

# Cranial Nerve Injury as an Initial Sign of Wegener Granulomatosis: Misdiagnosis and Fatal Course in Two Cases

## *Wegener Granülomatosisin Başlangıç Bulgusu Olarak Kranial Sinir Tutulumu: Yanlış Tanı ve Ölümcül Seyreden İki Olgu*

### ABSTRACT

Highest prevalence of all antineutrophil cytoplasmic antibody associated systemic vasculitides is the Wegener granulomatosis, and it's typically characterized by a necrotizing granulomatous vasculitis of the respiratory tracts, kidneys, and skin. Neurologic involvement in Wegener granulomatosis ranges from 22% to 54%, but central nervous system involvement is from 2% to 8%. Cranial nerve involvement as an initial sign with concomitant systemic disease is extremely rare. Involvement of one or more cranial nerves is generally a seemingly isolated finding in Wegener granulomatosis. We present WG cases that presented with treatment-resistant cranial nerve involvement and acute fatal pulmonary-renal syndrome.

**KEY WORDS:** Wegener's granulomatosis, Neurologic manifestation, Pulmonary-renal syndrome

### ÖZ

Wegener granülomatosis antinötrofil sitoplazmik antikorlarla ilişkili vaskülitlerde yüksek sıklıkla görülmekle beraber cilt, böbrek ve solunum sisteminin nekrotizan granülomatöz vaskülit ile karakterizedir. Wegener granülomatosisinde nörolojik tutulum %22 ile %54 arasında değişmektedir. Buna karşılık santral sinir sistemi tutulumu %2 ile %8 arasında değişmektedir. Sistemik hastalıkların başlangıç bulgusu olarak kranial sinir tutulumu oldukça nadirdir. Bir ya da daha fazla kranial sinir tutulumu Wegener granülomatosisinde nadiren görülür. Bu olguda kranial sinir tutulumlu, tedaviye dirençli, akut pulmoner-renal sendromlu Wegener granülomatosisi tartışmayı amaçladık.

**ANAHTAR SÖZCÜKLER:** Wegener granülomatosis, Nörolojik belirti, Pulmoner-renal sendrom

### INTRODUCTION

Systemic vasculitides is an extremely rare and many physicians still regard of them. However, they don't prepare for such a surprising come across. The most of organs such as upper and lower respiratory tracts, kidneys, and skin are affected by Wegener's granulomatosis (WG) which is typically characterized by a necrotizing granulomatous vasculitis (1). The frequency of neurologic involvement in WG ranges from 22 % to 54 %. While peripheral neuropathy is common in patients with WG (43.8 %), cranial nerve involvement is seen in only a small percentage (4.7%) (2). Cranial nerves 2, 6, and 7 are the most frequently involved, either by themselves

or in combination (3). In some prospective studies, the optic nerve was the most commonly affected cranial nerve in patients with WG (2). We present two patients with WG who presented with treatment-resistant cranial nerve involvement and acute fatal pulmonary-renal syndrome.

### CASE 1

A 40-year-old man presented at an otorhinolaryngology clinic because of tinnitus and sudden hearing loss, non-productive cough, pleuritic chest pain, and significant weight loss (7 %) for three weeks. He was initially diagnosed with bilateral otitis media, and treated with gentamycin for one week. His symptoms had not improved,

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Received : 26.02.2013

Accepted : 12.04.2013

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and progressive dysphagia and right-sided facial nerve paralysis had developed after 5 days of treatment. The patient had been hospitalized in the otorhinolaryngology clinic. Three days after, he had developed microscopic hematuria, generalized skin eruption, and oliguria and acute nephritic syndrome. The patient was referred to our clinic. Physical examination on admission revealed a blood pressure of 100/60 mmHg, pulse 96/min., body temperature 38.7 °C and respiratory rate 18/min. Neurological examination revealed 7th, 8th, and 10th cranial nerve dysfunction.

On admission, laboratory findings were as follows; white blood cell count 24.000/mm<sup>3</sup>, hemoglobin level 9.6 gr/dl, platelet count 224.000/mm<sup>3</sup>, serum creatinine 2.7 mg/dl; serum albumin 2.9 gr/dl; erythrocyte sedimentation rate 88 mm/h. Urinalysis revealed proteinuria, 150 mg/dl, and microscopic hematuria at 10 red blood cells/hpf. International normalized ratio (INR) was normal. C-reactive protein was 80 mg/L. Rheumatoid factor, anti-nuclear antibody, anti-ds-DNA-antibody, and cryoglobulin were all negative. Serum complement levels were normal. Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) was negative but c-ANCA was strongly positive. Decreased tonicity was found in the upper esophageal sphincter on endoscopic examination. Ear canal examination was normal. An audiogram demonstrated bilateral severe sensorineural hearing loss (SNHL), which is defined as both air and bone conduction below 15 dB with no significant air-bone gap (>10dB). Echocardiography, chest x-ray, and abdominal ultrasound on admission were normal. A computerized tomography (CT) scan of the temporal bone was normal. Paranasal regions, dura mater thickness, optic canals were all normal as detected by magnetic resonance image of the brain.

Renal biopsy was performed because of the acute nephritic syndrome and suspected systemic vasculitic syndrome. Diffuse crescentic glomerulonephritis was found on renal biopsy (Figure 1). The presence of upper respiratory symptoms, acute multiple cranial nerve dysfunction, acute nephritic syndrome and diffuse crescentic glomerulonephritis in renal biopsy, and the high c-ANCA positivity were suggestive of WG. The patient was therefore treated with plasmapheresis and pulse methylprednisolone for 3 days, followed by maintenance prednisolone and cyclophosphamide. The patient needed hemodialysis therapy 3 times during hospitalization. Although aggressive immunosuppressive treatment and plasmapheresis were performed, the patient developed diffuse alveolar hemorrhage and poor pulmonary function on his 10th inpatient day and died due to pulmonary-renal syndrome on 10th day of treatment.

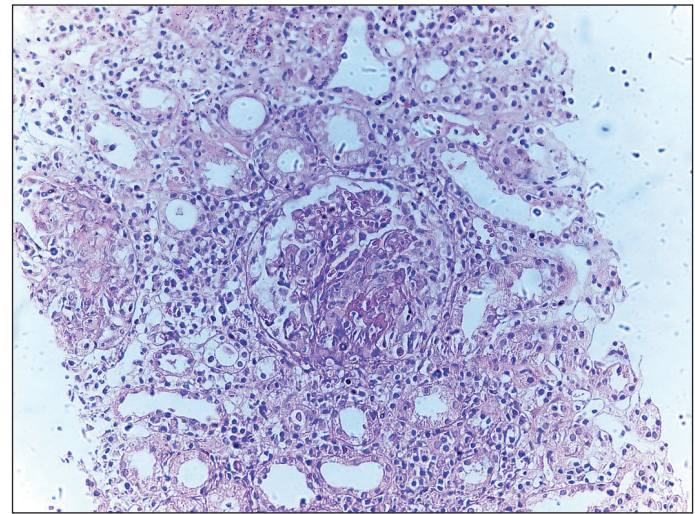
## CASE 2

A 38-year-old-female was admitted to our nephrology service because of tinnitus and progressive hearing loss for two weeks, and oliguria and dyspnea for two days. The patient had been diagnosed with otitis media and a nasolabial skin lesion in an outpatient clinic eight days before the admission, and treated

with cefuroxime axetil for a week. Her past medical history was unremarkable, and she did not smoke.

All vital findings were normal other than fever of 38.5 °C on admission. Lung examination revealed bilateral basilar late inspiratory crackles. Tympanic membranes and external ear canals were normal. She developed an ulcerated nasolabial skin lesion (Figure 2) and a purpuric eruption together with generalized edema (Figure 3) three days after admission. An audiogram demonstrated bilateral severe sensorineural hearing loss (SNHL), which is defined as both air and bone conduction below 15 dB with no significant air-bone gap.

Laboratory findings on admission as follows: white blood cell count 19.000/mm<sup>3</sup>, hemoglobin concentration 8.6 gr/dl, platelet count 186.000/mm<sup>3</sup>, creatinine 3.7 mg/dl, erythrocyte



**Figure 1:** Diffuse crescentic glomerulonephritis is shown here original magnification x200.



**Figure 2:** Ulcerated nasolabial skin lesion.



Figure 3: Vasculitic skin eruption on extremities.



Figure 4: Caviter lesion in right lung lower zone on chest x-ray.

sedimentation rate 76 mm/h. Urinalysis revealed microscopic hematuria (40/hpf) and proteinuria (75 mg/dl). 24-hour urine sample showed 2 gr/d of proteinuria. C-reactive protein was 45 mg/L. INR and activated Partial Thromboplastin Time (aPTT) were normal. Rheumatoid factor was negative. Strongly positive c-ANCA was found on admission. ANA, serum complement levels, and cryoglobulins were all normal. HIV, tuberculosis, subacute bacterial endocarditis, neoplastic disease and drug-induced conditions that can cause a false positive c-ANCA test were ruled out. Chest X-ray (Figure 4) and high-resolution computerized tomography (HRCT) (Figure 5) showed multiple pulmonary cavitary lesions. Primary lung or metastatic solid tumor, lymphoma, and tuberculosis were ruled out. Magnetic resonance imaging of the cranial bones and brain showed no abnormality. An audiogram confirmed bilateral SNHL. A CT

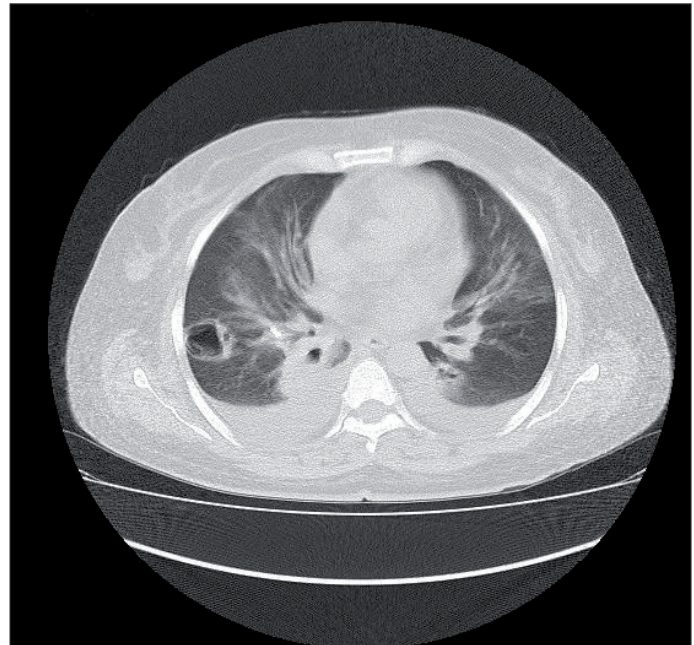


Figure 5: Multiple caviter lesions in lung on high resolution ct hrct.

scan of the temporal bone was normal. The patient underwent skin and renal biopsies. Renal biopsy revealed diffuse crescentic glomerulonephritis, and skin biopsy was compatible with leukocytoclastic vasculitis. Combined treatment with pulse methylprednisolone (1 gr/d for three days), pulse cyclophosphamide (0.5 gr/m<sup>2</sup>), and plasmapheresis was used. Oral corticosteroid therapy at 40 mg/d and cyclophosphamide at 100 mg/d were administered as the maintenance therapy. Hemodialysis was performed 11 times during the hospital stay. Her fever and creatinine level rapidly improved on the seventh day of treatment, but the hearing loss persisted. She developed sudden treatment-resistant massive hemoptysis, and died due to pulmonary-renal syndrome on the 35th day of treatment.

## DISCUSSION

WG is considered when its choose of the upper and lower respiratory tracts and the kidneys. The most important presenting features of WG are ear, nose, and throat involvement. Numerous patients with WG principally develop the disease by lesions of the upper airway region. Chiefly, the ear and nasal mucosa may be the first region of development disease (20 % to 40 %), and patients with WG frequently apply to otolaryngologists as was seen in our patients (4). The diagnosis of WG is based on the criteria published by the American College of Rheumatology in 1990. The distinctive features of our cases are the normal upper airway tract and external ear canals despite the hearing loss and tinnitus. We observed that these acute complaints had developed due to involvement of the cranial nerves. Nonetheless, the kidneys, skin, and lower respiratory tract were rapidly affected by WG, despite aggressive treatment.

One of the rare presenting feature of WG is neurological involvement. This involvement may progress usually while the course of the disease as appeared in 22-50 % of patients (2, 5). Although, multiple neurologic complications are appeared in up to 11 % of patients with WG, the most common single neurologic finding such as peripheral neuropathy is occurred in 16-43 % of patients (2, 5). On the other hand, involvement of the central nervous system has been reported rarely (2% to 8%) in WG patients. One or multiple cranial nerve involvement has been established either simultaneously with apparent vasculitic activity in other organs or as an appeared single manifestation. Another one has been intended to as non-systemic vasculitic neuropathy and the diagnosis is difficult. Cranial nerves 2, 6, and 7 are the most often affected, either singly or in combination (3). Lower cranial nerve palsies are very uncommon and usually occur during advanced stages of the disease (3). Furthermore, phrenic nerve involvement has been reported only once (6) and there are only a few causes of 11th cranial nerve palsy (7). Facial nerve palsy is one of the most important cranial neuropathies in patients with WG. Nikolaou et al. reported that three of their 7 patients showed only facial paresis (8) as was seen in our case 2. Additionally, similar facial nerve palsy findings were reported by Wierzbicka et al. in three of their 7 patients (9). Armani et al. (10) reported a WG case that presented with neurogenic dysphagia due to lower cranial nerve palsy and bilateral denervation of the 9th, 10th, 11th and 12th cranial nerves and right phrenic nerve. Isolated phrenic nerve involvement has also been reported by Pamuk et al. (6). Involvement of optic nerve may appear as exhaustive or ischemic neuropathy, optic nerve edema, and optic neuropathy (11).

Recently, Nishino et al. studied 324 patients in whom the diagnosis was made at the Mayo clinic, and multiple cranial nerve involvement was detected in only 8 patients (3). Groot et al. reported that cranial nerves including the 2nd, 3rd, 5th, and 7th nerve were damaged in only 6 of their 128 cases. Complete remission of CNS involvement was achieved in 6 of the 9 patients and the other 3 patients had a long-standing partial remission with pulse intravenous cyclophosphamide and corticosteroid treatment (2). Likewise, involvement of 7th, 8th, and 9th cranial nerves was found as an initial sign of the disease in our case 1, and involvement of the 8th cranial nerves was found in case 2. However, both of our patients died due to pulmonary-renal syndrome despite aggressive treatment. Some authors believe that cranial pathology without renal and pulmonary involvement suggests a variant of Wegener's granulomatosis called the "limited" form. We can speculate that combined systemic and cranial involvement may be fatal in patients with WG.

Hearing loss can be an initial sign of WG. Almost 50% of WG patients have otologic involvement, including both SNHL and conductive hearing loss (12). The reported frequency of SNHL in WG is from 2.8 % (12) to 13 % (13). SNHL is mostly significant because cranial nerve damage suggests a neurodegenerative

process that might warrant potent therapy (14). Furthermore, the occurrence of SNHL can be a warning of severe WG and is thought to require initial treatment with cyclophosphamide (14). The hearing loss in WG may progress quickly in days to weeks and can be accompanied by tinnitus (15). The acute onset of SNHL and the poor response to immunosuppressive therapy in our cases are very similar to the patients documented in the Wierzbicka et al. study (9). Furthermore, SNHL can be associated with other severe manifestations including renal disease (15), as seen in our patients.

## CONCLUSION

Lots of physicians still regard WG as uncommon and they don't prepare themselves for this disease. Physicians will encounter this compulsive disease when cranial neuropathies appear as sole finding of WG, and diagnostic procedure is requirement for not to miss this diagnosis. On the other hand, a multidisciplinary approach with dedicated clinicians is advised since direct histological proof or tests indicating active vasculitis are often not available in these patients.

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