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CASE REPORT

Rare Coexistence of Myelodysplastic Neoplasm and CD4 T-cell Lymphoproliferation

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SUMMARY

Background: **Myelodysplastic neoplasms (MDS) are characterized by cytopenia and morphologic dysplasia in myeloid cells and are considered a disease of the myeloid lineage. MDS with concurrent lymphoid clonality is rare and mostly occurs in CD8 T-cells.**
Methods: **We evaluated a 74-year-old man who presented with anemia and lymphocytosis using peripheral blood immunophenotyping, bone marrow examination, and next-generation sequencing.**
Results: **The patient was diagnosed with MDS with low blasts and an SF3B1 mutation (MDS-SF3B1), concurrent with clonal CD4 T-cell lymphoproliferative disorder, supported by TCR gene rearrangement and distinct mutation profiles.**
Conclusions: **This is the first reported case of MDS-SF3B1 coexisting with clonal CD4 T-cell proliferation.**
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KEYWORDS

myelodysplastic neoplasms, lymphoproliferative disorder, CD-4 T-cells

CASE PRESENTATION

A 74-year-old Korean man was referred to our institution after presenting with anemia and lymphocytosis. His complete blood count revealed the following: hemoglobin, 8.8 g/dL; mean corpuscular volume, 113.5 fL; white blood cells (WBC), 10.0 x 10^3/μL; and platelets, 277 x 10^3/μL. The differential WBC count was as follows: band neutrophils, 2%; segmented neutrophils, 38%; lymphocytes, 22%; atypical lymphocytes, 33%; and monocytes, 5%. The atypical lymphocytes were medium-to-large in size and had cleaved or bilobated nuclei with condensed chromatin patterns and a moderate amount of clear cytoplasm (Figure 1A). Flow cytometric immunophenotyping of the peripheral blood revealed that 96.8% of the lymphocytes strongly expressed CD45 (Figure 1B). Among these, 70.3% were

CD4-positive; 59.4% were positive for cytoplasmic CD2, CD3, CD4, and CD5 but were negative for CD7, CD8, and surface CD3, which suggested clonal CD4 T-cell proliferation (Figure 1C - F). Next-generation sequencing of peripheral blood DNA showed clonal rearrangements in *TCRB* (Vβ18 and Jβb2-5 in 51.42% of the clonal reads with *TCRB* rearrangements) and *TCRG* (Vγ10 and Jγ1/2 in 24.95% and Vγ2 and Jγ1/2 in 10.69%). Bone marrow (BM) aspirates showed increased erythropoiesis, relatively little granulopoiesis with a myeloid-to-erythroid ratio of 0.4, and adequate megakaryopoiesis. Dysplastic features were observed only in the erythroid lineage and included binucleation and karyorrhexis in more than 10% of the erythroid precursors (Figure 2A, B). Iron staining revealed an adequate amount of hemosiderin particles, whereas sideroblasts (including those that were ringed) were elevated (32% and 16% of BM erythroid precursors, respectively) (Figure 2C); no atypical lymphocytes were observed. A BM biopsy indicated 40% cellularity. Immunohistochemical staining for CD3 showed elevated levels of scattered and aggregated T-cells, while that for CD20, CD34, CD61, and CD117 revealed no remarkable findings; moreover, no reticulin fibrosis was observed. The patient's BM karyotype was 45,X,-Y[20]. Next-generation sequencing of the patient's BM aspirate using a 165-gene panel showed *SF3B1* K700E (variant allele frequency [VAF]: 39.4%), *TET2* splicing variant (VAF: 36.4%), and *STAT3* N647I (VAF: 2.0%). Based on these findings, he was diagnosed with MDS with ring sideroblasts and single-lineage dysplasia (MDS-RS-SLD) according to the revised 4th edition of the World Health Organization classification - which corresponds to MDS-*SF3B1* in the 5th edition of the same - with concurrent clonal CD4 T-cell lymphoproliferative disorder. He underwent a workup for T-cell malignancy, but no other lymphoid lesions were evident. After two years of conservative treatment, a follow-up BM biopsy showed no changes.

DISCUSSION

MDS is a clonal hematopoietic neoplasm that is classified as a myeloid malignancy [1]. Studies on lymphoid clonality in MDS are rare; while they may be categorized into three types, the distinction between them is unclear, given some overlap in their characteristics. Whether lymphoid cells show the same clonality as myeloid cells in patients with MDS, irrespective of the presence of lymphoproliferation, was mainly explored using fluorescence in situ hybridization, karyotyping, and flow cytometry techniques to elucidate the stages of cell differentiation at which clonal change occurred [2-7]; however, the results were equivocal. Studies demonstrated that myeloid and lymphoid cells share the same clonal abnormalities, suggesting that the clonal change occurred before lineage commitment and that the MDS clone originated from primitive transformed hematopoietic ancestor cells [2-5]. van Lom et al. reported a patient with MDS exhibiting monosomy 7 in both myeloid and B cells, whereas two other patients with this condition did not share monosomy 7 with lymphoid cells [2]. Miura et al. reported that monosomy 7 was present in pluripotent stem cells, B-progenitors, and T/NK progenitors in patients with MDS [3], while Ma et al. showed that both circulating myeloid and lymphoid precursor dendritic cells had the same chromosomal aberrations as BM myeloid cells [4]. Nilsson et al. reported that patients with 5q deletion syndrome showed this deletion in CD34+CD38- hematopoietic stem cells and in CD34+CD19+ pro-B cells [5]. In contrast, Bernell et al. and Saitoh et al. showed that clonal abnormalities such as monosomy 7, trisomy 8, and monosomy 17 were observed only in myeloid lineages (including granulocytic, monocytic, and erythrocytic cell lineages) but not in lymphoid cells among patients with MDS [6,7].

Other studies focused on the pathogenic role of the clonal expansion of cytotoxic CD8 T-cells in MDS [8-12]. Cytotoxic T-cell-mediated inhibition, an autoimmune process, suppresses hematopoiesis in patients with MDS as well as in those with aplastic anemia and large granular lymphocyte leukemia (LGLL) [8,9], which is the basis of immunosuppressive treatment for low-grade MDS (including hypoplastic MDS) [10]. Epling-Burnette et al. showed that CD8+/CD57+/CD28- effector T-cells are more common in patients with MDS than in age-matched controls (approximately 50% vs. 5%) [11]. They reported that Vβ1, Vβ9, Vβ11, Vβ18, and Vβ23 expansions were frequent; this is in the same context as autoimmunity being associated with the expansion of T-cell clones of restricted diversity that carry a limited T-cell receptor-Vβ (TCR-Vβ) repertoire [9]. Kochenderfer et al. reported that antithymocyte globulin treatment corrected the skewed spectratypes of TCR-Vβ in patients with MDS [8]. In contrast, Durrani et al. reported that patients with MDS and concurrent LGLL had a somatic STAT3/STAT5 mutation rate of 15%, while those with LGLL alone had a rate of 39% [12]. However, it remains unclear if LGLL and MDS share the same mutations, given that their group did not perform cell sorting.

Separate studies investigated concurrent or subsequent clonal lymphoproliferative conditions such as lymphomas or acute lymphoblastic leukemias [13-15]. Huang et al. reported a patient with concurrent T-cell lymphoma and MDS that expressed the common abnormality of a 20q deletion [13]. Disperati et al. summarized 21 patients with B- or T-acute lymphoblastic leukemia that exhibited the same cytogenetic abnormalities as the antecedent MDS, suggesting that the latter arose from pluripotent hematopoietic stem cells [14]. Yoshihara et al. reported a patient with angioimmunoblastic T-cell lymphoma who subsequently developed diffuse large B cell lymphoma and MDS and in whom samples from all three diseases shared common mutations in *TET2* and *DNMT3A*, suggesting multistep and multilineage tumor

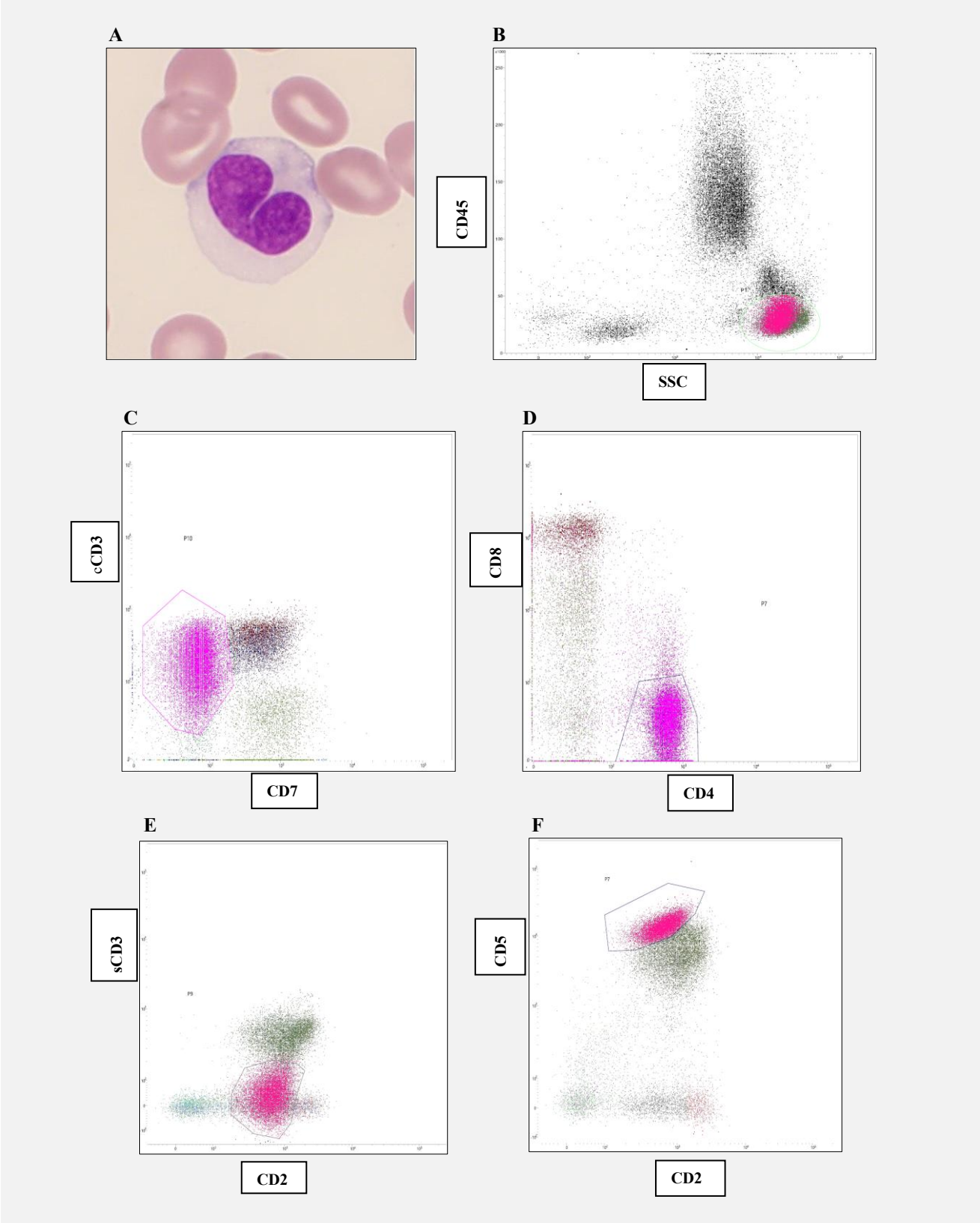

Figure 1. Morphologies and flow cytometric immunophenotyping of the patient's peripheral blood and bone marrow.

A Representative morphologies of atypical lymphocytes in the peripheral blood, showing medium-to-large cells with cleaved or bilobated nuclei, condensed chromatin patterns, and a moderate amount of clear cytoplasm (x 1,000). B - F Flow cytometric immunophenotyping: B Lymphocytes with bright CD45 expression. C Positive cytoplasmic CD3 and negative CD7 expression. D Positive CD4 and negative CD8 expression. E Positive CD2 and negative surface CD3 expression. F Positive CD2 and CD5 expression.

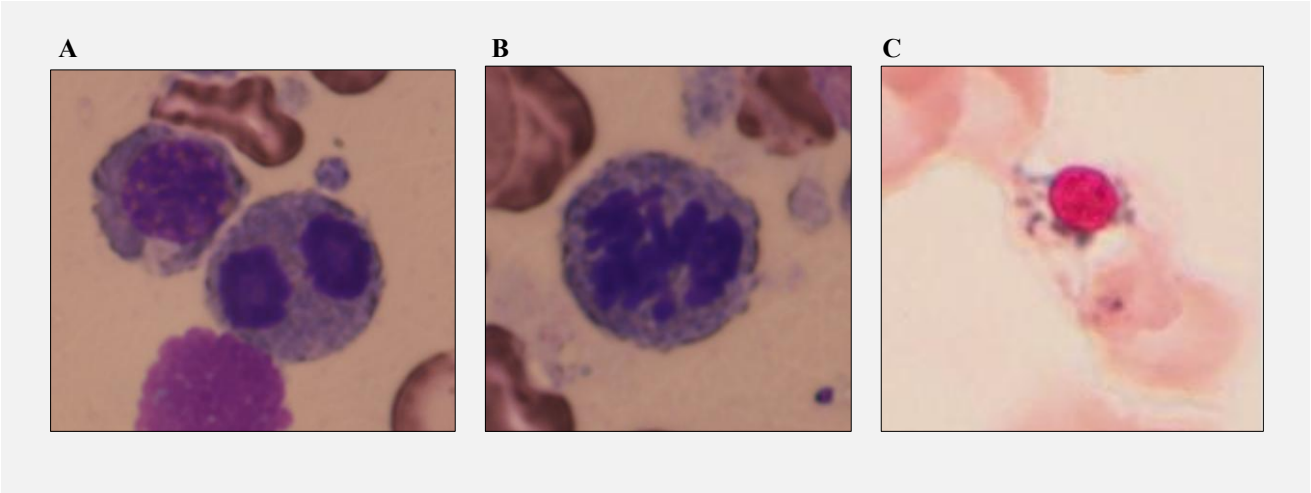

Figure 2. Microscopic images of dysplastic features in the erythroid lineage.

A Binucleation and B karyorrhexis observed in more than 10% of erythroid precursors. C Ring sideroblasts in the bone marrow. Magnification x 1,000.

igenesis from a common founder clone [15].

Our patient is the first diagnosed with MDS and concurrent clonal CD4-positive lymphoproliferation that could not be explained by an exaggerated cytotoxic T-cell response (as was the case in previous studies), even though his *TCR* gene rearrangement involved *TCRB* Vβ18, which is common in proliferating CD8-positive T-cells in patients with MDS [11]. Due to the increased cytotoxic T-cell response, the CD4:CD8 ratio is decreased in patients with MDS [16]. CD4 T-cell expansion has rarely been reported in these patients; although Fozza et al. reported such expansion, CD4 showed polyclonality, whereas CD8 exhibited oligoclonality [17]. The frequencies of interleukin (IL)-17-producing $CD4^{pos}$ T_H17 cells were increased in the peripheral blood of low-risk patients, suggesting a role for increased autoimmunity; however, T_H17 frequencies decreased concomitant with reduced IL-21 and IL-22 production [18,19]. Based on the VAF discrepancy between the myeloid malignancy genes (*SF3B1* and *TET2*) and lymphoid malignancy gene *STAT3*, we deduced that the MDS and CD4-positive T-cell lymphoproliferation had different genetic origins, although *TCRB* Vβ18 involvement is common. However, this hypothesis should be confirmed by cell sorting or single-cell genetic analysis, as such information would be helpful for disease management. Studying more patients with CD4-positive T-cell proliferation and concurrent MDS would help clarify the roles of the former in the latter.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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