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CASE REPORT

Myelodysplastic Neoplasm with Biallelic *TP53* Inactivation in a Well-Controlled HIV Patient

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SUMMARY

Background: **Human immunodeficiency virus (HIV) infection represents a chronic disease that must be treated with lifelong antiretroviral therapy (ART). Individuals with HIV are at increased risk of developing some cancers, including hematolymphoid malignancies. However, knowledge of myelodysplastic neoplasm (MDS) in HIV patients remains limited. Several studies have shown that HIV-positive MDS patients present at a younger age, progress more rapidly to acute myeloid leukemia (AML), and have poorer overall survival. Moreover, these patients have an increased prevalence of high-risk cytogenetic and molecular alterations. We report the first case of MDS with biallelic *TP53* inactivation according to the new WHO classification in an HIV patient in a well-controlled environment.**

Methods: **A bone marrow examination (BME) was performed to determine the cause of the patient's pancytopenia. In addition, karyotyping, FISH, and next-generation sequencing (NGS) were performed to diagnose the subtype of the disease.**

Results: **BME showed multilineage dysplasia and increased blasts, chromosome and FISH results were abnormal, and two *TP53* mutations were detected by NGS.**

Conclusions: **When considering the possibility of hematological malignancies in HIV patients with cytopenia, it is necessary to include MDS. Furthermore, more active investigations, including BME, especially genetic testing, are needed to determine the incidence, pathophysiology, and outcome of MDS in HIV patients.**

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KEYWORDS

HIV, MDS, *TP53*, complex karyotype

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CASE PRESENTATION

A 59-year-old male was diagnosed with HIV in 2012, and highly active antiretroviral therapy (HAART) was initiated. The patient remained on this treatment for 11 years with a long-term undetectable viral load (< 20 copies/mL) and CD4 cell counts > 400 cells/μL. In September 2023, the patient presented with progressive pancytopenia and dyspnea for 5 months. The laboratory results showed a leukocyte count of 1.26 x 10^9/L, a hemoglobin level of 73 g/L, and a platelet count of 39 x 10^9/L. Meanwhile, peripheral blood smears showed 1% blast-like immature cells. Bone marrow (BM) aspiration and biopsy were performed. The BM aspirate smear

Table 1. Clinical and genetic characteristics of HIV-positive patients with MDS in the literature.

Case	Age/ gender	MDS subtype	IPSS	Time from HIV (years)	Viral load (copies/mL)	CD4 count (cells/μL)	Gene mutations	Karyo-type	Treat-ment	Prog-ression to AML	Reference
1	66/F	MDS	Int-1	28	52	573	*ASXL1*, *DNMT3A*	normal	Len, Elt	no	Kaner et al., 2019 [4]
2	66/M	MDS	Int-2	13	73	383	*ASXL1*	-7	Aza	no	Kaner et al., 2019 [4]
3	70/M	t-MDS/AML	Int-2	20	247	76	*TP53*	-5,-7q,-2, marker chrom	Aza	yes	Kaner et al., 2019 [4]
4	66/M	MDS	Int-2	N/A	ND	304	*ASXL1*	-20q	Aza	no	Kaner et al., 2019 [4]
5	66/F	MDS	High	17	ND	781	*TP53*, *DNMT3A*	-7q,-5,+8,+9	Aza	yes	Kaner et al., 2019 [4]
6	52/F	t-MDS/AML	Int-2	12	N/A	140	*TP53*	N/A	Aza	yes	Kaner et al., 2019 [4]
7	64/F	MDS/AML	Int-2	15	< 40	931	*ASXL1*, *TET2*, *DNMT3A*, *U2AF1*	-7q	7+3	yes	Kaner et al., 2019 [4]
8	55/M	t-MDS/AML	High	24	< 40	275	*ASXL1*, *TP53*, *ETV6*	complex including -7	7+3/HiDAC, decitabine	yes	Kaner et al., 2019 [4]
9	65/F	MDS	Int-1	2	5,599	148	ND	-13q	untreated	no	Kaner et al., 2019 [4]
10	61/F	MDS-EB-1	Int-2	16	ND	929	*ASXL1*	+8	Aza	no	Mendes-de-Almeida et al., 2020 [5]
11	56/F	MDS-EB-1	very high (by IPSS-R)	N/A	174,920	12	*TP53*	complex including -5q,-7	decitabine	yes	Bijoy et al., 2022 [6]
12	54/M	MDS-bi*TP53* (by 5th ed. of WHO)	very high (by IPSS-R)	11	ND (< 20)	283.9	*TP53*, *TP53*	complex including -5q,+8	Aza	no	Present case

ND not detectable, N/A not available, IPSS international prognostic scoring system, Int-1 intermediate-1 risk, Int-2 intermediate 2 risk, IPSS-R revised international prognostic scoring system, HiDAC high dose cytarabine, Aza azacytidine, Len lenalidomide, Elt eltrombopag, MDS de novo MDS, t-MDS treatment-related MDS, t-MDS/AML treatment-related MDS that transformed to AML, MDS/AML MDS that transformed to AML, MDS-EB-1 MDS with excess blasts-1, MDS-bi*TP53* MDS with biallelic *TP53* inactivation.

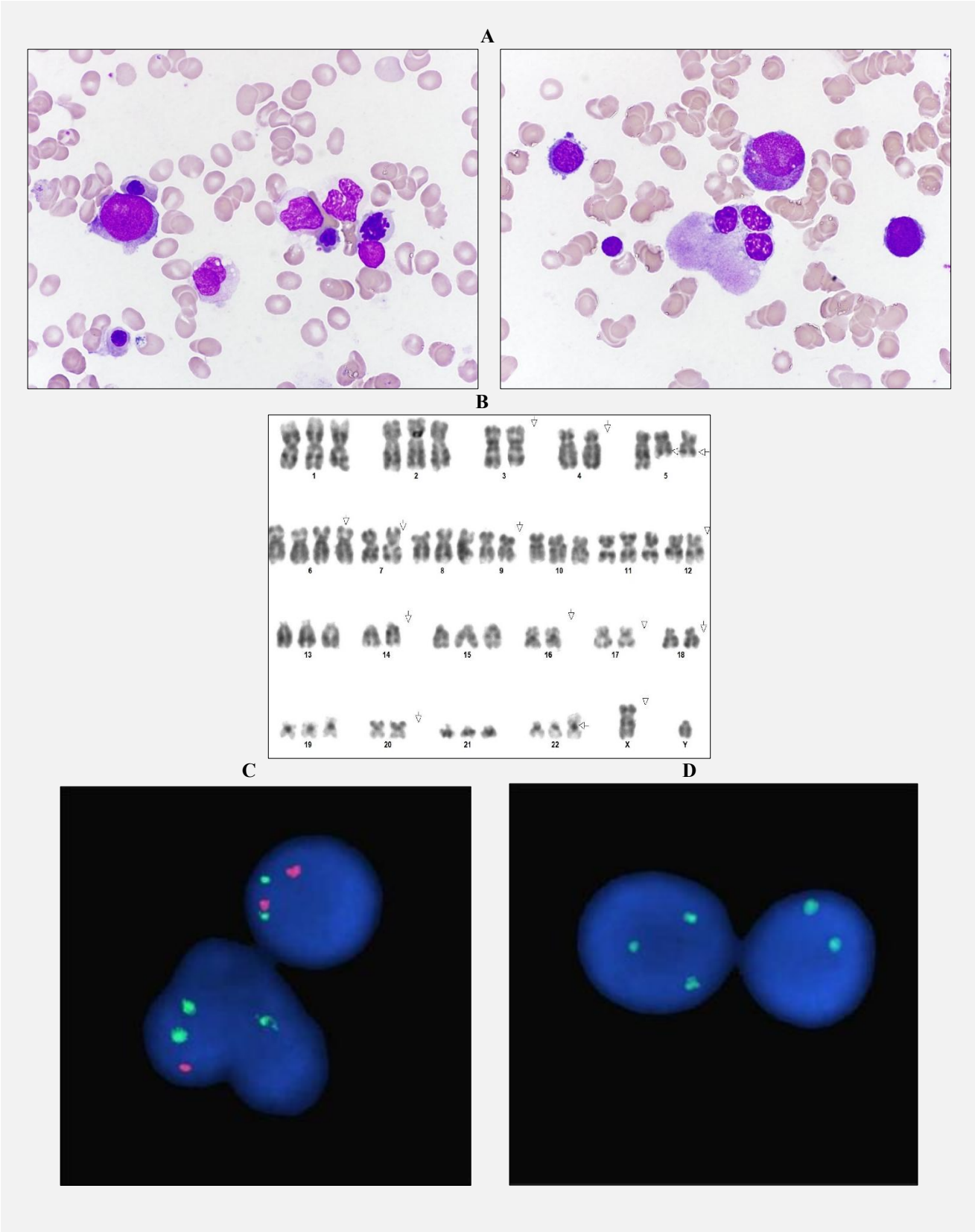

Figure 1. Morphologic and cytogenetic findings.

A) Bone marrow aspirate smear showing multilineage dysplasia and increased blasts (Wright stain, x 1,000). B) Karyotype of 59,XY,-X,-3,-4,del(5)(q22q35)×2,+6,-7,-9,-12,-14,-16,-17,-18,20,i(22)(q10)[8]/46,XY[12]. C) FISH analysis of one red (EGR1, 5q31.2) and three green (5p15.31) signals, indicating 5q deletion. D) FISH analysis of three green (D8Z2, 8p11.1-q11.1) signals, indicating trisomy 8.

showed multilineage dysplasia and 6.0% blasts (Figure 1A). The karyotype was 59,XY,-X,-3,-4,del(5)(q22q35) x 2,+6,-7,-9,-12,-14,-16,-17,-18,20,i(22)(q10)[8]/46,XY [12] (Figure 1B). The fluorescence in situ hybridization (FISH) analysis identified the 5q deletion (104/400, 26.0%) and trisomy 8 (90/400, 22.5%) (Figure 1C). Next-generation sequencing (NGS) using the oncomine myeloid research assay (Thermo Fisher Scientific Inc., Frederick, MD, USA) detected two *TP53* mutations of c.743G>A (p.Arg248Gln) and c.636del (p.Arg213 Aspfs*34) with allele frequencies of 12.75% and 10.86%, respectively. The patient was diagnosed with myelodysplastic neoplasm (MDS) with biallelic *TP53* inactivation, according to the fifth edition of the WHO classification of hematolymphoid tumours (MDS-EB-1, according to the revised fourth edition). He was at very high risk according to the revised International Prognostic Scoring System (IPSS-R) [1,2]. The patient was administered azacitidine alongside continuous ART. After 5 months, the BM aspirate smear showed persistent multilineage dysplasia with 3.0% blasts and a karyotype with similar abnormal findings:
57,XY,-X,add(2)(q11.2),-3,-4,del(5)(q22q35) x 2,+6,-7,-9,-12,-13,-14,-16,-17,-18,-20,-22[6]/46,XY[14].
Following a further 10 months, the BM aspirate smear showed persistent multilineage dysplasia with 5.5% blasts; meanwhile, the karyotype demonstrated a clonal evolution:
57~58,XY,-X,add(2)(q11.2),-3,-4,add(4)(q21),del(5)(q22q35) x 2, +6,-7,-9,-12,-13,-14,-15,-16,-7,8,der(18;22)(q10;q10),-19,-20,-21,-22,+1~2der(?)t(?;15)(?;q15)[cp12]/46,XY[8]. No dysplastic findings were observed in the BM aspiration in either biopsy, which were performed in 2012 and 2013.
Presently, the patient has been treated with ART, red blood cell and platelet transfusions, and eight cycles of azacitidine. However, the hematological parameters of the patient have deteriorated, with a leukocyte count of 0.88 x 10^9/L, a hemoglobin level of 84 g/L, a platelet count of 20 x 10^9/L, and circulating blasts.

DISCUSSION

HIV infection is a chronic disease that requires lifelong treatment with ART. People living with HIV have an increased risk of some cancers, including hematologic malignancies. However, studies investigating MDS in HIV patients remain limited, with fewer than 40 cases reported in the literature [4-7]. Jiamsakul et al. reported that malignancies occurred in 1.44% (107/7455) of Asian HIV patients; hematologic malignancies were 0.46% (n = 34), of which non-Hodgkin lymphoma was the most common (n = 26), and there was only one case of MDS [8].
MDS is a clonal hematopoietic disorder characterized by cytopenias, morphological dysplasia, and an increased risk of progression to AML [1]. Moreover, knowledge of the relationship between HIV and MDS remains limited, but several pathophysiological hypotheses have been proposed. The development of MDS in HIV patients may be related to chronic viral infection, with a disrupted inflammatory cytokine environment affecting immune system regulation. HIV infection itself or ART accelerates stem cell aging, leading to the acquisition of somatic mutations followed by clonal hematopoiesis and eventually MDS [4]. ART also has genotoxic effects [9] and is associated with hematopoietic progenitor cell dysplasia [10].
HIV-positive MDS patients present at a younger age, progress more rapidly to AML, and have poorer overall survival [4,5]. Additionally, these patients have an increased prevalence of high-risk cytogenetic alterations, such as complex karyotypes and deletions of chromosomes 5 or 7 [11,12], as observed in the present case. Molecular genetic testing has been included in relatively recent studies, and current data are summarized in Table 1. The most common somatic mutations were *ASXL1*, *TP53*, and *DNMT3A*. To our knowledge, the present case is the first to report two *TP53* gene mutations in an HIV-positive MDS patient, compared to previous cases with only one; according to the new WHO classification, this condition is classified as MDS with biallelic *TP53* inactivation. This subtype is regarded as very high risk in the IPSS-R, mostly associated with complex karyotype, and therapeutic considerations are similar to those for AML [1].
Cytopenias (anemia, leukopenia, or thrombocytopenia) and morphologic dysplasia are frequent findings in HIV patients who are at increased risk for hematological malignancies [13]. However, compared to non-Hodgkin lymphoma, MDS is relatively infrequent in HIV patients. In addition, the increased life expectancy of the patients who underwent ART has led to the presence of other age-related comorbid conditions that can confound the MDS diagnosis. In the present case, lymphoma was initially suspected when cytopenias occurred; however, MDS was finally diagnosed based on the obvious dysplasia in the BM along with chromosomal and genetic abnormalities consistent with the morphological findings. The importance of BM examination (BME), including BM aspiration, biopsy, and adjunctive testing, has been emphasized for investigating unexpected cytopenias in HIV patients [13,14]. The diagnostic yield of BME in HIV patients has been reported to be 19 - 47%, and when cytopenia was the main indication for BME, the diagnostic yield was 14.8 - 30.5% [14].
Recent advances in technology for detecting a wide range of genetic abnormalities have led to increased interest in clonal hemoblastosis (CH); meanwhile, several studies have reported that CH is more common in HIV patients compared to the general population [15,16]. These studies also showed that CH is associated with an increased risk of myeloid neoplasms, including MDS and AML, which are associated with particularly poor outcomes among HIV patients. In the present case, two *TP53* gene mutations were identified, which play a crucial role in determining diagnostic and prognostic clas-

sifications, highlighting the importance of genetic testing in monitoring HIV patients undergoing long-term treatment and the development of MDS.

In conclusion, to our knowledge, this is the first report on a case of MDS with biallelic *TP53* inactivation in a well-controlled HIV patient. When the possibility of hematological malignancy is considered in HIV patients with cytopenias, MDS, although rare, should be included. Additionally, more active investigations, including BME and especially genetic testing, are needed to determine the incidence, detailed classification, pathophysiology, and outcome of MDS in HIV patients.

Declaration of Interest:

The author has no potential conflicts of interest to declare.

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