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Acute promyelocytic leukemia: A rare presentation without systemic disease

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Abstract

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia characterized by an abnormal proliferation of promyelocytes. It is often associated with an aggressive clinical presentation involving complex coagulopathies including disseminated intravascular coagulation, with a significant risk of bleeding and/or thrombosis if treatment with all-*trans*-retinoic acid (ATRA) is not rapidly initiated. Here we present a unique case of APL which was isolated to femoral bone lesions, without definitive evidence of peripheral blood or bone marrow involvement, and without systemic sequelae.

Keywords

Acute myeloid leukemia; Acute promyelocytic leukemia; APL; Acute leukemia; Bone

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized classically by a t(15;17)(q24.1;q21.2), resulting in a *PML::RARA* fusion and a consequent abnormal proliferation of maturation arrested promyelocytes. It is more commonly diagnosed in young to middle aged adults and associated with an aggressive

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Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement
The patient has given written consent for the publication of this case.

Patient consent statement
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Nurfiza Ladak: Writing – original draft, Conceptualization. **Ying Liu:** Data curation. **Amanda Burke:** Investigation. **Oscar Lin:** Visualization, Investigation. **Alexander Chan:** Writing – review & editing, Visualization, Supervision, Conceptualization.

clinical presentation involving complex coagulopathies including disseminated intravascular coagulation (DIC), requiring prompt therapy with all-*trans*-retinoic acid (ATRA). The hypergranular variant has a characteristic cytologic morphology of bilobed abnormal promyelocytes with cytoplasmic granules and often Auer rods, as well as a characteristic flow cytometric (FC) immunophenotype. Here we present a unique case of APL which was isolated to femoral bone lesions, without definitive evidence of systemic involvement or sequelae.

Case Presentation

A 37-year-old man with no significant past medical history sustained an accident while go-carting at a speed of approximately 40 miles per hour (64.4 km/h), resulting in progressive right hip pain. Magnetic resonance imaging (MRI) was performed which revealed a right labral tear. He was treated with oral steroids with subsequent relief of symptoms. The patient remained asymptomatic for two months but represented with similar pain plus difficulty with ambulation and weight-bearing of the right lower extremity. Another MRI was performed out of concern for avascular necrosis. This interval MRI was notable for a new 17 cm marrow replacement process in the right proximal femur without cortical erosion and without associated edema (see Fig. 1A–B). In addition, there was a small right hip joint effusion with possible small labral tear. There was no evidence of an underlying fracture. On positron emission tomography/computed tomography (PET/CT) there were few F-fluorodoxyglucose (FDG) avid medullary lesions in bilateral femora, including a dominant lesion in the proximal right femur with a standardized uptake value of 3.3. A biopsy of this lesion was recommended.

Flow cytometry of the right femoral head aspirate was significant for an expanded abnormal immature myeloid precursor population, representing 18.3 % of white blood cells with the following immunophenotype: CD13 (dim), CD15 (negative), CD33 (bright), CD34 (negative), CD45 (dim), CD64 (dim), CD117 (dim), CD123 (bright), HLA-DR (variable – negative to dim), and MPO (bright), with increased side scatter in the abnormal population (see Fig. 1C–H). Although not entirely specific, the findings raised the possibility of an acute promyelocytic leukemia (APL) and fluorescence in situ hybridization (FISH) for t(15;17) *PML*::*RARA* was rapidly initiated.

Biopsy of the right femoral head demonstrated trabecular bone with sheets of immature mononuclear cells with oval to irregular/indented nuclei and granular cytoplasm (see Fig. 2A). The immature cells expressed weak CD117 in a subset of cells, strong and diffuse MPO, and variable CD45 while lacking CD34, TDT, CD3, CD20 and pancytokeratin (see Fig. 2B–D). Concurrent cytologic evaluation of the lesion demonstrated abnormal promyelocytes including numerous kidney shaped or bilobed forms with abundant large granules and Auer rods (see Fig. 2E–F). A diagnosis of APL was confirmed by FISH with translocation of *RARA* (17q21.2) detected in 86.1 % of cells and *PML*::*RARA* fusion / t(15;17) in 86.3 % of cells (see Fig. 2G–H).

The patient's complete blood count demonstrated WBC 5.1 K/mcL, RBC 4.92 M/mcL, HGB 14.2 g/dL, HCT 41.8 %, MCV 85 fL. No blasts or promyelocytes were seen on the

PB smear. Platelets were 248 K/mcL and fibrinogen, prothrombin time, and international normalized ratio were all within normal range. While PB FC demonstrated rare events (16 out of 670 thousand events) with a similar phenotype to those detected in the bone lesion, these were too few to definitively identify an abnormal population at the test's detection limit of 0.01 % or 20 events. FISH testing on the PB demonstrated *PML*::*RARA* fusion in 1 % of cells, which was within the normal range of variation. Reverse transcriptase polymerase chain reaction (RT-PCR) in the PB was negative for *PML*:: *RARA* fusion transcripts at a detection limit of 0.0047 % clonal cells.

Additionally, the BM was negative for involvement by APL, showing trilineage maturing hematopoiesis with no increase in blasts. Flow cytometry of the BM aspirate was negative for any abnormal immature myeloid precursor, mature B- or mature T-cell populations, with a total 428 thousand events evaluated. Karyotype analysis displayed a normal male karyotype, with no evidence of clonal chromosomal abnormalities observed. FISH for *RARA* rearrangement was negative in the bone marrow, as was RT-PCR for *PML*::*RARA* fusion transcripts.

The patient began ATRA and arsenic, with follow-up PET/CT demonstrating decreased avidity in the right femur. Follow-up right femur biopsy showed extensive necrosis, consistent with therapy effect. FISH showed 18 % *RARA* gene rearrangement in the femur on follow-up, and RT-PCR of material from this site demonstrated 0.024 % positivity for *PML*::*RARA* transcripts. Follow-up FC, FISH, and RT-PCR in the PB have been negative for abnormalities since the initial presentation.

Discussion

Acute promyelocytic leukemia is a subtype of AML characterized by an abnormal proliferation of maturation arrested promyelocytes and t (15;17)(q24.1;q21.2), resulting in a *PML::RARA* fusion. The disease predominately affects young to middle aged adults. Early recognition and prompt treatment with ATRA to promote promyelocyte maturation are imperative due to high risk of coagulopathy and DIC.[1] Myeloid sarcoma (MS) is a rare localized form of acute myeloid leukemia that usually presents concurrently with a leukemic diagnosis or at the time of relapse.[2] APL typically presents as a leukemic disease, and localized presentation as MS is exceedingly rare, with very few reports in the literature.[3–6].

Two morphologic variants of APL are described, hypergranular and microgranular. Hypergranular APL typically demonstrates abnormal promyelocytes with prominent cytoplasmic granules and Auer rods, with reniform or kidney shaped nuclei, some of which may be bilobed. Immunophenotyping by FC of hypergranular APL shows increased forward and side scatter with low or absent expression of CD34 and HLA-DR.[1] There is usually positivity for myeloid associated antigens CD13, CD33, CD64, CD117 and cytoplasmic MPO, while CD11a, CD15, CD18, CD65, CD66b and CD66c are typically negative. CD11b while commonly absent has been reported to be variably expressed in APL.[7–10].

Isolated bony presentation of APL without definitive evidence of systemic disease has been reported only very rarely in the English language literature. Interestingly, the patient in this single previous report of APL presenting solely as a localized bony lesion presented with systemic symptoms such as fever and fatigue, despite the absence of identifiable systemic disease.[11] While there are other reports of APL presenting as bone lesions, virtually all of the other reported cases showed either evidence of disease either in the PB or BM, or were not extensively tested for evidence of PB or BM disease with high sensitivity techniques.[3–6].

Classical cases of APL commonly present with leukopenia or pancytopenia secondary to promyelocyte expansion or alternatively with symptoms of coagulopathy including thrombosis and/or bleeding. [1] Our patient was an otherwise healthy 37 year old with no signs or symptoms of systemic involvement by APL presenting with isolated bone lesions detected by radiology after a motor vehicle accident. In retrospect, the APL in this patient's lesion was likely present before the accident, which may have led to earlier detection of the developing disease. Furthermore, there was no definitively detectable peripheral blood or bone marrow involvement, which has been present in other reported cases of isolated APL lesions.[3–6] This case shows notable absence of definitive systemic involvement; RT-PCR was negative, and while FC and cytogenetic testing detected minute abnormal populations in the PB, these were below the validated limits of detection and did not show definitive involvement.

Immunophenotyping by FC permitted the recognition of a phenotype that was compatible with APL: CD13 (dim), CD15 (negative), CD33 (bright), CD34 (negative), CD45 (dim), CD64 (dim), CD117 (dim), CD123 (bright), and HLA-DR (variable − negative to dim).[7–10] This led to rapid review of the histologic/cytologic morphology, as well as the rapid initiation of FISH, allowing for a prompt confirmation of the diagnosis. Due to its unique presentation the patient's clinical team did not suspect a leukemic process, highlighting the importance of recognizing the morphology and immunophenotype of APL.

Conclusion

Here we present a unique case of APL presenting as bone lesions without definitively detectable PB or BM involvement. Recognition of the immunophenotype by flow cytometry in the bone lesion and corresponding morphology prompted initiation of FISH studies which rapidly confirmed the diagnosis of APL, with initiation of therapy with ATRA and arsenic soon thereafter. This case emphasizes the need to recognize the morphology and immunophenotype of APL, and serves as a reminder that, though rare, APL can present as an isolated, localized lesion.

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Data availability

No data was used for the research described in the article.

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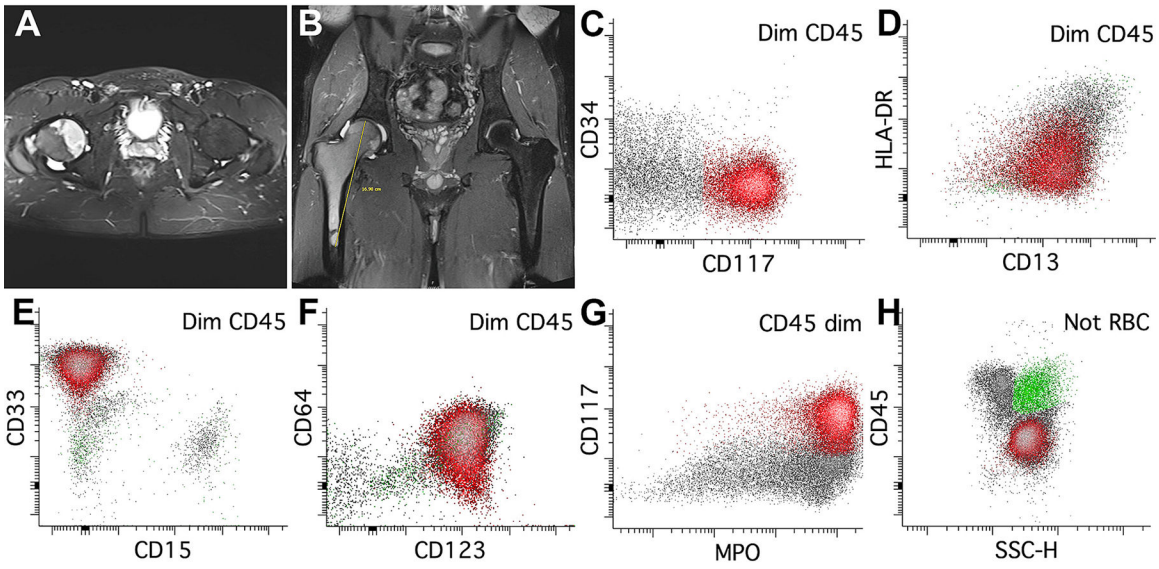

Fig. 1.

A-B. MRI images show right femoral bone lesion (yellow line in 1B) involving the femoral head and shaft. Flow cytometry of the right femoral head lesion shows that the abnormal cell population (red) demonstrates (**C**) expression of CD117 with absence of CD117, (**D**) positive CD13 with absent HLA-DR, (**E**) bright CD33 with absence of CD15, (**F**) bright CD123 with dim CD64, (**G**) bright MPO, and (**H**) dim CD45 expression with increased side-scatter similar to the side scatter of granulocytes (green).

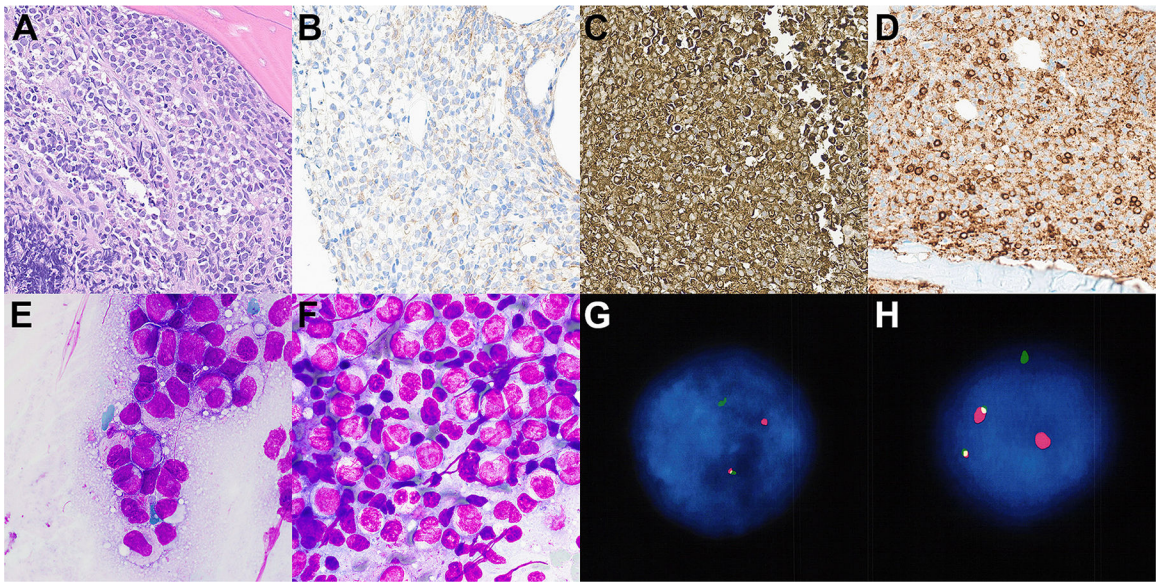

Fig. 2.

A. Biopsy of the right femoral head lesion shows sheets of immature appearing cells with small amounts of cytoplasm, irregular nuclei, and fine chromatin (hematoxylin and eosin stain, 400x magnification). Immunohistochemistry shows (**B**) weak expression of CD117 in a subset of cells, (**C**) strong diffuse myeloperoxidase expression, and (**D**) variable CD45 expression (immunohistochemistry, 400x magnification). **E-F**. Cytology evaluation of the aspirate material from the right femoral head lesion shows abnormal promyelocytes including numerous kidney shaped or bilobed forms with abundant large granules and Auer rods (Giemsa stain, 1000x magnification under oil). **G.** Cytogenetic fluorescence in situ hybridization (FISH) evaluation with *RARA* breakapart probe demonstrates split orange/green signals consistent with *RARA* gene rearrangement. **H**. Additional FISH testing with *PML*::*RARA* fusion probe demonstrates fusion signal of *PML*::*RARA* consistent with a t(15;17) translocation.