CASE REPORT

Atypical features in a patient with acute promyelocytic leukaemia: a potential diagnostic pitfall

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SUMMARY

Acute promyelocytic leukaemia (APML) is a malignancy with a high cure rate; however, delay in diagnosis or treatment can result in morbidity and mortality. APML has characteristic clinical, morphological, immunophenotypic and molecular features. In patients with acute leukaemia, a high index of suspicion is required to exclude APML. Very rarely APML patients at diagnosis can demonstrate atypical features. We reported a patient whose bone marrow features resembled acute myeloid leukaemia with predominantly agranular blasts, devoid of Auer rods and expressing CD34 and HLA-DR on flow cytometry. APML was not suspected initially but after cytogenetic and molecular genetic studies demonstrated t(15;17), appropriate therapy with ATRA+ chemotherapy was instituted and the patient showed remarkable and sustained response to treatment. This case highlights the fact that morphology and immunophenotyping are useful but not infallible indicators for these malignancies and, ultimate diagnoses will require detection of the characteristic molecular markers.

BACKGROUND

Acute promyelocytic leukaemia (APML) has characteristic clinical, morphological, immunophenotypic and molecular features. In patients with acute leukaemia, a high index of suspicion is required to exclude APML. This case report describes a patient with atypical clinical, morphological and immunophenotypic features of APML.

CASE PRESENTATION

A 44-year-old Caucasian woman presented with general weakness and purpuric spots in the skin of 2 weeks duration. She did not have any significant medical illnesses in the past. A clinical examination revealed purpuric spots all over the body; however, there were no bleeding from any other sites. Her cardiac, respiratory and neurological statuses were normal and there was no palpable lymphadenopathy or organomegaly. Her performance status by Eastern Cooperative Oncology Group score was 1.

INVESTIGATIONS

At presentation her full blood counts (FBC) showed pancytopenia with haemoglobin 72 g/L, total white cell count $3 \times 10^9/\text{L}$, neutrophil counts $0.8 \times 10^9/\text{L}$ and very low platelet count $8 \times 10^9/\text{L}$. There were a few blasts in the blood film. A bone marrow aspirate revealed 90% leukaemic blasts with mature

Figure 1 Bone marrow aspirates ($\times 1000$ magnification) showing M1-like blasts.

granulocyte component of 5%. The erythroid precursors and megakaryocytes were markedly reduced. Morphologically the blasts were medium to large-sized and mostly agranular with a few granular blasts, scanty cytoplasm, large nucleus, high nucleocytoplasmic ratio, delicate chromatin, prominent nucleoli and no Auer rods (figure 1, $\times 1000$ magnification). There were no abnormal promyelocytes in the blood film or bone marrow smears. These features were characteristic of M1 blasts by French American British (FAB) classification. Bone marrow trephine biopsy demonstrated a diffuse infiltrate of myeloblasts with scanty cytoplasm, large nucleus and prominent nucleoli with marked suppression of normal haematopoietic precursors (figure 2, $\times 400$ magnifications).

Figure 2 Bone marrow trephine ($\times 400$ magnification) showing diffuse infiltration by myeloblasts.

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Flow cytometric analysis showed an abnormal population of cells with low side scatter predominantly expressing surface antigens CD13, CD33, CD117 and myeloperoxidase. Among the myeloid markers, CD33 was more heterogeneously expressed when compared with CD13 and the granulocytic marker CD15 was negative in the leukaemic cells. CD34 and HLA-DR were positive in the majority of these leukaemic cells (figure 3). The monocytic markers, namely CD11c and CD14 were negative. At presentation the coagulation tests revealed normal prothrombin

time (PT) and activated partial thromboplastin time (aPTT) with a mildly reduced fibrinogen level (1.3 g/L, reference range: 2–4 g/L) and D-dimer level was 12 mg/L (normal range: <0.5 mg/L). The diagnosis of acute myeloid leukaemia was made based on the morphology and immunophenotype of leukaemic cells and induction treatment with Big-ICE (Idarubicin, high dose Cytarabine and Etoposide) chemotherapy was started.

After 48 h, a phone call came from the cytogeneticist with the information that bone marrow cytogenetics testing had

Figure 3 Flow cytometric analysis showing blasts with low side scatter which are predominantly CD13, CD33, CD117 and myeloperoxidase positive. CD34 and HLA-DR were also positive in the majority of the blasts.

Figure 4 Bone marrow cytogenetics showing t(15;17)(q22;q12) translocation (red arrows).

demonstrated an abnormal karyotype in 92% of the cells examined—46,XX,t(15;17)(q22;q12)(23)/46,XX(2), the cytogenetic translocation which is pathognomonic of APML (figure 4). Fluorescent in situ hybridisation (FISH) testing using the Vysis LSI PML/retinoic acid receptor α (RAR α) dual colour dual fusion probe also showed a PML/RAR α gene rearrangement (figure 5A). For comparison the FISH image of patient's normal cell without the gene rearrangement is shown (figure 5B). The

reverse transcriptase PCR (RT-PCR) result for PML-RAR α was also positive for APML (bcr-3 transcript). All these features confirmed the diagnosis of APML in our patient. The bone marrow slides were reviewed again carefully and there were no abnormal promyelocytes and no bilobed nucleus to suggest hypergranular or hypogranular APML.

DIFFERENTIAL DIAGNOSIS

Although initially suspected to be acute myeloid leukaemia (AML) without maturation (M1 by the FAB classification) based on clinical, morphological and immunophenotypic features, the genetic studies confirmed this to be AML with recurrent genetic abnormalities, APML with t(15;17); PML-RARA) by WHO classification, international classification of diseases for oncology (ICD-O) code: 9866/3.

TREATMENT

Soon after the confirmation of APML, Big-ICE chemotherapy was ceased and induction therapy with all-trans retinoic acid (ATRA) and idarubicin chemotherapy was introduced. During induction therapy, ATRA was given at a daily dose of 45 mg/m² for 5 weeks. She tolerated ATRA and chemotherapy well without any significant adverse effects.

OUTCOME AND FOLLOW-UP

FBC and coagulation parameters were monitored daily during the first 5 weeks. PT and aPTT levels were consistently within the normal range and fibrinogen levels were above 2 g/L on most occasions. D-dimer levels dropped to normal levels after 2 weeks. The patient did not require fresh frozen plasma or cryoprecipitate throughout the treatment. However, she required packed cells and platelet transfusions for top-up. The purpuric spots disappeared soon after platelet transfusions and there were no further bleeding manifestations. Five weeks after starting induction therapy, the patient attained complete morphological remission in the bone marrow biopsy and no detectable minimal residual disease by RT-PCR analysis. She underwent consolidation therapy (ATRA+ idarubicin) followed by maintenance therapy (ATRA+ 6-mercaptopurine). She is being monitored regularly with 3-monthly bone marrow biopsies and molecular testing for PML-RAR α in marrow specimens. Presently 2 years after diagnosis, she continues to be healthy with normal blood counts and is in molecular remission.

Figure 5 (A) Bone marrow fluorescent in situ hybridisation (FISH) showing dual PML retinoic acid receptor α (RAR α) fusion signals. (B) Bone marrow FISH on a normal cell showing two PML and two RAR α signals separately.

DISCUSSION

APML generally presents with pancytopenia and coagulopathy with or without disseminated intravascular coagulation (DIC). The most common morphological type is the hypergranular APML (M3 by FAB classification) characterised by an increase in abnormal promyelocytes and large blasts that will show an increased side scatter and commonly express the surface antigens CD33, CD13 and negative for HLA-DR and CD34 on flow cytometric analysis.^{1 2} Hypogranular APML (M3v by FAB classification) is less common and hyperbasophilic form is an extremely rare variant.³ In hypogranular variant the leukaemic cells commonly have bilobed nuclei and show low side scatter, CD34 negative and HLA-DR negative on flow analysis.^{2 4} APML should be suspected if these features are present and should be confirmed by urgent cytogenetics, FISH testing or RT-PCR assay for PML-RAR α .^{5 6} Atypical morphological forms of leukaemic cells have been reported in APML, including M1 like blasts.^{7–9} In such cases, there will be difficulties in diagnosing APML. The presence of PML/RAR α rearrangement in cases not having morphological features of M3 or M3v is extremely rare and was found to be approximately 0.2% in a study.⁹

Coagulopathy with or without DIC commonly occurs during the initial presentation of APML and can lead to life-threatening bleeding manifestations, including intracranial haemorrhage.¹⁰ The abnormalities in coagulation parameters include prolonged PT and aPTT, elevated D-dimers and low fibrinogen levels.¹¹ ATRA along with chemotherapy is the standard induction therapy for APML, which reduces the incidence of fatal bleeding manifestations. These complications are common during the first 2 weeks of induction therapy requiring close monitoring and pre-emptive management with products such as fresh frozen plasma and cryoprecipitates.¹²

Our patient did not have the characteristic features to suspect APML at diagnosis since the leukaemic cells appeared like M1 (FAB) with cell markers showing low side scatter with positive CD34 and HLA-DR antigens. At the time of presentation and during treatment, there were no clinically significant abnormalities in coagulation parameters, DIC or bleeding manifestations and she did not require fresh frozen plasma or cryoprecipitates. The diagnosis of APML would have been missed or delayed resulting in improper treatment and fatal outcome if the cytogenetic test had not been fast-tracked. In many centres worldwide, cytogenetic tests are prioritised for all patients who are diagnosed with acute leukaemia and the turn-around time will be usually less than 72 h. However if APML is suspected based on clinical features (DIC, bleeding), morphology or cell-surface antigen expression, urgent FISH testing is often performed which has a turn-around time of less than 24 h. In such situations, ATRA should be started early even before the diagnosis is confirmed by cytogenetic or molecular studies. This will be helpful to prevent the potentially fatal complications due to coagulopathy.¹²

Learning points

- ▶ Acute promyelocytic leukaemia (APML) is a haematological emergency in which early diagnosis and treatment is necessary to reduce morbidity and mortality.
- ▶ APML has characteristic clinical, morphological, immunophenotypic and molecular features.
- ▶ Atypical clinical or morphological manifestations can cause delay in diagnosis and treatment of APML.
- ▶ Rapid and high-quality cytogenetic testing with a potential cascade of specific molecular tests for t(15;17) should be conducted in all otherwise unremarkable acute myeloid leukaemia even if APML is not suspected. Positive results in these tests will dramatically impact therapy and outcomes.

Contributors MM was involved in clinician managing the patient, wrote manuscript and conducted the proof reading. KD performed cytogenetics and fluorescent in situ hybridisation test and correction of manuscript. JG helped in manuscript writing and proof reading.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Castoldi GL, Liso V, Specchia G, *et al*. Acute promyelocytic leukemia: morphological aspects. *Leukemia* 1994;8:1441–6.
- 2 Paietta E. Expression of cell-surface antigens in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol* 2003;16:369–85.
- 3 McKenna RW, Parkin J, Bloomfield CD, *et al*. Acute promyelocytic leukaemia: a study of 39 cases with identification of a hyperbasophilic microgranular variant. *Br J Haematol* 1982;50:201–14.
- 4 Golomb HM, Rowley JD, Vardiman JW, *et al*. "Microgranular" acute promyelocytic leukemia: a distinct clinical, ultrastructural, and cytogenetic entity. *Blood* 1980;55:253–9.
- 5 Grignani F, Fagioli M, Alcalay M, *et al*. Acute promyelocytic leukemia: from genetics to treatment. *Blood* 1994;83:10–25.
- 6 Borrow J, Goddard AD, Gibbons B, *et al*. Diagnosis of acute promyelocytic leukaemia by RT-PCR: detection of PML-RARA and RARA-PML fusion transcripts. *Br J Haematol* 1992;82:529–40.
- 7 Neame PB, Soamboonsrup P, Leber B, *et al*. Morphology of acute promyelocytic leukemia with cytogenetic or molecular evidence for the diagnosis: characterization of additional microgranular variants. *Am J Hematol* 1997;56:131–42.
- 8 Sainty D, Liso V, Cantu-Rajoldi A, *et al*. A new morphologic classification system for acute promyelocytic leukemia distinguishes cases with underlying PLZF/RARA gene rearrangements. *Blood* 2000;96:1287–96.
- 9 Allford S, Grimwade D, Langabeer S, *et al*. Identification of the t(15;17) in AML FAB types other than M3: evaluation of the role of molecular screening for the PML/RAR α rearrangement in newly diagnosed AML. The Medical Research Council (MRC) Adult Leukaemia Working Party. *Br J Haematol* 1999;105:198–207.
- 10 Rodeghiero F, Avvisati G, Castaman G, *et al*. Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia. A GIMEMA retrospective study in 268 consecutive patients. *Blood* 1990;75:2112–17.
- 11 Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. *Blood* 1992;79:543–53.
- 12 Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. *Blood* 2009;114:5126–35.

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