Unusual association of diseases/symptoms

Acquired factor VIII deficiency presenting as a floor of the mouth swelling

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Summary

The authors report the case of a patient with previously undiagnosed acquired haemophilia A who presented to the accident and emergency department with a swollen tongue and difficulty in swallowing. There were no signs of trauma or obvious dental infection. She was admitted onto a high dependency unit for observation. Over the course of the day, the floor of her mouth and neck became increasingly swollen to the extent that she developed breathing difficulties. She was transferred to an intensive care unit, where she was intubated to protect her airway from further compromise. Acquired factor VIII deficiency was diagnosed and appropriate treatment commenced. Despite intervention, her respiratory and cardiovascular functions deteriorated. Following discussions between the medical specialities involved in her care and her family, the decision was made to withdraw support. The patient passed away 96 h after admission.

BACKGROUND

Acquired haemophilia is a rare bleeding disorder that develops due to spontaneous autoantibody formation against a coagulation factor, usually factor VIII. It has a reported incidence of 1.48 per million/year.^{1 2} It typically occurs in the older and is associated with other auto-immune conditions, pregnancy and underlying malignancy.³ In most cases, the diagnosis is made during the investigation of abnormal bleeding, but a minority of patients are diagnosed from a deranged coagulation profile. The usual pattern of bleeding is different from that of inherited haemophilia, where haematuria as well as bleeding into muscles and joints are commonly observed.⁴

This case involves a rare disorder which had a very unusual presentation of an oral swelling, with no obvious signs of trauma or dental infection.

CASE PRESENTATION

A 65-year-old Caucasian female presented to the accident and emergency department with a swollen tongue and difficulty in swallowing. Her tongue began to swell after a coughing fit 2 days earlier. There was no history of trauma, toothache, change in medication or contact with new or unusual substances. She had no previous similar experiences.

She suffered from ischaemic heart disease, type II diabetes mellitus, hypercholesterolaemia and chronic obstructive pulmonary disease. There was no history of bleeding problems. Medication included aspirin, clopidogrel, simvastatin, rampril, sublingual nitroglycerine spray, furosemide and domperidone. She was allergic to penicillin.

On initial presentation, her airway was patent and she was able to complete sentences and speak clearly. There was no evidence of stridor or drooling of saliva.

Initial observations included a respiratory rate of 20 breaths per minute, oxygen saturations of 94% on room

air, pulse rate of 90 beats per minute and regular blood pressure was 134/91 mm Hg and a mild fever at 37.5°C. Cardiovascular, respiratory and gastrointestinal examination was unremarkable. She had a body mass index of 33.

She was fully alert and orientated. Examination of the head and neck revealed a firm, bilateral, uniform swelling of the submandibular and sublingual regions. There were no palpable enlarged cervical lymph nodes, and the thyroid gland was of normal size.

Intraoral examination revealed a swollen, bruised-looking floor of mouth, which was pushing the tongue into an elevated and protruded position. The tongue itself did not appear enlarged. There was no obvious sign of trauma or source of infection. There was no pooling of saliva.

INVESTIGATIONS

Her coagulation profile revealed a prolonged activated partial thromboplastin time (APTT) at 97 s. Thrombin time (TT) and Prothrombin time (PT) were normal, at 11 s and 13 s respectively. Her C reactive protein level was raised at 48 mg/ml. The rest of her blood tests were normal. CT showed thickening and oedema throughout the soft tissues of the floor of mouth and upper neck, consistent with infection (figure 1). However, no obvious source was demonstrated, and there was no drainable collection. A pan-facial radiograph supported the clinical findings of no obvious dental infection.

DIFFERENTIAL DIAGNOSIS

- ▶ Ludwig's angina (acute cellulitis of the submandibular region, usually due to infection)
- ▶ Trauma – to floor of mouth or neck
- ▶ Ace inhibitor related angioedema
- ▶ Allergic reaction – to foodstuff or other chemical
- ▶ Coagulopathy.

Figure 1 (A,B) CT images show sublingual swelling with no evidence of a discrete mass or collection.

TREATMENT

The patient was treated with oxygen, steroids, intravenous fluids and intravenous broad spectrum antibiotics. She was admitted onto a high-dependency unit for observation. Her aspirin, clopidogrel and ramipril were stopped.

Over the course of the day, her floor of mouth and neck became increasingly more swollen, to the extent that she developed breathing difficulties. She was transferred to an intensive care unit, where she was intubated to protect her airway from further compromise.

Further coagulation studies revealed a factor VIII autoantibody titre of 10.5 Bethesda units.

Acquired factor VIII deficiency was diagnosed, and she was treated with recombinant factor VII and systemic corticosteroids. She deteriorated over the next 24 h, with increased neck swelling and localised bleeding. An alternative clotting cascade bypassing agent, factor eight autoantibody bypassing activity (FEIBA), was therefore given. APTT improved transiently to 71 s, before deteriorating again to 91 s. She started to bleed into her lungs. Her neck and floor of mouth continued to swell. After another 24 h, there was still no improvement. Her factor VIII autoantibody titre levels fell to 4.2 Bethesda units, indicating that her autoantibody titres were falling in response to her immunosuppressive steroid therapy. However, as her clotting function was still abnormal, her respiratory and cardiovascular functions continued to deteriorate. Her arterial blood gas showed oxygen partial pressure of 6.2 kPa on 100% inspired oxygen. She developed a worsening bradycardia, despite maximal inotropic intervention. Regardless of all possible medical intervention, her clinical condition continued to worsen.

OUTCOME AND FOLLOW-UP

Following discussions between the medical specialities involved in her care and her family, the decision was made to withdraw support. The patient passed away 96 hours after admission.

DISCUSSION

Acquired haemophilia is a rare disorder with potentially life threatening complications. It classically presents with purpura or bleeding into soft tissue and muscle spaces.

Severe bleeding can cause complications such as compartment syndrome, haemorrhagic stroke and airway compromise.

Mortality from 8% to 22% are reported, with most deaths occurring within the first few weeks of initial presentation.^{5 6}

Conditions associated with acquired haemophilia are listed in table 1. In nearly half of the reported cases, it occurs spontaneously in older patients who do not have any of the recognised risk factors.

Establishing the diagnosis of acquired haemophilia

The most common screening abnormality seen in a patient with suspected acquired haemophilia is an isolated prolonged APTT, with a normal PT, TT, and platelet count.⁷

To confirm the diagnosis of acquired haemophilia, a mixing study can be performed; a mixture of normal control plasma and patient's plasma will correct the test value to normal range in the presence of a factor deficiency, but not in the presence of an inhibitory autoantibodies. If acquired haemophilia is still suspected, further tests should be carried out to rule out heparin contamination and lupus anticoagulant.^{8 9}

Clinical management

Treatment with factor VIII concentrates is ineffective. The main aims of treatment in acquired haemophilia are to control bleeding, eradicate the autoantibodies and identify and treat any underlying disorder. The severity of bleeding can vary greatly, and local measures should always be used in an attempt to achieve haemostasis. In cases where the autoantibody level is low (<5 Bethesda units), the administration of recombinant factor VIII products may control bleeding. If the autoantibody level is high (>5 Bethesda units), recombinant factor VIII products are ineffective. Instead, severe bleeding should be treated with bypassing agents such as FEIBA (FEIBAH; Baxter AG, Vienna, Austria) or recombinant activated factor VII (NovoSevenH; NovoNordisk A/S, Bagsvaerd, Denmark).¹⁰ Both products have a similar efficacy, stopping bleeding in around 80% of cases.¹¹

Administration of by-passing agents is not a long-term treatment option due to cost and mode of delivery. Alongside the by-passing agent, immunosuppression with corticosteroids should be started as soon as the diagnosis

Table 1 Factors associated with acquired haemophilia A

Pregnancy
Autoimmune disorders
Inflammatory bowel disease
Diabetes
Dermatologic disorders (pemphigus vulgaris)
Respiratory disease (asthma, chronic obstructive pulmonary disease)
Drug reactions
Acute hepatitis B or C
Malignant disease
Surgery

is confirmed. This will help eradicate any existing autoantibodies. A broad range of other treatment regimens are reported in the literature. Rituximab, cytotoxic agents such as cyclophosphamide and azathioprin, ciclosporin, intravenous immunoglobulins, immunoadsorption and FVIII immune tolerance induction have all been used to eradicate the neutralizing autoantibodies.

Unfortunately, in this case adequate, haemostasis was not achieved. The immunosuppressive agents were lowering the antibody titres, but this alone was not sufficient to produce a clinical improvement.

To date, there has not been a reported case of a patient with previously undiagnosed acquired haemophilia A, presenting with an oral swelling in the UK.

Learning points

- ▶ Acquired haemophilia is a rare disorder which can present with serious complications and be potentially fatal.
- ▶ This case highlights the importance of a coagulation screen and quick diagnosis of bleeding disorders for patients presenting to hospital with a recent and rapid oral swelling of unknown cause.
- ▶ Successful treatment requires both immediate haemostasis using bypassing agents to stabilise the patient's condition, and the prevention of further antibody production by immunosuppression to prevent further bleeding episodes.

Competing interests None.

Patient consent Obtained.

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