CASE REPORT

Development of acquired haemophilia A in a patient treated with alemtuzumab for multiple sclerosis

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SUMMARY

This case illustrates a 36-year-old man who presented with a factor VIII (FVIII) inhibitor (acquired haemophilia A) with cutaneous bleeding and a significant thigh haematoma. No traditional risk factors for the development of a FVIII inhibitor were identified. However, previous treatment with alemtuzumab for multiple sclerosis was noted in the patient's history. Alemtuzumab is an anti-CD52 monoclonal antibody and is known to be associated with the development of a number of autoimmune conditions, with a delay in onset of these conditions as long as 5 years after the cessation of treatment. To our knowledge, there have only been three previously documented cases of a FVIII inhibitor in the setting of alemtuzumab therapy. This case adds further evidence to the current body of literature suggesting alemtuzumab as a causative agent for the development of an FVIII inhibitor.

BACKGROUND

Alemtuzumab is an anti-CD52 monoclonal antibody which predominantly results in prolonged T-cell depletion, as well as much more rapidly recovering reduction of CD52 expressing B-cell, natural killer cell and mast cell populations. Alemtuzumab has many uses both in haematology as well as other medical specialties. It has been used for a wide variety of conditions including multiple sclerosis,[1] aplastic anaemia,[2] chronic lymphocytic leukaemia,[3] stem cell transplantation,[4] lung transplantation,[5] renal transplantation[6] and vasculitis.[7]

There has been an established association between alemtuzumab and the development of autoimmune conditions. Some authors have proposed that this is the result of depletion of regulatory T-cell populations allowing unregulated development of autoimmunity. The most commonly associated autoimmune conditions following treatment with alemtuzumab include Grave's disease and ITP.[4]

Here, we report what we believe to be the fourth documented case of a factor VIII (FVIII) inhibitor, occurring in a 36-year-old man following treatment with alemtuzumab for multiple sclerosis.

CASE PRESENTATION

Our patient is a 36-year-old man who presented to his general practitioner with a 4-week history of easy bruising and several episodes of epistaxis. On presentation, he described extensive bruising to his right forearm, as well as bruising to his right thigh with no antecedent trauma. He had no history of bleeding diatheses and had previously undergone an uncomplicated removal of wisdom teeth without excessive bleeding. His medical history included multiple sclerosis which was in remission following treatment with alemtuzumab, with one dose administered 5 years prior, and a subsequent dose administered 4 years prior. He had not received any other disease-modifying drugs prior to starting alemtuzumab, or in the period prior to this presentation.

INVESTIGATIONS

Initial investigation by the general practitioner revealed a prolonged activated partial thromboplastin time (APTT) of 88 s which corrected completely on mixing studies, a normal full blood count with no evidence of thrombocytopenia, as well as normal renal and liver function tests. Subsequent investigations were requested including repeat coagulation studies and FVIII and factor IX assays. A lupus anticoagulant was not performed as the patient had a bleeding diathesis and an APTT that corrected on mixing studies.

While awaiting the results of these investigations, the patient developed severe pain and swelling affecting his left thigh necessitating hospital admission. Evaluation in hospital revealed the presence of left thigh haematoma without evidence of compartment syndrome. His repeat APTT was again prolonged, at 96 s, and he was noted to have FVIII levels of <0.01. An FVIII inhibitor was suspected, and subsequently confirmed with Bethesda assay revealing an FVIII inhibitor level of 7 BU/mL.

DIFFERENTIAL DIAGNOSIS

Investigations were undertaken to identify a potential cause for the development of his FVIII inhibitor including CT neck/chest/abdomen/pelvis, anti-neutrophil cytoplasmic antibody (ANCA), antinuclear antibody, extractabel nuclear antigen, hepatitis B, hepatitis C, HIV, cytomegalovirus and Eptstein-Barr virus testing, flow cytometry for lymphoproliferative disorders, serum protein electrophoresis, free light chains and immunoglobulin levels. These investigations did not reveal any underlying cause and there was no evidence of an underlying rheumatological, malignant or autoimmune phenomenon.

TREATMENT

Treatment was initiated with recombinant factor VIIa (rFVIIa), as well as prednisolone at a dose of 1 mg/kg daily. After 4 days, there was improvement in his left thigh haematoma so his rFVIIa was

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ceased. Immunosuppression with prednisolone was continued. After 1 week, there was further bruising and bleeding, repeat testing revealed an undetectable FVIII level and rituximab was started at a dose of 375 mg/m^2 per week for 4 weeks.

OUTCOME AND FOLLOW-UP

Following the initiation of rituximab, there was both clinical and laboratory evidence of improvement. After 2 weeks of therapy, his APTT had normalised and his FVIII inhibitor was no longer detectable. After the four doses of rituximab, no further treatment was administered.

The patient has now undergone 4 years of follow-up with no clinical or laboratory evidence of relapse. No other potential cause has been identified during this follow-up period, and we believe that his development of an FVIII inhibitor may be attributable to his treatment with alemtuzumab; however, it is recognised that FVIII inhibitors may occur in patients with multiple sclerosis who have not been treated with disease-modifying drugs.[8–10]

DISCUSSION

FVIII inhibitors (acquired haemophilia A) represent the most common autoantibody directed against a clotting factor. It occurs at a rate of approximately one per million per year, and has an 80% risk of severe or life-threatening bleeding with a mortality rate of approximately 20%. Risk factors include female gender, pregnancy/postpartum, malignancy and presence of other autoimmune or rheumatological conditions. While approximately 40%–50% of cases are associated with these risk factors, the remainder of cases will occur in the absence of any clear precipitant.[11]

The development of an FVIII inhibitor is often heralded by the onset of easy bruising and prolonged bleeding times. In comparison with congenital haemophilia A, which commonly presents with spontaneous haemarthroses, the most common sites for bleeding in acquired haemophilia A include bleeding into the muscles, cutaneous bleeds and haematuria, with haemarthroses accounting for only 2% of bleeds in one case series.[12]

The typical abnormality seen on the coagulation profile is a prolonged APTT, occurring once FVIII activity levels fall below 45%. The APTT may initially correct on mixing with normal plasma but will not correct following prolonged incubation of 1–2 hours duration, due to the time-dependent function of FVIII inhibitors.[11] This is followed-up by checking factor levels, excluding interference from a lupus anticoagulant if the APTT does not fully correct prior to incubation, and a quantitative assay, most commonly the Bethesda assay, to check the level of FVIII inhibitor.[13]

There have been three previously reported cases of an FVIII inhibitor in a patient previously treated with alemtuzumab. The first case was in a patient treated for ANCA-associated vasculitis which demonstrated delayed onset of 5 years from the cessation of treatment.[7] The second case was a patient treated with alemtuzumab for multiple sclerosis who developed an FVIII inhibitor within 2 years of therapy.[14] The third case was in a patient treated with alemtuzumab for multiple sclerosis, again within 2 years of therapy.[15]

There have also been at least three reported cases of patients with multiple sclerosis who have developed an FVIII inhibitor without a history of alemtuzumab exposure. In two of these cases, there was no reported exposure to disease-modifying drugs.[8 9] The third reported case details a patient with multiple sclerosis who underwent autologous haematopoietic stem cell transplantation with busulfan and antithymocyte globulin. Post-transplant, this patient received therapy with interferon beta-1a (Avonex, Biogen) for 18 months prior to the development of an FVIII inhibitor. The authors in this study reported possible contribution of the interferon beta-1a; they did however acknowledge that this complication has previously only been observed with interferon-alpha.[10]

The development of an FVIII inhibitor as seen in this case adds yet another to the list of potential complications that clinicians need to be aware of when using alemtuzumab or treating patients with multiple sclerosis. Given the potentially life-threatening outcomes associated with this condition, it is prudent that clinicians recognise, and investigate for, FVIII inhibitors if there is any evidence of increased bruising, bleeding or abnormalities of the coagulation profile in patients being treated with alemtuzumab.

Learning points

- Alemtuzumab is an anti-CD52 monoclonal antibody which is becoming more commonly used across a wide range of disciplines.
- Alemtuzumab is known to cause multiple autoimmune side effects and the development of a factor VIII (FVIII) inhibitor appears to be one of them.
- Autoimmune side effects have been reported more than 5 years after the last administration of alemtuzumab.
- Clinicians need to be aware of the risk of FVIII inhibitors with alemtuzumab and we should remain vigilant in reporting such cases.
- FVIII inhibitors may also be seen in patients with multiple sclerosis in the absence of treatment with disease-modifying drugs.

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