Renal Involvement in Essential Mixed Cryoglobulinemia

FIGURE 9-16
The glomerulus showing only mild mesangial proliferation and mesangial matrix expansion. Thickening of the glomerular basement membrane is not evident. This picture frequently is present in cases clinically characterized only by mild urinary abnormalities (inactive phase). Moreover, in many cases in which a biopsy is taken during the acute phase of the disease with typical membranoproliferative patterns with or without thrombi, a second renal biopsy will show clear regression of the morphologically acute lesions with only mild mesangioproliferative alteration. (Trichrome × 250.)

FIGURE 9-17 (see Color Plate)
The pattern of immunohistologic glomerular staining varies according to the different glomerular patterns seen on light microscopy. A, Diffuse granular subendothelial deposits along the capillary walls, with or without very rare intraluminal thrombi. (Immunoglobulin M × 250.) B, Intense massive staining of the deposits totally filling the capillary lumina. Faint and irregular parietal deposits also are present. (Immunoglobulin × 250.) C, Parietal deposits with more evident peripheral lobular distribution. (Immunoglobulin × 250.) The components of mixed cryoglobulinemia immunoglobulin M and G, usually associated with C3, are the most frequently found immunoreactants.
Interstitial infiltrates having different degrees of intensity and diffusion. When present, these infiltrates are composed not only of T lymphocytes and monocyte macrophages, as in most glomerular diseases, but also of B lymphocytes. (Periodic acid–Schiff reaction × 100.)

Arteritis of small and medium-sized arteries. In about one third of cases an arteritis of small and medium-size arteries also is present. The artery shows diffuse fibrinoid necrosis of the vessel wall (in red) and intraparietal and perivascular leukocyte infiltration. It is worth emphasizing that even in the presence of renal arteritis we have never found in patients with cryoglobulinemia a picture of necrotizing crescentic glomerulonephritis, now considered a specific aspect of capillaritis in primary vasculitis (antineutrophil cytoplasm antibody-associated). This finding suggests that the vasculitic damage is limited to arterial vessels of larger size. (Trichrome × 100.)

### Renal Syndrome at Presentation in Patients with Cryoglobulinemic Glomerulonephritis and Associated Histologic Lesion

<table>
<thead>
<tr>
<th>Renal syndrome</th>
<th>Patients, %</th>
<th>Frequent histologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated proteinuria with microscopic hematuria, sometimes associated with moderate chronic renal insufficiency</td>
<td>55</td>
<td>Membranoproliferative glomerulonephritis (MPGN), with moderate infiltration of monocytes Lobular MPGN</td>
</tr>
<tr>
<td>Acute nephritic syndrome, sometimes complicated by acute oliguric renal failure</td>
<td>25</td>
<td>Mesangiocapillary glomerulonephritis (MCGN) with leukocytic infiltration, or intraluminal thrombi owing to abrupt massive precipitation of cryoglobulins, usually associated with renal and systemic vasculitis, or both</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>20</td>
<td>MPGN, frequently of lobular type, with some infiltration of monocytes</td>
</tr>
</tbody>
</table>

Renal syndrome at presentation in patients with cryoglobulinemic glomerulonephritis and associated histologic lesion. During the course of this disease, both the systemic and renal signs may vary remarkably, with periods of exacerbation alternating with periods of quiescence. Very often, exacerbation of the extrarenal signs is associated with exacerbation of renal disease (recurring episodes of nephritic or nephrotic syndrome); however, a flare-up of renal disease may occur even in the absence of exacerbation of the extrarenal signs. Partial or total prolonged remission occurs spontaneously or after treatment in 10% to 15% of patients. Arterial hypertension frequently is severe and is present in most patients with cryoglobulinemic nephropathy.
LABORATORY ABNORMALITIES IN ESSENTIAL MIXED CRYOGLOBULINEMIA

Circulating cryoglobulins
Cryocrits ranging from 2% to 70%, with large variations during the course of the disease
Hypocomplementemia
Very low levels of early C components (C1q and C4) and CH50; slightly low levels of C3; and high levels of late C components, C5 and C9

CLINICAL OUTCOMES OF 105 PATIENTS STUDIED IN THREE MILAN HOSPITALS FROM 1966 TO 1990

49% cumulative 10-year probability of survival, without renal failure
40% of patients died, mostly from cardiovascular diseases, liver failure, or infections
14% of patients progressed to chronic renal failure and required dialysis
14% of patients achieved complete and prolonged remission of renal symptoms

FIGURE 9-21
Relevant laboratory abnormalities in “essential” mixed cryoglobulinemia. During the course of this disease, cryoglobulins may temporarily become undetectable. Low levels of serum C4 cannot be corrected by treatment. Low levels of C3 frequently are found during clinical flare-ups and can be corrected by treatment.

FIGURE 9-22
The clinical outcomes in 105 patients studied in three hospitals in Milan, Italy, between 1966 and 1990. The medial total follow-up time from clinical onset was approximately 11 years [19].

TREATMENT OF ACUTE RENAL EXACERBATIONS OF CRYOGLOBULINEMIC GLOMERULONEPHRITIS AND VASCULITIS

Steroids are used to control inflammatory renal and systemic involvement
Cytotoxic drugs are used to block production of new cryoglobulins by the specific lymphocytic clone that produces the monoclonal immunoglobulin Mr RF, and therefore, the precipitating cryoglobulins
Plasma exchange is used to remove circulating cryoglobulins from the blood before they deposit in the glomerulus and arterial walls

FIGURE 9-23
This approach to treatment of the acute renal exacerbations of cryoglobulinemia and vasculitis used previously when the viral cause of the disease was unknown is still valid now that the viral cause is evident. It is a common experience that the antiviral agent interferon-α, when given alone, does not control renal complications in the acute stage of the disease [20].

PROPOSED TREATMENT FOR MIXED CRYOGLOBULINEMIA ASSOCIATED WITH HEPATITIS C VIRUS INFECTION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-α</td>
<td>3.0–6.0 MU, 3 times weekly</td>
<td>6–12 mo</td>
</tr>
<tr>
<td>Steroids</td>
<td>Methylprednisolone, 0.75–10 g/d, intravenously</td>
<td>3 d</td>
</tr>
<tr>
<td>Prednisone, 0.5 mg/kg of body weight tapered over a few weeks until maintenance dose of 10–15 mg/d is achieved</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 mg/kg of body weight</td>
<td>3–4 mo</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Exchanges of 3 L of plasma, 3 times weekly</td>
<td>2–3 wk</td>
</tr>
</tbody>
</table>

FIGURE 9-24
The proposed treatment for mixed cryoglobulinemia associated with hepatitis C virus infection in the presence of severe acute signs of renal involvement, ie, glomerulonephritis and vasculitis. Plasma exchange is used only when acute renal insufficiency caused by massive precipitation of cryoglobulins is present. Interferon-α is given for more than 6 months only when negation of hepatitis C virus RNA is achieved in the first months, suggesting a beneficial effect on the viremia. Only the antiviral treatment with interferon-α eventually associated with low doses of steroids to control the systemic signs of mixed cryoglobulinemias should be given if renal involvement is mild. The association of interferon-α with another antiviral agent ribavirin, 0.6 to 1.0 g/d orally, now is being tested in patients with hepatitis C virus infection, with promising results [20].
We thank Dr. M. P. Rastaldi of the Division of Nephrology and Drs. E. Schiaffino and R. Boeri of the Department of Pathology of the Hospital of San Carlo Borromeo for their help.

References