CASE REPORT

Microgranular acute promyelocytic leukemia presenting with leukopenia and an unusual immunophenotype

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Abstract
The microgranular variant (M3v) of acute promyelocytic leukemia (APL) is rare, and the diagnosis can be delayed due to variability in how this condition presents. M3v blasts often have folded nuclei, but unlike traditional APL blasts, they often possess faint granules without Auer rods. In addition, microgranular APL often presents with an elevated or normal white blood cell count in contrast with the leukopenia seen in traditional APL. In APL, delayed diagnosis can lead to early death from disseminated intravascular coagulation (DIC), which is the main cause of mortality in an otherwise treatable, and often curable, leukemia. We describe a 19-year-old male with microgranular APL who presented with leukopenia and many blasts resembling non-APL AML blasts with an unexpected immunophenotypic pattern. He was treated for DIC and initiated on all-trans-retinoic acid and arsenic trioxide; he achieved complete molecular remission after induction therapy. Suspicion for APL should always remain high in the presence of clinical manifestations of the disease in order that appropriate treatment can be initiated rapidly to prevent early death.

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Introduction

The microgranular variant (M3v) of acute promyelocytic leukemia (APL) is similar to classical APL in that it is characterized by the t(15;17) chromosomal abnormality. However, there are multiple features that set it apart. As opposed to the prominent granules typically seen in APL, M3v blasts possess a faint scattering of granules in the cytoplasm, and they often lack Auer rods [1]. However, as is the case in traditional APL, they often have folded nuclei [2]. Microgranular APL is rare, given that APL comprises approximately 5–10% of all acute myeloid leukemia (AML) cases, with the M3v accounting for only 10–25% of all APL [3]. Given the rarity of M3v, this disease can be misdiagnosed, as it can easily be confused with myelomonocytic or monocytic AML [4].

With the introduction of anthracyclines and subsequently all-trans retinoic acid (ATRA) for the treatment of APL, this form of leukemia has become curable in the majority of cases. The incorporation of arsenic trioxide (ATO) into APL treatment regimens has further increased remission rates and cure rates in APL, while decreasing toxicity [5]. Lo-Coco et al. [5] noted that 100% of low- and intermediate-risk APL patients treated with ATRA–ATO achieved complete remission, with 97% of patients achieving 2-year event-free survival.

The greatest cause of treatment failure in APL is early death, which affects an estimated 10–30% of patients [6]. More than half of early-death cases are ascribed to hemorrhagic-related complications of disseminated intravascular coagulation (DIC) [7,8]. Rapid initiation of ATRA therapy results in a significant decrease in early death [8]. Multiple factors correlate with delays in diagnosis and treatment, including admissions to facilities with little experience in acute leukemia and unusual presentations of APL, sometimes with the absence of DIC [6,9].

Misdiagnosis can occur with M3v due to its atypical clinical presentation and pathological characteristics. Traditional APL presents with leukopenia, whereas M3v is generally associated with a normal to elevated white blood cell (WBC) count [10]. Given the risk of misdiagnosis or delayed diagnosis of APL, flow cytometry has been widely adopted as a rapid method for diagnosis. APL blasts frequently express the myeloid antigens CD13, CD33, CD64, and CD117, and often lack expression of CD34 and human leukocyte antigen–D related (HLA–DR) [11–14].

In this report, we describe a patient who presented with microgranular APL with atypical clinical, morphological, and immunophenotypic features.

Case report

A previously healthy 19-year-old male developed epistaxis. After 3 days of persistent bleeding, he presented to a local emergency department and was treated with oxymetazoline nasal spray and right naris packing. He was found to be thrombocytopenic and coagulopathic and, therefore, was transferred to our institution for management. On presentation, WBC was 2.6 K/μL with 46% blasts, hemoglobin was 9.3 g/dL, and platelet count was 32 K/μL. Prothrombin time (PT) was 14.1 s, fibrinogen 99 mg/dL, D-dimer 8.32 μg/dL, haptoglobin 6 mg/dL, and lactate dehydrogenase (LDH) 316 IU/L. The patient was treated for DIC with cryoprecipitate infusions and platelet transfusions.

Peripheral blood smear showed normochromic, normocytic red blood cells with no schistocytes, microcytic cells, red-blood-cell fragments, or basophilic stippling. In addition, the circulating blasts were characterized by lacy chromatin with scant blue cytoplasm. Some had eosinophilic granules, but no Auer rods were seen. The occasional blast had a “folded” or cleft nucleus, but the majority did not (Figure 1).

Flow cytometry on the peripheral blood revealed a blast population uniformly positive for CD2, moderate-bright CD33, CD34, CD38, and CD117. There was heterogeneous expression of CD13, CD56, and dim CD123. There was also limited and heterogeneous expression of dim HLA–DR. These cells were negative for surface CD3, CD11c, CD14, and CD64. On account of the patient’s coagulopathy, ATRA was initiated as empiric therapy for APL.

Bone-marrow aspirate and biopsy (Figure 2) were performed. The core biopsy exhibited 100% cellularity with a leukemic cell infiltrate throughout, and the touch imprint showed 69.5% blasts that lacked conspicuous granulation or Auer rods. Fluorescent in situ hybridization revealed the presence of t(15;17)(q24;q21) in 72% of the cells. The

![Figure 1](https://example.com/figure1.png)
presence of this translocation was confirmed by conventional cytogenetics. ATRA was continued, and ATO was initiated. Polymerase chain reaction revealed the presence of the feline McDonough sarcoma (FMS)-like tyrosine kinase 3 (FLT3) internal-tandem-duplication mutation.

The patient developed a nonproductive cough 3 days into therapy; chest X-ray was consistent with interstitial pneumonitis. WBC rose to a peak of 26.8 K/µL, and the patient developed acute renal failure. The patient was initiated on dexamethasone for differentiation syndrome; ATRA and ATO were held until resolution of respiratory symptoms and renal failure. Treatment was subsequently resumed. The patient’s peripheral blood promyelocytic locus–retinoic acid receptor alpha (PML–RARA) polymerase chain reaction on day 30 of induction therapy revealed no molecular evidence of disease. The patient underwent bone-marrow aspirate and biopsy following the completion of induction, revealing complete morphological, immunophenotypic, cytogenetic, and molecular remission.

Discussion

M3v can offer a diagnostic challenge, particularly when it presents atypically. The incidence of M3v presenting with leukopenia is unknown, and to our knowledge, there are no previous reports that specifically address M3v in the setting of leukopenia. In an analysis of three APL trials, the WBC range among 155 M3v patients was 0.6—550 K/µL with a median of 15.8 K/µL, implying that it is unusual, but not impossible, for M3v patients to present with leukopenia [7].

While there is no universal APL phenotype, this condition is usually CD13, CD33, CD64, and CD117 positive, and CD34, HLA–DR, and CD2 negative [11–14]. Specifically, CD34 is expressed in 15–21% of APL cases with HLA–DR expressed in only approximately 3—9% of cases [4,12,13,15,16]. M3v has a more heterogeneous immunophenotype than traditional APL, expressing CD34 almost universally and expressing HLA–DR, CD56, and CD2 occasionally [11,13,17–20].

A number of the aforementioned markers associated with M3v have been associated with poorer outcomes. CD2 positivity correlates with leukocytosis, shorter complete remission duration, and a trend for shorter overall survival [13]. CD56 expression carries a poor prognosis with an increased risk of relapse following ATRA–anthracycline therapy [18,21,22]. Lastly, CD34 positivity has been shown in most, but not all, studies to carry a worse prognosis than CD34 negativity [9,23–25].

It is curious whether CD2, CD34, and CD56 expressions have an intrinsic, biologic effect on the increased risk of early death, or whether the diagnostic challenge that these features can pose is responsible for high rates of early death. In the largest study addressing outcomes in M3v, Tallman et al. [7] found that M3v carried a decreased overall survival compared to classical APL; however, when adjusting for WBC count, the difference disappeared. On
the basis of this finding, one could hypothesize that the adverse prognosis of M3v may be attributed entirely to the leukocytosis that accompanies it and/or the diagnostic challenge presented by M3v. Of note, this study did not directly evaluate immunophenotype as a variable in determining prognosis.

APL is a highly curable disease, but when death occurs, it is most often from early death, which can occur due to delayed diagnosis. Therefore, it is important to identify atypical presentations of APL. Our patient’s presentation highlights the significant clinical, morphological, and immunophenotypic heterogeneity with which APL can present. Moreover, this case illustrates that microgranular APL can present with a low WBC count and with leukemia cells that can resemble non-APL AML blasts. In addition, this case demonstrates that the immunophenotypic pattern in M3v can be different from the typical APL pattern. Until cytogenetic and/or molecular information is available, medical decision making must rely upon the clinical manifestations of the disease such as coagulopathy in a patient with abnormal blood counts—rather than the absence of typical morphological and immunophenotypic features of the disease.

Conflicts of interest

The authors declare no conflicts of interest. There was no financial support for the work in this paper.

References


