ORIGINAL ARTICLE

Ear, Nose and Throat Manifestations of Wegener’s Granulomatosis (Granulomatosis With Polyangiitis)☆

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KEYWORDS
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Abstract
Introduction and objectives: Granulomatosis with polyangiitis (GPA), previously called Wegener’s granulomatosis, is a small vessel vasculitis often associated with clinical head and neck manifestations, which are sometimes the presenting symptoms of the disease. The aim of our study was to identify ear, nose and throat (ENT) manifestations associated with GPA and propose a work-up for the management and diagnosis for patients with suspicion or confirmed diagnosis of this ENT pathology.

Patients and methods: Retrospective review of the medical records of all patients diagnosed with GPA who were seen at the Department of Otolaryngology from a tertiary public hospital in Cantabria (Spain) over a 20-year period. Clinical and laboratory data, in particular those concerning ENT manifestations, were retrieved from the patients’ medical records.

Results: Twenty-five patients (age range: 30–81 years) were included in the study. Of these, 88% had ENT manifestations at some point in the course of the disease. In 28% of the cases, ENT features were the presenting manifestations. The most frequent ENT manifestations were sinonasal symptoms (52%), followed by otological manifestations (32%).

Conclusions: Patients with GPA often present with clinical ENT manifestations. Consequently, routine ENT physical examination must be performed in patients with suspected vasculitis to establish a diagnosis of GPA or to better determine the degree of organ system involvement in patients with GPA.

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Introduction

Granulomatosis with polyangiitis (GPA), previously known as Wegener’s granulomatosis (WG), is a systemic autoimmune disease of unknown aetiology characterised by necrotising granulomatous inflammation and vasculitis affecting mainly small blood vessels. The prevalence of GPA ranges between 3 cases per 100 000 inhabitants in the U.S.A. and 16 cases per 100 000 inhabitants in southern Sweden. A collaborative European study suggested that the incidence of GPA has a North–South gradient, with a higher incidence in Scandinavian countries and a relatively lower incidence in southern Europe. In this sense, an epidemiological study conducted in Galicia described an incidence of 2.95 new cases per 1 000 000 inhabitants/year, which is below that observed in other European countries such as Norway (12 per 1 000 000 inhabitants/year) and the UK (8.4 per 1 000 000 inhabitants/year).

The most common ages of presentation of GPA are the sixth and seventh decades of life, but it can appear at any age, with similar frequency between genders in adult age.

The clinical manifestations of GPA can be very heterogeneous, often affecting the upper respiratory tract, lungs and kidneys. Localised forms of the disease in the head and neck region are not exceptional.

The diagnosis of GPA is complex, contributing to a delay in its confirmation and start of treatment. This often results in significant sequelae secondary to tissue destruction in affected areas of the head and neck.

The aim of our study was to determine the head and neck manifestations appearing in GPA, with particular emphasis on their presentation forms, in order to contribute to early diagnosis of the disease, and to propose a protocol for ENT diagnostic evaluation in these patients.

Materials and Methods

We conducted a retrospective study including patients diagnosed with GPA at a public tertiary care hospital in the Region of Cantabria, between January 1991 and April 2011. We reviewed the medical records of patients and collected the main clinical data associated with head and neck involvement.

The diagnosis of GPA was based on the presence of suspicious clinical lesions (e.g. head and neck manifestations along with systemic manifestations) with histological confirmation of WG or positive antineutrophil antibodies (ANCA). The histopathological criteria of GPA include the presence of necrotising granulomatous inflammation in arterial vessel walls or in the perivascular or extravascular region.

We excluded from the study those patients with GPA who were not examined at an Otorhinolaryngology Service (ENT). These were generally patients referred from other geographical regions for histological confirmation by lung or kidney biopsy.

Results

We reviewed the medical records of 70 patients with granulomatosis or systemic vasculitis. We excluded 30 patients who suffered a disease other than GPA and 15 patients who had not been examined by an ENT specialist. Of the 25 patients who met the inclusion criteria, 16 were male (64%)...
and 9 were female (36%). Age at diagnosis ranged between 30 and 81 years with a mean of 57 years. In total, 88% of patients presented ENT manifestations during the course of their disease, with sinonasal manifestations being the most frequent (52%).

Table 1 summarises the ENT involvement found. The first manifestation of the disease was an ENT symptom or sign in 28% of patients. A total of 18 patients (72%) suffered pulmonary involvement and 10 (40%) suffered renal involvement during the course of the disease. Except for 1 patient who presented granulomatosis localised in the head and neck region manifested as a sinus condition, the rest presented systemic involvement. A total of 10 patients (40%) underwent head and neck biopsy of suspicious lesions, generally nasal (only 1 case underwent biopsy of the laryngeal subglottis). In 5 cases (50% of those conducted in this region and 20% of the total patients included in the study) head and neck biopsy confirmed the presence of the disease by revealing histological criteria consistent with GPA. The 5 positive cases were obtained from biopsies of nasal mucosa.

A total of 23 patients (92%) underwent an ANCA study (through indirect immunofluorescence or else by ELISA), with 19 positive (76%) and 4 negative cases (16%). Among the positive cases, 15 were positive for antiPR3 with a cytoplasmic pattern (cANCA) and 4 were positive for myeloperoxidase with a perinuclear pattern (pANCA). Of the 4 patients with negative ANCA, 1 case presented localised disease and the remainder suffered systemic involvement.

All patients were treated with immunosuppressants and corticosteroids by the Rheumatology Service and in collaboration with the Nephrology Service in cases of renal involvement.

In total, 4 patients (16%) required surgical treatment for their ENT condition associated with GPA, which had not responded to medical treatment. Of these, 2 underwent tracheotomy due to subglottic stenosis (decannulation was not attempted in either case, due to the severity of stenosis, advanced age and/or general condition), 2 cases underwent tympanic tube placement (including the patient with subglottic stenosis) and another patient underwent dacryocystorhinostomy due to lachrymal-nasal duct obstruction. None of these patients presented postoperative complications.

One patient treated with cyclophosphamide and corticosteroids developed a nasopharyngeal carcinoma 3 years after diagnosis of GPA. This was treated with concomitant chemotherapy and radiotherapy and the patient is currently disease-free (2 years after diagnosis).

**Discussion**

GPA characteristically affects the upper respiratory tract, although the lower respiratory tract and kidneys are also frequently involved, completing the classic triad of this disease. Pulmonary involvement ranges from asymptomatic pulmonary nodules to pulmonary infiltrates and fulminating alveolar haemorrhage. The most common renal involvement is necrotising segmental glomerulonephritis, although proliferative glomerulonephritis is also frequently present. Renal manifestations may be present at the time of diagnosis in 18% of patients, although patients may develop renal involvement throughout their evolution.

GPA can also affect various other organs, resulting in articular, cutaneous (palpable purpura, ulcers, subcutaneous nodules) or neurological (mononeuritis multiplex, peripheral neuropathy, meningitis) symptoms and constitutional syndrome (fever, asthenia, anorexia and weight loss).

The presence of ENT involvement in patients with GPA ranges between 72.3% and 99% of cases depending on the performance or not of systematic head and neck studies upon suspicion or diagnosis of disease, as well as periodic reassessment of new outbreaks. These figures are similar to that found in the present study, despite its retrospective nature, which was 88%.

Although in our work ENT manifestations were the first symptom of the disease in 28% of cases, in other series these manifestations were the first symptom of the disease in between 63% and 72% of cases.

The fact that our study was retrospective coupled with the absence of a standardised study protocol for these patients in our service may have underestimated the true incidence of ENT manifestations of the disease. Moreover, since the course of this clinical entity is marked by frequent outbreaks, patients generally alternate silent phases in which there are no ENT manifestations, with phases of activity, and hence the importance of finding ENT symptoms in the previous history which may have disappeared spontaneously or after treatment.

Otolological manifestations appear in between 6% and 56% of patients with GPA. The most frequent are middle ear lesions, especially serous otitis. Acute otitis media
or chronic otitis media, which develop as a result of the presence of granulation tissue affecting the Eustachian tube, middle ear or nasopharynx, are less frequent.\textsuperscript{19} Facial paralysis, including bilateral cases, can also appear associated with the presence of otomastoiditis.\textsuperscript{20} Some GPA patients may present sensorineural or mixed hearing loss.\textsuperscript{13} Although hearing loss is usually described as having rapid onset, progressing over days or weeks and being compatible with the profile of typical autoimmune hearing loss, the 3 cases in our study who developed it suffered a slowly progressive evolution. In fact, we cannot rule out that their hearing loss was related to other environmental factors and neither can we confirm that sensorineural hearing loss in these patients had a true connection with GPA. It is postulated that sensorineural hearing loss is associated with the development of vasculitis affecting irrigation of the cochlea or by deposition of immune complexes within it.\textsuperscript{18,19} On the other hand, manifestations affecting the outer ear are exceptional, although there have been reports of auricular chondritis similar to those in recurrent polychnondritis.\textsuperscript{18}

Sinonasal manifestations are the most frequent in the head and neck region as shown in our study, in which 52\% of patients developed sinonasal symptoms. Typically, patients refer non-specific symptoms such as nasal dryness, purulent rhinorrhea, epistaxis, pain, smell disorders and nasal obstruction. Physical examination usually reveals the presence of nasal crusts and, occasionally, perforation of the anterior nasal septum. These lesions are often caused by vasculitis of the Kiesselbach area. The sequela known as "saddle nose" may occur in advanced stages as a result of extensive necrosis of the septal cartilage area.\textsuperscript{21} The appearance of chronic sinusitis due to obstruction of the drainage ostium is also a frequent.\textsuperscript{18}

Up to 8\% of patients may develop a retroorbital tumour, sometimes by extension of sinus lesions or else by the appearance of primary granulation tissue in that area.\textsuperscript{13} In 2\% of patients, GPA may initially appear as secondary proptosis.\textsuperscript{15} However, none of the patients in our series developed orbital disease.

Oral manifestations are rare in GPA, with "strawberry" gingival hyperplasia being the most characteristic in this disease.\textsuperscript{12} This finding was only observed in 1 patient in our study and represented one of the manifestations observed at the time of diagnosis of the disease which disappeared completely after medical treatment with immunosuppressants. Deep oral ulcers can also appear in the oropharynx or oral cavity (buccal mucosa, gums and tongue), and there were 2 cases in our series. Hypertrophy of the parotid and submandibular glands is very rare.\textsuperscript{22} There has been 1 case report of submandibular gland hypertrophy as the only manifestation of GPA.\textsuperscript{11}

Laryngotracheal manifestations are rare, with subglottic stenosis being the most common. These appear in 8\%–23\% of patients throughout their evolution, representing the first manifestation of the disease in between 1\% and 6\% of cases (4\% in our series).\textsuperscript{22} It is more common when the diagnosis of GPA takes place before 20 years of age.\textsuperscript{13} Patients with subglottic or tracheal stenosis may be asymptomatic in initial phases of the disease or suffer dyspnoea with exercise, but sometimes they may eventually develop acute respiratory obstruction.\textsuperscript{14} Between 22\% and 44\% of patients with subglottic stenosis suffer concomitant bronchial stenosis.\textsuperscript{12} In some cases, subglottic stenosis represents the only manifestation of the disease, as was the case in 1 of our patients, who debuted at 70 years of age with subglottic stenosis which required urgent tracheotomy.

Pharyngeal manifestations are exceptional in GPA. There has only been 1 case report of retropharyngeal tumour as initial manifestation of the disease.\textsuperscript{25} In our study we found 1 case of asymptomatic non-obstructive pharyngeal tumour.

The diagnosis of GPA is performed based on suggestive clinical symptoms (head and neck manifestations, characteristics associated with pulmonary and/or renal involvement), and is confirmed by a compatible histological study including: presence of small vessel vasculitis and necrotising granulomatous inflammation with giant multinucleated cells. These may occur together or in isolation. The presence of positive ANCA may contribute to the diagnosis in histologically dubious cases.

ANCA are antibodies whose target are the 2 main components of neutrophil granulocytes: PR3 serine and myeloperoxidase. Anti-PR3 antibodies are virtually pathognomonic for WG, while anti-myeloperoxidase antibodies are more suggestive of other necrotising primary vasculitis, mainly in microscopic polyangiitis.\textsuperscript{26} There are 2 types of tests to detect ANCA: immunofluorescence or ELISA (enzyme-linked immunosorbent assay). Immunofluorescence distinguishes between anti-PR3 and anti-myeloperoxidase based on staining pattern: the first are associated with cANCA and the second with pANCA.\textsuperscript{14} Detection through ELISA (presence of anti-PR3 or else anti-myeloperoxidase) provides greater specificity. However, when both methods are combined, the sensitivity and specificity for the diagnosis of GPA increase up to 90\% and 98\%, respectively.\textsuperscript{27} Up to 10\% of patients with GPA present a perinuclear pattern in immunofluorescence assays and up to 20\% of patients with active, untreated GPA present negative ANCA. This percentage increases up to 30\% in localised forms of the disease.\textsuperscript{15,18} In patients with suggestive clinical histories and negative cANCA tests, conducting serial serology studies may eventually demonstrate positive cANCA.\textsuperscript{18}

Biopsies of sinonasal lesions represent the best possibility for diagnosis in the head and neck region since they enable extensive sampling (generally, samples over 5 mm are required), thus facilitating the detection of histologically compatible lesions.\textsuperscript{28} Biopsy of granulation tissue in the middle ear is rarely diagnostic because of the limited amount of sample taken for diagnosis, except for those performed in the context of mastoidectomy. Subglottic biopsies are not very sensitive since it is also difficult to obtain large samples without causing subsequent scarring sequelae. In our study, 50\% of the samples obtained confirmed the presence of histological lesions compatible with GPA, all of them from the nasal mucosa.

Conducting complementary tests, such as sinus radiology, is useful in the initial ENT examination since some patients present sinus granulation tissue in the absence of symptoms. Performing tone audiometry is also useful in the initial evaluation of patients with GPA or suspected of it, since the development of bilateral sensorineural hearing loss throughout the evolution of the disease is not uncommon, as mentioned previously.\textsuperscript{13}
Performing computerised tomography (CT) or magnetic resonance imaging (MRI) may be indicated in some patients according to location of involvement and clinical manifestations. The most common findings on CT scans of the paranasal sinuses and fossae are the presence of mucosal oedema with bone destruction foci in the paranasal sinuses (Fig. 1), as well as foci of sclerosing osteitis and bone thickening in the same location.29 In severe subglottic/tracheal stenosis CT and MRI scans may also help to evaluate the characteristics of lesions. These tests are also indicated in patients with ear involvement who are unresponsive to treatment or in cases of facial paralysis.

Table 2 proposes a diagnostic protocol which we believe is useful in the initial assessment of patients with suspected or confirmed diagnosis of GPA.

In general, head and neck manifestations of patients with GPA usually respond well to immunosuppressive therapy (cyclophosphamide or methotrexate) associated with glucocorticoids for several months in phases of disease activity. Subsequently, patients require maintenance therapy in quiescent phases, with methotrexate and azathioprine being useful, as well as frequent boluses of glucocorticoids to control reactivations.18 Monoclonal antibodies against CD20 (rituximab) can also be useful.30

Surgical treatment does not change the course of the disease, but it can contribute to ameliorate the consequences of tissue destruction in the head and neck region. Caution should be exercised before conducting surgical indications in reactivation phases of the disease which may subsequently lead to greater sequelae. In our study, 5 patients required surgical treatment due to disease-related sequelae. Two patients underwent placement of trsympanic ventilation tubes without further complications, 1 patient underwent dacrocystorhinostomy and 2 patients underwent tracheotomy due to subglottic stenosis.

Generally, surgical treatment is not recommended in cases of septal perforation. However, “saddle nose” can be operated in the remission phase with good results.21

Subglottic stenosis only responds to medical treatment in 20% of patients, with the rest requiring surgical treatment, either tracheostomy, dilation with steroid injection, laser surgery or, in severe cases, laryngotracheoplasty.23 In our series, patients who suffered subglottic stenosis underwent tracheotomy exclusively due to severe airway obstruction, with decannulation not being attempted due to their advanced age.

There have been reports of malignant tumours appearing in patients with GPA treated with cyclophosphamide.31 One patient in our series developed a malignant nasopharyngeal tumour. We do not know if it could have been related to the medication.

<table>
<thead>
<tr>
<th>Type of examination</th>
<th>Involvement to be ruled out or indicated study</th>
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<tbody>
<tr>
<td>External examination</td>
<td>“Saddle nose”, parotid or submandibular gland hypertrophy</td>
</tr>
<tr>
<td>Otoscopy</td>
<td>Serous otitis/COM/granulation tissue in middle ear</td>
</tr>
<tr>
<td>Anterior rhinoscopy/nasal endoscopy</td>
<td>Nasal crusts/septal perforation/granulomatous tissue/sinusopathy</td>
</tr>
<tr>
<td>Exploration of oral cavity/oropharynx</td>
<td>“Strawberry” gingivitis, deep ulcers</td>
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<tr>
<td>Neck exploration</td>
<td>Parotid/submaxillary gland hypertrophy</td>
</tr>
<tr>
<td>Laryngotracheal exploration</td>
<td>Subglottic/tracheal stenosis</td>
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<tr>
<td>Radiography of sinuses</td>
<td>Sinusopathy</td>
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<tr>
<td>Tone audiometry</td>
<td>Conductive/mixed/sensorineural hypoacusis</td>
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<tr>
<td>Flow/volume curves</td>
<td>Laryngeal/tracheal stenosis</td>
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<tr>
<td>CT/MRI ear/sinonasal/larynx/trachea</td>
<td>Selected cases according to suspicion or location of granulomatous tissue/preoperative evaluation of head</td>
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<td>Biopsy of sinonasal/ear/subglottic granulomatous tissue</td>
<td>In non-confirmed GPA cases</td>
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COM, chronic otitis media; CT, computed tomography; GPA, granulomatosis with polyangiitis; MRI, magnetic resonance imaging.
Conclusions

Patients with GPA often present head and neck manifestations. It is important to perform a systematic ENT exploration of patients with suspected or confirmed diagnosis of GPA in order to contribute to an early diagnosis of these manifestations so as to prevent secondary complications which would worsen the quality of life of these patients.

Conflict of Interests

The authors have no conflicts of interest to declare.

References