CASE REPORT

Diabetes mellitus and acquired haemophilia: new association?

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Accepted 3 April 2017

SUMMARY

Diabetes mellitus encompasses a group of highly prevalent carbohydrate metabolic disorders with an increasing incidence. Some subtypes are thought to be associated with other immune-mediated diseases. Acquired haemophilia on the other hand is a quite rare autoimmune disease that is thought to be secondary to the emergence of inhibiting anticoagulation factor VIII antibodies (inhibitors) in patients with previously normal haemostatic function. More recently, numerous different diseases have been associated with acquired haemophilia namely immune-mediated diseases, drugs and solid and haematologic neoplasms. The authors report on a case of a patient with new onset acquired haemophilia arising in the setting of diabetic ketoacidosis.

and dyspnoea. At the hospital admission, hypotension (blood pressure 60/31 mm Hg), tachycardia (120 bpm), tachypnoea (35 cpm) and hyperglycaemia (blood glucose 282 mg/dL) were present. No fever was detected. Laboratory workup showed a high anion gap metabolic acidemia (pH 7.32; bicarbonate 7.7 mmol/L; anion gap 24 mmol/L), ketonaemia (6.4 mmol/L) and acute kidney injury (creatinine 1.34 mg/dL; urea 58 mg/dL). No electrolyte imbalance or evidence of infection was present. The diagnosis of diabetic ketoacidosis was established, and with vigorous intravenous hydration along with insulin infusion, the acidosis resolved and the clinical status improved.

On the second admission day, the patient presented with gross haematuria and easy bruising, despite no other evidence of haemorrhagic dyscrasia.

BACKGROUND

Diabetes mellitus is a highly prevalent condition that is characterised by elevated blood glucose levels and that is linked to both microvascular and macrovascular complications. Diagnosis is made using well-established clinical and laboratory criteria.¹ This condition encompasses a large group of disorders with different behaviour and pathophysiological mechanisms. Depending on the subtype, some may be associated with or be caused by many diseases/drugs.

Acquired haemophilia A on the other hand is a quite rare, poorly understood and underdiagnosed entity. It often has a severe clinical presentation of sudden onset, being associated with a high mortality rate.²

Data regarding the association between diabetes and acquired haemophilia in the literature are scarce and questionable.³ The authors report on a case of a 23-year-old patient in the setting of a hospital admission for diabetic ketoacidosis is diagnosed with acquired haemophilia.

CASE PRESENTATION

A 23-year-old African female with a known medical history of idiopathic oligoarthritis, iron deficiency anaemia, ciprofloxacin induced toxic hepatitis and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome secondary to salazopyrine (the latter diagnosed 5 months before admission) that was being treated with prednisolone 30 mg once daily (id), pantoprazole 40 mg id and calcium + vitamin D supplements, presented to the accident and emergency department for abdominal pain

INVESTIGATIONS

Coagulation studies revealed a prolonged activated partial thromboplastin time (aPTT—80.7 s; normal range 23–38) and low factor VIII activity (1.5%; normal range 50%–150%) with no other changes in prothrombin time, platelet count, factor IX levels or Von Willebrand factor studies. There was no history of prior exposure to blood products or previous pregnancy. Factor VIII inhibitor was present in low titre (1.1 Bethesda units (BU)). For the investigation of possible causes of the newly diagnosed haemophilia, the patient underwent extensive laboratory studies (full autoimmune panel and tumour markers), cross-sectional imaging (CT of chest, abdomen and pelvis) and mammography that were all unremarkable.

Regarding diabetes, admission glycated haemoglobin was high (8.9%) and basal urinary peptide C levels were below the normal range (15.7 µg/day; normal range 17.2–181). Anti-islet cells, glutamate decarboxylase antibodies were negative but anti-insulin antibodies were weakly positive (2.4 IU/L).

TREATMENT

Bladder saline lavage halted the bleeding in less than 24 hours. Haemoglobin levels significantly dropped from an initial value of 14 mg/dL to a minimum of 7.3 g/dL without requiring blood transfusion. Due to the identification of coagulation factor (CF) VIII inhibitor, prompt immunosuppression was initiated. Glucocorticoid dose was only slightly increased (to prednisolone 40 mg/day—0.6 mg/kg/day) to prevent further glycaemic decompensation

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To cite: Tavares Bello C, Vasylenko Y, Esteves J, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-219807

and due to the emergence of CF VIII inhibitors during preadmission glucocorticoid regimen. Cyclophosphamide (125 mg/day) was also given as soon as the diagnosis was established, and this combination treatment strategy was kept for 4 weeks. After the initial bleeding episode, with therapy, no further haemorrhage was documented despite worsening of the aPTT (80.7 to 120 s), residual factor VIII activity ($<0.5\%$) and inhibitor levels (2.39 BU). Due to first-line eradication treatment failure, weekly rituximab (375 mg/m^2) along with prednisolone (1 mg/kg/day) were started.

For diabetes mellitus, high-dose intensive insulin therapy regimen was required to control hyperglycaemia (daily insulin requirements of 78 units).

OUTCOME AND FOLLOW-UP

After 4 weeks of rituximab and prednisolone, disease remission was achieved. The patient was maintained on corticosteroids, being the dose tapered over 8 months, after which, due to novel worsening of coagulation parameters (rise in aPTT despite no evidence of inhibitor), prednisolone dose was increased (from 10 to 20 mg/day). This was followed by aPTT normalisation and maintenance of undetectable inhibitor levels until present day (10 months later). Currently, the patient remains under corticosteroid therapy (prednisolone 15 mg/day) with no clinical evidence or reported history of significant bleeding.

Concerning diabetes mellitus, the patient maintains elevated insulin requirements, high glycaemic variability despite reasonably improved glycaemic control.

DISCUSSION

Diabetes mellitus is highly prevalent, with an estimated prevalence of 13.1% in the Portuguese population.⁴ Diagnosis is made using well-established clinical and laboratory (glycaemic) criteria. This condition encompasses a large group of disorders with different behaviour and pathophysiological mechanisms and includes: type 1 and 2 diabetes, latent autoimmune diabetes of the adult, maturity onset diabetes of the young (MODY), secondary diabetes (pancreatic insufficiency, drug induced diabetes, Cushing's syndrome, paraganglioma, acromegaly, etc), among others.¹ Type 2 diabetes is by far the most frequent subtype and has an insidious, often subclinical course. Most of the patients are diagnosed in the setting of occasional blood tests. On the other hand, hyperglycaemic emergencies are more frequently the presenting features of type 1 diabetes. Therapy usually consists of the treatment of any identifiable underlying cause, however, in the majority of the cases hypoglycaemic pharmacological therapy is required, ranging from oral and injectable antidiabetics, insulin to islet cell transplantation. Diabetes is associated with disabling microvascular and macrovascular complications if undertreated and therefore deserves our full engagement.¹ The reported case had no clear features of any of the known diabetes subtypes despite behaving like type 1 diabetes. Laboratory investigation revealed low titre of anti-insulin antibodies and detectable c-peptide levels. Treatment demanded high insulin doses. Immunosuppressive treatment with glucocorticoids further worsened glycaemic control.

Acquired haemophilia (AH) is generally more prevalent in men and has a bimodal age distribution with the first peak in the postpartum period (mean age 33.9 years) and a second more pronounced peak in the eighth decade of life (mean age 73.9 years). It has an estimated incidence of 1.3 to 1.5 per million/year, although many authors believe that this may be an underestimation since up to 20% of all cases are never diagnosed.⁵

It develops due to an acquired deficiency of CF secondary to anti-CF antibodies ('inhibitor').⁶ These antibodies are usually polyclonal IgGs and target more frequently factor VIII. Associations have been made with other immune-mediated conditions such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroiditis and bullous pemphigoid. Drugs, pregnancy and alloimmunisation due to previous exposure to blood products are also known associations.⁷ The hallmark clinical manifestation is bleeding, involving usually the subcutaneous tissue compartment. Some authors have also described haemorrhage to occur in other locations such as muscle, retroperitoneum, brain, respiratory, gastrointestinal and urinary tracts. Unexpectedly, as opposed to what is seen in congenital haemophilia A, haemarthrosis are exceedingly rare in AH.

AH should be suspected in patients with bleeding diathesis and an isolated prolonged aPTT. Diagnosis is confirmed by the detection of low CF activity in mixing studies along with positive anti-CF antibodies. Mixing clotting studies in acquired haemophiliacs usually fail to show aPTT normalisation after mixing patient's serum with non-haemophilic patient's serum (that has an adequate amount of CF). Antibody activity/strength is quantified in BU, being considered 5 BU the cut-off between low and high inhibitor titre.⁸

Treatment includes control and prevention of the bleeding episodes, inhibitor eradication (with immunosuppression) and ultimately diagnosis and treatment of underlying disorder.

Not all bleeding episodes need haemostatic treatment and many subcutaneous bleeds can be managed conservatively. If indicated, bleeding should be promptly treated with bypass agents such as recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (FEIBA). If the initial bypassing agent is ineffective, the alternative one should be tried at an early stage. The use of these agents should be cautious and dosing should be calculated according to current recommendations. It is believed that rFVIIa at doses higher than 90 g/kg is associated with an increased risk for thrombosis. Therefore, except in cases where it is used as rescue therapy, the latter agent cannot be recommended at high doses. When first-line therapy fails or in the setting of severe bleeding, FVIII replacement combined with plasmapheresis and immunoadsorption can be considered. In addition to the described agents, tranexamic acid is an acceptable option for all bleeds, namely those involving mucosal surfaces.⁹

Inhibitor eradication strategies include high-dose corticosteroids, cyclophosphamide and/or rituximab and should be employed at the time of diagnosis. Current literature supports combination therapy with corticosteroids (prednisolone 1 mg/kg/day) and cyclophosphamide (1.5 mg/kg/day) as first-line therapy. The latter approach has a reported response rate of 80% and should be employed for a maximum of 6 weeks. Rituximab, a monoclonal chimeric antibody to the B-cell CD20 antigen, has recently been shown to be promising, with a reported response rate of at least 90%. The regimens were weekly intravenous rituximab (375 mg/m^2) for 4 weeks. Resistant cases were effectively treated either with a second rituximab cycle or pulse-dosed intravenous cyclophosphamide.⁷

Since patient follow-up guidelines have not been developed so far, follow-up strategies remain largely empirical and should include regular clinical and laboratory evaluation. Prognosis is unpredictable. Spontaneous remission has been reported in 25% of cases,¹⁰ namely those associated with pregnancy and prior antibiotic exposure. Mortality remains unfortunately high (9.7 to 33%) and severe bleeding may occur in up to 90% of the patients. Treatment-related complications,

namely infections, may also additionally increase morbimortality.^{7 11–13}

The reported case is noteworthy and challenging for many reasons:

The patient was much younger than what is reported in the literature, which refers AH to be a disease affecting the elderly and women in the postpartum period. The precipitating event is difficult to ascertain since there was an obvious previous systemic insult, salazopyrine-related DRESS syndrome 5 months before diabetes diagnosis and the patient was on systemic high-dose corticosteroids. Sulfa drugs (such as salazopyrine) have been associated with AH and this may have been the initiator event, being the clinical manifestations mitigated by concurrent high-dose glucocorticoids; however, no aPTT changes were detected at that time. Additionally, there was a history of long-standing inflammatory oligoarthritis possibly associated with an underdiagnosed immune-mediated disease. However, rheumatology evaluation was remarkable for the absence of clinical or radiological evidence of arthritis along with a negative autoimmune panel, not being consistent with any rheumatological diagnosis, namely systemic lupus erythematosus or rheumatoid arthritis. Seronegative arthritis was also considered unlikely due to the low erythrocyte sedimentation levels and lack of specific radiological findings. Haemophilic synovitis involving the weight-bearing joints was suggested as a possibility due to recurrent bleeding-induced joint injury, however, no suggestive clinical or radiological evidence was present. Hyperglycaemia and diabetic ketoacidosis could have also been favoured or even precipitated by the corticosteroid use. Hyperglycaemic emergencies are not only metabolic and haemodynamic but also inflammatory conditions. The question of whether the massive cytokine release (mostly interleukin (IL) 6, IL-8, IL-10) could create the ideal environment for new antibody formation and new onset AH is unfounded however likely in the presented report. Type 1 diabetes mellitus is thought to be an autoimmune disease associated with other organ-specific immune-mediated conditions such as thyroiditis, adrenocortical failure and coeliac disease. However, pancreatic islet cell damage in type 1 diabetes mellitus is believed to be mediated by cellular immunity (T cells) being antibodies considered mere disease markers, as opposed to what is seen in AH. Lastly, it should be mentioned that although the reported bleeding episode was promptly controlled with non-invasive haemostatic measures, disease remission was temporarily achieved only after a cycle of high-dose corticosteroids and cyclophosphamide followed by rituximab. Antibody titres were very low at disease presentation and increased transiently after 1 week of first-line treatment. Nevertheless after diagnosis and therapy no further significant bleeding episodes were reported questioning the

relevance of antibody titre measurement in disease activity assessment.

Learning points

- Acquired haemophilia is a rare life-threatening disease.
- It has been associated with many conditions such as immune-mediated diseases, drugs, hepatitis and malignancies.
- Diabetes on the other hand is quite frequent and usually has no obvious underlying or treatable cause.
- This is the first reported case of acquired haemophilia developing in the setting of a diabetic ketoacidosis to our knowledge and should raise the awareness for the possible disease association.

Contributors CTB: article writing, patient diagnosis and endocrinology clinic follow-up. YV: article writing and revision. JE: article revision and immunotherapy clinic patient follow-up. CAV: article revision.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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