Subacute Bacterial Endocarditis Masquerading as Type III Essential Mixed Cryoglobulinemia

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Abstract. An adult man presented severely ill with vasculitis of his lower extremities and with impaired kidney function. After detailed evaluation at a local hospital, a diagnosis of essential type III cryoglobulinemia was made. High-dose steroid and cyclophosphamide therapy was begun. The patient improved dramatically. However, 6 wk later when his steroid dose was reduced to 30 mg daily, vasculitis recurred. Intensifying his immunosuppressive therapy only worsened his condition. He was then transferred to the Ohio State University Medical Center for consideration for plasmapheresis for the presumed essential type III cryoglobulinemia. However, our evaluation showed that he had bacterial endocarditis causing his type III cryoglobulinemia. When immunosuppressive drugs were stopped and antibiotics were begun, his condition resolved completely. This case illustrates the difficulty of identifying infectious causes of cryoglobulinemia and emphasizes that an initial, highly favorable response of vasculitis to immunosuppressive therapy does not exclude an infectious cause for the vasculitis. (J Am Soc Nephrol 8: 1971–1976, 1997)

Cryoglobulins are immunoglobulins that remain in solution in warm temperature, but precipitate in the cold. Cryoglobulinemias can be divided into types I, II, and III. Types II and III are regarded as “essential” (idiopathic) when no cause for the cryoglobulinemia is found. Type II and type III cryoglobulinemia are referred to as “mixed” because the cryoglobulins contain two different immunoglobulin isotypes, usually IgG and IgM. Typically, the IgM is a rheumatoid factor (an antibody that binds specifically to the Fc region of other antibodies). If the rheumatoid factor is monoclonal, the mixed cryoglobulinemia is referred to as type II. If the rheumatoid factor is polyclonal, the cryoglobulinemia is referred to as type III (1). It is well established that infections can cause either type II or type III cryoglobulinemia. This case illustrates the difficulties in separating infectious from noninfectious causes of cryoglobulinemia.

Patients with essential mixed cryoglobulinemia usually benefit from immunosuppressive therapy and, perhaps, from the use of repeated plasmapheresis to physically remove the cryoglobulins (2). On the other hand, cryoglobulinemia due to infectious causes can be expected to be worsened by immunosuppression, although initial improvement may be seen. The present case illustrates this pitfall, as well as other classical and unusual manifestations of type III cryoglobulinemia due to infection.

Received December 12, 1996. Accepted June 16, 1997.
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1046-6673/0801-2 197 1 $03.00/0
Journal of the American Society of Nephrology
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Case Report

A 45-year-old white man presented to his family physician in September 1994 with profound fatigue, weight loss, shortness of breath, lightheadedness, and a rash on his lower extremities of at least 3 weeks duration. The appearance of the rash was consistent with palpable purpura of vasculitis. His past medical history included a known ventricular septal defect (VSD). In addition, he had corneal transplants both in 1974 and 1976. During examination, the patient appeared pale. Oral temperature was 98.2°F and BP was 126/88 mmHg. Cardiac examination revealed a grade III/VI basilar systolic murmur. The lungs were clear to auscultation. Abdominal examination was unremarkable. Painful, raised, nonblanching purpuric spots were scattered over his lower extremities beginning at the knees and ending at the ankles. There was no edema. Blood testing revealed hemoglobin 7.3 g/dl, white blood count (WBC) 7700 cell/mm³, platelet count 310,000/mm³, erythrocyte sedimentation rate 143 mm/h, blood urea nitrogen (BUN) 28 mg/dl, and serum creatinine 1.6 g/dl. Urinalysis showed microscopic hematuria and pyuria, and 30 mg/dl protein by dipstick. Antinuclear antibody was negative. Polyclonal IgM rheumatoid factor was positive in a titer of 1:1280. Serum protein electrophoresis showed a polyclonal gammopathy. Direct Coomb’s test was positive for IgG. IgG serum levels were elevated 3 times that of normal, and elevation of IgA and IgG levels was also observed. Thyroid function tests and liver function tests were normal. Monospot test, test for cytomegalovirus antibody, and antibody to HIV were negative. Blood cultures were negative. Testing for cryoglobulins was not done. An abdominal computerized axial tomography (CT) scan and a bone marrow exam were also normal. A surface echocardiogram was interpreted as showing mild pericardial effusion and mild-to-moderate aortic and tricuspid insufficiency.
Essential mixed cryoglobulinemia was diagnosed based on the positive rheumatoid factor and negative blood cultures. Treatment with prednisone (50 mg daily, orally) was initiated. Over the next 2 weeks, the patient experienced marked improvement in that his fatigue ameliorated and his rash disappeared. Six weeks later, as the prednisone dose was decreased to 30 mg daily, the patient developed marked weakness, fatigue, lower extremity edema, and dark red urine. Physical examination was remarkable only for the presence of soft systolic murmur at the left sternal border, and a palpable spleen tip. No rash was present. Blood testing showed that his hemoglobin was 7.8 g/dl and WBC count 19,000/mm³ with 95% segmented neutrophils on differential count. Platelet count was 96,000/mm³, and serum albumin was 2.5 g/dl. Urine analysis showed gross hematuria with >100 red blood cells (RBC), 5 WBC/high-powered field (hpf). Several RBC casts and 2+ proteinuria by dipstick were noted. BUN was 108 mg/dl and serum creatinine 6.0 mg/dl. Urine culture was negative. Plasma cryoglobulins were reported as +1. Rheumatoid factor was present in a titer of 1:320.

Because of acute renal failure, the patient underwent renal biopsy on October 27, 1994. The renal biopsy showed by light microscopy an occasional glomerulus with focal necrotizing glomerulonephritis and acute tubular necrosis (Figure 1). Immunofluorescence studies showed 1 to 2+ diffuse granular IgM and C1q in the mesangium and in capillary loops. C3 and C4 showed a similar pattern. Small amounts of fibrinogen were present within small crescents. Staining for IgA and IgG was negative. Staining for kappa and lambda light chains in a pattern similar to that noted for IgM was observed. There were no electron-dense deposits. The renal biopsy was interpreted as showing necrotizing glomerulonephritis (pauci-immune) and acute tubular necrosis. The patient’s relapse was thought to be due to inadequate immunosuppression. Methylprednisolone (1000 mg) was administered intravenously daily for 3 d followed by oral prednisone (100 mg daily) and cyclophosphamide (125 mg daily). On this treatment, renal function continued to deteriorate, gross hematuria persisted, and thrombocytopenia worsened. For these reasons, he was then referred to the Ohio State University Medical Center for consideration of plasmapheresis to treat essential mixed cryoglobulinemia.

At presentation to the Ohio State University Medical Center in November 1994, the patient complained of fatigue, dyspnea on exertion, orthopnea, easy bruising, epistaxis, and dark red urine. He was receiving oral prednisone (50 mg twice daily) and cyclophosphamide (125 mg daily). He was afebrile, with a pulse of 80 beats/min, BP 132/74 mmHg, and respiratory rate 16 breaths/min. Cardiac examination showed a grade III/VI systolic murmur at the left sternal border, pedal edema, but no rash. Blood testing showed BUN 198 mg/dl, serum creatinine 7.9 mg, WBC count 21,700/mm³, platelet count 69,000/mm³, hemoglobin 7.0 g/dl, hematocrit 20.2, serum lactate dehydrogenase 453 μM/ml, and serum phosphorous 11.7 mg/dl. Urinalysis showed a large amount of blood and 2+ protein by dipstick. Urine sediment showed >50 RBC/hpf and 1 to 2 WBC/hpf.

The urine sediment showed numerous casts and atypical cells. Proteinuria was 7.9 g/24 h. Antinuclear antibody was negative. Serum complement C3 was 37 mg/dl, C4 <10 mg/dl, and quantitative immunoglobulin G was elevated (2010 mg), whereas IgA (147 mg) and IgM (244 mg) were within the normal range. Plasma cryoglobulins and rheumatoid factor were positive. Hepatitis B and C serologies were negative. Blood cultures obtained on admission and 2 days later grew coagulase-negative staphylococci and streptococci-like organisms. Three days later, another blood culture showed growth of streptococcus-lie organisms and penicillinase-resistant staphylococcus epidermidis. The cyclophosphamide therapy was discontinued, and the prednisone dose was rapidly reduced to 10 mg daily. Intravenous vancomycin and gentamicin were begun. Fever developed to >102°F. Chest x-ray revealed cardiomegaly and lung infiltrates consistent with septic emboli from right-sided endocarditis. Transthoracic echocardiography demonstrated vegetations on the pulmonic valve with severe pulmonary regurgitation, aortic valve thickening with 2+ aortic regurgitation, a membranous VSD with a possible vegetation near the defect, and four-chamber enlargement. A subsequent transesophageal echocardiogram (TEE) (Figure 2) confirmed the presence of multiple vegetations on the pulmonary valve with severe pulmonary insufficiency, and a VSD with a possible vegetation at the defect. In addition, multiple aortic valve vegetations, moderate aortic regurgitation, and an atrial septal aneurysm with a secundum atrial septal defect were found. A review of the surface echocardiogram from September 1994 showed the presence of aortic and pulmonary valve vegetations.

Table 2 shows sequential changes in key clinical parameters before, during, and after therapy for endocarditis. As can be seen, with discontinuation of immunosuppression therapy and with initiation of antibiotic therapy, the patient’s condition gradually cleared. However, the patient was left with severe valvular deformities.

In March 1995, the patient underwent aortic valve and pulmonary valve replacement, Gore-Tex patch closure of

![Figure 1. Photomicrograph of glomerulus demonstrating segmental necrosis with fibrinogen deposition (hematoxylin and eosin; final magnification, ×100).](image-url)
Endocarditis and Glomerulonephritis

Discussion

This case is a classic example of a disorder in which the primary problem is a chronic infection. However, because of a strong immune response to an organism of low pathogenicity, the clinical manifestations and initial response to immunosuppressive therapy suggested a primary immune disorder. That is, our patient’s primary problem was bacterial endocarditis, but at presentation he lacked fever and leukocytosis, the usual manifestation of bacteremic infection. Instead, his clinical presentation was dominated by immune phenomena, including vasculitic skin lesions, a urine finding suggestive of glomerulonephritis, hypocomplementemia, Coomb’s positive hemolytic anemia, and the development of cryoglobulins with rheumatoid factor. Furthermore, the patient’s dramatic initial improvement while receiving anti-inflammatory and immunosuppressive medications suggested strongly that his primary problem was an immune disorder, not a chronic infection.

Other examples of chronic infection that can induce a syndrome suggestive of primary immune-mediated vasculitis/glomerulonephritis include previously reported cases of bacterial endocarditis (3); hepatitis B virus (4) or hepatitis C virus infection (5); bacterial infections causing osteomyelitis (6); ventriculo-atrial shunt infection (7-9); visceral abscess (10); and parasitic infections (11-16). The definitive treatment of these conditions and their concurrent immune manifestations is eradication of the infection. Control of the infection will remove the source of the antigen that drives the immune phenomenon.

In the present case, definitive treatment was delayed because the infection was covert. This led to an interesting series of events involving diagnosis and treatment that offer important insights into the pathogenesis and management of the cryoglobulinemia, which are classified as shown in Table 1.

The key discussion points of our case are as follows:

1. The diagnosis of right-sided endocarditis can be difficult.

Blood cultures are less likely to be positive in patients with

![Figure 2. Transesophageal echocardiogram demonstrating aortic and pulmonary valve vegetations. (A) Transesophageal short axis view demonstrating pulmonary valve vegetations (arrows) with destruction of the valve leaflets. (B) Same view (systolic frame) demonstrating vegetations (arrows) on the aortic valve. (C) Longitudinal view demonstrating aortic valve vegetations (arrows). AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RA, right atrium; RVOT, right ventricular outflow tract.](image-url)

the VSD, and suture closure of a patent foramen ovale. The native pulmonary and aortic valve were found to be almost completely destroyed. The microscopic examination of valves was consistent with infective endocarditis. Cultures from the tissues remained negative, and the patient enjoyed good recovery. In March 1995, his BUN was 21 mg/dl, serum creatinine 1.8 mg/L, platelet count 109,000/mm³, and blood hemoglobin 13 g/dl.

<table>
<thead>
<tr>
<th>Table 1. Cryoglobulinemias*</th>
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<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Type I: monoclonal Ig</td>
</tr>
<tr>
<td>Type II: monoclonal RF</td>
</tr>
<tr>
<td>Type III: polyclonal RF</td>
</tr>
</tbody>
</table>

* RF, rheumatoid factor; GN, glomerulonephritis; SLE, systemic lupus erythematosus.
right-sided endocarditis compared to those with left-sided endocarditis (17). Also, approximately 19% of patients with culture-negative endocarditis are afebrile (18). Endocarditis was suspected initially in our patient because of the cardiac murmurs; however, the presence of vegetations on the valves was not reported on the initial transthoracic echocardiogram. A subsequent transthoracic echocardiogram done at our institution clearly demonstrated pulmonic valve vegetations, a possible vegetation near the VSD, as well as aortic valve thickening. A TEE confirmed these findings and demonstrated definite aortic valve vegetations. A retrospective review of the initial surface echocardiogram showed that vegetations were present but were much smaller than those identified by us approximately 2 months later. Evidently, the vegetations grew in size during the 2 months that the patient received high-dose immunosuppressive medications. Also, identification of endocarditis can be facilitated by the use of TEE, because this technique is considered more sensitive than transthoracic echocardiography for the detection of vegetations (19).

2. Prednisone and cytotoxic therapy that produces prompt and dramatic improvement is not proof that the patient's condition is the result of a primary immune disorder. Our patient is a classic example of this principle. The initial improvement in this patient (disappearance of fatigue and vasculitis of the lower extremities) was almost certainly the result of the anti-inflammatory effects of prednisone. In addition, further temporary clinical improvement may have occurred, because the immunosuppressive effects of high-dose prednisone and cyclophosphamide decreased antibody levels (see Table 2), which decreased the immune-complex load. Nevertheless, immunosuppression did not produce sustained improvement. Indeed, it is likely that immunosuppression eventually led to the enhancement of the patient's infection, which manifested as recurrence of severe fatigue and the development of severe anemia and thrombocytopenia. The patient's anemia was both the result of bone marrow suppression (the patient's total reticulocyte count was only 2.1% when his hemoglobin was 7.3 g/dl) and severe intravascular hemolysis. The infection and the severe intravascular hemolysis were the mechanisms of impaired kidney function in our patient, as discussed below.

3. The acute renal failure was the result of intravascular hemolysis causing hemoglobinuria and acute tubular necrosis. Glomerular injury was minimal, and probably related to the bacteremia and not immune-complex deposition. The patient's rapidly progressive renal failure coincided with the development of marked intravascular hemolysis and hemoglobinuria. A renal biopsy of extensive acute tubular

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On Initial Presentation to Community Hospital</th>
<th>At Time of Relapse while Receiving Immunosuppressive Therapy</th>
<th>At Presentation to OSUMC when Immunosuppressive Therapy Was Stopped</th>
<th>After Completion of 6 wk of IV Antibiotics</th>
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<td>Hemoglobin/hematocrit</td>
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<td>7.8/23.7</td>
<td>7.0/20.2</td>
<td>8.7/26.0</td>
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<td>21,700</td>
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<td>ESR</td>
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<td>Reticulocyte count</td>
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<td>BUN</td>
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<td>198</td>
<td>19</td>
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<tr>
<td>Creatinine</td>
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<td>6.0</td>
<td>7.9</td>
<td>1.7</td>
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<td>U/A</td>
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<td>&gt;100 RBC, 15 to 20 WBC, 100 mg %protein, RBC cast, WBC cast, coarse granular cast</td>
<td>&gt;50 RBC, 1 to 2 WBC, 100 mg %protein</td>
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<td>1:320</td>
<td>249 U</td>
<td>97 U</td>
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<tr>
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<td>2010</td>
<td>1770</td>
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<td>IgA (nl 69 to 382)</td>
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<td>243</td>
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<td>244</td>
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<td>Complement (mg/dl)</td>
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<td>108</td>
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<tr>
<td>C4 (nl 17 to 58)</td>
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<td></td>
<td>&lt;10</td>
<td>&lt;10</td>
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</table>

* OSUMC, Ohio State University Medical Center; IV, intravenous; WBC, white blood cell; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; U/A, urinalysis; RBC, red blood cell; nl, normal range.
necrosis suggested that hemoglobinuria was the dominant factor in causing acute renal failure. Glomerular changes were also present, but they were focal and segmental in character, and not likely to significantly affect kidney function.

The mechanism of the focal necrotizing glomerulonephritis in our patient is unclear, but it apparently is not the result of deposition of circulating immune complexes. That is, examination of the glomerulus by immunofluorescence and by electron microscopy did not show evidence of conspicuous amounts of immune-complex deposition. These focal necrotizing lesions may represent emboli from the endocarditis that lodge in the glomerular capillaries and incite inflammation or the direct effect of bacterial toxins to activate inflammatory mechanisms, as we have reported previously (20).

Undoubtedly, our patient was forming large amounts of circulating immune complexes as the result of bacteremia, the strong antibody response to the bacteremia, and the formation of rheumatoid factors, which would enhance immune-complex formation (21). Cryoglobulins and associated rheumatoid factors are common in endocarditis (22). The failure to show significant glomerular accumulation of immune complexes under the circumstances of abundant circulating immune-complex formation is not clear. However, there is evidence that normally there is great capacity to clear immune complexes from the circulation (23). It is only when immune-complex uptake by the liver and spleen becomes impaired that excessive deposition of immune complexes in vulnerable organs such as the kidney begins to develop (21).

To our knowledge, our case is the first example of the association of autoimmune hemolytic anemia with endocarditis. The mechanism by which endocarditis might provoke an autoimmune hemolytic anemia is not clear. However, bacterial toxins are known to be potent B cell mitogens (24). Indeed, our patient had massively elevated IgG levels. Under the conditions of massive overproduction of immunoglobulins, it is possible that a high percentage of the B cell repertoire for IgG antibodies was developed in our patient. Some of these antibodies apparently had specificity for red cell antigens and led to the hemolytic anemia. This hypothesis is consistent with experimental models of massive B cell activation in mice by chronic administration of endotoxin (20). These mice developed immune-complex disease, in which the immune complexes are mainly the result of induction of autoreactive antibodies by the endotoxin, not by specific autoantigens.

In summary, cryptogenic endocarditis can give rise to a disorder that strongly resembles a primary immune-mediated vasculitis/glomerulonephritis. Thus, when evaluating patients presenting with a vasculitis/glomerulonephritis syndrome, it is important to maintain a high index of suspicion that the underlying disorder could be the result of an infectious disease, not a primary immunologic disease. As discussed, the management of these two conditions is markedly different.

References
Nephrology Training Program at the Ohio State University Medical Center

The nephrology division of the Ohio State University consists of 12 full-time faculty members, seven fellows, and more than 30 research and administrative staff members. The division’s clinical and research programs are located in the Ohio State University Medical Center. The Medical Center is the second largest hospital in the consortium of teaching hospitals and consists of 958 staffed medical and surgical beds. The Medical Center serves as the major referral hospital for a regional population of about 3.0 million. The two in-patient nephrology services receive more than 100 admissions per month. The in-patient acute dialysis center performs approximately 5000 in-patient hemodialyses and 250 continuous arteriovenous/venovenous hemodialyses per year. Clinical fellows are also trained in the performance of percutaneous native and transplant kidney biopsies (approximately 125 and 400 per year, respectively) and fiber optically guided percutaneous placement of peritoneal dialysis catheters (approximately 100 per year). The solid organ transplant program is one of the largest in the nation, conducting more than 200 kidney, 50 liver, and 50 pancreas/kidney transplants annually. The clinical research programs of the division include leadership roles in many clinical trials, including each of the four previous National Institutes of Health-sponsored controlled clinical trials in renal diseases and the current African-American study of kidney disease and hypertension (AASK). The basic research programs include: immune complex-mediated glomerulonephritis, delineation of complement-induced pathways of mesangial cell damage, the role of lipids and cytokines as inflammatory mediators, and the cellular basis for the development of diabetic nephropathy. Each year, we accept three nephrology fellows into our program for a period of 2 or 3 years. The first year of fellowship is largely a clinical experience. The second and third years are primarily research-oriented—either basic or clinical.