

BONE MARROW NECROSIS IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Clinical and laboratory findings

A 67-year-old man presented with fever and a 3-month history of bone pain, mainly localized in the lumbar vertebrae and in the pelvis, which was not associated with either movement or with recent trauma. On admission the patient was lethargic and physical examination revealed: pallor, and liver slightly tender and enlarged 3 cms. Vital signs were normal and neither lymphadenopathy nor splenomegaly was found. Hematologic values were: hemoglobin 12.5 g/dL; white-cell count $2.69 \times 10^9/L$ with 59% neutrophils, 2% basophils, 30% lymphocytes, 4% myelocytes, 5% erythroblasts; platelets $36 \times 10^9/L$. The erythrocyte sedimentation rate was 113 mm/h, LDH 1343 mU/mL, alkaline phosphatase 603 IU, SGOT 37 mU/mL, SGPT 73 mU/mL, while renal function tests were normal. Chest X-ray was normal, while radiography of the skeleton documented diffuse osteopenia; ultrasonography showed hepatomegaly and slight splenomegaly.

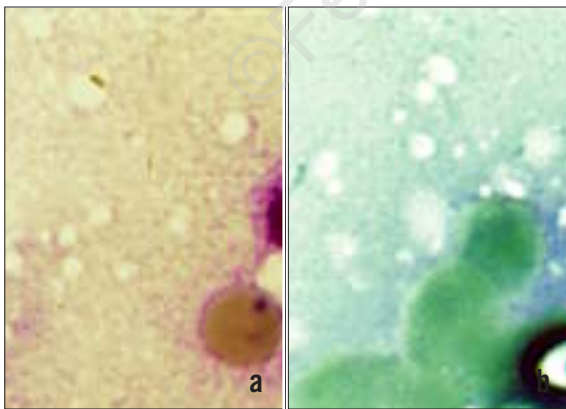


Fig. 1. Bone marrow smears, MGG. Necrotic cells with ill-defined cytoplasmic borders stand out on an amorphous background (a) (x480); rare intact blasts are present in this area (b) (x1200).

Bone marrow analysis

Bone marrow smears revealed hypocellularity with many impossible to identify degenerated cells that were dismissed as artefacts, and an amorphous pink-staining background (Figure 1a). Rare intact blasts were present in very few areas (Figure 1b). Marrow biopsy specimens showed several necrotic zones and some other with normal cellularity heavily infiltrated with blasts (Figure 2a, b).

Blast cells were PAS positive, Sudan B positive, peroxidase and α -naphthyl-acetate esterase negative. They expressed TdT and CD10, CD19, CD20 antigens, but not CD7, CD13 and CD33. Magnetic resonance imaging (MRI) confirmed marrow necrosis by revealing high signal dishomogeneity in all lombo-sacral metamers examined with both low and high intensity in T1 and T2 weighted images and in DP (Figure 3).

Conclusions

On the basis of these findings a diagnosis of acute lymphoblastic leukemia (ALL) of the common type, FAB L2, with bone marrow necrosis was made. The patient was treated with polychemotherapy according to the GIMEMA ALL 0288 protocol; both bone pain and lethargy disappeared, but only a partial remission was reached. The patient died four months later from myocardial infarction.

Bone marrow necrosis, often overlooked, is a well-described pathologic entity related to the death of bone marrow stromal and hemopoietic cells; it is rarely diagnosed *ante mortem* and has been associated with a poor prognosis.¹⁻⁴ Massive marrow necrosis is apparently very rare, and among hematologic diseases it is most often

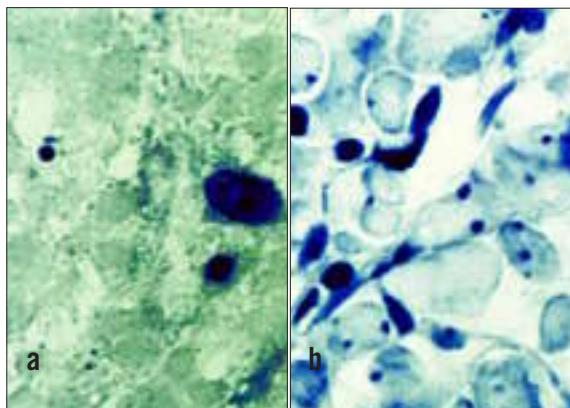


Figure 2. Bone marrow trephine biopsy. In this necrotic area the marrow architecture is destroyed and cells are scattered in a background of amorphous material (a); an adjacent area is heavily infiltrated with blasts (b). HE x300.



Figure 3. A sagittal MRI image of the lumbar spine shows extensive bright areas of necrosis in vertebral bodies.

associated with sickle cell anemia, leukemia and lymphoma. In the acute leukemias the incidence is much higher in the lymphoblastic type than in the myeloid type.⁵⁻⁶

The clinical picture is generally dramatic and when it occurs at onset, diagnosis of the underlying disease may be extremely difficult. Bone pain and fever appear frequently and extra-

medullary hemopoiesis may be present. The blood film shows pancytopenia and a leukoerythroblastic picture. Bone marrow necrosis is more often noted in trephine sections than in aspirates. Frequently only scanty amounts are obtained in marrow aspirates, and the necrotic cells, mixed with intact ones, are often dismissed as an artefact. Trephine sections show that in necrotic areas the marrow architecture is destroyed and the supporting connective tissue is absent. All cells are scattered in a background of amorphous eosinophilic staining material; in several cases increased fibrosis is observed.

In order to evaluate the extent of marrow necrosis scintigraphy was typically used in the past, but MRI is currently preferred.⁷

The pathophysiology of marrow necrosis is not known. The release of either toxins or soluble mediators by malignant cells may be an important etiologic factor.⁸ Cytokines like TNF may induce expression of leukocyte adhesion receptors on endothelial cells, granulocyte activation with generation and release of superoxide, and a prothrombotic effect on endothelial cells.

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