Case Report

Nephrotic syndrome and chronic renal insufficiency associated with essential cryofibrinogenemia

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Introduction

Cryofibrinogenemia (CF) is defined by the presence of circulating cold insoluble complexes of fibrin, fibrinogen, fibronectin, and fibrin split products with albumin, immunoglobulins and plasma proteins that precipitate from the patient’s plasma in the cold. Cryofibrinogen clots form when the patient’s plasma is cooled to 4°C and stored in the cold for up to 72 h [1,2]. Cryofibrinogen clots typically redissolve upon warming to normal body temperature down to 37°C.

Lesions in patients with symptomatic CF are attributed to cryoprecipitation of patient’s native fibrinogen in the small and medium sized arteries. Symptoms of CF are mainly cutaneous including purpura, ecchymosis, ulcerations, livido reticularis, ischaemic necrosis and rarely gangrene [3,4]. Cold exposed body areas like hands, feet, ears, and nose are commonly affected. While essential CF is a rare, non-fatal, often asymptomatic disorder that develops spontaneously in previously healthy persons, the secondary form occurs in patients suffering from underlying inflammatory and neoplastic disorders. The most common conditions associated with CF are malignancy, collagen vascular disease, diabetes mellitus, vasculitis and active infection. Renal lesions rarely develop in patients with essential CF [5–7]. Conversely, a high incidence of CF was identified in a cohort of French patients with IgA nephropathy [8]. CF has also been reported in patients on renal replacement therapy, either dialysis or transplantation [9,10]. This is the first reported case of chronic essential symptomatic CF in association with membrano-proliferative glomerulonephritis (MPGN).

Case report

A 66-year-old Caucasian male with a history of hypothyroidism, hypertension and essential cryofibrinogenemia was referred for the evaluation of nephrotic syndrome and generalized anasarca. He was diagnosed with essential CF five years previously, when he developed recurrent episodes of erythema and painful ulcerations of his extremities upon exposure to cold. Subsequent examination for an underlying cause of CF had not revealed any evidence of active infection, viral hepatitis, vasculitis, autoimmune disorder or haematologic dyscrasias. Cryofibrinogen was the only cryoprecipitate detected and the patient was subsequently placed on prednisone at a daily maintenance dose of 5mg. A year ago, low dose warfarin was added, providing relief from the flare-ups of the ischaemic skin lesions. Additional medications were: levothyroxine 100 mg/day, enalapril 40 mg daily, clonidine 0.1 mg three times daily and ferrous sulphate. For the past 5 months, he gradually developed increased swelling over his extremities, poor blood pressure control and difficulty breathing, all requiring hospitalization.

Physical examination showed blood pressure: 160/90 mmHg, pulse: 89 beats/min, respiratory rate: 24 breaths/min along with remarkable findings of generalized anasarca, 3+ pedal oedema, pale conjunctiva and erythematous purpuric lesions on the tip of his fingers.

Initial laboratory work-up indicated blood urea nitrogen of 20 mg/dl (7.14 mmol/l), serum creatinine of 1.4 mg/dl (123.76 µmol/l), and serum albumin of 1.8 g/dl. He had normochromic-normocytic anaemia with haemoglobin of 10 g/dl (100 g/l) and a haematocrit of 34%. Platelet count was 200 × 10⁹/µl and peripheral blood smear showed no evidence of microangiopathic haemolytic anaemia. The prothrombin time (PT) was 20.4 s, INR was 2.0, and partial thromboplastin time (PTT) was 28 s. Total cholesterol was 270 mg/dl (6.98 mmol/l), low-density lipoprotein cholesterol (LDL-C) 202 mg/dl (5.22 mmol/l), high-density lipoprotein cholesterol (HDL-C) 35 mg/dl

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(0.90 mmol/l), and triglyceride level 167 mg/dl (1.88 mmol/l). Tests including liver function, hepatitis B surface antigen, hepatitis C antibody, anti-nuclear antibody, anti-glomerular basement membrane antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, C3 and C4 complement levels, antistreptolysin O titre, serum cryoglobulin, anti-phospholipid antibodies were normal or undetectable. Plasma cryofibrinogen level was detectable (normal reference range: undetectable) though the testing laboratory did not report the quantity. Renal ultrasound showed normal-sized kidneys, while the chest X-ray findings were notable only for a moderate degree of bilateral pleural effusion. Spot urinalysis showed proteinuria >300 mg/dl and 8–10 dysmorphic red blood cells/high-power field without white blood cells, casts or crystals. A 24 h urine protein was >7 g. Urine and serum immunofixation studies did not demonstrate monoclonal proteins. He was started on continuous bumetanide drip and placed on 2 l of oxygen via nasal cannula. Interestingly, 24 h later, the patient was noted to have severe erythematous lesions and ecchymoses on the tip of nose, indicative of a flare-up of his ischaemic injury upon exposure to cold oxygen supplied by nasal cannula. Over the next 48 h, the patient achieved significant clinical improvement of his anasarca-related symptoms. Finally, he underwent kidney biopsy while serum creatinine was 1.4 mg/dl.

Light microscopic examination showed renal cortex containing 12 glomeruli, of which 4 (25%) were obsolescent. The remaining glomeruli showed accentuation of glomerular tuft lobulation due to combination of nodular mesangial sclerosis, variable increase in mesangial and endocapillary cellularity and global basement membrane thickening. Thickening of the glomerular capillaries was frequently produced by mesangial interposition, and by occasional intramembranous deposits of hyaline material (Figure 1). Double contours were detected in many of these capillaries by silver staining. Intracapillary fibrin thrombi were not identified. The podocytes were prominent and many contained prominent hyaline droplets. There was mild tubular atrophy, interstitial fibrosis, arteriolo- and arterial-sclerosis detected. There was no evidence of deposition of amyloid or fibronec- tin in the glomeruli by immunohistochemistry. Direct immunofluorescence study revealed focal coarsely granular segmental deposits of IgG (2+), IgM (2+) and C3 (2+) in the glomerular capillaries. A diffuse, peripheral, lobular pattern of fluorescence characteristic of MPGN was not detected.

Ultrastructural examination demonstrated mesangial matrix expansion in both diffuse and nodular patterns, with presence of cellular elements in the capillary basement membrane. The glomerular capillaries were very thick and irregular. Cellular fragments and matrix elements were trapped within expanded lucent lamina interna (Figure 2). Electron dense deposits were inconspicuous and only found in rare capillaries in the expanded lamina interna.

**Discussion**

We describe a rare case of essential CF associated with histological and functional evidence of chronic renal injury. The renal pathology showed chronic membranoproliferative pattern of glomerular injury (MPGN),
not associated with immuno-complex deposition disorder or paraproteinaemia and best classified as chronic microangiopathic changes (chronic thrombotic microangiopathy). The patient thus far, 1 year following the renal biopsy, shows no evidence of systemic illness to which the CF or the glomerulonephritis could be attributed. Essential CF is a relatively benign disorder, which could be asymptomatic or presents with recurrent and necrotizing ischaemic cutaneous lesions [11]. The secondary form, which develops with systemic disorders, is associated with increased mortality and morbidity risk related to the primary disease and is more commonly associated with cryoglobulinaemia (CG). Cryoglobulins differ from cryofibrinogens in that they are rich in immunoglobulins that could be polyclonal, monoclonal or mixed, and they could be precipitated from either the serum or plasma [12].

Renal involvement is more common in patients with CG, but rare in patients with CF. A report describing the spectrum of histopathologic lesions in 10 patients with symptomatic CF identified renal involvement in only one patient, who also had diabetic nephropathy [13]. Besides the diabetic changes in that patient, there were hyper-eosinophilic deposits in the mesangium, glomerular capillaries and renal tubules. The glomerular hyaline deposits consisted of mostly parallel arrays of densely packed fibrillary structures averaging 20 nm in diameter, without the evidence of either amyloid fibrils or cryoglobulin deposits. Lohlin et al. [14] reported the development of transient nontrophic syndrome in a 7-year-old girl with familial CF following anaesthesia-induced hypothermia but did not perform renal biopsy. Conversely, Nagy et al. [8] reported a 74% prevalence of CF in a cohort of patients with biopsy-proven IgA nephropathy and observed that patients with persistent CF were more likely to experience progressive deterioration of renal function.

MPGN is most frequently an immune complex-mediated phenomena, either idiopathic or associated with a number of systemic diseases, including autoimmune disorders and chronic infections [15]. Any of these conditions could also be associated with secondary CF and or CG. MPGN is the typical morphologic lesions identified in patients with cryoglobulinemic nephropathy. Typically cryoglobulinemic nephropathy presents with characteristic morphologic features of MPGN and with hyaline intraglomerular thrombi and monocyte margination in the glomerular capillaries [16]. Organized subendothelial deposits often show a fibrillar and a curvilinear pattern.

Renal biopsy in our patient showed a nodular pattern of glomerulosclerosis with frequent splitting of the glomerular capillaries (double-contour), along with variable mesangial and endocapillary proliferation. The light microscopy pattern was consistent with MPGN, while the immunofluorescence and electron microscopy did not reveal significant immune deposits. To that end, the immune deposits were focal and rather inconspicuous, and only rare subendothelial deposits could be found. Paucity of deposits in this case, in the context of the dominant chronicity of the glomerular pathology and the daily prednisone therapy, could be interpreted as representing partial resolution of glomerular immune complexes. Resolution of subendothelial immune complexes along with improved histology and improved renal function after treatment with prednisone and cyclophosphamide were documented by serial renal biopsies in a patient with MPGN associated with angiofollicular lymphoid hyperplasia (Castleman’s disease) [17]. There are reports of disappearance or partial resolution of immune deposits in cases of acute post-streptococcal glomerulonephritis and membranous nephropathy, concurrently with clinical improvement and remission [18,19].

MPGN-like renal pathology similar to that seen in our patient has been reported in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, and skin changes (POEMS) syndrome and Castleman’s disease [20,21]. The glomeruli display hypercellularity and thickening of the basement membranes with double contours, with no evidence of immunoglobulins or complement deposition. Ultrastructural findings are dominated by mesangiolysis and glomerular microangiopathy. It is believed that endothelial cell damage is central to the pathogenesis of the renal lesions in POEMS syndrome, but the mechanism of injury remains elusive. Studies have shown high serum levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), intraglomerular deposition of VEGF during renal dysfunction and a decline in IL-6 levels following successful therapy with corticosteroids, thereby implicating a cytokine-induced endothelial injury [22,23]. It is plausible that our patient may have developed MPGN-like lesions with microangiopathic changes as the result of endothelial damage. Mechanism at work could be attributed to the cryoprecipitation of the patient’s native fibrinogen in the glomerular capillaries resulting in the endothelial injury, especially aided by the procoagulant nature of CF. A possible immunologic mechanism may have initiated the initial cascade of events resulting from the interaction of various CF components, including fibronectin, fibrin and fibrinogen with the immune complex or the circulating immunoglobulins, signs of which may have diminished in response to long-term steroid therapy.

Our patient clearly fulfilled the diagnostic criteria for essential, isolated CF and had been having symptomatic cutaneous disease for a relatively long period of time. Although secondary MPGN and secondary CF share a list of common underlying diseases that could precipitate either disorder, thorough clinical investigation did not reveal any evidence of infection, malignancy or autoimmunity. Long-term steroid therapy could have modified the renal pathology and induced resolution of the immune deposits. This case raises the possibility of an association between essential CF and MPGN. Testing for CF is suggested as a
part of laboratory workup in MPGN of unknown aetiology.

Conflict of interest statement. None declared.

References


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