Treatment-relevant misdiagnosis of autoimmune myelofibrosis

Autoimmune myelofibrosis (AIMF) remains an underrecognized entity. Over three decades of myeloproliferative neoplasm (MPN) practice at the Mayo Clinic (1996-2025), a total of 14,580 patients underwent evaluation for myelofibrosis (MF), among whom only 30 cases (0.2%) were diagnosed with AIMF. Bone marrow fibrosis is a quintessential feature of primary myelofibrosis (PMF), but it can also occur secondary to infections, autoimmune disorders or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasms, metastatic cancer, or toxic myelopathies.[1,2] Among these entities, AIMF presents a diagnostic challenge, particularly in the absence of a prior history of autoimmune disorder. In the current report, we describe four patients with AIMF, initially misdiagnosed both clinically and morphologically as PMF, leading to incorrect treatment or treatment recommendations.

After obtaining Institutional Review Board approval, the Mayo Clinic clinical database was queried to identify patients who underwent evaluation for MF and tested negative for JAK2/CALR/MPL mutations i.e. triple-negative cases. Bone marrow fibrosis was graded according to the European Consensus Classification System which recognized three grades (MF-1 to MF-3).[3] A total of 30 patients with AIMF were identified, of whom four were misdiagnosed as PMF; these cases are summarized in Table 1.

A 19-year-old Caucasian college student presented with a history of exertional intolerance along with epistaxis and menorrhagia. Complete blood count (CBC) revealed pancytopenia with hemoglobin of 3.5 g/dL, white blood cell count 5.1x10^9/L (2% circulating blasts), and platelet count of 20x10^9/L. Vitamin B12, folic acid, and iron studies were adequate. Bone marrow biopsy demonstrated cellularity of 95% with moderate granulocytic hyperplasia, megakaryocytes were markedly increased in number with atypia and occasional loose clusters; fibrosis grade MF-1 was noted. Cytogenetic analysis revealed a diploid karyotype, and next-generation sequencing (NGS) (47-gene myeloid panel) did not detect any pathogenic mutations. She was diagnosed with PMF presenting with transfusion-dependent anemia, and thrombocytopenia. Risk stratification was classified as high risk by Molecular International Prognostic Scoring System (MIPSS 70 plus version 2.0). She subsequently underwent a myeloablative matched-unrelated donor allogeneic stem cell transplant (ASCT). However, retrospective re-evaluation of the diagnosis because of her young age and acute presentation with severe anemia (3.5 g/dL), marked thrombocytopenia (20x10^9/L), normal leukocyte count, and negative results on all genetic studies including a comprehensive myeloid gene panel, raised doubts about the initial diagnosis of PMF. Accordingly, a bone marrow re-review was performed by four expert hematopathologists (Figure 1A, B). Key findings included a markedly hypercellular marrow with marked megakaryocytic hyperplasia and moderate erythroid hyperplasia. Megakaryocytes lacked the atypical features characteristically seen in PMF. Importantly, a benign lymphoid aggregate and a subtle interstitial lymphoid infiltrate were identified. Reticulin fibrosis was best classified as MF-1, and no osteosclerosis was present. From a morphological standpoint, a MPN was considered in the differential diagnosis; however, the severity of the cytopenias was disproportionate to the degree of marrow fibrosis. A correlative assessment of clinical, laboratory, molecular genetics, and pathological features ultimately favored a diagnosis of AIMF.

The second patient was a 22-year-old African-American female who also presented with severe anemia (hemoglobin 5.4 g/dL), a white blood cell count of 4.8x109/L, and a platelet count of 389x10^9/L. Bone marrow biopsy was hypercellular with mild megakaryocytic atypia, slight erythroid hyperplasia, and morphologically unremarkable granulopoiesis. Minimal increase in reticulin fibrosis (MF 0-1) was observed (Figure 1C, D). The MPN driver mutation panel was negative for *JAK2*V617F, *MPL*, and *CALR* mutations. Karyotype was normal and myeloid NGS did not identify any pathogenic mutations. An initial diagnosis of triple-negative PMF with transfusion-dependent anemia was made and ASCT was recommended. However, further investigations including a positive direct Coombs test, presence of anti-dsDNA, and elevated inflammatory markers, were consistent with a diagnosis of systemic lupus erythematosus (SLE)-induced AIMF. Regarding anemia management, prednisone, azathioprine, rituximab, and hydroxychloroquine, were ineffective, leading to strong consideration of ASCT. However, tacrolimus administered at 1 g twice daily rendered her transfusion-independent, and she has maintained an ongoing anemia response for over 7 months.

The third patient was a 19-year-old female who presented with fatigue and headaches and was found to have pancytopenia; hemoglobin 9.2 g/dL, white blood cell count 1.2x10^9/L (absolute neutrophil count 0.46x10^9/L), and platelet count 59x10^9/L. Bone marrow biopsy revealed a hypercellular marrow with morphologically unremarkable trilineage hematopoiesis, and mild to moderate increase in reticulin fibrosis (MF grade 1-2) (Figure 1E, F). No clonal abnormalities were identified on chromosome analysis or NGS. She was initially referred for ASCT for presumed newly-diagnosed PMF. However, further evaluation revealed a positive anti-nuclear antibody (ANA), elevated anti-dsDNA IgG (160 IU/mL) and

Table 1. Salient findings in four patients with autoimmune myelofibrosis initially misdiagnosed as primary myelofibrosis.

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical features Age/sex	 19/F	 22/F	 19/F	 31/M
Splenomegaly on imaging, cm	Splenomegaly 15	No splenomegaly	No splenomegaly	Splenomegaly 14.4
Autoimmune disease	Absent	Present	Present	Absent
Laboratory features Pancytopenia Transfusion-depedent anemia C-reactive protein, mg/L (Ref range, <5 mg/L) Direct Coombs test Anti-nuclear antibody U (Ref range, <1 U)	 Present Present ND Negative ND	 Present Present 125.2 Weak positive 11.8	 Present Absent 6.2 Weak positive 5.1	 Absent Present 153.3 negative < 1
Bone marrow findings Bone marrow cellularity (%) Reticulin fibrosis	 Hypercellular (95) MF-1	 Hypercellular (95) MF-1	 Hypercellular (90) MF-1-2	 Hypercellular (90) MF-2
Osteosclerosis Benign lymphoid aggregates Plasma cells in bone marrow	None Present $CD3^+$ T cells, $CD20^+$ B cells Not ↑	NR Absent Not ↑	NR Present $CD3^+$ T cells, $CD20^+$ B cells Not ↑	NR Present $CD3^+$ T cells, $CD20^+$ B cells Not ↑
Diagnostic considerations and treatmet Iniitial diagnosis Treatment recommendation	 PMF ASCT	 PMF ASCT	 PMF ASCT	 PMF Clinical trial ASCT

F: female; M: male; Ref: reference; PMF: primary myelofibrosis, ASCT: allogeneic stem cell transplant; ND: not done; NR: not reported.

anti-RNP IgG (2.3 U), and low complement C4 (9 mg/dL), consistent with SLE. These findings confirmed a diagnosis of secondary AIMF. Treatment with prednisone and rituximab (1 g) was initiated, leading to rapid resolution of cytopenias. The fourth case involved a 31-year-old Caucasian gentleman who presented with syncope secondary to severe anemia (hemoglobin 5.5 g/dL). His white blood cell count was within normal limits (6.4x10^9/L) and platelet count was elevated (574x10^9/L). Peripheral smear showed no evidence of leukoerythroblastosis. Anemia work-up revealed adequate ferritin (486 mcg/L) and erythropoietin (499 mIU/L) levels. Bone marrow examination demonstrated a hypercellular bone marrow (90%) with increased trilineage hematopoiesis, <5% marrow blasts, no circulating blasts and moderate reticulin fibrosis (MF-2). Cytogenetic studies and NGS revealed no clonal abnormalities. The patient was initially diagnosed with triple-negative PMF, categorized as MIPSS 70 plus version 2.0 high risk and was enrolled in a clinical trial. After an exaggerated and unexpectedly favorable and unmaintained response to treatment, the possibility of AIMF was considered. Pathology re-review revealed mostly unremarkable megakaryocyte morphology and distribution, features most consistent with AIMF (Figure 2A, B). A repeat bone marrow examination demonstrated a normocellular

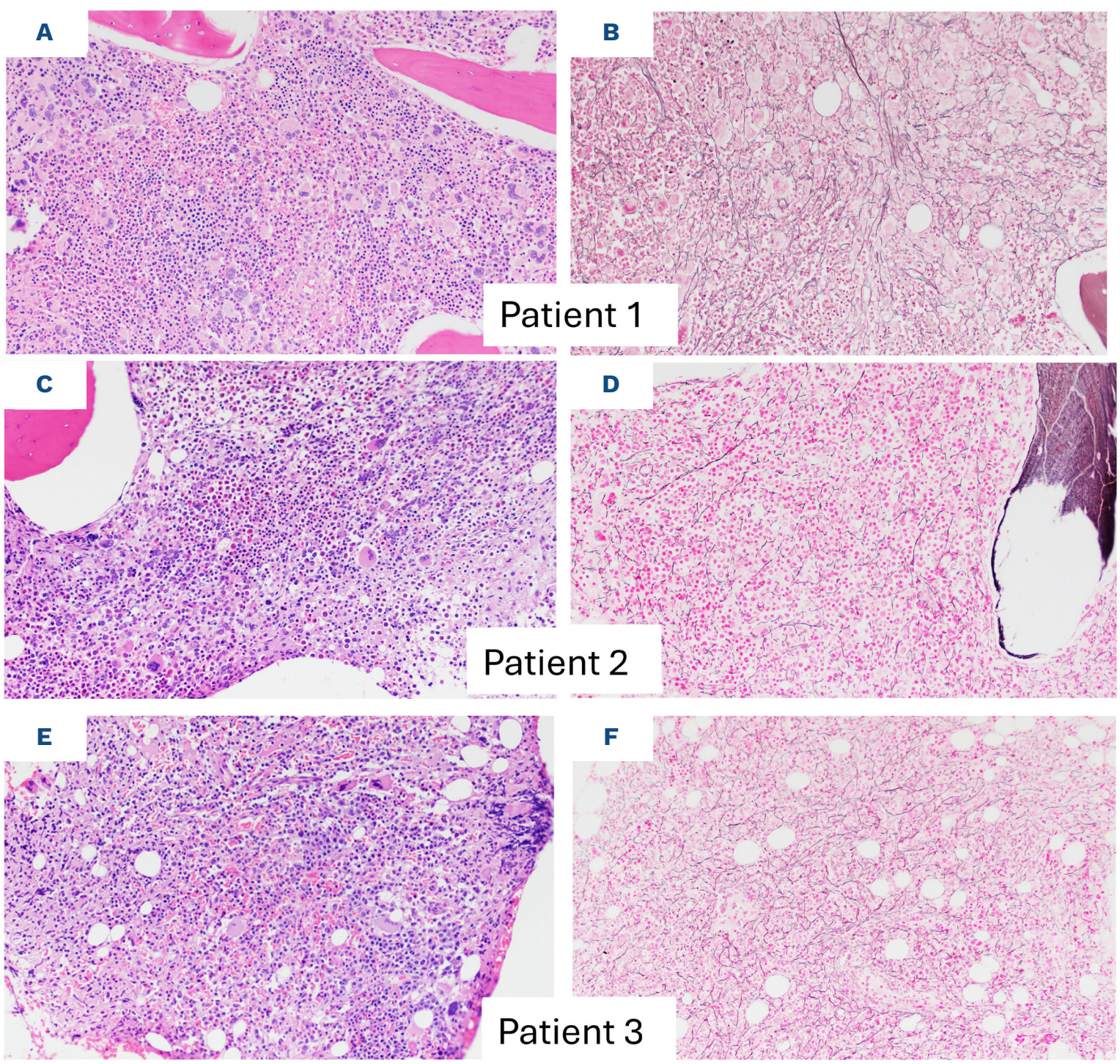

Figure 1. Bone marrow core biopsy findings and reticulin stain at the diagnosis of autoimmune myelofibrosis in three different patients (patient 1: panels A, B; patient 2: panels C, D; patient 3: panels E, F). (A-E) The bone marrow core biopsy findings from all 3 patients (A, C, E) demonstrate a markedly hypercellular bone marrow with increased trilineage hematopoiesis, degrees of cellular streaming (indicative of the presence of reticulin fibrosis) and megakaryocytic atypia including the presence of hyperchromatic and hyperlobated nuclei (C, E) and megakaryocytic hyperplasia with loose clusters and hyperlobulation (A). The reticulin stains from the 3 different patients show a range of reticulin fibrosis - no significant increase in reticulin fibrosis/focal mild reticulin fibrosis (MF-1) (D), moderately increased reticulin fibrosis (MF-2) (B), and a mild increase in reticulin fibrosis (MF-1) (F). (A, C, E) hematoxylin and eosin stain, 200x magnification; (B, D, F) reticulin stain, 200x magnification.

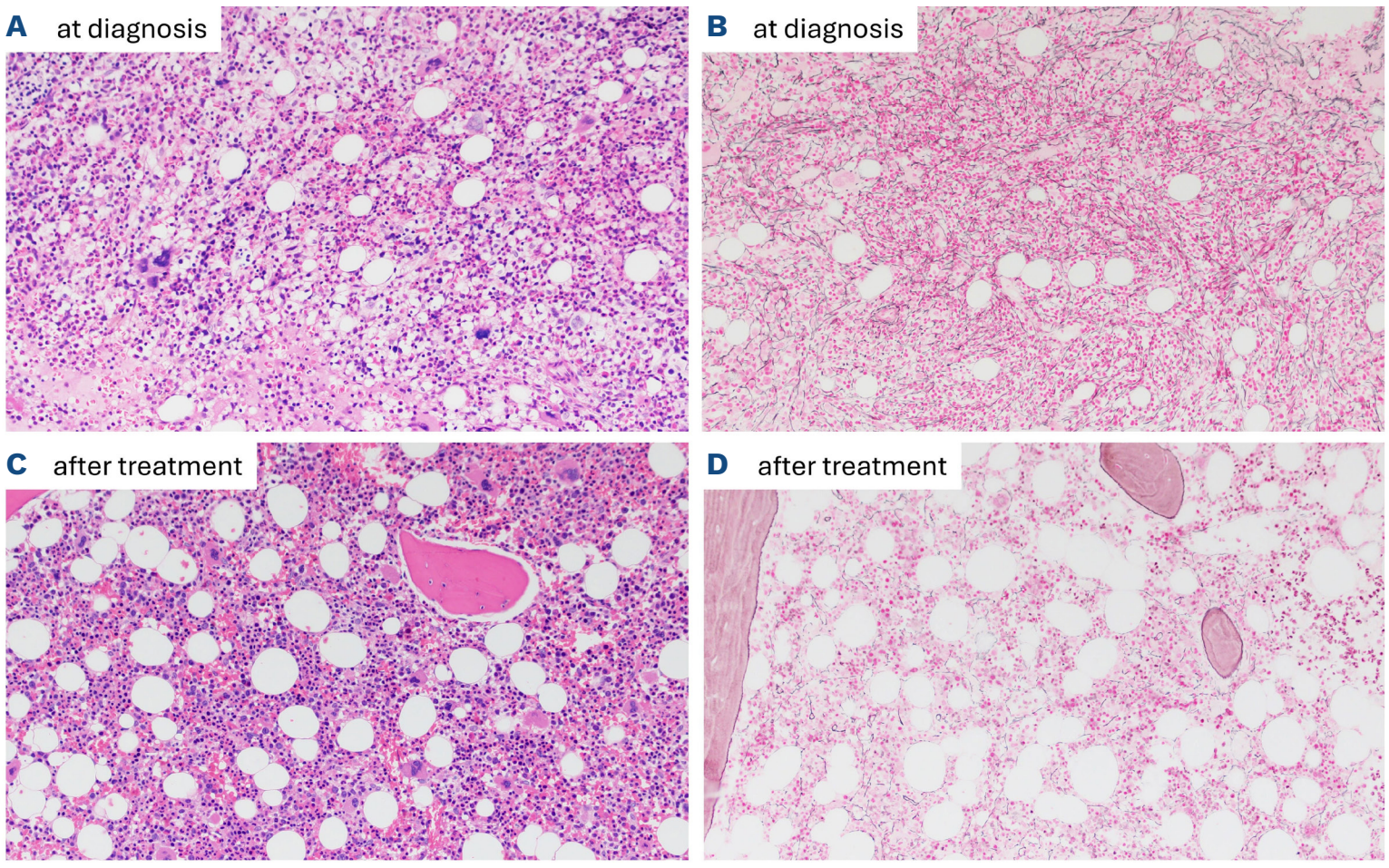

Figure 2. Bone marrow core biopsy findings at diagnosis (A, B) and after treatment (C, D) in a 31-year-old male patient diagnosed with autoimmune myelofibrosis. (A, B) Photographs at diagnosis illustrate a markedly hypercellular bone marrow for age (greater than 95% cellularity) with slight megakaryocytic hyperplasia with small clusters and occasional forms with hyperchromatic and atypical nuclear features. (B) Reticulin stain highlights a mild increase in reticulin fibrosis (MF-1). (A) Hematoxylin and eosin stain, 200x magnification; (B) reticulin stain, 200x magnification. (C, D) Photographs after treatment illustrate a normocellular bone marrow for age (60-70%) with intact trilineage hematopoiesis and resolution of the clusters and atypical morphologic features of the megakaryocytes as seen at diagnosis. A reticulin stain highlights no increase in reticulin fibrosis (MF-0). (C) Hematoxylin and eosin stain, 200x magnification; (D) reticulin stain, 200x magnification.

marrow with morphologically unremarkable trilineage hematopoiesis, no increase in blasts, and minimal reticulin fibrosis (MF-0 to MF-1) (Figure 2C, D).

These cases underline the importance of careful clinico-pathological correlation in distinguishing AIMF from PMF and MPN-unclassifiable (MPN-U).[4,5] Notwithstanding several overlapping pathological features, there are several diagnostic cues available to both hematopathologists and clinicians. From the diagnostic perspective, close attention to the presenting clinical features cannot be overemphasized. In cases of bone marrow fibrosis, it is important to correlate peripheral blood counts with characteristic features of MPN and maintain a high index of suspicion when findings are atypical. The presence of benign lymphoid aggregates and an interstitial lymphoid infiltrate in the bone marrow are supportive features of AIMF.[6] It is also important to recognize that lineage hyperplasia may result either from an underlying bone marrow proliferative neoplasm or as a reactive response to peripheral cell line destruction - often accompanied by atypia due to rapid cellular production. In the current era of widespread molecular testing, a re-evaluation of bone marrow morphology is recommended when molecular findings are incongruent with pathology, particularly in younger patients with negative NGS myeloid panel, given that clonality through cytogenetics or NGS is a key feature of PMF. It should be noted that rarer mutations may not be detected on a 47-gene myeloid panel. From a therapeutic standpoint, the prognosis for patients with AIMF as opposed to PMF is favorable. The majority of cases respond well to corticosteroids and rituximab therapy leading to hematologic improvement and bone marrow responses.[7-11] Taken together, our findings underscore the importance of accurate distinction between underlying causes of MF (AIMF *vs*. PMF or MPN-U), through integration of morphological findings with genomic profiling and clinical history, in order to avoid inappropriate treatments that may lead to both physical and psychological harm to patients. Future studies should explore mechanisms of AIMF, evaluate biomarkers of disease severity and investigate the role of anti-fibrotic agents.

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Contributions

NG wrote the manuscript and provided patient care. KKR, AO, DSV, CAH provided pathological expertise. AT edited the maunscript and provided patient care.

Data-sharing statement

Original data will be shared. Please contact the corresponding author.

References

1. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
2. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(5):801-821.
3. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90(8):1128-1132.
4. Amel Riazat-Kesh YJR, Maraveyas A, Martin L, Tremblay D. An overlooked mimic? Autoimmune myelofibrosis - A scoping review of the literature. Eur J Haematol. 2023;111(5):706-714.
5. Winer A, Bains A. Autoimmune panmyelosis with myelofibrosis. Blood. 2019;134(15):1269.
6. Bass RD, Pullarkat V, Feinstein DI, Kaul A, Winberg CD, Brynes RK. Pathology of autoimmune myelofibrosis. A report of three cases and a review of the literature. Am J Clin Pathol. 2001;116(2):211-216.
7. Gangat N, Reichard K, Orazi A, Tefferi A. Autoimmune myelofibrosis: A Mayo Clinic series of 22 patients. Br J Haematol. 2024;205(3):956-960.
8. Philippe M, Emilie C, Zahir A, et al. Clinical spectrum and therapeutic management of auto-immune myelofibrosis: a nation-wide study of 30 cases. Haematologica. 2020;106(3):871-874.
9. Pullarkat V, Bass RD, Gong JZ, Feinstein DI, Brynes RK. Primary autoimmune myelofibrosis: definition of a distinct clinicopathologic syndrome. Am J Hematol. 2003;72(1):8-12.
10. Vergara-Lluri ME, Piatek CI, Pullarkat V, et al. Autoimmune myelofibrosis: an update on morphologic features in 29 cases and review of the literature. Hum Pathol. 2014;45(11):2183-2191.
11. Piatek CI, Vergara-Lluri ME, Pullarkat V, et al. Autoimmune myelofibrosis: clinical features, course, and outcome. Acta Haematol. 2017;138(3):129-137.