Case Report

Nephrotic syndrome with spontaneous anticoagulant activity

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Introduction

The association between nephrotic syndrome (NS) and intravascular coagulation is well known, and thromboembolic disease is a relatively common complication of the condition. The association of NS with anticoagulant activity is less well recognized. Factor X deficiency, and sometimes Factor IX and Factor II deficiency, can rarely complicate AL amyloidosis, which may present with a NS. The mechanism is thought to be an interaction between the clotting factors and the amyloid fibrils. Amyloidosis can also be associated with bleeding through increased fibrinolysis [1]. We report a case of minimal change NS associated with profound clotting abnormalities due to an inhibitor of Factor V. Furthermore, the clotting abnormalities receded and then relapsed in tandem with the underlying disease, which eventually went into long-term remission with cyclosporine treatment.

Case report

A previously fit 76-year-old man presented in October 1999 with NS. When seen, he had a 1-week history of ankle swelling associated with heavy proteinuria (7.56 g/day), microscopic haematuria associated with granular casts (but no red cell casts), a serum albumin of 19 g/l, and renal impairment [serum creatinine of 127 μmol/l and an estimated glomerular filtration rate (GFR) of 51 ml/min]. There were no clues on super-ficial examination as to the cause of the NS and he was admitted to hospital for further investigation, with the intention of proceeding to percutaneous renal biopsy. He had been a heavy smoker throughout his adult life but his chest X-ray was normal.

Immunological tests were negative except for anti-nuclear antibodies in a titre of 1 in 100. Serological tests for hepatitis B and hepatitis C were negative. However, a clotting screen showed a prothrombin ratio (PTR) of 2.2, (normal <1.3) an activated partial thromboplastin time (APTT) of 63 s, (normal <39 s) and a thrombin time of 14 s. The fibrinogen level was raised at 10.96 g/l. The clotting screen was repeated the following day with similar results (PTR: 2.1, APTT: 55 s). Clotting Factor assays initially showed a Factor V level of 3%, Factor X assay of 62%, Factor VII assay of 84% and a Factor VIII assay of 143%. Further analysis showed that the apparent reduction of Factor V was due to the presence of an inhibitor in the blood.

Renal biopsy was deferred. The NS was managed with modest doses of diuretic and a high-protein, no-added-salt diet. Either despite or because of these measures, there was a rapid decline in renal function, with the serum creatinine rising to 325 μmol/l on day 13 after presentation. Treatment was started with intravenous methyl prednisolone (500 mg/day for 3 days) followed by high-dose oral prednisolone (60 mg/day), on the assumption that he had a rapidly progressive glomerulonephritis. The initial response to this treatment was gratifying with the serum creatinine peaking at 402 μmol/l on day 15 and then falling steadily (Figure 1).

Despite improvement in his renal function, the patient became unwell. His blood glucose, which had been raised on admission, rose sharply and he became symptomatic of hyperglycaemia. From day 17 he developed protracted diarrhoea. The diabetes was controlled with insulin but the diarrhoea worsened, and intravenous fluids had to be given. No pathogens or Clostridium difficile toxin was isolated from the stool. Repeated samples were sent to exclude the possibility of Strongyloides stercoralis hyper infection, as we were aware that the patient had spent several years in the Burmese jungle during World War II. All these tests, including subsequent cultures of stool on agar plates for Strongyloides sp. at our regional tropical disease centre, were negative. Empirical treatment with metronidazole was given, and pending

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bodies. He had developed well-marked Mees’ lines on day 42 with no oedema, a serum albumin of 35 g/l, a serum creatinine of 27 g/l, trivial proteinuria and a normal blood coagulation screen. Steroid treatment was withheld. He was discharged home on day 42 with no oedema, a serum albumin of 24 g/l. The results of strongyloides cultures, the steroids were stopped after 5 days.

He was confined to bed at this stage and required enteral feeding. Nevertheless renal function continued to improve, without steroids, as did the abnormalities of blood clotting. By day 26 PTR was 1.3, APTT was 33 s and bleeding time was 5 min (normal <10 min); a renal biopsy was thus performed.

The renal biopsy contained 13 glomeruli of which three were sclerosed. The remaining glomeruli showed evidence of some vascular engorgement, but no increased cellularity and no evidence of amyloid deposition. Immunofluorescent staining was uniformly negative. On electron microscopy, there was evidence of extensive podocyte foot-process fusion but no sign of any immune deposits. There was evidence of focal sclerosis in the mesangium but no immune deposits. On light microscopy, the interstitium was oedematous with a mild diffuse monocyte inflammatory infiltrate but more severe tubular damage. The vessels appeared normal. The biopsy was reviewed by several pathologists and the conclusion was that the changes were consistent with minimal change disease with superadded acute tubular necrosis and mild interstitial inflammation. (We reconfirmed at this stage that the patient had not had non-steroidal drugs before admission; he had no medication whatsoever). Steroid treatment was withheld. He was discharged home on day 42 with no oedema, a serum albumin of 27 g/l, trivial proteinuria and a normal blood coagulation screen.

When seen in the outpatient clinic 68 days after initial presentation, he was well with no proteinuria, a serum albumin of 35 g/l, a serum creatinine of 117 μmol/l and negative tests for anti-nuclear antibodies. He had developed well-marked Mees’ lines on his finger nails, but was otherwise in good health. When seen in clinic in March 2000, he reported an episode a few weeks before, when his legs had seemed to give way. He had had several falls but there were no definite neurological signs. There was a trace of protein in his urine but the serum albumin was 35 g/l. A coagulation screen showed a PTR of 1.2 and APTT of 35 s.

In August 2000, he attended for a routine outpatient review and was noted to have heavy proteinuria on dipstick testing but no oedema and no new symptoms. Repeat investigations showed the serum creatinine was 118 μmol/l with a 24 h creatinine clearance of 66 ml/min, but protein excretion of 3.63 g/day. The serum albumin was reduced at 28 g/l. By the end of that month, the serum albumin had fallen to 23 g/l and he had mild ankle oedema. Furthermore, there were mild abnormalities of blood coagulation with a PTR of 1.3 and APTT of 41 s. The Factor V level was 27% and the fibrinogen was raised at 8.43 g/l. Outpatient treatment with cyclosporine (4 mg/kg/day) was started. Eight days after starting cyclosporine he was admitted as an emergency, with an episode of confusion, dysphasia and weakness of legs. His symptoms improved rapidly the same day and a CT head scan showed no abnormality. Carotid Doppler studies showed diffuse intimal thickening but no significant stenoses. He still had ankle oedema and there was moderate proteinuria detected by dipstick with a serum albumin of 24 g/l. The serum creatinine was 130 μmol/l and there were mild abnormalities of blood coagulation with a PTR of 1.3 and APTT of 44 s. Factor V activity was once again reduced at 25%. Cyclosporine was continued and after 28 days of this treatment he had no oedema, a serum albumin of 30 g/l and 24 h urinary protein losses of 0.12 g. The coagulation screen at this stage showed a PTR of 1.2 and APTT of 36 s.

It was assumed that he had had a cerebrovascular accident associated with small vessel disease and the NS. Although the presenting abnormalities improved, there were difficulties getting him to mobilize and he spent 20 days in hospital. As the NS had resolved by the time of discharge (on cyclosporine), it was decided not to give him aspirin but 4 days later he was readmitted with a further minor stroke. The NS was in remission at this time and there were no abnormalities of the coagulation screen. A repeat CT head scan showed no abnormality and treatment with aspirin, pravastatin and ramipril were added to the cyclosporine. He gave up smoking. Since September 2000, he has remained in remission from the NS although he has had a fractured neck of right femur (June 2001), a myocardial infarction (August 2002) and several admissions with poor mobility. There has been a decline in renal function which has been attributed to ischaemic causes (small kidneys on scan in 2004, with no proteinuria) and this has led to reduction in the cyclosporine dose to 2 mg/kg/day. The coagulation screen has remained normal with a Factor V level measured at 102%.
Discussion

The coagulation protein, Factor V, is a glycoprotein synthesized mainly in the liver (plasma Factor V) and in the megakaryocytes (platelet Factor V). It is activated by both Factor Xa and thrombin to form Factor Va. The activated form plays an important part in the clotting pathway by combining with Factor Xa and forming the ‘prothrombinase complex’ which leads to the thrombin burst.

Factor V inhibitors occur most often spontaneously in older, previously healthy patients in the absence of a common underlying disease [2–8]. They are polyclonal IgG or polyclonal IgM and IgG antibodies in nature [9]. The most commonly described clinical association, seen in two-thirds of cases, is with a surgical procedure preceding the development of the inhibitor [9]. Many of these cases are associated with the use of bovine thrombin or fibrin glue. These substances contain thrombin and small amounts of Factor V that may result in production of anti-bovine thrombin and/or Factor V anti-bodies that cross-react with human thrombin and Factor V [10]. Other associations of Factor V inhibitors include malignant disease, autoimmune diseases such as Sjogren’s syndrome and celiac disease, antibiotics (especially aminoglycosides), blood transfusions, tuberculosis and pregnancy [2,9]. Very rarely Factor V inhibitors occur in patients with severe congenital deficiency after factor replacement [2]. In approximately 20% no association can be found [9] and probably represent true autoantibodies to Factor V.

The degree of clinical bleeding in patients with Factor V inhibitors varies from no clinical sequelae to fatal haemorrhage. Knöbl et al. [9] reviewed all 105 cases of Factor V inhibitor reported between 1955 and 1997 and found there was some bleeding in 60% of cases, which was fatal in 20%. This variability in bleeding tendency may be explained by the variable access of platelet Factor V to the inhibitor [8,9]. Platelet factor V may be relatively protected from an anti-Factor V antibody, even though plasma Factor V is completely neutralized. This hypothesis is also supported by the efficacy of platelet concentrates in a Factor V inhibitor patient [5].

The diagnosis of Factor V inhibitor is based on coagulation assays. The APTT and prothrombin time are prolonged, and plasma from a patient with normal factors fails to correct these assays. In the presence of a normal thrombin time, this should strongly suggest the presence of a Factor V inhibitor [2,6]. Factor V inhibitor developing after the use of topical thrombin will prolong the thrombin time; this can give a clue to the diagnosis especially with the history of recent surgery.

The treatment of Factor V inhibitors involves plasma and platelet transfusions to cover bleeding episodes and immunosuppressive measures to remove the antibodies. Removal of the antibody by plasmapheresis or immunoadsorption has been tried [10].

The administration of immunoglobulin has also proved helpful in the elimination of the antibody [10]. Whether steroids or other immunosuppressive agents influence the natural history of the inhibitors is unclear. The inhibitor may disappear spontaneously without specific therapy [2–4].

The patient in this case report had NS due to minimal change nephropathy, which is well documented to be due to an immune aetiology, supported by the response to immunosuppressive drugs, an association with atopy, and occurrence in Hodgkin’s disease with remission after successful treatment. The exact immune mechanism remains unclear, but the best hypothesis so far is that the disease is due to a defect of cell-mediated immunity and release of cytokines that increase the permeability of the glomerular basement membrane to protein [11]. In theory, such cytokines might also stimulate anergic lymphocytes to produce an autoimmune antibody response and the production of Factor V inhibitors. In our patient, the inhibitor appeared and disappeared in tandem with NS, and both conditions responded promptly to high-dose steroids in the first instance, and cyclosporine with the relapse. Our patient also had positive anti-nuclear antibodies, albeit in low titre, which disappeared after treatment. It is thus possible that the Factor V inhibitor was a manifestation of an autoimmune process, but this abnormality has not been reported previously in connection with NS.

Conflict of interest statement. None declared.

References


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