

Acquired Hemophilia A Associated with Post-Essential Thrombocytopenia Myelofibrosis: A Rare Autoimmune Bleeding Complication

Post-Esansiyel Trombositemi Miyelofibrozisi ile İlişkili Edinsel Hemofili A: Nadir Bir Otoimmün Kanama Komplikasyonu

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To the Editor,

Acquired hemophilia A is a rare autoimmune bleeding disorder caused by autoantibodies directed against factor VIII, with an estimated annual incidence of 1.48 cases per million population and a reported mortality rate of approximately 20% [1,2]. Patients typically present with sudden severe bleeding and isolated prolongation of activated partial thromboplastin time (aPTT) without a prior history of a coagulation disorder [3]. Although most cases are idiopathic, acquired hemophilia A may rarely occur in association with malignancies or autoimmune diseases [4]. The development of acquired hemophilia A in patients with myeloproliferative neoplasms is exceedingly rare [5].

A 64-year-old male with *JAK2V617F*-positive essential thrombocytopenia diagnosed in 2018 presented in March 2025 with hematuria and extensive ecchymosis after peripheral intravenous cannulation. He had no previous history of abnormal bleeding. Laboratory evaluation revealed prolonged aPTT, mildly prolonged prothrombin time, and elevated international normalized ratio (Table 1). Following fresh frozen plasma washout, coagulation studies again demonstrated prolonged aPTT. Mixing studies showed correction at 0 hours with prolongation at 2 hours, consistent with the presence of an inhibitor. Factor VIII activity was decreased (12.2%) and the factor VIII inhibitor titer was elevated (32 BU/mL) (Table 1). Screening for solid malignancies, including whole-body computed tomography, upper gastrointestinal endoscopy, and colonoscopy, revealed no evidence of malignancy. Antinuclear antibody/extractable nuclear antigen antibody profiles, anti-dsDNA antibodies, and serologic testing for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus were negative.

Treatment with methylprednisolone at a dose of 1 mg/kg was initiated. In response to recurrent oral bleeding, hemostasis was achieved with three doses of recombinant activated factor VII at 90 µg/kg. The patient had been under follow-up for essential thrombocytopenia since 2018. Laboratory evaluation revealed anemia and elevated lactate dehydrogenase (LDH) levels. Computed tomography showed a spleen length of 12.5 cm, and mild splenomegaly was detected on physical examination.

Bone marrow aspirate smear and imprint preparation were hypocellular and poor in particles. Numerous platelet aggregates and dysplastic megakaryocytes were observed. Megakaryocytes showed a marked increase, clustering, and abnormal localization; some were large with hyperlobulated morphology. Bone marrow biopsy demonstrated grade II-III reticulin fibrosis, collagen deposition, and marked megakaryocytic atypia. Based

Table 1. Laboratory parameters at diagnosis of acquired hemophilia A, including coagulation profile, factor VIII activity, inhibitor titer, hemoglobin, and LDH levels with corresponding reference ranges.

Laboratory parameter	Value at diagnosis	Reference range	Interpretation
aPTT (s)	53.3	22.5-31.3	Increased
PT (s)	15.2	10.9-14.7	Slightly increased
INR	1.34	0.9-1.2	Increased
Factor VIII activity (%)	12.2	70-150	Decreased
FVIII inhibitor (BU/mL)	32	<0.6	Increased
Hemoglobin (g/dL)	9.0	13.0-17.0*	Decreased
LDH (U/L)	287	135-225	Increased

aPTT: Activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; LDH: lactate dehydrogenase; *: reference range for male adults.

on a history of essential thrombocythemia, the fulfillment of the major criterion of grade II-III fibrosis, and fulfillment of three minor criteria (anemia, splenomegaly, and elevated LDH), a diagnosis of post-essential thrombocythemia myelofibrosis was established.

Activated prothrombin complex concentrate was administered prior to bone marrow biopsy. Forty-eight hours after its discontinuation, mucosal bleeding recurred, but it resolved following additional activated prothrombin complex concentrate administration. No thrombotic complications were observed. After 3 weeks of steroid therapy, factor VIII activity increased, and inhibitor titers declined and became undetectable (Figure 1). At the time of cyclophosphamide initiation, factor VIII activity was approximately 25%. Oral cyclophosphamide was administered at a dose of 1.2 mg/kg and continued for 8 weeks. In accordance with international recommendations [3], escalation

of immunosuppressive therapy was considered appropriate due to persistently suboptimal factor VIII levels despite inhibitor negativity. During a follow-up period of 9 months, inhibitor titers remained persistently negative, factor VIII levels stabilized between 10% and 20%, and no further bleeding episodes were observed. Myeloproliferative neoplasms rarely lead to factor VIII inhibitor development and only a limited number of cases have been reported [6,7,8,9]. Previously reported cases are summarized in Table 2. Reduced regulatory T-cells and increased proinflammatory cytokines in myelofibrosis may contribute to immune dysregulation [5,10]. In the present case, the exclusion of other secondary causes, together with the diagnosis of post-essential thrombocythemia myelofibrosis, suggests that inhibitor development may be related to the underlying hematological disorder. Acquired hemophilia A should be considered in patients with myelofibrosis presenting with unexplained bleeding and isolated prolonged aPTT.

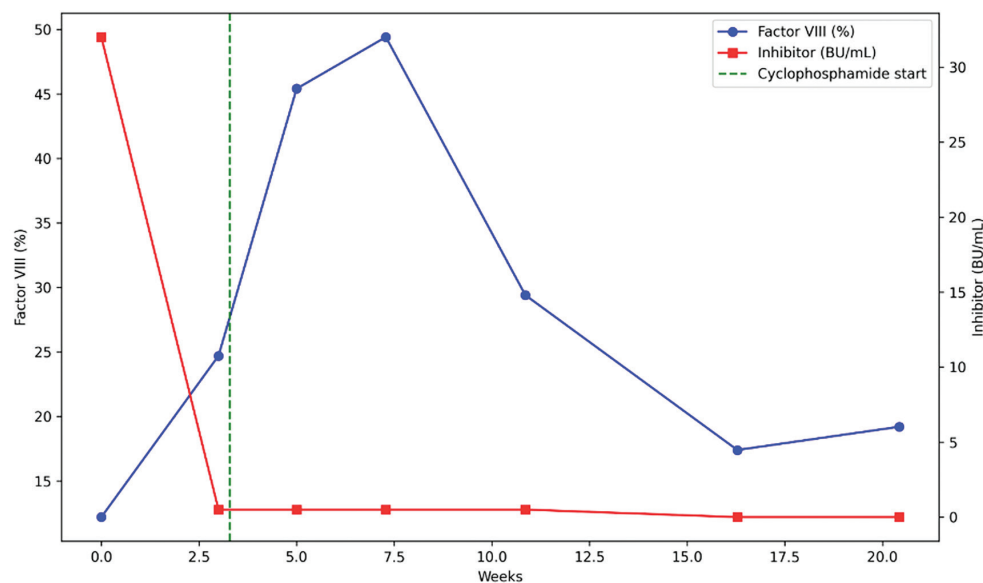


Figure 1. Trend of factor VIII activity and inhibitor titer during treatment. Factor VIII activity (left y-axis) and FVIII inhibitor titer (right y-axis) are shown over time in weeks. Inhibitor titers rapidly declined following corticosteroid therapy and became undetectable, whereas factor VIII activity initially increased and subsequently stabilized at lower levels during follow-up. Cyclophosphamide was initiated at week 3 due to persistently low factor VIII levels despite inhibitor negativity.

Table 2. Reported cases of acquired hemophilia A associated with myeloproliferative neoplasms.

Authors	Age	Sex	MPN subtype	Treatment	Outcome
Wrobel et al. [6]	66	Male	Myelofibrosis (leukemic transformation)	Steroid + rFVIIa + aPCC + Rituximab + Azacytidine	Remission
Prabhu et al. [7]	59	Male	Post-PV myelofibrosis	Prednisolone	Remission
Kremyanskaya and Aledort [8]	74	Female	Essential thrombocythemia (JAK2+)	Prednisone + aPCC (FEIBA®)	Remission
Mori et al. [9]	69	Female	Essential thrombocythemia	Supportive (RBCs + FFP)	Death

MPN: Myeloproliferative neoplasm; PV: polycythemia vera; rFVIIa: recombinant activated factor VII; aPCC: activated prothrombin complex concentrate; RBCs: red blood cells; FFP: fresh frozen plasma.

Keywords: Acquired hemophilia A, Factor VIII inhibitor, Myeloproliferative neoplasms, Post-essential thrombocythemia myelofibrosis, Autoimmune bleeding disorder, Bypassing agents

Anahtar Sözcükler: Edinsel hemofili A, Faktör VIII inhibitörü, Miyeloproliferatif neoplazmlar, Post-esansiyel trombositemi miyelofibrozis, Otoimmün kanama bozukluğu, Bypass edici ajanlar

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., D.Ç.P., Z.D., F.Ş.; Concept: S.K., D.Ç.P., F.Ş.; Design: S.K., D.Ç.P., F.Ş.; Data Collection or Processing: S.K., D.Ç.P.; Analysis or Interpretation: S.K., D.Ç.P., Z.D.; Literature Search: S.K., D.Ç.P., Z.D.; Writing: S.K., D.Ç.P., Z.D., F.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Received/Geliş tarihi: March 2, 2026

Accepted/Kabul tarihi: April 10, 2026

Epub: April 10, 2026

DOI: 10.4274/tjh.galenos.2026.84769



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