CASE REPORT

Acquired haemophilia A with a recalcitrant high-titre factor VIII inhibitor in the setting of interstitial lung disease

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SUMMARY

Acquired haemophilia A (AHA) is a bleeding disorder that results from autoantibodies against factor VIII (FVIII). A 70-year-old man with a history of interstitial lung disease presented with spontaneous bleeding into his thigh. He had undetectable FVIII levels and a high-titre FVIII inhibitor (>2000 Bethesda units/mL) and was diagnosed with AHA. He had several relapses, required multiple haemostatic and immunosuppressive treatments but eventually achieved a stable remission after 2 years of therapy.

Our patient matches the typical elderly male demographic of AHA. His relapsing course with remarkably high and persistent inhibitor titre highlights the need for close monitoring and aggressive upfront treatment. Whereas cyclophosphamide and steroids are often used first line in AHA, rituximab has also shown efficacy in refractory patients with high inhibitor levels. The FVIII and inhibitor concentration on presentation have been associated with treatment response and may be used as prognostic factors to tailor immunosuppressive regimens.

BACKGROUND

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by neutralising autoantibodies directed against human factor VIII (FVIII). Formation of these inhibitor autoantibodies is idiopathic in about half of cases but can be associated with underlying autoimmune conditions, malignancy or pregnancy.¹ The disorder exhibits a bimodal age distribution, occurring most commonly in men older than 60 years, as well as in young women, often in the postpartum period.^{2,3} Diagnosis is generally made following a bleeding event accompanied by laboratory confirmation of a prolonged activated partial thromboplastin time (aPTT) which does not correct with mixing, low FVIII levels and a positive FVIII inhibitor assay.

The bleeding episodes in AHA typically present as muscle or soft tissue bleeds, as opposed to the haemarthroses that characterise congenital haemophilia.⁴ Acutely, haemostasis is achieved with bypassing agents such as recombinant activated factor VII or activated prothrombin complex concentrate FVIII inhibitor bypassing activity (FEIBA). Recently, a recombinant porcine FVIII (OBI-1 or Obizur), which avoids neutralisation by human autoantibodies, has been explored as

a promising alternative haemostatic therapy for AHA.^{5,6} Antifibrinolytic agents, such as aminocaproic acid and tranexamic acid, can also be used.

Immediately following diagnosis, immunomodulatory agents including steroids, cyclophosphamide and rituximab are used with the goal of early eradication of FVIII inhibitor.^{7,8} First-line treatment commonly involves steroids either alone or in combination with cyclophosphamide, but comparative studies to inform treatment guidelines are limited and clinical experience often guides management.⁹ Further case reports and randomised studies will improve understanding and inform optimal immunosuppressive regimens in AHA patients with varying disease profiles.

CASE PRESENTATION

Here, we report a case of AHA in a 70-year-old man with interstitial lung disease (cryptogenic organising pneumonia), who required multiple haemostatic and immunomodulatory therapies over the course of 2 years, before eventually achieving a complete remission (figure 1). The patient presented in December 2013 (day 1) with gradual onset right flank and thigh pain, and was found to have a thigh haematoma on CT imaging, along with a drop in haemoglobin from 13.6 to 8.6 g/dL. He recalled bruising in his arms and a right eye periorbital haematoma dating back a few months, but both had resolved spontaneously; otherwise, there was no personal or family history of abnormal bleeding.

INVESTIGATIONS

The patient's aPTT was prolonged at 80 s, and did not correct in the context of a mixing study. FVIII activity was undetectable, and FVIII inhibitor was quantified at 1850 Bethesda unit (BU)/mL. His international normalised ratio and thrombin time, as well as factor IX and XI levels, were normal.

DIFFERENTIAL DIAGNOSIS

Several causes of bleeding diathesis were entertained on this patient's presentation. He could not recall any trauma, and he was not on any anticoagulant medication. Failure of the aPTT to correct with a mixing study ruled out congenital haemophilias (which were also unlikely given his age of presentation and lack of family history), as well as certain forms of von Willebrand Disease, which can also result in low FVIII levels and prolonged aPTT. The

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Figure 1 Timeline of bleeding events and therapies. FEIBA, factor VIII inhibitor bypassing activity; PTT, partial thromboplastin time.

diagnosis of acquired haemophilia A became clear with the result of undetectable FVIII level and high FVIII inhibitor titre.

TREATMENT

The patient did not require acute haemostatic therapy on his first presentation but was initiated on prednisone (60mg daily) and then oral cyclophosphamide (150mg daily). He was discharged after 5 days, but was readmitted on day 23 with a spontaneous left knee haemarthrosis in the setting of weaning his prednisone to 40mg per day. On this admission, he received FEIBA as well as four doses of weekly rituximab.

He was admitted a third time on day 135 with an abdominal wall haematoma in the setting of his peak inhibitor titre of 3936 BU/mL. He again received FEIBA, this time with the addition of aminocaproic acid. Oral cyclosporine 150mg twice daily was added to his regimen of cyclophosphamide and prednisone. Treatment with cyclophosphamide was complicated by neutropaenia, and this was ultimately discontinued on day 225; his neutrophil count recovered with administration of Neulasta.

On day 257, his inhibitor titre had fallen to 76, though he was experiencing increased bruising and received a second course of weekly rituximab. In the setting of a worsening tremor, most pronounced in his hands, cyclosporine was weaned and eventually discontinued in lieu of oral mycophenolate (500mg twice daily) on day 566.

OUTCOME AND FOLLOW-UP

With mycophenolate and low-dose prednisone as his maintenance medications, his aPTT continued to improve and then finally normalised in the setting of an undetectable inhibitor and normal plasma FVIII levels.

Of particular note, this patient's biopsy-proven cryptogenic organising pneumonia remained stable but did not appreciably improve (either symptomatically or radiographically) on the

various immunosuppressive regimens that were employed in the treatment of his AHA.

DISCUSSION

Autoimmune conditions such as lupus, rheumatoid arthritis and Sjogren's syndrome have been associated with approximately 18% of AHA cases^{10 11}; recent studies have also reported AHA associated with myasthenia gravis and TTP.^{12 13} Ours is a rare case of AHA in a patient with cryptogenic organising pneumonia. His lung disease, though not associated with a distinct underlying rheumatological condition, may reflect an underlying predilection to autoimmunity.

Though this older male patient fit a typical AHA demographic profile, his case was notable for a markedly and persistently elevated inhibitor titre (peak BU/mL 3936). The inhibitor assay can be technically challenging and depends on the expertise of one's laboratory staff, especially in the context of high-titre inhibitors where errors in preparing dilutions can greatly affect the numerical value ascribed to the Bethesda units. Also, since the relationship between inhibitor concentration and the effect on residual FVIII activity is not perfectly log-linear for type 2 inhibitors seen in AHA, the Bethesda assay can only provide a rough estimate of inhibitor potency.¹⁴ Nevertheless, this patient's markedly high inhibitor titre may have predicted his protracted and relapsing course.

Patient's perspective

I remember meeting you for the first time when you told me that I had acquired haemophilia. It was a very scary time. The second thing that I remember most was on my second visit to the haematology clinic when a nurse drew my blood and applied a dressing. I kept the dressing on for 3 days, but when I finally took it off at home, I was still bleeding and dripping blood.

I remember coming home from our daughter's home in Maine when I was bleeding into my stomach wall, and how painful this was driving from Maine to the hospital in Boston.

The one thing I remember most was when I stopped taking the cyclophosphamide because my white blood count had become so low. At this point I was given an injection (Neulasta) in my left arm. This injection caused the most pain that I had ever felt—through the front of both legs from my hips to my knees. I included this memory for some other patients with acquired haemophilia who may have to go through similar treatments and say to you: 'you will have to tough it out, and it will go away.'

Finally I must say that my team are the best medical professionals I have ever met. Thank you for saving my life.

Patient's wife

It was Christmastime when my husband began to show signs of his body swelling in his hip and legs and stomach. We went to the doctor and blood tests and exams showed nothing. By New Year, the local hospital took him by ambulance to Massachusetts General Hospital (MGH). It was at MGH that the team of doctors discovered his rare condition. We are grateful that my husband is here to celebrate our 50th anniversary this summer.

My husband's haematologist was the only one who took me aside, gave me a hug and asked 'how are you doing?' Most people forget that the patient isn't the only one suffering. My hope is that this medical journal article will be a learning tool and that no other family will have to go through a 'trial by error' treatment process to get through this strange and rare condition.

Learning points

- ▶ Acquired haemophilia A (AHA), a rare bleeding disorder caused by autoantibodies against factor VIII (FVIII), can be idiopathic (50%) or associated with underlying autoimmune disease, malignancy or pregnancy.
- ▶ The differential diagnosis for a spontaneous soft tissue or intramuscular haematoma in an elderly patient includes anticoagulant medications and acquired factor inhibitors, and should prompt a workup including complete blood count and coagulation parameters (international normalised ratio, partial thromboplastin time (PTT), thrombin time), followed by mixing study and coagulation factor levels if PTT is prolonged.
- ▶ Patients with AHA should receive upfront haemostatic therapy and immunosuppressive treatments (including steroids, cyclophosphamide and/or rituximab) to eradicate inhibitor autoantibodies and reduce the risk of future bleeding events.
- ▶ Given the risk of relapse (>20%, at a median of 7–9 months), patients require frequent monitoring of activated PTT and FVIII level after clinical remission.
- ▶ High-presenting inhibitor titre and low FVIII level may predict poor response to immunosuppressive treatments and be an indication for more aggressive combination regimens. More studies are needed to establish optimal immunosuppressive regimens for varying disease profiles.

A study of the European Acquired Haemophilia (EACH2) Registry showed that patients with lower FVIII and higher titre inhibitors at presentation were slower to achieve remission.⁷ Similarly, the GTH-AH 01/2010 study showed that low baseline FVIII levels were associated with lower likelihood of achieving clinical remission (CR), more prolonged and intensive immunosuppressive regimens and higher mortality rate.¹⁵ A 2009 meta-analysis of 377 AHA cases demonstrated a trend towards lower CR rates in patients with very high inhibitor titres, as well as an increased risk of death in patients with persistent inhibitor.¹⁶

Extending these results, Tiede *et al* suggest that FVIII level and inhibitor concentration at presentation can be used as prognostic factors to tailor immunosuppressive regimens in AHA.¹⁵ Certainly, these parameters in our patient contributed to our decision to treat with combination B-cell and T-cell-directed therapies rather than with steroid monotherapy. Though this approach seemed logical, evidence regarding optimal immunosuppressive regimens in different AHA disease profiles is limited. The EACH2 registry study showed that steroids and cyclophosphamide together were more effective than steroids alone or rituximab, with CR rates of 70% or higher after a median of 5 weeks.⁷ However, rituximab, while slower to achieve inhibitor eradication, may produce a more stable CR with fewer relapses⁷ and is recommended as second-line therapy for refractory patients, as well as in combination with other agents for patients with high inhibitor titres.^{8–11} Other third-line agents including azathioprine, calcineurin inhibitors and vincristine may also be used in refractory or relapsed patients.¹⁷ Recently, the proteasome inhibitor bortezomib has also been reported to successfully eradicate inhibitor in refractory acquired haemophilia.¹⁸

In our patient, initial steroid therapy along with cyclophosphamide, rituximab and cyclosporine were only transiently effective, with continued relapses for the first 6 months and a persistent inhibitor for almost 2 years. Though the transition

to mycophenolate late in his course preceded the normalisation of FVIII level and eradication of his inhibitor, its true role in his remission is unclear.

This case of persistent AHA, manifested by multiple bleeding events requiring both acute haemostatic and long-term immunosuppressive treatments, underscores the importance of frequent monitoring. Relapse rates in AHA exceed 20%, with median time to relapse of 7–9 months.^{19–20} After resolution of an acute episode, monitoring with physical exam, complete blood count, aPTT and FVIII level every month for the first 6 months, every 2–3 months up to 1 year and every 6 months thereafter is recommended.^{9–17}

This case also lends support to the notion that presenting inhibitor titre and factor VIII level may be useful parameters in predicting response to immunosuppressive treatments and tailoring therapies accordingly. More data are needed to establish optimal immunosuppressive regimens in AHA patients with varying disease profiles.

Contributors LS and DBS researched and drafted the entirety of the manuscript.

Competing interests None declared.

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