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Viral infections and the kidney: HIV, hepatitis B, and hepatitis C

■ ABSTRACT

Infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) can cause rapidly progressive renal disease, so prompt recognition and management are critical. Viral glomerulonephropathy can now often be successfully managed with a specific combination of antiviral therapy, immunosuppressants, plasmapheresis, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin 2 receptor blockers.

■ KEY POINTS

Each virus typically causes a characteristic histologic pattern: HIV infection often causes collapsing focal sclerosis (especially in African Americans), HBV causes membranous glomerulonephropathy, and HCV causes membranoproliferative glomerulonephritis.

Patients with HIV-associated nephropathy should be treated with highly active antiretroviral therapy as well as an ACE inhibitor, an angiotensin 2 receptor blocker, or both. Some patients also benefit from corticosteroid therapy.

In adults, HBV glomerulopathy should be treated with lamivudine (Epivir), possibly combined with pegylated interferon. In children, HBV glomerulopathy tends to remit spontaneously without treatment.

HCV glomerulonephritis should be treated with plasmapheresis, immunosuppressants, ribavirin (Rebetol), and pegylated interferon, depending on the severity and progression of the renal disease.

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TEN YEARS AGO, viral glomerulonephritis was usually regarded as untreatable. Now, treatments are available for the top three causes of viral glomerulonephritis: human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Infections with these viruses have become so common worldwide that even if only a small percentage of infected patients develop glomerular disease, the absolute number of cases is large.

This article covers the epidemiology, pathophysiology, diagnosis, and management of the three most common viral glomerulopathies. It also discusses how to distinguish nephropathy caused by antiviral therapy.

■ VIRUSES AND THE KIDNEY

Besides HIV, HBV, and HCV, some less-common viruses can also cause kidney problems: parvovirus is associated with a specific pattern of focal sclerosis, polyomavirus BK is associated with tubular injury in kidney transplant recipients, and hantavirus causes acute interstitial nephritis and perhaps also chronic interstitial disease.

How viruses damage kidneys

Viruses can damage the kidneys in a number of ways that are often characteristic of the specific infection.

Circulating immune complexes (consisting of viral antigens or endogenous antigens induced by the virus and the host antibodies that develop in response) may precipitate in the kidney.

In situ immune complexes form from viral or endogenous antigens that first lodge in the glomerular basement membrane and then

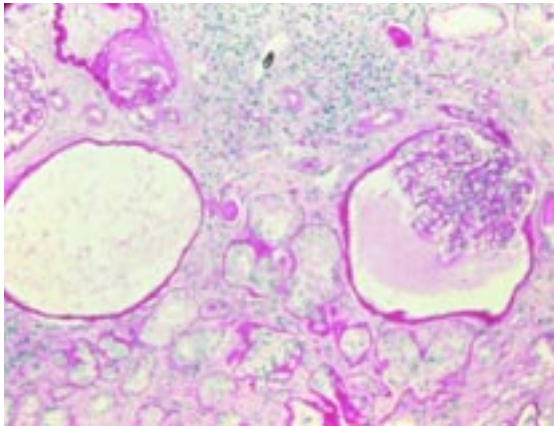


FIGURE 1. Collapsing focal sclerosis.

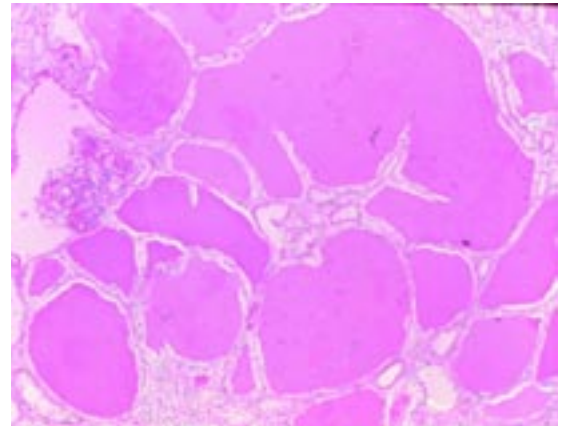


FIGURE 2. Giant microcystic tubules.

combine with antibodies that also enter the glomerulus.

Circulating and in situ immune complexes commonly occur with HBV or HCV infection.

Viral proteins or inflammatory factors are commonly expressed in HIV-associated nephropathy.

Viruses can also have direct cytopathogenic effects on glomerular cells.

Tubulointerstitial injury occurs from hantavirus infection and polyomavirus BK.

Hemodynamic disturbances, such as septic shock due to disseminated intravascular coagulation, can occur in patients with large viral loads.

Rhabdomyolysis associated with viral illness can cause acute renal failure, especially in association with influenza A2.

Antiviral therapy itself can cause nephrotoxicity, and it is sometimes difficult to determine whether a problem is due to the disease or the therapy.

■ HIV INFECTION

Worldwide, acquired immune deficiency syndrome (AIDS) has killed more than 25 million people,¹ and an estimated 4.9 million people are newly infected per year.² The United States has about 1 million infected people, and about 40,000 people are newly infected each year.² AIDS is the leading cause of death in African Americans 25 to 44 years old.

HIV-associated nephropathy

HIV-associated nephropathy is a unique pattern of glomerular disease that is often found

in African Americans and sometimes in Hispanics. It is, however, so unusual in non-Hispanic white people that another cause of nephropathy should be sought if this lesion is found.

Most patients with HIV-associated nephropathy have a high viral load, but the disease is not associated with any other specific risk factor, including age of the patient, duration or stage of HIV infection, or concurrent opportunistic infections. It is most common in cities in the eastern United States with large African American populations.

At New York-Presbyterian Hospital, we obtained renal biopsy specimens from 112 patients with HIV infections and found that 93% had glomerular disease. Focal segmental sclerosis was the pattern in most cases.³ Series performed elsewhere in the United States and in other countries would likely reveal a different pattern, depending on the racial background of the patients.

Casanova et al⁴ obtained 26 renal biopsies from patients in Italy who had HIV infection and glomerular disease but were white: most had proliferative and immune complex glomerulonephritis, and there was no evidence of HIV-associated nephropathy.

Clinical features. HIV-associated nephropathy typically presents with heavy proteinuria, full-blown nephrotic syndrome, and renal insufficiency. Serum creatinine levels may be remarkably elevated at presentation. Ultrasonography typically reveals large, echogenic kidneys.

Histologic features. Under light microscopy, the focal sclerosis shows a collapsing form:

AIDS is the leading cause of death in African Americans 25 to 44 years old

capillary loops in the glomeruli appear closed, with visceral epithelial cell proliferation in Bowman's space (FIGURE 1). Typical focal sclerosis associated with other diseases is segmented and has areas of normal-appearing glomeruli. HIV-associated nephropathy may develop very quickly, so that many of the glomerular filters are collapsed.

Giant microcystic tubules are abundant under light microscopy (normally, tubules in the tubulointerstitial area are much smaller than the glomeruli; see FIGURE 2). The large spaces in the microcysts cause the echogenicity found by ultrasonography.

Under electron microscopy, the endoplasmic reticulum of the endothelial cells of capillary loops contain many tubular reticular inclusions. These inclusions are also known as "interferon footprints" because they can be induced by exposing a number of cell types to interferon.

Other patterns of glomerular disease

Other patterns of glomerulonephropathy can also be associated with HIV infection:

Membranoproliferative glomerulonephritis (typically in association with concurrent HCV infection)

Lupus-like glomerulonephritis (although other lupus-like systemic manifestations usually do not occur)

Thrombotic microangiopathy due to thrombocytopenic purpura and hemolytic uremia syndrome pattern

Immunglobulin A (IgA) nephropathy and immune complex glomerulonephritis (often seen in white patients infected with HIV).

Murine models of HIV-associated nephropathy

Transgenic mice have been created that, without being infected, develop clinical and pathologic features similar to those of HIV-associated nephropathy, increasing proteinuria, and end-stage renal disease. They have a biopsy picture similar to that of humans with HIV-associated nephropathy. The transgene is expressed in glomerular and tubular epithelial cells, which proliferate, lose differentiation markers, and become more primitive, losing contact inhibition.

TABLE 1

Treatment of viral glomerular diseases

HIV-associated nephropathy

Highly active antiretroviral therapy
Angiotensin-converting enzyme inhibitors or angiotensin 2 receptor blockers, or both
Corticosteroids (in select cases)

Hepatitis B virus glomerular disease (adults)

Lamivudine (Epivir)
Possibly, pegylated interferon
Corticosteroids (controversial)

Hepatitis C virus glomerular disease

Plasmapheresis
Rituximab (Rituxan)
Corticosteroids
Pegylated interferon
Ribavirin (Rebetol)

In humans, the kidney is a reservoir for HIV-1 infection, and when glomerular and tubular cells become infected, they also proliferate and lose differentiation markers. Visceral epithelial cells proliferate, glomeruli collapse, and microcystic tubulointerstitial disease develops.

Treatment of HIV-associated nephropathy

HIV-associated nephropathy is treated in three ways (TABLE 1).

Antiviral therapy. Almost all HIV patients now receive highly active antiretroviral therapy (HAART) unless they have specific contraindications to it. The benefit of treating HIV-associated nephropathy with HAART is supported by retrospective data and nonrandomized series.

Winston et al⁵ reported a classic case of HIV-associated nephropathy that dramatically illustrates HAART's benefits. A 35-year-old man presented with a 6-week history of fatigue, weight loss, diarrhea, and night sweats. Laboratory tests were positive for HIV with a high viral load (HIV-1 RNA > 750,000 copies/mL) and a CD4 count of 459 cells/mL. The patient had two previous tests for HIV that were negative, making this a new infection. He had acute renal failure: his urinary protein excretion was 17 g/24 hours, and his serum creatinine concentration was 3.8

Treatment of HIV-associated nephropathy: HAART, ACE inhibitors, ARBs, and sometimes steroids

mg/dL. Renal biopsy revealed collapsed glomeruli and microcystic formation in the tubules.

The patient was treated with HAART and no other therapy. Six weeks later, his viral load was less than 50 copies/mL, his serum creatinine level was 1.4 mg/dL, and his urinary protein excretion was 1.5 g/24 hours. A repeat biopsy showed vast improvement, with mostly normal glomeruli and no dilated tubules.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers. Regardless of the cause, heavy proteinuria is generally treated with one or a combination of these medications.

Burns et al⁶ studied 20 patients with HIV-associated nephropathy. Of these, 11 did not have nephrotic syndrome: 7 of them were treated with the ACE inhibitor fosinopril (Monopril) 10 mg/day. Untreated patients developed progressive proteinuria over 24 weeks, while treated patients did not. Of the 9 patients who started the study with nephrotic syndrome, the 5 who were treated with fosinopril had a decline in urinary protein excretion from an average of 5.4 g/day to 2.8 g/day over 12 weeks; the 4 untreated patients had an increase in protein excretion from an average of 5.2 g/day to 10.5 g/day. Serum creatinine levels did not increase in the treated group over 12 weeks, while they increased from 1.9 mg/dL to 9.2 mg/dL in the untreated group.

This study and others strongly indicate that treatment with either an ACE inhibitor or an angiotensin 2 receptor blocker slows progression to renal failure. However, these drugs must be used with caution in patients who present with elevated serum creatinine and potassium levels.

Immunosuppression is the most controversial treatment for HIV-associated nephropathy and is recommended only in certain cases.

Smith et al⁷ gave prednisone 60 mg/day to 19 patients who had HIV-associated nephropathy and serum creatinine levels greater than 2 mg/dL. Two patients progressed to end-stage renal disease in 4 to 5 weeks, but in the other 17 the average serum creatinine levels decreased from 8.1 mg/dL to 3.0 mg/dL. Thirteen patients were tested for 24-hour urinary protein excretion: 12 had reductions from an average of 9.1 g/day to 3.2 g/day.

Although this study demonstrates dramatic gains from prednisone therapy, it has significant drawbacks: it was in a very select group of patients who did not have ongoing infections and were early in their disease course.

In other individual cases and small series, patients with HIV-associated nephropathy with heavy proteinuria and massive nephrotic syndrome dramatically improved with other immunosuppressants such as cyclosporine. Patients often stayed in remission for years until relapsing after being forced to stop therapy because of an opportunistic infection.

Eustace et al⁸ retrospectively examined 21 patients who had biopsy-proven HIV-associated nephropathy and progressive azotemia; 13 of them had received prednisone 60 mg for 1 month followed by a several-month taper. After 3 months, renal failure developed in 6 of the 8 patients who received no treatment, and 3 progressed to end-stage renal disease. Of the 13 patients treated with steroids, only 2 developed renal failure, none of whom developed end-stage renal disease. Average proteinuria levels were reduced by about 5.5 g/day in the treatment group. Improvement in the treatment group was evident even after adjusting for baseline creatinine, 24-hour proteinuria, CD4 count, history of intravenous drug use, and concurrent HBV or HCV infection. In long-term follow-up, there was no significant difference in the incidence of hospitalizations or of serious infections, leading the authors to conclude that steroids were useful in certain populations of patients with HIV-associated nephropathy.

Renal adverse effects of HAART

Some of the antiretroviral drugs have adverse effects on the kidney.

Tenofovir (Viread), **adefovir** (Hepsera; not available in the United States), and **cidofovir** (Vistide) can produce acute renal failure of the acute tubular necrosis type or a Fanconi-like syndrome by poisoning the mitochondria of proximal tubular cells, rendering them unable to reabsorb filtered proteins. Patients may develop amino aciduria, uricosuria with low uric acid levels, and glycosuria, and some develop renal dysfunction.

Indinavir (Crixivan) can cause acute or chronic renal failure. About 20% of the drug

**Corticosteroids
are the most
controversial
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HIV-associated
nephropathy**

is cleared by the kidney, and it is mostly insoluble at the normal urinary pH of 5 to 7. A crystalline precipitate can form, causing tubular obstruction. About 20% to 30% of patients taking the drug have crystals visible in urinalysis, stone formation occurs in about 3%, and papillary necrosis can also develop.

A patient treated with indinavir may present with acute renal failure, typically without shock or hypotension. Many have microscopic or gross hematuria, dysuria, back or flank pain, and renal colic.

Most cases of nephrotoxicity are mild and reversible by discontinuing indinavir. Most renal effects can be prevented by maintaining a high urine output to avoid crystalluria.

■ HEPATITIS B

Hepatitis B infects some 400 million people worldwide, including an estimated 1.25 million in the United States. In areas where it is endemic, vertical transmission (from mother to child) is common; elsewhere it is transmitted predominantly through blood products, contact with mucous membranes, and needle-sharing.

HBV renal involvement can occur at any age but is more common in children.

Children typically present with nephrotic syndrome and microscopic hematuria. The glomerular filtration rate is usually normal, as are the serum levels of alanine aminotransferase and aspartate aminotransferase.

Adults typically present with proteinuria, nephrotic syndrome, hypertension, renal dysfunction, and, often, clinical evidence of liver dysfunction.

HBV glomerulonephritis is ideally diagnosed by detecting the virus in the blood, excluding other causes of glomerulonephritis, and detecting HBV antigens in glomeruli. Even many large medical centers, however, cannot test for HBV in the kidney, so the diagnosis is usually presumptive and based on the clinical picture, elevated aminotransferase levels, HBV in the blood, and the typical glomerular pattern. Most patients are also positive for hepatitis B “e” antigen (HBeAg). Only a small percentage of patients with HBV glomerulonephritis have a low complement level; in contrast, most patients with HCV glomerulonephritis have low complement.

Three forms of HBV glomerulonephritis

Three forms of glomerulonephritis are associated with HBV infection:

Membranous nephropathy is the most common form, especially in children. Membranous nephropathy is rare in children without HBV infection or systemic lupus erythematosus. But in adult white Americans, membranous nephropathy is the most common pattern of idiopathic nephrotic syndrome.

Membranoproliferative glomerulonephritis is also common, especially combined with membranous glomerulonephritis.

Under light microscopy, some of the capillary loops appear normal, with thin basement membranes. Other capillary loops have apparently split basement membranes, which appear as a “tram track” pattern. Having both abnormal and normal segments of the glomerulus is typical of secondary forms of membranoproliferative glomerulonephritis and is usually caused by HBV or HCV.

Immunoglobulin A nephropathy is seen most often in children and in Asians.

Prognosis of HBV glomerulonephritis

Children and adults typically have different disease courses.

In children, HBV glomerulonephritis has a favorable prognosis with a high spontaneous remission rate if renal function is stable. Reports of successful treatment with antiviral medications should be regarded with skepticism unless a placebo-controlled, randomized study was performed.

In adults, HBV typically progresses. A series in Hong Kong found that 29% of patients developed renal failure and 10% developed end-stage renal disease within 5 years. Adults with nephrotic syndrome and abnormal liver function tests have an even worse prognosis: more than half develop end-stage renal disease within 3 years.

Treatment of HBV glomerulopathy is uncertain

Corticosteroids. Many fear that steroids and other immunosuppressants may cause more harm than good by enhancing viral replication and precipitating hepatic flares. Patients typically develop exacerbations of both renal disease and liver disease either dur-

Children with HBV glomerulonephritis have a high rate of spontaneous remission

TABLE 2

Laboratory indicators of hepatitis C virus glomerulonephritis

Serum antihepatitis C virus antibody
 Serum hepatitis C virus RNA by polymerase chain reaction
 Elevated serum aminotransferases
 Cryoglobulinemia (mixed type II with monoclonal immunoglobulin M kappa)
 Cryocrit (2%–70%)
 Low C4, C1q, CH₅₀
 Normal or only slightly low C3

3.2 million people in the United States are thought to have HCV—and that is probably an underestimate

ing therapy or soon afterward.

Pegylated interferon (Pegasys, Peg-Intron) has been shown to benefit children, but they tend to improve anyway without treatment. Results in adults have been mixed.

Lamivudine (Epivir) has been beneficial in small series. Tang et al⁹ treated 10 patients with lamivudine who had HBV infection and biopsy-proven membranous nephropathy and elevated serum alanine aminotransferase; 12 similar patients before lamivudine was available served as a control group. At 6 months, 4 patients had entered complete remission in the treated group compared with 1 patient in the control group; at 12 months the numbers were 6 vs 3. The 3-year rate of survival free of end-stage renal disease was 100% in the treated group vs 58% in the control group. Lamivudine was well tolerated with no adverse events.

Unfortunately, resistance to lamivudine with long-term use is commonly reported. Combining lamivudine with interferon alfa is now being tried.

Other drugs. Entecavir (Baraclude) has been approved for treating HBV infection, but whether it benefits glomerular disease is not yet known. Other possible drugs that are still unproven for treating HBV glomerular disease include adefovir (Hepsera) (which can be nephrotoxic), tenofovir (Viread), and clevudine (which is experimental).

■ HEPATITIS C VIRUS

HCV infection is also very common, with an estimated 170 to 200 million people chronically infected worldwide. The National Health and Nutrition Examination Survey

estimated that 4.1 million people in the United States have antibodies to HCV and 3.2 million are chronically infected.¹⁰ These numbers probably underestimate the true prevalence; the survey was conducted in households, thereby excluding those at highest risk of infection such as the homeless, prisoners, and those in other institutions.

Hepatitis C typically has a slow, prolonged course, which progresses to chronic liver disease and cirrhosis in about 10% to 20% of those infected. Glomerulonephritis, which is usually membranoproliferative with or without cryoglobulinemia, is more commonly associated with HCV infection than with HBV.

HCV evades immune elimination, so the infection becomes chronic, and circulating immune complexes accumulate over many years. HCV also stimulates the production of monoclonal rheumatoid factor, causing type II cryoglobulinemia and vasculitis. Frank, symptomatic cryoglobulinemia affects about 1% of infected patients.

A typical patient may present with hyperpigmented skin. Biopsy of the skin reveals small-vessel vasculitis with inflamed vessels and cryoglobulins. Several series have shown that what was once diagnosed as “essential mixed cryoglobulinemia” is usually HCV-related.^{11–13}

Laboratory and clinical features

Johnson et al,¹⁴ in an early series of 34 patients infected with HCV, found that 56% were exposed through intravenous drug abuse, 18% through blood transfusions, and 6% through sexual intercourse; 20% had no identified risk factor. Cryoglobulins were initially detectable in the serum of 59% but did not correlate well with symptoms of essential mixed cryoglobulinemia: of the 15 patients with symptoms, 11 (73%) had detectable cryoglobulinemia, and of the 19 patients without symptoms, 9 (47%) had detectable cryoglobulinemia. Eventually, cryoglobulinemia was detectable in 22 of 23 patients. Clinical signs of liver disease were evident in 18% of patients, serum aminotransferases were elevated in 68%, and rheumatoid factor was positive in 72%.

C4, which is part of the primary complement pathway, was low in 69% of patients and was eventually low in all of them: low C4 lev-

els continue to serve as a diagnostic clue for HCV infection. HCV infection typically involves a normal C3 level, which is typically low in systemic lupus erythematosus and streptococcal infection. Other typical laboratory features of HCV glomerulonephritis are shown in **TABLE 2**.

HCV glomerulonephritis is rare in children and most often develops in infected adults in their 40s and 50s after a long history of HCV infection and subclinical liver disease. Symptoms of cryoglobulinemia include palpable purpura and arthralgias. Many of these patients develop proteinuria and microscopic hematuria, about half develop renal dysfunction, which is usually mild, and 20% develop nephrotic syndrome. Hypertension develops in 80%, but only about 15% progress to end-stage renal disease.

Histologic features of HCV glomerulonephritis

Under the light microscope, every capillary loop typically has the tram-tracking pattern of membranoproliferative disease (**FIGURE 3**). Precipitates of cryoglobulins can often be seen in the glomeruli. Blood vessels in the kidney may contain cryoglobulins with inflammation around them: cryoglobulin vasculitis can also be found on skin biopsy. Immunofluorescence of glomeruli reveals immunoglobulin M and immunoglobulin G deposits.

Electron microscopy reveals electron-dense deposits with a characteristic substructure. At very high magnification, tubular annular formation of particles is sometimes visible. These are not the virus itself but are probably virally related.

Prognosis of HCV glomerulonephritis

Tarantino et al¹⁵ followed 105 patients with mixed cryoglobulinemic glomerulonephritis for more than 25 years. The study was completed more than 10 years ago, when all subjects were diagnosed with “essential” disease, and antiviral agents were not available. Patients were treated with plasmapheresis, steroids, and cytotoxic agents. After 10 years, only 49% were still alive, the rest having died of heart disease, liver disease, and infection. Fifteen patients developed chronic renal failure, 15 patients had remission of renal disease,

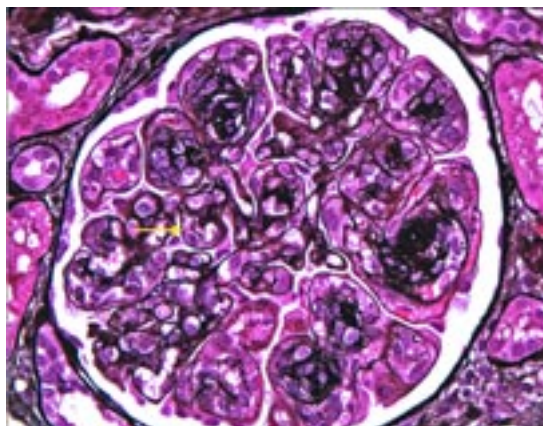


FIGURE 3. Membranoproliferative glomerulonephritis.

and 2 had complete disease remission. Retrospectively, blood samples from 34 patients were studied for HCV antibody: 85% were positive.

Treatment

Treatment of HCV glomerulonephritis involves several approaches.

Plasmapheresis removes cryoglobulins.

Corticosteroids and cytotoxic drugs inhibit the immune response.

Interferon and ribavirin (Rebetol) suppress viral replication. Combination therapy offers higher initial and sustained responses than monotherapy.

Pegylated interferons have greater biological activity than regular interferons because their absorption and clearance are delayed, providing a more potent and longer-lasting antiviral effect. Several studies have shown the advantage of using pegylated interferon for patients with chronic HCV infection, either alone or in combination with ribavirin.^{16–20}

Alric et al²¹ studied 25 patients with HCV with mixed cryoglobulinemia and nephrotic syndrome. Patients were all initially treated with prednisone, furosemide, and plasmapheresis, then 18 patients were treated with standard or pegylated interferon alfa plus ribavirin for an average of 18 months, and the remaining 7 patients received no antiviral therapy. Patients were followed for at least 6 months after treatment withdrawal. Of the 18 treated patients, 12 had a sustained clearance of HCV RNA, and reduced proteinuria and cryoglobulinemia. Serum creatinine levels

‘Essential mixed cryoglobulinemia’ is usually HCV-related

remained stable in all treated patients, regardless of whether they responded to antiviral therapy.

New immunosuppressants are also proving useful against HCV cryoglobulinemia.

Sansonno²² studied 20 patients who had mixed cryoglobulinemia and HCV-positive chronic active liver disease and were resistant to interferon alfa therapy. All were treated with an intravenous infusion of rituximab (Rituxan) 375 mg/m² once a week for 4 weeks. Sixteen patients (80%) had a complete response, with rapid improvement of clinical

signs and a reduced cryoglobulin level. The response was sustained throughout the 12 months of follow-up. The drug appeared safe, with no severe side effects reported.

Comment. For patients who present with HCV infection and progressive disease, elevated serum creatinine levels, and heavy proteinuria, I typically initially treat with plasmapheresis to reduce the cryoglobulinemia and steroids, with or without another agent—often rituximab. After several months, when the serum creatinine level is lower, I use interferon plus ribavirin for antiviral therapy. ■

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