ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 9, Issue – 1, February - 2026, Page No.: 53 – 57

MPL and TP53 Co-Mutated Primary Myelofibrosis in A 55-Year-Old Woman: A Rare Case Report

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How to citation this article: Dr. B. Kasthuri Bala, Dr. A. Rajesh, Dr. G. Rathnakumar, Dr. B. H. Prawin, "MPL and TP53 Co-Mutated Primary Myelofibrosis in A 55-Year-Old Woman: A Rare Case Report", IJMACR- February - 2026, Volume – 9, Issue - 1, P. No. 53 – 57.

Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

Primary myelofibrosis (PMF) is a rare myeloproliferative neoplasm typically diagnosed in patients over 65 years, characterized by bone marrow fibrosis, extramedullary hematopoiesis, and driver mutations such as MPL. We report case of a 55-year-old female who presented with easy fatiguability, low-grade fever, low back pain. Examination revealed pallor, angular stomatitis, Hepatosplenomegaly With investigations showing pancytopenia leucoerythroblastic peripheral smear, elevated LDH, and RPI O.4. BM biopsy- hypercellular marrow with fibrosis alongside MPL gene mutation and TP53 positivity. This case atypical presentation of PMF in 5th decade with dual MPL/TP53 mutations, highlighting diagnostic challenges, rapid progression risks, optimized risk stratification and management

Keywords: Primary myelofibrosis, MPL mutation, TP53 mutation, Myeloproliferative neoplasm, Genetic mutations in PMF, Pancytopenia, Splenomegaly, Bone marrow fibrosis.

Introduction

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis, extramedullary hematopoiesis, splenomegaly, leukoerythroblastic peripheral blood smear, and driver mutations such as JAK2 V617F (50-60%), CALR (20-25%), or MPL (5-10%), with a median diagnosis age of 65-70 years and incidence of 0.5-1 per 100,000. The diagnostic pathway—starting from recognition of pancytopenia and massive splenomegaly,

proceeding to bone marrow biopsy with reticulin staining, then to cytogenetics and NGS—is aligned with contemporary PMF guidelines that emphasize integrated morphologic and molecular criteria.

High-risk mutations like TP53 (<5% prevalence) predict aggressive disease, leukemic transformation, and inferior survival, independent of IPSS/DIPSS-plus scores. PMF rarely manifests in middle-aged women (<20% under 55 years), and concurrent MPL/TP53 positivity is exceptionally rare, posing diagnostic and prognostic challenges.

Diagnostic Criteria Mentioned in Table

Primary myelofibrosis, early/prefibrotic stage (prePMF)	**Primary myelofibrosis, overt fibrotic stage**
Major criteria	**Major criteria**
1. Bone marrow biopsy showing megakaryocytic proliferation and atypia[a], bone marrow fibrosis grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2*, *CALR*, or *MPL* mutation[b] or Presence of another clonal marker[c] or Absence of reactive bone marrow reticulin fibrosis[d] 3. Diagnostic criteria for *BCR::ABL1*-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met	1. Bone marrow biopsy showing megakaryocytic proliferation and atypia[a], accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2*, *CALR*, or *MPL* mutation[b] or Presence of another clonal marker[c] or Absence of reactive myelofibrosis[d] 3. Diagnostic criteria for essential thrombocythemia, polycythaemia vera, *BCR::ABL1*-positive chronic myeloid leukemia, myelodysplastic syndrome, or other myeloid neoplasms[e] are not met
Minor criteria	**Minor criteria**
▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥11 x 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range	▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥11 x 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range

This report details a 52-year-old postmenopausal woman with type 2 diabetes presenting with pancytopenia, massive hepatosplenomegaly, and PMF confirmed by bone marrow biopsy showing grade 3 reticulin fibrosis, MPL mutation, and TP53 positivity, underscoring the value of comprehensive genetic profiling in atypical demographics.

Case Presentation

A 55-year-old postmenopausal nulliparous female homemaker from Kallidaikurichi, known case of type 2 diabetes mellitus for 1 year on irregular medications, presented with easy fatiguability for 2 months, intermittent low-grade fever for 10 days without chills/rigor, and insidious-onset persistent low back pain. Pallor and angular stomatitis were noted; no icterus, cyanosis, clubbing, lymphadenopathy, or pedal edema.. Abdominal exam revealed hepatomegaly (4-5 cm below right costal margin, soft, non-tender, moves with respiration) and massive splenomegaly (10 cm below left costal margin, 20 cm span, firm, smooth, non-tender, moves with respiration); divarication of recti present, abdominal girth 90 cm. Spine tender at lumbar region; other systems (CVS, RS, CNS) unremarkable.

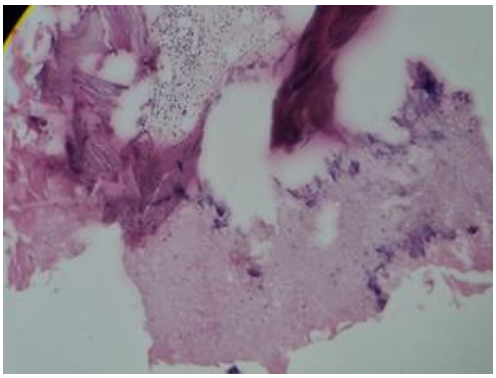
Investigations confirmed pancytopenia with leucoerythroblastic features; no hemoparasites or hemolysis (negative Coombs, dengue, widal, HIV, HBsAg, HCV). Bone marrow aspiration was inadequate; biopsy showed hypercellular marrow, megakaryocytic atypia/clustering, grade 3 reticulin fibrosis (reticulin stain), consistent with overt PMF, plus MPL mutation and TP53 positivity.

Parameter	28/08/25	30/08/25	31/08/25	01/09/25	05/09/25	Reference Range
Hb (g/dL)	5.4	4.9	5.3	5.8	6.1	12-16
RBC (×10^6/µL)	2.27	2.93	2.29	2.97	2.42	4-5.2
Platelets (×103/µL)	42	98	27	115	61	150-405
TC (×103/µL)	4.5	4.1	3.2	3.7	4.5	4-11
Retic Count (%)	-	-	-	2.2	-	0.5-1.5
RPI	-	-	-	0.4	-	>2
LDH (U/L)	718	-	-	-	573	<250
ESR (mm/hr)	60	-	73	-	-	<20

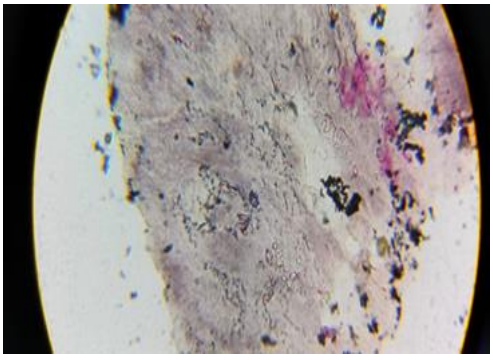
Peripheral smear: Leucoerythroblastic anemia, anisopoikilocytosis.

Bone marrow aspiration- dry tap

Bone marrow biopsy/reticulin stain: Grade 3 fibrosis, megakaryocytic atypia.



Bone Marrow Biopsy



Bone Marrow Biopsy/Reticulin Stain

X-ray (long bones/skull/lumbar spine): No lytic lesions.

USG Abdomen

USG abdomen revealed moderate hepatomegaly and massive splenomegaly.

CT Abdomen

Contrast-enhanced CT abdomen confirmed gross hepatomegaly and massive splenomegaly multiple splenic infarct noted. No focal lesions or ascites noted. Additionally, diffuse sclerosis was noted in vertebral bodies, pelvis, proximal femur, and femoral heads, with few lytic lesions—characteristic skeletal changes in advanced PMF.

As Per Diagnostic Criteria Above Mentioned

My patient has met 3 major and 4 minor criteria

Molecular Genetics / NGS Panel

Targeted leukemia gene panel by next-generation sequencing (NGS) performed on peripheral blood (MedGenome Labs, collection date 14 September 2025, reported 25 September 2025) detected clinically relevant variants in MPL and TP53. The test was reported as POSITIVE for pathogenic/likely pathogenic variants, with the following details:

MPL: p.Trp515Leu (missense), variant allele frequency (VAF) 38%. Classified as Tier IB (variant of strong clinical significance with well-documented association), reported as a diagnostic marker for a subset of myeloproliferative neoplasms and prevalent in essential thrombocythemia and primary myelofibrosis.

TP53: p.Cys275Phe (missense), VAF 41.07%. Classified as Tier IID (variant of potential clinical significance) with prognostic relevance; TP53 mutations are described as a risk factor for progression to accelerated/blast phase in chronic-phase myeloproliferative neoplasms.

No clinically significant small insertions/deletions (INDELs) or copy number variants (CNVs) were detected in the remaining genes on the panel.

Discussion

This case illustrates an uncommon molecular profile of primary myelofibrosis (PMF) in a middle-aged woman, integrating clinical, histopathologic, cytogenetic, and next-generation sequencing (NGS) data. PMF usually presents in older adults and is driven by JAK2, CALR, or MPL mutations in about 90% of cases, with additional high-risk mutations modulating phenotype and prognosis. MPL W515 variants are established driver lesions that activate JAK–STAT signaling, while TP53 mutations occur in a small minority of PMF patients and

are linked to clonal evolution, leukemic transformation, and shortened survival.

Integration with existing literature

Reports on TP53-mutated PMF consistently emphasize their rarity but adverse biology. Large series have found TP53 mutations in roughly 1–4% of chronic-phase PMF, often enriched in patients with complex karyotypes or additional myeloid mutations and associated with higher rates of progression to acute myeloid leukemia and reduced overall survival. In contrast, this patient shows dual MPL (p.Trp515Leu) and TP53 (p.Cys275Phe) mutations with a normal 46,XX karyotype, underscoring that high-risk molecular lesions may precede or occur without overt cytogenetic evolution. Existing cytogenetic-based risk models for PMF categorize normal karyotype as favorable, but more recent integrated genomic studies highlight that TP53 and other high-risk mutations can override otherwise low-risk clinical or cytogenetic features.

The skeletal and abdominal imaging in this case—massive hepatosplenomegaly, diffuse bony sclerosis with focal lytic lesions— align with the described spectrum of PMF-related extramedullary hematopoiesis and bone remodeling. However, published imaging series typically do not correlate such findings with detailed NGS profiles, so this report adds clinicoradiologic granularity to the small body of literature on MPL- and TP53-co-mutated PMF. By documenting variant allele frequencies around 40% for both MPL and TP53, the NGS data also support a substantial clonal burden, echoing observations that TP53-mutant subclones often expand as disease progresses.

Key strengths of this case approach include

Comprehensive phenotyping: systematic correlation of symptoms, examination, laboratory indices, bone marrow histology, conventional karyotyping, and targeted NGS reflects current recommendations for integrated genomic evaluation in myeloid neoplasms.

Molecular precision: reporting exact MPL and TP53 variants with allele frequencies and AMP-tier classification allows comparison with emerging genotype-phenotype data and supports reproducible risk assessment.

Imaging–genotype linkage: detailed USG/CT description of hepatosplenomegaly and bone changes alongside molecular findings helps clinicians recognize radiologic patterns that should prompt extended genomic work-up in cytopenic splenomegaly.

Limitations

Should also be acknowledged. This is a single-patient observation, so causal inferences about the interaction between MPL and TP53 mutations and specific clinical features are hypothesis-generating only. Longitudinal follow-up, including clonal dynamics under therapy and at potential progression, is not yet available, limiting prognostic conclusions. Furthermore, the NGS panel did not capture all possible cooperating mutations (e.g., epigenetic or splicing genes not on the assay), so additional high-risk lesions may be present but undetected, as described in large MF genomic cohorts. Finally, the normal karyotype was based on a finite metaphase number; small subclones below the detection threshold of conventional cytogenetics cannot be excluded.

Conclusion

This case describes a middle-aged woman with primary myelofibrosis driven by an MPL p.Trp515Leu mutation

and a co-occurring TP53 p.Cys275Phe mutation, in the setting of a normal 46, XX karyotype. Integrated clinical, morphologic, cytogenetic and NGS assessment established the diagnosis of overt PMF and revealed a high-molecular-risk profile despite favorable cytogenetics, mirroring contemporary data that TP53 mutations, even as single-hit events, signal increased risk of progression and inferior outcomes in myelofibrosis. Such mutations may identify a subgroup at high risk for progression who could benefit from closer surveillance or early referral for allogeneic transplantation. For future research, integrative genomic and functional studies are needed to clarify how MPL-driven JAK–STAT activation interacts with TP53 pathway disruption to promote fibrosis, osteosclerosis, and leukemic transformation. Clinically, this case supports a paradigm in which PMF management shifts from morphology- and karyotype-based risk alone toward individualized strategies anchored in high-resolution genomic profiling.

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