Rapidly Fatal Hepatitis C Virus–Related Periarteritis Nodosa with Associated Pericarditis

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In the medical literature, hepatitis B virus (HBV) is the best-known etiologic factor of periarteritis nodosa (PAN). Since the advent of the HBV vaccine and the elimination of transfusion-related HBV infections, the frequency of HBV as an etiologic agent of PAN is on the decline. Cases of HBV-related PAN dropped from 36% in 1985 to fewer than 7% in recent years.[1] Conversely, the importance of hepatitis C virus (HCV) has been underrecognized as an etiologic agent of PAN.[2] The prevalence of HCV antibodies in patients with PAN has been reported as insignificant.[3] In a recent retrospective review of systemic vasculitis in patients with HCV, PAN emerged as an important distinct entity.[4] We report a fulminant case of PAN related to HCV infection that supports the latter observation. We suggest that in the absence of a vaccine, HCV is liable to displace HBV as the best-known etiologic factor of PAN.

CASE PRESENTATION

Initial Presentation and Case History

A 53-year-old man was admitted to the hospital because of fever, shortness of breath for 4 to 5 days, weight loss, and bilateral pedal edema. The patient's history included intravenous heroin addiction; he had been in a methadone maintenance therapy program for the past 15 years. The patient had a history of HCV infection with slightly elevated liver function tests. The patient's history also included arterial hypertension that was poorly controlled with hydrochlorothiazide, felodipine, and atenolol. He was a smoker (33 pack-years), and consumed 5 to 6 bottles of beer daily for the past 10 to 15 years. He tested negative for HIV infection 2 years ago.

One week earlier the patient was admitted to the same hospital because of chest pain and palpitations. The patient's electrocardiogram (ECG) showed a normal sinus rhythm with nonspecific ST-segment and T-wave changes. The chest radiograph was within normal limits, and troponin I levels tested at 8-hour intervals were less than 0.3 ng/mL. Results of thyroid function testing were normal. Myocardial infarction was ruled out, and the patient was discharged the following day.

Physical Examination

Physical examination of the patient revealed a well-built, well-nourished man. His temperature was 101.6°F, blood pressure was 160/90 mm Hg, heart rate was 100 bpm, and respiratory rate was 18 breaths/min. He had no skin lesions and no peripheral lymphadenopathy. Auscultation of the chest revealed mild crepitations of the lower lobe of the right lung, and the right hypochondrium was slightly tender with no guarding, rigidity, or organomegaly. Bilateral pitting pedal edema of +1 was noted. The neurologic examination was negative, and arterial oxygen saturation was 97% on room air.

Laboratory Evaluation

The serum and blood laboratory results of the patient over the course of his hospitalization are shown in **Table 1**. Urinalysis on admission showed a large amount of blood, a small amount of leukocyte esterase, and 500 mg/dL of protein. The ECG still showed nonspecific ST-segment and T-wave changes. Blood and urine cultures were collected, and the patient was started empirically on levofloxacin. Computed tomographic (CT) scan of chest, abdomen, and pelvis showed pericardial thickening, borderline splenomegaly, bilateral renal

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Table 1. Routine Blood and Serum Laboratory Findings of Case Patient

Laboratory Parameter (normal value)	1 Month Prior to Admission	On Admission	Day 4	Day 6	Day 10	Day 12	Day 14
Glucose (70–109 mg/dL)	94	108	129	102	94	134	115
Total protein (6.0–8.3 g/dL)	6.2	5.9	NP	5.3	NP	NP	NP
Albumin (3.3–5.0 g/dL)	3.3	3.1	NP	2.4	NP	NP	NP
Sodium (136–145 mmol/L)	138	138	133	136	135	136	137
Potassium (3.5–5.1 mmol/L)	3.7	4.7	3.7	4.5	4.5	4.0	4.4
Chloride (96–108 mmol/L)	108	108	104	106	104	106	105
Carbon dioxide (22–31 mmol/L)	25	20	22	19	20	20	20
Urea nitrogen (7–23 mg/dL)	18	45	61	69	104	105	107
Creatinine (0.5–1.3 mg/dL)	1.2	2.3	2.8	3.7	5.7	5.1	5.0
Calcium (8.4–10.5 mg/dL)	8.7	8.2	7.8	NP	8.1	8.4	8.4
Alkaline phosphatase (30–120 U/L)	47	48	NP	64	NP	NP	NP
Aspartate aminotransferase (10–40 U/L)	43	65	NP	45	NP	NP	NP
Alanine aminotransferase (10–45 U/L)	52	61	NP	29	NP	NP	NP
Leukocyte count (3.8–10.5x10^3/uL)	3.8	8.1	9.3	14.0	18.2	16.5	17.3
Hemoglobin (13.0–17.0 g/dL)	10.7	10.4	10.4	11.2	8.5	8.7	8.1
Platelets (150–400 x 10^3/uL)	170	122	107	96	179	207	240
Erythrocyte sedimentation rate (Westergren)(0–20 mm/h)	NP	NP	NP	NP	910	105	100
Angiotensin-1 converting enzyme (9–67 U/L)	NP	NP	NP	NP	65	NP	NP
Troponin I (0.0–1.9 ng/mL)	< 0.3	NP	3.7	1.8	0.3	NP	NP

NP = not performed.

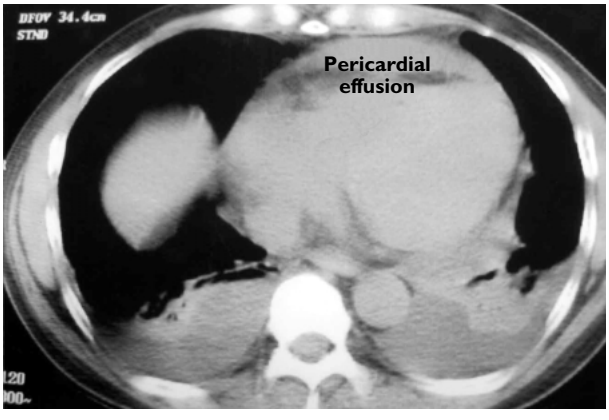

Figure 1. Chest computed tomography scan of the case patient on hospital day 6 showing a large pericardial effusion.

calculi, benign prostatic hypertrophy, and thickening of the colonic wall.

Clinical Course

On hospital day 4, the patient complained of chest pain. His temperature was 100.7°F, and there was no growth in any of the cultures. Blood pressure was 180/100 mm Hg despite antihypertensive medication, and arterial oxygen saturation was 96%. A repeat ECG showed ST-segment depression and T-wave inversion in leads V_1 and V_2. Troponin I level was 3.7 ng/mL. The patient was placed on heparin anticoagulation therapy. The troponin I levels decreased gradually; however, the heparin had to be stopped because of gross hematuria.

On hospital day 6, the patient complained of abdominal pain, nausea, and indigestion. The patient's temperature was 102°F. The blood pressure fluctuated between 170/100 and 190/100 mmHg, and renal function started to deteriorate (Table 1). A repeat CT scan of chest and abdomen revealed bilateral pleural effusions and a pericardial effusion (**Figure 1**). A transesophageal echocardiogram failed to show any evidence of endocarditis. Blood cultures still showed no growth. Measurement of fibrin split products on day 7 showed an elevation (≥ 5 < 20 μg/mL; normal, < 5 μg/mL).

On hospital day 10, thoracentesis yielded straw-colored fluid with a total protein level of 1.6 g/dL and lactate dehydrogenase level of 163 U/L. No organisms or growth were noted. Meanwhile, an asymmetrical pruritic skin rash appeared on the patient's trunk. At

Table 2. Immunologic Laboratory Findings for the Case Patient

Laboratory Parameter (Normal Value)	Hospital Day	Result
C3 complement (80–180 mg/dL)	10	99 mg/dL
C4 complement (10–45 mg/dL)	10	< 6 mg/dL
Cytoplasmic ANCA antibody (< 21 EU = negative)	10	< 21 EU
Perinuclear ANCA antibody (< 21 EU = negative)	10	< 21 EU
Rheumatoid factor (> 19.9 = positive)	10	71.3 IU/mL
Sjögren's A antibody IgG*	10	Not detected
Sjögren's B antibody IgG*	10	Not detected
Cryoglobulins*	13	Positive
Cryocrit (0 mm)	13	3 mm
Autoantibodies		
Antinuclear antibody *	10	Negative
Anti–double-stranded DNA antibody*	10	Negative
Anti-RNP antibody*	10	Negative
Anti-Smith antibody*	10	Negative
Anti-glomerular basement membrane antibody*	12	Negative

*Normal value is negative or not detected.

ANCA = antineutrophil cytoplasmic autoantibody; EU = ELISA units; RNP = ribonucleoprotein.

this point, systemic vasculitis with multi-organ involvement was suspected, and the patient was started on steroid therapy. The patient's rash worsened and spread to the groins and extremities. Hepatitis viral testing at this time showed the patient negative for hepatitis A, hepatitis B surface antigen, and hepatitis B anti-surface antigen IgM antibody, but positive for hepatitis C antibody. Hepatitis C RNA level was 521,000 IU/mL. The patient also tested negative for HIV. The patient's condition continued to deteriorate. Results of immunologic studies performed at this time are shown in **Table 2**.

On day 12, the patient underwent a subxiphoid pericardial window procedure. Pathologic examination of fragments of parietal pericardium showed organizing fibrin, perivascular lymphoplasmacytic infiltrates, and focal fibrinoid necrosis of the walls of several arteries diagnostic of PAN (**Figure 2**). Plans for exchange plasmapheresis were made. On day 13, serum protein electrophoresis revealed a small monoclonal protein spike (0.2 g/dL).

Unfortunately, on hospital day 14, the patient had a sudden change of mental status with seizures and lost consciousness. CT scan of the brain confirmed massive intracranial hemorrhage, with brainstem herniation. The patient died several days later. Consent for an autopsy was not granted.

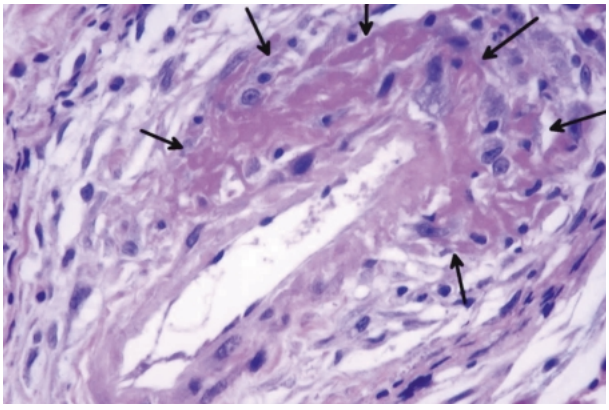

Figure 2. Photomicrograph of the case patient's parietal pericardium biopsy sample demonstrating focal transmural fibrinoid necrosis of a medium-sized artery (*arrows*). Hematoxylin-eosin stain, magnification of ×400.

DISCUSSION

Multi-organ system involvement without evidence of infection brings systemic vasculitis to the forefront of any differential diagnosis.[5] The classification of vasculitides according to the size of the involved vessels is still the most widely accepted, most useful classification.

The definition of PAN as originally described by Kussmaul and Maier[6] in 1866 has withstood the test of time.[2] The basic histopathologic finding is a focal and segmental fibrinoid necrotizing arteritis of medium sized arteries resulting in vessel wall destruction, pseudoaneurysm formation, and ischemic infarction. Curiously, PAN does not involve the lungs.

The 1994 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis[7] confirmed this definition. This conference also listed microscopic polyangiitis as the umbrella entity for cases of necrotizing vasculitides in which arterioles, capillaries, and venules (including glomerular capillaries) are primarily involved with little or no immune deposits. The latter requirement is meant to exclude cryoglobulinemic vasculitis and other forms of immune complex–mediated small vessel vasculitis.

Mixed cryoglobulinemia is the most widely cited extrahepatic vasculitic manifestation of chronic hepatitis C infection.[8,9] However, in a series of 17 patients with HCV presenting as systemic vasculitis, Cacoub et al[4] showed that 10 patients fulfilled the criteria for a histopathologic diagnosis of PAN, whereas only

7 patients could be classified as symptomatic cryoglobulinemia, even though all 17 had detectable levels of cryoglobulins (as in the case patient). The patients with HCV-associated PAN were notable for the presence of life-threatening manifestations, including malignant hypertension, cerebral angiitis, renal insufficiency, and ischemic abdominal pain. Another interesting observation was that none of the 17 patients had positive anti-neutrophil cytoplasmic antibody titers, a common finding in microscopic polyangiitis.

Our case presentation supports the findings of Cacoub et al.[4] We support their conclusion that early recognition of HCV-related PAN is crucial in order to institute the proper sequence of therapeutic modalities.[10] The treatment is administration of corticosteroids in conjunction with exchange plasmapheresis to control the severe life-threatening manifestations and antiviral therapy to control viral replication—the same strategy used in the treatment of HBV-associated PAN. Unfortunately, our case patient did not survive long enough for the institution of exchange plasmapheresis and antiviral therapy.

It is worth noting that the present case is the second published report in which the antemortem diagnosis of PAN was made on the basis of a pericardiectomy specimen. The other case involved a 74-year-old woman who succumbed to PAN unrelated to HBV or HCV.[11]

Lastly, HBV surface antigen has been detected in the vessel walls of the skin of some patients with chronic HBV infection, including 2 patients with PAN.[12] We were not able to demonstrate HCV antigen using immunohistochemical methodology on paraffin blocks.

CONCLUSION

HCV infection is capable of inducing a fulminant systemic necrotizing vasculitis in the form of PAN, which is characterized by fever, weight loss, severe systemic hypertension, rapidly progressive renal failure, ischemic abdominal pains, and markedly elevated erythrocyte sedimentation rate. Owing to the frequent presence of mixed cryoglobulins in PAN, it may be easily confused, early in its course, with the more indolent HCV-related symptomatic mixed cryoglobulinemia. Familiarity of the treating clinician with HCV-related PAN increases the likelihood that a correct diagnosis will be made in a timely manner. Prompt treatment with a combination of immunosuppressive and antiviral therapies can then be initiated along with exchange plasmapheresis and careful long-term followup. **HP**

ACKNOWLEDGMENT

The authors thank Ms. Paula Green for her invaluable bibliography search.

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