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Case Report

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

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Key words: IgG cryoglobulinaemia; leukocytoclastic vasculitis; monoclonal cryoglobulinaemia; membranoproliferative glomerulonephritis (MPGN)

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 manifestations in their study of 21 patients with type I cryoglobulinaemia in 25% of cases. The renal manifestations may result from massive subendothelial deposits of cryoglobulons, or diffuse glomerulonephritis with subendothelial deposits similar to those seen more commonly in association with type II or III cryoglobulins [4].

We recently diagnosed a patient having a type I cryoglobulinaemia with renal involvement. Because we were struck by the indolent cause of her illness and the response to therapy, we describe her disease with a review of other cases of type I cryoglobulinaemia with renal involvement, which were identified by searching Medline from 1990 until the present and using relevant references.

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, T₄78 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 cryoglobulons, 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. Immunoelctrophoresis 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
approach was outlined.

In 1992, she was referred to an outpatient clinic for
hypercholesterolaemia resistant to dietary measures-
ments 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 hyperten-
sion 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, chole-
terol 10.1 mmol/l, HDL cholesterol 1.24 mmol/l, tri-
glyceride 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 immuno-
fixation showed a weak band for paraprotein IgG type
kappa. Cryoglobulins were again present: further
typing revealed a type I cryoglobulinoma. ANF was
negative, immunofluorescence test and ELISA were
negative for ANCA. HCV and HBV were negative.

Urinary 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 deterior-
ated. 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), cryo-
globulins 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 deteriora-
tion 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 deposits. 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 osteo-
litic 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.

![Figure 1. Light-microscopy of one of the representative glomeruli: double contours of the capillary walls, mesangial expansion with hypercellularity and sclerosis and eosinophilic, PAS-positive thrombi occluding the capillary loops provide the diagnosis of MPGN secondary to cryoglobulinaemia (methenamine silver, 200 x).](image)
**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>
<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>
<td>MPGN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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