Clinical Case Report

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Hemorrhagic pericardial effusion as the debut of acquired hemophilia in a chronic lymphocytic leukemia patient

A case report, and a review of acquired hemophilia A-related hematological malignancies

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Abstract

Background: Acquired hemophilia A (AHA) is a rare bleeding disease caused by autoantibodies against factor VIII. Spontaneous bleeding symptoms usually affect the skin and muscle, while pericardial effusion is an extremely rare manifestation. In the elderly, anticoagulant treatment is frequent and bleeding symptoms are usually associated with this.

Clinical findings: We report a hemorrhagic pericardial effusion as the AHA debut in a patient with untreated chronic lymphocytic leukemia and anticoagulated with apixaban for atrial fibrillation and chronic arterial ischemia. The patient was treated with recombinant activated factor VII to control the active bleeding and corticosteroids and cyclophosphamide to eradicate the inhibitor. In addition, a briefly review of hematological malignancies associated to acquired hemophilia was performed.

Particularities: a) anticoagulant treatment may confuse the suspicion of AHA and its diagnosis; b) hemorrhagic pericardial effusion is an extremely rare presentation; c) bypassing agents raise the risk of thromboembolism; d) hematological malignancies rarely cause AHA (<20% of cases).

Conclusion: A multidisciplinary team is needed to diagnose and manage AHA effectively. The use of anticoagulants may lead to the misdiagnosis of clinical symptoms. Chronic lymphocytic leukemia is one of the main causes of hematological malignancies associated. The specific treatment of CLL is still recommended in the event of active disease.

Abbreviations: AF = atrial fibrillation, AHA = Acquired hemophilia A, aPCC = activated prothrombin complex concentrate, aPTT = activated partial thromboplastin time, ASA = Acetylsalicylic acid, AVK = antivitamin K, BA = Bethesda assay, BU = Bethesda units, CAI = chronic arterial ischemia, CC = corticosteroids, CLL = chronic lymphocytic leukemia, CR = complete remission, DOACs = direct oral anticoagulants, DVT = deep vein thrombosis, EACH2 = United Kingdom and the European Acquired Hemophilia, FVIII = factor VIII, IgG = immunoglobulin G, INR = International Normalized Ratio, IST = immunosuppressive therapy, LA: lupus anticoagulant, LAA = left atrial appendage, LAAO = LAA occlusion, LWMH = low-weight molecular heparin, PR = partial response, PT: prothrombin time, rFVIIa = recombinant activated factor VII.

Keywords: Acquired hemophilia A, chronic lymphocytic leukemia, hemorrhagic pericardial effusion

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VEV, MTCM, SMG, FLC, DGC, JC, AAM, FMH, PP, and JMB diagnosed and treated the patient; CSM carried out and interpreted the imaging test; JATH undertook the femoral bypass and DVT; MG was responsible for CLL; JRGP performed and interpreted the laboratory data; JMB wrote the manuscript, which was critically reviewed by JRGP, FMH and FP; all authors read and approved the final manuscript.

The authors report no conflicts of interest.

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1. Introduction

Acquired hemophilia A (AHA) is a rare bleeding disorder characterized by spontaneous hemorrhage or prolonged bleeding after surgery, trauma, or other invasive procedures in patients without a family or personal history of hemorrhagic diathesis.[1] Its incidence is heterogeneous, but probably underestimated because of undiagnosed and unreported cases.[2] The most important prospective studies featured in the United Kingdom and the European Acquired Hemophilia registry concluded that AHA usually develops in the elderly (median age 64–78 years), but can be associated with pregnancy and autoimmune disease in younger cohorts.[2,3] AHA is usually caused by the spontaneous production of neutralizing immunoglobulin G (IgG) autoantibodies, also known as inhibitors, targeting endogenous factor VIII (FVIII).[4,5] Recent research suggests that the breakdown of immune tolerance is caused by a combination of genetic and environmental factors.[6] In addition, the age distribution of FVIII autoantibodies is typically biphasic, with a small peak between 20 and 30 years, owing to post-partum occurrence, and a major peak in elderly patients.[2,7] It is well known that around 50% of AHAs are idiopathic, whereas known causes include malignancy and autoimmune disorders.[2,8] In contrast to congenital hemophilia A, joint bleeding is infrequent with AHA. However, subcutaneous bleeding is most common (in >80% of cases), followed by muscle bleeding (>40%), gastrointestinal bleeding (>20%), and genitourinary, retroperitoneal bleeding and that from other sites (<10%).[3] Bleeding into the thoracic cavity (e.g., hemorrhagic pleural effusion or pericardial effusion) and intracranial hemorrhage may be fatal, but are very uncommon, occurring in only approximately 1% of cases.[9] AHA should be suspected in patients with a recent onset of abnormal bleeding, an isolated prolongation of activated partial thromboplastin time (aPTT) and normal prothrombin time (PT).[10] Laboratory tests indicating AHA include a mixing study consistent with an inhibitor, a negative result for lupus anticoagulant (LA), and low levels of FVIII. The FVIII inhibitor must be confirmed and quantified by the Bethesda assay (BA) or the Nijmegen Bethesda assay.[11] However, in patients under treatment with anticoagulants, such as antivitamin K (AVK), direct oral anticoagulants (DOACs), or heparins, the diagnosis may be challenging.[12] Here, we describe a hemorrhagic pericardial effusion as the AHA debut in a patient with untreated chronic lymphocytic leukemia (CLL) and anticoagulated with apixaban for atrial fibrillation (AF). We also review the literature on cases with AHA associated with hematological malignancies.

2. Case material

A 77-year-old male was diagnosed with asymptomatic CLL in May 2015. The most relevant clinical history findings were: prostate cancer treated with radiotherapy in 2005; chronic arterial ischemia (CAI), which needed a femoral bypass since 1999; AF that had been treated with AVK since 2013 (CHA_2DS_2-VASc = 4); and vitamin B12 deficiency secondary to chronic atrophic gastritis. A hemolytic anemia secondary to a warm autoantibodies episode was resolved with corticosteroids (CC) treatment in May 2016. One month later, the patient was hospitalized for a community-acquired pneumonia, which required intravenous antibiotics, and for a posttraumatic hematoma in the left leg, which appeared to be related to the AVK treatment. In February 2017, a labile international normalized ratio (INR), the need for vitamin B12 intramuscular treatment and the intramuscular hematoma prompted a change of treatment from AVK to apixaban (5ï¿½mg/12ï¿½h), and later, to occlude the left atrial appendage (LAA). One week later, following the LAA occlusion, the patient attended an A&E department with dyspnea, orthopnea, oliguria, and edemas. Physical examinations revealed a grade III/VI aortic systolic murmur. The hemoglobin level was 10.8 g/dL (previously 13.5 g/dL) without reticulocytes and leucocytes, and platelet counts were normal (5.4×10^9 cells/L, 184×10^9 cells/L, respectively). The patient's aPTT was isolated prolonged (89.8 seconds; normal range: 29 to 40 seconds) and he had taken the 5-mg dose of apixaban at least 12 hours before. No other abnormalities were found in laboratory tests. A chest radiograph showed an enlarged cardiac silhouette and a globular heart shape ("water bottle" sign) (Fig. 1), whereas echocardiography revealed a severe large circumferential pericardial effusion (Fig. 2). As the clotting test results were attributed to the DOAC and were associated with a significantly higher risk of hemorrhage, drainage of the pericardial effusion was postponed to reduce this risk. Twenty-four hours later, a pericardial window surgery was performed and 1250 L of hemorrhagic liquid was drained. The next day,

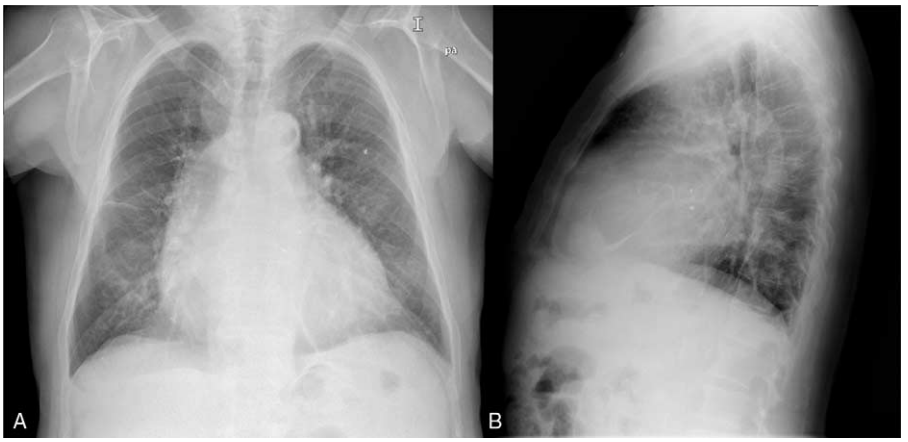

Figure 1. Chest radiograph. Frontal (A) and lateral (B) chest radiographs showed an enlarged cardiac silhouette with an increase in the transverse diameter but no increase in its height, creating a globular morphology ("water bottle" sign). This sign is present when there is a large pericardial effusion.

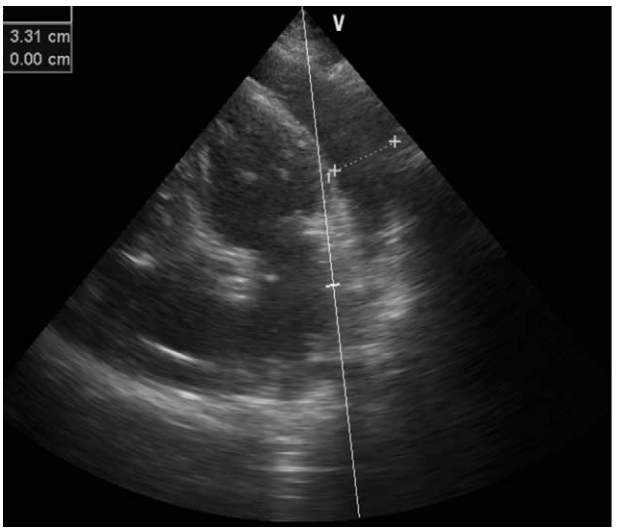

Figure 2. Transthoracic echocardiography in apical 4-chamber view showing pericardial effusion. The echocardiograph showed a large circumferential pericardial effusion (>25 mm at end-diastole).

aPTT remained significantly prolonged (77.7 seconds) and a hematoma appeared at the base of the tongue (Fig. 3). At that time, a coagulation disorder was therefore suspected. The patient's plasma was mixed with normal pooled plasma in a ratio of 1:1 and incubated, which partially corrected the aPTT, reducing it to 58.6 seconds).[11] Further investigation revealed FVIII activity of 1.67% (normal range: 70%–150%) and anti-factor VIII inhibitor antibodies of 7 Bethesda units (BU) per mL (normal range: 0 BU/mL) was performed according to standard recommendations.[11,13] Once AHA has been diagnosed, the patient was treated with recombinant activated factor VII (rFVIIa, 90 μg/kg/4 h) to control the active bleeding. Treatment with CC (Prednisone 1 mg/kg/day) and cyclophosphamide (50 mg/day) was initiated to eradicate the inhibitor. After 15 days, the inhibitor had disappeared, FVIII activity was 90%, and the aPTT was normalized (35.8 seconds). CLL was re-evaluated by computed tomography, which revealed no evidence of progression. Then, the CC dose was tapered and completely stopped 3 months after the disappearance of the inhibitor, by which time complete remission (CR) had been achieved.[8] Acetylsalicylic acid (ASA) was also introduced because of CAI on the recommendation of the vascular surgery department (Fig. 4). In May 2017, the patient went to an A&E with leg pain and

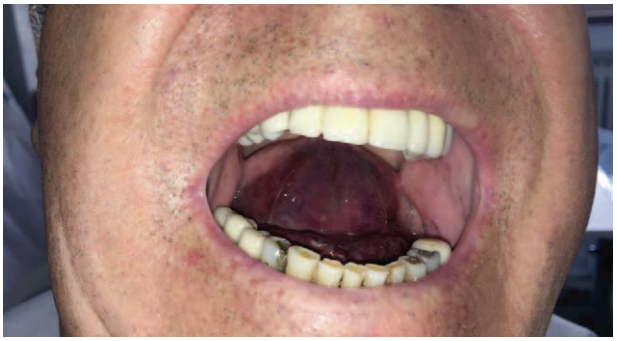

Figure 3. Spontaneous sublingual hematoma.

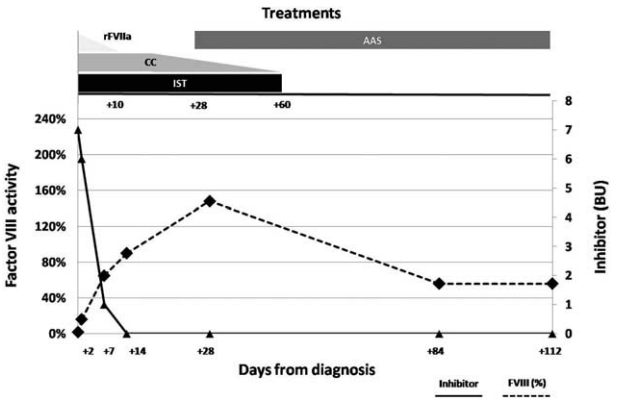

Figure 4. Changes in FVIII activity and inhibitor levels related to hemostatic and immunosuppressive therapy. Patient presented hemorrhagic pericardial effusion and a spontaneous sublingual hematoma. Inhibitor (7 BU) was detected and acquired hemophilia A was confirmed. Hemostatic treatment with rFVIIa (90 μ/kg/4 h) and corticosteroids (1 mg/kg) and cyclophosphamide (50 mg/day) (IST) was started. Due to favorable evolution, rFVIIa was reduced and stopped on day 10. Until the inhibitor had been eliminated by immunosuppressive therapy therapy, factor VIII activity levels did not increase. On day 14, corticosteroids were tapered. CC and immunosuppressive therapy were stopped on day 60 and complete remission was maintained. AAS was restarted on day 30 when hemostasis was safe and the inhibitor had been eradicated. rFVIIa = recombinant activated factor VII.

edema. Duplex ultrasound indicated a distal deep vein thrombosis (DVT) in the gemellar veins (Fig. 5). A full dose of low-weight molecular heparin (LWMH) was used successfully treat the patient during the course of 1 month. At the last follow-up (6 months after the AHA diagnosis), the patient maintained CR with no associated complications.

3. Discussion

Our case report has several particularities related to the manifestation of bleeding, thrombosis risk in the context of hemostatic treatment, the laboratory challenge associated with anticoagulant therapies, and the hematological cause of AHA.

First, we describe an extremely rare bleeding manifestation at the beginning of AHA. Bleeding symptoms usually occur in a spontaneous recent-onset and/or traumatic context, although dental or nondental surgery and other medical procedures are involved on very rare situations.[2,5,14] Hemorrhages typically occur on the skin and mucosa, and in muscles and the oral cavity (in almost 50% of the patients).[2,5,14] However, intracranial bleeding and bleeding into the digestive tract, genitourinary system, and retropharyngeal and retroperitoneal spaces were observed (Table 1).[2,5,14] In the course of this disease, bleeding into the thoracic cavity is very uncommon (I approximately 1% of cases); 3 cases of hemorrhagic pleural effusion or hemothorax have been reported in the literature.[9] Potentially fatal bleeding into the thoracic cavity caused by AHA may appear after surgical procedures performed on the chest.[15] Previously, in 1 patient diagnosed with myeloma multiple, hemarthrosis and hemorrhagic pericardial effusion were in association with AHA[16] (Table 1). In this context, before his diagnosis of pericardial effusion, our patient underwent an LAA occlusion (LAAO), which may have been partially responsible for the bleeding. In addition, the hypersensitivity to anticoagulants, multiple falls, adherence to a diet to maintain a stable INR, fluctuating renal function (which can affect anticoagulation with DOACs), and

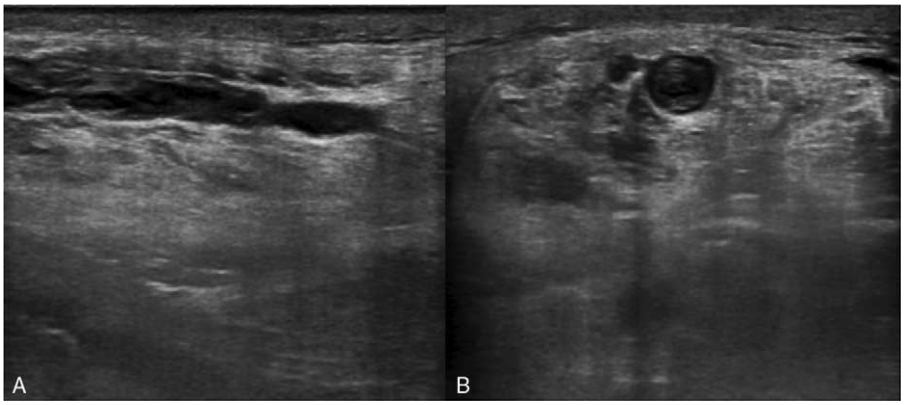

Figure 5. Acute deep vein thrombosis revealed by gray-scale ultrasound. Longitudinal (A) and transverse (B) gray-scale ultrasound images of the gemellar vein demonstrated an enlarged noncompressible vein with intraluminal echoes.

patient compliance with the medication regime are obstacles to effective therapeutic anticoagulation.[17] These factors are associated with high risk of stroke and hemorrhage for our patient. Nonpharmacological methods, such as LAAO, have emerged as valid alternatives for the treatment of such patients.[18] Before starting the LAAO, transesophageal echocardiography must be performed to assess LAA anatomy, to aid in the selection of a suitable device and size, and to identify anatomic contraindications.[19] The device is introduced into the right atrium via the right femoral vein and is then passed into the left atrium through a transseptal puncture. A small sheath is placed in the femoral artery to control pressure.[19] To facilitate successful implantation of the LAAO device, the site of the transseptal puncture should be in the inferior and posterior part of the fossa ovalis. Although the feasibility and safety of LAAO have been recently been evaluated and published,[20] there are specific complications that are known.[21] The most frequent complications of these are the thrombus formation on the device and chest pain/pericarditis (up to 14% of cases), and the residual flow into the LAA (up to 32%). However, pericardial effusion and cardiac tamponade are rare (<3%).[18,21]

The administration of other anticoagulants, for example, AVK or DOACs, could be a confounding factor and may delay the diagnosis of AHA in an emergency situation.[12] The median time from the first hemorrhage event to diagnosis is 1.5 months.[22] Reviewing the medical history of our patient revealed that 3 months earlier, when he was hospitalized with pneumonia, he showed a post-traumatic intramuscular hematoma that was considered to be the consequence of concomitant AVK and LMWH treatment. However, his aPTT had already been prolonged by this time (aPTT: 84.3 seconds, INR: 1.5) but had not been investigated further. Moreover, CCs were administered in the context of pneumonia, so the aPTT was normalized. Thus, the location and severity of the hematoma and the laboratory findings were atypical in this respect. AVK treatment was subsequently ended and, somewhat later, enoxaparin was replaced by a therapeutic dose of apixaban. Finally, the LLAO procedure was carried out.

It is important to note that a prolonged aPTT may be attributable to the presence of LA, coagulation factor deficiencies, and other anticoagulants (e.g., heparin, DOACs). The clinical context of bleeding or thrombosis may help us achieve an accurate diagnosis.[8,23] The laboratory hallmark for the diagnosis of AHA is a prolonged aPTT, that is not corrected by normal plasma (mixing test), and that has a normal PT.[8,23] This type of test allows us to distinguish between factor deficiency and the presence of an inhibitor. The presence of LA can then be confirmed by specific tests, such as the diluted Russell viper venom time.[8,11] However, many of these tests, along with anti-Xa assay, are not usually available in emergency situations. These factors contribute to the delay in AHA diagnosis.

For hemostatic treatment, the bypassing agents rFVIIa (NovoSeven) and activated prothrombin complex concentrate (aPCC, FEIBA) are both appropriate first-line therapies. Overall, bleeding was most successfully controlled with a bypassing agent (91.8%), there are no difference between rFVIIa (91.8%) and aPCC (93.3%). Recently marketed, recombinant porcine FVIII is a promising alternative therapeutic option.[23] Patients who receive bypassing agents, especially the elderly, the immobile, and those with malignancy, AF, or vascular grafts, among others, are at risk for arterial and venous thromboembolism, as we observed in our patient.[24–26] The patient was monitored closely and ASA was started when the hemostatic system was safe (Fig. 4); the DVT was not related to rFVIIa.

Although inhibitors can disappear spontaneously after several months in some cases, bleeding-related morbidity and mortality are substantial while they are present. Thus, immunosuppressive therapy (IST) is recommended for all adults with AHA.[27] IST achieves remission in 60% to 80% of patients after a median of 5 to 6 weeks. The evidence suggests that time to remission may be shorter in patients receiving a combination of CC and cyclophosphamide, although long-term survival does not differ.[27,28] With this regimen, our patient achieved partial response (PR) in the first month and CR in the third month (Fig. 4). Another regimen, based in anti-CD20 (Rituximab) therapy, was useful as a first-line treatment in combination with CC if IST was avoided.[8] Many factors have been investigated to assess the extent to which they predict the response to IST and which they are associated with the risk of relapse. Anti-FVIII autoantibodies of the IgA class appear to have a particularly high risk of relapse, but we could not determine this in our patient.[29] In accordance with other registers, whose median observation time was 9 months, the proportion of patients who were alive and inhibitor-free was 60% to 70%.[3,27] Our patient, who had been under observation for 8 months at the last follow-up, maintained stable CR.

Finally, several large registers have established that idiopathic AHA is the most frequent type, accounting for up to 50% of the

Table 1

Hematological malignancies involved in AHA, by disease (literature reviewed).

Ref	Year	Age/Sex	HM	Type of bleeding	FVIII:C (%)	Inhibitor, BU/mL	Hemostatic treatment	IS treatment	Outcome
[33]	1974	47/M	NHL	Skin, hematuria	<1	—	HFVIII	CC + CY	CR
[33]	1998	40/M	NHL	Skin, hematuria	3	4	HFVIII	CC	CR
[33]	2000	51/M	NHL*	Bruising	—	250	aPCC	IVIG + CY or CO	NR
[34]	2000	53/F	NHL	Dental extraction	5	12	—	CC + CY	CR
[33]	2002	70/M	NHL	GI	6.8	8.6	aPCC	IVIG	Died
[33]	2001	61/M	NHL*	Post-surgery	—	22	rFVIIa	CC	CR
[35]	2015	46/M	NHL	Muscle, retroperitoneal	<1	20.8	rFVIIa + tranexamic A	IVIG + R + CY + CC	CR
[36]	2015	81/M	NHL	Skin, muscle	<1	5	—	CC and specific NHL	CR
[33]	1982	66/F	CLL	Skin, hematuria, retropharyngeal	<1	100	CP + PE	CC + CY	CR
[33]	1993	82/F	CLL	Skin, retroperitoneal	4	9	DDAVP	IVIG + CC	CR
[33]	1995	68/M	CLL	Dental extraction	11	1	—	IVIG	CR
[33]	1997	59/M	CLL	Skin, GI	—	38	aPCC	—	CR
[33]	1999	65/F	CLL	Skin, retroperitoneal	4	20	PFVIII + PE	CY + fludarabine	CR
[34]	2000	71/M	CLL	Skin	<1	64	PFVIII	—	Died
[34]	2000	57/M	CLL	Skin	2	28	PFVIII	IVIG	CR
[34]	2000	74/M	CLL	Skin, hematuria	6	8	—	CC + IVIG	CR
[33]	2001	77/F	CLL	Bruising	4	2	—	CC	CR
[33]	2001	64/F	CLL*	Muscle	—	46	aPCC	CC	CR
[33]	2007	80/F	CLL	Muscle	2	10	—	CC + CY	CR
[37]	2015	55/M	CLL	Bruising, hemothorax	5	66	HFVIII + rFVIIa/aPCC	CC + CY	PR
[38]	2017	75/M	CLL	Muscle	<1	18.4	rFVIIa	CC + CY + R	CR
[39]	2015	62/F	LGLL	—	—	—	rFVIIa or aPCC	CC + R	CR
[33]	2001	50/F	HL†	Muscle	1	123	—	CC	CR
[33]	2000	65/M	WM	Skin	2	700	aPCC + HFVIII + PE	CC + CY	—
[33]	1994	52/M	MM†	Muscle	2	17.8	HFVIII + PE + CP	CC	Died
[34]	2000	58/F	MM	Skin, GI	<1	28	PFVIII + aPCC + PE	CC	Died
[33]	2005	58/M	MM	Post-surgery	6	20	aPCC	CC + CY	Died
[16]	2012	43/F	MM	Post-surgery	6	—	—	Specific MM	CR
[16]	2012	70/M	MM	Skin, retinal	<1	—	—	Cytoxan	PR
[16]	2012	65/M	MM	Skin, pericardial effusion	5	9.5	aPCC	IVIG + R	CR
[40]	2015	67/F	MM	—	2	4.85	—	CC	CR
[41]	2015	64/M	MM	Skin, hemoptysis	17.3	5	rFVIIa	VTD	CR
[42]	2016	45/M	MM	Muscle	7	2.6	rFVIIa	R + CY + V	CR
[43]	2017	67/M	MM	—	28	—	HFVIII	Specific MM	CR
[44]	2017	87/M	MM	Skin, muscle	1.4	18.4	aPCC	CC + CY or V	CR
[33]	1986	55/F	AML	Skin	4	10	—	CC	CR
[34]	2000	53/F	AML	Skin, GI	<1	86	PFVIII	—	Died
[33]	2005	64/F	AML	GI	3.9	1.7	PFVII + DDAVP + aPCC	CC	CR
[33]	1991	75/F	MDS	Skin	2	420	—	CC	CR
[34]	2000	79/M	MDS	Post-surgery	1	22	PFVIII	—	Died
[33]	2003	71/M	MDS	Skin, muscle	24	9	rFVIIa/aPCC + HFVIII	—	CR
[45]	2012	84/M	MDS	Skin, muscle	3	3	rFVIIa	CC	Died
[46]	2014	58/M	CMML	Skin, muscle	<1	200	rFVIIa/aPCC	CC + CY	CR
[46]	2015	79/F	CMML	Bruising	—	120	rFVIIa	CC	Died
[46]	2015	41/M	CMML	Post-surgery	—	107	—	CC + CY	Died
[46]	2015	54/M	CMML	Skin	—	21	—	CC	CR
[46]	2015	71/M	CMML	Skin, hematuria	6.7	7.4	HFVIII	HU, IVIG	CR
[33]	2000	58/M	CML†	Muscle	2	58	rFVIIa	CC	CR
[33]	2001	52/F	CML†	GI	—	29	PFVIII	CC	CR
[47]	2012	80/M	CNL	Muscle	<1	190	aPCC + rFVIIa	CC + R	CR
[34]	2000	74/F	PMF	Retroperitoneal	<1	386	PFVIII + aPCC	—	Died
[48]	2013	77/M	PMF/AML	Skin	—	—	rFVIIa	CC + CY + R	CR‡
[49]	2016	66/M	PMF	Post-surgery, muscle	<1	17.3	rFVIIa/aPCC	CC + R	PR
[50]	2003	71/M	MPN/MDS	Skin, muscle	24	9	HFVIII + rFVIIa + aPCC	CC + CY	CR
[51]	2011	74/F	ET	Skin	4	5.8	DDAVP + aPCC	CC	CR
[52]	2012	69/F	ET	Skin, stroke	<1	17	FFP	—	Died

A = acid, AML = acute myeloid leukemia, APCC = activated prothrombin complex concentrates, C = cryoprecipitate, CC = corticosteroids, CO = cyclosporine, CR = complete response, CY = cyclophosphamide, CLL = chronic lymphocytic leukemia, CML = chronic myeloid leukemia, CMML = chronic myelomonocytic leukemia, CNL = chronic neutrophilic leukemia, D = dexamethasone, DDAVP = desmopressin, ET = essential thrombocythemia, F = female, FFP = fresh frozen plasma, GI = gastrointestinal, HFVIII = human factor VIII, HL = Hodgkin lymphoma, HM = hematologic malignancy HU = hydroxyurea, IVIG = intravenous immunoglobulins, LGLL = Large granular lymphocyte leukemia, M = male, MDS = myelodysplastic syndrome, MM = multiple myeloma, MPN = myeloproliferative neoplasm, NHL = non-Hodgkin lymphoma, NR = not response, PE = plasma exchange, PFVIII = porcine FVIII, PMF = primary myelofibrosis PR = partial response, R = rituximab, rFVIIa = recombinant activated FVII, T = thalidomide, V = bortezomib, WM = Waldenström macroglobulinemia.

* Patient also received fludarabine.

† Patient also received interferon-α.

‡ Died to infection.

cases.[2,3,5] Underlying malignancy is present in 10% to 20% in the most important registers.[2,3,5,14] The majority are related to solid tumors, especially carcinoma of the prostate and lung, each of which accounts for about 25% of cases of AHA.[30] Of the hematological malignancies, which are less frequently associated with AHA than are solid tumors, lymphoid neoplasms were the most frequent.[30] We have briefly reviewed the published cases of hematological malignancies associated with AHA and described the main disorders, the bleeding manifestation, and their inhibitor eradication and outcome responses (Table 1). CLL is well known to be associated with several autoimmune phenomena, such as autoimmune hemolytic anemia, pure red cell aplasia, and immune thrombocytopenia.[31] A few cases with CLL have been reported since 2007.[31] The median age at diagnosis of AHA was 68 years (range, 55–82 years) and half of the CLL patients (n=7; 54%) were male. The main locations of bleeding were the skin and muscle (n=7; 54%); gastrointestinal and retroperitoneal bleeding and hematuria were other noted symptoms. The median FVIII activity was 4% (range, 0–11) and the initial inhibitor level was 20 BU/mL (range, 1–100 BU/mL). Almost 70% of the patients required hemostatic treatment to control the bleeding manifestation consisting of bypassing agents and FVIII infusions. All except 2 patients were treated by immunosuppressive therapy, based on a combination of corticosteroids and cyclophosphamide. The underlying CLL should be treated if concomitant disease progression is documented.[32] Finally, only 1 patient died without achieving any type of response (Table 1). Lymphoid neoplasms (non-Hodgkin lymphoma and CLL) are the most frequent causes of AHA, although in recent years more cases with myeloid neoplasm (acute myeloid leukemia, myelodysplastic syndrome, chronic myeloproliferative neoplasm) have been published (Table 1).

In conclusion, a multidisciplinary team is required to diagnose and manage AHA. The use of anticoagulants may lead to the misdiagnosis of clinical symptoms. CLL is one of the main causes of hematological malignancies. The specific treatment of CLL is still recommended in the event of active disease.

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