

Use of prothrombin complex concentrate for prophylaxis of bleeding in acquired factor X deficiency associated with light-chain amyloidosis

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Dear Sir,

We describe here the effects of infusions of prothrombin complex concentrate (PCC) given to treat and prevent bleeding in a case of systemic light-chain amyloidosis (AL) with factor X deficiency.

Amyloidosis occurs when there is extracellular deposition of fibrillar proteins in organs or tissues; in biopsies, these proteins are positively stained by Congo red. There are various forms of the disease: AL amyloidosis is caused by the deposition of immunoglobulin light chains, which is associated with a clonal proliferation of plasma cells in the bone marrow but not necessarily with overt multiple myeloma¹. Bleeding complications are commonly encountered in AL amyloidosis² as a consequence of amyloid deposition in the vessel wall causing vascular fragility and a deficiency of coagulation factors, usually factor X³, because of absorption onto amyloid fibrils, particularly in the hepatic and splenic regions⁴.

A diagnosis of factor X deficiency due to systemic light-chain AL amyloidosis was made in a 70-year old patient who was referred to the Emergency Room of our hospital in November 2011 because of the appearance of spontaneous bruising and haemorrhagic suffusions of the skin.

The laboratory tests showed a normal blood cell count and prolonged prothrombin time (ratio, 1.35) and activated partial thromboplastin time (ratio, 1.8), which normalised in the mixing test. An isolated factor X deficiency was detected (12% of normal values). Searches were made for serum monoclonal gammopathy and urinary Bence-Jones proteins, with only the latter being positive for a very small amount of lambda chains. Ultrasound examination of the abdomen was normal; computed tomography (CT) of the chest and abdomen showed a right axillary lymph node, impalpable in the physical examination. Echocardiography showed left ventricular hypertrophy with hyper-echoic walls and a normal ejection fraction. Mild bleeding from a pigmented skin lesion was observed in the left retro-auricular area; the lesion was removed surgically and diagnosed as melanoma skin cancer on histological examination.

A bone marrow trephine biopsy showed a low percentage of clonal plasma cells (5%) and was positive for the Congo red stain, as were a biopsy of periumbilical fat and histological sections of the right axillary lymph node, which did not provide alternative diagnoses. All the surgical procedures were complicated by prolonged bleeding, despite vitamin K infusions. Pressure dressings and transfusions of solvent/detergent-treated plasma were necessary to control the bleeding.

Moreover, during hospitalisation the patient developed hypovolaemic shock, due to a retroperitoneal haematoma, as detected by CT angiography of the abdomen. The haemorrhage ceased after the administration of solvent/detergent-treated plasma (15 mL/kg) and transfusions of packed red blood cells.

The patient underwent chemotherapy with steroids and bortezomib, without improvement of the level of serum factor X. Subsequently, he was repeatedly admitted to our hospital for spontaneous intramuscular and gastrointestinal haemorrhages. Briefly, the patient was readmitted in December 2011 twice, once for a rectal haemorrhage and the other time for spontaneous left retro-auricular bleeding; treatment with solvent/detergent-treated plasma (15 mL/kg) and fibrinogen became necessary. In February 2012, the patient was readmitted because of bleeding gums, which was followed a few days later by severe spontaneous bleeding in the left thigh. Considering the last spontaneous event as a major bleed, infusions of activated PCC (FEIBA, containing factor II, IX, X concentrates) were started (1,000 U daily for 12 days). Transfusions of packed red blood cells were also necessary. Since chemotherapy was ineffective in preventing haemorrhagic episodes and splenectomy was not feasible, because the patient was considered to be at very high surgical risk, a prophylactic regimen with PCC 20 U/kg three times a week was started after the patient had been discharged from hospital in April 2012. This regime was effective in preventing bleeding events. In October 2012, the PCC dosing regimen was changed such that PCC 20U/kg was infused twice a week.

A few weeks later, the patient was admitted to hospital because of a spontaneous intramuscular haematoma in the right leg, as shown by CT scan. The patient was treated with PCC 20 U/kg daily until stabilisation of the haematoma.

After discharge, the infusion regimen with PCC 20 U/kg three times a week was restarted. The patient subsequently had some limited bleeding episodes. In December 2012, he developed a post-traumatic right limb haematoma and a spontaneous new haematoma in the left shoulder. In February 2013, he had a left shoulder haematoma. The last haemorrhagic episode was observed in May 2014 when a haematoma located at the hepatic hilum was detected by CT scan. In all these cases the patient was successfully treated with PCC 20 U/kg and solvent/detergent-treated plasma infusions (15 mL/kg) every other day. Since May 2014, the patient has not had any obvious bleeding.

Notably, the initially assessed plasma level of factor X changed from a basal value of 15 to 32 and 18%, 1 hour and 24 hours, respectively, after infusion. Given that recovery of factor X after infusion was poor and brief, we could argue that the reduction of bleeding also depended on the frequency of PCC administration. Since there was concern about the risk of thrombosis following PCC infusions, the patient's D-dimer levels and platelet counts were monitored. D-dimer levels were above the normal range during bleeding, but returned to normal values after resolution of the haemorrhage. No relevant variations in platelet counts were detected during or after bleeding. In spite of this, and even if no thrombotic events were observed, chronic activation of coagulation due to PCC infusions cannot be totally excluded.

Chemotherapy and splenectomy are the most frequently used treatments in cases of systemic light-chain amyloidosis with factor X deficiency; although amyloid deposition is reduced and the main site of its absorption is removed, improvement of factor X levels is not observed in all cases. In order to treat or prevent bleeding events, infusions of fresh-frozen plasma, PCC, activated PCC, recombinant activated factor VII or factor X are suggested options in cases with persistent factor X deficiency⁵. In our experience, PCC infusion at a dosing regimen of 20 U/kg three times a week in factor X deficiency secondary to amyloidosis was effective and followed by a reduction in the frequency and extent of major bleeding requiring hospitalisation, while a dosing regimen of PCC 20 U/kg twice a week proved to be less effective in preventing severe bleeding.

The Authors declare no conflicts of interest.

References

- 1) Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. *J Clin Oncol* 2011; **29**: 1924-33.
- 2) Mumford AD, O'Donnell J, Gillmore JD et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. *Br J Haematol* 2000; **110**: 454-60.
- 3) Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in amyloidosis. A critical review. *Am J Hematol* 1981; **11**: 443-50.
- 4) Furie B, Voo L, McAdam KP et al. Mechanism of factor X deficiency in systemic amyloidosis. *NEJM* 1981; **304**: 827-30.
- 5) Mahmood S, Blundell J, Drebes A et al. Utility of factor X concentrate for the treatment of acquired factor X deficiency in systemic light-chain amyloidosis. *Blood* 2014; **123**: 2899-900.

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