

Anaphylactic reaction with prothrombin complex concentrate in a patient with IgA deficiency and anti-IgA antibodies

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Immunoglobulin A (IgA) deficiency with anti-IgA antibodies is not listed as an absolute or relative contraindication for the use of prothrombin complex concentrates (PCCs). We discuss a patient who developed an anaphylactic reaction to PCC on a background of selective IgA deficiency with anti-IgA antibodies and with a history of anaphylactic reaction to other blood products. Further analysis of PCCs revealed the presence of variable quantities of immunoglobulins of all classes, including IgA. Although the summary of product characteristics for PCCs from various manufacturers does not list IgA deficiency with anti-IgA antibodies as an absolute or relative contraindication, our findings suggest that PCCs are not devoid of IgA and great caution must be exercised with their use in patients with IgA deficiency with anti-IgA antibodies and with previously documented

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Introduction

Immunoglobulin A (IgA) deficiency with anti-IgA antibodies is not listed as an absolute or relative contraindication for the use of prothrombin complex concentrates (PCCs). We report our experience of an anaphylactic reaction in a patient with IgA deficiency with anti-IgA antibodies following the administration of a PCC (Octaplex; Octapharma Limited, Manchester, UK) for reversal of over anticoagulation with warfarin and with previous documented reactions to plasma in the past. This is particularly relevant and important, as the current British Committee for Standards in Haematology and other national and international guidelines for anticoagulation recommend that PCCs be used in preference to fresh frozen plasma (FFP) in patients who require reversal in the context of over anticoagulation and bleeding [1]. Whereas it is clearly recognized that standard FFP is contraindicated in patients with IgA deficiency with anti-IgA antibodies and documented clinical reactions, there is no such contraindication for the use of PCCs in the above-described group of patients. To our knowledge, there have been no publications so far reporting on reactions to the use of PCCs in patients with IgA deficiency and anti-IgA antibodies. Written consent has been obtained from the patient involved.

Case report

Our patient is a 55-year-old woman with a diagnosis of systemic lupus erythematosus (SLE), chronic renal failure, IgA deficiency with anti-IgA antibodies and on indefinite anticoagulation with warfarin for a previous life-threatening venous thromboembolic event. She presented with intermittent right-sided abdominal pain of

5 days duration radiating to the back, which was associated with nausea and vomiting. The pain was made worse by food and there were no obvious relieving factors. On admission, there was tenderness in the upper mid-abdomen and epigastrium with normal blood pressure, pulse rate and respiratory rate. Investigations revealed a haemoglobin (Hb) of 13.6 g/dl, platelet count of $181 \times 10^9/l$ and an international normalized ratio of 7.6 and a decision was made to omit further warfarin. Eight hours after admission, her general condition deteriorated and investigations showed that her Hb had dropped to 8 g/dl. An urgent abdominal ultrasound revealed a sub-hepatic haematoma and a computed tomography scan confirmed a large 15×8 cm heterogeneous haematoma within the right upper quadrant, displacing and compressing the stomach and the first part of the duodenum.

In view of the severe intra-abdominal bleeding and according to our hospital guidelines, in addition to intravenous vitamin K, a decision was made to administer a PCC (Octaplex) for the rapid correction of anticoagulation. During the administration of the initial 20 ml of PCC, she complained of chest tightness with breathlessness and became hypotensive. Administration of Octaplex was immediately discontinued and the patient's breathlessness recovered partially with oxygen, gelofusine and piriton. A repeat Hb was further down at 5.5 g/dl and in view of the anticipated delay for organizing administration of IgA-depleted blood products, that is, washed red cells, the patient went on to receive two doses of NovoSeven 90 µg/kg (Novo Nordisk, Crawley, West Sussex, UK), 2 h apart. Resuscitation was continued with appropriate blood products, and owing to ongoing bleeding and haemodynamic instability, the patient was

intubated for an angiogram. Three bleeding points were identified, including two small bleeding points arising from the pancreaticoduodenal branches of the gastroduodenal artery and a third from a proximal branch of the right hepatic artery. All were selectively embolized with microcoils (Boston Scientific, Natick, Massachusetts, USA). The mesenteric angiogram did not reveal any evidence of significant vasculitis, but the appearances were suggestive of severe atheromatous disease. The coagulation screens 2 days after vitamin K during her inpatient stay showed a normal prothrombin time of 14 s (12–16) and activated partial thromboplastin time of 30 s (26–36), suggesting the absence of any specific inhibitors to other coagulation factors. She was subsequently anticoagulated with unfractionated heparin for the remainder of her inpatient stay without bleeding complications and discharged on warfarin.

The patient was diagnosed with SLE at age 25 in 1982 when she presented with a 2-month history of joint pains, pleuritic chest pain, fever, proteinuria, haematuria, diarrhoea and deteriorating renal function requiring haemodialysis. A renal biopsy revealed proliferative glomerulonephritis, which was treated with cyclophosphamide and prednisolone. In addition to immunosuppression, plasma exchange was attempted with albumin. However, after the first infusion of albumin, she became hypotensive and further infusion was stopped. This was followed a day later by a severe anaphylactic reaction with shortness of breath, loin pain, fever, chills, rigors and hypotension following infusion of half a unit of packed red cells. All further use of blood products was stopped and she received treatment with hydrocortisone and piriton. Subsequent investigations confirmed IgA deficiency with levels of less than 0.1 g/l and more recent repeat analysis after the reaction to PCC showed no detectable IgA by a haemagglutination/inhibition technique. Antibodies to IgA were detected by haemagglutination with a titre of 1:128.

In 1997, an initial laparotomy for a large pelvic abscess was followed by total colectomy and ileostomy for a necrotic area in the ascending colon and purulent peritonitis, believed to be due to vasculitis. The post-operative period was complicated by deep vein thrombosis, pulmonary embolism, right atrial thrombus and pulmonary hypertension. Investigations revealed the presence of IgG anticardiolipin antibodies at low titres, with no evidence of IgM anticardiolipin antibodies or anti- β_2 glycoprotein 1 antibodies. She had also been noted to be positive for lupus anticoagulant intermittently. In view of the life-threatening venous thromboembolism and her history and investigations, indefinite anticoagulation was recommended. Since diagnosis, she has been persistently positive for antinuclear antibodies, but has always been

negative for extended nuclear antibody screen. Over the years, she has been intermittently positive for IgG anticardiolipin antibodies just above the upper limit of normal and for lupus anticoagulant, suggesting a diagnosis of secondary antiphospholipid syndrome.

Selective IgA deficiency (IGAD) is the most common primary antibody deficiency. It is defined by serum levels of IgA of less than 0.05 g/l in the presence of normal IgG and IgM in a patient older than 4 years. The incidence of IGAD varies from 1:396 to 1:15 000 in different regions. Most affected individuals are asymptomatic, but symptomatic patients suffer from recurrent mucosal infections, allergies and autoimmune diseases. In patients with IGAD, the frequency of anti-IgA antibodies has been reported to be from 20 to 40%, but the frequency of reactions to blood products is not of the same magnitude [2].

Following the reaction described, IgA and other immunoglobulins were detected in a sample of Octaplex by the Immunoturbidometric method (measuring range 0.50–8.00 g/l) (Roche Diagnostics, Burgess Hill, West Sussex, UK) and similarly IgA was detected in Beriplex (CSL Behring UK Limited, Haywards Heath, West Sussex, UK) and FEIBA (Baxter, Newbury, Berkshire, UK) – another two PCC products available in the UK. All samples were subsequently analyzed with a haemagglutination/inhibition technique using anti-IgA and IgA-coated cells and IgA was detected in all the three reconstituted products, and the levels were between traces and normal serum concentration. The lower limit of detection for this technique is quoted at 0.0016 g/l [3]. Indeed, this confirms a recent analysis of PCCs with modern proteomic technologies showing traces of various plasma coagulation proteins [4].

Conclusion

We conclude that PCCs are not devoid of IgA and great caution must be exercised with their use in patients with IgA deficiency and anti-IgA antibodies known to react to blood products with IgA. We recommend a more detailed analysis of the individual PCCs for the IgA content with a view to issuing a warning in similar situations in the individual product summary of product characteristics.

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