ANCA-Negative Wegener’s Granulomatosis with Multiple Lower Cranial Nerve Palsies

Sung-Hee Kim,1 Jin Park,1 Jung Ho Bae,2 Min-Sun Cho,3 Kee Duk Park,3 and Jee Hyang Jeong1

Departments of 1Neurology, 2Otolaryngology, and 3Pathology, Ewha Womans University School of Medicine and Ewha Medical Research Institute, Seoul, Korea

Received: 8 March 2013
Accepted: 16 May 2013

Address for Correspondence:
Jee Hyang Jeong, MD
Department of Neurology, Ewha Womans University School of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 158-710, Korea
Tel: +82.2-2650-2776, Fax: +82.2-2650-5958
E-mail: jeong@ewha.ac.kr

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI10C2020).

INTRODUCTION

Wegener’s granulomatosis (WG) is a rare autoimmune disease of localized granulomatous inflammation of the upper and lower respiratory tract and systemic small and medium-sized vessels with granulomatous formation. Though it is known for respiratory tract and kidney involvement, neurologic manifestation has been also reported. Herein we report a patient who suffered pansinusitis with multiple lower cranial nerve palsies but reached remission by immunosuppressant after the diagnosis of WG. A 54-yr-old female visited with headache, hearing difficulty, and progressive bulbar symptoms. She experienced endoscopic sinus surgeries due to refractory sinusitis. Neurologic examination revealed multiple lower cranial nerve palsies. Vasculitic markers showed no abnormality. Nasal biopsy revealed granulomatous inflammation and vasculitis involving small vessels. Given cyclophosphamide and prednisolone, her symptoms were prominently improved. WG should be considered in the patient with multiple cranial nerve palsies, especially those with paranasal sinus disease. Because WG can be lethal if delayed in treatment, prompt immunosuppressant is warranted after the diagnostic tissue biopsy.

Key Words: Wegener Granulomatosis; Cranial Nerve Diseases; Refractory Sinusitis; c-ANCA Negative

CASE DESCRIPTION

A 54-yr-old female was referred for neurologic consultation due to progressive dysarthria, dysphagia and left facial palsy for past 5 month in January 2011. She had no underlying medical illness such as diabetes mellitus, and had underwent first functional endoscopic sinus surgery (FESS) for bilateral maxillary sinusitis 4 yr ago. She had remained tolerable after the surgery for about 3.5 yr then the symptoms of headache, hearing difficulty, dysarthria and dysphagia slowly emerged and progressed for about 6 months. Under the diagnosis of recurrent sinusitis involving frontal, ethmoid, sphenoid and maxillary sinuses, second FESS and broad-spectrum antibiotics were treated. Although these surgical and medical treatments were adequately performed, her symptoms worsened as aggravated hearing problem, severe bulbar symptoms and newly developed left facial palsy. The first brain MRI with using contrast enhancement was performed, only to reveal still existing bilateral otomastoiditis and extensive sinufinite (Fig. 1A-D). Cerebrospinal fluid (CSF) had no cell counts and normal protein level. The empiric steroid therapy (methylsol 2 mg/kg/day) without definite diagnosis has somewhat stabilized these series of aggravating symptoms. At then, she was referred to our clinic for more detailed evaluation.

In January 2011 when she was admitted in our clinic, all the...
vital signs including body temperature were stable. Accompanied by severe bulbar symptoms of dysarthria and dysphagia, she complained of constitutional symptoms such as general weakness, poor oral intake and weight loss of up to 12 kilograms during past 6 months. Neurologic examination revealed various lower cranial nerve palsies of both sides, which were overall more prominent on left side than right side. Demonstrated clinical manifestations and positive neurologic findings are; facial diplegia, progressive hearing difficulty resulting in near-deafness, bilateral tinnitus and hyperacusis, right deviation of uvula, bilateral decreased gag reflexes, flaccid dysarthria with breathy voice and hypenmasia, dysphagia especially in liquid food, left vocal cord palsy, left sternocleidomastoid muscle weakness, impaired tongue protrusion and gigglng, and fasciculation with slight atrophy on the left side tongue. In contrast to these various lower cranial nerve involvements, there was no afferent pupillary defect, and no limitation in extraocular eye movements. Otolaryngology report was given as extensive sinusitis involving bilateral frontal, sphenoid, and maxillary sinuses with nasal cartilage erosion and bilateral chronic otitis media.

Laboratory studies revealed increased C-reactive protein (CRP) of 29.90 mg/dL (normal range 0-0.3 mg/dL), increased erythrocyte sedimentation rate (ESR) of 67 mm/hr, mild anemia (hemoglobin 10.8 g/dL), but no eosinophilia and mild leukocytosis (12,800/μL). Renal function (BUN 15 mg/dL, creatinine 0.6 mg/dL, glomerular filtration rate 111 mL/min) and microscopic urine analysis were normal. Serology test for anti-Ro/SSA, anti-La/SSB, antinuclear, anticiardioplin antibody, and ANCA were negative. Neither immunofluorescence method nor direct enzyme-linked immunosorbent assay method for proteinase 3 and myeloperoxidase antigens could detect ANCA. FANA screening and VDRL were also negative, and angiotensin converting enzyme was within normal as 28 U/L (normal range 18-55 U/L). Rheumatoid factor was minimally elevated up to 20.4 IU/mL (normal range 10-18 IU/mL). Serum folate, vitamin B12 and vitamin B12 were measured as normal level. Tumor markers including AFP, CEA, CA19-9, and CA125 were normal.

Chest CT revealed no hilar enlargement or parenchymal lung lesion. Neck CT showed high density lesions in the nasopharynx with enhancement, penetrating the skull base and extensive sinusitis expanding into orbit and retromaxillary fat-pad (Fig. 2). Whole body positron emission tomography (PET) showed hypermetabolic lesion in bilateral tonsil area with multiple lymph nodes in level II/III of neck and also in bilateral frontal, ethmoid, sphenoid, and maxillary sinuses (Fig. 3).

In the facial nerve conduction study, the compound muscle action potential (CMAP) amplitude of left facial nerve was decreased to 60% that of right side. Blink reflex test showed delayed ipsilateral R1 and R2, but normal contralateral R2 responses on both supraorbital nerve stimulations. These electrophysiological findings were indicative of bilateral facial neuropathies, more severe in the left side.

Endoscopic biopsy was performed twice due to failure to obtain pathologic confirmation at first biopsy. The first biopsy specimen was obtained from nasopharyngeal wall layer through a punch biopsy under local anesthesia, but the second endo-
Kim S-H, et al. • Wegener’s Granulomatosis with Lower Cranial Nerve Palsies

Fig. 2. Neck CT. (A to C) Quite extensive sinusitis expanding to orbit and retromaxillary fat pad is observed. Note that massive swollen lesions of nasopharynx with positive enhancement penetrated the skull base.

Fig. 3. 18F-FDG PET. (A to C) Prominent hypermetabolism in bilateral tonsil area of nasopharynx and multiple lymph nodes of neck level II and III were shown. (D-F) Multiple sinusitis were also demonstrated as hypermetabolic lesions. 18F-FDG PET: 18F-fluorodeoxyglucose positron-emission tomography.

scopic biopsy was performed far deeper layer of retropharyngeal area under general anesthesia. Tissues obtained from the second biopsy showed granulomatosus inflammation and vasculitis involving small sized blood vessels with ischemic necrosis and destruction of cartilage (Fig. 4). Period acid-Schiff, Gomori methenamine silver and acid-fast bacilli stains showed no histological evidence of fungal organism or mycobacterium. Immunostains for CD3 and CD56 had no abnormal infiltration of natural killer T cells. Epstein-Barr virus-encoded RNA in situ hybridization resulted in negative findings.

All the clinical manifestations, laboratory and imaging studies indicated ANCA negative WG involving otolaryngeal space,
upper respiratory tract and multiple lower cranial nerves. She was transferred to the rheumatology department and began therapy with steroid (methylprednisolone 1 mg/kg/day) and cyclophosphamide (2 mg/kg/day). Within the ten days of these treatments, the patient stated that her sufferings of headache and constitutional symptoms were prominently diminished. The hearing difficulty, which compelled her to wear a hearing aid, improved dramatically leaving no more need of the device. After three months of combination therapy of tapering steroid (prednisolone 0.6 mg/kg/day) and steady cyclophosphamide (2 mg/kg/day), the patient restored to almost her normal bulbar function and removed nasogastric tube for oral intake. Further repeated ANCA study was negative. Brain MRI was re-evaluated with a time interval of five months from the first MRI study, and showed persistent sinusitis of both frontal, ethmoid, sphenoid, and maxillary sinuses, in despite of marked improvement of clinical symptoms. Moreover, focal thickening with enhancement of the meninges around the area of tentorium cerebelli, inferior aspect of frontotemporal lobe adjacent to sinuses and nasopharynx were newly observed (Fig. 1E-H). Clinical significance of these imaging findings was somewhat debatable because previous neurologic defects such as dysarthria, dysphagia, and hearing impairment had improved remarkably. However, re-evaluated CRP was still high as 5.75 mg/dL, which implied for further immunotherapy. Ultimately, potent immunotherapy consisting of high dose steroid (methylprednisolone 2 mg/kg/day) and cyclophosphamide (3 mg/kg/day) was performed. Three weeks later, the follow up CRP fall to 0.39 mg/dL and ESR normalized as 3 mm/hr. Taking only cyclophosphamide (0.25 mg/kg/day) after tapering steroid, she is still in a remission state for more than a year.

**DISCUSSION**

The initial clinical symptoms and neurologic signs of the patient have shown bilateral multiple lower cranial neuropathies with chronic, insidious and progressive course, coexisting with chronic sinusitis, rhinitis and otitis media refractory to usual treatments. These symptoms and signs requires careful differential diagnosis within chronic inflammatory disease such as sarcoidosis, systemic vascular conditions including WG and antiphospholipid syndrome, infectious disease such as tuberculosis or fungal infection, diffuse infiltrative lymphoma mainly involving in head and neck, and meningitis carcinomatosis secondary to unknown primary malignancy. A series of CSF analysis, laboratory test, brain MRI, neck CT and whole-body PET were strongly suggestive of diffuse infiltrating malignancy or vasculitic disease mainly involving in upper respiratory tract. Eventually, histopathologic study by two endoscopic biopsy of nasopharynx confirmed granulomatous inflammation and vasculitis involving small sized blood vessels. To conclude, WG was the final diagnosis through the course of exclusion of differential diagnosis.

The vasculitis is defined histologically as inflammation within the wall of the blood vessels, which can be granulomatous or associated with fibrinoid necrosis of the vessel wall. Classification of systemic vasculitis is mainly based on histological features and the size of the vessel involved predominantly (4). WG and Churg-Strauss syndrome (CSS) are two main systemic vasculitides, both affecting mainly small-sized vessels and involving the upper respiratory tract. In the case of our patient, WG was far more possible diagnosis rather than CSS since the coexisting refractory sinusitis and otitis media could be more integrally explained under a single disease entity.

Although WG is one of the most common forms of systemic vasculitides, a reported annual incidence is merely 10 cases per one million people (2). Systemic vasculitides are relatively rare disease to encounter, particularly in the neurological field. The diagnostic difficulty is much more serious if clinical manifesta-
Cranial neuropathy can be the first obvious clinical manifestation in many various vasculitides including WG. Unfortunately, no single diagnostic modality can be reliable in the diagnosis of limited WG of CNS involvement. CSF analysis often shows only a slight rise in protein and a mild lymphocytic pleocytosis. Therefore, the diagnosis of CNS involvement in WG is based upon the combination of neurologic symptoms and signs, brain MRI, and histopathology.

A study of imaging in WG reported about 30% of meningeal thickening and contrast enhancement, 26% meningeal involvement by extracerebral granulomatous disease, 20% cerebral infarcts, and about 50% non-specific white matter lesions (12). Enhancing diffuse or focal dural thickening and multiple non-specific white matter lesions with increased signal on T2-weighted and fluid attenuated inversion recovery (FLAIR) images are relatively common imaging findings (13). Remote brain parenchymal granulomatous lesions of brain MRI are extremely rare.

Nasal biopsy is useful for confirming the diagnosis with a reported sensitivity of about 53% (14, 15). Classically, a triad of microscopic findings of vasculitis, granulomatous inflammation and tissue necrosis is the histologic characteristic of WG (8). However, rarely will all three histologic features be present at the same time, particularly in limited WG. One study reported that only 16% of biopsies in head and neck WG have all three defining criteria and in most cases only one criterion is found (16). In spite of these limitations, the biopsy remains as a crucial component of the diagnostic workup in suspected WG.

Anti-neutrophilic cytoplasmic antibodies with a cytoplasmic staining pattern (c-ANCA) is an established diagnostic tool of WG more easily used than biopsy. ANCA is known as a pathogenic factor in inflammatory processes that underlies necrotizing vasculitis. The sensitivity of c-ANCA in active Wegener’s disease is up to 91% and a specificity of 99% (17). However, its titer depends on the extent and phase of the disease. In complete remission status, c-ANCA is not detectable. In the limited form, when WG is localized to the respiratory tract or the adjacent CNS, c-ANCA confers about 40 to 50% specificity. On the other hand, it has the specificity is 85%-100% in the generalized form (18, 19). Our patient corresponded as the limited form of WG confined to the upper respiratory tract and CNS, without the evidences of renal or lung involvement. Thus our laboratory result of negative c-ANCA could be explained well by the previous reports that a detection rate of c-ANCA is low in the limited WG than generalized. Despite the attraction of using c-ANCA as a diagnostic test due to its ease, in almost every case it should not be placed in for biopsy to diagnose WG.

Current management of WG is based upon the regimen of oral prednisolone 1 mg/kg/day in combination with oral cyclophosphamide 2 mg/kg/day for remission induction. Daily prednisolone is continued for four weeks and tailed down gradually over 1 to 2 months before converting to an alternate day regi-
men. Then the dose is further tapered down till patient is solely on cyclophosphamide. Long-term experience with cyclophosphamide provided many evidences for its efficacy of 80% survival rate, with 91% of patients having significant improvement and 75% achieving complete remission (20). In severe disease, however, cyclophosphamide is started at higher dose of 3-5 mg/kg/day, and prednisolone is also given higher from 2 to 15 mg/kg/day. A few case studies of limited WG confined to CNS showed relatively favorable clinical response to standard protocol consisting of steroid and cyclophosphamide. Though some case reported that there was only halting of further progression without definite neurological improvement after standard immunotherapy (21), and others reported that some clinical improvement was followed by rapid deterioration leading to fatal outcome (9, 22). The case reports of dramatic response or near full recovery after a standard therapy was not uncommon (6, 10, 23, 24). For few progressive cases in spite of the combination therapy of cyclophosphamide and prednisolone, other agents including methotrexate, leflunomide, etanercept, mycophenolate, tumor necrosis factor, and anti-lymphocyte directed therapy have been tried (25, 26). Eventhough, no specific regimen has been established for those refractory cases or focally localized cases of WG (4), several studies reported of successful treatments of focal meningeal involved WG by using infliximab or rituximab (27–29).

In summary, we described a limited WG presenting with refractory sinusitis and various cranial neuropathies having slowly progressive feature. WG should be considered in patients with multiple cranial nerve palsies, especially those with underlying chronic paranasal sinus disease, with or without systemic involvement. Since WG could be lethal if untreated, prompt treatment with potent immunosuppressants including cyclophosphamide is necessary promptly after the tissue biopsy to confirm the diagnosis.

REFERENCES

1. Martinez Del Pero M, Sivasothy P. Vasculitis of the upper and lower airway. Best Pract Res Clin Rheumatol 2009; 23: 403-17.
2. Rodrigues CE, Callado MR, Nobre CA, Moura FE, Vieira RM, de Alburquerque LA, Vieira WP. Wegener’s granulomatosis: prevalence of the initial clinical manifestations: report of six cases and review of the literature. Rev Bras Reumatol 2010; 50: 150-64.
3. Cattaneo L, Chierici E, Pavone L, Grasselli C, Manganelli P, Buzio C, Agarwal PK, Gogia A. Wegener’s granulomatosis: lessons from clinical cases. J Neurol 2009; 256: 455-7.
4. Pagnoux C, Wolter NE. Wegener’s granulomatosis of nose: a case report. Indian J Otolaryngol Head Neck Surg 2011; 63: 4-5.
5. Müller S, Del Buono EA, Flint A. Diagnostic usefulness of nasal biopsy in Wegener’s granulomatosis. Hum Pathol 1991; 22: 107-10.
6. Spísek R, Kolouchová E, Jensovský J, Rusina R, Fendrych P, Plas J, Bartůnková J. Combined CNS and pituitary involvement as a primary manifestation of Wegener granulomatosis. Clin Rheumatol 2006; 25: 739-42.
7. Akahoshi M, Yoshimoto G, Nakashima H, Miyake K, Inoue Y, Tanaka Y, Tsuchamoto H, Horiuchi T, Otsuka T, Harada M. MPO-ANCA-positive Wegener’s granulomatosis presenting with hypertrophic cranial pachymeningitis: case report and review of the literature. Mod Rheumatol 2004; 14: 179-83.
8. Warnatz K, Peter HH, Schumacher M, Wiese L, Prasse A, Petschner F, Vaith P, Vold B, Weiner SM. Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature. Ann Rheum Dis 2003; 62: 50-7.
9. Allen SD, Harvey CJ. Imaging of Wegener’s granulomatosis. Br J Radiol 2007; 80: 757-65.
10. Del Buono EA, Flint A. Diagnostic usefulness of nasal biopsy in Wegener’s granulomatosis. Hum Pathol 1991; 22: 107-10.
11. Madhira S, Hamid QA, Prayaga SM, Kolloff S. Limited Wegener’s granulomatosis with predominant otological presentation. Indian J Otolaryngol Head Neck Surg 2011; 63: 4-5.
12. Agarwal PK, Gogia A. Limited Wegener’s granulomatosis with p-ANCA positivity. J Indian Acad Clin Med 2004; 5: 348-50.
13. Sayd MS. Upper respiratory tract symptoms, renal involvement and vasculitis: a case report and review of Wegener’s granulomatosis. J Clin Med Res 2010; 2: 189-93.
14. Swain S, Ray R. Wegener’s granulomatosis of nose: a case report. Indian J Otolaryngol Head Neck Surg 2011; 63: 402-4.
15. Langford CA. Cyclophosphamide as induction therapy for Wegener’s granulomatosis and microscopic polyangiitis. Clin Exp Immunol 2011; 164: 31-4.
16. Daderian AD, Chayasirisobhon S. An unusual case of multiple cranial nerve palsies in Wegener’s granulomatosis. J Naf Med Assoc 2000; 92: 455-7.
17. Nordmark G, Boquist L, Rönnblom L. Limited Wegener’s granulomatosis with central nervous system involvement and fatal outcome. J Intern Med 1997; 242: 433-6.
18. Nowack R, Wachtler P, Kunz J, Rasmussen N. Cranial nerve palsy in Wegener’s granulomatosis: lessons from clinical cases. J Neurol 2009; 256: 298-304.
19. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged appro-
ach to the treatment of Wegener’s granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum 1999; 42: 2666-73.
26. Langford CA. Wegener’s granulomatosis: current and upcoming therapies. Arthritis Res Ther 2003; 5: 180-91.
27. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010; 363: 221-32.
28. Hermann J, Reittner P, Scarpatetti M, Graninger W. Successful treatment of meningeal involvement in Wegener’s granulomatosis with infliximab. Ann Rheum Dis 2006; 65: 691-2.
29. Just SA, Knudsen JB, Nielsen MK, Junker P. Wegener’s granulomatosis presenting with pachymeningitis: clinical and imaging remission by rituximab. ISRN Rheumatol 2011; 2011: 608942.