CASE REPORT
OLGU SUNUMU

A case of HCV positive cryoglobulinemic focal necrotizing glomerulonephritis with generalized purpura

Jeneralize ekzantemi bulunan kriyoglobulinemik fokal nekrotizan glomerulonefritli HCV pozitif vakası

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SUMMARY

Hepatitis C, in addition to chronic liver disease, can cause many non-hepatic symptoms and signs such as hematological, dermatological, renal, autoimmune and neurological disorders. The accumulation of the immune complex and complement unit in small vessels causes vasculitis. Hepatitis C infection is the most obvious secondary cause of the disease. Immune complexes settle in endothelial cells and activate all pathways of the immune system and cause damage accordingly. They also cause some systemic diseases in the central nervous system, kidneys, skin and other internal organs. Membranoproliferative glomerulonephritis has been reported in more than a quarter of hepatitis C cases. Results obtained from patients followed for 21 years indicate that renal involvement is a sign of malignant prognosis. However, end-stage renal disease is not common in these patients. Detection of circulating cryoglobulins in the laboratory, hypocomplementemia and rheumatoid factor positivity help in the diagnosis of hepatitis C serology. These patients typically show low C4 values and normal or near-normal C3 values. In our case, active chronic hepatitis C positivity was discussed over the patient who was consulted to the nephrology service because of nephrotic level proteinuria, hematuria, renal failure and generalized exanthema.

Keywords: Focal necrotizing glomerulonephritis, HCV, mixed cryoglobulinemia, rituximab

ÖZET

Hepatit C, kronik karaciğer hastalığının yanı sıra hematolojik, dermatolojik, renal, otoimmün ve nörolojik bozukluklar gibi karaciğer dışı birçok semptom ve bulguya neden olabilir. Hepatit C enfeksiyonuna sekonder bağışıklık kompleksi ve komplemanların birikmesi nedeniyle küçük damarlarda vaskülit meydana gelir. Membranoproliferatif glomerülonefrit, hepatit C vakalarının dörtte birinden fazlasında görülebilir. Yirmi bir yıldır takip edilen hastalardan elde edilen sonuçlar böbrek tutulumunun malign prognoz belirtisi olduğuna işaret etmektedir. Ancak bu hastalarda son dönem böbrek yetmezliği sık görülmemektedir. Dolaşımdaki krioglübülinlerin laboratuvarda saptanması, hipokomplementemi ve romatoid faktör pozitifliği hepatit C serolojisinin teşhisine yardımcı olur. Bu hastalar tipik olarak düşük C4 değerleri gösterirken, normal veya normale yakın C3 değerleri gösterirler. Olgumuzda aktif kronik hepatit C pozitifliği nefroloji servisine nefrotik düzeyde proteinüri, hematüri, böbrek yetmezliği ve jeneralize ekzantem nedeniyle konsülte edilen hasta üzerinden tartışılmıştır.

Anahtar kelimeler: Fokal nekrotizan glomerülonefrit, HCV, mikst kriyoglobulinemi, rituksimab

INTRODUCTION

The most common extrahepatic manifestation of Hepatitis C (HCV) is mixed cryoglobulinemia, which often causes leukocytoclastic vasculitis due to type II and III cryoglobulinemia (1). The most important causes of cryoglobunemic vasculitis are infections (70%), autoimmune (24%) and lymphoproliferative (6%) diseases. It is parallel with the frequency of HCV infection, which is the most common infection (2). Cryoglobulinemic vasculitis occurs in 54% of patients with HCV, and 5% of these develop cryoglobulinemic vasculitis. While cryoglobulinemic vasculitis typically affects the skin, musculoskeletal, nervous system, and kidneys, Raynoud's phenomenon may develop in 20-50% of cases. Arthritis and arthralgia often accompany vasculitides, characterized by multiple joint involvement in more than 70% of mixed cryoglobulinemic vasculitis cases. Although nervous system involvement can be seen in 40% of cases, it is of peripheral type and causes sensory defects. Membranoproliferative glomerulonephritis (MPGN) can be seen in more than a quarter of cases and is the most important cause of morbidity. Also, end-stage renal disease may not be common. Significantly low serum C4 levels are valuable for the diagnosis of hypocomplementemia (3). ANCA (-) is a distinction from small vein vasculitis. Rheumatoid Factor (RF) positivity can be seen in 70% of patients and should remind the presence of cryoglobulinemia. Leukocytoclastic vasculitis are typical histology of skin lesions, and granular deposition of type IgM and complement C3 in the vein walls is detected by immunofluorescent staining (4). Rituximab is a human-mouse chimeric monoclonal antibody (IgG1/κ) specific for the CD20 antigen, a transmembrane protein found on the surface of normal and malignant B lymphocytes. Rituximab is used in the treatment of many autoimmune diseases by suppressing autoreactive B cell cloning (5). Our patient with chronic HCV hepatitis shows a very low complement C4 level as required by cryoglobulinemic vasculitis ANCA stained negative, RF positive (RF 70%, ANA 90% and ANCA positive, less than 5% probability). Rituximab administration to the patient significantly reduced vasculitides and organ damage.

CASE REPORT

A 60-year-old female patient was admitted to the emergency department with complaints of dyspnea and diffuse exanthema throughout the body (Figure 1). In the

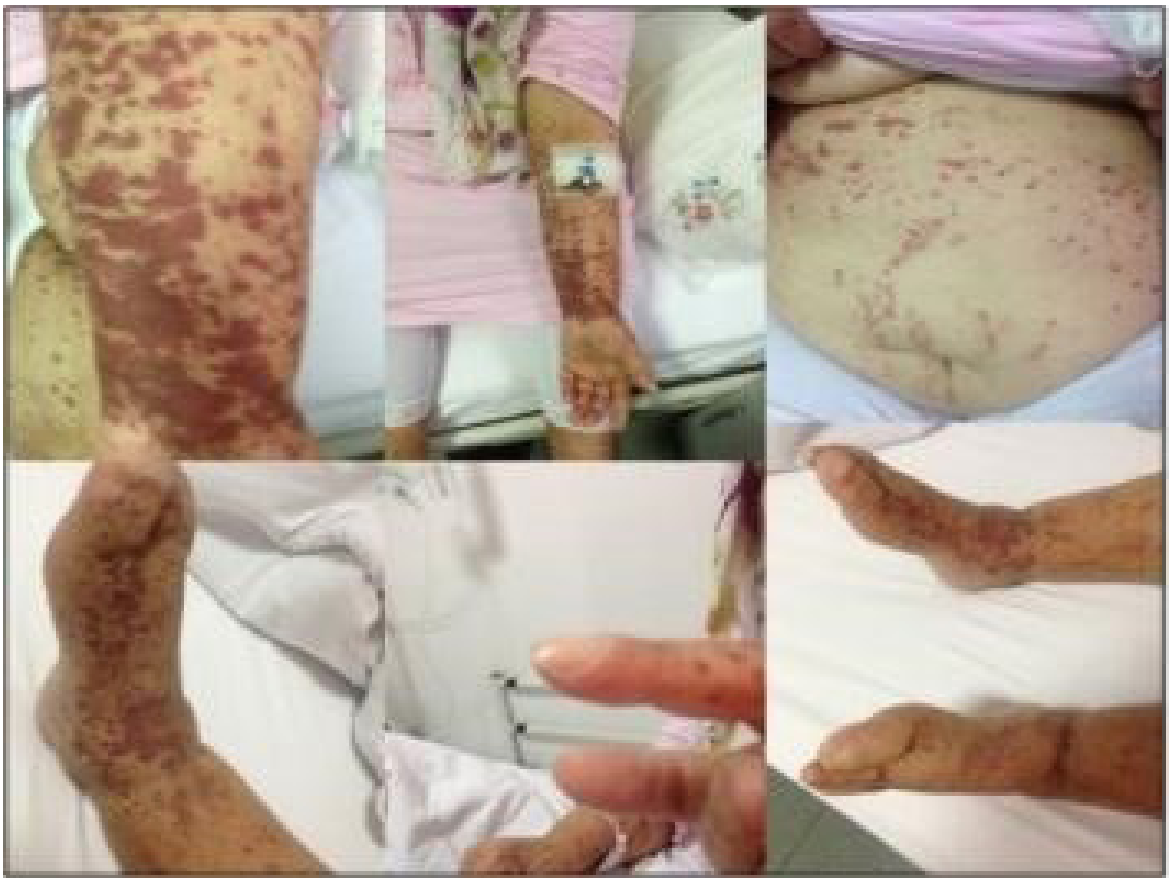

Figure 1. Generalized palpable purpura and clubbing of fingers that tend to partially coalesce and do not fade with application of pressure.

tests performed, hematuria and uremia were detected. The patient was diagnosed with hypertension and Chronic Obstructive Pulmonary Disease (COPD) in his anamnesis. A detailed examination of the generalized exanthema that started in the legs and spread to the whole body in 1997 was diagnosed as HCV. The patient informed us that the exanthema attacks were intermittent and resolved after 3 days. Liver biopsy and punch biopsy from the exanthema region were performed in January 2013 because of the patient's elevated transaminase levels and exanthema lesions on the skin. In liver biopsy; portal changes showed chronic hepatitis consistent with HCV with moderate activity. In the lesion punch biopsy; Immunohistochemical examination showed IgA, IgG, IgM negative C3: vessel membrane positive, that is, "leukocytoclastic vasculitis". The cryoglobulin test sent to another testing center gave a negative result. It was understood that he applied 180 mcg/week peg-interferon (peg-INF) and 1000 mg/day ribavirin treatment for 48 weeks. In the physical examination of the patient who was admitted to the service for further examination and treatment; vitals were stable, general condition was moderate-poor, conscious was oriented and cooperative, sclera was subicteric, both hemithorax were equally involved in breathing, respiratory sounds were coarse, and widespread rhonchi were present. The abdomen is comfortable and there is no rebound, Traube is closed. There were diffuse purpuric lesions on the whole skin that did not fade with pressure. Pretibial 2+ bilateral edema was present.

24-hour urine creatinine clearance was 36.48 (45-123) and proteinuria was 3.75 g/day. In blood tests, total protein 4.9 g/dL (6.4-8.3), albumin: 1.9 g/dL (3-4.5), BUN: 26 mg/dL (<23), creatine: 1.37 mg/dL (0.5-1,11), WBC:14.5 (4.0-10), Hg: 9.62 g/dl (12-15), Hct:28.6 % (36-46) MCV:79.2 fL (80-92), PLT: 410 (150)-400), ALT: 15 U/L (<37), AST: 15 U/L (<37), billuribin (total): 2.09 mg/dL (0-1.2), bilirubin (direct): 1.86 mg /dL (0-0.5), amylase: 263 U/L (<125), lipase: 197 U/L (<78), ALP: 213U/L (<135), GGT: 150 U/L (<36) , LDH : 296 U/L, iron: 5 mcg/dL (37-145), iron binding capacity: 197 mcg/dL (170-370), ferritin: 486.26 ng/dL (5-204), sedimentation 1 h: 45 mm, CRP: 17.9 mg/dL. Anti-ds DNA (-), direct-indirect Coombs test (-), ANA (+), RF: 293 IU/mL (<20) Anti-HBs (+), HBsAg (-), Anti-HIV (-), Anti- HCV (+), HCV-RNA 961993 IU/mL result. HCV genotype 1b was identified . The cryoglobulin test is repeated for the 5th time and detected positive.

On the 7th day of his hospitalization, with the complaint of widespread abdominal pain, a direct abdominal X-ray was taken and surgical consultation was requested. Direct graphy, no air-fluid level. The patient was consulted to general surgery, and abdominal tomography was performed; No acute pathology was observed. In the abdominal ultrasonography of the patient, the liver parenchyma was heterogeneous, splenomegaly, and minimal ascites in the abdomen. Kidney sizes and parenchyma were normal and there were no signs of pelviectasis. In the portal Doppler ultrasonography of the patient, the portal flow velocity was normal and its direction was hepatopetal, and it was physiologically determined. Due to uremia and hematuria, the patient was consulted with nephrology and kidney biopsy was performed. Fluid overload findings in the patient; Due to intense edema, lung effusion and oliguria , ultrafiltration and hemodialysis were performed by inserting a subclavian catheter. Renal biopsy revealed focal necrotizing glomerulonephritis vasculitis, and immunohistochemical examination revealed IgG, IgM and C3 positive fibrinoid necrotization. There was no crescent formation.

In echocardiography; ejection fraction: 60% and left ventricular grade 1 diastolic dysfunction was present. EMG was performed on the patient with diffuse peripheral pain. EMG examination revealed electrophysiological findings consistent with sensorimotor axonal polyneuropathy in the lower extremities. A combination of 1.125mg (3 tablets) telaprevir, 180 mcg/week peg-interferon (peg-INF) and 1000 mg/day ribavirin was administered to the patient. This combination therapy was discontinued due to intolerance in the patient and it was planned to administer rituximab (anti-CD20 monoclonal antibody). 275 mg/m2 was administered twice as much as 450 mg with an interval of 2 weeks. The patient's stomach pain and all exanthema disappeared and his oliguria continued for a while. The patient underwent 7 sessions of hemodialysis ultrafiltration. Rituximab treatment was administered 3 more times at 6-month intervals. After the patient's uremia and fluid accumulation disappeared, sofosbuvir-velpatasvir, one of the new oral antivirals, was started for 12 weeks and HCV cure was provided. In the 12-month follow-up of the patient, a decrease in liver enzymes and an increase in creatinine clearance were observed after rituximab treatment. The patient continues his social life.

DISCUSSION

While renal involvement is a serious complication in mixed cryoglobulinemia (MC), it is due to thrombosis or immunocomplex deposition. It is frequently observed as histological MPGH. Clinically, moderate proteinuria and hematuria can be seen. However, in some cases, a marked proteinuria can be seen at the nephrotic level. The disease progresses with relapse and remission, and if left untreated, it causes kidney failure. There is no standardized diagnosis of MC (5). Instead, classification criteria, which are clinical and serological tests, are used. The patient had negative results for both different cryoglobulin tests. Cryoglobulin will be obtained in the laboratory at 37 °C and must be kept at the same temperature until processed. It is also known that the cryoglobulin concentration can be determined by spectrophotometric analysis and the incubation time of the serum sample at 4 °C will vary according to the cryoglobulin type. Type I cryoglobulins tend to precipitate in the first 24 hours, whereas type III cryoglobulins require 7 days to not precipitate (6).

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HCV treatment should be started before starting MC treatment. HCV seronegative patients have less purpura and arthralgia, nonsteroidal anti-inflammatory drugs may be preferred for treatment. Peg:INF or pegINF+ ribavaring combinations should be applied as the first choice in HCV seropositive patients. The therapeutic efficacy of HCV-associated vasculitis mostly depends on the virological response. In studies with peg-interferon, significant improvement in skin, kidney and joint findings and a decrease in the amount of cryoglobulin were observed. In addition, patients with peripheral neuropathy should avoid the administration of peg-INF due to the negative effects of peg-interferon on peripheral neuropathy. Low doses of corticosteroids are preferred in mild skin and joint diseases, and higher doses are preferred in kidney and neurological diseases (7). In severe organ involvement, combination of cytotoxic agents with systemic corticosteroids or plasmapheresis, corticosteroid and cytotoxic agents is recommended. Other treatment options include IVIG and r ituximab. Rituximab therapy is a new treatment but has proven to deliver good results and improve patients (8). If the response to steroids is not as desired in organ involvement, immunosuppression will be the preferred method. Rituximab (anti CD20 monoclonal antibody) is recommended in patients with vasculitic lesions that are resistant to or intolerant to Peg-INF therapy, and who have organ involvement for whom it is contraindicated to start new antiviral therapies. There is no fixed treatment protocol for the disease. Treatment is decided according to the predominant symptom. Prognosis depends on kidney involvement and underlying disease.

CONCLUSION

In case of end-organ damage caused by immüne complexes such as generalized palpable purpura and renal involvement, we should rapidly apply immunosuppressive therapy to patients with HCV positive cryoglobunemic vasculitis. In addition, new oral anti-viral agents should be administered in order to provide HCV seroconversion, if possible. Since our patient had renal impairment, we started HCV treatment after ritiksumab treatment and provided HCV seroconversion.

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