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Acute lower limb ischemia revealing hypo granular acute promyelocytic leukemia

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A B S T R A C T

Introduction: Acute promyelocytic leukemia (AML-M3), classified as acute Myeloid leukemia with PML RARA according to the 5th edition of the World Health Organization classification of haematolymphoid tumors 2022 [1], is marked by abnormal promyelocyte proliferation and is known for high risks of bleeding and thromboembolic complications. We present a case where lower limb ischemia revealed this leukemia in a child.
Case report: An 11-year-old with minor ankle trauma developed severe lower limb ischemia, leading to the discovery of subtotal femoral artery thrombosis. Blood tests revealed hyperleukocytosis, thrombocytopenia, and anemia with 88 % blasts, confirming acute myeloid leukemia (AML-M3). Karyotyping showed a t(15;17) translocation, and the child was started on emergency chemotherapy.
Discussion: Acute promyelocytic leukemia (APL), classified as AML-M3 with PML-RARA, is characterized by abnormal promyelocytes and accounts for about 10 % of acute leukemias, mostly in middle-aged adults. It has two variants: common hypergranular and rare hypogranular forms. APL can present with bone marrow failure, anemia, bleeding, and occasionally thromboembolic events, as seen in this case. The ischemia mechanism is not fully understood but may involve vessel obstruction by blasts or hypercoagulability. Diagnosis relies on clinical, morphological, phenotypic, and cytogenetic evidence, with treatment involving all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).
Conclusion: Hypogranular acute promyelocytic leukemia (AML3v) is a rare form and is even rarer when it is discovered following an ischaemic event, which is what makes our case so special.

1. Introduction

Acute promyelocytic myeloid leukemia AML 3 or acute Myeloid leukemia with PML RARA according to the 5th edition of the world health organization Classification of haematolymphoid tumors 2022) [1] is a subtype of acute leukemia characterized by the proliferation of abnormal promyelocytes, known for its increased risk of disseminated intravascular coagulation (DIC)and its enormous bleeding potential, but also for its thromboembolic complications, although the latter rarely reveal the disease [2]. We report a case of a child who consulted for lower limb ischemia revealing acute promyelocytic leukemia.

2. Observation

An 11-year-old child with no previous pathological history came to the emergency room with benign trauma to the right ankle following a sports accident. The somatic examination was unremarkable except for a slightly oedematous right ankle with pain. The radiological examination did not show any fracture. The child was given analgesic treatment and then declared discharged. Three days later he returned to the emergency room with severe pain in the right lower limb, clinical examination revealed an ischaemic right limb. An emergency Doppler ultrasound showed a subtotal thrombosis of the superficial femoral artery. The patient was admitted urgently to the operating theatre for thrombectomy under general anesthesia. In the preoperative work-up, the haemogram (Cell Blood Count) showed a hyperleukocytosis of 24,000/µL with monocytosis of 18,000/µL, thrombocytopenia of 39,000/µL, microcytic hypochromic anaemia (hemoglobin 9.7 g/ dl, MCV GMV 69fl, MCHT MCH 24 pg); reticulocytes 35,500/µL. In view of the thrombocytosis and monocytosis, a blood smear was performed showing 88 % blasts with bilobed, bissac, and butterfly wing nuclei (Fig. 1).

The myelogram showed a very richly cellular marrow, 92 % of which was composed of medium-sized blasts, with a high nucleocytoplasmic ratio, with a sometimes irregular, bilobed nucleus with fine nucleated chromatin. The remainder of the count is made up of 3 % neutrophils, 3 % erythroblasts, and 2 % lymphocytes. The myeloperoxidase (MPO)

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reaction was strongly positive in 100 % of the blasts (Fig. 2). The diagnosis of acute myeloid leukemia (variant AML3) was made.

The immunophenotypic profile showed 83 % proliferation expressing CD34, CD33, CD13, CD117, C64, and intra MPO markers, and were negative for HLA DR, TdT, and CD 14 Fig. 3.

A karyotype was performed on a marrow aspiration showing a 46-chromosome pseudodiploid clone with a clonal structural abnormality: t (15; 17) (q24.1; q21.2) on twelve cells examined.

The haemostasis work-up suspected disseminated intravascular coagulation (DIC) marked by a decrease in PT to 53 %, hypo fibrinogenemia to 1.9 g/L. D-dimer levels were 24.37 mg FEU/L. Postoperatively the child was referred to the paediatric ward for the initiation of emergency chemotherapy.

3. Discussion

Acute promyelocytic leukemia which corresponds to acute promyelocytic leukemia with PML-RARA according to the revised WHO 2022 classification, is an acute myeloid leukemia in which abnormal promyelocytic cells predominate. It accounts for 10 % of acute leukemias and can occur at any age, but most patients are middle-aged adults [3]. A distinction is made between the typical leukopenic or normoleukocytic AML 3, known as hypergranular, and the much rarer hypo or agranular variant AML 3 [4].

The circumstances of discovery of the disease are numerous, bone marrow failure syndrome, especially in the classic form, anaemic syndrome, alteration of the general state, haemorrhagic syndrome and rarely thromboembolic attacks as in our case, indeed very few cases of ischaemia reveal an acute leukemia have been reported in the literature [5].

The mechanism of this ischemia remains poorly understood, there are several hypotheses that could explain these ischaemias such as the obstruction of vessels by blasts and the formation of a white thrombus [6]. Or as a result of the hypercoagulable state that is often present in these patients secondary to activation of blood coagulation and platelet function and or suppression of fibrinolysis leading to thrombosis and or DIC. This is explained by the presence of the t (15;17) translocation which induces hyperexpression of tissue factors favouring interaction with other coagulation factors and other circulating procoagulants leading to thrombin formation. Other mechanisms are also involved. For example, the release of cytokines (IL-1B, TNFa, by blasts that convert the endothelium into a pro-coagulant state; the release of fibrinolytic proteins and proteolytic enzymes [7,8].

The diagnosis is based on a combination of clinical, morphological, phenotypic, molecular and cytogenetic evidence. However, if there is even the slightest suspicion of AML 3, a very rapid diagnosis can be made based solely on a blood and/or marrow smear. The haemogram, depending on whether it is the classic or the variant form, detects one or more cytopenias, sometimes pancytopenia, whereas in the variant form a hyperleukocytosis is noted [6]. The blood smear shows large blasts (20 to 30 μm in diameter) and differ in appearance according to their cytological form. In the classic form, the blast nucleus is variably reniform or bilobed, and its cytoplasm is filled with azurophilic or purple granules, sometimes coalescing, even masking the nucleus, which becomes invisible; the granules may sometimes form a rod-like structure 10 known as an "Auer body», needle-like structure. Some cells contain a large number of Auer bodies, giving rise to the characteristic "faggot cells" appearance that is pathognomonic of AML 3. In the hypogranular form, the cytoplasm contains fine, loosely scattered, and less prominent granulations. Auer bodies may be present but are less abundant than in the classic form. The hypo granular appearance of the cytoplasm is due to the submicroscopic size of the azurophilic granules. The shape of the nucleus is characteristic, it can be bilobed, bissac, or butterfly which most often allows the diagnosis [2,9,10].

The myelogram may show blasts of the same appearance as the blood smear, except that they are often slightly more granular than in the peripheral blood smear. Myeloperoxidase is strongly positive in acute promyelocytic leukemia.

Immunophenotyping is also important for the diagnosis of AML 3. Promyelocytic blasts are characterized by the expression of the CD33 marker. Expression of the CD13 marker is variable, while expression of the CD14 and CD64 markers is often low or absent. Expression of the CD117 marker is also negative or low. CD15 and CD65, which are markers of granulocyte differentiation, are negative or weakly expressed. In the classical form, CD 34 is negative and HLA DR is positive, whereas in the hypogranular form, CD 34 is often positive and HLA DR negative [9,11]. Approximately 10 % of cases may express CD 56 which is associated with a poor prognosis. [12]

>95 % of AML 3 cases are characterized by a balanced translocation between chromosomes 15 and 17, which can be detected by standard cytogenetic techniques. The translocation results in a fusion of the RARα and PML genes, with breakpoints typically at the q22 locus on chromosome 15 and q21 on chromosome 17. The resulting fusion protein disrupts differentiation and maturation signals and blocks myeloid differentiation at the promyelocytic stage. In particular, the breakpoint in the RARA gene is located in the second intron, while the PML gene has three distinct breakpoints(intron 6, exon 6, and intron 3), thus identifying the most common regions for the stop points (bcr-1, −2, and −3 respectively). These regions correspond to the different PML-RARA isoforms [12]. Although the bcr-1 (also known as the "long" or "L" isoform) and bcr-3 (also known as the "short" or "S" isoform) isoforms account for the majority of PML cases (90–95 %), the bcr-2 isoform is a

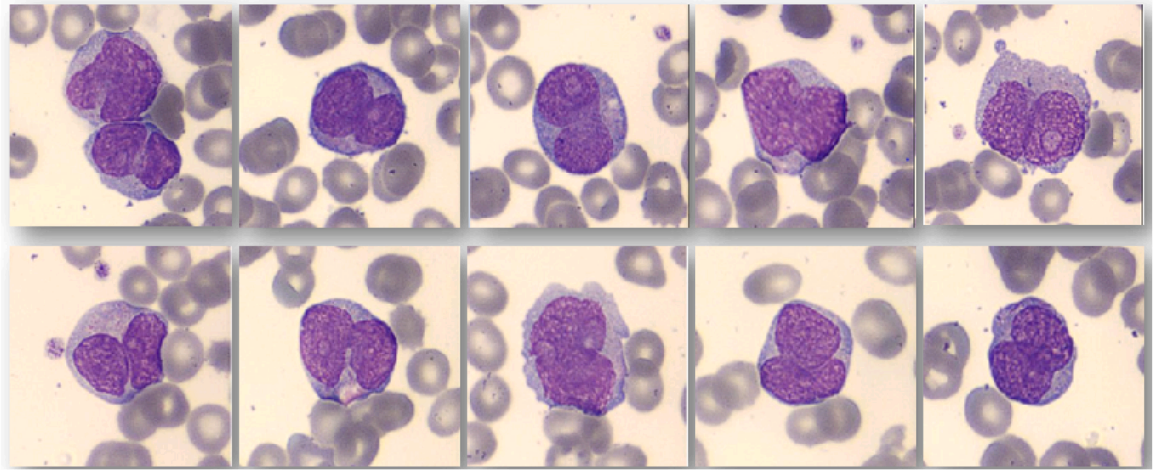

Fig. 1. Images of the different aspects of the blasts of the peripheral blood smear stained with MGG: ×100.

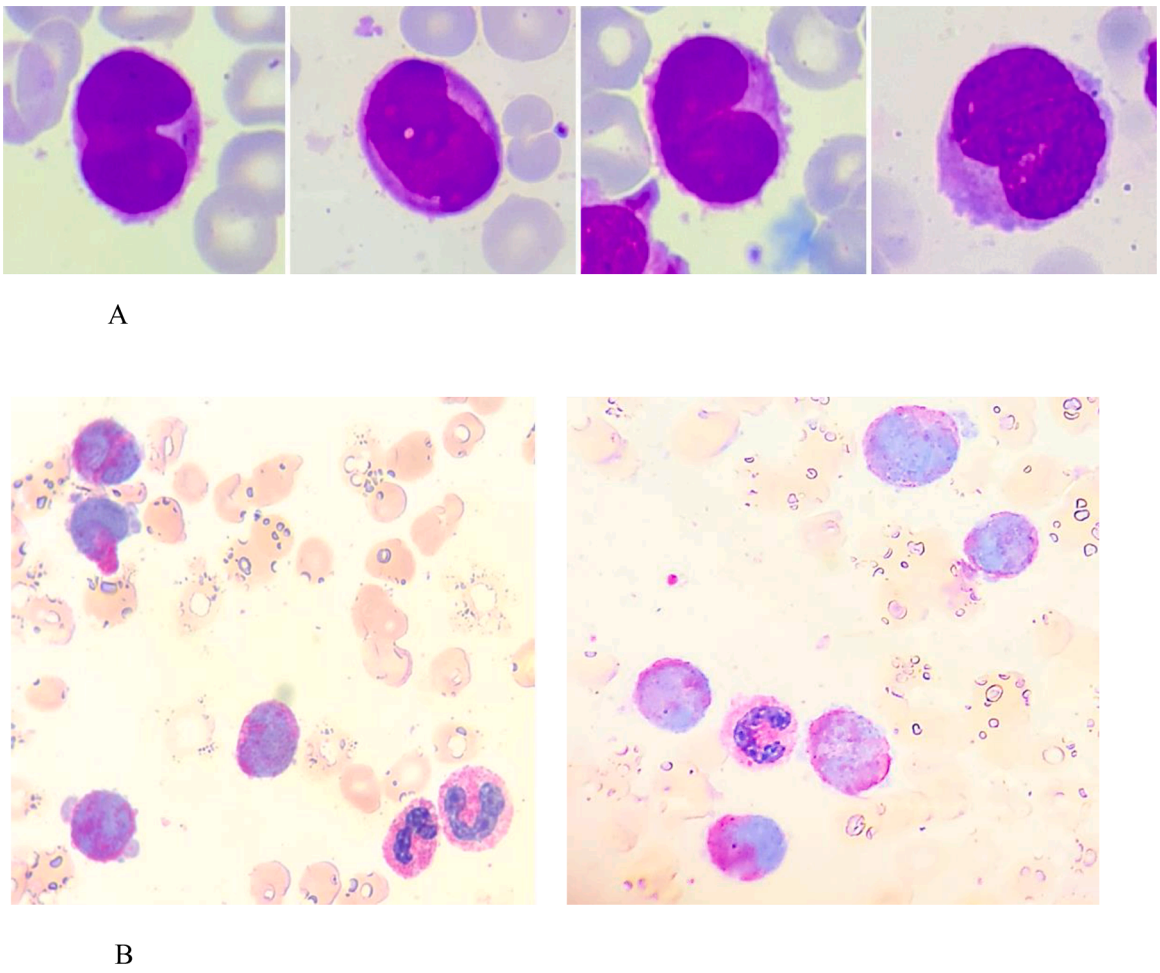

Fig. 2. a Images of blasts on medullogram stained with MGG ×100.
b: Images of blasts on medullogram stained with MPO ×100.

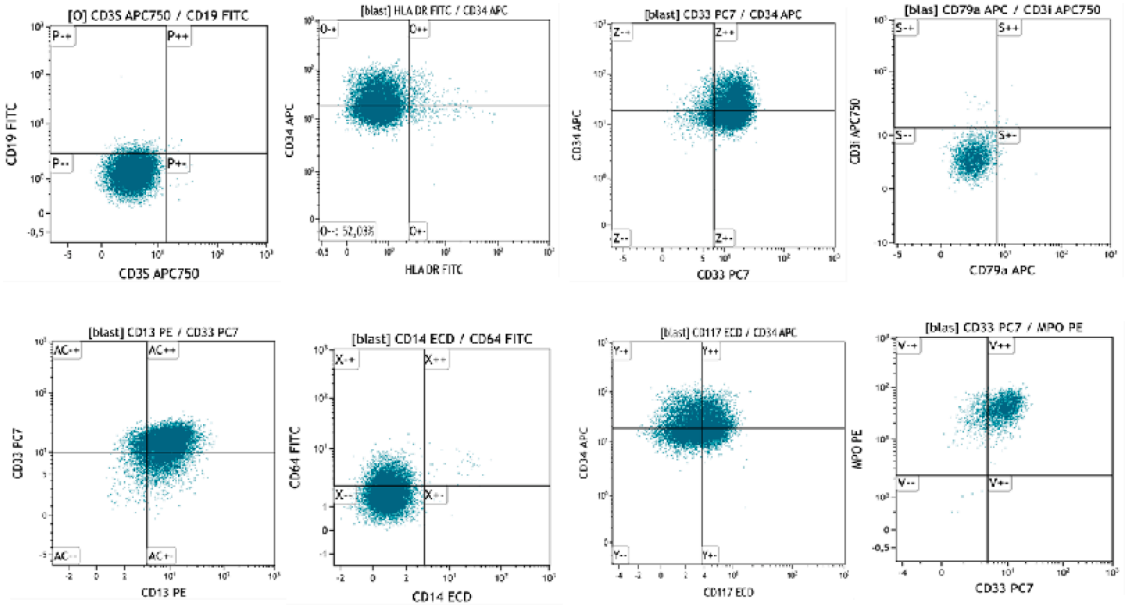

Fig. 3. Immunophenotyping of blasts found in the medulla.

rarer variant, also known as the "V" isoform. Other complex translocations and masked translocations can also be seen in AML3 [13,14].

The treatment of variant AML3 is similar to that of classical AML3, which involves the use of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). ATRA induces the differentiation of promyelocytic cells into mature cells, while ATO induces apoptosis of leukemic cells. Both drugs are administered in combination to treat AML3 [15]. The incorporation of ATO into APL treatment has transformed the therapeutic scenario, allowing the establishment of a regimen devoid of traditional chemotherapy, yet yielding impressive success rates. If ATO is not accessible or unavailable, combining ATRA with idarubicine(IDA) or gemtuzumab (GO) or Atra with Daunorubicine (DNR) and cytarabine (ARA-C) after risk stratification, serves as a viable alternative [16].

4. Conclusion

Hypogranular acute promyelocytic leukemia (AML3v) is a rare form and is even rarer when it is discovered following an ischaemic event, which is what makes our case so special.

Ethical approval

Not applicable, this is a case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Sabrina Belmahi: Writing – original draft, Investigation, Conceptualization. **Zainab Kajeiou:** . **Loubna Yacoubi:** . **Noussaiba Azzi:** . **Mounia Slaoui:** . **Abdelilah Berhili:** . **Mohammed Bensalah:** . **Rachid Seddik:** .

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.

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