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Case records of the Massachusetts General Hospital. Case 31-2005. A 60-year-old man with skin lesions and renal insufficiency

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Case 31-2005: A 60-Year-Old Man with Skin Lesions and Renal Insufficiency

Jonathan Kay, M.D., and Robert T. McCluskey, M.D.

Presentation of Case

A 60-year-old man was evaluated in the rheumatology clinic because of a rash and worsening renal function.

He had been well until three months earlier, when he began to have fatigue and weight gain, one week after returning from a visit to his son in Colorado. He could not fit into his shoes, and his wife noticed that he had facial swelling. Three days later, a rash appeared over his buttocks and feet. He saw his primary care physician. The blood pressure was 154/82 mm Hg. There was 1+ bilateral pretibial and pedal edema. Tests for antineutrophil cytoplasmic antibodies and anti–streptolysin O were negative; a test for antinuclear antibodies was weakly positive (8 U; normal, less than 7.5 U). Other laboratory-test results are listed in Tables 1 and 2. The results of chest radiography showed no abnormalities, except for blunting of the costophrenic angles that was thought to represent small effusions. An ultrasonographic study of the kidneys revealed hypoechoic areas in the left kidney and a normal-appearing right kidney. Furosemide and metolazone were started. A low titer of IgM antibody to Rocky Mountain spotted fever was present, but this value did not change on follow-up testing.

Despite increasing doses of furosemide, the patient continued to gain weight over the course of the next 10 days. He was referred to a nephrologist at another hospital. The blood pressure was 175/95 mm Hg, and he had gained more than 9 kg since the start of his illness. Palpable purpuric lesions were present on the buttocks and feet, including the soles. The serum creatinine level was 2.1 mg per deciliter (185.6 µmol per liter), and the urinalysis revealed 3+ protein, 4+ blood, 10 to 15 red cells per high-power field, 5 to 10 white cells per high-power field, and many coarse and fine granular casts. Treatment with atenolol was started. A skin-biopsy specimen showed a leukocytoclastic vasculitis. Direct immunofluorescence staining of the biopsy specimen showed granular deposits consisting primarily of IgM and C3 in a vascular pattern in the papillary dermis, with very faint deposits of IgG and no IgA.

A renal biopsy was performed one week later at that hospital, and a diagnosis of endocapillary proliferative glomerulonephritis, immune-complex type, was made. Immunofluorescence studies were reported to show mesangial and focal capillary-loop deposits of IgG, C3 (trace to 1+), and IgM (1+). Electron-microscopical examination revealed small mesangial and subendothelial electron-dense deposits. The findings were con-
sidered consistent with postinfectious glomerulonephritis, provided that other types of immune-complex glomerulonephritis could be ruled out—in particular, lupus nephritis. Over the next two weeks, the patient continued to be fatigued, with a poor appetite; the serum creatinine level rose to a peak of 2.9 mg per deciliter (256.4 µmol per liter).

Treatment with prednisone (60 mg per day), lisinopril, amlodipine, and omeprazole was started, and treatment with metolazone was discontinued. The patient was also still taking furosemide and atenolol. Over the next four weeks, the serum creatinine level fell to 1.9 mg per deciliter (167.9 µmol per liter), the patient’s edema improved, the rash gradually resolved, and he felt more energetic. During the next week, however, the edema increased, and over the course of the next four weeks the creatinine level rose to 2.4 mg per deciliter (212.2 µmol per liter). A 24-hour urine collection yielded 5.7 g per deciliter of protein. Three weeks later, the patient was seen in the rheumatology clinic of this hospital.

The patient was a retired management consultant who lived in New Hampshire. He did not have photosensitivity, hair loss, Raynaud’s phenomenon, keratoconjunctivitis sicca symptoms, or arthritis. An appendectomy had been performed two years earlier because of acute appendicitis. He drank approximately five alcoholic beverages per week and did not smoke cigarettes. He had no allergies. There was no family history of renal disease or autoimmune disorders. He was married, and his wife and a son and a daughter were well. He knew of no exposures to toxins or ill persons and did not recall tick bites. He had traveled recently only to Colorado and Connecticut.

On examination, he appeared chronically ill. The blood pressure was 170/100 mm Hg, the pulse 60 beats per minute, and the respiratory rate 14 breaths per minute. He had a cushingoid appearance, and there was diffuse anasarca. There was marked (4+) pitting edema of both forearms and of both legs, extending up to the thighs. The results of the remainder of the physical and neurologic examinations were normal.

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Laboratory-test results are shown in Tables 1 and 2. A diagnostic test was performed.

Differential Diagnosis

Dr. Jonathan Kay: I participated in the care of this patient and am aware of the diagnosis. This 60-year-

* GPL denotes IgG phospholipid, and MPL IgM phospholipid.
old man had a sudden onset of constitutional symptoms; leukocytoclastic cutaneous vasculitis; facial, arm, and leg edema; and hypertension, within two weeks after returning from a visit to Colorado. Laboratory evaluation revealed anemia and renal insufficiency, with microscopic hematuria and proteinuria in the nephrotic range. Serum complement levels were decreased, and he had low titer of antinuclear antibodies and of IgM antibodies to Rocky Mountain spotted fever. Testing for cryoglobulins and antineutrophil cytoplasmic antibodies had been negative.

The development of a palpable purpuric rash shortly after the patient’s return from Colorado raised the possibility of Rocky Mountain spotted fever. Early symptoms of Rocky Mountain spotted fever, which usually occur several days to two weeks after the bite of a common dog tick (Dermacentor variabilis) infected with Rickettsia rickettsii, include fever, headache, malaise, myalgias, nausea with or without vomiting, and abdominal pain. The patient did not describe any of these symptoms. The patient’s rash was located on his chest, buttocks, and legs, in contrast to the typical distribution of the rash of Rocky Mountain spotted fever, which usually begins as a maculopapular eruption that evolves into a petechial rash on the arms and legs and then spreads centrally and also distally to the palms and soles. About 20 percent of patients have renal involvement. The diagnosis can be made by serologic testing that shows a titer of 1:128 or higher. This patient’s titer of IgM antibodies was 1:64, and the result did not change on follow-up testing, suggesting that Rocky Mountain spotted fever was not the cause of his illness.

This patient’s urinary sediment contained red cells, suggesting glomerular disease. The presence of nephrotic-range proteinuria, hypertension, edema, and elevated serum levels of creatinine imply diffuse glomerulonephritis, in which inflammatory lesions are present in most or all of the glomeruli on light microscopical examination. The results of a renal biopsy reportedly showed endocapillary proliferative glomerulonephritis with immune complexes containing IgG, IgM, and C3.

The pathologist who interpreted the renal biopsy raised the possibility of either postinfectious glomerulonephritis or lupus nephritis. Antistreptolysin O antibodies were not detected, which ruled out a diagnosis of poststreptococcal glomerulonephritis. Although the initial test for antinuclear antibodies was weakly positive, the test repeated at this hospital was negative. About 5 percent of patients with systemic lupus erythematosus present without detectable serum antinuclear antibodies; however, these patients typically do not have renal involvement. When nephrotic-range proteinuria develops in a patient with lupus nephritis, serum antinuclear antibodies may become undetectable because they are excreted with other proteins in the urine; this scenario was a possibility in this patient. He reportedly had IgM antcardiolipin antibodies and hypocomplementemia, both of which are features associated with lupus. If the findings of the renal biopsy had been consistent with lupus nephritis, he would have met only three of the four criteria necessary for a diagnosis of systemic lupus erythematosus, as defined in 1997 by the American College of Rheumatology. Thus, a diagnosis other than systemic lupus erythematosus should be considered.

The 1994 Chapel Hill consensus conference on the nomenclature of systemic vasculitides divided this group of disorders into large-vessel vasculitis, medium-sized–vessel vasculitis, and small-vessel vasculitis (vasculitis involving vessels smaller than arteries). The disease in the patient under discussion clinically involved arterioles, capillaries, and venules, since there was cutaneous leukocytoclastic vasculitis and glomerulonephritis. Many causes of small-vessel vasculitis could be ruled out in this patient because of the absence of predisposing factors, such as exposure to drugs or documented infections, or the absence of associated diseases. There was no evidence of cancer, inflammatory bowel disease, rheumatoid arthritis, or Sjögren’s syndrome. He did not have urticaria, which might have suggested hypocomplementemic urticarial vasculitis. There were no oral or genital ulcerations, involvement of the central nervous system, or uveitis to suggest Behçet’s disease, and no pulmonary involvement to suggest Goodpasture’s syndrome. Microscopic polyangiitis, Wegener’s granulomatosis, and the Churg–Strauss syndrome are unlikely diagnoses in the absence of antineutrophil cytoplasmic antibodies. Thus, the most likely diagnosis was Henoch–Schönlein purpura or cryoglobulinemic vasculitis.

Henoch–Schönlein purpura typically affects children, with the peak incidence at around five years of age, but it also may affect adults. The disease usually occurs not only with nephritis and palpable purpura that typically involves the lower extremi-
ties, but also with gastrointestinal symptoms, such as abdominal pain, which this patient did not have. In both Henoch–Schönlein purpura and cryoglobulinemic vasculitis, cutaneous involvement occurs in about 90 percent of patients and renal involvement in about 50 percent. However, IgA deposition in the skin, which is pathognomonic of Henoch–Schönlein purpura, was not present in this case.

Laboratory findings in this patient that support a diagnosis of cryoglobulinemic vasculitis include hypocomplementemia with low levels of C4 and the presence of rheumatoid factor without antinuclear antibodies. In patients with mixed cryoglobulinemia, serum complement activation results in selective depression of the C4 level, often to below the limit of detection; this occurs most frequently in those with type II cryoglobulins. Type II cryoglobulins contain a monoclonal component, often an IgM rheumatoid factor, and polyclonal IgG. Renal involvement is three times as prevalent in patients with type II mixed cryoglobulinemia as in those with type III mixed cryoglobulinemia, in which the cryoglobulins contain a combination of polyclonal IgM rheumatoid factor and polyclonal IgG. However, cryoglobulins were not detected in this patient’s blood.

Since the hallmark of cryoglobulinemia is the presence of cryoglobulins, how could a negative cryoglobulin determination be consistent with this diagnosis? The assay for cryoglobulins involves careful handling of the blood sample: the specimen must be maintained between 37°C and 41°C from the time of its withdrawal until the serum is isolated in the laboratory. After centrifugation at 37°C to remove red cells and fibrin, the serum is transferred at room temperature to a cryocrit tube, which then is stored at 4°C for a week and observed daily for seven days. If the serum becomes cloudy, the cryocrit tube is centrifuged in the cold and the cryocrit is measured. The cryoglobulin is washed and then assessed for monoclonality by immunofixation and for the presence of rheumatoid factor. If the specimen is exposed to temperatures lower than 37°C at any time before the serum is obtained, the cryoprecipitate may be lost. Thus, improper handling of the specimen before it reaches the clinical laboratory or improper processing in the laboratory can result in a false negative cryoglobulin test.

In summary, my diagnosis in this case is type II mixed cryoglobulinemia, with a false negative cryoglobulin assay. I requested that the renal-biopsy specimen be reviewed by our renal pathologists.

Dr. Nancy Lee Harris (Pathology): Dr. Franklin Segall referred the patient to Dr. Kay. Could you comment on your thinking?

Dr. Franklin D. Segall (Nephrology, Mount Auburn Hospital): When I first saw the patient, the urine sediment suggested glomerular inflammation. Because of the rash, I considered Henoch–Schönlein purpura and obtained a skin-biopsy specimen, which showed no IgA deposition. When the renal biopsy suggested lupus nephritis, I started the patient on steroid treatment; he had initial improvement, but his renal function continued to deteriorate, and I sent him to see Dr. Kay.

**Clinical Diagnosis**

Glomerulonephritis due to systemic lupus erythematosus.

**Dr. Jonathan Kay’s Diagnosis**

Mixed cryoglobulinemia type II.

**Pathological Discussion**

Dr. Robert T. McCluskey: The diagnostic procedure was a review of the renal biopsy performed at the other hospital. All of the glomeruli in the specimen were globally hypercellular, owing almost entirely to intracapillary cells with the appearance of monocytes or macrophages (Fig. 1A). Periodic acid–Schiff (PAS) preparations showed generally normal-appearing glomerular basement membranes, with rare segmental duplication of the glomerular basement membrane and without an appreciable increase in mesangial matrix. Several glomeruli had one or more intracapillary amorphous, eosinophilic, PAS-positive globules, which are characteristic of pseudothrombi (Fig. 1A). There was mild, focal interstitial mononuclear-cell infiltration and edema. Two small arteries had features of vasculitis (Fig. 1B and 1C). A review of the electron micrographs of one glomerulus revealed amorphous, electron-dense subendothelial and intracapillary deposits, as well as segmental duplication of the glomerular basement membrane (Fig. 1D). Intracapillary mononuclear cells were also seen. Immunofluorescence microscopical studies were reported as showing trace to 1+ granular staining for IgM, IgG, and C3, without IgA, in the mesangium and along the glomerular basement membranes.

The renal-biopsy findings are highly character-
The characteristic of active, acute type II mixed cryoglobulinemic glomerulonephritis (Table 3). The key features are massive accumulation of monocytes and macrophages in glomeruli and the presence of pseudothrombi.8-10 Although the intracapillary leukocytes have the appearance of monocytes or macrophages in histologic preparations, more definitive cell identification might have been obtained through the use of a monocyte marker, notably CD68.8 The finding on immunofluorescence microscopy of granular deposits in glomeruli containing IgM and IgG is consistent with mixed cryoglobulin complexes. The finding of small-vessel vasculitis adds additional support to the diagnosis; in particular, the accumulation of amorphous eosinophilic material in a vessel wall (Fig. 1C), which probably represents cryoprecipitates, is characteristic of early cryoglobulinemic vasculitis. The electron-microscopical findings also favor the diagnosis of cryoglobulinemic glomerulonephritis by showing intraluminal and subendothelial deposits, as well as intracapillary cells with the appearance of monocytes. In this case, the glomerular electron-dense deposits were amorphous, which is not unusual in cryoglobulinemic glomerulonephritis. However, in many cases the deposits have distinctive fibrillar or cylindrical structures that are virtually diagnostic of type II mixed cryoglobulinemic glomerulonephritis.11

The initial pathologic diagnosis made in the present case was endocapillary proliferative glomerulonephritis. This is a descriptive term that...
Evidence of healed vasculitis

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<th>Table 3. Distinctive Pathological Features of Type II Mixed Cryoglobulinemic Glomerulonephritis.</th>
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<td><strong>Acute stage (as in first biopsy specimen)</strong></td>
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<td>Massive infiltration of glomeruli by activated monocytes and macrophages (CD68 positive, esterase positive)</td>
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<tr>
<td>Intracapillary deposits testing positive on periodic acid–Schiff staining; containing IgM and IgG, characteristic of cryoglobulin precipitates (pseudothrombi)</td>
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<tr>
<td>Electron-dense intracapillary, intramonicyte, and subendothelial deposits, some with fibrillar or cylindrical structure</td>
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<td>Segmental duplication of glomerular basement membrane and mild-to-moderate mesangial increase</td>
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<tr>
<td>Small-vessel vasculitis</td>
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<td>IgG and IgM deposits in the interstitium (not described in this case)</td>
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<td><strong>Chronic stage (as in second biopsy specimen)</strong></td>
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<tr>
<td>Pattern of membranoproliferative glomerulonephritis type I</td>
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<tr>
<td>Moderate increase in mesangial cells and matrix, with prominent duplication of glomerular basement membranes; tubular atrophy and interstitial fibrosis</td>
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<tr>
<td>Few or no monocytes in glomeruli</td>
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<td>Few, if any, pseudothrombi</td>
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<td>Deposits in mesangial cells and in glomerular basement membrane containing IgM, IgG, and C3 (often sparse)</td>
</tr>
<tr>
<td>Subendothelial and mesangial electron-dense deposits, with or without fibrillar or tubular substructure</td>
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<td>Evidence of healed vasculitis</td>
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was introduced in early studies of renal-biopsy specimens, when it was believed that glomerular hypercellularity resulted mainly from proliferation of mesangial and endothelial cells. However, it was later shown that infiltration by circulating mononuclear cells, rather than the proliferation of endothelial cells, largely accounts for endocapillary hypercellularity in various forms of glomerulonephritis. The numbers of intraglomerular monocytes and macrophages are far greater in acute type II mixed cryoglobulinemic glomerulonephritis than in other so-called proliferative conditions, notably post-streptococcal glomerulonephritis, diffuse proliferative lupus nephritis, and idiopathic membranoproliferative glomerulonephritis type I. The mononuclear cells phagocytose and degrade the IgM and IgG mixed cryoglobulin complexes within glomeruli, thus helping to bring about resolution, but they also contribute to glomerular injury through a variety of mechanisms, including the release of proteases, reactive oxygen species, eicosanoids, and nitric oxide.

A skin-biopsy specimen of a purpuric lesion showed leukocytoclastic vasculitis (Fig. 2). The absence of IgA in the vascular lesions argues against the diagnosis of Henoch–Schönlein purpura, and the finding of deposits of IgM, IgG, and C3 supports the diagnosis of mixed cryoglobulinemic vasculitis. However, the diagnostic pathological findings were in the kidney. A biopsy specimen of the bone marrow obtained at this hospital was normal.

Dr. Kay: After Dr. McCluskey’s review of the renal biopsy, blood was drawn under appropriate conditions to assess for cryoglobulins. The cryocrit was 3 percent, with a cryoglobulin that consisted of homogeneous IgM kappa and heterogeneous IgG protein — findings that established the diagnosis of type II mixed cryoglobulinemia.

Since the association between hepatitis C virus infection and mixed cryoglobulinemia was first reported, type II mixed cryoglobulinemia associated with hepatitis C virus infection has become the type of cryoglobulinemia that is most commonly encountered in clinical practice (in 80 percent of the cases). This patient’s serum contained no antibodies to hepatitis C virus and no hepatitis C viral messenger RNA (mRNA) was detectable by polymerase-chain-reaction assay of his serum. However, because hepatitis C viral mRNA may be concentrated up to 1000 times within the cryoprecipitate, the polymerase-chain-reaction assay for hepatitis C viral mRNA was performed on the cryoprecipitate by Dr. Vincent Agnello at the Lahey Clinic in Burlington, Massachusetts, and was negative. This result confirmed that the patient had type II mixed cryoglobulinemia, unassociated with hepatitis C virus infection.

**DISCUSSION OF MANAGEMENT**

Dr. Kay: A prospective randomized, controlled clinical trial of treatment for cryoglobulinemia associated with hepatitis C virus infection found that interferon alfa-2a resulted in disappearance of detectable hepatitis C viral mRNA from the serum and improvement in the serum levels of cryoglobulin and signs and symptoms of cryoglobulinemia in 15 of 25 patients (60 percent) who were treated with interferon alfa-2a. However, treatment of cryoglobulinemia without hepatitis C virus infection remains based on empirical clinical experience, although one study showed a response to recombinant interferon alfa-2a in two patients.

If the patient has an underlying condition that is contributing to cryoglobulin production, such as a hematologic cancer, that condition should be treat-
Plasmapheresis may be used as short-term treatment to remove circulating cryoglobulins and to prevent their deposition in tissues. Immunosuppressive therapy with prednisone and cytotoxic drugs, such as cyclophosphamide, usually is initiated to suppress cryoglobulin production.

Rituximab, an anti-CD20 chimeric monoclonal antibody that depletes B cells, was used recently to treat patients who had mixed cryoglobulinemia that was unresponsive to other medications. In two prospective, uncontrolled case series involving 35 patients, including 3 without hepatitis C infection, serum levels of cryoglobulin decreased, serum levels of C4 increased, and there was clinical improvement in the majority of the patients. However, hepatitis C viral mRNA levels increased in some of the patients in each of these series. Thus, caution must be used when treating patients who have hepatitis C virus infection with rituximab.

Despite treatment with 20 mg of oral prednisone three times daily, this patient’s creatinine level rose to 2.4 mg per deciliter (212.2 µmol per liter) after eight weeks of the drug. Cyclophosphamide (800 mg) was administered in a single intravenous dose, and plasmapheresis was begun (total, six treatments). The course of his disease was complicated with an infection with *Staphylococcus aureus* that caused septic prepatellar bursitis, requiring hospitalization for intravenous penicillin therapy for the penicillin-sensitive *S. aureus* and closed drainage; an episode of bronchiolitis obliterans with organizing pneumonia that was diagnosed by video-assisted thoracoscopy; an empyema of the right lung associated with *Escherichia coli* that required chest-tube drainage and intravenous antibiotics; and a perforated sigmoid diverticulum that required sigmoid resection and colostomy.

The patient’s serum creatinine level continued to rise to 3.8 mg per deciliter (335.9 µmol per liter), and his cryocrit remained at 3 percent. Because of his active infections, the planned oral cyclophosphamide treatment was contraindicated. Thus, we referred him to Dr. Philip C. Amrien of the Hematology and Oncology Unit to be considered for rituximab therapy. At Dr. Amrien’s recommendation, the patient was treated with rituximab (375 mg per square meter of body-surface area, intravenously) weekly for four weeks, according to the standard protocol. One month later, his creatinine level had risen to 4.0 mg per deciliter (353.6 µmol per liter). However, his cryocrit fell to less than 1 percent. Treatment with mycophenylate mofetil was initiated, on the basis of the hypothesis that it might serve as an immunosuppressive agent with less risk of infection than was associated with cyclophosphamide. Oral prednisone (30 mg daily) was continued.

Dr. McCluskey: A second renal biopsy was performed here about nine months after the first. The glomeruli showed mild-to-moderate mesangial hydropellularity and matrix increase, as well as segmental duplication of the glomerular basement membrane (Fig. 3A and 3B). There were no intracapillary monocytes or pseudothrombi. Several small arteries showed changes that were indicative of healed arteritis (Fig. 3C). Interstitial fibrosis and tubular atrophy involved about 40 percent of the sample. Immunofluorescence microscopical examination revealed segmental granular glomerular basement membranes and mesangial staining for IgM (1+) and C3 (1+ to 3+).

The findings from the second biopsy show some features of membranoproliferative glomerulonephritis type I (Table 3). Lesions such as those in the specimen can be found in patients with type II mixed cryoglobulinemic glomerulonephritis who have had remissions, but similar pathological findings are
seen in a variety of conditions that have been diagnosed as idiopathic or secondary membranoproliferative glomerulonephritis type I.\textsuperscript{20} Thus, whenever a pathological diagnosis of membranoproliferative glomerulonephritis type I is made, tests to rule out mixed cryoglobulins and hepatitis C infection, and tests for other infectious agents, should be performed before the condition is labeled idiopathic.

\textbf{Dr. Kay:} Four months after the patient completed the course of rituximab, his cryocrit again rose to 3 percent, and he received a second course of rituximab. Cryoglobulins again became undetectable, and he was able to taper off prednisone. One year after the diagnosis, he was feeling well and began to be physically active, although he remained on hemodialysis.

Unfortunately, about 18 months after the diagnosis, an enterococcal infection of his hemodialysis line developed that resulted in bacterial endocarditis of the aortic valve, causing aortic insufficiency and requiring replacement of the aortic valve with a bovine bioprosthesis. The patient recovered quickly and now, one year later, is remarkably well, with an undetectable cryocrit, on chronic hemodialysis. He is awaiting renal transplantation.

\textbf{Dr. Harris:} The patient and his wife are here at the conference. Would you like to comment?

\textbf{The Patient:} Until the age of 60, I had been very healthy and active. Very suddenly, that all changed. The past three years have been a physical and emotional roller coaster, filled with unpleasant procedures, hope, despair, feeling awful, and feeling almost human. The most difficult times have been the long hospital stays, the endless hours attached to a dialysis machine, and the stress and frustration of waiting for answers that didn’t always come quickly.

I have come to appreciate the professionalism and honesty of my physicians. If they didn’t know the answers, they kept searching. They were very open in their discussions about my illness, knowing that what they said wasn’t always what I wanted to hear. They made my wife and me feel an integral part of a team effort. Throughout this illness, however, my most valuable asset has been my wife. She has studied, has learned, has challenged when necessary, and has been an advocate for me — something all patients should have. I, in turn, have learned to question and to accept or reject certain procedures, drugs with unknown results, and physicians’ opinions and to know that ultimately medical decisions are mine alone.

\textbf{Type II cryoglobulinemia with renal disease.}

\textbf{Dr. Kay:} reports having served on two advisory boards for Genentech (after this case was completed).
REFERENCES


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