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Review

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Ear, nose, and throat in ANCA-associated vasculitis: a comprehensive review

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Abstract

Ear, nose, and throat (ENT) involvement is a common feature in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), particularly in granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Over the last decade, substantial advancement has been made in understanding AAV pathogenesis, classification, and treatment. Typical ENT symptoms may include sinonasal, otologic, pharyngeal, and laryngeal manifestations. The otolaryngologic symptoms of AAV sometimes might be misdiagnosed in etiology as infectious or allergic. Thus, rapid recognition and early diagnosis of AAV as the cause of the symptoms prevent the risk of irreversible organ damage. The high impact of ENT symptoms on the quality of life of AAV patients confirms the importance of their early treatment through specific local and systemic approaches. Appropriate interdisciplinary management to early recognition of AAV and initiation of treatment may reduce morbidity in these patients. The purpose of this comprehensive review is to describe the clinical, histological, and radiological findings of ENT involvement in AAV and to update their surgical and therapeutic management, with a focus also on the role of a multidisciplinary team, involving the otorhinolaryngologist.

Keywords: Antineutrophil cytoplasmic antibody, ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, ear, nose, throat

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of multi-system autoimmune disorders, characterized by inflammation of small - to medium-sized vessels, endothelial injury, and tissue damage. According to the 2012 revised Chapel Hill Consensus Conference nomenclature of vasculitides and the American College of Rheumatology (1990) classification criteria[1,2], AAV are classified into three distinct disease phenotypes: granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).

Autoimmunity is documented by serum antibodies targeting cytoplasmic component of neutrophils, specifically proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA), due to loss of tolerance to neutrophil primary granule proteins[3]. ANCAs appear more closely associated with a vasculitic inflammation[4,5], while granulomatous phenotype is predominantly linked to ANCA-negative serology and localized disease[6,7].

Any organ or tissue may be involved in AAV, with clinical presentation ranging from severe organ-threatening or life-threatening disease to less severe presentation or organ-limited manifestations[8]. GPA and MPA commonly affect the upper respiratory tract, lungs, and kidneys, often at the same time, while EGPA is characterized by asthma, hyper-eosinophilia, and heart and peripheral nervous system involvement[9]. However, EGPA is characterized by two different subsets, reflecting distinct underlying pathogeneses: a predominant "vasculitic phenotype" closely associated to ANCA and an "eosinophilic phenotype", which is interleukin-5 (IL-5) driven[10].

Ear, nose, and throat (ENT) represent some of the most common sites of AAV manifestations, more often in GPA and EGPA, which generally precedes pulmonary or renal involvement. Although patients with ENT symptoms have better survival[7,11] and less renal involvement[7,12], they typically present a relapsing disease[13].

Typical ENT symptoms may include sinonasal, otologic, pharyngeal, and laryngeal manifestations [Figure 1]. Up to 95% of GPA patients show evidence of head and neck features and 85% have evidence of nasal or sinus problems[7,14]. In EGPA, head and neck manifestations could occur in 48%-96% of the cases at diagnosis[15,16]. Finally, involvement of head and neck organs in MPA is less common, being reported in 20%-30% of the patients[17].

The otolaryngologic symptoms of GPA sometimes might be misdiagnosed in etiology as infectious or allergic. Thus, rapid recognition and early diagnosis of AAV as the cause of the symptoms prevent the risk of irreversible organ damage. Appropriate interdisciplinary management for early recognition of AAV and initiation of treatment may reduce morbidity in these patients.

The purpose of this comprehensive review is to describe the clinical, histological, and radiological features of ENT involvement in AAV and to update their surgical and therapeutic management, with a focus also on the role of a multidisciplinary team, involving the otorhinolaryngologist.

SINONASAL MANIFESTATIONS

The most frequently observed ENT manifestation of GPA is sinonasal involvement, being present in 60%-85% of patients[7,18]. One of the first manifestations is nasal blockage, in association with hyposmia or anosmia when mucosal swelling occurs[19]. Purulent nasal drainage associated with the growth of

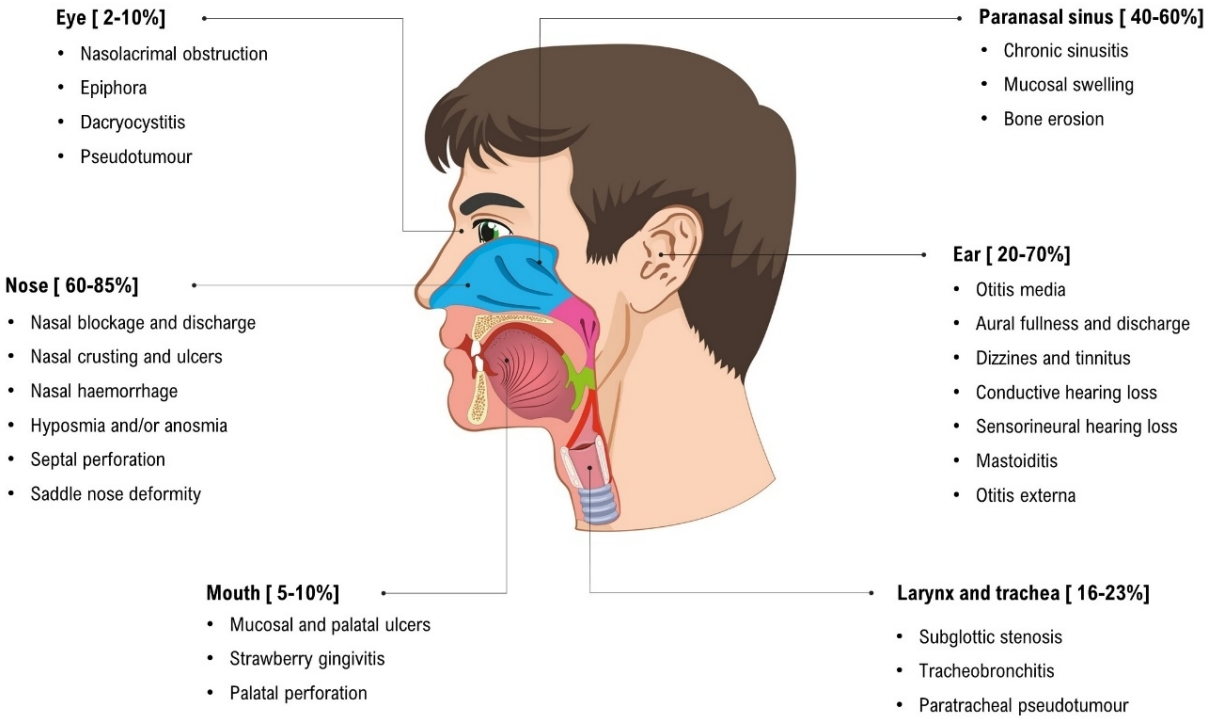

Figure 1. Ear, nose, and throat features in granulomatosis with polyangiitis according to the anatomical region and frequency of involvement.

Staphylococcus aureus or *Pseudomonas aeruginosa* can cause cacosmia. Epiphora may present as a sign of nasolacrimal duct and lacrimal sac involvement, as a result of granulomatous involvement, infection, or compression caused by mucosal inflammation[20].

The nasal mucosa exhibits diffuse crusting, hemorrhage, and purulent discharge during active disease, resulting in nasal blockage, with symptoms reported by patients ranging from mild to very severe[19] [Figure 2]. The most common site of disease activity is the anterior portion of the nasal septum, where all vessels of the septal cartilage converge and the septal perforation usually starts and extends over the entire cartilage[14]. Other structures of the nose, e.g., turbinates, might also be involved. At endoscopic examination, the nasal mucosa could appear granulating, with bloody submucosal patches or ulcerations, vulnerable, and covered with crusts[21]. In advanced stages, synechiae may also be observed. In the long term, inflammation and destruction of the nasal cartilage can lead to the typical saddle nose deformity[19] [Figure 2].

The involvement of paranasal sinuses is also very common and could be detected by computed tomography (CT) or magnetic resonance imaging (MRI)[22] [Figure 3]. However, during active disease, imaging is not capable of differentiate granulomatous inflammation from non-specific inflammation or infection[23]. The sinuses are likely to fill with scar tissue in the chronic stages of the disease, particularly after many relapses, and the maxillary sinuses also become narrower, with gradual ossification of the maxillary bone.

In MPA patients, involvement of the head and neck region is less common, but, when present, it resembles that of GPA. In a study conducted by Wojciechowska *et al.*[24], comparing GPA and MPA patients, the most frequently reported manifestation in the ENT area in both groups was chronic rhinosinusitis, followed by

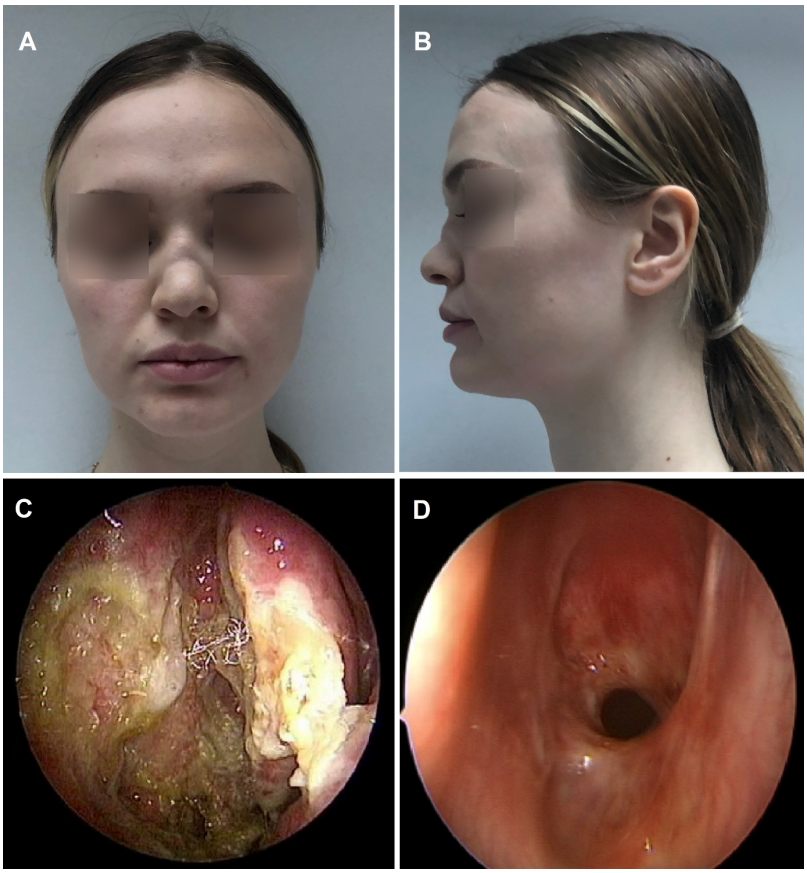

Figure 2. Clinical features of granulomatosis with polyangiitis manifestations in the ENT region. Frontal and sagittal view of saddle-nose deformity (A, B). Nasal endoscopy (C) showing subtotal septal perforation, bone erosion of the right middle and inferior turbinates, and diffuse crusting covering the nasal mucosa. Endoscopic view of a concentric subglottic stenosis (D).

epistaxis and purulent nasal discharge.

A significant proportion of EGPA patients suffer from ENT symptoms, usually manifesting as allergic rhinitis and chronic rhinosinusitis with or without polyps[25]. Olsen *et al.*[26], in a series of 32 patients with EGPA, reported nasal disease in 69% of the cases, nasal polyps in 50%, and nasal crusting in 36.3%. They also found pansinusitis in 80% of patients. Another study on 28 EGPA patients[25] demonstrated that ENT involvement was present in 75% of the cases, with allergic rhinitis and nasal polyposis as the most frequently observed manifestations at disease diagnosis, being observed in 42.8% and 76.1% of the patients, respectively. A history of chronic rhinosinusitis was present in 14.2% of the subjects. Chronic rhinosinusitis with diffuse and bilateral nasal polyps in EGPA is characterized by intense eosinophil tissue infiltration and a chronic-relapsing course in almost one-third of cases, despite surgery and medical treatment[27]. However, in EGPA nasal polyps, in addition to tissue eosinophil aggregates, a diffuse neutrophilic infiltration can be observed, supporting the hypothesis of neutrophils' entanglement in the inflammatory process, even in the absence of histological signs of vasculitis[28-30]. The role of neutrophil infiltrate in the nasal mucosa might be to amplify eosinophil tissue recruitment, in addition to contributing to inflammation[28], and thus leading to a more refractory manifestation.

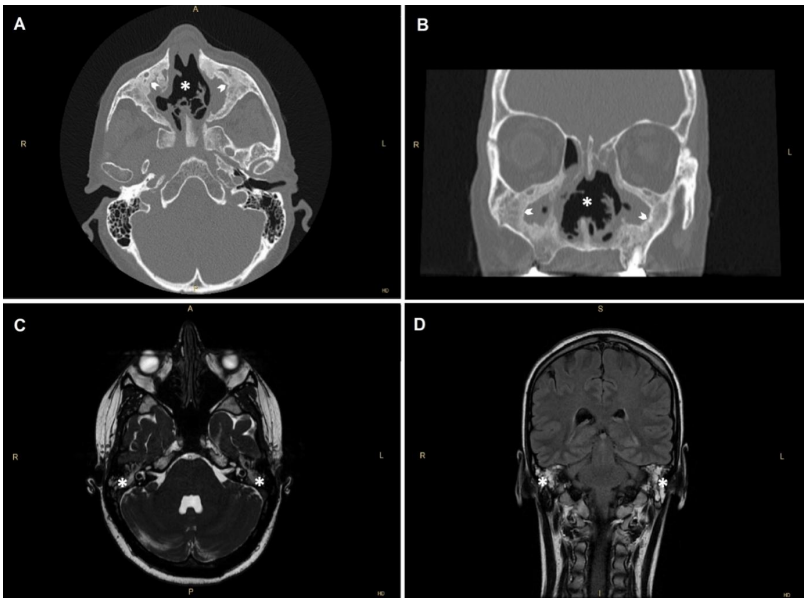

Figure 3. Radiological aspect of chronic rhinosinusitis, anterior septal perforation (asterisks), and maxillary sinus osteitis (arrowhead) in a patient diagnosed with granulomatosis with polyangiitis [CT scan, axial (A) and frontal (B) views]. T2-weighted MRI axial scan (C) and fluid attenuated inversion recovery (FLAIR) coronal scan (D) showing diffuse hyperintense opacification of the middle ear and mastoid cells in bilateral mastoiditis (asterisks).

OTOLOGIC MANIFESTATIONS

Otologic manifestations in systemic GPA are common, occurring in 20%-70% of the cases and representing the second most frequent symptoms of head and neck involvement[7,24,31]. The most involved site is the middle ear (23%-70%), leading frequently to hearing loss[21,32], which could be the presenting symptom of GPA. The vast majority of patients have relapsing or refractory otitis media, which does not respond to regular treatment, such as antibiotics and insertion of tympanic vent tubes [Figure 3]. Other common symptoms are tinnitus, otalgia, aural fullness or discharge, and dizziness[21,33]. Hearing loss may be conductive, sensorineural, or mixed. Fluid or granulation in the middle ear induces conductive hearing loss, while the exact mechanisms of sensorineural hearing loss are not clear. It has been hypothesized that a vasculitic inflammation of the inner ear may be responsible for sensorineural deafness, although deposition of immune complexes in the cochlea or toxic effects of inflammatory byproducts passing through the membrane into the inner ear cannot be excluded[34]. The majority of patients are PR3-ANCA positive, although recently a high rate of ENT symptoms in MPO-ANCA-positive GPA patients was reported, which differs from the classic microscopic polyangiitis phenotype for presenting with a limited or milder disease and lower rate of renal involvement[35,36].

Otoscopy examination can detect fluid in the middle ear and drum perforation. The audiometric pattern has been described as typically flat, although sometimes additional high frequency losses may coexist[37]. CT images of the temporal bone show soft tissue shadows and opacification in the middle ear and mastoid, while bone destruction may be observed in the tympanum and mastoid sinuses[21].

Hearing loss and middle ear effusions are also the most common presenting otologic manifestations of EGPA. The typical manifestation is represented by a granulomatous otitis with chronic, thick discharge, which leads to a conductive hearing loss in patients with chronic paranasal abnormalities, eosinophilia, and asthma[38,39].

Less commonly, localized AAV may presents only with otologic symptoms, without evidence of other AAV-related organ lesions. In these patients, not fulfilling the classification criteria for systemic vasculitis, the term OMAVV (otitis media with AAV) has been proposed[40,41]. Clinical criteria for OMAVV are reported in Table 1. Hearing loss represents the most common initial symptom, often associated with otorrhea, tinnitus, and vertigo or dizziness. Pachymeningitis or facial palsy may complicate the clinical course of OMAVV. An irreversible complete deafness despite treatment may develop in 3.5%-7.2% of patients[40].

TRACHEOBRONCHIAL MANIFESTATIONS

Large airways involvement, in the form of tracheobronchial disease, is a less common GPA manifestation[42]. Subglottic stenosis (SGS) is the most frequent tracheobronchial stenosis type, with an estimated frequency of 16%-23% in adult patients with GPA, while it can be considered uncommon or even exceptional in EGPA[42-44] [Figure 2]. It is one of the most common manifestations of ENT involvement in pediatric subjects[45]. SGS is defined as narrowing of the subglottic area within the cricoid cartilage[46] that can lead to upper airway obstruction and potentially life-threatening consequences[47]. Involvement of the glottic and supraglottic larynx may less frequently occur, resulting in multilevel airway stenosis[48]. Stenosis may also extend into the distal trachea and bronchi[48] including ulcerating tracheobronchitis with or without inflammatory pseudotumors[49].

SGS patients are commonly female and younger (26-40 years) than patients with tracheobronchial stenosis[45,47].

The pathogenesis of subglottic stenosis in GPA remains unclear[50,51], but the association of a vasculitic process in the setting of active inflammation due to laryngopharyngeal reflux[44,52] and mechanical forces related to turbulent subglottic airflow[53] may synergistically produce a hyperactive healing response that leads to cartilaginous fibrotic scarring and stenosis[50].

Subglottic stenosis likely increases gradually, allowing the patient to adjust his breathing pattern until a critical stenosis is reached. Typically, patients remain mild symptomatic or asymptomatic until about 75% of airway stenosis (60% in children) is reached[50]. Some patients report "asthmatic-like" symptoms for many years before diagnosis[43]. Patients with SGS may develop symptoms gradually, from non-specific cough, hoarseness, shortness of breath, pharyngodynia, hemoptysis, or vocal changes, finally to stridor or dyspnea on exertion when a critical point of stenosis is reached[18,54,55]. As the airway caliber narrows, obstruction may result from crusts, mucous plug, and thick secretions caused by inflammation of the mucosa or infections, as well as the subglottic lesion itself[50,56]. Unilateral or bilateral vocal cord fixation can be a consequence of cricoarytenoid joint involvement[57]. Occasionally, patients presenting with acute obstruction require emergency tracheostomy[18]. Recognition of active tracheobronchial or SGS in GPA can be challenging because SGS seems to progress irrespective of systemic GPA disease activity[43,53]. It may present as the first symptom or as a late manifestation of the disease[48]. Patients with subglottic inflammation are more likely to be ANCA negative[47] and to have endobronchial disease, ENT manifestations (destructive sinonasal disease as well), pulmonary manifestations, and constitutional symptoms[47], and they less frequently have nervous system and renal involvement[49]. The presence of SGS must be urgently investigated in patients with GPA who develop respiratory symptoms, even in the absence of another disease flare[47,50].

Even though SGS in GPA is a serious and potentially life-threatening complication, no standardized diagnostic and therapeutic approach exists. It is still debated which diagnostic methods should be recommended (serial bronchoscopies, lung function tests, and virtual endoscopy) for diagnosis and follow-

Table 1. Diagnostic criteria of otitis media with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV)

Diagnostic criteria of OMAAV
OMAVV is diagnosed if the following three criteria (A, B, C) are fulfilled
(A) At least one of the following clinical courses: · Intractable otitis media with effusion or granulation, which is resistant to antibiotics and insertion of tympanostomy tube · Progressive deterioration of bone conduction hearing levels
(B) At least one of the following features: · Already diagnosed as AAV (GPA; MPA; EGPA) based on the involvement of others organs · Positivity for serum MPO-or PR3-ANCA · Histopathology consistent with AAV i.e., necrotizing vasculitis predominantly affecting small vessels with or without granulomatous extravascular inflammation · At least one of the following accompanying sig/symptoms of AAV-related involvement: a. Involvements with upper airway tracts other than ear, scleritis lung and/or kidney b. Facial palsy c. Hypertrophic pachimeningytis d. Multiple mononeuropathy e. Transient alleviation of symptoms/sign with administration of 0.5-1 mg/Kg prednisolone and relapse with discontinuation of treatment
(C) Differential diagnosis: · Cholesteatoma, cholesterol granuloma, eosinophilic otitis media, tuberculosis, otitis externa, skull base osteomyelitis, neoplasms (malignancy, inflammatory myofibroblastic tumor, *etc.*) otitis media or inner ear inflammation caused by autoimmune diseases and vasculitis other than AAV

ANCA: Anti-neutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiits. MPO: myeloperoxidase; PR3: proteinase 3.

up[54].

Laryngeal endoscopy, using a flexible laryngoscope, should be performed as part of routine initial evaluation. Endoscopy typically reveals a circumferential narrowing associated with friable, erythematous mucosa or a inelastic fibrotic thickening, depending on the inflammatory state of the stenosis[18] but without specific findings for vasculitis[53]. Biopsy of the SGS should be performed cautiously because it can lead to exacerbation of the stenosis secondary to edema and progression of the scarring[58]. Among imaging techniques, MRI has a sensitivity of 87.5% and a specificity of 60% in recognizing inflammatory activity in SGS. It can detect circumscribed intramural granulomatous lesions or discriminate between regional and circumferential wall thickening[43]. Because 15%-55% of GPA patients have additional bronchial stenotic segments, spiral CT with three-dimensional reconstruction of the laryngotracheal lumen is useful to allow the assessment of the entire tracheobronchial pathway[50].

Dynamic expiratory CT has been proposed as a screening method to assess tracheal stenosis, being able to evaluate dynamic pathological changes during respiration in addition to detecting fixed stenoses[47].

Most cases of non-vasculitic subglottic stenosis are secondary to post-intubation scarring or laryngotracheal trauma[43]. Differential diagnosis should also include neoplastic and infectious factors[51]. It is important to distinguish these patients from congenital or idiopathic SGS[48]. Subglottic laryngotracheal stenosis has been reported in other forms of vasculitis such as relapsing polychondritis[46].

ORAL MANIFESTATIONS

Oral lesions in GPA could be observed at disease onset in around 2% of cases and could appear in about 5%-10% of patients during disease course[14]. These manifestations can be characterized by rapidly evolving ulceration, necrosis with neutrophil-rich infiltrates, or chronic granulomatous localized process slowly leading to mucosal and bone destruction[59]. Oral lesions include mucosal palatal and lingual ulcerations, aphthae, and non-healing extraction sockets[59,60]. Finally, specific gingival lesions, known as "strawberry gingivitis", can be observed, and they are characterized by exophytic gingival swelling of reddish purple

color with petechial hemorrhages that resemble strawberries[61-64]. The differential diagnosis of mucosal ulcers should include sarcoidosis, Crohn's disease, infections (mycobacterial, leishmaniasis, and paracoccidioidomycosis), and drug abuse[14]. Finally, in GPA and other granulomatous infectious diseases, palatal perforation is exceedingly unusual[65].

TUMOR-LIKE MANIFESTATIONS

Atypical lesions are often the presenting feature in GPA, including mass lesion. This manifestation may present as parapharyngeal mass, parotid mass, sinonasal and maxillary sinus lesions, and subglottic paratracheal mass[66-69]. Typically, masses are associated with PR3-ANCA and occur at early stage of the disease, usually as part of a systemic disease (lung and kidney). Pseudotumor in the ENT region may present with secondary cranial neuropathies. Nerve palsy may occur as single or multiple cranial nerve involvement. Evolution to osteomyelitis by invasive mass is possible[70]. Parapharyngeal involvement is reported by description of a parapharyngeal mass or secondary to local extension from contiguous parotid mass.

Tumor-like lesions in the ENT region are associated with a higher rate of partial response or refractory disease. Furthermore, surgical procedures can be difficult in this region.

HISTOLOGICAL FINDINGS

As the nose and paranasal sinuses are frequently involved in AAV and easily accessible, an intranasal biopsy is believed to be the one of the best ways to achieve histological confirmation. Thus, diagnostic biopsies of the nasal mucosa can be performed under local anesthesia, being relatively minimally invasive; however, the maxillary and ethmoid sinuses are also alternative regions for representative biopsies[14].

However, biopsy specimens from the ENT region are often small, making it therefore difficult to achieve a conclusive histological diagnosis of AAV. It is recommended to take multiple large biopsies (> 5 mm) from the edge of the inflamed area, in order to maximize the chance of obtaining a diagnostic biopsy[71]. It is rare to see at the same time all the typical features, including necrotizing granulomata with giant cells and neutrophil-predominant vasculitis[72]. Indeed, non-specific features, such as acute or chronic inflammation, are usually found in most head and neck biopsy specimens, which does not help in confirming the diagnosis of AAV[73]. Only in up to 16% of GPA cases can the classic triad of vasculitis, necrosis, and granulomatous inflammation be seen, while vasculitis and granulomas are found 21% of cases and vasculitic and necrosis in 23% of specimens[74]. However, when the clinical picture fits the diagnosis of AAV despite a negative histopathological result, a high index of suspicion must be preserved.

Although intranasal biopsies are the most common way to validate a diagnosis in GPA and EGPA, intranasal biopsies from MPA patients seldom reveal the existence of vasculitis and therefore are of limited value[73].

It is not recommended to perform biopsy of middle ear or mastoid region, given the technical difficulty of obtaining an appropriate biopsy specimen and the high rate of inconclusive histological findings[74].

In EGPA patients, during the prodromal phase, it is extremely difficult to clearly distinguish chronic rhinosinusitis from inflammation due to vasculitis. Histologically, nasal specimens usually show diffuse eosinophilic tissue infiltration[75], as in eosinophilic-type nasal polyposis, while only less than 10% of specimens reveal necrotizing vasculitis or eosinophilic granuloma. The diagnostic yield can be increased up to 50% if histological examination is performed on deep biopsy or surgical specimens of sinus tissue

obtained under general anesthesia[76]. Recent data demonstrate that, alongside the well-known eosinophil-rich inflammation, there may be other cells contributing to the inflammatory process, such as neutrophils[28], but specific markers are still lacking.

RADIOLOGICAL FINDINGS

Performing CT or MRI scans may be used and recommended on an individual basis, according to the location of the involvement and the clinical manifestations.

In a systematic review[77] carried out on sinus imaging findings in GPA, 92.6% of the patients had abnormalities on sinus CT: mucosal thickening of the paranasal sinuses and nasal fossae (87.7%), bony destruction (59.9%), and osteoneogenesis with foci of sclerosing osteitis and bone thickening (46%-59%) [Figure 3]. Bony obliteration of sinuses is relatively rare. Septal erosion was observed in 59.4% of the patients and 27.1% had orbital involvement. MRI imaging showed similar rates of mucosal thickening (89.9%) and granulomas in 14.5% of the patients, while conversely bony erosion was reported in only 10.1% of the cases. In EGPA patients, mucosal thickening, nasal polyps, and pansinusitis are commonly reported, while bony destruction is absent[78]. An alternative diagnosis, rather than AAV, should be suspected in the presence of bone erosion of the hard palate or the maxillary wall and alveolus. However, even though CT or MRI features are often non-specific, imaging might improve management of AAV patients, for example by quantifying the extent of sinus involvement.

Finally, CT and MRI scans can also be used to better define lesions in subglottic/tracheal stenosis. These tests are also suggested for patients with ear involvement who are refractory to treatment or in cases of cranial nerve palsy[79].

DIFFERENTIAL DIAGNOSIS

Many of the clinical features of AAV are non-specific, and, thus, the potential differential diagnoses are several. In the presence of ulcerative lesions of the ENT region, AAV should be included in the differential diagnosis; in addition, infections, inflammatory autoimmune diseases, malignancies, and substance abuse conditions can also cause granulomatous inflammation, which may lead to extensive damage [Table 2]. Complete and careful examination is warranted, as well as looking for evidence of different organ involvement other than the head and neck region. Moreover, all patients presenting with ENT symptoms resembling GPA should be evaluated with flexible endoscopy and imaging (CT and/or MRI) in order to quantify disease extent and identify the best area to biopsy. Additionally, serologic assessment should be performed; firstly, ANCA testing can lead to the proper diagnosis. An increasing presence of clinical, serological, and histological factors should enforce clinical suspicion of AAV, if there are no signs or symptoms that lead to a different diagnosis.

TREATMENT OPTIONS

Local treatment

Tissue damage caused by inflammation represents one of the major sources of morbidity for patients with AAV and ENT involvement. Some of these symptoms need adequate treatments, administered alone or in combination with systemic medical treatment, such as surgical or endoscopic repair or the delivery of topical or injectable medications directly to the site of disease[80].

Sinonasal symptoms can be relieved with vigorous nasal irrigation and topical medications applied directly to the nasal mucosa. This can be achieved in combination with glucocorticoids. Nasal irrigation with saline on a regular basis can help to dissolve crusts that can become a pablum for bacterial proliferation and block

Table 2. Differential diagnoses of ear, nose and throat inflammatory, granulomatous and necrotizing lesions

Infections	Inflammatory autoimmune diseases	Malignancies	Substances
Bacterial Tuberculosis Leprosy Syphilis Rhinoscleroma Actinomicosis	ANCA-associated vasculitis 1. Granulomatosis with polyangiits 2. Eosinophilic granulomatosis with polyangiits 3. Microscopic polyangiits	Nasal NK-T-cell lymphoma (midline lethal granuloma)	Cocaine-induced midline destructive lesions (CIMDL)
Fungal Zygomycosis Dermatacietes Rhinosporidiosis Blastomycosis Histoplasmosis Sporotrichosis Coccidioidomycosis	Other autoimmune diseases 1. IgG4-related disease 2. Sarcoidosis 3. Rheumatoid arthritis 4. Relapsing polychondritis 5. Systemic lupus erythematosus		Levamisole-induced Vasculitis (LIV)
Protozoal Leishmaniasis			Propylthiouracil-induced vascultis

nasal passages. Nasal lubricants applied directly to the mucosa or emollients added to nasal saline washes can help reduce dried nasal mucus and soften crusts, making them easily removable[81]. Topical application of antibiotics may be useful to eradicate *Staphylococcus aureus* from the nose.

Systemic treatment

The combination of corticosteroids and immunosuppressants is the mainstay of AAV treatment. Among immunosuppressive agents, cyclophosphamide is the conventional induction treatment for systemic or diffuse GPA[82], while methotrexate is an alternative for forms of GPA that are not life-threatening[83]. Induction treatment allows remission to be achieved in more than 80% of cases. For maintenance treatment, azathioprine is the most widely used[84]. In localized disease, in addition to methotrexate and trimethoprim, sulfamethoxazole also appears to be effective, with a reduction in the relapse rate, mainly in ENT, possibly for action against *Staphylococcus aureus*[85].

Rituximab (RTX), a chimeric human-mouse monoclonal antibody against CD20, is nowadays approved and widely used in the treatment of AAV[82], with a good safety profile[86]. RTX can be used in combination with corticosteroids as a first-line treatment for severe AAVs, particularly when cyclophosphamide is not recommended[87].

Regarding ENT manifestations, RTX is not usually recommended in patients without life- or organ-threatening manifestations[82]. However, RTX as rescue therapy has been administered in GPA with refractory ENT manifestations. A recent case series reported a good response of refractory OMAAV after RTX treatment[88].

In a large retrospective cohort of 59 AAV patients with orbital masses, RTX resulted highly effective (remission rate: RTX 91% *vs.* cyclophosphamide 52%). However, in this study, all patients received glucocorticoids without a standardized protocol, RTX was administered only in 19% of the patients, and there was no subgroup analysis between patients treated with RTX and patients treated with other immunosuppressive agents to assess if other features/treatments could have influenced the outcome[89]. In a previous case series of refractory GPA treated with RTX, Holle *et al.*[90] reported a much lower remission/improvement rate in patients with orbital masses (44.4%). Nevertheless, it is important to stress that the retroorbital disease is not recommended to be treated with a mild immunosuppressive regimen (e.g., methotrexate or mycophenolate)[82].

RTX was reported to be effective in the management of tracheobronchial stenosis (SGS and bronchial stenosis). Girard *et al.*[42] reported a remission rate in 80% in GPA patients with tracheobronchial stenosis when treated with RTX. However, the remission rate was lower with SGS (67%) and in patients requiring local treatment (67%)[42].

Other SGS case reports treated with RTX have been published, in addition to the French case series. Most reported a good outcome even in pediatric cases, but there are reports of no response. Moreover, most patients received glucocorticoids and were also locally or surgically treated, so the real effect of RTX alone is difficult to assess[91-93].

Despite aggressive immunosuppressant treatment, SGS seems to respond less than other GPA manifestations and to be burdened with a high risk of relapse. In these cases, the patients could require a surgical treatment, so an expert laryngologist is crucial in the patient's monitoring and management[49].

For EGPA management, treatment is usually borrowed from the GPA/MPA experience, because EGPA is frequently excluded from AAV randomized clinical trials, and, when included, EGPA patients are only a minority. Moreover, very few clinical trials are specifically designed for EGPA and only one considered a monoclonal antibody (mAb)[94-96]

Upper and lower airway involvement management in EGPA is challenging because ENT and asthma exacerbations are an expression of non-severe disease but very common and dependent on glucocorticoids (up to 84% of patients)[97].

In the last years, new treatments have been proposed for these manifestations; however, more evidence is focused on refractory and glucocorticoid-dependent asthma than ENT manifestations such as chronic rhinitis and nasal polyposis.

The pathogenesis of EGPA is still not fully clarified, but a direct pathogenic effect of eosinophil infiltration into different tissues has been demonstrated. Eosinophils are strongly activated and regulated by IL-5, which is primary produced by Th2 cells[98].

Recently, a phase 3 randomized controlled trial including relapsing, refractory, or glucocorticoid-dependent EGPA, the MIRRA trial, was published. This trial demonstrates that mepolizumab, an anti-IL-5 mAb, significantly reduced the frequency of disease relapses, including asthma and sinonasal relapses, and allowed the tapering or reduction of glucocorticoids[94].

Regarding mepolizumab, a large observational respective study confirmed the efficacy of this drug for EGPA patients with severe glucocorticoid-dependent asthma. The study included patients treated with mepolizumab (100 mg monthly, compared to the 300 mg monthly dosage administered in the MIRRA trial). Canzian *et al.*[99] reported some benefit even with the low dosage that could be acceptable as first-line therapy, but they highlighted that it has not been compared to the validated dosage of 300 mg monthly.

Since the results of the MIRRA trial were published, other anti-IL-5 medications have been considered promising in EGPA. Reslizumab, for example, has been investigated in an open label pilot study in EGPA with apparent favorable outcome on disease exacerbations[100]. Similarly, a prospective open label pilot study on benralizumab, an anti-IL-5 receptor mAb, was recently published considering a few EGPA patients, which reported a good glucocorticoid sparing effect and improvement of EGPA exacerbations, including

airway symptoms[101]. Interestingly, a recent case series reported a good steroid sparing effect of benralizumab on EGPA asthma, even in patients with no or poor response to mepolizumab. Moreover, in this study, the authors reported a significant improvement of patients' reported outcomes on ENT symptoms[102].

Up to now, it has been widely demonstrated that the systemic increase of IL-5 is crucial for promoting eosinophilia; however, IL-5 increase is not always sufficient to cause eosinophil-mediated tissue damage or pathological condition[98]. In specific tissues, local inflammatory environment and tissue-specific IL-5 concurrently contribute to full eosinophil activation[103]. *In situ* activation and differentiation of eosinophils might be associated with eosinophil heterogeneity and thus inconsistent response to treatment, according to specific organs. Although significant differences in efficacy of anti-IL-5 treatments have not been demonstrated, benralizumab extensively depleted eosinophils via antibody-dependent cell-mediated cytotoxicity, compared with that of mepolizumab[104]. However, despite deep depletion of eosinophils, a post-hoc analysis of the randomized controlled trial did not show significant differences between mepolizumab and benralizumab[105]. The reason for the discrepancy between the eosinophil depletion and clinical improvement is still unclear.

Another interesting drug is omalizumab, an anti-human immunoglobulin E murine mAb, which was demonstrated to be effective against allergic asthma, refractory chronic rhinosinusitis with nasal polyps, and refractory chronic spontaneous urticaria[106-108]. Some authors reported a favorable experience with omalizumab as steroid sparing agent in EGPA with persistent asthma and ENT manifestations, but half of the patients suffered asthma exacerbations[109-112].

However, there is also evidence of new onset or worsening of EPGA during omalizumab treatment[113,114]. It should be noted that the majority of studies on omalizumab in EGPA patients are case reports and case series with a low level of evidence, and they focus on asthma and ENT disease, while no data are available on the benefit of the drug in vasculitis manifestation and severe EGPA that is considered to be limited[115].

However, the real efficacy on vasculitis manifestations of anti-IL-5 medications is also debated because the MIRRA trial included asthma and sinonasal exacerbations as EGPA relapses, which is usually not recommended[116].

With regard to vasculitis manifestations in EGPA patients, RTX seems to be highly effective, especially for ANCA-positive patients[117], but data on asthma or ENT manifestations are still limited. One study reported a beneficiary effect of RTX on EGPA asthma, however the small size and the lack of a control group do not allow drawing final conclusions[118].

Surgical treatment

The mainstay of treatment in AAV is medical, being surgical interventions delayed if possible given the potential risk of complications[119]. However, considering the ENT involvement, surgery may play a major role in at least four different settings: (1) diagnosis; (2) symptoms relief; (3) management of complications; and (4) reconstruction. Each of these surgical purposes finds its different weight and importance in relation to the underlying disease (GPA, EGPA, and MPA) and the different anatomical regions involved.

A recent systematic review on the role of surgery in AAV affecting the nose and sinuses demonstrated that most reports dealt with GPA in comparison with EGPA and MPA[73]. Although far from being considered surgical procedures, endoscopic nasal biopsies represent mini-invasive interventions frequently performed

in the outpatient clinic and probably the easiest way to histologically confirm diagnosis in GPA and EGPA. Endoscopic sinus surgery should be indicated in GPA patients presenting with complications (e.g., mucoceles, fungal infections, and orbital/lacrimal pathways involvement). In cases unresponsive to medical treatments, endoscopic sinus surgery should be cautiously considered in GPA patients, since recent evidence suggests that sinus surgery is associated with osteitis progression and an increase in nasal space and crust formation[120].

Reconstructive surgery in GPA (e.g., septal perforation or saddle nose repair) is controversial and needs careful planning. Although no consensus exists on the best time to perform it, it should be indicated when the disease is in complete remission, with Unadkat *et al.*[121] suggesting waiting for further 6-12 months after disease stabilization.

Surgical measures for symptoms relief are reserved for refractory otologic manifestations in GPA. Patients with recurrent otitis media with persistent symptomatic middle ear effusions or eustachian tube dysfunction may benefit from myringotomy tube placement[122]. In the case of recurrent mastoiditis, mastoidectomy is advisable. An external approach and/or endonasal procedures may be used to perform dacryocystorhinostomy for epiphora and/or chronic infection in the lacrimal sac.

Although laryngo-tracheal manifestations of GPA are extremely rare (around 10%-15%), the subglottic stenosis is the most frequently observed. Failure of glucocorticoids and immunosuppressive treatment in symptoms relief is the main indication for surgical treatment of subglottic stenosis. Endoscopic intervention or dilation are preferred. Treatment failures are relatively high, ranging from 49% after one year to 80% at five years after the first procedure, according to a multicenter study including 47 patients[49].

Considering EGPA patients, the role of endoscopic sinus surgery is still a matter of debate, with a controversial opinion reported in the literature[73]. In the future, surgery in EGPA will probably collide with the introduction of new monoclonal antibodies in the treatment regimens.

Surgical indications and proper timing of procedures is critical in AAV patients and should always be planned in a multidisciplinary setting in conjunction with all the medical figures involved to avoid poor outcomes and potential surgical complications.

CONCLUSIONS

ENT involvement in AAV, especially in GPA and EGPA, represents one of the most frequent symptoms. Although patients with ENT symptoms have better survival and less renal involvement, they typically experience persistent or relapsing disease together with long-term exposure to therapies, leading to irreversible damage.

The burden of sinonasal morbidity on quality of life is significant and comparable to other common chronic diseases, with an impairment especially of social functioning and well-being perception, perhaps as a result of the stigma of constant purulent rhinorrhea, embarrassing epistaxis, or nasal deformity from cartilage destruction[123,124]. The high impact of ENT symptoms on quality of life of AAV patients confirms the importance of their early treatment through specific local and systemic approaches[124].

The otorhinolaryngologist is often one of the first physicians to see patients with GPA. The most frequent clinical manifestation of GPA is related to ENT involvement, in all of its forms, which may be the first or the only symptom. Thus, a close collaboration between the otorhinolaryngologist and rheumatologist is

crucial for readily arriving at the proper diagnosis, which allows the timely initiation of appropriate therapy. Therefore, AAV patients must be followed up regularly and frequently, in order to detect early relapses and reduce damage accrual of the affected areas.

DECLARATIONS

Authors' contributions

Conceptualization: Padoan R, Campaniello D, Felicetti M, Cazzador D, Schiavon F
Investigation: Padoan R, Schiavon F
Writing review: Padoan R, Campaniello D, Felicetti M, Cazzador D, Schiavon F
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Drafting and revising figures: Padoan R, Cazzador D
Supervision of ENT surgery topics: Cazzador D, Schiavon F

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