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– CASE REPORT –

TP53-Mutated Myelodysplastic Syndrome with Bone Marrow Fibrosis in a Young Adult: A Rare Diagnostic and Therapeutic Challenge

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Abstract

Introduction: *Myelodysplastic syndrome with fibrosis (MDS-F) is a rare and biologically aggressive subtype of myelodysplastic syndrome associated with severe cytopenias, poor prognosis, and increased risk of progression to acute myeloid leukemia. The coexistence of TP53 mutation further confers adverse disease biology, therapeutic resistance, and inferior survival outcomes. Occurrence of TP53-mutated MDS-F in young adults is exceptionally uncommon and poses significant diagnostic and therapeutic challenges.*

Case presentation: *A 22-year-old female presented with transfusion-dependent pancytopenia and progressive pallor. Bone marrow aspiration resulted in a dry tap, while trephine biopsy revealed markedly hypercellular marrow with dysplasia involving erythroid precursors and megakaryocytes and grade 2 reticulin fibrosis. Immunophenotyping identified approximately 5% CD117-positive myeloid precursors. Cytogenetic analysis showed a normal female karyotype, whereas next-generation sequencing detected a TP53 exon 5 mutation, c.536A>G (p.His179Arg), with variant allele frequency of 22.6%. The patient was diagnosed as MDS-F, and classified as moderate high risk according to the IPSS-M. She received azacitidine therapy and achieved complete remission with bilineage recovery after four cycles, which subsequently deepened to complete remission after six cycles, following which she was planned for allogeneic hematopoietic stem cell transplantation.*

Conclusion: *This case highlights the rare occurrence of TP53-mutated MDS-F in a very young adult and demonstrates that azacitidine can induce meaningful hematologic remission despite adverse molecular and morphologic features. Early molecular profiling and timely referral for allogeneic transplantation remain essential in such high-risk disease.*

Keywords: *Myelodysplastic syndrome; TP53 mutation; Fibrosis; Azacitidine; Hematopoietic stem cell transplantation*

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Introduction

Myelodysplastic Syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, dysplasia, and peripheral cytopenias, with a risk of progression to Acute Myeloid Leukemia (AML).[1] Contemporary classification systems categorize MDS into genetically defined and morphologic subtypes. Genetic subtypes include entities associated with *TP53* mutation, SF3B1 mutation, and del(5q), whereas morphologic variants include low-blast,

hypoplastic, increased-blast, and fibrotic forms of MDS. MDS with fibrosis and increased blasts (MDS-F) is characterized by 5–19% blasts with grade 2–3 marrow fibrosis within the marrow microenvironment and is frequently associated with multilineage dysplasia, transfusion dependence, inferior survival outcomes, and adverse-risk features including *TP53* mutations. The pathogenesis of marrow fibrosis is thought to involve cytokine-mediated stromal activation induced by abnormal hematopoietic progenitors. Elevated levels of profibrotic cytokines such as transforming growth factor-beta and platelet-derived growth factor contribute to increased reticulin deposition within the marrow microenvironment. Unlike primary myelofibrosis, MDS-F generally lacks classical myeloproliferative driver mutations such as JAK2, CALR, and MPL, suggesting distinct pathogenic mechanisms.[2] *TP53* is a critical tumor suppressor gene encoding the p53 transcription factor, often referred to as the "guardian of the genome" because of its central role in maintaining genomic stability and regulating apoptosis. *TP53* is among the most frequently mutated genes across human malignancies and is consistently associated with adverse prognosis and poor response to conventional therapies.[3] Mutations in *TP53* occur in ~10–12% of MDS and are linked to poor prognosis, higher risk of progression to AML, and limited treatment response; although most involve the DNA-binding domain, they can occur throughout the gene.[4, 5] Although *TP53* mutations are more frequently identified in elderly patients with therapy-related disease or complex karyotypes, their coexistence with significant marrow fibrosis in young adults is exceedingly uncommon.[6] The rarity of young-onset *TP53*-mutated MDS-F poses both diagnostic and therapeutic challenges, particularly in resource-limited settings where early molecular testing may not always be readily available. Hypomethylating agents such as azacitidine remain standard frontline therapy for higher-risk MDS and are frequently used as bridging treatment prior to allogeneic hematopoietic stem cell transplantation (HSCT).[7] However, outcomes in *TP53*-mutated MDS remain unsatisfactory, and literature describing therapeutic responses in young patients with *TP53*-mutated MDS-F remains limited. We present a case of MDS-F in a young female, a rare finding at this age, treated with azacitidine.

Case presentation

A 22-year-old female presented with progressively worsening pallor, generalized weakness, and easy fatigability of two months duration. During this period, she required eight units of packed red blood cell transfusions because of persistent symptomatic anemia. There was no history of fever, recurrent infections, bleeding manifestations, bone pain, weight loss, night sweats, or significant drug intake. Family history was non-contributory. On examination, she was hemodynamically stable but had marked pallor. There was no icterus, petechiae, lymphadenopathy, hepatosplenomegaly, or sternal tenderness.

Initial laboratory investigations demonstrated pancytopenia with hemoglobin 6.3 g/dL, total leukocyte count 1.81 × 10^9/L, absolute neutrophil count (ANC) 0.72 × 10^9/L, and platelet count 32 × 10^9/L. Peripheral blood smear revealed normocytic normochromic anemia with mild anisopoikilocytosis, neutropenia, thrombocytopenia, and occasional circulating myeloid precursors without overt blasts. Corrected reticulocyte count was markedly reduced at 0.4%, suggesting ineffective erythropoiesis. Serum ferritin was elevated at 607 ng/mL, likely reflecting repeated transfusions. Serum iron, vitamin B12 and folate levels were within normal limits, thereby excluding nutritional deficiency–related marrow dysplasia. Renal and liver function tests were normal. Viral serologies including hepatitis B, hepatitis C, and human immunodeficiency virus were negative.

Given the patient's young age and severe pancytopenia, an initial differential diagnosis of aplastic anemia and acute leukemia was considered. Bone marrow aspiration, however, resulted in a dry tap, raising suspicion for marrow fibrosis or densely packed marrow infiltration. Consequently, a trephine biopsy was performed, which revealed a markedly hypercellular marrow with multilineage dysplasia. Erythroid precursors showed megaloblastoid changes, nuclear irregularity, and nuclear budding, while megakaryocytes demonstrated marked dysplastic features including hypolobated nuclei, abnormal nuclear contours, and micromegakaryocytic forms. There was relative erythroid and megakaryocytic hyperplasia with markedly suppressed myelopoiesis and left-shifted maturation **(Figure 1A).** Reticulin staining demonstrated grade 2 fibrosis **(Figure 1B).**

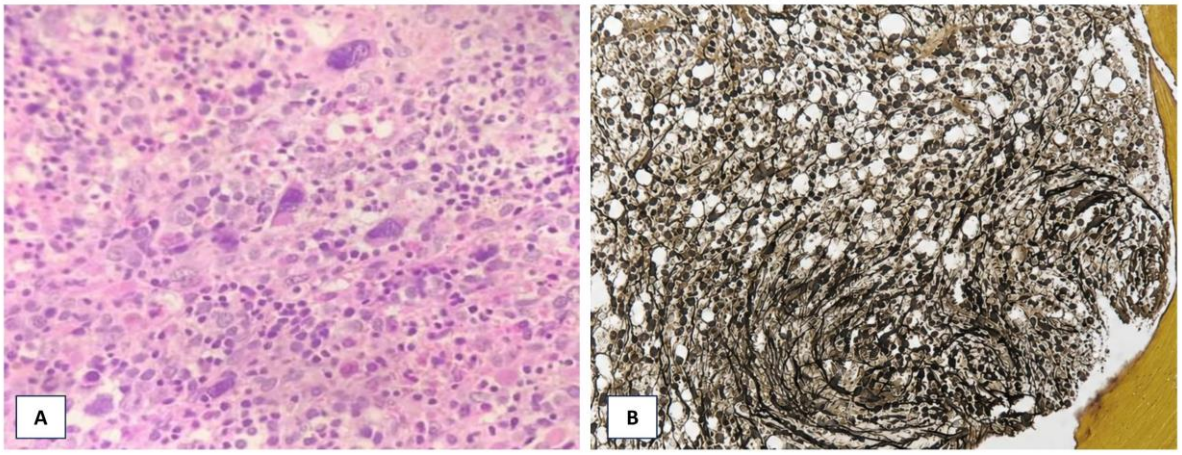


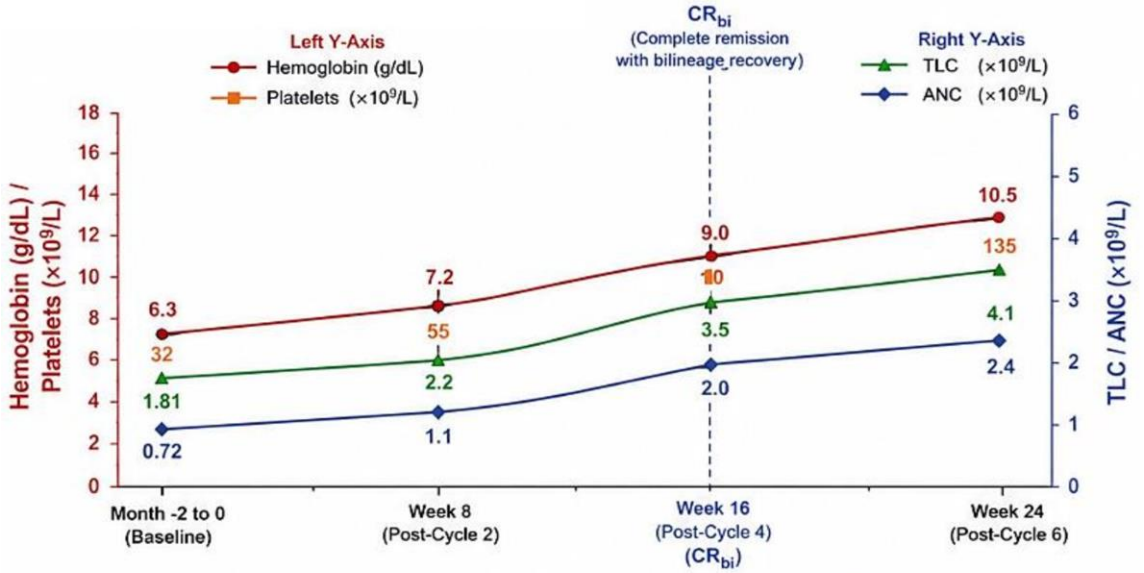
Figure 1. *Histopathological findings in TP53-mutated myelodysplastic syndrome with fibrosis. Bone marrow biopsy (A) H&E stain (400×), showing hypercellular marrow and multilineage dysplasia, including dysplastic megakaryocytes with hypolobated nuclei, abnormal nuclear contours, and micromegakaryocytic forms, along with dyserythropoiesis characterized by megaloblastoid changes, nuclear irregularity, and nuclear budding; (B) Reticulin stain (400×) demonstrating diffuse increased reticulin fibre deposition with intersecting coarse fibres, consistent with grade 2 marrow fibrosis.*

Immunophenotyping identified ~5% CD117-positive, CD34-negative myeloid precursors. Conventional cytogenetics showed a normal female karyotype (46, XX). Because of the unusual presentation and fibrotic marrow morphology in a young adult, next-generation sequencing (NGS) was performed for further molecular characterization. Molecular analysis by NGS revealed a *TP53* mutation, c.536A>G (p.His179Arg) in exon 5 (NM_000546.6), with a variant allele frequency of 22.6% **(Figure 2).**

Figure 2. *Molecular findings in TP53-mutated myelodysplastic syndrome with fibrosis. Integrative Genomics Viewer snapshot demonstrating TP53 exon 5 mutation, c.536A>G (p.His179Arg), identified by next-generation sequencing.*

Based on morphologic, immunophenotypic, cytogenetic, and molecular findings, a final diagnosis of MDS-F was made and categorized as Moderate high risk as per IPSS-M (Molecular International Prognostic Scoring System for Myelodysplastic Neoplasms).[8]

The patient was initiated on azacitidine therapy at a dose of 75 mg/m²/day for 7 days every 28 days along with supportive transfusion support, antimicrobial prophylaxis, and close monitoring for infectious complications. Following two cycles, transfusion requirement gradually decreased with early hematologic recovery. After four cycles, she achieved complete remission with bilineage recovery (CRbi) as per the revised International Working Group 2023 response criteria.[9] Hemoglobin improved to 9 g/dL, total leukocyte count to 3.5 × 10⁹/L, ANC to 2.0 × 10⁹/L, and platelet count to 110 × 10⁹/L. Continued azacitidine therapy resulted in complete remission (CR) after six cycles, with hemoglobin increasing to 10.5 g/dL, ANC to 2.4 × 10⁹/L, and platelet count to 135 × 10⁹/L. Longitudinal hematologic response kinetics following azacitidine therapy is outlined in **Figure 3.** She subsequently became transfusion independent and remained clinically stable. In view of the high-risk molecular profile and young age, she is currently planned for allogeneic HSCT as definitive curative therapy.



Clinical Milestone	Pre-Treatment Baseline (Month -2 to 0)	Post-Cycle 2 (Week 8)	Post-Cycle 4 (CR_{bi}) (Week 16)	Post-Cycle 6 (Week 24)
Hemoglobin (g/dL)	6.3	7.2	9.0	10.5
Platelets (×10⁹/L)	32	55	110	135
TLC (×10⁹/L)	1.81	2.2	3.5	4.1
ANC (×10⁹/L)	0.72	1.1	2.0	2.4
Intervention / Notes	Requires ~8 units PRBC	Transfusion frequency slowing	Transfusion independent	Sustained response, bridging to HSCT

Figure 3. *Longitudinal hematologic response kinetics following azacitidine therapy. Multi-line graphical representation demonstrating serial improvement in peripheral blood counts during treatment. The left Y-axis depicts hemoglobin concentration (g/dL) and platelet count (×10⁹/L), while the right Y-axis represents total leukocyte count (TLC) and absolute neutrophil count (ANC) (×10⁹/L). Progressive hematologic recovery was observed across six cycles of azacitidine, culminating in complete remission with bilineage recovery (CRbi) after cycle four, along with achievement of transfusion independence. Complete response was achieved after six cycles, following which she was planned for planned allogeneic hematopoietic stem cell transplantation (HSCT).*

Discussion

MDS-F represents a biologically aggressive and rare subset of myelodysplastic neoplasms associated with severe cytopenias, transfusion dependence, excess blasts, and inferior clinical outcomes. Increasing grades of marrow fibrosis correlate with adverse prognostic features including severe anemia, higher marrow blast percentage, unfavourable cytogenetics, and higher IPSS-R risk categories, with progressively reduced overall survival. Molecular studies have additionally demonstrated enrichment of high-risk mutations such as *TP53*, U2AF1, and KMT2D in patients with advanced fibrosis,

supporting a close relationship between marrow fibrosis and aggressive disease biology.[10] The presence of fibrosis also contributes to diagnostic overlap with myeloproliferative neoplasms, although classical driver mutations (*JAK2, CALR, MPL*) are uncommon in MDS-F, suggesting distinct pathogenic mechanisms.[11]

TP53-mutated myeloid neoplasms are recognized for their aggressive clinical behaviour and poor therapeutic outcomes. Most TP53 mutations in MDS and AML are missense mutations involving hotspot regions within the DNA-binding domain, resulting in loss of normal p53 tumor suppressor activity. *TP53*-mutated clones exhibit resistance to apoptosis and may undergo clonal expansion under treatment-related selective pressure. Clinically, *TP53* mutations are associated with chemotherapy resistance, rapid disease progression, higher risk of leukemic transformation, and markedly inferior survival outcomes.[12] The prognostic impact appears independent of cytogenetic risk, and higher variant allele frequency has been associated with increased resistance and inferior outcomes.[13] In the present case, the identified *TP53* exon 5 mutation with a variant allele frequency of 22.6% likely contributed to the high-risk disease biology despite the presence of a normal conventional karyotype.

Therapeutic outcomes in *TP53*-mutated MDS remain unsatisfactory. Conventional approaches including intensive chemotherapy, hypomethylating agents, and venetoclax-based regimens have demonstrated limited ability to improve long-term overall survival.[12] Novel targeted therapies have also produced disappointing results in advanced clinical studies. Eprenetapopt (APR-246), a p53-reactivating agent evaluated in combination with azacitidine, showed encouraging activity in early-phase studies but failed to demonstrate significant survival benefit in phase III trials. Similarly, magrolimab, an anti-CD47 monoclonal antibody investigated in *TP53*-mutated MDS and AML, did not show meaningful superiority in subsequent analyses.[12] Consequently, allogeneic HSCT continues to represent the only potentially curative therapeutic option for eligible patients.[10, 12]

Although marrow fibrosis itself is traditionally considered an adverse prognostic feature, available evidence suggests that fibrosis may not significantly impair response to azacitidine therapy. Hammond et al. evaluated azacitidine-treated MDS cohorts and observed that while higher fibrosis grades were associated with elevated ferritin levels, transfusion dependence, and adverse baseline clinical features, fibrosis did not significantly influence response rates, leukemic transformation, leukemia-free survival, or overall survival.[14] Similarly, Juvadi et al. reported an overall response rate of 63% in MDS-F patients treated with azacitidine, including complete remission and hematologic improvement rates comparable to those observed in non-fibrotic MDS. Importantly, treatment response did not significantly differ according to fibrosis grade, supporting the continued role of hypomethylating therapy in fibrotic MDS.[15]

Overall, this case underscores the diagnostic challenges posed by young-onset MDS-F presenting with pancytopenia and dry tap marrow aspiration. It also highlights the importance of integrating morphologic, cytogenetic, and molecular evaluation for accurate diagnosis and risk stratification. The observed hematologic remission following azacitidine further supports its role as an effective bridging therapy before allogeneic HSCT in high-risk *TP53*-mutated disease.

Conclusions

MDS-F with *TP53* mutation is a rare and highly aggressive clinicopathologic entity, particularly in young adults. The present case highlights the diagnostic complexity and therapeutic challenges associated with this uncommon disease phenotype. Azacitidine induced significant hematologic remission and served as an effective bridge to allogeneic HSCT despite adverse molecular and morphologic features. Early molecular characterization, careful morphologic evaluation, and timely referral for HSCT remain crucial for optimizing outcomes in such high-risk patients.

Article information and declarations

Ethics statement: The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was not required. Appropriate informed consent was obtained from the patient. Patient confidentiality has been maintained, and the data do not permit identification of the individual.

Author contributions: MP — conceptualization; MP, TKD, KG — writing—original draft, investigation, data curation; TKD— review of data and critical input; KG — manuscript review and final editing; MP, TKD, KD— writing, review and editing, final draft preparation. All authors have read and approved the final manuscript.

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