Unusual Case Presentations of Wegener's Granulomatosis

Wegener Granülomatozu: Olağandışı Klinik Seyirli İki Olgu

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ABSTRACT

Wegener's granulomatosis (WG) is an uncommon condition characterized by necrotizing granulomatosis of the upper and lower respiratory tract and glomerulonephritis. Clinical symptoms and organ involvement of the disease vary widely. In this report we describe two cases of WG with unusual clinical presentations: one presented with erosive monoarthritis of the right knee and the other with serous otitis media. These symptoms were preceded by renal and pulmonary involvement. We think that this report will increase the awareness about the unusual clinical presentations of WG. This report also highlights the importance of early aggressive management to avoid further severe complications in WG.

KEY WORDS: Wegener's granulomatosis, Arthritis, Otitis media, Rapidly progressive glomerulonephritis, Immunosuppressive therapy

ÖZ

Wegener granülomatozu (WG), üst ve alt solunum yolunda nekrotizan granülomlar ve glomerülonefrit ile karakterize, nadir bir hastalıktır. Hastalığın klinik belirtileri ve organ tutulumu büyük ölçüde değişmektedir. Bu olgu sunumunda, akciğer ve böbrek tutulumu belirtileri ve bulguları meydana çıkmadan once, nadir klinik bulguları olan, biri sağ dizde eroziv monoarthrit ve diğeri seröz otitis media ve nazofarengeal kitle bulunan iki vaka takdim etmek istedik. Bu raporun WG'nun alışılmadık klinik başlangıcı hakkında farkındalığı arttırıcı etkisi olacağını düşünüyoruz. Ayrıca WG'da daha ciddi komplikasyonları önlemek için erken agresif tedavinin önemini vurgulamayı amaçlıyoruz.

ANAHTAR SÖZCÜKLER: Wegener granülomatozu, Artrit, Otititis media, Hızlı ilerleyen glomerülonefrit, İmmünsüpresif tedavi

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INTRODUCTION

Wegener's granulomatosis (WG) is a rare form of anti-neutrophil cytoplasm autoantibody (ANCA)-associated systemic vasculitis characterized by necrotizing granulomatosis of the upper and lower respiratory tract and glomerulonephritis (1). Clinical symptoms and organ involvement of the disease vary widely (2,3). Rapidly progressive deterioration of renal function is a frequent but clinically unfavorable feature of WG (4). In this report we describe two cases of WG with unusual presenting symptoms, one with erosive monoarthritis and the other with serous otitis media, preceded by renal and pulmonary involvement.

CASE PRESENTATIONS

Case 1

A 76-year-old white male patient presented to the orthopedics outpatient clinic complaining of right knee pain and swelling that had started 3 weeks prior to the clinic visit. On his physical examination, right knee swelling with limited range of motion (ROM), tenderness and joint warmth was detected. His past medical history was unremarkable. Laboratory investigation showed elevation

of serum creatinine from 0.8 mg/dl (70.4 μmol/L) to 6.7 mg/dl (589.6 μmol/L) and drop in hemoglobin values from 12.1gr/dl to 8.2gr/dl in the last 3 weeks. A urine analysis revealed hematuria without proteinuria. Renal Ultrasound with Doppler study showed patent vessels with no evidence of hydronephrosis. The presence of dismorphic red blood cells and red blood casts in the urine sediment suggested glomerulonephritis. No other organ involvement was found in further studies. Serologic demonstrated a positive c-ANCA (anti-PR3). Following blood transfusion and a hemodialysis session, a renal biopsy was performed. Renal biopsy showed segmental glomerular necrosis and crescent formation in 60% of the glomeruli but no immune complex deposition. By the 16th day of admission, cough, breathlessness and hemorrhagic expectoration started. Micronodular opacities were detected by chest radiogram and alveolar hemorrhage was reported on a pulmonary high-resolution computed tomography. After determining a diagnosis of rapidly progressive glomerulonephritis, pulse steroid therapy with methylprednisolone (1000 mg/day for 3 days) was started. Pulse therapy was followed by oral prednisolone (1mg/kg/day). We continued oral therapy with tapering the dose for four weeks. Until the end of the first month, the patient was treated with intravenous pulse cyclophosphamide (750mg, monthly, six courses) and six cycles of plasmapheresis. Two months following remission, right knee arthroplasty was performed. Histopathologic examination of the tissues removed from the knee joint revealed interstitial edema, moderate active chronic inflammatory reaction and mild fibrosis (Figure 1). One year after the treatment, creatinine was 1.3 mg/dl (114.4 μmol/L), urinary protein excretion was 235 mg/day and the patient was symptom free.

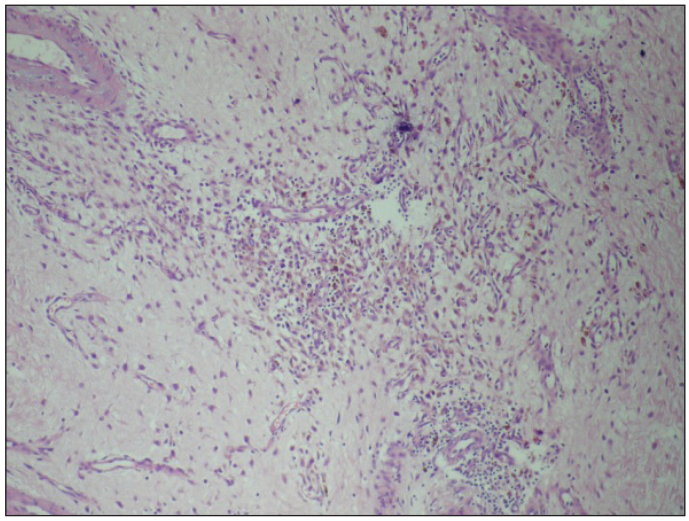

Figure 1: *Arthroplasty material; interstitial edema, moderate active chronic inflammatory reaction and mild fibrosis (H&E, x40).*

Case 2

A 40- year-old white female was presented with bilateral earache, sore throat, rhinorrhea and low-grade fever. MRI revealed a nasopharyngeal mass and bilateral osteomastoiditis (Figure 2). Microscopic findings of biopsies from nasopharyngeal lesions did not show any necrotizing or granulomatous lesions. She was diagnosed with serous otitis media, Broad-spectrum antibiotics were prescribed and ventilation tubes were inserted bilaterally. After 2 months, she presented with joint pain, sore throat, nonproductive cough and rash of one week duration. Upon admission, laboratory tests were performed in the emergency unit. Chest radiography findings were normal; CRP:283 mg/L, AST:174 U/L, ALT:123 U/L, sedimentation rate: 104/h and serum creatinine: 86.24 μmol/L. Laboratory

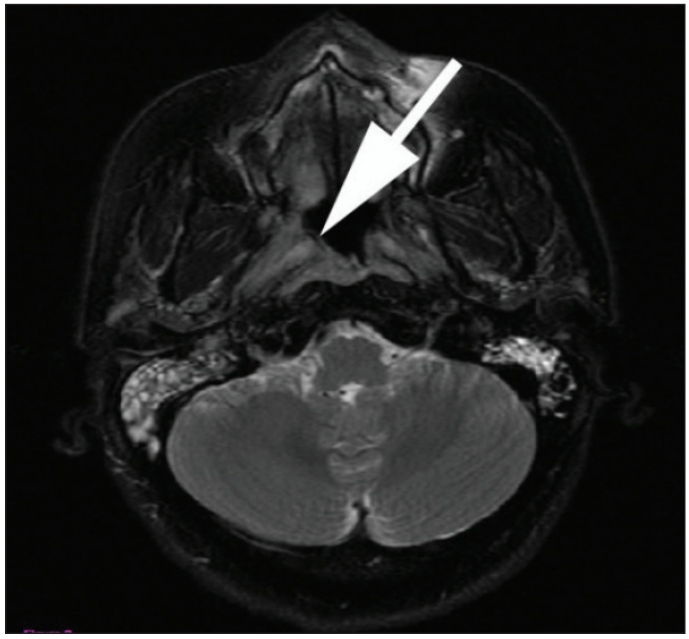

Figure 2: *Magnetic resonance image showing nasopharyngeal mass (arrow) and bilateral osteomastoiditis.*

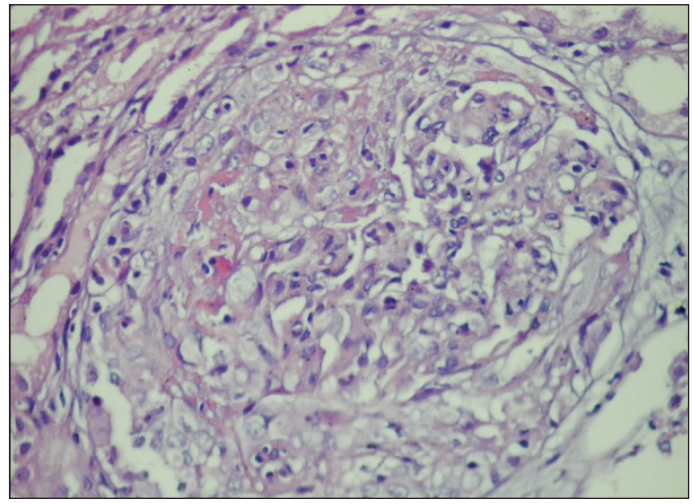

Figure 3: *Kidney biopsy showing segmental glomerular necrosis and fibrocellular crescent formation in a glomerulus (H&E, x100).*

workup showed EBV specific IgM and IgG antibody positivity. EBV infection was confirmed by EBV PCR. Palpable purpura was detected on both legs. A skin biopsy was performed. The patient's symptoms persisted for five days and in this time period her serum creatinine level rose to 5.56 mg/dl (489.28 μmol/L) from 0.98 mg/dl (86.24 μmol/L). Her hemoglobin level dropped to 7.3 g/dL. Urine sediment showed 5-7 red blood cell/high-power field with no dysmorphic features. 24 hour urine protein excretion was 1.23 g/day. Abdominal ultrasound showed that the size, form and echo texture of the kidneys were normal while the liver was enlarged. Subsequent to packed red blood cell transfusion and hemodialysis, a renal biopsy was performed. The biopsy specimen revealed segmental glomerular necrosis and crescent formation with no immune complex deposition in 60% of the glomeruli (Figure 3). Light microscopy of the skin biopsy specimen showed leucocytoclastic vasculitis. An immunofluorescence analysis for antineutrophil cytoplasmic antibodies (ANCA) was found to be positive in a cytoplasmic (C-ANCA) pattern, with antibody specificity for proteinase-3. Due to these results, the patient was diagnosed with rapidly progressive glomerulonephritis. Pulse steroid therapy with methylprednisolone (1000 mg/day for 3 days) was started. Pulse therapy was followed by oral prednisolone (1 mg/kg/day) plus intravenous cyclophosphamide (750 mg, six times/3 weeks). Progression of cough and hemorrhagic expectoration were noted by the seventh day of the treatment. Micronodular opacities were detected on the chest radiogram and alveolar hemorrhage was reported on pulmonary high-resolution computed tomography. Four cycles of plasmapheresis with citrate anticoagulation was performed as alternative day therapy. Hematuria was observed after each plasmapheresis session and because of hemoptysis we changed plasmapheresis to therapeutic immunoadsorption. Three weeks after initiating therapy, creatinine level dropped to 1.6 mg/dl (140.8 μmol/L) and patient became symptom free. At the end of the second month of therapy her serum creatinine level rose to 2.1 mg/dl (184.8 μmol/L) and her urinary sediment became active again. Due to early relapse, pulse steroid (1 gram per day for 3 days) plus 5 cycles of immunoadsorption therapy was started. We continued oral steroid therapy with tapering the dose over six months and thereafter continued at a dose of 5 mg per day. The latest serum creatinine level was 1.3 mg/dl (114.4 μmol/L), urinary sediment revealed only 3-4 dimorphic erythrocytes and the patient was symptom free.

DISCUSSION

We report two cases of Wegener's Granulomatosis (WG) with unusual presenting symptoms (one with erosive monoarthritis and the other with serous otitis media), preceded by renal and pulmonary involvement. WG is a rare systemic disorder and affected patients may seek help from physicians of diverse specialties (3). Clinical symptoms and organ involvement of the disease vary widely. The upper respiratory tract is the area where initial symptoms appear more often and generally precede pulmonary or renal involvement. More than 70% of the symptoms include nasal, sinus, ear, or tracheal manifestations. These presenting symptoms of WG are commonly misdiagnosed as infectious or allergic in etiology (4).

The initial symptoms of the second patient are consistent with the most common symptoms of WG. Due to the upper respiratory tract complaints, the patient was monitored until two months prior to the appearance of renal symptoms. However, possibility of systemic diseases was not taken into consideration. The first sign suggesting vasculitis was purpuric lesions that appeared five days before detection of kidney failure, which did not fade on pressure and began spreading from the lower extremity to the rest of the body. Similarly to our case, leukocytoclastic vasculitis is the most common cutaneous pathologic pattern (5). Skin involvement is more frequent in generalized WG and may be an early premonitory sign of renal disease. Renal involvement occurs in 15% of patients as a primary symptom, while it develops in 70-75% of patients during the course of the disease. Most of the patients are symptom free until advanced uremia develops.

Arthralgias and myalgias are the most common symptoms that are present in two thirds of the patients. However monoarticular and polyarticular arthritis are less common. Since rheumatoid factor is often positive in WG, it is sometimes misdiagnosed as rheumatoid arthritis (6). Although musculoskeletal symptoms are frequent, only a few cases have reported erosive arthritis as presenting symptom of WG (7,8). In our first case, renal failure was detected through a pre-operative laboratory work up for right partial knee replacement surgery (due to ankylosis). He was diagnosed as WG during renal failure etiology investigation. This is one of the rare cases reported with this unusual course of the disease. It should be kept in mind that WG has a spectrum of clinical presentations. Severity and presenting symptoms of the disease varies for each patient. Although, the diagnosis is based on clinical, laboratory and tissue biopsy findings, ideally the diagnosis is established through biopsy of an involved organ. Characteristic histological findings in non-renal tissues show granulomatous inflammation, necrosis and necrotizing or granulomatous vasculitis (9). Biopsies of abnormal pulmonary parenchyma yield diagnostic changes in 91% of cases (10), while biopsies of the upper respiratory tract show diagnostic features only 21% of the time (11). In the second case, even though MRI findings revealed a nasopharangeal mass, no findings other than reactive tissue changes were reported. In both of our cases, the diagnosis was established through biopsy of the kidney. Interestingly, both the diagnostic and late manifestation was kidney involvement in both cases.

Kidney biopsy typically reveals a segmental necrotizing glomerulonephritis that is usually pauci-immune on immunofluorescence (12). The pathogenesis of WG is a complex process, leading to an inflammatory damage to blood vessels. Infectious agents have been linked to the pathogenesis

of vasculitis via diverse mechanisms (13). In a recent study, an increased prevalence of otorhinolaryngeal manifestations in WG patients positive for EBV early antigen IgG have also been observed (14). In our second case, due to long standing sore throat and fever of unknown etiology, infectious mononucleosis was considered as an initial diagnosis and EBV antigen was found to be positive. Two days later the first rash appeared and subsequently renal failure was diagnosed. Acute renal failure and hemoptysis are potentially life-threatening conditions and must be aggressively treated during or even before further diagnostic evaluation. There are many causes of acute renal failure or hemoptysis but those that could explain other features of this patient's complex presentation are limited. Hemoptysis developed dramatically in both of the cases; nonetheless, it did not result in death in either of them.

Therapy of WG has two components; induction of remission by initial immunosuppressive therapy and maintenance immunosuppressive therapy for a variable period to prevent relapse. Immunosuppressive therapy is a combination of corticosteroids and cytotoxic agents. Induction of complete remission is the goal of immunosuppressive therapy and complete remission is achieved in more than 90% of the cases. Plasma exchange has been performed for WG patients who are dependent on dialysis and those who have rapidly progressive glomerulonephritis (RPGN) (15). In both of our patients, remission was achieved by glucocorticoids plus cyclophosphamide treatment supported by plasmapheresis.

CONCLUSION

Wegener's granulomatosis is a form of ANCA associated systemic vasculitis. Clinical symptoms and organ involvement of WG vary widely. Early recognition and treatment is of crucial importance in preventing severe organ damage in WG. In this report we describe two cases of Wegener's granulomatosis with unusual presentations. We think that this report will increase the awareness about the unusual clinical presentations of WG. This report also highlights the importance of early aggressive management to avoid further severe complications in WG.

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