Lupus-like glomerulonephritis: an autoimmune complication of hepatitis C infection

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Abstract Lupus-like glomerulonephritis in patients with negative lupus serologies and no extra-renal manifestations of lupus can create a diagnostic dilemma. We describe a 53-year-old gentleman with chronic hepatitis C virus (HCV) infection who presented with dialysis-requiring renal failure, renal histologic findings of “full-house” immunofluorescence label and tubuloreticular inclusions on electronic microscopy, but no extra-renal or laboratory signs of systemic lupus erythematosus. Attempted treatment with cyclophosphamide and corticosteroids was limited by cyclophosphamide hypersensitivity. The patient remained dialysis-dependent over 18 months of observation and did not develop extra-renal clinical or biological manifestations of lupus. Mimics of seronegative lupus with isolated renal involvement can include HCV-related autoimmunity. Treatment of acute glomerulonephritis may be similar initially, but other concerns in patients with HCV infection include excluding cryoglobulinemia, the potential impact of immunosuppression therapy on liver disease and

consideration of subsequent use of antiviral therapy. Given the increasing prevalence of HCV globally, the recognition of extra-hepatic autoimmune manifestations of HCV infection will likely increase.

Keywords Glomerulonephritis · Hepatitis C · Immune deposits · Immunofluorescence microscopy · Immunosuppression · Tubuloreticular inclusions

Introduction

“Full-house” immunofluorescence staining is defined as simultaneous detection of IgA, IgG, IgM, C3 and C1q deposits in renal biopsy specimens. Association of tubuloreticular inclusions (TRIs) on electronic microscopy with a “full-house” immunofluorescence pattern is considered to be highly suggestive of lupus nephritis [1, 2]. Lupus-like glomerulonephritis in patients with negative lupus serologies and no extra-renal signs of lupus can create a diagnostic dilemma. Typical renal complications of infections with the hepatitis C virus (HCV) include membranoproliferative glomerulonephritis with or without cryoglobulinemia. Less often, HCV causes membranous, proliferative, fibrillary and immunotactoid glomerulopathies as well as focal segmental glomerulosclerosis [3, 4]. We describe a case of lupus-like glomerulonephritis in a patient with HCV infection.

Case presentation

A 53-year-old African-American man presented to the emergency department complaining of several weeks of worsening malaise, nausea and lower extremity edema. His

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medical history was notable for a diagnosis of HCV infection made during routine medical evaluation approximately 3 years previously. At that time he was told he did not have evidence of clinically significant liver disease. He received infrequent medical follow-up over the intervening years because of lack of health insurance. However, he saw a doctor 1 month prior to the current admission for evaluation of fatigue, and laboratory data included a serum creatinine level of 1.6 mg/dL. On presentation to our institution, physical examination demonstrated blood pressure of 186/113 mmHg, mild bibasilar rales and 3+ lower extremity pitting edema. Pertinent negative examination findings included the absence of sclera icterus, skin rash and synovitis; the liver was not enlarged and was non-tender. Laboratory data included hemoglobin of 13.6 mg/dL, blood urea nitrogen of 62 mg/dL, serum creatinine of 6.2 mg/dL, serum albumin of 3.0 mg/dL and normal transaminase

levels. The C3 level was low at 53 mg/dL, and C4 was normal at 20 mg/dL. Urinalysis showed 3+ protein, 3+ blood and dysmorphic red blood cells on microscopy; spot quantitative urine protein was 13 g/g creatinine. Serologic evaluation was negative for lupus anticoagulants and for antinuclear (ANA), anti-double stranded DNA, anti-neutrophil cytoplasmic (ANCA), anti-SSA, anti-SSB, anti-Smith, anti-ribonucleoprotein, anti-topoisomerase I, anti-glomerular basement membrane, human immunodeficiency virus (HIV) and hepatitis B antibodies. Cryoglobulins were undetectable on two occasions. HCV viral load was 4.5 million IU/mL with genotype 1a.

Renal needle core biopsy, performed after three dialysis sessions to control uremic platelet dysfunction, revealed cellular crescents in two of six glomeruli, and minimal interstitial inflammation and fibrosis (Fig. 1a). Neither membrane reduplication with mesangial interpositioning

Fig. 1 Renal biopsy specimen in the current case. Light microscopic examination showed cellular crescents in 2 of 6 glomeruli: (a) Jones' silver stain shows a cellular crescent (*thick arrow*) above the glomerular capillary tuft (*thin arrow*). Immunofluorescence analysis demonstrated “full-house” granular mesangial and glomerular

basement membrane label: shown are immunofluorescence labeling for IgG (b) and C1q (c). Ultrastructural analysis revealed TRIs (*thick arrow*) in glomerular endothelial cells (d). (Electron photomicrograph courtesy of Nancy Galvin, Ph.D., Saint Louis University School of Medicine)

typical of membranoproliferative glomerulonephritis nor glomerular basement membrane thickening with epimembranous spikes typical of membranous nephropathy were observed within the glomerular capillary tufts. Immunofluorescence demonstrated “full-house” global diffuse granular label of the glomerular basement membrane and mesangium with 3+ IgG, 2+ IgA, 1+ IgM, 2+ C3 and 1+ C1q (Fig. 1b, c). Electron microscopy showed immune complexes in the subepithelial, subendothelial and mesangial compartments, as well as TRIs in glomerular endothelial cells (Fig. 1d).

The patient was treated with methylprednisolone 500 mg intravenously daily for 3 days followed by oral prednisone (1 mg/kg daily) and cyclophosphamide (150 mg daily). As he did not have insurance coverage to continue oral cyclophosphamide, after 2 weeks of therapy, his regimen was changed to intravenous cyclophosphamide (500 mg/m²). Several days after intravenous infusion he developed daily spiking fevers and mild transaminase elevation (peak alanine transaminase 80 mg/dL). Liver biopsy showed stage IV (cirrhosis) chronic hepatitis C with grade 2 activity; pan-cultures were negative for infection. Cyclophosphamide hypersensitivity was suspected as the cause of fevers. The patient remained oliguric, and, given the absence of appreciable renal recovery and suspected treatment toxicity, cyclophosphamide was discontinued, and prednisone was tapered to discontinuation. Fevers and transaminase elevation resolved. The patient received interferon alpha-2a monotherapy, dosed for hemodialysis, for approximately 3 months, but it was subsequently discontinued because of thrombocytopenia and bleeding from his dialysis access site. The bleeding and thrombocytopenia resolved, but the patient continued to be hemodialysis-dependent over 18 months of follow-up. He did not develop extra-renal clinical or laboratory manifestations of lupus.

Discussion

Hepatitis C is well established as a cause of kidney disease, most commonly manifest as membranoproliferative glomerulonephritis with or without cryoglobulinemia. Autoimmune syndromes mimicking lupus in patients with HCV infections have been reported and can create diagnostic and treatment dilemmas. Some patients with seronegative “full house” nephropathy become seropositive for lupus markers and/or develop extra-renal manifestations of systemic lupus erythematosus over time. For example, Gianviti et al. [2] described three children who presented with clinical glomerulopathy (proteinuria and/or hematuria) without other clinical or immunological evidence of lupus who were found to have a “full-house” immunofluorescence

pattern on renal biopsy specimens, along with cytoplasmic TRIs by electron microscopy in two of the three cases. All three patients developed antinuclear and anti-double-stranded DNA antibodies, at 3, 5 and 10 years after original presentation, respectively; one also developed clinical symptoms of lupus. In contrast, retrospective review of histological and medical records for 14 additional children at the same institution who presented with idiopathic “full-house” immunofluorescence glomerulonephritis (including TRIs in 1 of 14) identified no serological or clinical evidence of lupus after a mean follow-up of 5.8 years. Reported causes of “full-house” nephropathy with negative lupus serologies have included post-hepatic cirrhosis (shrunken liver), diabetic nephropathy, de novo membranous nephropathy and post-infectious glomerulonephritis [1, 5, 6].

Renal biopsy findings of TRIs on electron microscopy, along with “full-house” findings on immunofluorescence, appear to be more strongly associated with lupus nephritis than “full house” nephropathy alone [2, 5, 7, 8]. TRIs are subcellular organelles characterized by small clusters of anastomosing tubule-like structures within cisternae of endoplasmic reticulum that may develop in glomerular endothelial cells. While associated with lupus and the risk of clinical disease progression, glomerular TRIs have been identified in other pathological conditions such as HIV-associated nephropathy [9–12]. Glomerular TRIs are often found in HIV-infected patients without clinical renal disease; in the presence of HIV-associated nephropathy, the prevalence of TRIs is up to 90 % [13, 14]. Similarly, patients with lupus erythematosus may have TRIs whether or not they have glomerulonephritis, but prevalence increases to up to 80 % in the context of nephritis [9, 12]. The morphogenesis of TRIs might relate to biological activities of alpha or beta interferons, and correlates clinically with endogenous overproduction of interferons or exogenous administration such as treatment for HCV [15, 16]. Our patient had not received antiviral therapy for HCV prior to presentation.

The pathogenesis of HCV-mediated renal diseases may include indirect and direct renal injuries. HCV may elicit autoimmune responses against self-antigens, in some cases by “molecular mimicry,” resulting in production of auto-antibodies [17]. HCV infection has been associated with the development of cryoglobulins, hypocomplementemia, ANA, ANCA and rheumatoid factor, as well as a systemic lupus-like syndrome [18, 19]. Confirmed HCV infection was documented in a markedly higher proportion of a consecutive, unselected sample of 134 Spanish lupus patients compared with healthy controls (11 vs. 1 %), prompting the authors to suggest consideration of HCV testing in the evaluation of lupus, as well as lupus serology testing in patients with chronic HCV infection and

extrahepatic features of lupus [20]. Hepatic injury from HCV may decrease clearance of circulating immune complexes, decrease synthetic function of many serum proteins, and disturb systemic hemodynamics and renal perfusion. Although renal tropism has not been documented, some authors have raised theoretical possibility of direct renal infection similar to a mechanism proposed for HIV nephropathy [21]. However, the reasons why some HCV-infected patients develop membranoproliferative/cryoglobulinemic glomerulonephritis, membranous glomerulopathy, lupus-like syndromes or other renal lesions have not been defined.

In the current case, several consulting teams worked together including nephrology, rheumatology and hepatology. While the opinion of rheumatology was for seronegative lupus, the nephrology service favored “lupus-like” glomerulonephritis from HCV, but treatment of acute glomerulonephritis with either primary diagnosis is similar. In rapidly progressive glomerulonephritides, oral cyclophosphamide along with corticosteroid therapy is often part of the initial treatment [22, 23]. However, adverse effects of corticosteroid therapy are well known, and cyclophosphamide toxicity may result in hepatotoxicity or leukopenia with a resultant increased risk of infection. Intravenous cyclophosphamide preparations have shown similar rates of remission in lupus nephritis with less toxicity due to a lower cumulative dose; however, there is a greater risk of relapse [24].

Successful corticosteroid and cyclophosphamide treatment of patients with HCV vasculitis has been reported. In a retrospective analysis of 16 patients with HCV-related vasculitis and low levels of viremia treated with corticosteroids and intravenous cyclophosphamide, all demonstrated a virologic response including suppression of viral loads to undetectable levels in 75 % (12/16) [25]. Despite successful treatment, 44 % (7/16) of patients relapsed, and there were 2 deaths (1 from sepsis, 1 from renal failure) [25]. Quigg et al. [26] described successful cyclophosphamide treatment of a case of cryoglobulinemic membranoproliferative glomerulonephritis associated with HCV infection. The patient experienced disappearance of cryoglobulins within 1 month and an improvement in creatinine clearance by 3 months, and there was no evidence of cyclophosphamide-related hepatotoxicity during 1 year of therapy. Canada et al. [23] described successful treatment of a case of life-threatening HCV-related vasculitis with pulse methylprednisolone followed by oral prednisone and intravenous cyclophosphamide for 6 months. During the period of immunosuppression, there was no deterioration in hepatic function, but HCV RNA levels markedly increased. Immunosuppression was successfully followed with interferon for antiviral therapy. In contrast, fibrosing cholestatic hepatitis (an aggressive and usually fatal form of viral

hepatitis in immunocompromised patients) in a previously immunocompetent patient with previously stable chronic HCV infection has been described after treatment with steroids and cyclophosphamide for active glomerulonephritis [27]. In our patient, use of cyclophosphamide was limited to 2 weeks because of hypersensitivity, during which time he did not demonstrate improvement of renal function.

Patients with a history of HCV infection who are initiated on immunosuppressive therapy for glomerulonephritides must be closely monitored biochemically by HCV load and/or alanine transaminase levels. Corticosteroid therapy, with or without cyclophosphamide, has been shown to increase HCV viremia in HCV antibody-positive individuals [23, 28]. In addition to a worsening of baseline liver function, patients with prolonged viremia are at increased risk of liver-related mortality [29]. After 2–4 months of immunosuppression for HCV-associated glomerulonephritis, antiviral therapy with combination alpha-interferon and ribavirin has been recommended [30]. Treatment with interferon-alpha has been shown to improve proteinuria, suppress viremia and stabilize renal function; however, patients often relapse after discontinuing antiviral therapy [30]. In the 2008 KDIGO “Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease,” therapeutic recommendations are guided by glomerular filtration rate (mL/min/1.73 m^2): >50 , pegylated interferon and ribavirin; $15\text{--}50$, pegylated interferon monotherapy; <15 , renally dosed standard interferon [31]. In our case, use of renally dosed interferon was limited by hematologic toxicities. The KDIGO guidelines also recommend consideration of plasma exchange, rituximab or cyclophosphamide plus methylprednisolone pulses among patients with rapid loss of kidney function from HCV glomerulonephritis and an acute flare of cryoglobulinemia [31].

Conclusion

This case illustrates that renal histological findings of “full-house” immunofluorescence even with TRIs may not be primary lupus nephritis. Although lupus can present with isolated renal involvement and be seronegative, mimics of autoimmunity include HCV infection. Treatment of acute glomerulonephritis may be similar initially, but other concerns in patients with HCV infection include excluding cryoglobulinemia, the potential impact of immunosuppression therapy on liver disease and consideration of subsequent use of antiviral therapy. Given the increasing prevalence of HCV globally [32], recognition of extrahepatic autoimmune manifestations of HCV will likely increase.

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