 Gy/15 hours over 3 weeks), and showed complete response.

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Figure 3. FNAC from skin nodule showing immature myeloid cells and a megakaryocyte (arrow). Haematoxylin and eosin, Transformation x 200

Figure 4. Skin involvement in agnogenic myeloid metaplasia. Radiotherapy caused lesion to regress. to acute leukaemia occurred 5 months later

At this time, a marrow aspirate yielded a dry tap while the biopsy showed no hemopoietic activity and reticulin fibrosis. In March 2000 the patient was hospitalized with fever, generalized lymphadenopathy and signs and symptoms of raised intracranial tension. Ophthalmoscopic examination showed bilateral papilledema and preretinal haemorrhages. CSF examination showed a WBC count of $1500 /\text{mm}^3$ with a majority of blast cells. Bone marrow aspiration smears showed 48% blasts and 8% promyelocytes with reduced megakaryocytes and erythroid cells. Blasts were monocytoid (Fig. 5), and showed moderate nonspecific esterase activity. FNAC of a skin nodule also showed numerous blast cells. A diagnosis of transformation of AMM to acute myeloblastic leukemia was made.

Figure 5. Monocytoid blasts seen in transformation to acute myeloid leukaemia. Wright's stain, x1000

Chemotherapy with high-dose cytarabine 3 g/m² BID on days 1,3,5,7 and idarubicin 12 mg/m² daily for 3 days) and intrathecal triple therapy (methotrexate, cytarabine and hydrocortisone) was started. However the patient's condition continued to worsen and he died shortly thereafter.

DISCUSSION

AMM is a relatively uncommon disorder in Bahrain. In an analysis of 213 haematological malignancies diagnosed between 1986 to 1995 at Salmaniya, only 3 cases were detected⁵.

In AMM, extramedullary haematopoietic foci can cause organ enlargement or tumour formation in almost any tissue. Common sites are spleen liver, lymph nodes, kidney and adrenal glands. Less often involved are bowel, breast, lungs pleura, mediastinum, mesentery, skin, synovium, thymus, lower urinary tract, ovaries and intra-cranial or intra-spinal epidural space^{1,2,6}. In this case histological evidence of such haematopoiesis was seen in the liver biopsy and spleen, with skin involvement in the later stages. Our patient showed several poor prognostic features at presentation: anaemia, high WBC count and high numbers of circulating blasts. Presence of hepatomegaly is a debatable indicator of poor prognosis in AMM⁷.

Skin involvement in AMM may occur in the form of erythematous plaques, nodules, diffuse or papular erythema, ulcers or bullae⁴. Transition to acute leukaemia preceded by the development of granulocytic sarcomas, as seen in this case, is a rare event^{8,9}. Another notable feature was that transformation to myeloblastic leukaemia occurred simultaneously in the marrow and cutaneous tumours along with CNS involvement.

Clonality studies in AMM have shown that the trilineage proliferation (myeloid, erythroid and megakaryocytic) which occurs in varying degrees, is actually monoclonal and is due to involvement at stem cell level⁷. Fibroblastic proliferation with collagen deposition, often the most prominent feature in the marrow, is a secondary reaction¹⁰. Fibrosis is induced by cytokines released by the proliferating hemopoietic cells, principally megakaryocytes¹⁰ that are prominently seen in fibrotic areas. Increased marrow collagen may be due to both decreased breakdown and increased synthesis of the protein. Degradation of collagen may be retarded by platelet factor 4, which inhibits collagenase¹¹. Among factors that stimulate fibrosis are platelet-derived growth factor (PDGF) and calmodulin (stimulate fibroblast proliferation) and transforming growth factor β (TGF- β , increases collagen synthesis)^{7, 12}. Levels of both PDGF and TGF- β are increased in circulating megakaryocyte fragments and platelets in AMM¹³. TGF- β may be the principal mediator of collagen accumulation in AMM¹².

Understanding of these pathogenetic mechanisms forms the rationale of treatment with agents that suppress the action TGF- β (Interferon- α , suramin) or with anti-proliferative action on megakaryocytes (Vitamin D analogs, anagrelide)^{7, 12}.

Interferon- α may ameliorate bone pain, splenomegaly and thrombocytopenia but its use is limited by its side-effects such as flu-like symptoms and worsening anemia¹⁴,¹⁵. In the present case too, Interferon- α was used, but could not be adequately tried because of flu-like symptoms.

CONCLUSION

Cutaneous tumours (granulocytic sarcomas) developing in AMM is a rare and ominous sign and may precede acute leukaemic transformation of the disease. This should alert the clinician to investigate the marrow and suspicious extramedullary sites for such transformation of the disease.

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