

CASE REPORT

Brucellosis with p-ANCA-associated renal failure, leukocytoclastic vasculitis and endocarditis: Case report

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ABSTRACT

The relationship between brucellosis and p-antinuclear cytoplasmic antibody (p-ANCA)-associated vasculitis (pAAV) is a rare condition. Herein, we report a 52-year-old man who was diagnosed as rapidly progressive glomerulonephritis (RPGN) and endocarditis due to brucellosis. He was treated with antimicrobial agents, steroids, plasmapheresis, renal replacement therapy and aortic valve replacement. According to our best of knowledge, no similar case has been reported previously in the literature in regard to p-ANCA anti-lactoferrin antibodies associated-glomerulonephritis with brucellosis and endocarditis. *J Microbiol Infect Dis 2011;1(1):31-34.*

Key words: Brucellosis, endocarditis, glomerulonephritis, leukocytoclastic vasculitis, p-ANCA

p-ANCA ilişkili böbrek yetmezliği ile birlikte Bruselloz, lökositoklastik vaskülit ve endokardit: Olgu sunumu

ÖZET

Bruselloz ve p-antinükleer sitoplazmik antikor (p-ANCA) ile ilişkili vaskülit (pAAV) birlikteliği nadir görülen bir durumdur. Bu yazıda; brusellozise bağlı gelişen hızlı ilerleyen glomerülofrit (RPGN) ve endokardit tanısı alan 52 yaşındaki erkek hasta tartışıldı. Hasta antimikrobiyal ajanlar, steroid, plazmaferez, renal replasman tedavisi ve aort kapak replasmanı ile tedavi edildi. Bildiğimiz kadarıyla, literatürde bruselloz ve endokardit ile glomerülofrit ilişkili p-ANCA anti-laktoferrin antikorlar yönünden daha önce rapor edilmiş benzer bir olgu bulunmamaktadır.

Anahtar kelimeler: Brusellozis, endokardit, glomerulonefrit, lökositoklastik vaskülit, p-ANCA

INTRODUCTION

Brucellosis is a systemic infectious disease and still poses a serious health problem in developing countries. The disease can affect virtually any organ system.¹ For this reason, brucellosis shows variability in clinical presentation. It most frequently can affect the musculoskeletal system. Cardiac involvement occurs in less than 2% of the cases.^{2,3} Endocarditis is a severe and lethal complication and is more frequent in men than women. In endocarditis, there is usually aortic valve involvement.^{1,3,8} During the course of brucellosis, microorganism could be isolated from urine 9, but serious renal involvement is uncommon.^{2,10,11} Skin manifestations could be manifest less than 5% of the patients, but there are no characteristic skin lesions in brucellosis infections.^{2,12,13} Palpable purpura indicates the presence of leukocytoclastic vasculitis related with accumulation of

immune complexes.¹⁴ The relationship between brucellosis and p-antinuclear cytoplasmic antibody (p-ANCA)-associated vasculitis (pAAV) is a rare condition. Herein, we reported a case that was diagnosed as rapidly progressive glomerulonephritis (RPGN) and endocarditis due to brucellosis.

CASE

A 52-year-old man admitted to the Emergency Department with a three months history of progressively worsening fatigue, intermittent fever reaching 39°C, night sweating, diffuse arthralgia, myalgia, abdominal pain, swelling and purpuric rashes on his legs. His blood pressure was 140/90 mmHg, body temperature was 38.4°C, pulse was regular, 110 beats/min. Physical examination revealed a palpable purpura on the legs and hips,

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systolic murmur in the aortic valve area. He had lost 8 kg weight in the last three months. In his history, there was no previous illness, dyspnea and palpitations on exertion. Laboratory examination revealed erythrocyte sedimentation rate (ESR) 52 mm/h, C-reactive protein (CRP) 20.0 mg/L (reference level 0-3 mg/L), hemoglobin (Hb) 7.8 g/dl, white blood cell count (WBC) 7,950/mm³ (72% neutrophile, 19% lymphocyte), microscopic hematuria and proteinuria (1,000 mg/dl). In the stool examination, occult stool blood was found negative. Hemoptysis or melena was not detected. The patient was discharged with a treatment of methylprednisolone 40 mg/day after skin biopsy.

A week later, he applied to the Department of Rheumatology and hospitalized with the diagnosis of leukocytoclastic vasculitis. His neurologic, respiratory, gastrointestinal and musculoskeletal examinations gave no abnormality. An aortic systolic murmur (grade II/VI) and mitral systolic murmur (grade I/IV) were audible. Palpable purpura was the most prominent on the legs and hips and fewer on the upper arms. Laboratory evaluation revealed Hb as 7.1 g/dl, WBC 5,560/mm³ (granulocyte 81%, lymphocyte 12%), ESR 34 mm/h, CRP 11.4 mg/dL, serum creatinine 1.1 g/dl (reference range 0.7-1.1 mg/dl), serum albumin 2.9 g/dl (reference range 3.5-5.2 g/dl). Urine analysis revealed 20-25 erythrocytes per microscopic area. Twenty-four hour urinary protein excretion was found as 1,800 mg and the urine culture was unfavorable. C3 complement (C3) was 0.764 g/L (reference range 0.9-2.0 g/L). There is no evidence of monoclonal gammopathy in the protein and urine immunoelectrophoresis. Rheumatoid factor, anti-nuclear antibody, anti-dsDNA and cryoglobulin were negative. At the same time, p-ANCA was positive and anti-lactoferrin antibody level was 16.8 U/ml (reference range 0-15 U/ml). Chest X-Ray and renal ultrasonography were normal. Electrocardiography revealed a sinus tachycardia. Brucella serum agglutination test was favorable as titer of 1/1280. Anti-Brucella IgG and IgM antibodies were favorable by ELISA. He stated that he has eaten non-pasteurized dairy products. He was diagnosed as brucellosis and rifampin 600 mg/day and doxycycline 200 mg/day were started for treatment. Skin biopsy taken from purpuric lesions was histopathologically reported as leukocytoclastic vasculitis with vascular deposition of IgM, IgA and C3. There was

no eosinophilia in the histopathological examination (Figure 1). Blood cultures yielded as *Brucella* species. Therefore it was accepted as the cutaneous manifestation of brucellosis. Transthoracic and transesophageal echocardiography revealed vegetation on the aortic valve and a second degree aortic regurgitation (Figure 2). After these findings, his medical therapy was rearranged as doxycycline (200 mg/day), rifampin (600 mg/day) and ceftriaxone (2 g/day).

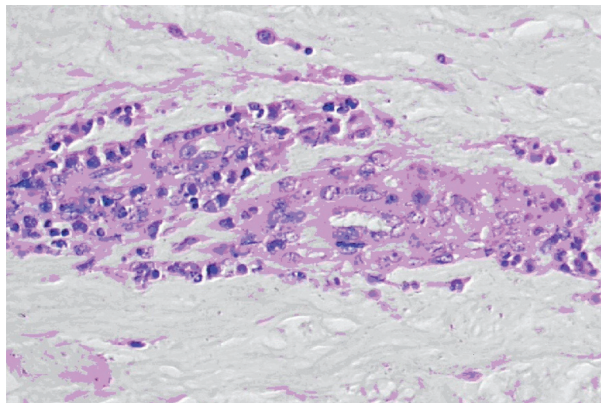


Figure 1. Skin biopsy revealed small dermal vessels with infiltration of polymorphonuclear leukocytes. The endothelial lining is reactive and the walls are thickened. There is scattered nuclear fragment in the vascular wall (400x H&E).

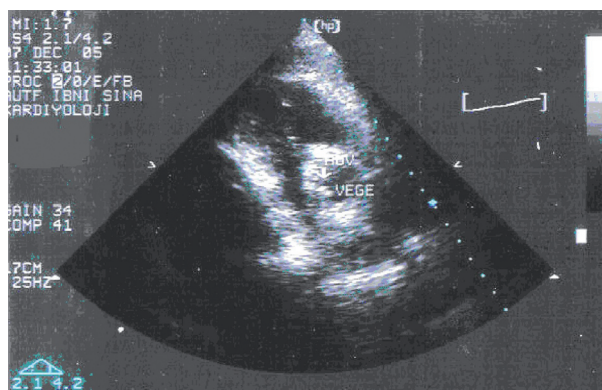


Figure 2. Transthoracic echocardiography revealed second degree aortic regurgitation and 1x0.8 cm mobile vegetation over the aortic valve.

In the clinical follow-up his renal functions diminished day by day. He was consulted to the Department of Nephrology. Renal biopsy was planned due to persistent proteinuria, hematuria and rapidly deteriorated renal functions, but the patient refused renal biopsy. BUN and serum creatinine levels were increased day by day reaching

values of 98 mg/dl and 4.5 mg/dl respectively. He was accepted as p-ANCA-associated rapidly progressive glomerulonephritis (RPGN) and 1 g/day intravenous pulse methylprednisolone was given for three days once and then continued 2 mg/kg/day. Plasmapheresis was started as three times in the consecutive days for controlling the renal function impairment. The renal functions started to improve after plasmapheresis. Serum C3 level returned to normal value and proteinuria regressed to 600 mg/day. Renal replacement therapy was planned and administered. Fifteen days after the beginning of brucellosis therapy thrombocytopenia (60,000/mm³) was detected. Brucella associated bone marrow involvement was excluded by bone marrow biopsy. It was accepted as rifampin-induced thrombocytopenia. The antibiotic therapy was switched to ciprofloxacin (1 g/day). After six weeks of medical treatment, he underwent aortic valve replacement. The patient was discharged with doxycycline (200 mg/day) and ciprofloxacin (1 g/day) therapy for 6 months. He has not any problem during follow-up.

DISCUSSION

Although cutaneous manifestations are not common in Brucellosis, these lesions include extensive purpuric rash (7%) and diffuse maculopapular rash (11%).^{2,9,12,14} There are some reports on leukocytoclastic vasculitis in brucellosis.^{2,12-14} Cutaneous lesions could be result of direct inoculation, hypersensitivity phenomenon, deposition of immune complexes or direct invasion by the organism.² Cryoglobulinemia has been described very rarely in brucellosis and may be the cause of cutaneous vasculitis.^{13,14}

Our patient had palpable purpura and the skin biopsy revealed leukocytoclastic vasculitis. The presence of brucella endocarditis implied that leukocytoclastic vasculitis might be related with immune complex accumulation.

Hematologic alterations are common in brucellosis. These are mostly leukopenia, relative lymphocytosis and thrombocytopenia. Pancytopenia occurs in 5-20% of the patients.^{2,15} Thrombocytopenia was developed in the present patient after rifampin treatment. The thrombocytopenia was accepted as side effect of rifampin.

During the course of brucellosis a mild proteinuria is common, but biopsy-proven glomeru-

lonephritis is very uncommon.^{2,9,11} The cause of renal involvement could be with multiple mechanism. Interstitial nephritis caused by directly invasion of bacteria is the most frequent pathology. Therefore, glomerulonephritis due to accumulation of circulating immune complexes may occur. In present case, co-existence with endocarditis was present.

RPGN is a clinical syndrome with an abrupt onset or an insidious onset of hematuria, proteinuria, anemia, and rapidly progressing renal failure. Yamagata reported beneficial effects of plasmapheresis in RPGN.^{11,16} Infections induce glomerulonephritis by formation of immune complexes and their deposition in the kidney.^{11,14,17} The diagnosis of RPGN was clear in our case. His renal functions returned to normal levels following plasmapheresis. The improvement of renal functions after medical therapy and plasmapheresis, supported that the idea that brucella infection was the cause of glomerulonephritis.

Lactoferrin is one of the targets for ANCA. Lactoferrin exerts antimicrobial activity, immunomodulatory and anti-inflammatory functions and may contribute to neutrophil activation by the organisms.^{18,19} Anti-lactoferrin antibodies may hamper these functions, leading to an increased inflammatory condition. Anti-lactoferrin antibodies may be detectable in patients with infections.¹⁸ Our patient had p-ANCA and anti-lactoferrin antibody positivity with RPGN. The negativity of ANCA after 6 week of therapy supported that brucella infection as the cause of RPGN.

Brucella endocarditis is an uncommon but a serious and lethal complication.^{3,6,7} The aortic valve is the most frequently affected cardiac valve.^{3,5,7} In Turkey, the rate of endocarditis among brucellosis was reported as 0.7%.¹ Blood cultures are usually negative in uncomplicated chronic brucellosis and positive blood cultures indicate probability of endocarditis.⁶ Cure of brucella endocarditis with medical treatment alone has been reported occasionally.^{3,6,8} Antibiotic therapy followed by surgery seems to be the most effective treatment.^{1,4,6,7} In the present patient the surgical and medical treatment were performed together.

We present a patient with brucella and p-ANCA associated renal failure, endocarditis and leukocytoclastic vasculitis. Clinical and laboratory evidence of vasculitis, and ANCA-associated renal failure disappeared after corticosteroid and

antibiotic treatment combined with plasmapheresis. No similar case has been reported previously in regard to brucellosis with p-ANCA associated glomerulonephritis in the literature, so according to our best of knowledge our case is the first.

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