The unexpected hematological diagnosis during investigation of back pain: a case report

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ABSTRACT

Background: Acute promyelocytic leukemia is a subtype of acute myeloid leukemia most noted for a high rate of cure with prompt treatment and high early mortality if unrecognized, typically presenting with symptoms of bone marrow failure and life-threatening coagulopathy.

Case Presentation: We report the case of a patient who was found to have this unexpected diagnosis during workup of persistent back pain following a fall. In this example, the incidental finding of abnormal bone marrow signal on magnetic resonance imaging prompted a bone marrow biopsy which confirmed the diagnosis.

Conclusion: This case highlights the significance and emerging role of imaging techniques in identifying abnormalities in the bone marrow which may provide the initial clues and support the timely diagnosis of hematological malignancies.

Keywords: Acute promyelocytic leukemia, case report, magnetic resonance imaging.

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Background

Acute promyelocytic leukemia (APL), a rare subtype of acute myeloid leukemia, is characterized by translocations of the retinoic receptor alpha gene (RARA) with other genes and in the vast majority with the promyelocytic leukemia protein (PML) gene. This results in the characteristic *t*(15:17), PML-RARA fusion protein with downstream signaling effects leading to the differentiation block of myeloid progenitors at the promyelocyte stage which consequently dominate the bone marrow landscape [1]. It is uncommon for APL to present with incidental findings. This is one of the very few case reports which explores when to perform more invasive tests such as bone marrow biopsy in cases of altered bone marrow signal during imaging studies when the clinical presentation is unusual.

Case Presentation

A 61-year-old man presented to the emergency department complaining of severe lower back pain preceded by a fall where he slipped and landed on his sacrum. Clinical examination and systems review were unremarkable. Significant past medical history included hypertension, hypercholesterolemia, sciatica, obesity, and family history of breast cancer.

Laboratory investigations on presentation showed hemoglobin 148 g/l, white blood count 3.0 × 10^9/l, neutrophils 1.8 × 10^9/l, lymphocytes 0.8 × 10^9/l, and platelets 247 × 10^9/l. Magnetic resonance imaging (MRI) of the whole spine demonstrated an acute L2 superior end-plate fracture with no cord compression or abnormal bone marrow signal.

The initial management plan included analgesia, thoracolumbosacral orthosis brace, and follow up with the neurosurgery team.

A second MRI spine was performed 5 months later in view of persistent back pain which revealed new abnormal bone marrow signal in multiple vertebrae levels (Figure 1). A

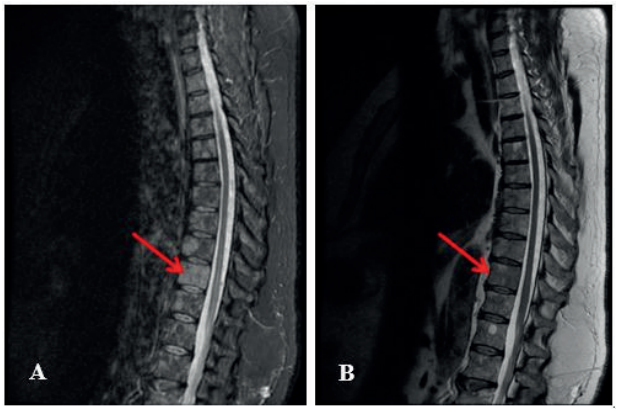

Figure 1. *MRI thoracolumbar spine. Sagittal T1-weighted (A) and fat-suppressed short T1-inversion recovery (B) images showing diffuse abnormal marrow signal in T10 vertebrae (red arrow).*

repeat full blood count (FBC) showed neutrophils of 1.0 × 10^9/l, Lymphocytes 0.7 × 10^9/l, hemoglobin 135 g/l, platelets 192 × 10^9/l with normal renal, liver, and coagulation profile. Blood film examination revealed reactive lymphocytes and neutropenia with no evidence of blasts. Supporting investigations including prostate-specific antigen level, serum protein electrophoresis, and free light chains were within the normal range. Serology for the human immunodeficiency virus, hepatitis B and hepatitis C viruses was negative. The patient remained otherwise well with no history of bleeding, fevers, night sweats, or weight loss.

At this stage, a referral to the hematology clinic was made which prompted a bone marrow aspiration with trephine biopsy. Surprisingly, the bone marrow aspirate showed a marked increase in blasts (52%, normal range 1%-5%) with a dominant population of abnormal promyelocytes, many of which contained Auer rods (Figure 2). Immunophenotyping with flow cytometry showed an abnormal population of cells positive for the surface markers Cluster of differentiation (CD13), CD33, CD56 and myeloperoxidase and negative for CD34, Human Leukocyte Antigen – DR isotype (HLA-DR), and CD11c, consistent with immature myeloid precursors. Fluorescent in-situ hybridization analysis of the aspirate was positive for the *t*(15;17) translocation of the PML/RARA gene product which is diagnostic for APL.

Prior to performing the bone marrow biopsy, the differential diagnosis of altered bone marrow signal associated with mild neutropenia included infective causes such as tuberculosis or viral infection, systemic inflammatory disorders such as rheumatoid arthritis and malignant infiltration.

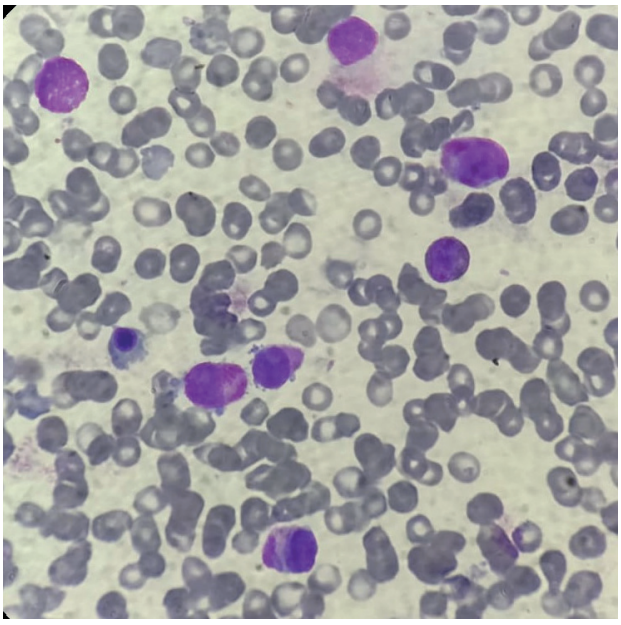

Figure 2. *Bone marrow aspirate. Microscopy at ×40 magnification revealed high frequency of myeloid precursors with eccentric nuclei and prominent primary granules with multiple Auer rods, characteristic of abnormal promyelocytes.*

The bone marrow aspirate results were communicated to the duty hematologist and urgent treatment with oral all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) infusion was commenced.

The patient remained in complete remission at the 6-month follow-up visit and is completing consolidation therapy with ATRA and ATO. His symptom of lower back pain is improved pending follow up imaging studies.

Discussion

APL is characterized by a high early (within 1 month) mortality rate of 17.3% which plateaus significantly after the first 2 months, thus making a prompt diagnosis in these cases is of the essence [2].

In clinical practice, APL should be suspected in any patient presenting with laboratory or clinical features of an acute leukemia such as pancytopenia or leukocytosis, deranged clotting, bleeding, weakness, or infections. A provisional diagnosis can be made on the basis of the peripheral blood film followed by a bone marrow aspirate which confirms the presence of the featured RARA-translocation by fluorescence *in situ* hybridization or polymerase chain reaction.

APL should be dealt as a medical emergency as it can be rapidly complicated by life-threatening events such as disseminated intravascular coagulation or bleeding and has a dismal prognosis (<1 month) if left untreated. However, in the era of modern medicine, patients may present at an earlier pathogenetic stage during incidental findings before presenting with a fully developed clinical syndrome such as subtle changes in blood test parameters or imaging tests.

In a recent study of 1,004 consecutive patients diagnosed with leukemia following incidental findings, only 23% of the APL patients were diagnosed following incidental results in contrast to about 68% of the chronic lymphocytic leukemia (CLL) cases which has a more indolent course. In the same patient cohort, the APL patients were most likely to report symptoms (mostly bleeding) when directly asked and uniformly had some abnormality in the FBC albeit abnormal radiological findings were discovered in only one third [3]. This was in contrast with CLL where imaging abnormalities were discovered in over two thirds of the patients.

An abnormal bone marrow signal on MRI can be identified using various sequences (T1, T2, diffusion-weighted imaging) and reflects the replacement of abundant yellow marrow which is rich in fat from red marrow which is rich in water which can be a feature of hematological malignancies [4]. Despite its well-established clinical utility in other conditions such as multiple myeloma, its role in other hematological malignancies is less well understood and remains the subject of clinical trials [5]. In a recent study of four cases in Norway, incidental findings on MRI following musculoskeletal symptoms resulted in the

timely diagnosis of acute leukemia of the non-plasma cell type when not otherwise suspected on the basis of clinical signs or FBC results [6].

There is no current consensus on whether a bone marrow assessment is indicated after an incidental finding of altered bone marrow signal on MRI. In a retrospective study of MRI scans which evaluated the bone marrow about 1.5% had an incidental finding of abnormal signal and of those only 6% led to a diagnosis of malignancy [7]. A number of non-malignant causes such as hemangiomas, hypoxia, smoking, obesity, and benign hematological conditions were also identified as alternative causes.

Therefore, an initial clinical assessment which includes baseline laboratory investigations with a focus on the FBC and blood film review can select the patients requiring more invasive tests. This was confirmed by a further study which selected patients to undergo bone marrow biopsy for incidental MRI changes based on the additional clinical or laboratory features indicative of leukemia. That led to a much higher yield of primary hematological disorders discovered in 7 out of 15 patients [8].

Conclusion

This case highlights the dilemma of when to perform more invasive investigations when incidental bone marrow signal changes on MRI scans raise the suspicion of hematological malignancies. An individualized approach and multi-disciplinary assessment of each case should be applied in order to timely recognize these potentially life-threatening conditions.

List of Abbreviations

APL	Acute promyelocytic leukemia
ATO	Arsenic trioxide
ATRA	All-trans-retinoic acid
CD	Cluster of differentiation
CLL	Chronic lymphocytic leukemia
FBC	Full blood count
MRI	Magnetic Resonance Imaging
RARA	Retinoic receptor alpha

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this
article.

Funding

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 61 years old
2	**Final diagnosis**	Acute promyelocytic leukaemia
3	**Symptoms**	Back pain
4	**Medications**	Paracetamol, ATRA, Arsenic trioxide
5	**Clinical procedure**	Biological therapies
6	**Specialty**	Hematology