

Case Report

Wegener's granulomatosis with otitis media as starting symptom and multi-system involvement: case report and literature review

Bing-Zhong, Jin-Tao Du, Ya-Feng Liu, Xue-Ling Qin

Department of Otolaryngology-Head and Neck Surgery, West China Hospital of Sichuan University, Chengdu, China

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Abstract: Wegener's granulomatosis (WG) is an autoimmune disease characterized by necrotizing granulomatous vasculitis. The causes of WG are unclear, and all body systems can be affected by this disease. The diversity of WG indications often causes misdiagnosis. This paper reports a type of rapid WG case, in which otitis media emerged and developed into unilateral facial paralysis, as well as caused many organ lesions in the nose, heart, liver, and kidney.

Keywords: Wegener granuloma, middle ear mastoiditis, diabetes insipidus, anti-neutrophil plasma antibodies

Introduction

Wegener's granulomatosis (WG) is characterized by necrotizing granulomatous vasculitis and classified as an autoimmune disease [1]. The upper and lower respiratory tracts, as well as the kidneys are mainly affected by WG. Granulomatous inflammation of the nasal mucosa and lung tissues presents the first clinical manifestations of WG, which can develop into diffused necrotizing granulomatous inflammation; this condition is characterized by nasal sinusitis, lung lesions, and progressive renal failure [2, 3]. The diagnostic criteria of WG in the 1990 ACR classification standards are (1) painful or painless oral or nasal ulcer and purulent or hemorrhagic nasal secretions; (2) nodules, fixed infiltration lesions, or cavities that can be seen on chest X-ray; (3) microscopic hematuria (RBC > 5 per high power field of vision) or red blood cell tube type; (4) pathological granulomatous inflammatory changes; and (5) neutrophil infiltration of arterial walls or areas outside the blood vessels (arteries or arterioles). Patients experiencing two or more of these criteria can be diagnosed with WG. The diagnostic sensitivity of this method is 88.2%, and the specificity is 92.0%.

Case report

A 49-year-old female patient was admitted in June 2014 for earache and otopyorrhea on both ears. Other symptoms included persistent tinnitus, aural fullness, hearing loss, dizziness, headache, and dry mouth. Antibiotic treatment was not effective in the local hospital.

In July 2014, the patient was admitted to our hospital following complaints of a month-long earache, pus on bilateral ears, and 10-day mouth distortion. Her body temperature declined from 38°C to 36.9°C after taking levofloxacin. Ear CT scans showed soft tissue shadows in the mastoid of the middle ear (**Figure 1A, 1B**). Audiology tests revealed severe hearing loss in both ears. Chest X-ray film showed three nodules in the right upper, right lower, and left lower lobes. Head CT scans showed bilateral maxillary sinusitis, sieve sinusitis on the left side, and bilateral mastoiditis (**Figure 1C**). Nasal endoscopy revealed bilateral nasal mucous secretions, turbinate swelling, and pus. Routine blood test results are as follows: Hb = 106 g/L, PLT = 401×10^9 /L, WBC = 8.84×10^9 /L, neutrophil percentage = 87% and lymphocyte percentage = 8.9%. Urea and creati-

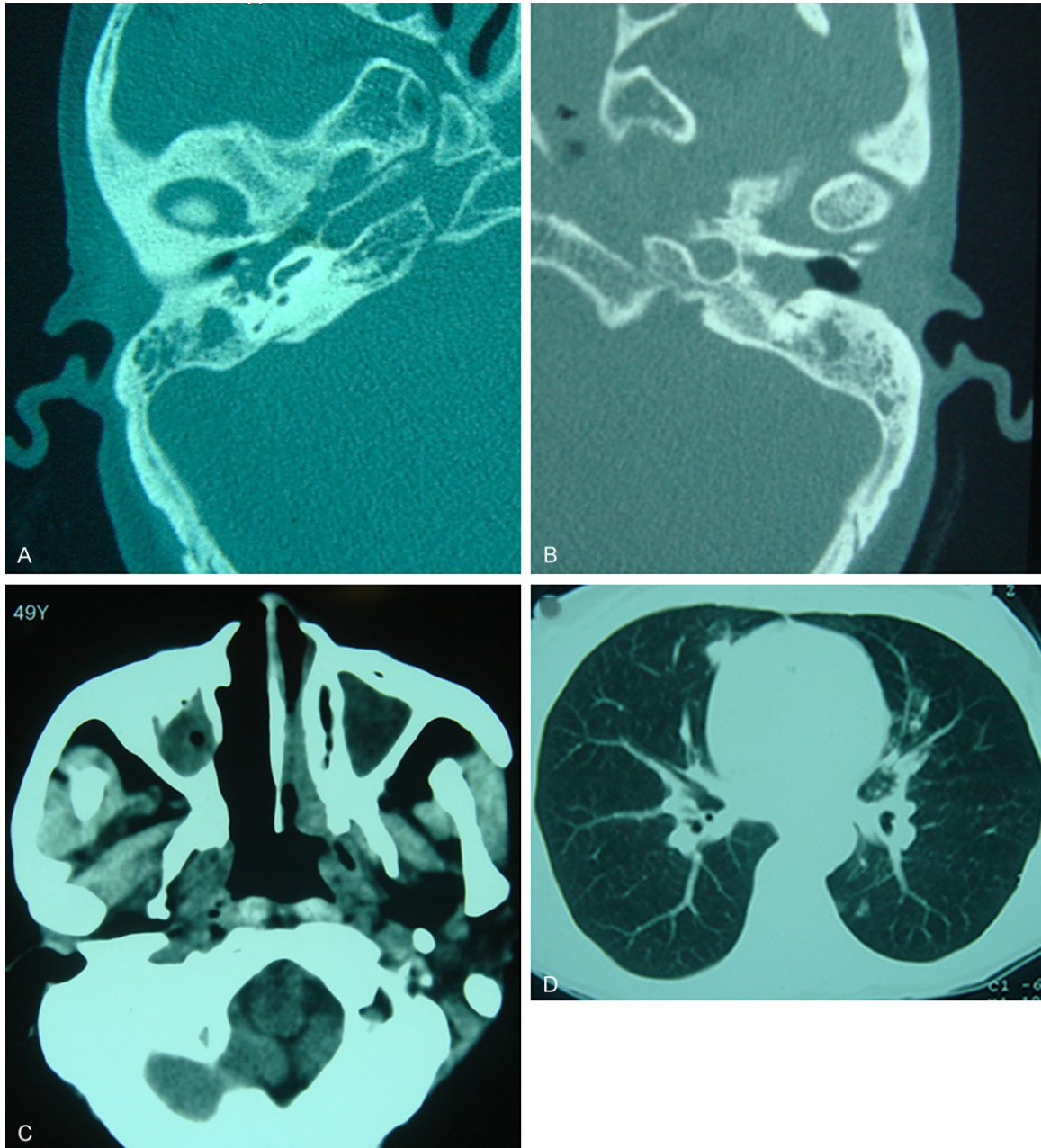


Figure 1. CT Scans. A, B. Ear CT scans showed soft tissue shadows in the mastoid of the middle ear. C. Head CT scans showed the density of bilateral maxillary sinusitis had increased; the bone of left side esmoid had been fuzzy. D. Chest CT examination showed scattered multiple nodules and masses in bilateral lungs, and some small holes of lesions can be seen in the film.

nine levels were normal. Diagnosis results are as follows: (1) bilateral middle ear mastoiditis, (2) left peripheral facial paralysis, (3) sinusitis, and (4) left marginal keratitis.

The patient had mastoidotomy and facial nerve decompression on the left side on the third day of admission. During surgery,

granulation tissues of the middle ear were observed, and the auditory ossicle chain had been damaged. Middle ear pathological examination results revealed chronic suppurative inflammation, necrosis with foreign body granulomatous response (**Figure 2A**) and neutrophil infiltration with vascular inflammation (**Figure 2B-D**). Chest CT examination showed scattered

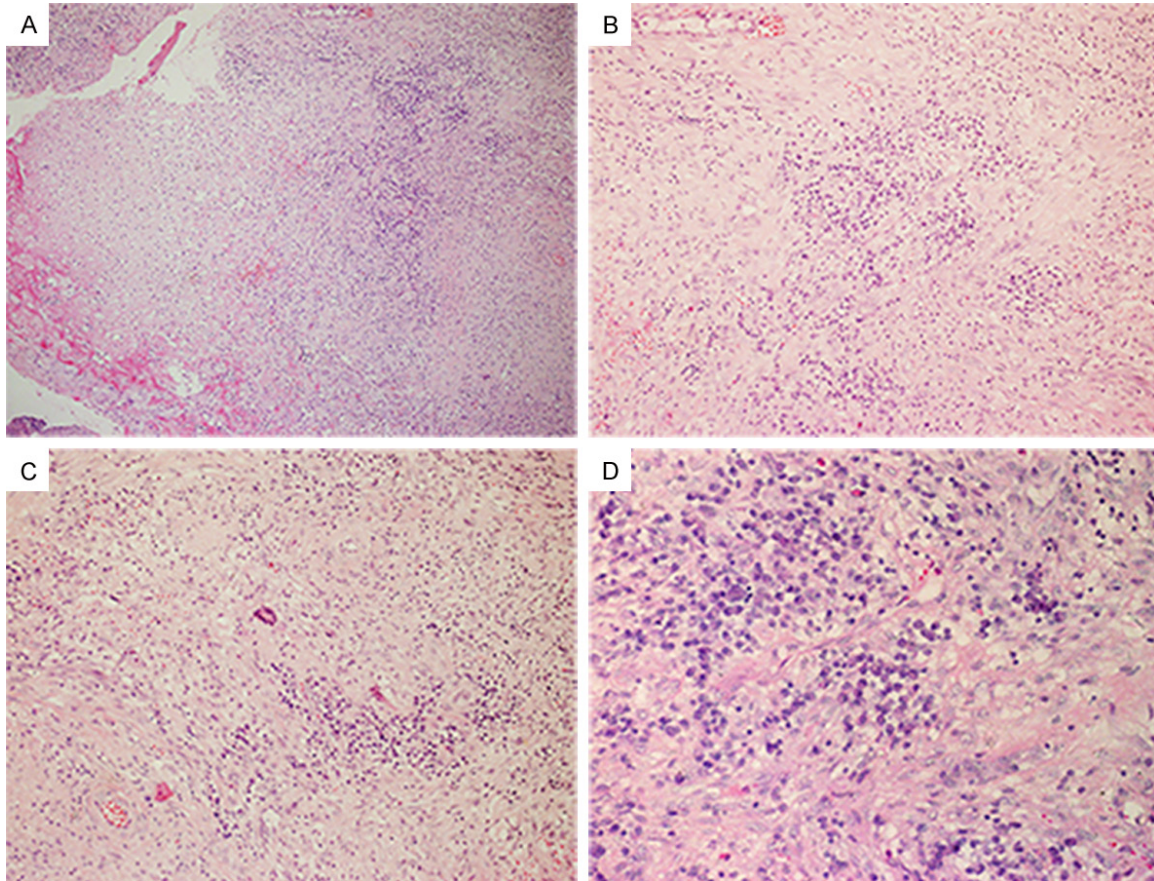


Figure 2. Pathology. (A) HE×100, Middle ear pathological examination results revealed chronic suppurative inflammation, necrosis with (B, HE×200) foreign body granulomatous response and neutrophil infiltration with (C, HE×200, D, HE×400) vascular inflammation.

multiple nodules and masses in bilateral lungs, with sizes ranging from 0.3 cm to 3.5 cm. Boundaries were clear, and some small holes of lesions can be seen in the film (**Figure 1D**). The bronchial walls thickened in the bilateral upper lobes and left lower lobes. Tubes underwent stenosis, and some small lymph nodes can be seen in the mediastinum. Slight effusion was observed in the pericardium. Abdominal ultrasound results showed liver damages. Bronchoscopy showed that the lower part of the tracheal mucosa suffered roughness, erosion, infiltrating changes, and unobstructed lumens; the carina became broader, and surface infiltration and erosion were observed; the mucosa also suffered roughness, erosion, and infiltrating changes at all levels. Routine urine test results are as follows: low proportion of urine, urine occult blood, urine WBC, and proteinuria; urinary sediment showed red blood cells (5/HP), white blood cells (126/HP), and pus cells.

The patient's maximum urine volume was 4500 ml/day, and her quantity of water intake was 5000 ml/day. Remittent fever was observed. On the eighth day after surgery, the breathing rate was 25 times/min, and later, more than 30 times/min. A large amount of secretions were present in the airway. Combined with hypostatic infection, pulmonary encephalopathy was observed. Clinical immunology results showed c-ANCA (+), and protease-3 (ANCA-PR3) 7.7. The final diagnosis was WG, accompanied by multisystem damages (ear, nose, eyes, heart, lung, liver, kidney, and pituitary gland). High-dose prednisone 50 mg/d was used for treatment, but high fever appeared again post-treatment. The patient fell into a coma. The blood oxygen saturation fluctuated to around 80 mmHg under masked oxygen inhalation. The patient's family then gave up the treatment, and she was discharged from the hospital.

Discussion

In WG, ears are affected in approximately 19% to 61% of cases [4], and ear damages are the starting symptoms in approximately 33% [5]. Outer ear involvement is rare, and the middle ear was involved in about 40% to 70% of cases. Bilateral or unilateral secretory otitis media is the most common symptom of WG that involves the ears [6, 7]. Generally, WG affecting the middle ear and mastoid cavity may cause suppurative otitis media. WG affecting the temporal lobe may cause complications such as cranial nerve palsy and meningitis. The infringement of the inner ear can cause sensorineural deafness, and hearing loss may appear in a few days to several weeks [8]. The possible mechanism of WG involves depositing immune complex to cochlea, and granulation tissues compress and damage the auditory nerve or cochlear nerve blood vessels [5]. Hormonal therapy and chemotherapy drugs are still recommended in cases of sensorineural deafness [9]. Vertigo may be caused by central nervous system involvement or immune complex deposit to the vestibular system [10]. Rare cases of WG are accompanied by single or bilateral flank nerve palsy, in which the facial nerve is damaged directly [11].

Early diagnosis and treatment of WG is important. Approximately 82% of patients die within a year, and more than 90% die within two years [12]. In many cases, ear involvement may be the only early sign of WG. However, involvement of the lungs and kidneys may indicate late-stage WG. Early stages are often indicated by ear and upper respiratory tract involvement alone [12].

Manifestations of WG starting with ear symptoms are few, and many of the indications begin with otitis media or facial paralysis [12-14]. The majority of WG cases are usually characterized by the following: (1) Antibiotic treatment is ineffective, and the condition aggravates gradually under conventional treatment. ANCA is a very useful early diagnosis index, but the testing time lasts for a week. Thus, bilateral otitis media should be considered if the treatment is ineffective. (2) Bilateral otitis media with short history can be associated with inductive nerve deafness. Some cases reported by Kloeckl, Shuto J, and Jordanl J [14-16] indicated that

many courses lasted less than 3 months, and some of the cases presented inductive nerve deafness. Histories of 3 cases that lasted for 1 week, 2 weeks, and 2 months were part of the 15 cases retrospectively studied by Dai Takagi MD [4].

Early diagnosis relies on c-ANCA and local biopsy. In 1985, c-ANCA was first reported by Van der Woude as a highly specific indicator of WG, particularly in the active stage. Hence, the occurrence of c-ANCA in WG demonstrates a diagnostic significance. The positivity rate of c-ANCA in the sinus region is high, and 14 out of the 15 cases with ear symptoms reported by Dai Takagi MD also exhibited nasal symptoms [17]. Biopsies of the nose or sinuses of the cases with nasal symptoms yielded a higher positive rate.

WG may be detected by differential diagnosis of atypical inflammation in the ear. Dai Takagi MD [17] reported that target therapies of three patients exerted significant effects on the first month of symptom appearance. The treatment of two patients diagnosed with the disease for more than 3 months is invalid. Two cases involved death by complications.

The treatment of WG can be divided into three periods: remission induction therapy, remission maintenance therapy, and recurrence control. Evidence-based medicine shows that glucocorticoid and cyclophosphamide (CTX) combination therapy exerts a significant effect, especially in patients with kidney damage and severe respiratory disease. For some recurrence and toxic treatment cases, CTX may not be successful. Naoto Tamura reported that the use of Rituximab MabThera (CD20 mouse chimeric monoclonal antibody) to consume beta cells was valuable for recurrence cases, and this drug can reduce the titer of ANCA; moreover, hormone dosage is reduced without any side effects [18].

Surgical treatment should be performed with caution because the symptoms may worsen after myringotomy and mastoidotomy. Up to 25 recently reported cases were successfully treated by drugs without surgery [4].

The main factors influencing the prognosis of WG are incoercible infection and irreversible kidney damages. The factors of poor prognosis

include serum creatinine > 150 mmol/L and ages older than 57. Jacques-Eric Gottenberg's prospective study showed that a survival rate of 10 years may reach 89% probability for patients with a serum creatinine of < 150 mmol/L upon diagnosis. The survival rate will decline without dialysis when the serum creatinine is > 150 mmol/L or the kidney function is damaged [19]. The type of ANCA may not be related to the treatment response and prognosis, but WG in patients who carry PR3 antibodies can worsen without treatment [20]. Therefore, early diagnosis and active treatment before renal damage can improve the prognosis of WG.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ya-Feng Liu, Department of Otolaryngology-Head and Neck Surgery, West China Hospital of Sichuan University, 37 GuoXue Lane, Chengdu 610041, Sichuan Province, China. Tel: +86 18980601411; Fax: +86 288-5423627; E-mail: liuyafengent@qq.com

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