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Delayed onset of membranoproliferative glomerulonephritis in a patient with type I cryoglobulinaemia

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Introduction

Cryoglobulins are immunoglobulins that precipitate or gel when serum is cooled to below 37°C [1]. The precipitate will disappear if serum is heated to 37°C. This phenomenon of cold-induced precipitation was first described in vitro in 1929, and its association with disease was first recognized 4 years later by Wintrobe and Buell [2]. In 1947, Lerner et al. introduced the term cryoglobulins to describe this subset of immunoglobulins [3]. Cryoglobulins were later divided into three major types: in type I the cryoglobulin fraction is a single monoclonal immunoglobulin component, type II has mixed monoclonal and polyclonal immunoglobulin components, and type III has exclusively polyclonal components [4].

Type I cryoglobulins are mostly seen in combination with or as a result of multiple myeloma (M Kahler) or Waldenström’s macroglobulinaemia, and rarely in other lymphoproliferative disorders [4,5]. Types II and III cryoglobulinaemias are mostly seen in combination with autoimmune and infectious diseases like hepatitis C virus, and lymphoreticular malignancies. Manifestations in cryoglobulinaemia include glomerulonephritis, arthritis, neuropathies, cirrhosis, and skin lesions such as vasculitis and thrombosis. Cutaneous manifestations are present in 67–100% of patients with cryoglobulinaemia and are frequently the first reason to seek medical advice [4,6].

Although particular forms of glomerulonephritis, such as membranoproliferative glomerulonephritis, are frequently seen in types II and III mixed cryoglobulinaemias, renal disorders are relatively infrequent in type I cryoglobulinaemia [5]. Brouet et al. report renal mani-

Case report

Our 56-year-old patient had a 10-year history of extreme skin rashes on both arms and legs provoked by cold exposure before she sought medical advice for this complaint in 1985. Furthermore she had a history of sinusitis and upper respiratory infections for which she was regularly seen and treated by the department of ENT. On physical examination she had a blood pressure of 155/90 mmHg and no signs of vasculitis. Laboratory examination revealed a normal ESR (9 mm/h), and normal white and red blood cell counts and platelet counts. Serum creatinine was 74 µmol/l, T₄ 78 nmol/l, serum cholesterol 7.1 mmol/l, serum total protein 60 g/l, and serum albumin 39 g/l. Protein spectrum: albumin 64%, alpha-1 4%, alpha-2 12%, beta 13%, gamma 7%. Immunoelectrophoresis showed no abnormalities, especially no paraprotein. Serum was positive for cryoglobulins, which were not further typed. Syphilis serology was negative. Urine was negative for albumin.

During the following years the patient developed overt skin lesions in addition to rashes. Skin biopsy revealed leukocytoclastic vasculitis. She had no general symptoms like fatigue, night-sweats, fever or weight loss. On physical examination in 1989 blood pressure was 140/90 mmHg, both legs showed healing vasculitic...
skin lesions. Routine laboratory findings were similar to those in 1985. Immunelectrophoresis revealed a IgG-kappa paraprotein. Cryoglobulins were strongly positive (3.58 g/l) and consisted of IgG-kappa.

C1q-binding test was 30% (normal <10%), complement proteins C1q, C3, C4 were normal. Anti-DNA was doubtful on qualitative analysis and negative on quantitative analysis. ANCA was negative. Urine examination showed no protein in urine.

Skeletal survey indicated no osteolytic lesions. Bone marrow examination revealed normal maturation of red and white precursor cells. Plasma cells accounted for 7.8%. Immunological typing revealed monoclonal IgG-kappa, though not sufficient for multiple myeloma (M. Kahler) minor criteria.

Since the patient had already recovered from the skin lesions and was in good condition an expectant policy was outlined.

In 1992, she was referred to an outpatient clinic for hypercholesterolaemia resistant to dietary measurements and simvastatin therapy. She was overweight (length 154 cm and weight 66 kg) and had a blood pressure of 180/100 mmHg. Laboratory evaluation showed an ESR of 23 mm/h, normal full blood count, cholesterol 8.0 mmol/l, HDL 1.38 mmol/l, total serum protein 57 g/l, Waaler-Rose and ANF were negative, protein loss in urine was 1–3 g/l in 24 hours with slight erythrocyturia. Simvastatin therapy was continued and atenolol was added to control blood pressure.

Throughout 1992 values for serum cholesterol and urine protein loss fluctuated. In April 1993 she was referred to our outpatient clinic because of hypertension and proteinuria. She had a blood pressure of 230/90 mmHg, no signs of peripheral oedema. Detailed laboratory evaluation revealed an ESR of 60 mm/h, normal full blood count, creatinine 88 μmol/l, cholesterol 10.1 mmol/l, HDL cholesterol 1.24 mmol/l, triglyceride 1.48 mmol/l, total serum protein 55.7 g/l, albumin fraction 34.9, alpha-1, alpha-2, beta-globulins in normal range, gamma-globulin 4.5 (normal, 7–15) and paraprotein. Agar electrophoresis and immunofixation showed a weak band for paraprotein IgG type kappa. Cryoglobulins were again positive: further typing revealed a type I cryoglobulinaemia. ANF was negative, immunofluorescence test and ELISA were negative for ANCA. HCV and HBV were negative. Urine protein loss was 4.3 g/l, erythrocyturia was 30–40 per high-power field. Drug therapy was changed to simvastatin, atenolol, and hydrochlorothiazide.

In the following years renal function slowly deteriorated. In 1995, creatinine clearance fell to 33 ml/min while protein loss had increased to 7 g/24 h. In late 1995, laboratory evaluation showed an ESR of 101 mm/h, Hb 6.3 mmol/l, creatinine 169 μmol/l, total serum protein 61 g/l, serum albumin 35 g/l, alpha-1, alpha-2, beta-globulins within the normal range, gamma-globulins 3 g/l, paraprotein 1 g/l, IgA 0.47 (normal, 0.6–3.82 g/l), IgG 2.06 (normal, 6.94–16.2 g/l), IgM 1.08 (normal, 0.6–2.63 g/l), cryoglobulins were strongly positive, C1q-binding assay 121 (normal, 75–125 mg/l), C3 complement 808 (normal, 880–2000 mg/l), C4 complement 387 (normal, 160–470 mg/l), CH50 titre 135 (normal, 68–133%), B2 microglobulin 4.0 (normal <2.5 mg/l), ANCA was negative. Urine protein loss still was 7 g/l, while urine protein analysis showed the same monoclonal IgG type kappa as in serum.

Renal biopsy was performed because of deterioration of kidney function. Microscopic evaluation revealed 18 glomeruli, eight of which were sclerosed (Figure 1). The other glomeruli showed an increase of mesangial matrix and cells, a thickening of the capillary walls with double contours of the basal membrane. Several glomeruli showed adhesions and proliferation of visceral and parietal epithelium. Accumulation of homogeneous, granular eosinophilic, PAS-positive material was found in the mesangium, the capillary lumina and in the thickened capillary walls. Immunofluorescence demonstrated this material to be IgG and kappa depositions. Furthermore, IgG was observed around the peritubular capillaries as well as in the tubular epithelium. The findings were diagnostic for a membranoproliferative glomerulonephritis due to IgG kappa cryoglobulinaemia.

Bone marrow cytology showed increased plasma cells (plasma cells were 24% of total nuclear cells of the marrow). Skeletal X-ray did not show any osteolytic areas. CT scan of both abdomen and thorax did not show enlarged lymph nodes. Again, no definite diagnosis of multiple myeloma (M. Kahler) could be made.

Because of deterioration of renal function and the histopathological findings, we started with melphalan and prednisone therapy.

During therapy, renal function increased (creatinine 133 μmol/l, clearance 47 ml/min), protein loss in urine fell to 1.3 g/l, while blood pressure normalized. Clinically, no signs of vasculitis recurred, although a severe Raynaud phenomenon was still present.

![Image](https://example.com/image1.png)

**Fig. 1.** Light-microscopy of one of the representative glomeruli: double contours of the capillary walls, mesangial expansion with 600 μm. Secondary to cryoglobulinaemia (methenamine silver, 200 ×).
Literature review

Searching the recent literature on cryoglobulinaemia, we found only seven studies with well-defined, histologically confirmed renal involvement (Table 1). In total, seven patients were described. Six of them were male, only one of them was female. Their mean age was 50 years, the youngest being 35 years old, the oldest being 68 year of age at the onset of disease.

Signs of vasculitis were the presenting symptom in four of seven patients. One patient was diagnosed with Raynaud’s phenomenon in the early phase of his cryoglobulinaemia. Oedema was the presenting symptom in three patients.

Histologically all biopsies showed a membranoproliferative glomerulonephritis. In the case described by Pais et al. [8], capillary obstruction was observed in addition. Immunological typing revealed IgG cryoglobulinaemia in more than half of the cases. Kappa chains were detected by immunological typing in three of seven patients. The interval between the onset of the cryoglobulinaemia and renal involvement differed from less than 1 year in three cases to 7 years in the case described by Ezzat et al. [11]. Except for the fatal case described by Pais [8], all patients showed initial improvement on immunosuppressive treatment. Unfortunately, in three cases [10,12,14], the initial response did not result in a remission and the deterioration in kidney function led to the start of peritoneal or haemodialysis. In Ezzat’s case [11], remission was obtained by treating the underlying non-Hodgkin lymphoma with combination chemotherapy. In the cases described by Bengtsson et al. [13] and Ponticelli et al. [9], remission was followed by maintenance on immunosuppressive therapy.

In three of seven patients a malignant lymphoma could be diagnosed as the underlying disease of the cryoglobulinaemia [8,11,14]. In the four other patients an underlying disorder could not be found or was at least not mentioned in the report. Diagnosing the underlying disease did not improve or amend the prognosis and the course of the cryoglobulinaemia.

Discussion

In this report we describe a 56-year-old woman with a more than 10-year history of Raynaud’s phenomenon, a well-documented cryoglobulinaemia type I, and renal involvement documented 7 years after her first symptoms. Although a monoclonal IgG kappa production was found a definite diagnosis of multiple myeloma could not be made. Nine years after her first disease manifestations renal function deteriorated. Renal biopsy revealed a membranoproliferative glomerulonephritis. Treatment with melphalan and prednisone was successful.

In one of the first studies [4] published in 1974, 21 patients of the 86 patients with cryoglobulinaemia had a type I cryoglobulinaemia (25%). IgM cryoglobulins were the most frequent within the group of type I cryoglobulinaemia. Twenty-five per cent of the patients with type I cryoglobulinaemia developed renal symptoms. Since the authors did not specify the renal disease and the moment of its occurrence, this study is of limited value for our case.

Several other studies and case reports on cryoglobulinaemia with renal involvement published in the last two decades could not be used because of lack of typing of the cryoglobulins or because of lack of specification of the renal involvement due to the type of cryoglobulinaemia. In fact, we only found seven studies with well-defined, histologically confirmed renal involvement, all of them being a membranoproliferative glomerulonephritis. In only three of seven patients medication resulted in remission of the renal disease.

Compared to the other studies published on renal involvement in type I cryoglobulinaemia our case report is conspicuous for the very late onset of kidney involvement. Seven years after the first presentation of symptoms, our patient developed proteinuria. Two years later renal function deteriorated.

In the literature only Ezzat et al. [11] described a case in which renal involvement was diagnosed 7 years after the development of a leukocytoclastic vasculitis. However, this patient had been lost for follow up for several years. When first diagnosed he already had a severe nephrotic syndrome.

Table 1. Cases of type I cryoglobulinaemia with renal involvement in the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex/age</th>
<th>Presenting symptoms</th>
<th>Onset of renal disease</th>
<th>Renal disease</th>
<th>Immunological typing</th>
<th>Course of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pais [8]</td>
<td>M 68</td>
<td>Lymphadenopathy, oedema</td>
<td>&lt;1 year</td>
<td>MPGN + capillary obstruction</td>
<td>IgM-lambda</td>
<td>Died</td>
</tr>
<tr>
<td>Ponticelli [9]</td>
<td>F 42</td>
<td>Vasculitis, proteinuria</td>
<td>&lt;1 year</td>
<td>MPGN</td>
<td>IgG-kappa</td>
<td>Remission</td>
</tr>
<tr>
<td>Ishimura [10]</td>
<td>M 54</td>
<td>Oedema, vasculitis</td>
<td>2 years</td>
<td>MPGN</td>
<td>IgG-kappa</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Ezzat [11]</td>
<td>M 35</td>
<td>Oedema, vasculitis</td>
<td>7 years</td>
<td>MPGN</td>
<td>IgM-kappa</td>
<td>Remission</td>
</tr>
<tr>
<td>Kaplan [12]</td>
<td>M 45</td>
<td>Malaise, polyuria</td>
<td>5 years</td>
<td>MPGN</td>
<td>IgG</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Bengtsson [13]</td>
<td>M 49</td>
<td>Cold intolerance, vasculitis</td>
<td>&lt;1 year</td>
<td>MPGN</td>
<td>IgA-lambda + IgG-lambda</td>
<td>Dialysis</td>
</tr>
<tr>
<td>Rollino [14]</td>
<td>M 59</td>
<td>Raynaud phenomenon</td>
<td></td>
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</tbody>
</table>
Therapeutic regimens varied considerably among the cases described. Almost all patients were treated with a combination of prednisone and other drugs like cytostatics, depending on the underlying disease. Because of the small and heterogeneous population reported here, no conclusion can be drawn as to which therapy is superior. Prednisone alone was found to be ineffective in the cases described by Kaplan and Kaplan [12] and Bengtsson et al. [13].

In summary, we described the eighth case of well-defined renal involvement due to type I cryoglobulinaemia. Our patient differed from the previously published cases due to the very long interval between the demonstration of cryoglobulinaemia and the renal involvement. Therapy with melphalan and prednisone was effective in preserving kidney function. In the literature, type I cryoglobulinaemia is strongly associated with MPGN and leads to terminal renal failure in 50% of the cases. Adding cytostatics to prednisone seems to be additive in preserving renal function.

References

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