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CASE REPORT

Hypercalcemia and diffuse osteolytic lesions in a 45-year-old patient with myeloid sarcoma with megakaryocytic differentiation

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Acute megakaryocytic leukemia is a rare form of acute myeloid leukemia that carries a poor prognosis. As most cases of osteolytic lesions are due to plasma cell and myeloid malignancies, maintaining a broad differential directly influences clinical course. We document a 45-year-old patient with progressive constitutional symptoms, osteolytic bone lesions in the setting of hypercalcemia, who developed acutely worsening pancytopenia. The diagnosis of myeloid sarcoma with megakaryocytic differentiation was made after obtaining tissue from osteolytic bone that stained strong for CD34. Immunohistochemical testing underscores the importance of how serologic and urine testing remains limited and can delay early diagnosis in this disease.

Keywords: *myelofibrosis*; *AML*; *acute panmyelosis*; *acute megakaryoblastic leukemia*

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Acute megakaryocytic leukemia is a rare form of acute myeloid leukemia (AML) with a poor prognosis. Its clinical and pathological features may make it difficult to distinguish from other marrow disorders with a prominent fibrotic component such as acute panmyelosis with myelofibrosis. Here, we report the case of a 45-year-old patient with an unusual presentation of osteolytic lesions and hypercalcemia and no evidence of a plasma cell disorder.

Case report

A 45-year-old Hispanic woman presented to a local hospital with a 2-week history of progressively worsening diffuse back pain, fatigue, a generalized sense of weakness, and daily fevers and sweats. She denied any parasthesias, or dyasthesias, but the pain was severe enough to limit some of her activities of daily living. She reported no specific aggravating or relieving factors. Of note she did have a significant history of von Willebrand's disease diagnosed at the age of 35 and had otherwise been in good health without major medical problems thus far. Physical examination revealed a palpable, non-mobile, 2×2 centimeter mass at the level of the left 10th rib with no overlying cutaneous changes. No lymphadenopathy or hepatosplenomegaly were present. Neurological examination was grossly normal. The complete blood count (Table 1) revealed leukocytosis of 33.8×10^9/L, 2% blasts with a left shifted differential without thrombocytosis (416×10^9/L), or anemia (9.0 g/dL). The chemistry panel was significant for hypercalcemia (13.8 mg/dL), an elevated lactate dehydrogenase (LDH) level (4,823 IU/L), and an elevated alkaline phosphatase (257 IU/L). A bone scan demonstrated increased uptake in the left hip felt to be a degenerative left acetabulum (Fig. 2). Plain radiographs (Fig. 1) and MRI imaging of the left hip showed lytic lesions in the left femoral neck. Both a marrow biopsy and a tissue sample of the rib mass were non-diagnostic.

For the hypercalcemia, the patient was treated with pamidronate and intravenous fluids. Broad-spectrum intravenous antibiotics were started since the patient had

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Table 1. Progression of CBC, LDH, and alkaline phosphatase during hospital stay

	Day 1	Day 4	Day 8	Day 14	Day 17
WBC $\times 10^9$/L	33.8	17.5	7.2	1.7	1.5
Hb (g/dL)	9.0	9.9	10.6	10.6	8.9
Platelets $\times 10^9$/L	416	248	119	72	54
% blasts	2	2	1	3	NA
LDH (IU/L)[a]	4,823	4,111	5,942	6,309	5,557
Alkaline phosphatase (IU/L)[b]	257	212	150	231	201

[a]Upper limit of normal 618 IU/L; [b]upper limit of normal 126 IU/L. WBC, white blood cell count; Hb, hemoglobin; NA, not available; LDH, lactate dehydrogenase.

a low-grade fever of 99.6°F. The patient was transferred to our institution suspecting a diagnosis of multiple myeloma.

On presentation to our institution, the white blood cell count (WBC) was 33.7×10^9/L consisting of 80% neutrophils and a left shift including 2% metamyelocytes and 2% blasts. Tear drop cells were not identified and there were no schistocytes. The hemoglobin was 9 g/dL and the platelet count was 416×10^9/L. LDH levels were elevated at 4,823 IU/L (upper limit of normal [ULN] 618 IU/L), corrected calcium was 11.94 mg/dL, and alkaline phosphatase levels were 257 IU/L (ULN 126). The renal function was within normal limits.

A bone survey shortly after transfer showed normal bone mineral content, multiple discrete lytic lesions in the skull, ribs, pelvis, and shoulder girdle and a lytic lesion in the adjacent left supra-acetabular ilium and femoral neck (Fig. 1). A PET/CT scan showed diffuse activity of the marrow spaces throughout the axial skeleton and extending into the appendicular skeleton as well as throughout the spleen. Large lytic lesions were also noted within several regions including the left femoral neck and left acetabular roof which corresponded to the lesions seen on the bone survey (Fig. 2). However, serum protein electrophoresis and immunofixation did not show evi-

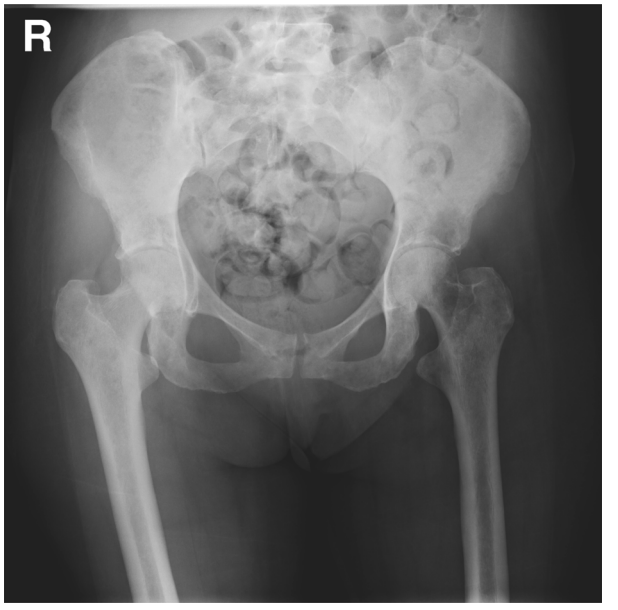

Fig. 1. Hip view shows multiple discrete myelomatous lesions in the pelvis and a lucent lesion in the left femoral neck.

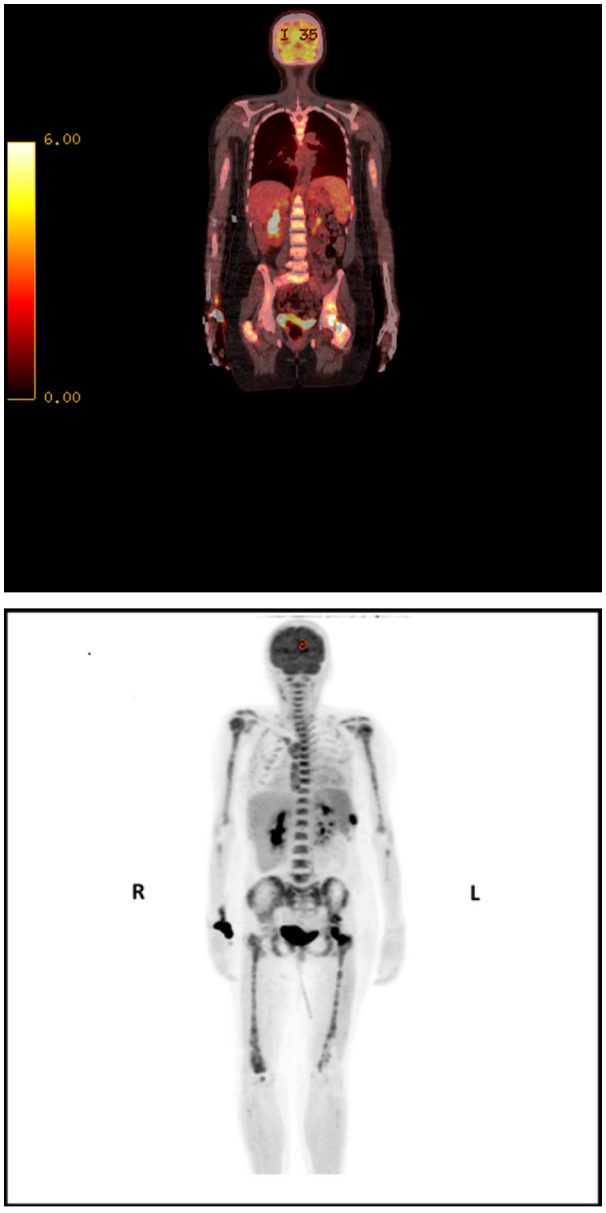

Fig. 2. FDG PET/CT scan. (A) Extensive nodular increased activity most evident in long bones such as both humeri and femurs. (B) Conspicuous foci with intense activity are seen in the medial condyle of the right femur (SUV 3.3) and left acetabular roof and femoral neck where a 3 cm lytic lesion is seen with cortical destruction (SUV 15.8).

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dence of a monoclonal protein. Kappa and lambda light chain ratio was normal (1 : 1.62). Urine was not tested.

During the course of hospitalization her temperature remained elevated between 99.3°F and 102.4°F despite the use of broad-spectrum antibiotics. Blood and urine cultures remained consistently negative and no source of infection was identified. Within 2 weeks of admission, the blood counts deteriorated and the patient became increasingly anemic, thrombocytopenic, and leukopenic (Table 1). A repeat marrow biopsy and curettage of the left femoral neck region were performed (Fig. 3).

The marrow biopsy was characterized by marked fibrosis with many crushed large cells and diminished hematopoietic elements. Immunohistochemical staining was limited with CD34 highlighting a few vessels and CD61 positive in some of the crushed cells. Tumor cells were negative for myeloperoxidase (MPO) and non-specific esterase (NSE). The left femoral neck showed a malignant tumor infiltrate composed of large mononucleated to anaplastic cells with moderate cytoplasm and some multinucleated forms (Fig. 3). In addition, many mature forms of megakaryocytes were present. The tumor cells were negative for CD138, CD20, CD3, cytokeratin, S-100, and CD30. In contrast they were strongly and diffusely positive for CD34 and CD43. Immunohistochemical stains which were positive on subset of cells included Factor VIII (megakaryoctyes and some of the mononucleated tumor cells), CD61 (mononucleated tumor cells), CD117 and MPO, and CD31 (some mononucleated cells and some megakaryocytes). The infiltrate was associated with marked stromal fibrosis and significant tumor necrosis. In combination, these features suggested a diagnosis of myeloid sarcoma with megakaryocytic differentiation (AML FABM7). Cytogenetic analysis based on the marrow sample revealed translocation t(1;13)(p22;q12) in 3 metaphases and del(13)(p12q22) in one. The remaining 16 metaphases were diploid. No sample for molecular studies could be obtained.

The patient received induction chemotherapy consisting of idarubin and intermediate dose cytarabine in combination with clofarabine as part of an investigational induction program for patients younger than 60 years old. On day 4 of chemotherapy the patient was taken for a prophylactic closed intramedullary nailing of the left femur. An allogenetic stem cell transplant is being considered early in the treatment course for her myeloid sarcoma with megakaryocytic differentiation.

Discussion

Acute panmyelosis with myelofibrosis is a rare form of AML which presents acutely with constitutional

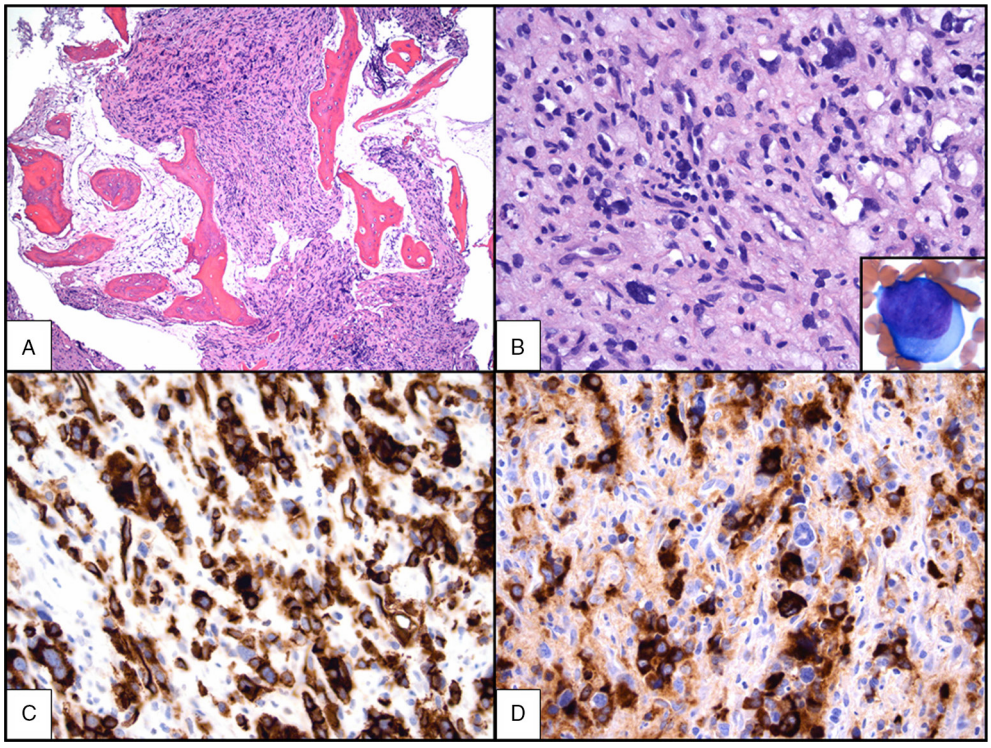

Fig. 3. Histological examination of the lytic femoral lesion. (A) The lesion is infiltrative and bone destructive (hematoxylin&eosin, ×100). (B) A higher power view of the infiltrative tumor cells and admixed megakaryocytes (hematoxylin&eosin, ×500). Inset: a tumor cell on touch imprint. (C) The tumor cells are uniformly CD34 positive. (D) Many tumor cells which are positive for Factor VIII-related antigen.

symptoms, fevers and bone pain, and pancytopenia (1). In general, osteolytic lesions are rare in leukemias and lymphomas and are seen more frequently in plasma cell disorders and metastatic solid tumors. The initial suspicion was a diagnosis of multiple myeloma. However, further work up did not reveal the presence of plasma cells or a population of monoclonal proteins. Although non-secretory myeloma was a consideration, it is very rare (only about 3% of plasma cell disorders), involves neoplastic plasma cells (which could not be detected in this case including by immunohistochemical stains), and in up to two-thirds of cases demonstrates abnormal light chain levels or ratio. Furthermore, presentation with hypercalcemia is less common in non-secretory myeloma than its more frequent secretory variants (2, 3).

The diagnostic procedure which ascertained the diagnosis was a left femoral biopsy pointing strongly toward a diagnosis of a myeloid sarcoma with megakaryocytic differentiation akin to AML FABM7 when taking into consideration the marrow biopsy results as well. Skeletal radiological manifestations in patients with myelofibrosis may range from normal to osteoporosis and osteosclerotic changes (the latter in 30 to 70% of cases). Osteolytic lesions on the other hand are exceedingly rare (4, 5). In combination with hypercalcemia, occurrence of lytic lesions has been associated with accelerated and blastic phases of myelofibrosis ('acute myelofibrosis'), a rapid disease course, and poor prognosis (6).

It typically occurs as de novo and is not preceded by a lengthy prodrome of the clinical manifestations of myelofibrosis. Criteria for diagnosis include panmyelosis (marrow hypercellularity with multilineage involvement), severe marrow fibrosis, pancytopenia with absence of tear-drop-shaped red blood cells, and lack of splenomegaly (7, 8). Using a panel of antibodies such as MPO, lysozyme, erythroid markers, and megakaryocytic markers allows demonstration of the multilineage nature of the proliferation. Marrow blast percentage varies but often does not exceed 20%. Megakaryocytic populations can be prominent. Although most patients' marrow will show an abnormal karyotype, no specific cytogenetic abnormalities have been described. According to one series of 12 patients with acute panmyelosis structural abnormalities of chromosome 12 were most frequent whereas abnormalities of chromosomes 3 and 13 have been associated with myelofibrosis in previous observations (7, 9). The most important distinction is from acute megakaryoblastic leukemia (AML M7). According to WHO criteria, the diagnosis in this case requires at least 20% blasts of which at least 50% are of megakaryocytic lineage. Markers to identify megakaryocytic forms are mainly antibodies with reactivity against platelet glycoproteins (CD41, CD42, CD61) or against von Willebrand factor VIII although not all of them are equally apt for use in routinely processed tissue sections (8, 10). Blasts in acute megakaryoblastic leukemia are less heterogeneous than in acute panmyelosis which may reflect a less immature and more committed cell of origin in the former. Whereas CD34 is nearly always expressed in panmyelosis, many cases of acute megakaryocytic leukemia lack expression of CD34 and HLA-DR. Although extensive, marrow fibrosis is less pronounced in the megakaryocytic variant than in panmyelosis. Hypercalcemia itself in the absence of osteolytic lesions is a very rare feature as well and has only be described in one previous case report of an 8 month-old non-Down syndrome infant with a diagnosis of acute megakaryocytic leukemia and hypercalcemia at presentation (11).

Other diagnoses with overlapping clinical and pathologic features that need to be considered include primary myelofibrosis, fibrotic subtypes of myelodyplastic syndrome, and tumors of other tissues of origin that metastasize to the marrow. These distinctions can usually be reliably made based on the degree of fibrosis, percentage and marker expression of blasts, level of dysplasia, and presence or absence of solid tumor cells in the marrow.

The prognosis of patients with either acute megakaryocytic leukemia or acute panmyelosis is nearly equally poor. Median survival times following AML type induction therapy are measured in few months and outside use of allogeneic stem cell transplant. Only a few long-term survivors have been identified (7, 8, 12). How alternative treatment modalities and newer drugs may influence future prognosis is unknown and only occasional case reports are described (13).

Conclusion

In conclusion, this is a 45-year-old patient with progressive constitutional symptoms, osteolytic bone lesions with hypercalcemia, and a rapidly worsening pancytopenia. The final pathological diagnosis is that of an acute megakaryocytic leukemia (AML M7) weighing in identification of megakaryocytic markers in the tissue section and the diffuse and strong staining for CD34. Presentation of patients with osteolytic lesions should not automatically be assumed to be of plasma cell origin and myeloid malignancies should be kept in the differential diagnostic considerations.

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Disclosure

None of the authors have any financial or personal bias that would inappropriately compromise the publication of this work.

Consent

Informed consent was obtained from the patient and her family for educational use of the data and no personal patient information has been disclosed.

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