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Acquired hemophilia A as rare complication in course of myeloproliferative syndrome

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Introduction

Acquired hemophilia A (AHA) is an autoimmune disorder in which antibodies against factor VIII (FVIII) are produced, decreasing its activity. This leads to massive bleeding. AHA often affects people over 60 years of age, in 11% of cases it accompanies solid tumors, while hematological malignancies and predominant lymphoproliferative malignancies account for 3.8% of cases. The clinical manifestation is spontaneous bleeding, and the mortality rate reaches 20% [1]. AHA has been estimated to occur in 1.5 per 1,000,000 people, although the latest research suggests that this percentage may in fact be 2–3 times higher [2]. Clinically, AHA manifests as sudden bleeding; laboratory tests show isolated prolongation of activated partial thromboplastin time (APTT), a decrease in FVIII activity, and the presence of an inhibitor [measured in Bethesda units (BU)] [2, 3]. A 1-to-1 plasma mixing test is used in diagnostics, wherein incomplete or no correction is observed [4]. Myeloproliferative neoplasms (MPN) include essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and pre-fibrotic PMF (pre-PMF). MPN are characterized by the presence of the JAK2 *V617F* mutation [5, 6]. MPN is a rare disease (2.17 cases/100,000) [7], and the coexistence of AHA in the course of MPN has only rarely been described in the literature. This report focuses on the diagnostic dilemmas of AHA in a patient with massive bleeding and a history of polycythemia vera.

Case report

A 76-year-old man with polycythemia vera being treated with hydroxycarbamide and anagrelide visited his family doctor because of a subcutaneous and intramuscular hemorrhage on the right side of his trunk. Due to enlargement of the hematoma, the patient was referred to the emergency department of his district hospital, where imaging tests were performed. Chest tomography showed hyperdense thickening (max. 6–7 cm) of the soft tissues, i.e. lateral and posterior parts of the chest, abdominal cavity, and pelvis. The image suggested the presence of an extensive intramuscular and subcutaneous hematoma.

The patient began to become anemic, despite numerous transfusions of red blood cell concentrate and plasma, demonstrating resistance to the transfusions, and the growth of clinical bleeding symptoms with a further decrease in hemoglobin (data in the table) and extending the time to APTT to 60 s. A control chest tomography showed (Figure 1) enlargement of the dimensions of the hematoma. In addition, the patient presented hepatosplenomegaly. Laboratory tests showed reduced FVIII activity with an inhibitor titer of 0.6 BU, allowing the AHA diagnosis.

The patient was treated with inhibitor eradication therapy: cyclophosphamide at 1 mg/kg body weight and prednisone at 1 mg/kg body weight. Due to thrombocytosis and a history of a stroke, activated prothrombin complex concentrate (aPCC), which is associated with a slightly higher prothrombotic risk, was not administered. Treatment with

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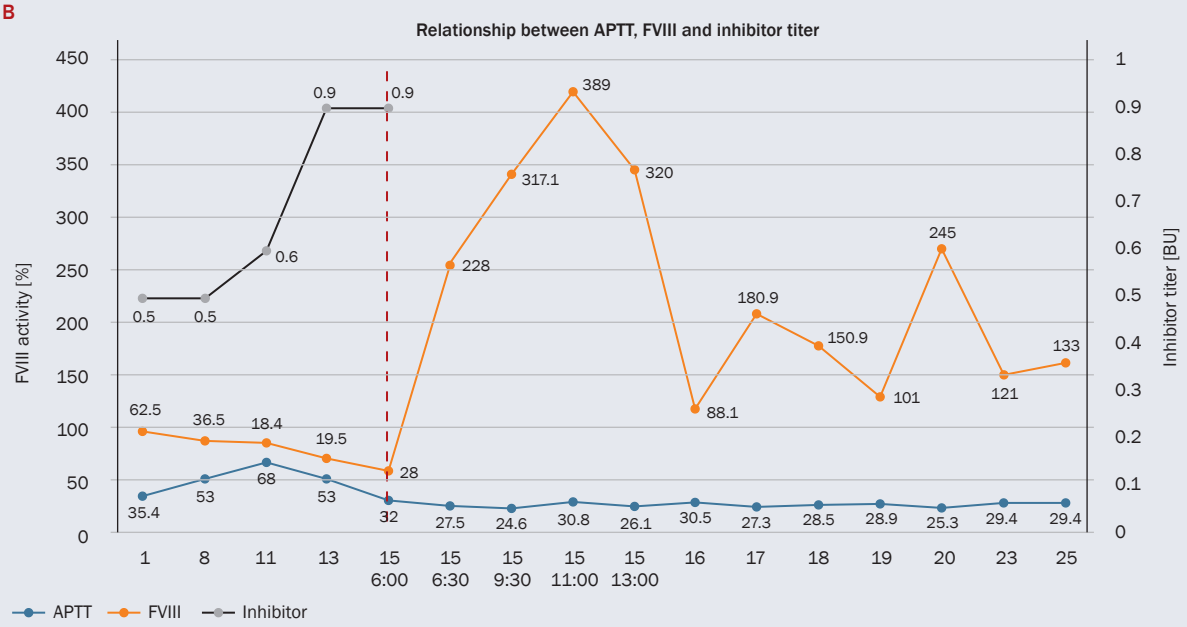
A

Day	WBC [10^9/L]	Hb [mmol]	PLT [10^9/L]	FFP [U]	RBCC [U]
1	35.36	6.1	733		
2	32.07	6.0	741		
3	27.23	5.5	623		2
4	27.00	6.3	647		
5	28.34	5.8	679		
6	30.19	4.5	701	2	4
7	34.17	4.2	678	2	4
8	33.57	5.1	708		
9	31.67	4.7	701	2	3
11	32.87	4.4	687	2	2
13	30.00	5.5	699	4	

FIX	FXI
99.80%	62.80%
N: 63–150	N: 65–150

B



C

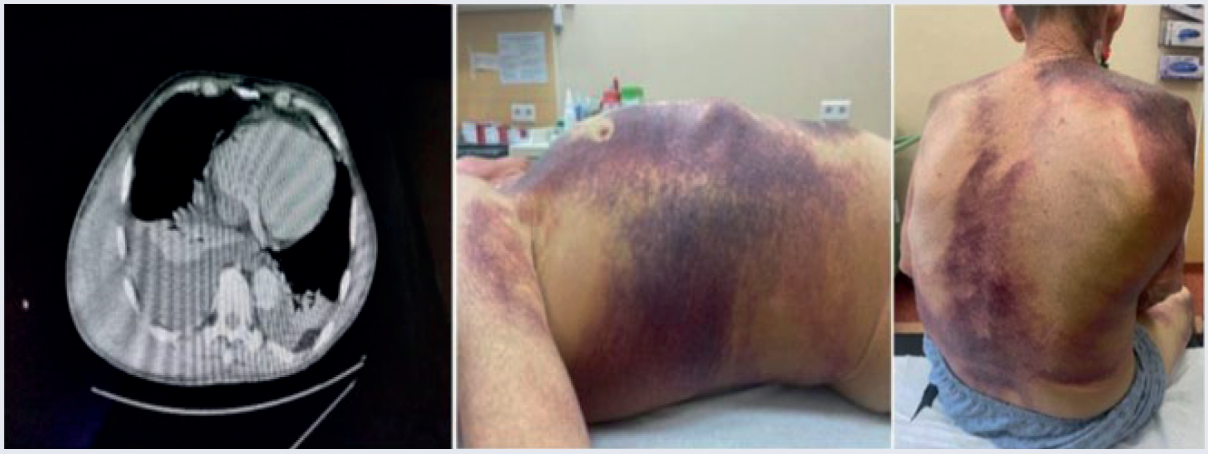


Figure 1A–C. Relationship between activated partial thromboplastin time (APTT), factor VIII (FVIII) activity, and inhibitor titer. Tables show test results (morphology, factor activity and number of transfusions); WBC — white blood cells; Hb — hemoglobin; PLT — platelets; FFP — fresh frozen plasma; RBCC — red blood cell concentrate; FIX — factor IX; FXI — factor XI; rpFVIII — porcine factor VIII

recombinant factor VII (FVII) was initiated via injection — repeated doses of 90 µg/kg body weight were introduced as life-saving therapy. Before recombinant porcine factor VIII administration, the anti-recombinant porcine factor VIII (anti-rpFVIII) inhibitor titer was determined to be 0.9 BU. Then, rpFVIII was presented at an initial dose of 200 U/kg

body weight. Finally, we adjusted the quantity to 80 U/kg body weight depending on factor VIII activity above 100%, as preparation for invasive surgery, obtaining a gradual increase in FVIII activity. The imagefrom a trepanobiopsy confirmed the presence of post-PV myelofibrosis. The presence of JAK2 mutations was demonstrated. In the course of hospitalization, gradual absorption of the hematoma was observed, and the inhibitor-eradicating treatment was reduced.

RpVIII has high hemostatic efficiency and a low risk of thromboembolic complications. Therefore, rpVIII is used as rescue therapy in AHA patients, regardless of age and comorbidities [8]. Due to the patient's progression, a ruxolitinib treatment program has been included in the treatment, and the inhibitor is improving, gaining improvement in the field of bleeding control.

Discussion

Single cases of AHA in the course of a myeloproliferative syndrome have been reported in literature reviews. Biss et al. [9] described the case of a 71-year-old patient with acquired FVIII inhibitor with an inhibitor titer of 9 BU and manifesting massive bleeding. The accompanying myeloproliferative syndrome was characterized by splenomegaly and erythropoiesis disorders [9]. Vener et al. [10] described the case of a 42-year-old patient with diagnosed PV and AHA who had intramuscular bleeding and a massive hematoma of the retroperitoneal space. Studies showed an uncorrected APTT prolongation in the mixed plasma test and an inhibitor titer of 90 BU [10]. Epidemiological data shows that PV, ET, and primary myelofibrosis occur in 0.84, 1.03, and 0.47 cases per 100,000, respectively [7].

On the basis of the diagnostic difficulties in the presented, rarely reported, case of AHA in the course of post-PV myelofibrosis, the successful preparation of the rpVIII before trepanobiopsy allowed us to confirm the diagnosis of Philadelphia-negative myeloproliferative neoplasm.

Article information and declarations

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Author contributions
PG — manuscript preparation. EW — data collection, laboratory tests. JRM — study design, coordination, conceptualization, language edition, final approval. MS — data collection.

Conflict of interests
The authors declare no conflict of interests.

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