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

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1. Introduction

The use of antiretroviral therapy (ART) 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.

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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), in the context of 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.
(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 (H2O); 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, AVT was changed for dolatregravir (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 nuclei 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 ceftizime for febrile neutropenia. He reached 117,000/μL leukocytes in one week, followed by mild leukopenia and tumor 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.
| HIV Case | Age/ Sex | Time from HIV diagnosis (yrs) | ART | CD4\(^+\) count (cels/mm\(^3\)) | Viral load | APL Diagnosis | Morphologic variant/Risk group* | WBC/Platelets (/\(\mu\)L) | 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 | NA/NA | NA/NA | NA/NA | CR not achieved | Gatshoph et al. [11] |
| 4        | 27/M    | 8                             | IDV, NFV, AZT, EFV, TDF, STC | 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                             | >500 | <50 | RT-PCR PML-RARA | M3/intermediate | 5,090/150 | ATRA, Ida | ATRA, Ida, Mitox | ATRA, MTX, 6-MP ND | CCR at 21 months | De Vita et al. [13] |
| 6        | 35/M    | 10                            | AZT, STC, D4T, LPV/RTV, STC, NVP, DDI | 184 | <50 | FISH t(15;17) and RT-PCR PML-RARA | M3/intermediate | 1,600/2,800 | ATRA, Ida | ATRA | | | Botan et al. [14] |
| 7        | 37/M    | 7                             | ATV, TVD, RAL, PPV, ABC/STC, RTV, TVD, ATV, STC, FTC, TDF | >800 | ND | RT-PCR PML-RARA | M3/intermediate | 1,600/112,000 | ATRA, Ida | NA/NA | NA/NA | CR at day 77; 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, ABC/STC, RTV | 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/STC, RTV, ATV, FTC, TDF | 38 | 75.4 | Morphology | M3/intermediate | 4,000/2,200 | ATRA, Ida | ATRA, Ida, Mitox | ATRA, MTX, 6-MP | CCR at 38 months | Kunitomi et al. [2] |
| 10       | 46/M    | 0,4                           | RPV, FTC, TVD | 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, STC, 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; EPV- Efavirenz; NVP- Nevirapine; DDI- Didanosine; TDF- Tenofovir; FDC- Fosamprenavir; ATRA- all-trans-retinoic acid; ATO- Arsenic trioxide; Dauno- Daunorubicin; Ida- Idarubicin; 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 low metabolism, and in absence of primary resistance, 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; BFG performed the immunophenotyped 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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