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 brief 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 venous 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
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. Its incidence is heterogeneous, but probably underestimated because of undiagnosed and unreported cases. 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. AHA is usually caused by the spontaneous production of neutralizing immunoglobulin G (IgG) autoantibodies, also known as inhibitors, targeting endogenous factor VIII (FVIII). Recent research suggests that the breakdown of immune tolerance is caused by a combination of genetic and environmental factors. 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. It is well known that around 50% of AHAs are idiopathic, whereas known causes include malignancy and autoimmune disorders. 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%). 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. 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). 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. However, in patients under treatment with anticoagulants, such as antithrombin K (AVK), direct oral anticoagulants (DOACs), or heparins, the diagnosis may be challenging. 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 (CHA2DS2-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 (5 mg/12h), 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 × 10^11 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,
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. 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. Once AHA has been diagnosed, the patient was treated with recombinant activated factor VII (rFVIIa, 90 mg/kg/4h) 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. 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 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. Hemorrhages typically occur on the skin and mucosa, and in muscles and the oral cavity (in almost 50% of the patients). However, intracranial bleeding and bleeding into the digestive tract, genitourinary system, and retropharyngeal and retroperitoneal spaces were observed (Table 1). 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. Potentially fatal bleeding into the thoracic cavity caused by AHA may appear after surgical procedures performed on the chest. Previously, in 1 patient diagnosed with myeloma multiple, hemorrhoidis and hemorrhagic pericardial effusion were in association with AHA (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 diet to maintain a stable INR, fluctuating renal function (which can affect anticoagulation with DOACs), and
and cardiac tamponade are rare \((18,21)\) from the first hemorrhage event to diagnosis is 1.5 months.\(^{[22]}\) The patient was monitored closely and ASA 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.\(^{[27-29]}\) 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.\(^{[3]}\) 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%. In 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
### 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 |
|-----|------|---------|----|-----------------|------------|----------------|---------------------|-------------|---------|
| [31] | 1974 | 47/M | NHL | Skin, hematuria | <1 | — | HFVIII | CC + CY | CR |
| [32] | 1998 | 40/M | NHL | Skin, hematuria | 3 | 4 | HFVIII | CC | CR |
| [33] | 2000 | 51/M | NHL | Brusing | — | 250 | aPCC | IMV + CO | NR |
| [34] | 2000 | 53/F | NHL | Dental extraction | 5 | 12 | — | CC + CY | CR |
| [35] | 2001 | 61/M | NHL | Post-surgery | — | 22 | rFVIIa | CC | CR |
| [36] | 2005 | 46/M | NHL | Muscle, retropitoneal | <1 | 20.8 | rFVIII + tranexamic A | IMV + R + CC | CR |
| [37] | 2015 | 81/M | NHL | Skin, muscle | <1 | 5 | — | CC and specific NHL | CR |
| [38] | 1982 | 66/F | CLL | Skin, hematuria, retropitoneal | <1 | 100 | CP + PE | CC + CY | CR |
| [39] | 1993 | 82/F | CLL | Skin, retropitoneal | 4 | 9 | DDVAP | IVG + CC | CR |
| [40] | 1995 | 68/M | CLL | Dental extraction | 11 | 1 | — | IVG | CR |
| [41] | 1997 | 59/M | CLL | Skin, Gl | — | 38 | aPCC | — | CR |
| [42] | 1999 | 65/F | CLL | Skin, retropitoneal | 4 | 20 | PFVIII + PE | CY + fludarabine | CR |
| [43] | 2000 | 71/M | CLL | Skin | <1 | 64 | PFVIII | — | Died |
| [44] | 2000 | 57/M | CLL | Skin | 2 | 28 | PFVII | — | CR |
| [45] | 2003 | 70/M | PMN/MDS | Skin | 4 | 10 | — | — | — |
| [46] | 2005 | 58/M | PMF/AML | Skin | 4 | 10 | — | — | — |
| [47] | 2000 | 56/M | MM | Skin, muscle | <1 | 18.4 | rFVIIa | CC + CY + R | CR |
| [48] | 2015 | 82/F | LGLL | Skin, glomerulonephritis | 6 | 8 | — | CC + MG | CR |
| [49] | 2001 | 77/F | CLL | Skin, retinal | 6 | 2 | — | CC | CR |
| [50] | 2017 | 81/M | NHL | Muscle | <1 | 46 | aPCC | CC | CR |
| [51] | 2007 | 80/F | CLL | Skin, muscle | 2 | 10 | — | CC + CY | CR |
| [52] | 2015 | 55/M | CLL | Brusing, hemoptaxia | 5 | 66 | HFVIII + rFVIIa/aPCC | CC + CY | PR |
| [53] | 2017 | 75/M | CLL | Muscle | <1 | 18.4 | rFVIIa | CC + CY + R | CR |
| [54] | 2015 | 82/F | LGLL | Skin, retinaxia | 6 | 2 | — | — | — |
| [55] | 2000 | 65/M | WM | Skin | 2 | 700 | aPCC + HFVIII + PE | CC + CY | — |
| [56] | 1994 | 52/M | MM | Skin, muscle | 2 | 28 | HFVIII + PE + CC | CC | Died |
| [57] | 2000 | 58/F | MM | Skin, Gl | <1 | 28 | PFVIII + aPCC + PE | CC | Died |
| [58] | 2005 | 56/M | MM | Post-surgery | 6 | 20 | aPCC | CC + CY | Died |
| [59] | 2012 | 45/M | MM | Post-surgery | 6 | — | — | Specific MM | CR |
| [60] | 2012 | 70/M | MM | Skin, retinaxia | <1 | 11.2 | — | Cytotoxan | PR |
| [61] | 2012 | 65/M | MM | Skin, pericardial effusion | 5 | 9.5 | aPCC | IVG + R | CR |
| [62] | 2015 | 67/F | MM | Skin, bone | — | 2 | 4.85 | — | CC | CR |
| [63] | 2015 | 64/M | MM | Skin, hemoptaxis | 17.3 | 5 | rFVIIa | VTD | CR |
| [64] | 2016 | 45/M | MM | Muscle | 2 | 2.6 | rFVIIa | R + CY + V | CR |
| [65] | 2017 | 67/M | MM | Skin, muscle | 28 | — | HFVIII | — | CR |
| [66] | 2017 | 67/M | MM | Skin, muscle | 1.4 | 18.4 | aPCC | CC + CY + V | CR |
| [67] | 1986 | 55/F | AML | Skin | 4 | 10 | — | — | — |
| [68] | 2000 | 53/F | AML | Skin, Gl | 1 | 123 | — | CC | CR |
| [69] | 2005 | 64/F | AML | Gl | 3.9 | 1.7 | PFVIII + DAVAP + aPCC | CC | CR |
| [70] | 1991 | 75/F | MDS | Skin, muscle | 2 | 420 | — | CC | CR |
| [71] | 2000 | 79/M | MDS | Post-surgery | 1 | 22 | PFVIII | — | Died |
| [72] | 2003 | 71/M | MDS | Skin, muscle | 24 | 9 | rFVIIa/apCC + HFVIII | — | Died |
| [73] | 2012 | 84/M | MDS | Skin, muscle | 3 | 3 | rFVIIa | CC | Died |
| [74] | 2014 | 58/M | CMML | Skin, muscle | <1 | 200 | rFVIIa + aPCC | CC + CY | CR |
| [75] | 2015 | 79/F | CMML | Brusing | — | 120 | rFVIIa | CC | Died |
| [76] | 2016 | 51/M | CMML | Post-surgery | — | 107 | — | CC + CY | Died |
| [77] | 2015 | 54/M | CMML | Skin | — | 21 | — | CC | CR |
| [78] | 2015 | 71/M | CMML | Skin, hematuria | 6.7 | 7.4 | HFVIII | HU, IVG | CR |
| [79] | 2000 | 58/M | OML | Muscle | 2 | 58 | rFVIIa | CC | CR |
| [80] | 2001 | 53/F | OML | Gl | — | 29 | PFVIII | — | CR |
| [81] | 2012 | 80/M | OML | Muscle | <1 | 200 | aPCC | — | CR |
| [82] | 2004 | 74/F | PMF | Retropitoneal | <1 | 386 | PFVIII + aPCC | — | Died |
| [83] | 2013 | 77/M | PMF/AML | Skin | — | — | rFVIIa | CC + CY + R | CR |
| [84] | 2016 | 66/M | PMF | Post-surgery, muscle | <1 | 17.3 | rFVIIa/apCC | CC + R | PR |
| [85] | 2003 | 71/M | MPN/MDS | Skin, muscle | 24 | 9 | HFVIII + rFVIIa + aPCC | CC + CY | CR |
| [86] | 2011 | 74/F | ET | Skin | 4 | 5.8 | DDVAP + aPCC | CC | CR |
| [87] | 2012 | 68/F | ET | Skin, stroke | <1 | 17 | FFP | — | Died |

A = acid, AML = acute myeloid leukemia, APCC = activated prothrombin complex concentrates, C = cryoprecipitate, CC = cryocorticoids, CO = cyclosporine, CR = complete response, CY = cyclophosphamide, GI = gastrointestinal, HFVIII = human factor VIII, HU = hydroxyurea, MDS = myelodysplastic syndrome, MM = multiple myeloma, NHL = non-Hodgkin lymphoma, NR = not response, PE = plasma exchange, PFVII = porcine factor VII, PMF = primary myelofibrosis, PR = partial response, R = rituximab, rFVIIa = recombinant activated FVII, T = thalidomide, V = bortezomib, WM = Waldenström macroglobulinemia.

† Patient also received interferon-α.

‡ Patient also received fudarabine.

* Patient also received cytoxan.

1 Died to infection.
cases.\textsuperscript{12,3,5} Underlying malignancy is present in 10\% to 20\% in the most important registers.\textsuperscript{12,3,5,14} 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.\textsuperscript{30} Of the hematological malignancies, which are less frequently associated with AHA than are solid tumors, lymphoid neoplasms were the most frequent.\textsuperscript{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.\textsuperscript{31} A few cases with CLL have been reported since 2007.\textsuperscript{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.\textsuperscript{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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