RESEARCH ARTICLE

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Role of the Hemostasis and Thrombosis Unit in the Management of Patients with Acquired Hemophilia A

Edinsel Hemofili A Hastalarının Yönetiminde Hemostaz ve Tromboz Ünitesinin Rolü

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Abstract

Objective: Acquired hemophilia A (AHA) is a rare autoimmune disease characterized by the presence of autoantibodies against coagulation factor VIII, leading to spontaneous hemorrhage in patients without a prior family or personal history of bleeding. This study describes the demographics, diagnosis, underlying disorders, bleeding characteristics, treatment, and outcomes of 41 AHA patients together with specific case reports.

Materials and Methods: Diagnosis and treatment of these patients occurred between 2005 and 2023. The median age at diagnosis was 67.8 (range: 15-93) years. Among the 41 patients, 10 (24%) cases were idiopathic, 4 (10%) were postpartum, 18 (44%) involved autoimmune diseases, and 9 (22%) involved a diagnosis of cancer.

Results: The diagnostic delay exceeded 30 days in 15 of the 41 cases (36.5%). A total of 38 of the 41 (93%) patients presented with spontaneous bleeding, with mucocutaneous bleeding being the most common presentation (23/41, 56%). Four patients experienced postpartum bleeding. Clinical remission was achieved by 100% of patients and no patients died.

Conclusion: Hemostatic and immunosuppressive therapy is essential in AHA, and it should be started as soon as possible in patients with bleeding. However, a significant delay in diagnosis was observed in these cases. The absence of mortality is likely attributable to the management of the disease within a specialized hemostasis and thrombosis unit, which offers a clinical ward, a specialized laboratory, and a dedicated ambulatory service. The Italian Society for the Study of Haemostasis and Thrombosis is working to secure recognition of this essential role in every hospital.

Keywords: Acquired hemophilia A, Factor VIII inhibitors, Bleeding, Bypassing agents, Inhibitor eradication

Öz

Amaç: Edinsel hemofili A (AHA), daha önce ailesinde veya kişisel kanama öyküsü olmayan hastalarda kendiliğinden kanamaya yol açan, koagülasyon faktörü VIII'e karşı otoantikorların varlığıyla karakterize nadir bir otoimmün hastalıktır. Bu çalışma, 41 AHA hastasının demografik özelliklerini, tanısını, altta yatan bozukluklarını, kanama özelliklerini, tedavisini ve sonuçlarını belirli olgu raporlarıyla birlikte açıklamaktadır.

Gereç ve Yöntemler: Bu hastaların tanısı ve tedavisi 2005 ile 2023 yılları arasında gerçekleşti. Tanı anındaki medyan yaş 67,8'di (aralığı: 15-93). Kırk bir hastanın 10'u (%24) idiyopatikti, 4'ü (%10) doğum sonrası gelişmişti, 18 olgu (%44) otoimmün hastalığa sahipti ve 9 olguda (%22) kanser tanısı mevcuttu.

Bulgular: Tanı gecikmesi 41 olgunun 15'inde (%36,5) 30 günü aştı. Kırk bir hastanın 38'inde (%93) kendiliğinden kanama görüldü ve en sık görülen tablo mukokutanöz kanamaydı (23/41, %56). Dört hastada doğum sonrası kanama görüldü. Hastaların %100'ünde klinik remisyon sağlandı ve hiçbir hasta ölmedi.

Sonuç: AHA'da hemostatik ve immünosüpresif tedavi esastır ve kanaması olan hastalarda mümkün olan en kısa sürede başlanmalıdır. Ancak bu olgularda tanıda önemli bir gecikme gözlemlendi. Mortalite olmamasının nedeni muhtemelen hastalığın özel bir klinik servis, laboratuvar ve ayaktan tedavi servis hizmeti sunan uzmanlaşmış bir hemostaz ve tromboz ünitesinde yönetilmesidir. İtalyan Hemostaz ve Tromboz Çalışmaları Derneği, her hastanede bu temel rolün tanınmasını sağlamak için çalışmaktadır.

Anahtar Sözcükler: Edinsel hemofili A, Faktör VIII inhibitörleri, Kanama, Bypass ajanları, İnhibitör eradikasyonu

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Introduction

Acquired hemophilia A (AHA) is a rare autoimmune disease with an estimated incidence of 1.34-1.48 per million per year [1]. The incidence increases with age, being particularly uncommon in children, among whom it is estimated at 0.045 per million per year, compared to 14.7 per million per year in individuals over 85 years [2]. The age distribution of autoantibodies is typically biphasic with a minor peak between 20 and 30 years due to postpartum inhibitors and a major peak in patients aged 68 to 80 years. The distribution of AHA in men and women is similar, except in the age range of 20-40 years, when pregnancy has a significant impact on the rates [3]. In approximately 50% of cases, factor VIII (FVIII) autoantibodies occur in patients without any identifiable concomitant disease, while the remaining cases may be associated with the postpartum period, autoimmune diseases, underlying hematological or solid cancers, infections, or medication use [4]. Bleeding manifestations can occur at various sites, either spontaneously or following trauma or invasive procedures, and vary greatly in severity, sometimes being life-threatening. The bleeding is typically mucocutaneous, involving soft tissue, muscles, the gastrointestinal tract, and the urogenital system, rather than hemarthrosis, which is more common in congenital hemophilia [5]. AHA is characterized by the development of antibodies against coagulation factors, primarily FVIII. These autoantibodies (IgG1 and IgG4) are polyclonal and target epitopes in domains A2, A3, and C2 of the FVIII molecule, interfering with factor IX (FIX), phospholipids, and von Willebrand factor [6]. The onset of the disease can be dramatic, exposing patients to hemorrhagic shock or severe bleeding, with a mortality risk ranging from 3% to 9% [7,8]. However, in about 30% of patients, bleeding is mild and does not necessitate hemostatic treatment [5]. AHA is suspected in patients with unprovoked bleeding, a negative personal and family history of hemorrhages, and a prolonged activated partial thromboplastin time (aPTT) that is not corrected after a mixing test with normal plasma. A low FVIII level and the presence of FVIII inhibitor titers, confirmed by the Nijmegen-Bethesda method, establish the diagnosis [9]. AHA is often unrecognized, exposing patients to a higher risk of death due to the prolonged time between the onset of bleeding and correct diagnosis and treatment. This study analyzes and discusses the clinical and laboratory data, treatment, outcomes, and long-term follow-up of 41 AHA patients diagnosed in our Hemostasis and Thrombosis Unit between 2005 and 2023. Treatment decisions were tailored to the severity of bleeding and all patients were monitored in long-term follow-up to document treatment success, relapse, or death from any cause. Additionally, specific cases are presented and discussed.

Materials and Methods

Between 2005 and 2023, 41 AHA cases were diagnosed in the Hemostasis and Thrombosis Departmental Unit (HTDU). All 41 patients identified in this study were adults. The population of Sardinia was 1,575,028 in 2023, with South Sardinia having 753,000 and Central Sardinia having 348,000 (via the Italian National Institute of Statistics, 1 January 2023). For our study population in South and Central Sardinia (41 cases), the estimated incidence of AHA is 2 cases per million per year (ranging from 0.9 to 5.4 cases per million). In 2016, 2018, and 2023, a relatively high number of patients (6, 5, and 6 cases, respectively) were diagnosed (Figure 1). The median age at diagnosis was 67.8 (range: 15-93) years.

All patients in this series were admitted to our unit's clinical ward. Electronic registration forms captured data on age at diagnosis, sex, clinical manifestations, type of bleeding at diagnosis, duration of diagnostic delay, laboratory results, and the hemostatic and immunosuppressive treatment approach.

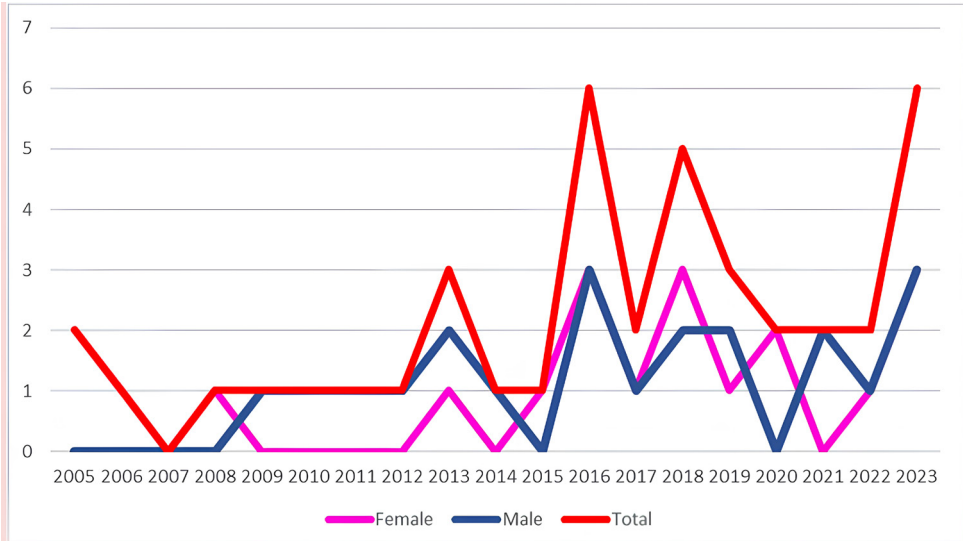

Figure 1. Number of patients diagnosed from 2005 to 2023 (n=41).

Follow-up was conducted in the ambulatory section of the unit. Coagulation screening tests, including prothrombin time (recombinant thromboplastin, Werfen, Barcelona, Spain), aPTT (silica-based, Werfen), FVIII one-stage assay, and an inhibitor assay using the Bethesda method, were performed in the laboratory of the HTDU. A mixing study was conducted to demonstrate the presence of inhibitors prior to the FVIII coagulant and inhibitor assays. All patients were admitted to the HTDU ward. Hospitalization required each patient to accept the protocol outlined by Law 196/2003 (personal data treatment). This protocol informed patients that their sensitive data would be treated anonymously and could be used for scientific purposes (e.g., in scientific publications) and/or educational presentations during congresses, symposia, conferences, lectures, refresher courses, and any scientific and educational discussions with medical and healthcare personnel, including lessons for medical and nursing students.

Statistical Analysis

All statistical analyses were performed using MedCalc software (version 14.8.1, MedCalc Software, Ostend, Belgium). As this was a retrospective study and all patients were treated according to international guidelines, exemption from the ethical committee was deemed appropriate. All variables were described as medians and ranges. Linear regression was also used. Finally, percentages were employed to describe the obtained results.

Results

All results are summarized in Table 1.

Demographic and Coagulation Profile

Our patient group consisted of 19 men and 22 women, indicating an approximately equivalent incidence between the sexes. The median age at diagnosis was 67.8 (range: 15-93) years. There was no significant correlation between FVIII inhibitor titer and FVIII level (correlation coefficient: r=0.4, p=0.9).

Etiology

Ten of the 41 patients (24%) had no identifiable underlying etiology for the inhibitor (i.e., idiopathic), 4 (10%) were postpartum, 18 (44%) had autoimmune diseases (including rheumatic polymyalgia, rheumatoid arthritis, Sjogren syndrome, celiac disease, and systemic lupus erythematosus), and 9 were diagnosed with cancer.

Clinical Presentations and Hemostatic Treatment

The median time from the first bleeding episode to diagnosis (diagnostic delay) was more than 30 days in 15 of the 41 cases (36.5%) and between 7 and 30 days in 22 cases (54%), while only 4 (10%) patients received a diagnosis within the first week of bleeding onset. All patients presented with active bleeding at diagnosis, with spontaneous bleeding in 38 of the 41 cases (93%). The most common presentation was mucocutaneous bleeding (23/41, 56%), followed by muscle hematoma (25/41, 61%). One patient presented with compartment syndrome, and two patients with muscle hematoma were initially mismanaged as experiencing deep venous thrombosis. Gastrointestinal bleeding and hemarthrosis were uncommon. Three patients had hemorrhagic bullae. Four patients experienced postpartum bleeding. In one (2.4%) case, we observed femoral-popliteal vein thrombosis during the first 7 days of hospitalization while the FVIII:C was 3%.

Management of Bleeding

Management of bleeding in AHA depended on the type and severity of the bleeding. To arrest acute bleeding, patients were treated with one or both of the following agents: activated prothrombin complex concentrate (APCC) (FEIBA, Baxter Immuno AG, Vienna, Austria) and recombinant human activated factor VII (NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark). Acute bleeding was defined as new-onset bleeding requiring treatment, while severe bleeding was defined as bleeding from visceral organs or the retroperitoneal compartment, or as life-threatening bleeding. Hemostatic parameters, bypass agents, and immunosuppressive therapies are reported in Table 1. Other hemostatic agents included fresh frozen plasma, which was used for two patients before a correct diagnosis was made. Tranexamic acid was also used for mucocutaneous bleeding and as adjunctive hemostatic treatment for all patients. Seven (17%) patients received more than one type of hemostatic agent.

Six of the 41 patients (16%) were using antiplatelet drugs due to a personal history of arterial ischemic events, particularly coronary artery disease. Atrial fibrillation was documented in one patient on anticoagulant therapy (dabigatran). Once FVIII:C levels recovered (>30%), primary or secondary antithrombotic prophylaxis was restarted if the criteria for anticoagulation or antiplatelet therapy were still met.

Steroids were the most frequently used immunosuppressive agent, particularly in combination with cyclophosphamide. Rituximab, in conjunction with other immunosuppressive agents, including steroids, was the second choice for two patients. Five (12%) patients who did not respond to a combination of steroids and cyclophosphamide were treated with immunoglobulins; three (7%) patients received plasmapheresis and one (2.4%) patient received methotrexate.

Clinical remission was achieved by all 41 (100%) patients. No patient died during hospitalization. Two patients died 1 month after discharge due to neoplastic disease and one patient died 20 days after discharge due to infectious complications. Furthermore, we observed only one relapse a year later after

Table 1. Characteristics of patients with acquired hemophilia A.

No.	Sex	Year of diagnosis	Age, years	aPTT, s	FVIII, IU/dL	Inhibitor, BU/mL	DD (days)	Hemostasis management	Immunosuppressive therapy
1	F	2005	59	125	0.5	150	24	RFVIIa, TXA, FFP	Prednisone, CP, CsA, RTX, IVIG, PEX
2	F	2005	15	97	1	29.6	72	RFVIIa, TXA	Prednisone, CP
3	F	2006	39	82	1	12	57	RFVIIa, TXA	Prednisone, CP
4	F	2008	81	87	0.7	48	16	APCC, TXA	Prednisone, CP
5	M	2009	45	130	0.2	20	99	RFVIIa, TXA, FFP	Prednisone, CP, CsA, RXT, IVIG
6	M	2010	68	108	0.4	21	7	APCC, TXA	Prednisone, CsA
7	M	2011	82	110	0.1	17	10	APCC, TXA	Prednisone
8	M	2012	78	103	1.4	22	28	APCC, TXA	Prednisone, CP
9	M	2013	82	118	0.1	416	26	RFVIIa, APCC, TXA	Prednisone, CP
10	F	2013	50	114	1	25.6	20	RFVIIa, TXA	Prednisone, CP
11	F	2013	34	108	0.6	17	34	RFVIIa, TXA	Prednisone, CP
12	M	2014	82	125	0.6	18	23	APCC, TXA	Prednisone, CP
13	F	2015	77	56	4	22.4	26	APCC, TXA	Prednisone, CP
14	M	2016	56	83	0.3	224	14	APCC, TXA	Prednisone, CP
15	F	2016	84	68	2	96	24	APCC, TXA	Prednisone, CP
16	F	2016	29	66	0.4	4	42	APCC, TXA	Prednisone, CP, RTX, IVIG, PEX
17	M	2016	91	84.7	0.1	224	23	APCC, TXA	Prednisone, CP
18	M	2016	75	66	5.9	5.4	18	APCC, TXA	Prednisone
19	F	2016	93	52	7.8	12	7	TXA	Prednisone
20	M	2017	73	55.9	4.3	3.2	13	TXA	Prednisone
21	F	2017	29	53	4.3	2.7	12	RFVIIa, TXA, plasma-derived FVIII, FFP	Prednisone
22	M	2018	91	101	0.2	22.4	17	RFVIIa, APCC, TXA	Prednisone, CP
23	F	2018	84	97	0.1	9.6	54	RFVIIa, TXA	Prednisone, CP
24	M	2018	84	123	0.7	112	50	RFVIIa, TXA	Prednisone
25	F	2018	81	79	10	38	9	TXA	Prednisone
26	F	2018	60	119	0.1	52	28	APCC, TXA	Prednisone, CP
27	M	2019	84	49	3.9	26	35	APCC, TXA	Prednisone, CP
28	F	2019	52	64	4	35	31	TXA	Prednisone
29	F	2019	45	52	4.3	16	10	TXA	Prednisone, CP
30	F	2020	88	56	10	25	19	TXA	Prednisone
31	F	2020	72	196	0.3	24	29	APCC, TXA	Prednisone, CP
32	M	2021	83	74	8	36	10	TXA	Prednisone, CP, IVIG
33	M	2021	78	140	4	35	8	APCC, TXA	Prednisone, CP
34	M	2022	76	125	1.2	35	30	APCC, TXA	Prednisone, CP
35	F	2022	46	145	4	38	60	RFVIIa, TXA	Prednisone, CP
36	M	2023	59	125	0.5	150	24	APCC, TXA	Prednisone, CP
37	F	2023	80	135	2	64	27	APCC, TXA	Prednisone, CP
38	M	2023	78	92	4.7	47	30	RFVIIa, TXA	Prednisone
39	M	2023	87	73	1	229	65	RFVIIa, TXA	Prednisone, CP, IVIG, MTX, PEX
40	F	2023	31	155	1	30	40	RFVIIa, TXA	Prednisone, CP
41	F	2023	46	75	4	15	30	APCC, TXA	Prednisone, CP

APCC: Activated prothrombin complex concentrate; DD: delay of diagnosis; RFVIIa: activated recombinant factor VII; TXA: tranexamic acid; FFP: fresh frozen plasma; CP: cyclophosphamide; CsA: cyclosporine; RXT: rituximab; PEX: plasma exchange; IVIG: intravenous immunoglobulin; MTX: methotrexate; PEX: pexidartinib; F: female; M: male; aPTT: activated partial thromboplastin time.

complete remission in a patient with an autoimmune disease (rheumatic polymyalgia).

Discussion

This paper presents our case series managed according to the international guidelines available in the literature [10,11]. All aspects related to the diagnostic approach and the hemostatic and immunosuppressive treatment were appropriately addressed [12]. It is worth noting that immunosuppressive therapy is essential in AHA, and it should be started as soon as possible in patients with bleeding. Our results align closely with those published on FVIII levels, bleeding characteristics, and inhibitor levels. However, we observed some differences upon comparison with data from the largest registry on the disease [13]. Our percentage of idiopathic AHA is significantly lower (24%) than that of the registry (51%). Similarly, the incidence of thrombotic events is lower in our data: 2.4% (1 out of 41) versus 4.8% in the registry. No drug-induced AHA was present in our series and no patient died. The incidence of AHA was higher in our series compared to general data reported, attributable to the genetic characteristics of Sardinia, where the incidence of autoimmune diseases is relatively high [14]. The complex genetic landscape of Sardinia may stem from malaria, which was endemic until the 1950s, favoring the selection of genetic variants that mitigate disease severity, such as G6PD deficiency and thalassemia traits. However, other variants have been selected that confer a propensity for autoimmune diseases such as type 1 diabetes, multiple sclerosis, and autoimmune thyroiditis [15]. Our series clearly demonstrated a delay in diagnosis of AHA, with nearly 40% of patients experiencing a delay of over 30 days from the onset of the disease to the final diagnosis. This delay may occur because AHA is rare and often overlooked by both general and specialized physicians. Additionally, there is a disconnect in linking a major hemorrhagic event with prolonged aPTT, which is frequently disregarded. Another concern is that many general laboratories do not perform the aPTT mixing test, significantly limiting accurate diagnostic approaches. These issues were well documented by Pardos-Gea et al., who described the causes of diagnostic delay in their 20-year experience [16]. They also reported instances where calf swelling without external signs of hemorrhage was misinterpreted as deep vein thrombosis, leading to the use of low-molecular-weight heparin and resulting in a worse bleeding scenario. This occurred in two of our patients. In one case, a compressive muscle hematoma developed in both arms, resulting in compartment syndrome characterized by an ischemic clinical picture that necessitated surgery. Surgery was associated with a significantly worse bleeding scenario, requiring much larger quantities of activated FVII. Figure 2 illustrates the main points for suspecting the presence of the disease, which could be distributed among general practitioners to enhance awareness. Another notable aspect of this series is that no patient died before attaining complete remission. This outcome contrasts with literature reports indicating mortality rates between 3% and 9% [7]. We assert that this remarkable result was achieved because all patients received care within the same specialized ward of the HTDU, where the personnel were consistently specialized in the field of hemostasis and thrombotic diseases within an internal medicine department. Additionally, the unit includes a specialized laboratory. We believe that an internist approach to the disease has played a favorable role, facilitating the management of the adverse effects of various therapies and the frequent underlying conditions associated with AHA. Interestingly, we observed that activated FVII was used more frequently than APCC. However, it is worth noting that both bypass agents have been found to yield similar results in controlling bleeding, allowing for the use of either

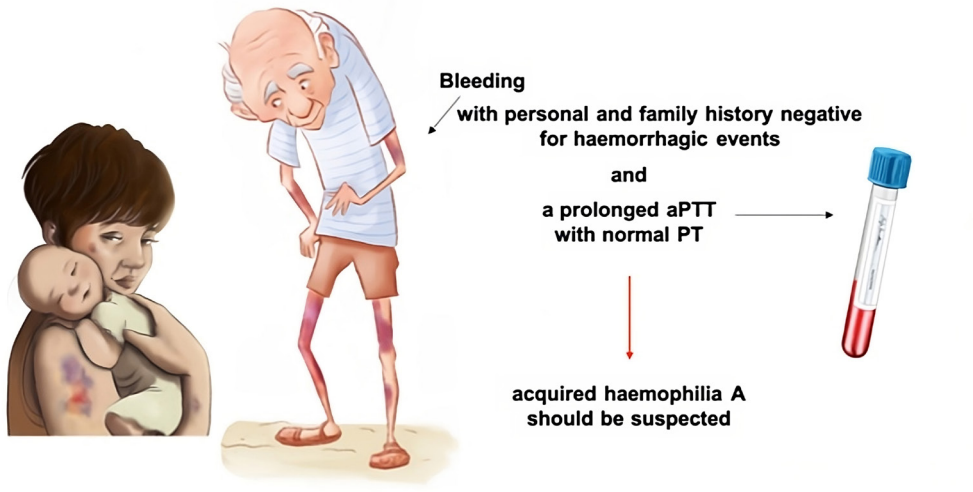

Figure 2. A simple drawing to help remember when to suspect acquired hemophilia A.
aPTT: Activated partial thromboplastin time.

agent [17]. We would like to briefly describe and comment on three patients from this series. The first was a patient with a very low FVIII level (nearly 0%) and a very high inhibitor level (229 BU), which was reduced to 28 BU by plasmapheresis. This patient was treated with immunosuppressive and bypass agents, but FVIII levels remained near 0% for several weeks despite the absence of overt bleeding. Given the high risk of bleeding, we decided to introduce emicizumab, a monoclonal bispecific antibody that bridges both factor IX and X, mimicking FVIII activity [18]. The results were optimal, with FVIII levels rising to 11% without any bleeding during the second weekly administration of this drug. The use of emicizumab is off-label in AHA. Nevertheless, several studies have demonstrated its efficacy and safety in these patients [19,20]. The second patient developed mantle cell lymphoma after a year and a half of complete remission. Neoplastic disease was suspected during follow-up and confirmed by lymph node biopsy. Complete remission was achieved following chemotherapy and autologous and allogenic bone marrow transplantation [21]. Other cases of malignant lymphoma following AHA have been documented in the literature [22], suggesting that long-term follow-up is advisable for these patients. The third case involved a 66-year-old woman who was a Jehovah's Witness. She was admitted to our internal medicine department with a large hematoma in her left thigh, ecchymosis, and another large hematoma in her right shoulder. She had a history of Sjogren syndrome and type 2 diabetes. Laboratory parameters indicated prolonged aPTT (FVIII: 4.4%) and a hemoglobin level of 6 g/dL. She also had severe renal failure with Modification of Diet in Renal Disease glomerular filtration rate (MDRD) of 28 mL/min. Although management of bleeding with bypass agents and the immunosuppressive treatment commenced immediately, treating her anemia proved challenging due to her refusal of blood transfusions [23]. Our approach involved infusions of saline and gelatin-colloid solutions, along with intravenous iron and erythropoietin. Her hemoglobin fell to 4.0 g/dL, coinciding with an increase in creatinine levels (4.97 mg/dL for an MDRD value of 9 mL/min). Nevertheless, she was discharged after 16 days, having attained complete remission (aPTT within the normal range without any new bleeding), improved hemoglobin (7.5 g/dL), and MDRD of 24.1. Her hemodynamic condition was stable. Days after discharge, her hemoglobin level increased to 9.8 g/dL and her MDRD value remained stable. She was followed for 2 years, during which no relapse was observed.

Study Limitations

This study has some limitations that warrant discussion. It is a retrospective single-center study, albeit covering 18 years and including a relatively large cohort of 41 patients. We emphasize that single-center studies, while limited, can provide valuable insights into local medical approaches, thereby enhancing experience in a specific field. Local studies should be encouraged without undermining the importance of establishing large registries dedicated to rare diseases such as AHA. Another limitation is the non-use of recombinant porcine FVIII (Obizur), which could have been beneficial for more critical cases [24,25]. However, in our series, bleeding was effectively managed, as evidenced by the absence of mortality. Another reason for not using this treatment was the lack of a round-the-clock laboratory availability for measuring FVIII activity to administer appropriate drug doses.

Conclusion

This study demonstrates that a single specialized center for hemostasis and thrombosis can effectively manage patients with AHA. We observed a significant delay in diagnosis by non-specialized or general practitioners, who often overlook the disease and the fundamental principles of the hemostatic system. This issue could be mitigated by disseminating educational materials in a straightforward format to facilitate the recognition of AHA. We emphasize that no patient died because the management of the disease was conducted in a specialized unit equipped with a clinical ward, a specialized laboratory, and a dedicated ambulatory service. This is crucial for optimal patient care. Furthermore, we believe that having an expert in hemostasis and thrombosis is essential. Several patients in our series were referred to our unit from other hospitals lacking experience in managing the disease. The Italian Society for the Study of Haemostasis and Thrombosis is working to secure recognition for this essential role in every hospital.

Ethics

Ethics Committee Approval: Exemption from the ethical committee was deemed appropriate.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.M., F.M., D.B.; Design: A.M., F.M.; Data Collection or Processing: M.F.R., S.C.; Analysis or Interpretation: D.B.; Literature Search: L.F., F.M. P.S.; Writing: F.M., D.B.

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

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