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Case Report

Acute megakaryocytic leukemia presenting as hypercalcemia with skeletal lytic lesions

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Abstract: Acute megakaryocytic leukemia (AML M7) is a rare type of acute myelogenous leukemia in adults, commonly presenting with myelofibrosis. This report describes a case of a 32-yr-old male who presented with hypercalcemia and bony lytic lesions, in the absence of myelofibrosis. The diagnosis of AML M7 should be considered in a patient with pancytopenia, lytic lesions and hypercalcemia.

Acute megakaryocytic leukemia (AML M7) is a rare subtype of acute myelogenous leukemia. It is usually associated with extensive bone marrow fibrosis, and its presentation with radiographic lytic lesions or periosteal reaction in long bones has been described in four case reports involving children (1–4). Destructive lytic bone lesions in the setting of AML M7 in an adult patient have been described only in one other case report (5). Hypercalcemia has been reported in association with other types of acute myelogenous leukemia (AML) (6). The causative factors of the hypercalcemia associated with myeloid malignancy are poorly defined. In this report we describe a case of an adult patient who presented with both diffuse lytic lesions and hypercalcemia, and was diagnosed with *de novo* AML M7.

The morphologic diagnosis of AML M7 can be difficult, which prompted the French-American-British cooperative group to add specific flow cytometric and cytogenetic criteria for the diagnosis of AML M7. The presence of such markers as IIb/IIIa (CD41/61), CD42b or factor VIII related antigen is usually needed to establish the diagnosis. Abnormalities of chromosomes 3 are common (7), and an association with Down's syndrome has been described (8).

The clinical presentation of AML M7 can also be variable. Patients in whom the disease evolves from a pre-existing myeloproliferative disorder may present with hepatosplenomegaly, anemia and leukopenia. Sixty percent of patients presented with leukopenia (WBC $< 3000\ mm^{-3}$), 55% with anemia (hemoglobin $< 9\ g\ dL^{-1}$) and 60% with thrombocytopenia (platelets $< 100 \times 103\ mm^{-3}$) at the time of diagnosis (7). Extensive myelofibrosis resulting in a 'dry tap' on a bone marrow biopsy is a well recognized feature reported in 17 out of 17 patients in whom a bone marrow biopsy could be assessed (7). Survival after treatment with conventional chemotherapy is extremely poor, with the median survival ranging between 7 and 10 months (7, 9).

This report describes the clinicopathologic findings of an unusual case in which the diagnosis of *de novo* AML M7 was made in an adult patient who presented with hypercalcemia, pancytopenia and lytic bone lesions.

Case report

The patient was a 32-yr-old man with a prior history of a motorcycle accident requiring several orthopaedic surgeries on his legs, who presented

to a community hospital with back pain in his lumbar area. Plain radiographs and a computerized tomography (CT) scan revealed a lytic lesion in the L3 vertebral body. A biopsy of the lesion was performed at the time of decompression laminectomy. An initial review of the biopsy specimen was felt to be consistent with an extramedullary myeloid cell tumor with megakaryocyte differentiation (Fig. 1), and a brief course of radiation therapy to the involved area of the lumbar spine was given. On subsequent follow-up patient presented with confusion, lethargy and weakness. Laboratory values obtained are shown in Table 1 and included hypercalcemia and an elevated serum alkaline phosphatase and lactate dehydrogenase. As an indirect measure of bone turnover, the elevated serum alkaline phosphatase enzyme was fractionated and was found to consist almost entirely of the bone isoenzyme type. A repeat plain radiographical survey revealed new lytic lesions in the skull, right acetabulum, L1 and L5 vertebrae (Figs. 2A–D). Serum protein electropheresis revealed no evidence of a monoclonal protein, and a Bence-Jones urine screen was negative. Over the course of the next 4 d, the patient's platelet count decreased to 61 K mm^{-3}. The patient was transferred to our hospital, and a bone marrow biopsy was performed. The bone marrow was packed by blasts and atypical megakaryocytes (Fig. 3). Immunostains showed that the blasts and abnormal megakaryocytes were strongly positive for CD43 (not shown), CD 61 and a factor VIII related antigen. They were positive for CD31 and CD117 (not shown), but negative for multiple B- and T-cell markers (Fig. 4). Cytochemical stains on the bone marrow aspirate showed that the blasts and megakaryocytes were focally positive for non-specific esterase-b but negative for myeloperoxidase. These findings were felt to be consistent with acute myelogenous leukemia with megakaryocytic differentiation (AML FAB M7). Cytogenetic analysis revealed multiple complex cytogenetic abnormalities in a single clone of cells, but the inv(3)/t(3 3); previously reported in AML M7, was not present (Table 2). The peripheral smear at the time of transfer to our center revealed normochromic, normocytic red blood cells, an absence of schistocytes or fragmented red blood cells, a decreased number of platelets and an absence of blasts.

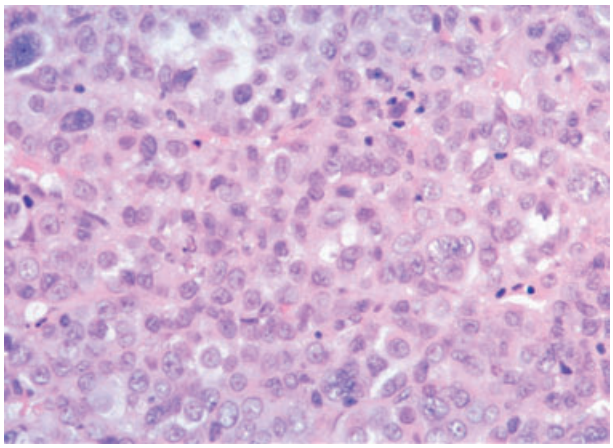

Fig. 1. Core needle biopsy of the lumbar spine lesion, showing extramedullary myeloid cell tumor. Immunostains revealed megakaryocytic differentiation with expression of CD31 and CD61 on blasts (40 × magnification, hematoxylin and eosin).

The patient underwent induction chemotherapy with idarubicin and ARA-C regimen. The patient's hypercalcemia resolved shortly after initiation of

Table 1. Laboratory values on presentation

Test	Result	Reference	Test	Result	Reference
Serum calcium	17.3	8.8–10.6 mg dL^{-1}	Bicarbonate	36	21–32 mmol L^{-1}
Ionized calcium	1.91	1.10–1.30 mmol L^{-1}	Phosphorus	4.8	2.5–4.9 mg dL^{-1}
Serum albumin	2.5	3.5–5.5 g dL^{-1}	BUN	66	7–18 mg dL^{-1}
Serum protein electropheresis	No monoclonal M protein present		Creatinine	3.4	0.6–1.3 mg dL^{-1}
24 h urine collection	Negative for Bence-Jones protein		Uric acid	9.5	2.5–7.2 mg dL^{-1}
Alkaline phosphatase total	1753	98–251 U L^{-1}	LDH	647	100–190 U L^{-1}
Alkaline phospatase bone fraction	1735	24–146 U L^{-1}	WBC	11.6	4.5–11.0 K mm^{-3}
Fibrinogen	738	150–450 mg dL^{-1}	Hemoglobin	11.9	12–17.3 g dL^{-1}
PT	10.9	10.1–11.6 s	Hematocrit	33.9	36–53%
PTT	32.5	25–32.6 s	Platelet	154	140–440 K mm^{-3}
D-Dimers	<0.2	<0.2 μ mL^{-1}	Prostate-specific antigen (PSA)	0.3	0.0–2.5 ng mL^{-1}

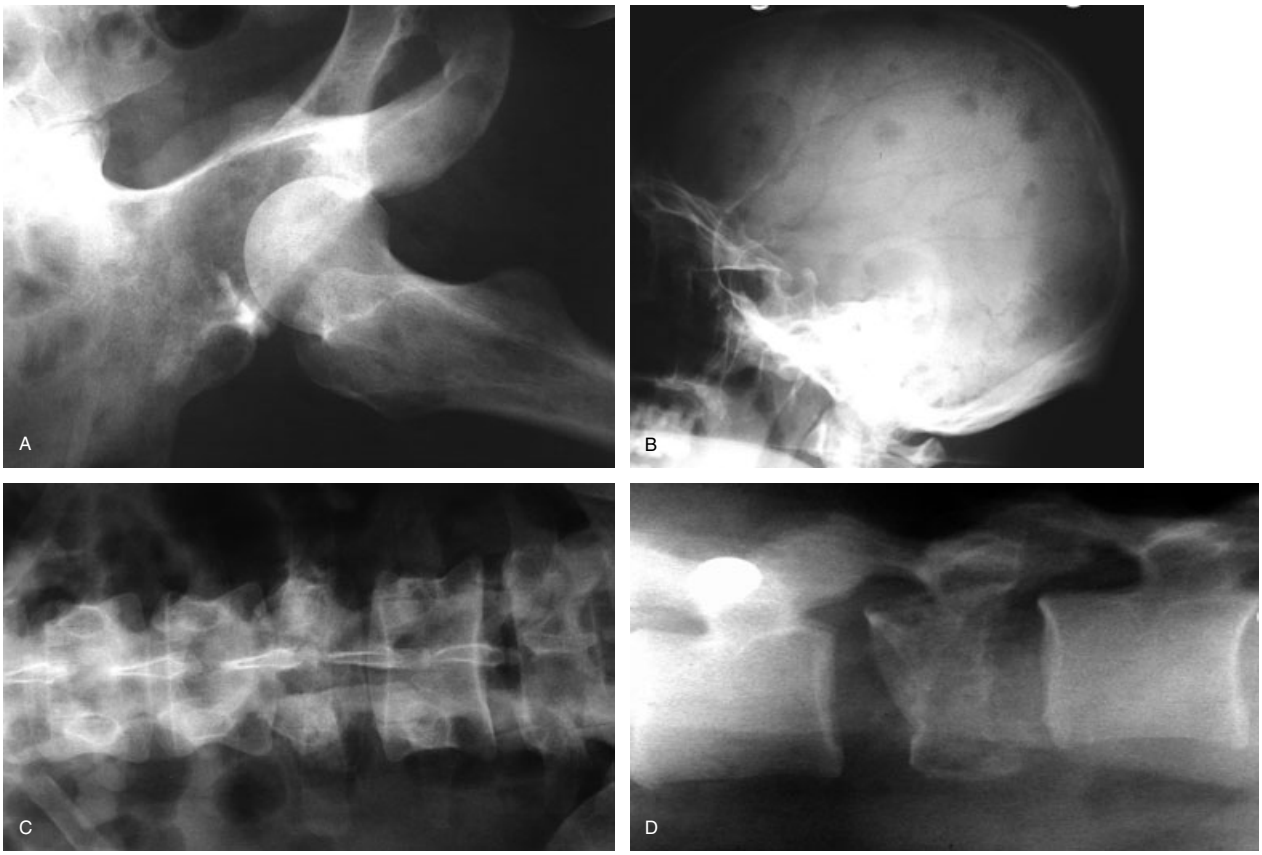

Fig. 2. Images of skeletal survey demonstrating lytic lesions in the right acetabulum (A), skull (B) and pathologic fractures of lumbar spine vertebrae (C) and (D).

induction and required no further treatment. Even though a pretreatment level of serum parathyroid level was not obtained, its value after acute treatment of hypercalcemia, with a single dose of 90 mg of intravenous pamidronate and saline hydration, was 28 pg mL^{-1} (normal 12–75 pg mL^{-1}, post-treatment serum calcium 8.1 mg dL^{-1}). A repeat bone marrow biopsy on day 14 revealed a hypocellular marrow ($<5\%$ cellularity) with no evidence of residual leukemia, and a day 28 bone marrow biopsy confirmed the absence of leukemia with restored trilinear hematopoesis and trilinear maturation.

Discussion

In this report, we describe a 32-yr-old man with acute megakaryocytic leukemia (AML M7) who presented with hypercalcemia and lytic bony lesions (features not unlike those seen with multiple myeloma). The diagnosis of AML M7 was made based on bone marrow morphology, immunohistochemistry, and flow cytometry data. The blasts were positive for CD43. This was an expected finding given that almost all hematopoetic cells, including benign and malignant megakaryocytes, will express this antigen. We did not examine the blasts for CD41 expression as we had other evidence of megakaryocytic differentiation (expression of CD61 and Factor VIII related antigen).

Skeletal X-ray abnormalities in the setting of AML M7 have been described in four case reports of pediatric patients (1–4). They included periosteal thickening of long bones either with (2, 3) or without (1, 4) diffuse lytic lesions. Only one of the patients had trisomy 21 (3). None of the case reports mentioned the presence of hypercalcemia in any of the patients. Dharmasena *et al.* (5) has described the only report of an adult patient with lytic lesions in the setting of AML M7. No hypercalcemia was present in that case, and the bone marrow had extensive fibrosis.

Diffusely lytic lesions have been described in the setting of myelofibrosis evolving from previous polycythemia vera (10). Interestingly, in that case the diffuse pain from lytic lesions disappeared after the patient underwent a splenectomy.

Previous case reports of hypercalcemia in AML M7 have described patients in whom acute

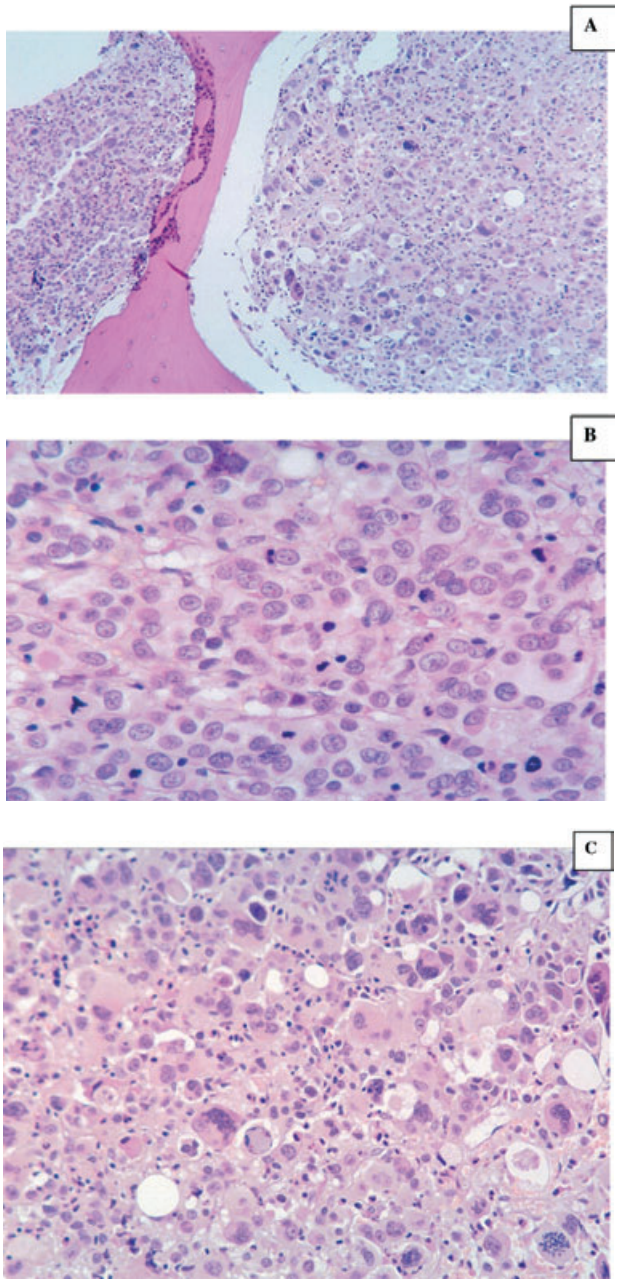

Fig. 3. Bone marrow core biopsy showing marked hypercellularity due to a proliferation of blasts and abnormal megakaryocytes. Fibrosis is notably absent. (A, hematoxylin, 20× magnification; B–C, hematoxylin and eosin, 40× magnification).

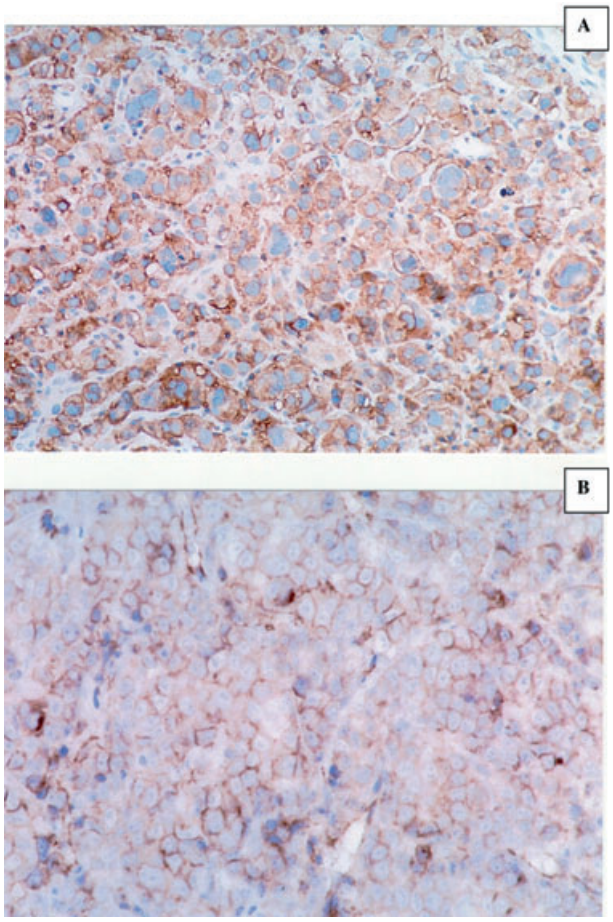

Fig. 4. Immunostains for the expression of CD61 (A) and CD31 (B) by the leukemic blasts indicating the megakaryocytic differentiation of the acute leukemia (40× magnification).

Table 2. Cytogenetic abnormalities

	Cells	Result	
	14	XY, −X, +del(Y)(q11q12),der (1)i (1)(q10) inv (1)(q23q42), −4, −5, +6, +8, +8, −9, −11, der (13)t (13,17)(p13;q21), −17, −17, −18, +19, +19, +21, +21, +i (21) (p10), +del (22) (q12q13)[cp14]	Clone 1
	6	46, XY	Normal
Total cells analyzed	20		

megakaryocytic leukemia evolved from a preexisting myeloproliferative disorder such as polycythemia vera (11), agnogenic myeloid metaplasia (12) or chronic myelogenous leukemia (13). Our report describes a *de novo* presentation of AML M7 with hypercalcemia and lytic lesions.

The etiology of hypercalcemia in myeloid malignancies remains poorly defined. One study demonstrated abnormal production of parathyroid hormone by the malignant myeloid cells (14). Stimulated promyelocytic leukemia cell lines have been reported to produce PTH-related protein (PTHrP) (15), and elevated levels of 1,25-dihydroxyvitamin D_3 levels have been implicated in hypercalcemia reported with idiopathic myelofibrosis (16). Given the numerous lytic lesions in our patient, one of the possible explanations for the hypercalcemia is extensive bony destruction by the leukemic cells. Similiar to other reports of hypercalcemia in M7 leukemia (12), our case also had an elevated lactate dehydrogenase level, probably indicating a high tumor turnover rate. Elevated levels of

alkaline phosphatase bone isoenzyme levels could be attributed to either bony destruction or high bone turnover rate. Another unique feature of this case is the absence of bone marrow fibrosis, a finding reported to be almost universal in one series on AML M7 (7).

We conclude that acute megakaryocytic leukemia should be considered in the differential diagnosis when managing a patient with hypercalcemia and bony lytic lesions. The exact etiology of hypercalcemia in myeloid malignancies awaits further studies.

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