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Case Report

Giant Retroperitoneal Hematoma-A Life-Threatening Complication in a Young Patient with Type A Hemophilia Presenting with Inhibitors: Case Report

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Abstract

Spontaneous retroperitoneal hemorrhage is a rare complication in patients with severe type A hemophilia. The diagnosis is made based on high clinical suspicion in the context of an existing pathology with predisposing potential, such as congenital hemophilia. This type of bleeding is associated with a high rate of morbidity and mortality secondary to massive bleeding, and hemostasis is a challenge in hemophilic patients who present it. We report the case of a 19-year-old patient diagnosed with a severe form of hemophilia, who developed inhibitors and suffered a giant retroperitoneal hematoma spontaneously. The patient was treated with active recombinant factor VII according to the therapeutic protocol. His response to the hemostatic treatment was favorable and he was safely discharged after 16 days of hospitalization. The rarity of these life-threatening hemorrhagic complications and the difficulties in achieving hemostasis justify their reporting in the international literature.

Keywords: Type A haemophilia; Coagulation anti-factor VIII antibodies; Retroperitoneal hematoma; Active recombinant factor VII

Abbreviations: **rFVIIa:** active recombinant factor VII; **Hb:** Haemoglobin; **WBC:** White Blood Cells; **PLT:** Platelets; **apTT:** activated partial Thromboplastin Time

Introduction

Retroperitoneal hemorrhage is defined as an accumulation of blood in the retroperitoneal space; spontaneous forms are rare and may occur in the context of congenital coagulopathies such as type A hemophilia, type B hemophilia, or von Willebrand disease [1-3]. The literature on this type of bleeding is limited. However, other etiologies of spontaneous retroperitoneal hemorrhage are cited and include the rupture of retroperitoneal organs, antithrombotic, anticoagulant, or fibrinolytic drugs, renal and adrenal invasive or metastatic tumors, aneurysms of the major blood vessels, as well as iatrogenic and idiopathic causes [4-11]. The physiopathology of retroperitoneal hematomas is not fully understood and, as such, optimal management is a challenge. Their occurrence may be due to atherosclerotic manifestations [12,13]; another mechanism involved could be the stretching of the sheath of intraabdominal muscles during physical exertions such as cough, which has been reported in cases of patients with severe hemophilia [2,5,14,15]. The diagnosis of spontaneous retroperitoneal hemorrhage is usually prompted by high clinical suspicion in the context of a preexisting condition which creates a predisposition to this type of bleeding, such as congenital hemophilia.

The production of inhibitors in such patients is a major problem, as it may lead to severe complications and even threaten life, especially in cases of severe type A hemophilia. The incidence of inhibitor production in greater in type A hemophilia compared to type B, as well as in patients previously treated with various coagulation factors; increasing age is also a contributing element [16]. Statistical data has shown that 23-33% of patients with severe type A hemophilia will present substantial titers of inhibitors secondary to repeated substitution therapy with coagulation factor VIII. In moderate and mild forms of hemophilia, the rate is lower [16,17]. The management of patients with hemophilia who develop inhibitors must address two objectives: stopping the bleeding and neutralizing the inhibitors. In recent decades, treatment has consisted in the administration of active recombinant factor VIIa (rFVIIa, NovoSeven®), a by-pass agent which acts on the extrinsic coagulation pathway, facilitating the formation of thrombin and stable fibrin clots [16]. This type of coagulation factor is frequently used to control bleeding in the context of surgical interventions on adults with severe type A hemophilia who present inhibitors [16,18]. Numerous studies have proven the safety and efficacy of active recombinant factor VII (rFVIIa), including for patients who are concurrently administered antifibrinolytic agents [19,20-22]. The usual active recombinant factor VII (rFVIIa) dose is 90 µg/kg of body weight every 2-4 hours. Alternatively, the administration of a single large dose of 270 µg/kg of active recombinant factor VIIa (rFVIIa) appears to be equally effective and with a similar safety profile [23-25].

Case Report

We present the case of a young, 19-year-old patient known to the Hematology Department of the Regional Emergency Hospital "St. Spiridon" Iași following his diagnosis of severe type A hemophilia (factor VIII activity level of less than 1%, reference range 50-150%) since the age of 8 months. The patient presented at the Emergency Department with diffuse abdominal pain especially in the lower abdominal area, irradiating posteriorly. The symptoms had started two days before and had aggravated in the past 12 hours. The patient was also known to be suffering from chronic arthropathy in the right knee associated with relative motor deficit in the right leg, for which he was monitored regularly at the Orthopedics Department of the same Emergency Hospital. On admission, the clinical examination revealed that the patient was in serious condition, hemodynamically unstable, with sclerotegumentary pallor, high blood pressure (systolic blood pressure= 95 mmHg), tachycardia (heart rate = 120 beats/min), tachypnea (respiratory rate = 22 breaths/min), abdominal distension and sensitivity upon both superficial and deep palpation, mobility slightly hindered by breathing movements, and macroscopic hematuria.

The blood test samples were processed urgently, and the results were: hemoglobin (Hb) 8.9 g/dl, white blood cells (WBC count) 27.360/mmc, platelets (PLT) 355.000/mmc, activated partial thromboplastin time (apTT) 109.1 sec. And abdominal ultrasound was carried out and revealed a non-homogenous buildup of fluid in the right hypochondrium (192/85/165 cm, 1224 cm^3), and no fluid in the Morrison's pouch and in the pouch of Douglas. The patient was therefore diagnosed with giant retroperitoneal hematoma and hemoperitoneum. The patient was admitted for emergency laparotomy with peritoneal lavage, after which he was transferred to Intensive Care Unit in critical condition. He was administered substitution treatment with coagulation factor VIII at 12-hour intervals, according to the protocol, in order to maintain 100% factor VIII. Despite the initial drop, the level of activated partial thromboplastin time (apTT) resumed its escalation (see Table 1).

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
109.1 sec	51.7 sec	40 sec	50.2 sec	63.5 sec	126.6sec

Table 1: The level of apTT during the first 6 days of hospitalization.

This pattern of activated partial thromboplastin time (apTT) values (relative to the reference range of 28-38) in spite of the

substitution treatment with coagulation factor VIII prompted the suspicion that the patient's body was producing anti-coagulation antibodies. The hypothesis was confirmed when antibody titration on day 7 of hospitalization revealed very high levels of anti-factor VIII antibodies (573.4 Bethesda units/ml). Subsequently, the treatment was adjusted to include by-pass agents in order to stop the hemorrhagic syndrome and neutralize the inhibitors. To achieve the first objective, the patient was given 90 µg/kgbw of active recombinant factor VIIa (rFVIIa) every 2-4 hours for 16 days until the bleeding stopped. For the latter, we administered immunosuppressive treatment with corticosteroids and cyclophosphamide. The new treatment led to the gradual decrease of activated partial thromboplastin time (apTT) values and the normalization of hematological parameters (see Table 2).

	Day 7	Day 8	Day 10	Day 12	Day 13	Day 14	Day 15	Day 16
Hb (g/dl)	9.3	9	9.2	9.8	10.2	11.3	12.3	13.6
WBC	12,200	9,600	6,700	6,160	5,080	4,800	5,920	7,830
PLT	3,79,000	3,36,000	3,57,000	3,60,000	3,79,000	3,99,000	3,56,000	3,71,000
apTT (sec)	145.5	109.4	107.8	105.8	102.1	102.5	98.7	95.5

Table 2: The paraclinical evolution in response to adjusted rFVIIa therapy.

The ultrasound scans done during the hospitalization and treatment period showed the slow but favorable reduction in size of the retroperitoneal hematoma, as can be seen in Table 3 below.

	Day 1	Day 7	Day 11	Day 14	Day 16
Size of hematoma	192/85/165 mm	162/80/149 mm	137/82/95 mm	115/69/106 mm	115/79/84 mm

Table 3: The ultrasound appearance of the size of the retroperitoneal hematoma during hospitalization.

After the 16th day of treatment, the patient was discharged in a good general state, with a prescription of continued corticotherapy in small doses and the recommendation to present for intermittent prophylactic treatment with rFVIIa. The patient complied and, 8 weeks later, he returned for intermittent prophylaxis with 90 µg/kgbw of active recombinant factor VIIa (rFVIIa) 3 times a week. The size of the hematoma was monitored after discharge at 2-month intervals until the complete resorption was noted after 6 months of treatment (see Table 4).

	After	After	After	After
	2 months	4 months	6 months	9 months
Size of hematoma	80/65 mm	60/57 mm	No free fluid in the peritoneal cavity	No free fluid in the peritoneal cavity

Table 4: The ultrasound appearance of the retroperitoneal hematoma after discharge.

Regarding the level of inhibitor production, repeated titration showed a gradual decline down to 11.4 BU (see Table 5).

On diagnosis	After 2 months	After 6 months	After 9 months
573.4 Bethesda units/ml	358.4 Bethesda units/ml	65 Bethesda units/ml	11.4 Bethesda units/ml

Table 5: The evolution of inhibitor titer levels.

Discussion

It is well known that patients with moderate to severe type A hemophilia are more predisposed to developing anti-factor VIII antibodies [26]. This is attributed to a range of factors among which genetic mutations, ethnicity, aging, as well as exposure to treatment [27-30]; the case of our patient, who had been exposed to treatment for over 70 days, support this hypothesis. The spontaneous occurrence of a giant hematoma in such a young patient (19 years old) is rare even when considered internationally. In addition, achieving hemostasis is extremely difficult and elicits a guarded prognosis. Although the mortality rate secondary to such complications is high, our patient

responded very well to the hemostatic treatment administered in the doses recommended by the therapeutic guides (90 μg/kgbw of active recombinant factor VIIa (rFVIIa) every 2-4 hours until the bleeding stops) [26]. Given the substantial financial costs of the treatment and the large number of tubes used, as well as the unpredictability of the hematoma, we believe that saving this patient was a significant clinical achievement for our hospital. It is worth mentioning that, prior to this hemorrhagic episode, the patient had only been treated on demand, and the life-threatening giant retroperitoneal hematoma made the therapeutic management all the more difficult. Unlike the kind of bleeding usually seen in hemophilic patients, our patient bled heavily, and his condition required more than standard hemophilia management.

In this case, the ultrasound scan played a decisive role in establishing the diagnosis [29,30]. During the 16-day hospitalization period, four units of packed red blood cells were transfused. The patient was discharged once his hemoglobin and activated partial thromboplastin time (apTT) levels normalized, and the inhibitor titer and size of the hematoma decreased.The details and outcomes of this case are in support of the idea that early diagnosis and hemostatic assistance with active recombinant factor VIIa (rFVIIa) are two crucial elements in the successful management of atypical forms of bleeding and, as such, in saving the lives of patients with severe hemophilia and presentation of inhibitors.

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OV Badulescu, N Filip and C Delianu acquired, analyzed, and interpreted all the patient data. OV Badulescu, N Filip, MC Badescu, C Delianu, M Ciocoiu and PD Sirbu contributed to the conception and design of the current manuscript. OV Badulescu, N Filip and MC Badescu acquired, analyzed, and interpreted the literature references. OV Badulescu and N Filip drafted the manuscript and PD Sirbu and M Ciocoiu revised it critically for important intellectual content. OV Badulescu, N Filip and C Delianu confirm the authenticity of all the raw data. All authors have read and approved the final version to be published.

Ethics approval and consent to participate: Ethics approval was not needed as the manuscript is a case report. Informed signed consent to participate was obtained from the patient.

Patient consent for publication: As personal data were published, informed signed consent for publication was obtained from the patient.

Competing interests: The authors declare that they have no competing interests.

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