HCV Infection Complicated with Nephrotic Syndrome, Immune Complex Crescentic Glomerulonephritis and Acute Renal Failure: A Case Report

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There is ample evidence suggesting that hepatitis C virus (HCV)-associated autoimmunity plays a role in a broad spectrum of autoimmune diseases, which are usually overlooked. We report on a case of nephrotic syndrome, palpable purpura, cryoglobulinemia, hypocomplementemia, and acute renal failure complicated by immune complex glomerulonephritis (GN). The patient is a 64-year-old man with HCV infection, who was initially considered to present only an HCV-associated cryoglobulinemic GN. However, renal biopsy revealed a "full house" immune complex crescentic GN, which led to our subsequent investigation. The attending clinicians faced what is a common dilemma, where an HCV-associated autoimmune disease inevitably switches to a lupus-like GN. Hence, we also discuss treatment.

Key Words: HCV infection, HCV-associated autoimmune disease, nephrotic syndrome, crescentic glomerulonephritis, renal failure
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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 erythematous, 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,

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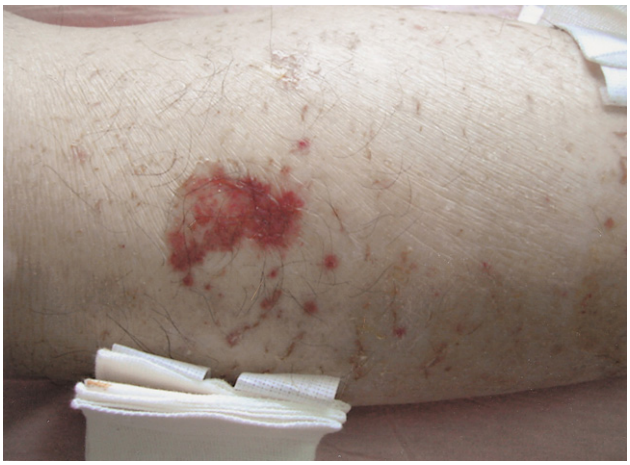

Figure 1. *Palpable purpura over right lower leg.*

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 (41.4 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.

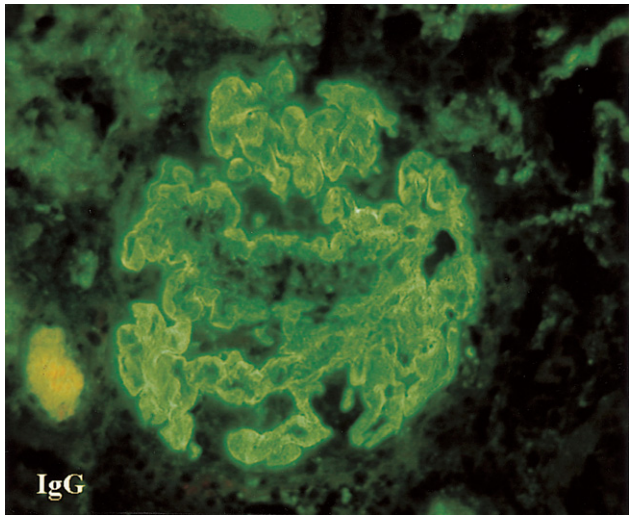

Figure 2. *In immunofluorescence study, the strongest granular pattern of staining shows where IgG (3+) collects along the glomerular basement membrane (40×).*

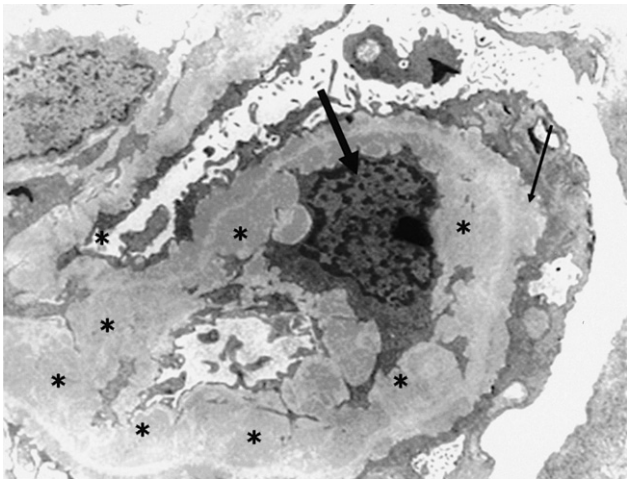

Figure 3. *Electron micrograph showing irregular thickening of glomerular basement membrane (GBM), subepithelial (thin arrow) and predominant subendothelial (*asterisk*) electron dense deposits. Mesangial cells interposition (thick arrow) with GBM duplication was indicative of membranoproliferative glomerulonephritis transition (4000×).*

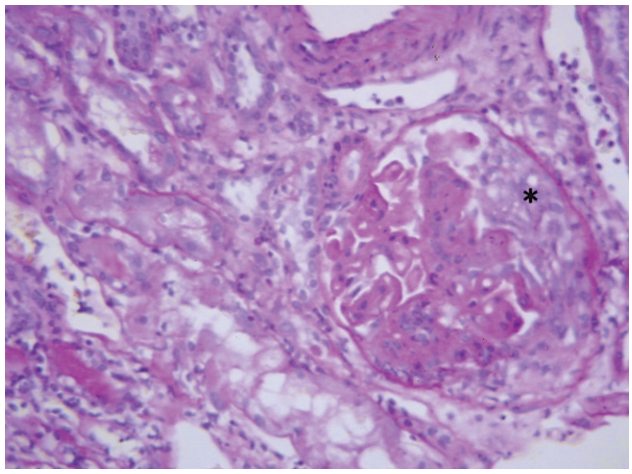

Figure 4. *Light microscopy showing cellular crescent (asterisk) formation in three of the glomeruli (periodic acid-Schiff reaction) (400×).*

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.

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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、可摸性紫癜、冷凝球蛋白血症、低補體血症、併發免疫性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激奇（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面臨的“ 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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