REVIEW ARTICLE

Otolaryngologic Manifestations of Systemic Vasculitis

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Received 19 July 2011; accepted 30 September 2011

KEYWORDS
Systemic vasculitis; ENT manifestations; Wegener granulomatosis

Abstract Systemic vasculitis is a heterogeneous group of diseases of various aetiologies and manifestations. In general, the clinical results derive from ischemia caused by vascular inflammation, which depends on the organ affected. Such vasculitis cases are classified according to the classification of the Chapel Hill conference. They can present with relative frequency as ENT manifestations in both their debut and throughout their evolution. Consequently, the ENT specialist should include them in the differential diagnosis in patients with ENT manifestations that are difficult to control or of atypical presentation. Our objective was to review the most common ENT clinical signs and symptoms in each of these diseases.

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PALABRAS CLAVE
Vasculitis sistémicas; Manifestaciones otorrinolaringológicas; Granulomatosis de Wegener

Manifestaciones otorrinolaringológicas de las vasculitis sistémicas

Resumen Las vasculitis sistémicas son un grupo muy heterogéneo de enfermedades de diversas etiologías y manifestaciones. En general, la clínica se deriva de la isquemia producida por la inflamación vascular de la cual depende el órgano afecto. Se clasifican según el consenso de la conferencia de Chapel Hill. Se pueden presentar con relativa frecuencia como manifestaciones otorrinolaringológicas tanto en su debut como a lo largo de su evolución, por lo tanto deben incluirse en el diagnóstico diferencial del especialista en otorrinolaringología en pacientes de difícil control o presentación atípica de manifestaciones ORL. Es nuestra intención revisar la clínica otorrinolaringológica más frecuente en cada una de estas enfermedades.

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Introduction

Systemic vasculitis comprises a heterogeneous group of diseases with varied aetiologies and clinical manifestations which often overlap, making their differentiation very complicated. The common feature to all cases is inflammation of the lining of blood vessels, causing occlusion of the lumen.
and, consequently, tissue necrosis and ischemic phenomena. This, in turn, results in a deterioration of the function of the affected organ.\(^1\)

Numerous pathogenic mechanisms have been described, including immunocomplex-mediated vascular damage, production of antineutrophil cytoplasmic antibody (ANCA), anti-endothelial cell antibodies, cellular immunity, etc. Often, these mechanisms coexist.

Clinical manifestations may be varied, depending on the size, number and type of affected vessels and the organs involved. Most patients present obvious constitutional symptoms, such as weakness, fever, and weight loss, which are associated with others such as limb pain in cases of peripheral neuropathy, arthralgia or arthritis in cases of musculoskeletal involvement, abdominal pain or even visceral perforation in cases of gastrointestinal involvement or different types of elementary lesions in cases of skin involvement. Patients often present otolaryngological (ENT) clinical manifestations which, occasionally, are the initial symptoms. Therefore, it is important for ENT specialists to become familiar with these diseases.

In this review we have carried out a description of the ENT symptoms of the most common types of vasculitis, thus complementing a previous review in this publication of audiovestibular manifestations in cases of systemic vasculitis.\(^2\)

**Classification of Vasculitis**

There are numerous possible classifications of vasculitis. For example, from the standpoint of their aetiology they are classified into primary or secondary, depending on whether they appear in isolation or as part of another condition (systemic lupus erythematosus, rheumatoid arthritis, infections, drugs, etc.). However, from the practical standpoint, the most widely used classification is the so-called Chapel Hill classification, published in 1992, which is based on the size of the affected vessels (Table 1). This gives rise to characteristic clinical manifestations, not only from the general point of view, but also from standpoint of ENT (Table 2).

Moreover, in 1990, the American College of Rheumatology (ACR) developed a set of classification criteria for systemic vasculitis. These were intended to standardise clinical definitions for epidemiological and therapeutic use, rather than for diagnosis, but they are sometimes used for this purpose.

**Presentation Forms According to the Type of Vasculitis**

**Large Vessel Vasculitis**

**Giant Cell Arteritis (Temporal Arteritis)**

This type of vasculitis is common in our environment, with an annual incidence around 12/100000 population, mainly in subjects aged over 50 years and predominantly in females.\(^3\)

It mainly affects the branches of the extracranial carotid artery, and 2 out of 3 patients suffer headache at the beginning of the disease. In general it is a headache of recent onset which, if the patient has a previous history of headache, is reported as having different characteristics from the usual. It is generally located in the temporal region, but may also appear in the frontal and occipital regions, so a differential diagnosis with ENT pathologies should be conducted. Half of patients suffer jaw claudication, characterised by rapid onset from the start of mastication. Sometimes, patients downplay this symptom, so it must be searched for explicitly.

Jaw claudication was the most specific symptom of giant cell arteritis (GCA) in a study which correlated positive biopsies with clinical symptoms.\(^4\) Of a total of 134 patients who underwent biopsy, jaw claudication was present in 54% of those who tested positive, compared with only 3% of those whose biopsies were negative.

Approximately 10% of patients with GCA present symptoms related to the upper respiratory tract. In particular, non-productive cough is a common symptom which can lead to diagnostic confusion.\(^5\) It is believed to be an effect of vasculitis on cough receptors, which are found throughout the respiratory tree.

Other symptoms are lingual pain or lingual infarction (Fig. 1),\(^6,7\) odynophagia,\(^6,7\) sensorineural hearing loss,\(^8\) vestibular dysfunction, benign peripheral positional vertigo (BPPV) of ischemic origin, smell alterations and even pain, swelling, redness and necrosis of the face or scalp (Fig. 2), oral mucosa and/or nose.

It was observed that, out of 44 patients with GCA who were monitored for 2 years, 20 developed BPPV, with the majority associating nystagmus, compared with 2.3% out of the healthy population.\(^9\)

Loss of vision due to optic nerve ischemia is among the most important complications. About 50% of patients present polymyalgia rheumatica.

**Table 1** Classification of Systemic Vasculitis According to the Size of the Affected Vessels.

<table>
<thead>
<tr>
<th>Primary vasculitis</th>
<th>Large vessel vasculitis</th>
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<tbody>
<tr>
<td></td>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td></td>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td></td>
<td>Cogan syndrome</td>
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<tr>
<td>Medium vessel vasculitis</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
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<tr>
<td>Small vessel vasculitis</td>
<td>Mediated by immunocomplexes:</td>
</tr>
<tr>
<td></td>
<td>• Cutaneous leukocytoclastic vasculitis</td>
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<tr>
<td></td>
<td>• Schönlein–Henoch purpura</td>
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<tr>
<td></td>
<td>• Essential cryoglobulinemia</td>
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<tr>
<td></td>
<td>• Associated to ANCA:</td>
</tr>
<tr>
<td></td>
<td>• Wegener’s granulomatosis</td>
</tr>
<tr>
<td></td>
<td>• Microscopic polyangiitis</td>
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<tr>
<td></td>
<td>• Churg-Strauss syndrome</td>
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</tbody>
</table>

**Secondary vasculitis**

- Connective tissue diseases (rheumatoid vasculitis, lupus erythematosus, Sjögren syndrome and inflammatory myopathies)
- Paraneoplastic
- Infections
- Intestinal inflammatory disease
- Drugs
Table 2  Clinical and Diagnostic Characteristics of Systemic Vasculitis.

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Symptoms</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis</td>
<td>Differences in arterial pressure. Absent or decreased pulse in limbs. Arterial hypertension.</td>
<td>Pathological arteriography.</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Arthralgia, intermittent purpura in lower limbs. Renal involvement, sensitive peripheral neuropathy. Pulmonary (asthma, haemoptysis) and CNS involvement.</td>
<td>Cryoglobulins in blood. Skin biopsy. Hypocomplementemia. Determination of HCV or HBV.</td>
</tr>
</tbody>
</table>

ANCA: antineutrophil cytoplasmic antibodies; CNS: central nervous system; ESR: erythrocyte sedimentation rate; HBV: hepatitis B virus; HCV: hepatitis C virus.
According to the ACR classification, its diagnosis requires at least 3 of the following 5 criteria: age over 50 years, characteristic headache, temporal artery alterations, elevated ESR and compatible biopsy of the temporal artery.

**Takayasu Arteritis**

Takayasu arteritis (TA) is a rare vasculitis in our environment, with only 1–3 cases per million population each year. It mainly affects women younger than 40 years, and usually damages the aorta and its major branches.

There have been reports in the literature of patients with ENT manifestations. These appear especially with symptoms of sinusitis, such as persistent localised headache and purulent rhinorrhea. In most cases, findings are incidental and are revealed after an imaging study, whose result shows the sinus involvement.

The has been one report of confirmed TA in which the presence of vasculitis was correlated with the nasal deformity known as ‘saddle nose’. The finding of differences in blood pressure in both arms, decreased brachial artery pulse or a pathological arteriography (Fig. 3) are useful for its diagnosis.

**Medium Vessel Vasculitis**

**Polyarteritis Nodosa**

The prevalence of this type of vasculitis is currently declining (its incidence in Spain is 1 case per million population). It is occasionally associated to infection by hepatitis B virus (HBV) and, more rarely, by hepatitis C virus (HCV). The otorhinological condition of polyarteritis nodosa (PAN) is relatively common, since it appears in up to 30% of cases.

PAN may affect the middle ear; the main symptom is hearing loss, which may be conductive or sensory. Facial paralysis may be associated with loss of hearing. Based on the foregoing, PAN should be included in the differential diagnosis of patients with otic disease which is difficult to control.

The main diagnostic test is to obtain histological material which confirms vasculitis or, in its absence and in an appropriate clinical setting, a pathological arteriography (aneurysms, usually of small size). The presence of subcutaneous nodules or livedo reticularis in the limbs, especially the lower ones (Fig. 4), may guide the diagnosis.

**Kawasaki Disease**

This type of vasculitis has a very low prevalence and mainly affects children. Classically, the disease is characterised by the appearance of erythema and fissures in the lips and oral mucosa, leading to a characteristic image of ‘strawberry tongue’, caused by the detachment of the filiform papillae. The appearance of oral lesions such as vesicles or ulcers and tonsillar exudate is also common.

Between 50% and 70% of cases present cervical lymphadenopathies which tend to involve all the anterior cervical lymph nodes covering the sternocleidomastoid muscle. About 35% of patients report cough and rhinorrhea.

In a retrospective series, Yoskovitch et al. collected the ENT manifestations of 155 patients with Kawasaki disease (KD). The totality of patients (100%) presented changes in the oral mucosa and "strawberry tongue", 97% suffered pharyngitis, 65% cervical lymphadenopathies, 29% rhinitis, 15% otitis media and less than 1% presented epiglottitis, trismus and external otitis.
Otolaryngologic Manifestations of Systemic Vasculitis

Figure 4  Livedo reticularis in a patient with polyarteritis nodosa.

Other manifestations of this disease include mastoiditis, glossitis, airway obstruction, retropharyngeal and parapharyngeal abscesses, external otitis, supraglottitis, sialadenitis and facial nerve palsy.

In addition to the classical ones, KD may be manifested through a wide variety of symptoms including diarrhoea, hepatomegaly, jaundice, arthritis, myocarditis, pericarditis, etc.

Diagnosis should be based on the presence of a number of criteria: fever, rash, scaling and erythema multiforme in the limbs, bilateral conjunctival injection, cervical lymphadenopathies, and changes in the oral mucosa.

Small Vessel Vasculitis

This group includes 3 entities with a characteristic serological marker: ANCA. This marker may appear in different percentages, depending on each variety. In addition to its role in the pathophysiology of the disease, it is essential due to its importance during diagnosis and monitoring.

Wegener’s Granulomatosis

This is an idiopathic systemic vasculitis characterised by the formation of necrotising granulomas which are sometimes accompanied by small-vessel vasculitis, leading to the classic triad of kidney and upper and lower airway involvement. Its incidence in our environment is 3 cases per million population.13

There are limited forms of the disease, with clinical findings located in the upper airways or lungs in about a quarter of patients, although most of these patients (up to 80%) subsequently develop systemic involvement.

Both Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) may present ENT symptoms, although they are far more common in the former than in the latter, 90% versus 35% of cases.

In most cases, the disease debuts with an involvement of the upper respiratory tract which does not improve with the usual treatments and becomes the reason for patient referral to ENT consultation. Hence, the importance of a rapid and correct diagnosis and treatment by the otolaryngologist, in order to prevent the natural progression of the disease.13

This entity should be taken into account in all cases of repeated sinusitis, otitis media or rhinitis which do not improve with treatment. Nevertheless, it may also debut as repeated epistaxis, nasal ulcers, septal perforations and ”saddle nose” deformities (Fig. 5). Furthermore, up to 25% of cases may present subglottic stenosis.24

Separating by organs, the most representative ENT manifestations in WG are:

External Ear. The disease rarely affects the outer ear. External otitis may appear in the context of chronic otitis media and it rarely occurs in isolation. Auricular chondritis can sometimes appear along with oedema, erythema and pain, in a similar manner to relapsing polychondritis.

Middle Ear. Otitis media with effusion is the most common otological manifestation of WG. It is the result of a dysfunction of the Eustachian tube, derived from granulomatous involvement of the nasopharynx, nasal cavity or the Eustachian tube itself. Chronic otitis media with effusion may be complicated by contiguity with mastoiditis and this is associated with facial nerve palsy in up to 8%–10% of cases.25

Inner Ear. After renal failure, sensorineural hearing loss is the most common long-term morbidity in these patients (affecting 35% of patients).26 Hearing loss may develop quickly or gradually, over several days or weeks. Sensorineural hearing loss has been postulated as the result of vasculitic involvement of the cochlear blood supply or deposition of immunocomplexes within the cochlea. Surprisingly, vertigo is exceptional.25,26

Nose. Patients with WG may present nonspecific symptoms, such as nasal congestion, rhinorrhea and anosmia,
which may be misinterpreted as nasal allergies or viral infections of the upper respiratory tract. They may develop rhinitis, sinusitis (Fig. 6), septal perforation or stenosis of the nasal airway. A nasal examination may reveal ‘‘cobblestone mucosa’’, oedema and formation of crusts. 27 The anterior nasal septum, within the vascular convergence region known as the Kiesselbach area, is one of the most commonly affected regions.

Patients with advanced disease may present scarred areas in the nasal mucosa or erosion of the turbinates and septum. In cases where a septal perforation progresses substantially, the structural framework of the nose may become compromised, leading to nasal deformity and even to total nasal collapse. 27

Oral Cavity and Salivary Glands. Oral involvement is relatively rare, although a classic type of presentation is ‘‘strawberry’’ gingival hyperplasia (Fig. 7). 28 There may be ulcerations of the oropharyngeal mucosa. Involvement of the parotid and submandibular glands is infrequent. 28 Larynx and Trachea. Unlike most other ENT manifestations of WG, laryngeal and tracheal symptoms may become fatal if left untreated. Subglottic and tracheal stenosis is present in approximately 16% of patients. The most common symptom is progressive breathing difficulty, although patients may also present acute stridor, requiring urgent tracheostomy. 29 Subglottic stenosis is 5 times more common among children. 28

According to ACR criteria, in order to diagnose WG, a patient must show at least 2 of these 4 criteria: nasal or oral inflammation, altered chest radiograph, altered urinary sediment and granulomatous inflammation visualised in a biopsy. However, these criteria did not take ANCA into account. Their presence, especially the cytoplasmic type (c-ANCA) and with anti-proteinase 3 (PR3) specificity, in a patient with compatible clinical symptoms has a sensitivity of 85% and a specificity of 98%. 30 Nevertheless, in patients with limited forms, the prevalence of ANCA (+) may be as low as 60% in cases limited to ENT manifestations.

Sinusal biopsy is the best option when a biopsy is required for the diagnosis of WG and there is ENT involvement. 30

Churg–Strauss Syndrome

This type of vasculitis occurs in patients between the second and fourth decades of life and has a prevalence in our environment of 1.3 cases per million population. 19 It is often associated with eosinophilia, bronchial asthma and allergic rhinitis. The typical presentation is in the form of migratory infiltrates, unlike WG which presents fixed infiltrates which usually cavitate (Fig. 8).

ENT symptoms are frequent in Churg–Strauss syndrome (CSS), the most common being paranasal sinus and nasal involvement, appearing with nasal obstruction, recurrent sinusitis and nasal polyposis. In a series of 29 patients with this disease, nasal polyposis was detected in 60% of them. 31

Chronic serous otitis media and sensorineural hearing loss appear occasionally and may be reflective of the severity of rhinosinusitis. 32, 33

Classification requires the presence of at least 4 of these 6 criteria: asthma, eosinophilia, neuropathy, migratory pulmonary infiltrates, involvement of the paranasal sinuses and the finding of extravascular eosinophils in a histological sample.

In other types of vasculitis, such as essential mixed cryoglobulinemia and cutaneous hypersensitivity vasculitis, sensorineural hearing loss is the main ENT symptom, appearing in up to 22% of cases of the former.

Cogan Syndrome

Although it is not a form of vasculitis, this syndrome may appear as such throughout its development. It is a rare, inflammatory and autoimmune entity, which predominantly affects young adults. Ocular involvement (in 50% of cases), especially in the form of interstitial keratitis (Fig. 9) and otopathological involvement (in 30% of cases) are typical, with both coinciding in 15% of cases. It may give rise to systemic manifestations, such as abdominal pain, diarrhoea, peripheral neuropathy, vasculitis or heart failure.

The inner ear manifestations of Cogan syndrome (CS) may appear as a Meniere’s crisis in the form of vertigo, ataxia, nausea, vomiting, tinnitus, and hearing loss. 34 Vestibular dysfunction may also cause oscillopsia, which consists of the perception of objects swaying back and forth abruptly after turning the head sideways. Frequently repeated involvement of the inner ear may lead to profound hearing loss.
Figure 8  Multiple cavitated pulmonary nodules in a patient with Wegener’s granulomatosis.

In a retrospective series of 60 patients, hearing loss was typically sudden, bilateral, fluctuating and progressive, leading to complete hearing loss in 73 of the 120 ears. Hearing loss in both ears was reported at some point in all patients. Two, smaller studies found bilateral hearing loss in approximately two thirds of patients. Recurrent episodes of the disease may also lead to cochlear hydrops.

Diagnosis is based on symptoms, requiring only ocular and inner ear involvement.

Figure 9  Interstitial keratitis in a patient with Cogan syndrome.

Conclusions

Vasculitis includes a group of diseases which may appear with otolaryngological manifestations with relative frequency, both in their debut and during their evolution. Therefore, they should be considered by ENT specialists during the differential diagnosis of patients suffering ENT manifestations which are atypical or difficult to control.

Conflict of Interests

The authors have no conflicts of interest to declare.

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