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Aleukemic Acute Promyelocytic Leukemia: How Concomitant HIV, Hepatitis C, and Chronic Alcohol Use Disorder May Have Hidden an Underlying Malignancy

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Male, 67-year-old
Final Diagnosis: Acute promyelocytic leukemia
Symptoms: Exertional dyspnea • nocturia • orthopnea • weight gain
Clinical Procedure: —
Specialty: General and Internal Medicine • Oncology

Objective: Rare disease

Background: Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia (AML) and is characterized by a genetic translocation affecting the retinoic acid receptor-alpha gene, leading to blockage in the differentiation of granulocytic cells. The accumulation of promyelocytes in bone marrow leads to cytopenias and life-threatening coagulopathies. Definitive diagnosis is made with bone marrow biopsy. Differentiation of APL from other leukemias is important to appropriately treat with all-trans retinoic acid (ATRA) and arsenic trioxide. Patients with HIV are at a higher risk to develop AML. This article identifies how multiple comorbidities and social factors can contribute to difficulties in diagnosing AML.

Case Report: We present a 67-year-old man with a past medical history of hypertension and substance use disorder who presented with progressive exertional dyspnea and was found to have HIV, chronic hepatitis C, and APL with pancytopenia. His bone marrow biopsy confirmed AML. This was a case of co-existing HIV and aleukemic leukemia.

Conclusions: APL can present with pancytopenia, weakness, failure to thrive, or bleeding complications, which can be similar to presentations of those diagnosed with HIV. Diagnosis of APL can be differentiated between hypergranular and hypogranular; our patient demonstrated APL with only 52% blasts, which can make for a challenging diagnosis. Given increased mortality of APL, immediate ATRA therapy is warranted. Aleukemic leukemia is a rare presentation typically accompanied by skin manifestations. Our case highlights the importance of having high clinical suspicion for malignancy in patients with comorbidities that can interfere with the classic presentation of leukemia.

Keywords: Alcoholism • Hepatitis C • HIV • Leukemia, Promyelocytic, Acute • Pancytopenia

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Background

Acute promyelocytic leukemia (APL), also referred to as AML-M3 or APML, is a type of acute myeloid leukemia. The mechanism behind the development of APL is the translocation of chromosomes 15 and 17 [1]. This leads to fusion of chromosomes leading to the formation of a fusion gene called promyelocytic leukemia (PML)/retinoic acid receptor alpha (RARA) [1,2].

While the real cause of AML is unknown, evidence suggests there are multiple factors that can cause genetic changes and increase a person's risk of developing AML. Patients with HIV are at high risk of developing AML [3]. Real causes are unknown but possible development of immunosuppression due to exhaustion in T-cell expression and several leukemogenic mechanisms lead to a 2-fold higher risk of AML in HIV patients than in the general population [3-5]. Due to the rare occurrence of APL in patients with HIV, guidelines for management of these 2 diseases together are not well defined.

Here, we present a 67-year-old man with a past medical history of hypertension and substance use disorder, who presented with progressive exertional dyspnea and was found to have HIV, chronic hepatitis C, and APL with pancytopenia. We discuss our patient's hospital course and management plan for coexisting APL and HIV.

Case Report

A 67-year-old man with a past medical history of hypertension and substance use disorder (alcohol, tobacco, heroin, and cocaine use) presented to the Emergency Department (ED) with a chief complaint of chronic and progressive exertional dyspnea of a 1-year duration. The patient endorsed orthopnea, nocturia, and unintentional weight gain. He endorsed the capability to ambulate approximately half a block prior to feeling short of breath. In terms of his substance use, the patient endorsed using heroin daily and cocaine every few days, with alcohol consumption of 5 to 6 beverages weekly.

Initial laboratory studies were significant for pancytopenia with macrocytic anemia, leukopenia with an absolute neutrophil count of 90, and moderate thrombocytopenia. The patient's initial complete metabolic panel showed normal electrolyte and liver function test results. A coagulation profile was performed on the day of admission, which was in the normal limits as well. A urinary drug screen was positive for cocaine and opioids, and HIV testing resulted positive, with a CD count of 491 and HIV RNA PCR of 1920 (**Table 1**). The hepatitis and sexual disease panel was sent as well (**Table 1**). The hepatitis panel showed chronic hepatitis C infection (HCV) and resolved hepatitis B infection.

Table 1. Laboratory studies.

Laboratory studies	Values on admission	Values on discharge	Reference range
Complete blood count			
White blood cell count	1.2×10^3/mm^3	4.4×10^3/mm^3	4.5-11.0
Red blood cell count	1.89×10^6/mm^3	2.5×10^6/mm^3	4.33-5.83
Hemoglobin	6.6 g/dL	8.2 g/dL	13.5-17.5
Hematocrit	19.5%	24%	41.0-53.0
Mean corpuscular volume	103.2 fL	96.0 fL	80.0-100.0
Mean corpuscular hemoglobin	34.9 pg	32.8 pg	26.0-32.0
Mean corpuscular hemoglobin concentration	33.8 g/dL	34.2 g/dL	31.0-37.0
Red cell distribution width	21.3%	19.9%	0.5-16.5
Platelet count	45 K/mm^3	249 K/mm^3	140-440
Coagulation profile			
Prothrombin time	13.4 seconds		12.2-14.9
International normalized ratio	1.0		N/A
Partial thromboplastin time	28 seconds		21.3-35.1
Fibrinogen level	289 mg/dL		183-503

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Table 1 continued. Laboratory studies.

Laboratory studies	Values on admission	Values on discharge	Reference range
Anemia profile			
Iron Level	156 mcg/dL		50-212
Total iron binding capacity	270 mcg/dL		250-450
Iron saturation	58%		15-50
Ferritin level	458 ng/mL		16.4-294
Folate level	11 ng/mL		≥4.1
B12 level	>1500 pg/mL		211-911
Cardiac markers			
B-type natriuretic peptide	587 pg/mL		1-100
Troponin-I	17 pg/mL		3-23
Toxicology			
Alcohol level	<10		≤10
U Amphetamine Scr	Negative		Negative
U Barbiturate Scr	Negative		Negative
U Benzodiazapine Scr	Negative		Negative
U THC Scr	Positive		Negative
U Opiate Scr	Positive		Negative
U PCP Scr	Negative		Negative
Human immunodeficiency virus testing			
HIV 1,2 Ag/Ab Combo	548.71 s/co		N/A
HIV 1,2 Index	≥1.00		<1
HIV 1,2 Ag/Ab Interpretation	Reactive		Non-reactive
%CD4 Pos Lymph	54.6%		30.8-58.5
%CD8 Pos Lymph	33.4%		12.0-35.5
Abs CD4 Helper	491/mcL		359-1519
Abs CD8 Suppressor	301/mcL		109-897
Hepatitis studies			
HCV Ab	> 11.0 s/co		0.0-0.9
HCV Load	1890000		
Hep B Core IgM Ab	Negative		Negative
Hep B Core Total Ab	Positive		Negative
Hep B Surf Ab	Non-reactive		Non-reactive

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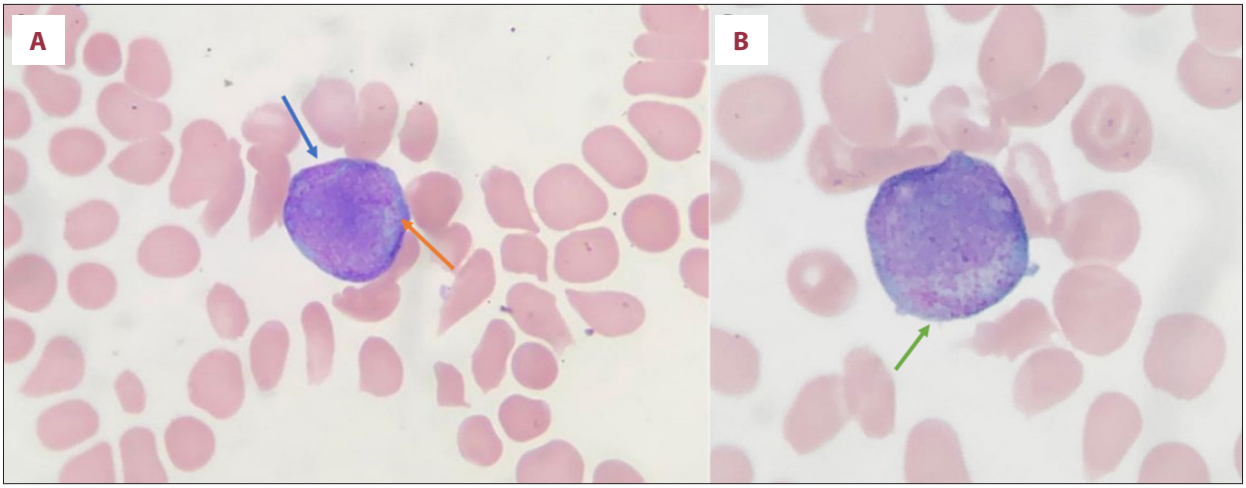

Figure 1. Peripheral blood smear images **A** and **B**, demonstrating increased promyelocytes (**A**, blue arrow), with some hyper granularity with azurophilic granules (**B**, green arrow) with Auer rods visualized (**A**, orange arrow).

The patient received intravenous (i.v.) furosemide to help with diuresis and 1 unit of red blood cells for anemia in the ED. The patient was admitted for further management and was placed on neutropenic precautions. The Hematology-Oncology team was consulted for pancytopenia. Initially, HIV and bone marrow suppression from chronic alcohol use was thought to be the cause of the patient's pancytopenia. The Infectious Disease Department was consulted, and the patient was started on Biktarvy 1 mg oral tablet daily for newly diagnosed HIV. In our institution, it was decided that patients would be initiated on appropriate treatment for HCV as outpatients.

During hospitalization, the patient's cell count continued to decline; thus, he was given 1 dose of granix on day 4 of hospitalization, which increased the white cell count. However, he developed severe thrombocytopenia. A coagulation profile was done, which showed an elevated prothrombin time and decreased fibrinogen and fibrinogen degradation products, which raised concern of disseminated intravascular coagulation; however, the patient had no active bleeding.

Peripheral blood smear was notable for increased promyelocytes and hypergranularity with azurophilic granules, and Auer rods were visualized (**Figure 1**). Initially, our plan was to perform an outpatient bone marrow biopsy; however, due to worsening of pancytopenia, the bone marrow biopsy was performed on day 5 of hospitalization. Flow cytometry study revealed increased CD117+ immature myeloid cells. Fluorescence in situ hybridization was positive for PML/RARA rearrangement. These results supported a diagnosis of APL.

The patient was started on all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) for APL. He received prophylactic antibiotics, including acyclovir, fluconazole, and ciprofloxacin, and once his platelet count improved, he was started on bactrim as well. The patient's electrocardiogram was monitored for possible QTc prolongation while he was on ATRA. He was also given i.v. thiamine supplementation to prevent Wernicke's encephalopathy in the setting of ATO administration. The patient received a total of 4 cycles of ATO (with thiamine supplementation to prevent Wernicke's encephalopathy), with plans to receive ATRA, for a total of 7 cycles as an outpatient. Given the patient's clinical improvement and the established treatment plan for his malignancy, he was discharged home with close outpatient follow-up after the completion of the induction phase of 28 days.

Discussion

APL can present with complications of pancytopenia, such as weakness, failure to thrive, or infections, as well as with hemorrhagic complications, including gingival bleeding, ecchymoses, epistaxis, and menorrhagia [4,5]. Complications can occur, including disseminated intravascular thrombosis or fibrinolysis, which manifest as a result of the bone marrow malignant cells provoking dysfunction of the coagulation cascade [6]. This complication represents a medical emergency because, if untreated, approximately 40% of patients demonstrate cerebrovascular hemorrhage, with approximately 10% to 20% of patients at risk for death due to hemorrhage [7]. In our patient's case, he presented with exertional dyspnea and pancytopenia, which prompted further investigation; however, he fortunately did not develop subsequent complications of APL, such as bleeding or thrombosis, because he was diagnosed quite early.

In terms of diagnosis, there are 2 main forms of APL. Hypergranular (also referred to as "typical") represents the most common form (75% of patients), in which promyelocytes contain densely packed granules with Auer rods [8]. The

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hypergranular forms have a high expression of cytoplasmic myeloperoxidase, CD13, and CD33 and do not express or only dimly express both HLA-DR and CD11b. APL cells express low CD15 and CD117 levels compared with normal promyelocyte cells [9]. Diagnosis can be confirmed by PML-RARA fusion gene and/or chromosomal translocation. Patients with APL have a reciprocal translocation of t(15;17)(q24.1;q21.2) and have the fusion gene PML-RARA, which acts to connect the RARA gene on chromosome 17 with the PML gene on chromosome 15 [9]. In our patient's case, he was found to have an increase in CD117+ immature myeloid cells, with a FISH-positive PML/RARA rearrangement, suggestive of APL. Our patient's case was unique because his bone marrow was notable for only 52% blasts, which may be indicative that the patient was in the process of converting to APL. As in our patient's case, APL can be difficult to diagnose, because, in the early phases, patients can be asymptomatic despite having bone marrow replacement.

Given the high mortality rate of APL, immediate tretinoin treatment should be initiated based on cytologic and clinical criteria, prior to definitive genetic, cytogenetic, or immunostaining confirmation [10]. If APL is not diagnosed following more confirmatory studies, ATRA can be discontinued, and treatment can be transitioned to treat alternative types of AML [10]. When comparing alternate types of AML, age greater than 60 years does not represent a predictor of poor prognosis with APL [11]. Given our patient's demographics and early diagnosis, this may be indicative of good prognosis; however, as he was found to have concomitant HIV and hepatitis, the patient's comorbidities could complicate management.

Pancytopenia can be multifactorial, especially in our patient's case. For instance, with HIV, cytopenias are the most common hematologic abnormality, with thrombocytopenia typically presenting first [12]. In addition, HCV infection can lead to aplastic anemia, since CD8 Kupffer cells have cytotoxic and myelopoiesis effects on bone marrow cells [13]. Fortunately, the literature has demonstrated that, with adequate treatment for HCV, there can be partial reversibility of the bone marrow suppression [14]. Lastly, chronic alcohol use can also contribute to bone marrow suppression, with data suggesting acetaldehyde as the contributing factor [15]. Given our patient's comorbidities of HIV, HCV, and chronic alcohol consumption, his source for pancytopenia is likely multi-contributory. However, the significantly low blood levels and further investigation revolving this may have led to earlier diagnosis of his malignant process, given his asymptomatic state.

Leukemia has been found to occur in the absence of leukocytosis, with rare variants in which patients also have an absence of splenomegaly and some variants demonstrating aplastic anemia [16]. The etiology regarding leukopenia versus leukocytosis in APL remains poorly understood; however, patients can present with leukopenia prior to developing leukocytosis with this disease [17]. In a case series, many patients with aleukemic myelosis endorsed dyspnea, weakness, and palpitations [16]. Aleukemic leukemia cutis is a manifestation in which patients develop cutaneous manifestations of the disease, generally preceding the development of systemic leukemia [18]. In our patient's case, he was diagnosed with APL; however, he had an absence of leukocytosis, splenomegaly, and cutaneous features. This unique clinical presentation may have been masked and complicated by his diagnosis of HIV and history of polysubstance use disorder.

Conclusions

Given the high mortality rate of APL due to complications, which include life threatening coagulopathy, patients with persistent cytopenia should be evaluated for AML promptly. APL in the presence of HIV infection would lead to delayed diagnosis because these patients present with pancytopenia instead of the typical presentation of leukocytosis in AML patients. It is important to determine the diagnosis of these specific patient populations in a timely manner, with a high clinical index of suspicion, even when the laboratory studies do not initially align with the classic picture. Fastidious accurate diagnosis and management of APL (especially in our patient's case) led to quick treatment and may have improved, among other things, mortality.

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Institution Where Work Was Done

All work was performed at St. Joseph's University Medical Center, Paterson, NJ, USA.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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