Parotitis as the Presenting Symptom of Wegener’s Granulomatosis: Case Report and Meta-Analysis

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Wegener’s granulomatosis is a systemic disease characterized by necrotizing granulomatous lesions and vasculitis of small and medium-sized blood vessels. First reported by Klinger in 1931 \cite{1}, the syndrome classically involves the upper airways, lungs and kidneys. Involvement of other organs such as the skin, eyes or the musculoskeletal system is also common \cite{2,3}. Patients often present with severe upper respiratory tract findings such as sinus pain and purulent or bloody nasal discharge. Specific autoantibodies against the neutrophil cytoplasmic enzyme proteinase-3 can be detected and aid in the diagnosis of WG, which is confirmed by the typical granulomatous inflammation seen in biopsies of the affected tissues.

Parotid involvement in WG is unusual and only a few cases have been reported \cite{4-6}. We describe the case of a 57 year old man who developed parotitis, which was the presenting symptom of WG, and review the literature on this unusual presentation and its possible implications.

**PATIENT DESCRIPTION**

A 57 year old healthy male was admitted to the ear, nose and throat department because of complaints of right ear pain associated with a mucopurulent discharge that lasted a month. He denied fever, night sweats or joint pain. His appetite was good and he was not on any regular medication. He had been treated empirically with antibiotics by his family physician without any improvement.

On admission the patient was stable with a low grade fever. Examination revealed a deviation of the left mandibular angle with a fluctuating mass on the anterior wall of the right external auditory canal and discharge. There was no lymphadenopathy, hepatosplenomegaly, signs of arthritis or rash. His blood tests revealed a normocytic-normochromic anemia (hemoglobin 12.7 g/dl) and leukocytosis of 15,600 cells/µl, with a differential count of 80% neutrophils. He had normal levels of electrolytes, and kidney and liver function were intact. Laboratory investigations were significant for anemia (hemoglobin decreased from 12.7 to 7.9 g/dl), leukocytosis (white blood cells 15,080 with 89.2% neutrophils), acute renal failure (urea 27 mg/dl and creatinine 7.95 mg/dl), and erythrocyte sedimentation rate 56 mm/hr. Urine specimen was positive for red blood cells, white blood cells (0–4 per field), nitrites and protein. A 24 hour urine collection yielded 8.7 g/L of protein. Blood and urine cultures were sterile. Chest and neck computed tomography revealed necrotizing parotitis, bilateral nodules in the lungs, and pleural effusion. Kidneys and collecting ducts were normal on renal ultrasonography.

Based on the clinical picture, radiological findings, laboratory results, and the biopsy finding of necrotizing granuloma, the diagnosis of Wegener’s granulomatosis was suspected and elevated titers of anti-
PR3 antibodies confirmed the diagnosis. The patient was started on methylprednisone 500 mg/day and cyclophosphamide 50 mg/day with gradual mitigation of symptoms and improvement of his renal function up to normalization.

Many conditions are associated with parotid gland diseases, including: a) bacterial, viral, fungal, chlamydial, mycobacterial and helminthic infections; b) hypersensitivity to organic dusts; c) immune mediated diseases such as rheumatoid arthritis, temporal arteritis, Sjogren’s syndrome, and sarcoidosis; and d) malignancies including lymphoma. Parotid involvement in WG is rare and can mimic malignancy, abscess, viral infection or unspecified gland enlargement [3].

Since there is no classic characteristic suggesting parotid involvement, the recognition of WG becomes a diagnostic challenge. In the case described here, the initial presentation was restricted to the parotid gland and the biopsy was inconclusive, leading to a 3 month delay until the diagnosis of WG was reached. The mean time for diagnosing vasculitis is 2 months [6,7], but in certain cases the delay is much longer, up to 20 months. The time for diagnosis in this case is reasonable especially when considering the unusual presentation.

**METHODS**

With the aim of identifying additional cases of salivary gland involvement in WG and analyzing its impact on disease morbidity and outcome, we performed a MEDLINE (National Library of Medicine, Bethesda, MA) search for additional cases in adult patients reported in the literature. Search terms included “Wegener’s granulomatosis” and “parotitis,” “parotid gland,” “salivary glands,” “submandibular gland” or “sublingual gland.” The search was last performed in March 2012. Additional reports were obtained by checking the references from the selected studies, case reports and review articles. Publications included in our analysis were case reports of Wegener’s granulomatosis involving salivary glands. The initial search algorithm resulted in 65 potential publications of which 36 met our inclusion criteria and were included in our analysis. The following data were extracted from the selected papers: age, gender, symptoms at presentation, additional organ involvement, and outcome.

**RESULTS**

We found 42 cases (including this case report) of parotid involvement in WG [Table 1]. Epidemiological data were available for 39 patients, 60% men and 40% women, with a mean age of 52 years. The parotid gland was the most common salivary gland involved in WG (78%), followed by the submandibular (36%) and the sublingual gland (2.5%). Only three cases presented with isolated parotid gland involvement [27,28,33]. In most of the cases salivary gland enlargement was accompanied by other organ involvement such as upper respiratory (72%), lower respiratory (61%) and renal (47%). Analysis of the incidence of renal involvement in WG patients with salivary involvement by decades, since 1950, revealed a trend of decrease in renal involvement in the last decades [Figure 1]. A high frequency of neurological manifestations (hearing loss, nerve palsy, etc.) and specifically facial nerve palsy (44% and 17% respectively) were reported among the WG patients with parotid gland involvement. Data on patient survival were available for only 33 patients, and among them 6 deaths occurred (18%).

Among the 41 cases reported in the medical literature, 20 were published in ENT-related journals, 8 in general internal medicine, 9 in rheumatology, 2 in pathology and one in a radiology journal.

**DISCUSSION**

Parotid gland involvement is a rare manifestation of WG, with a reported incidence of 4% to <1% [7,31,33]. Among 85 patients with WG described by Fauci et al. [11] in 1983, only one patient had parotid gland involvement. But even though this presentation is rare, several cases of WG associated with salivary gland involvement have been reported [5,9,10,16]. Our MEDLINE search focused on the occurrence of parotid and other salivary gland involvement in WG. Besides our patient, we found 41 additional cases. A mild gender predilection (60% vs. 40% male/female ratio) was found in the patients in our analysis, slightly higher than the ratio reported in the literature [14]. The disease developed in the fourth or fifth decade of life, as described in the literature [39].

The parotid gland was the most common salivary gland involved, followed by the submandibular and the sublingual. Isolated parotid disease as the presenting symptom of WG is extremely rare. Our patient is the fifth patient reported [27,28,33,37], but of five cases three eventually developed upper or lower respiratory tract manifestations, indicating that isolated parotid involvement is rarely the sole manifestation of WG.

Upper respiratory and lower respiratory tract involvement was found in the majority of cases (72% and 61% respectively), but renal involvement was described in only 47%, rates lower than those described by Hoffman et al. [7] for 158 patients with WG, where 93% had upper respiratory involvement, 66% pulmonary involvement, and 77% renal failure [7]. Although the classic triad of WG (upper respiratory symptoms, lower respiratory symptoms, kidney vasculitis) is not always present at the time of the initial evaluation, approxi-
Table 1. Wegener’s granulomatosis with parotid involvement

<table>
<thead>
<tr>
<th>Case [Ref]</th>
<th>Journal</th>
<th>Year of publication</th>
<th>Age/gender</th>
<th>Salivary gland involvement</th>
<th>Presenting symptom</th>
<th>Renal disease</th>
<th>Other organ involvement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindsay et al. [8]</td>
<td>Am J Pathol</td>
<td>1944</td>
<td>67/F</td>
<td>+</td>
<td>ENT, lung</td>
<td>+</td>
<td>Parotitis (unilateral), eye, heart, pituitary</td>
<td>Died</td>
</tr>
<tr>
<td>Berman et al. [1]</td>
<td>Ann Intern Med</td>
<td>1963</td>
<td>34/M</td>
<td>+</td>
<td>Parotid &amp; submaxillary (bil), ENT, eye</td>
<td>+</td>
<td>Percard</td>
<td>Died</td>
</tr>
<tr>
<td>Murty et al. [18]</td>
<td>J Laryngol Otol</td>
<td>1990</td>
<td>23/M</td>
<td>+</td>
<td>ENT, arthralgia, submandibular (lt)</td>
<td>–</td>
<td>–</td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55/F</td>
<td>+</td>
<td>Parotid mass (lt), ENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specks et al. [19]</td>
<td>Arch Otol Head Neck Surg</td>
<td>1991</td>
<td>60/M</td>
<td>+</td>
<td>Submandibular (bil), lung, ENT, hearing loss (bil), prostate</td>
<td>–</td>
<td>–</td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64/M</td>
<td>+</td>
<td>ENT, submandibular (rt)</td>
<td>–</td>
<td>Scleritis</td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24/F</td>
<td>+</td>
<td>ENT, submandibular (rt)</td>
<td>–</td>
<td>Lung</td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27/M</td>
<td>+</td>
<td>ENT, parotid (rt)</td>
<td>–</td>
<td>–</td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75/F</td>
<td>+</td>
<td>Parotid (bil), lung</td>
<td>–</td>
<td>–</td>
<td>Remission</td>
</tr>
<tr>
<td>Benson-Mitchell et al. [21]</td>
<td>J Laryngol Otol</td>
<td>1993</td>
<td>34/F</td>
<td>+</td>
<td>Parotitis (unilateral) and arthralgia</td>
<td>–</td>
<td>–</td>
<td>Remission</td>
</tr>
<tr>
<td>Vanhaevert et al. [22]</td>
<td>Post Grad Med</td>
<td>1993</td>
<td>60/F</td>
<td>+</td>
<td>Submandibular (bil), ENT, eye, pancreatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh et al. [25]</td>
<td>Sarcoidosis Vasc Diff Lung Dis</td>
<td>1997</td>
<td>+</td>
<td></td>
<td>Parotitis</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Although the diagnosis was periarteritis nodosa, on reviewing the report it seems that the patient had WG. The lower incidence of renal involvement in our analysis suggests that these patients may be at a lower risk for development of renal disease. There may be several explanations for this finding: a) parotid involvement belongs more to a local or restricted disease phenotype than to a systemic one, b) parotid involvement may be an early feature of the disease which probably explains the sparing of the kidney on presentation [26], and c) since the parotid gland is a superficial and easily visible organ, it may serve as a marker for early disease evaluation and is more accessible for biopsy (with lower morbidity as compared to lung or kidney biopsy), hence promoting earlier diagnosis and treatment and preventing disease progression. Specks et al. [19] also recognized the lower morbidity and mortality associated with parotid involvement at presentation of WG and assumed that the earlier the patient receives treatment the lesser the likelihood of developing irreversible loss of organ function (early diagnosis and treatment may prevent the progression to systemic disease). In agreement with these speculations, our analysis of the incidence of renal involvement by decades revealed a trend of decrease in renal involvement in recent decades, probably reflecting earlier diagnosis and treatment [Figure 1].

On the other hand, biopsies from extra-pulmonary sites, such as the parotid gland, frequently show only non-specific inflammatory changes (as in our patient), and often an open lung biopsy is required to reach a definite diagnosis [16,17]. Devaney and co-authors [17] found that vasculitis, necrosis and granulomatosis were present in only 16% of all head and neck biopsies. Furthermore, interpretation of head and neck biopsies has a wide differential diagnosis, making the diagnosis even more
difficult [17]. Lustman et al. [23] reported similar results, with only 30% of parotid gland biopsies showing the presence of vasculitis.

An increased frequency of neuropathy, especially facial nerve palsy, was reported in the patients with parotid disease as compared to patients with typical WG (41% vs. 22%) [14]. The facial nerve involved was on the same side as the involved salivary gland in all cases that the side was mentioned, pointing to an anatomic connection between the two symptoms. A similar observation was reported by Yamamoto and team [36], who found facial neuropathy in 35% of patients with WG and parotitis.

Interestingly, half of all cases with WG and parotid involvement were reported in ENT journals, and one-quarter in internal medicine and in rheumatology journals each, illustrating the lack of awareness of this unusual presentation.

Although WG is considered an autoimmune disease, several authors have suggested a role for infection and specifically for S. aureus in disease development and in relapses [40]. Since S. aureus is an important etiological cause of parotid gland infections, it has been suggested that S. aureus phosphatase acts as an antigen and an initiator of autoimmune responses leading to vasculitis and glomerulonephritis [25]. The parotid involvement in WG reinforces the possible role of infections and specifically of S. aureus in this disease.

In summary, we present a patient and an analysis of an additional 41 cases of WG with parotid involvement. Our analysis demonstrates that parotitis can be the initial symptom of systemic WG and should be considered in the differential diagnosis of parotid disease. As such, titers of C-anti neutrophil cytoplasmic antibodies and anti-PR3 antibodies should be measured during the evaluation of parotid enlargement since early treatment and diagnosis may lower the risk for renal involvement.

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References


