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Acute promyelocytic leukemia in a long-standing HIV-positive patient: Case report and literature review

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ABSTRACT

The use of antiretroviral therapy has drastically improved the life quality and prognosis of people living with the human immunodeficiency virus (HIV). The risk of acute myeloid leukemia (AML) currently does not appear to be significantly increased compared to the general population. Acute promyelocytic leukemia (APL), infrequent in people with HIV, is a distinct subtype of AML with unique molecular pathogenesis, clinical manifestations, and treatment. Herein we describe a fatal case of APL hypogranular variant in an HIV-positive patient presenting with hyperleukocytosis. Also, we conducted a literature review of the ten cases reported so far.

1. Introduction

The use of antiretroviral therapy (ART) has drastically improved the prognosis and quality of life of people living with the human immunodeficiency virus (HIV). Due to longer life expectancy in the ART era, aging has increased the incidence of non-AIDS-defining malignancies [1]. Several factors, including immune system deregulation, chronic stimulation, and direct viral pathogenicity, may play a role in this predisposition [2]. Acute myeloid leukemia (AML) is the most common subtype of acute leukemia in adults and is considered a non-AIDS-defining hematological malignancy. The precise frequency of AML occurrence in HIV-positive patients remains uncertain. Although studies present epidemiologic limitations because of undetailed subclassifications, the risk of leukemia doesn't seem higher in people living with HIV than in those without [3]. Acute promyelocytic leukemia (APL), also known as French- American-Britain (FAB) classification of AML-M3, has been described in a few HIV case reports.

APL is a biologically and clinically distinct subtype of AML with unique molecular pathogenesis, clinical manifestations, and treatment. Cytogenetically, it is characterized by a balanced translocation t(15;17)

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(q22;q21). This abnormality involves the promyelocytic leukemia gene (*PML*) located on chromosome 15q24 and the retinoic acid receptor alpha (*RARA*) gene on chromosome 17q21, resulting in a *PML-RARA* fusion gene, which is responsible for cellular transformation. This fusion confers a particular sensitivity to treatment with all-trans-retinoic acid (ATRA) plus chemotherapy or ATRA plus arsenic-trioxide (ATO). The hypogranular variant (M3v), or microgranular, accounts for approximately 10–25% of all APL cases [4]. M3v cells are typically large, have a bilobed nucleus, and show no apparent granules or Auer rods on microscopy. In addition, M3v often presents with an elevated or normal white blood cell (WBC) count compared to the leukopenia seen in traditional APL [4]. Early death affects 10–30% of APL patients, and half of them occur due to hemorrhagic-related complications of disseminated intravascular coagulation (DIC) [5].

As APL incidence in patients with HIV is sporadic, the therapeutic approach is challenging and often individualized. Here, we describe a fatal case of AML M3v in a long-standing HIV-positive patient presenting with hyperleukocytosis (HL), complicated by leukostasis, tumor lysis syndrome, and DIC during induction therapy. We include a literature review of the ten cases reported to date.

2. Case description

A 49-year-old black man was diagnosed with HIV infection in 2004. He went four years without treatment and started ART in 2008 with lamivudine (3TC), tenofovir (TDF), lopinavir, and ritonavir (LPV/r). He presented neurotoxoplasmosis, HIV copies higher than the upper limit, and a nadir $CD4^{+}$ count of 14 cells. After that, he developed right hemiparesis as sequelae. He remained in this scheme until 2016 when the assistant physician changed it to atazanavir (ATV), TDF/3TC, and

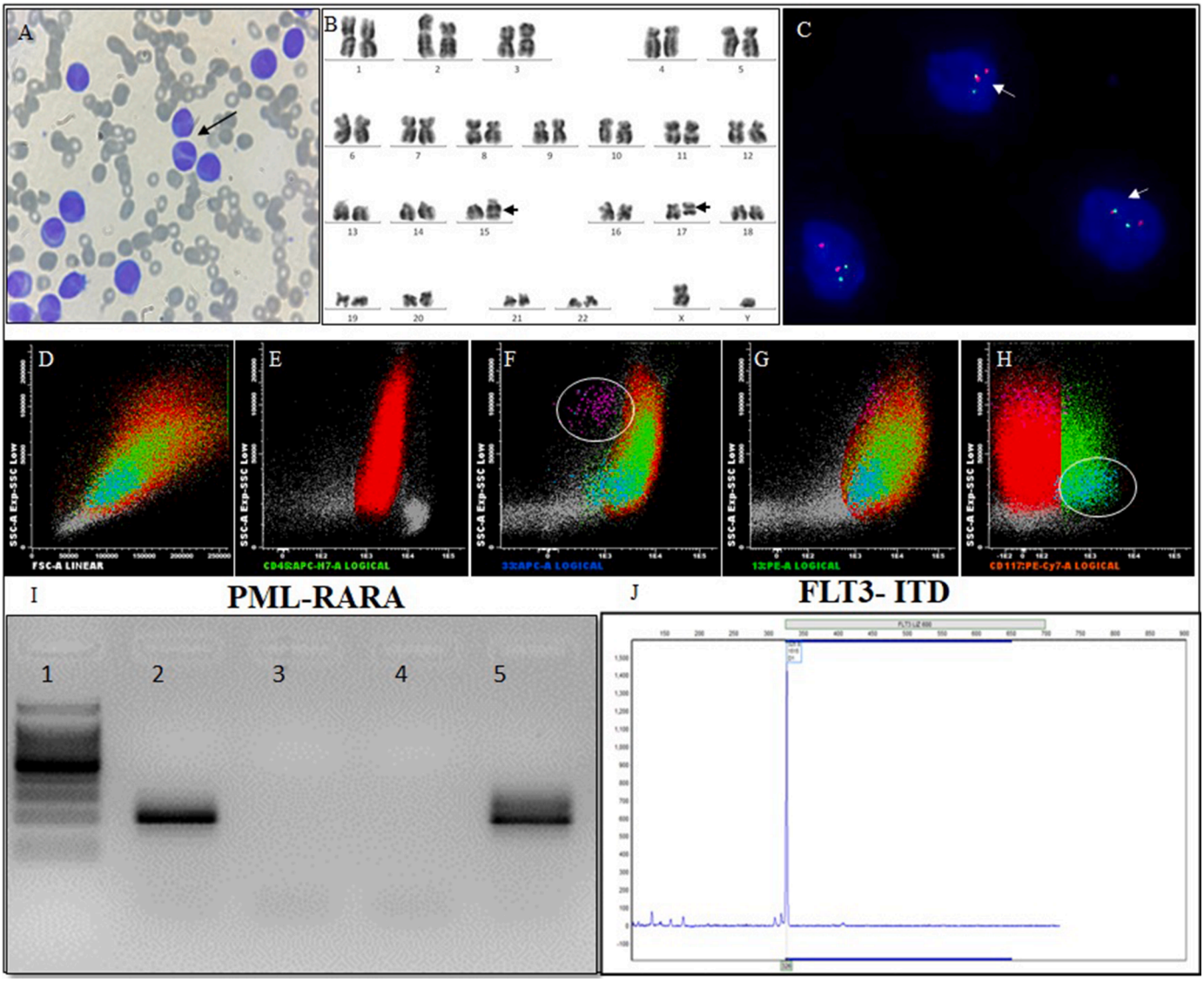

Fig. 1. Laboratory findings at diagnosis of acute promyelocytic leukemia in patient with HIV. (A) Peripheral blood smear morphological showing the large neoplastic promyelocytes with no azurophilic granules or Auer rods, containing a hypogranular variant typical bilobed or reniform nucleus (black arrow); (B) Cytogenetic analysis by G-banding showed the karyotype: 46,XY,t(15;17)(q22;q21). (C) FISH analysis of interphase nucleus confirming the rearrangement involving the *PML/RARA* genes indicated by the arrows and a typical nucleus, showing two orange and two green signal patterns; (D–H) Analysis by flow cytometry showed: (D) The relationship between cell size and its complexity; (E) CD45 showing hypergranularity; (F) High expression of CD33 on blast cells; (G) Overexpression of CD13 in the blast population. (H) Partial expression of CD117 on blast cells; (I) *PML-RARA* fusion gene detection using RT-PCR, followed by 2% agarose gel electrophoresis. The amplification of a 214 bp product identified *PML-RARA* long transcript. 1- 100 bp ladder; 2- Patient's sample; 3- Healthy donor negative control; 4- No amplification control (H_2O); 5- Positive control (NB4 cell line) (J) *FLT3*-ITD was investigated by DNA PCR using fluorescent primers, followed by fragment analysis. Wild-type *FLT3* gene amplification generated a product (peak) of 326 pb.

ritonavir because of 11,176 HIV copies/mL but 1065 $CD4^+$ cells/μL. He continued regular ART with undetectable viral load up to admission in 2022. He sought a primary care unit with fever, fatigue, odynophagia, respiratory distress, and gum and ear bleeding for one month was referred to our hospital and diagnosed with APL based on peripheral smear findings. On admission, ATV was changed for dolutegravir (DTG), ritonavir was suspended, and 3TC and TDF were maintained. His-initial laboratory studies indicated anemia (Hb 5.9 g/dL), elevated WBC counts (85,900/μL) with 80% abnormal cells, decreased platelets (55,000 /μL), low fibrinogen levels (80 mg/dL), high lactate dehydrogenase (3092 U/L) and prolonged prothrombin time test (44 s, INR 1.8) with normal partial thromboplastin time activated.

Abnormal promyelocytes were large, had bilobed nucleoli with basophilic cytoplasm, presented fine granules, and did not exhibit Auer rods, as shown in Fig. 1A. His-HIV RNA was 63 copies/mL, and his CD4+ cell count was 673/μL. Cytogenetic analysis of peripheral blood cells by G-banding showed 46,XY,t(15;17)(q22;q21)[10] (Fig. 1B). Fluorescence *in situ* hybridization (FISH) was performed using LSI PML/RARA dual color single fusion probe (Vysis, Abbott, USA). FISH analysis showed cells with one allele with the fusion involving the *PML/RARA* genes nuc ish (PML, RARA x2), (PML con RARA x1)[80]/ nic ish (PML,RARA)x2 [20] (Fig. 1C). The immunophenotype was characterized by CD33, CD13, CD64, CD117, CD34, and CD15 positivity, while CD11b, CD16, HLA-DR, CD14, and CD7 were negative (Fig. 1D–H). *PML-RARA* long transcript was detected by reverse transcription-polymerase chain reaction [6]. *FLT3* internal tandem duplications (ITD) were investigated by fragment analysis and were not found (Fig. 1I-J).

The patient evolved to dyspnea, hypoxemia, diffuse alveolar infiltrates, respiratory failure due to pulmonary leukostasis, and required orotracheal intubation three days after admission (Fig. 2A). Hydroxyurea was started for cytoreduction, along with ATRA. Supportive measures, such as vigorous hydration and allopurinol, were also initiated while awaiting confirmation of APL diagnosis. He was a high-risk patient and received cytarabine and daunorubicin protocol (7 + 3) (idarubicin was unavailable nationally). He received dexamethasone to prevent differentiation syndrome and ten days of cefepime for febrile neutropenia. He reached 117,000/μL leukocytes in one week, followed by mild leukopenia and tumoral lysis syndrome. Fig. 2B shows the clinical course. Physicians suspended TDF and started hemodialysis because of renal failure but maintained DTG and 3TC. Despite multiple fresh frozen plasma, cryoprecipitate, platelet, and red blood cell transfusions, he presented refractory DIC with severe pulmonary bleeding and died ten days after admission.

3. Discussion

Although the risk of myeloid malignancies is not substantially increased among people living with HIV, some cases have been described. Recently, our group reported a myelodysplastic syndrome evolved with clonal karyotype associated with trisomy 8 and *ASXL1* mutation in a well-controlled HIV patient [7]. AML is identified in HIV-positive patients with a predominance of FAB M2, M4, and M5 subtypes [8]. APL is infrequent in the setting of HIV, and, to our knowledge, only ten other cases have been reported in the literature [2, 9–16] (Table 1).

Nine out of the ten reports documented no notorious risk factors for AML. Only in one case did the patient carry a previous lymphoma diagnosis and receive irradiation before developing APL [14]. *In vitro* studies showed a controversial ATRA effect reducing HIV viral load with ATO potentially suppressing T cell [1]. We identified that only three cases did not undergo successful treatment with ATRA regimens, but one was rescued with ATO and achieved complete remission after 17 months. Our patient exhibited the most prolonged time from HIV diagnosis (18 years). Also, he is the second HIV-positive reported case of M3v and the first one presenting with HL. He didn't show an appropriate virologic control during the first four years of his treatment, and this fact may potentially have favored leukemia pathogenesis.

APL comprises approximately 5–10% of all AML cases, with relapse occurring in 20% of the cases [4]. Hypogranular variant morphology may mislead the FAB AML-M4 subtype and delay correct treatment. In our case, cytogenetics, FISH, and molecular analysis confirmed the APL diagnosis. The morphology was typical of the hypogranular variant, CD34 was positive but CD2 was not tested. Although the expression of CD34 was initially considered uncommon in APL, studies have shown that it occurs in about 20–30% of newly diagnosed cases. The significance of CD34 expression in APL is unclear but seems to indicate immature cells. Additional studies associated CD34 positivity with leukocytosis, micro/hypogranular morphology, expression of CD2 and bcr3isoform [17,18].

Coagulopathy in APL is the primary cause of death and morbidity within the first 30 days, presenting mainly as intracerebral and pulmonary hemorrhages. Consumptive coagulation and primary and secondary fibrinolysis are implicated in the pathophysiology and, less often, thrombotic phenomena. Management consists of initiating ATRA as soon as APL is suspected, as it can reverse the coagulopathy by the fifth day [5]. Transfusional measures are recommended daily or more than once a day based on laboratory levels. The supportive therapy should be continued until the symptoms and laboratory findings balance throughout the induction.

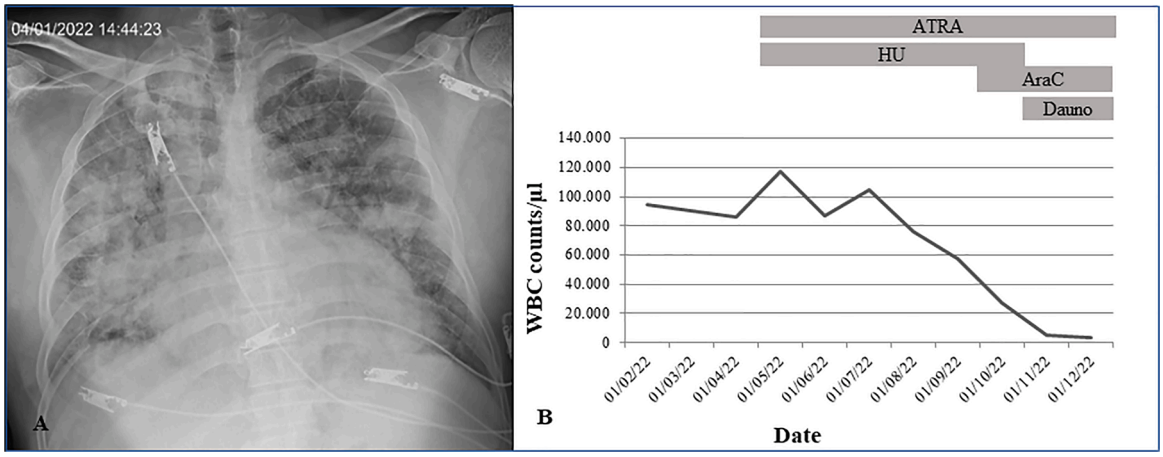

Fig. 2. Pulmonary hyperleukocytosis finding and clinical evolution. (A) Chest radiograph showing bilateral interstitial and alveolar opacities; (B) Schematic diagram indicating the evolution of white blood cells (WBC) over time and treatment. ATRA- All-trans-retinoic acid; HU- Hydroxyurea; Ara-C- Cytarabine; Dauno- Daunorrubicin.

Table 1
Literature review of clinical, cytogenetic, and molecular features, treatment, and outcome of HIV-positive patients with APL

HIV Case	Age/ Sex	Time from HIV diagnosis (yrs)	ART	CD4$^+$ count (cels/ mm^3)	Viral load	APL Diagnosis	Morphologic variant/Risk group*	WBCPlatelets (/μL)	Induction	Consolidation	Maintenance	Outcome	Ref
1	30/M	2	Not started	240	NA	RT-PCR *PML-RARA*	M3/intermediate	4,800 200	ATRA	DNR +Ara-C x 2 Mitox + Ara-C	Nil	CCR at 8 months	Calvo et al. [9]
2	36/ M	0	Not started	400	NA	Cytogenetics t (15;17)	M3/low or intermediate	4,000 NA	ATRA	Nil	6-MP, MTX	Relapsed; died at 305 days	Sutton et al. [10]
3	22/F	NA	Not started	ND	ND	Morphology	M3/high	16,000 3,000	NA	NA	NA	CR not achieved	Gatphoh et al. [11]
4	27/M	8	IDV, NFV, AZT, D4T, 3TC	356	ND	Cytogenetics t (15;16;17) FISH t (15;17)	M3v/ intermediate	0.8 19,000	ATRA, Dauno, Ara-C	HD Ara-C; IDA x 2	ATRA, 6-MP, MTX	CR molecular at weeks 9; CCR at 40 months	Kudva et al. [12]
5	46/F	2	EFV, TDF, 3TC	>500	<50	RT-PCR *PML-RARA*	M3/intermediate	5,090 150	ATRA, Ida	ATRA, Ida, Mitox	ATRA, MTX, 6-MP	CCR at 21 months	De Vita et al. [13]
6	35/M	10	AZT, 3TC, D4T, LPV/RTV	184	<50	FISH t(15;17) and RT-PCR *PML-RARA*	M3/intermediate	1,600 2,800	ATRA, Ida	ATRA	ND	CCR at 14 months	Boban et al. [14]
7	37/M	7	3TC, NVP, DDI	>800	ND	RT-PCR *PML-RARA*	M3/intermediate	1,600 112,000	ATRA, Ida	NA	NA	CR at day77; relapsed at 1 year and retreated with ATO CR at 3 months and CCR at 17 months	Malik & Levine 2009 [15]
8	43/F	0	ATV, TVD, RAL, FPV	118	>500,000	Cytogenetics t (15;17) and RT-PCR *PML-RARA*	M3/high	40,700 1,500	ATRA, Ida	ATRA, Ida, Mitox	ATRA, MTX, 6-MP	CR at day 29; CCR at 8 months	Drilon et al. [16]
9	32/M	0,4	DRV, ABC/ 3TC, RTV	38	75.4	Morphology	M3/intermediate	4,000 2,200	ATRA, Ida, Ara-C	ATRA, Ida, Mitox	ATRA, MTX, 6-MP	CCR at 38 months	Kunitomi et al. [2]
10	46/M	0,4	RPV, FTC, TDF	264	325	NA	M3/intermediate	10,000 1,900	ATRA, Ida	ATRA, Ida, Mitox	Impossible due to liver dysfunction	CCR at 30 months	Kunitomi et al. [2]
11	49/M	18	ATV, 3TC, TDF	673	63	Cytogenetics t (15;17), FISH t (15;17) and RT- PCR (*PML-RARA*)	M3v/high	85,900 55,000	ATRA, Ara-C, Dauno	Nil	Nil	Died at day 10	This report

M- Male; F- Female; ART- Antiretroviral treatment; WBC- White blood cells; Ref- References; IDV- Indinavir; NFV- Nelfinavir; AZT- Zidovudine; D4T- Stavudine; ABC- Abacavir; 3TC- Lamivudine; RVP- Rilpivirine FTC- Emtricitabine; EFV- Efavirenz; NVP- Nevirapine; DDI- Didanosine; TDF- Tenofovir; TVD- Tenofovir/Emtricitabine; LVR- Lopinavir; RTV- Ritonavir; FPV- Fosamprenavir; ATRA- all-trans-retinoic acid, ATO- Arsenic trioxide; Dauno- Daunorrubicin; Ida- Idarrubicin; Ara-C- Cytarabine, Mitox: Mitoxantrone, MTX: Methotrexate; 6-MP- Mercaptopurine; CR- Complete remission, CCR- Continuous complete remission; NA- Not available; ND- Not detected;

* Risk group- According to the PETHEMA protocol.

HL occurs when WBC count reaches 100,000 cells/mm^3, carries a dismal prognosis, and is present in 5–20% of untreated AMLs [19]. Although less frequently, typical symptoms can also occur with lower WBC levels. Studies showed an association between HL with FAB M4 or M5 AML subtypes, chromosomal KMT2A rearrangement 11q23, and the FLT3-ITD mutation [19]. However, our patient did not present *FLT3*-ITD. The outcome of M3v patients appears to be influenced more by the WBC than the specific morphology. It is recommended not to delay the initiation of cytoreductive treatment for HL. Also, red cell transfusions should be given only if inevitable in HL patients to avoid further increase in blood viscosity [19]. In APL, leukapheresis might worsen the coagulopathy and is therefore not recommended [19].

Studies combining ATRA and chemotherapy have shown a virtual absence of primary resistance, 90–95% complete remission rates, and 85–90% long-term survival rates in APL [1]. Best results with ATRA plus chemotherapy are obtained with simultaneous administration of ATRA and anthracycline-containing chemotherapy for induction. ART is recommended during anti-leukemic treatments in HIV-positive individuals to facilitate immune reconstitution, reducing infection mortality [1]. Regimens containing integrase inhibitors, such as raltegravir or DTG, without pharmacologic boosters are currently favored because of their low potential for drug-drug interactions. Anthracyclines and antimetabolite agents, frequently used for AML treatment, generally undergo non-CYP450 routes of elimination, and their metabolism is unlikely to be significantly altered by ART [1]. Prophylactic strategies with agents against bacterial, fungal, and opportunistic infections allow acceptable infectious morbidity and mortality, even during neutropenia [1].

4. Conclusion

Despite all measures, our high-risk patient succumbed due to HL's complications. Its description and the literature review highlight the importance of APL's early diagnosis and treatment in patients living with HIV. It is difficult to establish a definite association between HIV and APL due to the scarcity of cases. Multicenter clinical studies are needed to define epidemiology, standardize cytogenetic/molecular features, and improve therapeutic management.

Authors' contributions

DPMA, TSF, and BG designed the study; DPMA, JB, MTGA, JM, and JPSCC attended the patient; DPMA, JB, and AGV analyzed the clinical data; DPMA, VLL, DTV, and JB wrote the manuscript. VLL and MMR performed the cytogenetic and FISH analysis; BEG performed the immunophenotypical assay, and BCRMM and DTV conducted the molecular study. VGO provided pharmaceutical assistance. TSF, EPN, and BG revised the manuscript and supervised the study. All authors have seen and approved the manuscript and its submission.

Declaration of Competing Interest

The authors declare no competing financial interests.

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