Unexpected outcome (positive or negative) including adverse drug reactions

Acquired haemophilia secondary to ivabradine presenting with acute respiratory distress syndrome

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The authors present the case of a 72-year-old patient who presented with severe dyspnoea, scant haemoptysis, pronounced desaturation and bilateral haematomas on the upper limbs. Chest radiography showed bilateral infiltrates mainly in the lower lobes. The patient's prothrombin time, and platelet count were normal. However, the activated partial thromboplastin time showed a prolongation that was not reversed on a correction study. Factor VIII (FVIII) levels were very low and evidence of FVIII inhibitor was found. The patient had started taking ivabradine 2 months earlier, and the diagnosis of idiosyncratic acquired haemophilia was established. The patient was treated with volume expansion therapy, high levels of oxygen, multiple transfusions, methylprednisolone, desmopressine and rituximab. On the 3rd day, the patient showed progressive amelioration of his dyspnoea, oxygen needs and chest infiltrates. On the 7th day, the patient was discharged.

BACKGROUND

Acquired haemophilia is a rare but potentially life-threatening bleeding disorder. Diagnosis of acquired haemophilia can be difficult, because the condition is rare and the patient does not have the usual personal or family history of bleeding episodes. In our case, acquired haemophilia manifested with alveolar haemorrhage mimicking acute respiratory distress syndrome (ARDS).

Acquired haemophilia results from the development of autoantibodies directed against clotting factors. Numerous conditions have been associated with acquired inhibitors to Factor VIII (FVIII). Rarely, FVIII autoantibodies arise as idiosyncratic reactions to medications as it was in our case with the new drug ivabradine. Ivabradine, the first selective and specific If inhibitor, has received marketing authorisation in 27 European countries from the European Medicines Evaluation Agency for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication or intolerance to β -blockers.

CASE PRESENTATION

A 72-year-old patient presented to our department on 21 December 2010 with severe dyspnoea evolving over 3 weeks, low-grade fever, cough with scant haemoptysis and pronounced desaturation (SaO₂ 92% on room air).

His vital signs showed low blood pressure (95/60 mm Hg), pulse rate 130 beats/min and respiratory rate 36 breaths/min.

The patient also had bilateral haematomas in both upper limbs extending from the wrists to the elbows and in the left thigh.

His medical history revealed two coronary artery bypass graft back in 1998 and 2008, mitral valve replacement in 2008. His usual treatment included esomeprazole 40 mg/day, telmisartan 10½ tab/day; desloratadine 1 tab/day;

furosemide 40 mg two times per day and levothyroxine 125 1 tab/day.

On September 2010, the patient suffered from atrial flutter treated by radiofrequency ablation and ivabradine 5 mg two pills/day.

The patient had hypothyroidism treated with levothyroxine and also suffered from obstructive sleep apnoea treated by continuous positive airway pressure. He also had chronic renal failure.

INVESTIGATIONS

Chest radiograph showed bilateral patchy infiltrates predominating in the lower lobes. The patient's prothrombin time, and platelet count were normal. However, the activated partial thromboplastin time (aPTT) showed a prolongation that was not reversed on a correction study. FVIII levels were very low (3%) and evidence of FVIII inhibitor was found.

DIFFERENTIAL DIAGNOSIS

Lupus like anticoagulant was negative.

TREATMENT

The patient was treated with volume expansion therapy, high level of oxygen using non-rebreathing mask (15 l/min), multiple transfusions of red blood cells and fresh frozen plasma. The patient was also given high-dose corticosteroids (methylprednisolone 80 mg intravenously/12 h), desmopressine (23 µg intravenously) and rituximab 700 mg repeated after 2 weeks.

OUTCOME AND FOLLOW-UP

On the 3rd day, the patient showed progressive amelioration of his dyspnoea, oxygen needs and chest infiltrates. On the 7th day, the patient was discharged on rituximab

700 mg after 1 week and prednisone 1 mg/kg to be gradually decreased.

DISCUSSION

Acquired haemophilia is a rare but potentially life-threatening bleeding disorder caused by the development of autoantibodies directed against plasma coagulation factors, most frequently FVIII.¹ Diagnosis of acquired haemophilia can be difficult, both because the condition is rare and because the patient does not have the usual personal or family history of bleeding episodes, such as is seen in congenital haemophilia.¹ Moreover, the clinical signs and symptoms of acquired haemophilia differ from those of hereditary haemophilia.

Acquired haemophilia results from the development of autoantibodies directed against clotting factors.² Numerous conditions have been associated with acquired inhibitors to FVIII. Rarely, FVIII autoantibodies arise as idiosyncratic reactions to medications as it was in our case.

An isolated prolongation of the aPTT that was not corrected when the patient's plasma was incubated with equal volumes of normal plasma in a mixing study was the key component of the diagnosis of acquired haemophilia.

Because the most common cause of isolated prolonged aPTT is lupus anticoagulant,³ it is essential to consider the presence of a lupus anticoagulant in patients with a prolonged aPTT. The absence of lupus anticoagulant was confirmed by a specific test.

The severity of acquired haemophilia at clinical presentation can also make its management challenging. Treatment strategies for acquired haemophilia have two major objectives. During acute bleeding episodes, effective control of bleeding manifestations is the primary objective. However, the ultimate therapeutic goal is to eliminate the inhibitor and cure the disease.

Patients with very low inhibitor titres and residual FVIII activity, as in our case may benefit from treatment with desmopressin. In healthy individuals, intravenous infusion of desmopressin (0.3 µg/kg) may result in a two to three-fold temporary increase in FVIII and von Willebrand factor plasma levels.⁴ However, in most patients with acquired FVIII inhibitors, desmopressin treatment alone will not provide haemostasis.⁵

Guidelines suggest that as soon as the diagnosis of acquired haemophilia is established, elimination of the inhibitor should be attempted by means of immunosuppression.⁶ Eradicating the inhibitor is important to restore normal haemostasis and minimise the patient's risk of bleeding.⁶ Patients who achieve complete remission (eradication of the inhibitor) have been shown to have a better outcome in terms of overall survival than patients who do not achieve complete remission.⁴

First-line therapy for eradicating inhibitors usually includes methylprednisolone at a dose of 1 mg/kg/day (or an equivalent dose of prednisone), which results in the abolition of inhibitors in approximately 60–70% of patients.^{4 6} And that what was done in our case.

Rituximab, an anti-CD20 monoclonal antibody, has shown promising results in eradicating inhibitors in acquired haemophilia.⁷ At present, there are no results from randomised controlled trials to confirm the usefulness of rituximab as a first-line or salvage therapy for acquired haemophilia, but rituximab showed to be a powerful therapeutic option in our case.

In general, the prognosis of patients with acquired haemophilia depends on the patient's response to immunosuppression.¹ In our case, the patient responded well to immunosuppression and was able to leave the hospital after 1 week.

As far as we know, this is the first idiosyncratic acquired haemophilia to be documented with ivabradine.

Learning points

- ▶ Diagnosis of ARDS aetiology poses a particular challenge for clinicians.
- ▶ Acquired haemophilia can manifest with alveolar haemorrhage mimicking ARDS.
- ▶ Acquired haemophilia can be induced by ivabradine.
- ▶ Rituximab is a powerful therapeutic option to eliminate the inhibitor of FVIII.

Competing interests None.

Patient consent Obtained.

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