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Acute promyelocytic leukemia presenting with features of metastatic osseous disease

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A B S T R A C T

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia defined by a balanced translocation between chromosomes 15 and 17 resulting in fusion of the promyelocytic leukemia gene (PML) on chromosome 15 with the retinoic acid receptor-alpha gene (RARα) on chromosome 17. APL often presents with pancytopenia and is associated with a life threatening coagulopathy making prompt diagnosis and initiation of therapy critical. We report an unusual case of APL in a 59 year old female without peripheral blood abnormalities or diffuse marrow involvement. Clinical and radiographic findings were initially interpreted as metastatic osseous disease but ultimately found to be APL.

1. Introduction

APL was first described as a distinct entity in 1957 and accounts for about 5–8% of AML cases [1]. For many years the disease was universally fatal, usually due to hemorrhagic death associated with disseminated intravascular coagulopathy (DIC). The introduction of all-trans retinoic acid (ATRA) which binds RARα and induces differentiation of blasts has revolutionized treatment of APL, making it a highly curable disease. Arsenic trioxide (ATO) binds and degrades the PML-RARα fusion protein and works synergistically with ATRA; cure rates with ATRA + ATO now exceed 90% [2]. Although APL is considered the most curable form of AML, there remains a significant risk of death early in the disease course due to coagulopathy and bleeding. Early recognition of the disease with prompt initiation of therapy is critical. APL is more common in young adults and patients typically present with symptoms related to pancytopenia. APL blasts may be rare in the peripheral blood but in general, are easily detected in the bone marrow. APL blasts exhibit distinctive morphologic (bilobed nuclei, Auer rods) and immunophenotypic features, facilitating the diagnosis. In most cases, recognition of the characteristic clinical and morphologic findings allows for a presumptive diagnosis of APL at which point ATRA therapy is initiated empirically. The diagnosis is confirmed by testing for the pathognomic PML-RARα fusion using fluorescent in situ hybridization, karyotype or reverse transcription polymerase chain reaction (RT-PCR). We present an unusual case of APL, in which the patient had radiologic findings thought to be metastatic osseous disease, a normal CBC, and variable involvement of the marrow, including one bone marrow biopsy with no morphologic evidence of disease.

2. Case report

A 59 year old female with a history of chronic back pain presented with worsening back pain after lifting heavy furniture. A spinal X-ray showed degenerative joint disease. The pain persisted and an MRI was performed three months later. The MRI demonstrated abnormal marrow signal at multiple levels (L3-L5 and S1), most pronounced in the L4 vertebral body. The radiographic findings were highly suspicious for metastatic osseous disease (Fig. 1A). A CT guided biopsy of the L4 lesion revealed atypical cells with monolobated or bilobed nuclei and abundant eosinophilic cytoplasm (Fig. 1B). Immunohistochemical stains were performed; the cells expressed MPO (Fig. 1C), lysozyme and CD68 while CD117 was negative. Her CBC showed a mildly decreased WBC of 4.1 K/uL (normal range, 4.8–10.8 K/uL) with a normal differential of 66% neutrophils (normal range, 35–70%), 26% lymphocytes (normal range 25–45%), 6% monocytes (normal range, 3.5–9%), 1% eosinophils (normal range 0–7%) and 0.5% basophils (normal range, 0–2%). Coagulation studies were normal; INR = 1 (normal range 0.9–1), PTT = 32 s (normal range 23–34 s) and PT = 11.3 s (normal range 10–13 s), and the patient was clinically stable. A diagnosis of atypical myeloid proliferation was rendered and the patient was referred to our institution for further evaluation.

A repeat bone marrow biopsy (standard iliac crest) was performed, which was without morphologic or immunohistochemical evidence of a neoplastic population; however karyotype revealed an apparently balanced translocation between the long arms of chromosomes 15 and 17 in 3/20 metaphase cells, 46,XX,t(15;17)(q22;q21)[3]/46,XX[17. This was confirmed by fluorescence in situ hybridization (FISH) to result in PML-RARα fusion (26/200 cells positive for dual-fusion). In light of this

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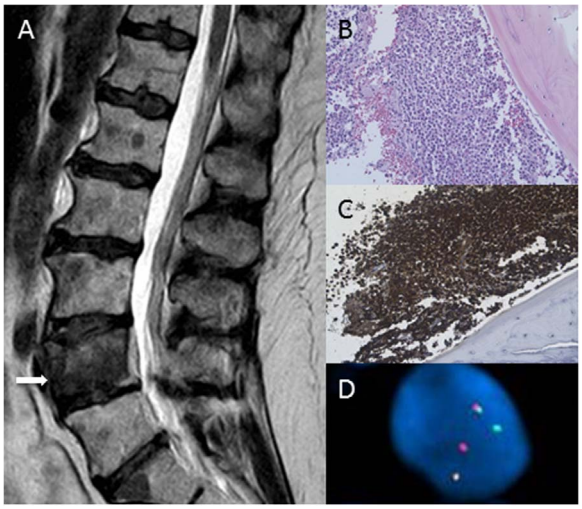

Fig. 1. (A) MRI of lumbar spine showing multiple foci of decreased signal most pronounced at L4 (arrow) (B) Hematoxylin and Eosin stained section of L4 biopsy, 20× (C) MPO immunohistochemical stain on L4 biopsy, 20× (D) Fluorescence in situ hybridization showing PML-RARα fusion in L4 biopsy orange = PML Green = RARα.

finding, FISH was retrospectively performed on the L4 biopsy and showed PML-RARα fusion in 79% of cells (Fig. 1D) and a diagnosis of APL was made. RT-PCR on peripheral blood revealed a low level of the PML-RARα fusion product (0.4% allele burden relative to ABL). At diagnosis, 60 days after the initial L4 biopsy, the patient's leukopenia was slightly worse (WBC 3.29 K/uL, absolute lymphocyte count 0.8) and she remained clinically stable. By risk-stratification, her APL was low risk (WBC < 10 and platelets > 40) and given her overall low burden of disease compared to most APL patients, she was started on ATRA /arsenic based regime as an outpatient. She tolerated induction and 4 cycles of consolidation well and entered into a molecular complete remission (PML- RARα undetectable by RT-PCR). The patient remains disease free 14 months after initial diagnosis.

3. Discussion

This case illustrates an unusual presentation of APL. Our patient presented with back pain but was otherwise asymptomatic. Her CBC was normal and MRI showed focal lesions in her lumbar spine that were assumed to be metastatic. The initial L4 biopsy revealed an atypical infiltrate of myeloid cells although an immunohistochemical stain for CD117 was negative which is very unusual for APL and further obscured the diagnosis. It is possible this was a false negative result related to technical artifact or poor antigen preservation in decalcified paraffin embedded tissue. Retrospectively, the L4 lesion was clearly APL, with 79% of cells containing the PML- RARα fusion. Interestingly, the subsequent iliac crest bone marrow biopsy contained no morphologic or immunohistochemical evidence of APL, although FISH did show the PML-RARα fusion indicating bone marrow involvement at the genetic level.

We reviewed the literature to identify rare presentations of APL. APL presenting as an isolated myeloid sarcoma (extramedullary APL) has been increasingly recognized, although this is more often with relapse. Skin and CNS are the most common sites although heart [3], breast [4], and various other sites [5] have been described. There are rare reports of APL presenting as destructive bone lesions, although in most of these, concurrent peripheral blood abnormalities [6], significant extramedullary involvement [7], or detectable disease on pelvic biopsy [8] were also described. We found one report of APL presenting as isolated lytic lesions in a 16 year female with a normal CBC and normal iliac crest bone marrow biopsy [9]. Bone lesions in other subtypes of AML are also infrequently reported, most of which have been described in association with acute megakaryoblastic leukemia [10] and rarely in acute myeloid leukemia transformed from a myeloproliferative neoplasm [11,12].

Osseous radiographic abnormalities in children with lymphoblastic leukemia are common and include osteopenia, lytic lesions, metaphyseal bands, periosteal new bone and sclerotic lesions [13]. In contrast, bone lesions in AML/APL are rare and when encountered are often accompanied by systemic manifestation of disease. The biological underpinnings of bone abnormalities in acute leukemia are not well understood. There is evidence to suggest that AML cells are able to remodel the local microenvironment to support growth and studies have shown that AML cells can suppress osteoblast growth in the bone marrow niche [14]. Furthermore, leukemia cells including promyelocytic leukemia cell lines are capable of producing parathyroid hormone related protein (PTHrP), potentially leading to hypercalcemia and lytic bone lesions [15]. In some cases APL cells may be less prone to entering the circulation and proliferate locally before seeding the rest of the marrow. This pattern of local proliferation and then systemic expansion is certainly true in relapsed APL where patients can present with a focal extramedullary mass lesion and/or with low levels of circulating PML-RARα transcript prior to development of marrow disease and overt clinical relapse. It is remarkable that several months elapsed between the patient's presentation with back pain and the initiation of treatment, and still she was without circulating blasts, significant cytopenias, or the coagulopathy that is characteristic of this disease. In patients presenting with focal bone marrow lesions, it is important to keep a diagnosis of acute leukemia in the differential.

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