Hepatitis C virus (HCV) is a recognized culprit in the etiology of many glomerular diseases, which include the principal membranoproliferative glomerulonephritis (MPGN) type 1 disease, the less common acute proliferative and exudative GN, as well as mixed MPGN type 1 with overlapping membranous features [1]. HCV infection has also been found to be strongly associated with autoimmune disorders and immunologic abnormalities, such as with antinuclear antibodies (ANA), cryoglobulin, antineutrophil cytoplasmic antibody (ANCA), cutaneous lesions, and hypocomplementemia [2–4]. HCV may also act as a triggering factor in the pathogenesis of systemic lupus erythematosus, or the “lupus-like syndrome” [5]. Thus, there is considerable overlap in the clinical features of HCV infection and lupus nephritis. We hereby report on a case that initially represented an HCV-associated cryoglobulinemic GN. However, in view of the progressive renal-function deterioration, a renal biopsy was performed. This biopsy revealed an intriguing “full house” immune complex crescentic GN, which presented us with a further dilemma.

Case Presentation

A 64-year-old man was admitted because of proceeding nephrotic syndrome. He presented with anasarca, dyspnea, decreased urine amount, persistent heavy proteinuria, and a 7-kg gain in body weight over the past 6 months. The patient also had palpable purpura of his legs for the last month (Figure 1). He denied having had trauma, surgery,
exposure to Chinese herbal medicines, or systemic diseases, except for a 10-year history of chronic hepatitis C and a 1-year history of nephrotic syndrome. One year previously, hypertension did not develop, and the initial laboratory data revealed total protein, 4.6 g/dL; albumin, 1.2 g/dL; glutamic-oxaloacetic transaminase (GOT), 84 U/L; glutamic-pyruvic transaminase (GPT), 71 U/L; total cholesterol, 412 mg/dL; blood urea nitrogen (BUN), 28.2 mg/dL; serum creatinine, 1.3 mg/dL; ANA test, 1:40; normal complement component C3 and C4 (139 mg/dL and 28.1 mg/dL, respectively) levels; and negative serum cryoglobulin. Abdominal sonography demonstrated renal parenchymal disease, normal liver appearance and a small amount of ascites. However, he refused to undertake renal biopsy and was lost to follow-up due to the emergence of severe acute respiratory syndrome.

On admission, blood pressure was 160/90 mmHg, and a massive amount of right-sided pleural effusion and ascites were also noticed. No lymphadenopathy was present. The laboratory data showed that BUN was 80 mg/dL; serum creatinine, 1.6 mg/dL; albumin, 1.59 g/dL, total protein, 3.86 g/dL; total cholesterol, 201 mg/dL; triglyceride, 75 mg/dL; GOT, 19 U/L; GPT, 12 U/L; serum sodium, 133 meq/L; and potassium, 4.2 meq/L. Serology showed an ANA titer of 1:40 (speckled); depressed C3 and C4 levels (13.4 and 10.1 mg/dL, respectively); positive serum cryoglobulin and positive p-ANCA; negative rheumatoid factor, antistreptolysin O titer and venereal disease research laboratory test; anti-HCV(+); HBsAg(-). Daily protein loss (DPL) was 3.5 g, and the creatinine clearance was 66.5 mL/min.

The tentative diagnosis was HCV-related cryoglobulinemia. In the course of treatment, urine amount gradually increased and body weight decreased at a rate of less than 1 kg reduction per day, after albumin plus furosemide infusion. However, serum creatinine increased to 3.24 mg/dL within 1 month. Because precipitating factors of overdiuresis and bleeding were excluded, a renal biopsy was performed.

To our considerable astonishment, renal pathology showed a “full house” immune complex GN (Figure 2) with membranous nephropathy superimposed on membranoproliferative transition (Figure 3), and crescentic transformation (Figure 4).

Additional studies revealed: anti-dsDNA(-), and a low titer of ANA (1:40). The patient only fulfilled one of the 11 American Rheumatism Association (ARA) diagnostic criteria for systemic lupus erythematosus. One the other hand, HCV RNA was negative, and skin pathology revealed intact vascular wall with dense perivascular lymphocytic infiltration in the dermis, which is inconsistent with the characteristic of HCV-associated leukocytoclastic vasculitis.

Much evidence for HCV-associated autoimmune diseases was at hand, including cryoglobulinemia, positive p-ANCA and low ANA titer, in concurrence with palpable purpura and the full house immune complex GN. Therefore, we prescribed IV methylprednisolone 500 mg for 3 days, following oral prednisolone 20 mg/day and cyclophosphamide 100 mg/day for renal function deterioration.
Surprisingly, the ascites and right-sided pleural effusion disappeared after 3 days of pulse steroid therapy, and renal function remained stable. Moreover, neither abnormal liver function nor increased viral load developed. However, the patient died of severe infection, 1 month later.

**DISCUSSION**

We present an unusual case of probable membranous nephropathy, superimposed on membranoproliferative transition, and crescentic transformation, in concurrence with a full house immune complex GN, in an older man with HCV infection and who developed acute renal failure and marked extrarenal manifestations. Careful analysis and correlation of clinical and pathologic findings allowed us to speculate that HCV may have been an original culprit in the development of HCV-related autoimmune disease, with a switch to lupus-like GN. In this case, however, the possible development of true lupus nephritis was difficult to dismiss offhand. The full house immune complex GN, however, seemed to have negated the pathognomonic features to lupus nephritis in follow-up [6,7].

HCV-associated cryoglobulinemia, in conjunction with hypocomplementemia and palpable purpura, led us to conclude that MPGN should be the target lesion. However, the association with positive ANA and ANCA, as well as the full house staining on immunofluorescence, also suggested a possible autoimmune disorder [8]. In such cases, cryoglobulinemia may be the source of a false negative polymerase chain reaction result in patients with HCV-positive liver disease [9]. Therefore, we were initially facing a therapeutic dilemma, due to the concurrence of HCV infection and lupus-like GN. Due to the elevated DPL of 12 g/day, which spontaneously subsided to 4.5 g after conservative treatment, interferon-α therapy did not appear to be of paramount importance. Furthermore, it was noted that autoimmune disease may complicate antiviral therapy for HCV infection [10], and steroid therapy is not contraindicated in patients with HCV-associated nephropathy [11]. Hence, it was urgent to decrease the crescent formation via pulse steroid therapy.

To our surprise, the right-sided pleural effusion and ascites dramatically decreased, renal function remained stable, and the viral load did not flare up. Despite these responses, however, the patient died of infection 1 month later.

In conclusion, this case underlies the importance of recognizing HCV-associated autoimmunity, which usually is overlooked. Although immunosuppression and potential infections are often contingent to pulse steroid plus cyclophosphamide therapy, careful supervision may overcome these problems.
REFERENCES

1. Markowitz G, Kaur P, Orazi A, et al. A 51-year-old female with nephrotic syndrome, renal failure, and hepatitis C virus infection. *Am J Kidney Dis* 2001;37:442–7.

2. McMurray RW, Elbourne K. Hepatitis C virus infection and autoimmunity. *Semin Arthritis Rheum* 1997;26:689–701.

3. Ohira H, Tojo J, Shinzawa J, et al. Antineutrophil cytoplasmic antibody in patients with antinuclear antibody-positive chronic hepatitis C. *Fukushima J Med Sci* 1998;44:83–92.

4. Agarwal N, Handa R, Acharya SK, et al. A study of autoimmune markers in hepatitis C infection. *Indian J Med Res* 2001;113:170–4.

5. Ramos-Casals M, Font J, Garcia-Carrasco M, et al. Hepatitis C virus infection mimicking systemic lupus erythematosus: study of hepatitis C virus infection in a series of 134 Spanish patients with systemic lupus erythematosus. *Arthritis Rheum* 2000;43:2801–6.

6. Jones E, Magil A. Nonsystemic mesangiopathic glomerulonephritis with “full house” immunofluorescence. *Am J Clin Pathol* 1982;78:29–34.

7. Smet AD, Kuypers D, Evenepoel P, et al. “Full house” positive immunohistochemical membranoproliferative glomerulonephritis in a patient with portosystemic shunt. *Nephrol Dial Transplant* 2001;16:2258–62.

8. Fisher ME, Rossini M, Simmons E, et al. A woman with chronic hepatitis C infection and nephritic syndrome who developed multiple renal lesions after interferon alfa therapy. *Am J Kidney Dis* 2004;44:567–73.

9. Van Thiel DH, Fagiuli S, Caraceni P, et al. Cryoglobulinemia: a cause for false negative polymerase chain reaction results in patients with hepatitis C virus positive chronic liver disease. *J Hepatol* 1995;22:464–7.

10. Wilson LE, Widman D, Dikman SH, Gorevic PD. Autoimmune disease complicating antiviral therapy for hepatitis C virus infection. *Semin Arthritis Rheum* 2002;32:163–73.

11. Komatsuda A, Imai H, Wakui H, et al. Clinicopathological analysis and therapy in hepatitis C virus-associated nephropathy. *Intern Med* 1996;35:529–33.
感染 HCV 男性併發腎病症候群、免疫複合體、半月狀腎絲球腎炎以及急性腎衰竭之一 — 病例報告

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已有廣泛的證據指出 HCV 相關的自體免疫性在一群自體免疫疾病中扮演的角色，但常被忽略。在此我們提出一位 HCV 感染之男性，表現出腎病症候群、可複性紫瘢、冷凝球蛋白血症、低補體血症及併發免疫複合體腎絲球腎炎以及腎衰竭。起初認為只是 HCV 相關性冷凝球蛋白血症腎絲球腎炎；然而，腎臟切片顯示全盤性惑奇（full house）腎絲球腎炎，不禁令人思索：此病的元兇是誰？此外針對臨床醫師無可避免而臨的“HCV 相關性自體免疫疾病出現似狼瘡性腎炎之轉換”，提出治療之經驗。

關鍵詞：HCV 感染，HCV 相關性自體免疫疾病，腎病症候群，腎絲球腎炎，腎衰竭
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