Review

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 ANCA-associated vasculitis (AAV), particularly in granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Over the last decade, substantial advance 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 aetiology 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 quality of life of AAV patients confirms the importance of their early treatment through specific local and systemic approach. 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, histologic 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 polyangiits, eosinophilic granulomatosis with polyangiitis, ear nose and throat

INTRODUCTION

Anti-neutrophil cytoplasmic antibody associated (ANCA) 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 (CHCC) nomenclature of vasculitides and the American College of Rheumatology (ACR 1990) classification criteria[1,2], AAV are classified in 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, heart and peripheral nervous system involvement[9]. However, EGPA is characterized by two different subsets, reflecting distinct underlying pathogenesis: a predominant "vasculitic

phenotype" closely associated to ANCA and an "eosinophilic phenotype", interleukin-5 (IL-5) driven[10].

Ear, nose and throat (ENT) represents one of the most common site of AAV manifestations, more often in GPA and EGPA, and 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 patient 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 aetiology 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 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, histologic 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 the patients[7,18]. One of the first manifestation is nasal blockage, in association with hyposmia or anosmia when mucosal swelling occurs[19]. Purulent nasal drainage associated with the growth of Staphylococcus aureus or Pseudomonas aeruginosa can cause cacosmia. Epiphora may presents 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, haemorrhage 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 the vessels of the septal cartilage converge and where 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 with ulcerations, vulnerable and covered with crusts[21]. In advanced stages synechiae may be also 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 head and neck region is less common, but when present 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 epistaxis and purulent nasal discharge.

A significant proportion of EGPA patients suffer of 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%, while nasal crusting was observed in 36.3% of them. They also found pansinusitis in 80% of the 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.

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 mostly 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 has 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 of sensorineural deafness, although deposition of immune complexes in the cochlea or toxic effects of inflammatory by-products passing through the membrane into the inner ear cannot be excluded[34]. The majority of patients are PR3-ANCA positive, although recently it was reported a high rate of ENT symptoms in MPO-ANCA positive GPA patients, which differ 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. 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, 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 lead to a conductive hearing loss, in patient 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 terms OMAVV (otitis media with AAV) was proposed[40,41]. Clinical criteria for OMAVV are reported in **Table 1**. Hearing loss represents the most common initial symptoms, 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 can be considered uncommon or even exceptional in EGPA[42-44] **[Figure 2]**. It is one of the most common manifestation of ENT involvement in paediatric 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 pseudo-tumours[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, pharyngodinia, haemoptysis or vocal changes, finally to stridor or dyspnoea on exertion when a critical point of stenosis is reached[18,54,55]. As the airway calibre 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 presents 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 also), pulmonary manifestations and constitutional symptoms[47] and less frequently 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 other disease flare[47,50].

Despite 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, virtual endoscopy) for diagnosis and follow-up[54].

Laryngeal endoscopy, using a flexible laryngoscope, should be performed as part of routinely 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 oedema 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 3-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 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 colour with petechial haemorrhages 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 in other granulomatous infectious diseases, palatal perforation is exceedingly unusual[65].

TUMOUR-LIKE MANIFESTATIONS

Atypical lesions are often the presenting feature in GPA, including mass lesion. This manifestation may presents 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 part of a systemic disease (lung and kidney). Pseudotumor in ENT district 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.

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

HISTOLOGIC FINDINGS

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

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

show usually 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 histologic examination is performed on deep biopsy or surgical specimens of sinus tissue obtained under general anaesthesia[76]. Recent data demonstrated 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.

RADIOLOGIC FINDINGS

Performing CT or MRI scans may be used and recommended on individual basis, according to the location of the involvement and to 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 only in 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 of the maxillary wall and alveolus. However, despite CT or MRI features are often non-specific, imaging might improve management of AAV patients, for example quantifying extent of sinus involvement.

Finally, CT and MRI scans can be used also 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 DIAGONSIS

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, alongside with 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, and 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 to identify the best area to biopsy. Additionally, serologic assessment should be performed, first and foremost 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 into 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 pabulum for bacterial proliferation and block nasal passages. Nasal lubricants applied directly to the mucosa or emollients added to nasal saline washes can help to 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

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 in 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, trimetropim sulfamethoxazole also appears

to be effective, by a reduction in the relapse rate, mainly ENT, possibly for an 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].

About the 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 patients and there is no subgroup analysis between patients treated with RTX and patients treated other immunosuppressive agents to asses if other features/treatment could have influenced the outcome[89]. In a previous case series of refractory GPA treated with RTX, indeed, Holle et al reported a much lower remission/improvement rate in patients with orbital masses (44.4%)[90]. Nevertheless, it is important to stress that the retro orbital disease is not recommended to be treated with a mild immunosuppressive regimen (e.g. methotrexate or mycophenolate)[82].

Rituximab (RTX) was reported to be effective in the management of tracheobronchial stenosis (SGS and bronchial stenosis). Girard et al. reported a remission rate in 80% of 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, other than the French case series. The most reported a good outcome even in paediatric 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 this cases, the patients could require a surgical treatment, so an expert laryngologist is crucial in the patient's monitoring and management[49].

About EGPA management, treatment is usually borrowed from the GPA/MPA experience, because EPGA 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 expression of non-severe disease but very common and glucocorticoids dependent (up to 84% of patients)[97].

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

The pathogenesis of EGPA is still not fully clarified, however, 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 or refractory or glucocorticoid- dependent EGPA, the MIRRA trial, was published. This trial demonstrates that mepolizumab, an anti-IL5 mAb, significantly reduced the frequency of disease relapses, including the asthma and sinonasal relapses and allowed the glucocorticoids tapering or reduction[94].

About mepolizumab, a large observational respective study confirmed the efficacy of this drug on EGPA patients with severe glucocorticoid-dependent asthma. The study included patients treated with mepolizumab 100 mg monthly other than 300 mg monthly (dosage administered in MIRRA trial). The Authors 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[99].

After the results of MIRRA trial, other anti-IL5 medications have been considered promising in EGPA. Reslizumab, for example, has been investigated in an open label pilot study in EGPA with apparent favourable outcome on disease exacerbations[100]. Similarly, it has been recently published a prospective open label pilot study on benralizumab, an anti-IL5 receptor mAb, in few EGPA patients reporting a good glucocorticoid sparing effect and improvement of EGPA exacerbations, including airways symptoms[101]. Interestingly, a recent case series reported a good steroid sparing effect of benralizumab on EGPA asthma, even in patients with lack or poor response to mepolizumab. In this study, moreover, the Authors reported a significant improvement of patients' reported outcomes (PROs) 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 an eosinophil-mediated tissue damage or pathological condition[98]. In specific tissues, local inflammatory environment and tissue-specific IL-5 concurrently contribute to full eosinophils 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-IL5 treatments have not been demonstrated, benralizumab extensively depleted eosinophils via antibody-dependent cell-mediated cytotoxicity (ADCC), 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 eosinophils' depletion and clinical improvement is still unclear. Another interesting drug is omalizumab, an anti-human immunoglobulin E (IgE) murin mAb, that demonstrated to be effective against allergic asthma, refractory chronic rhinosinusitis with nasal polyps and refractory chronic spontaneous orticaria[106-108]. Some author reported a favourable experience with omalizumab as steroid sparing agent in EGPA with persistent asthma and ENT manifestations, but half of 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 the studies on omalizumab in EGPA patients are case reports and case series with a low level of evidence and focuses 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 the anti IL5 medications is also debated, because MIRRA trial included the asthma and sinonasal exacerbations as EGPA relapses, that is usually not recommended[116].

About vasculitis manifestations in EGPA patients, RTX seems to be highly effective especially on 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 does not allow to draw final conclusions[118].

Surgical treatment

The mainstay of treatment in AAV is medical, being surgical interventions procrastinated if possible, give the potential risk of complications[119]. However, considering the ENT involvement, surgery may play a major role in at least four different settings: i) diagnosis, ii) symptoms relief, iii) management of complications, and iv) reconstruction. Each one of these surgical purposes find its different weight and importance in relation to the underlying disease (GPA, EGPA, and MPA), and to the different anatomical districts 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, orbital/lacrimal pathways involvement). In cases unresponsive to medical treatments, endoscopic sinus surgery should be cautiously weighted in GPA patients, since recent evidence suggests that sinus surgery is associated with osteitis progression, with 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 timing to perform it, it should be indicated when the disease is in complete remission, with some authors suggesting waiting for further 6 to 12 months after disease stabilization[121].

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 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% to 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 1 year, to 80% at 5 years after the first procedure, according to a multicentre study on 47 patients[49].

Considering EGPA patients, the role of endoscopic sinus surgery is still a matter of debate, with controversial opinion reported in 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

To conclude, ENT involvement in AAV, especially in GPA and EGPA, represent 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 rhinorrhoea, 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 approach[124].

The otorhinolaringologist is often one of the first physicians to see patients with GPA first. 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 otorhinolaringologist and rheumatologist is crucial for readily arrive at the proper diagnosis that 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
Editing: Padoan R, Cazzador D, Schiavon F
Drafting and revising figures: Padoan R, Cazzador D
supervision of ENT surgery topics: Cazzador D, Schiavon F

Availability of data and materials

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1 Lionaki S, Blyth ER, Hogan SL, *et al.* Classification of antineutrophil cytoplasmic autoantibody vasculitides: The role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum* 2012;64:3452–62.

2 Fries JF, Hunder GG, Bloch DA, *et al.* The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum* 1990;33:1135–6.

3 Kallenberg CGM. Usefulness of antineutrophil cytoplasmic autoantibodies in diagnosing and managing systemic vasculitis. *Curr Opin Rheumatol* 2016;28:8–14.

4 Lyons PA, Rayner TF, Trivedi S, *et al.* Genetically distinct subsets within ANCA-associated vasculitis. *N Engl J Med* 2012;367:214–23.

5 Nishi R, Koike H, Ohyama K, *et al.* Differential clinicopathologic features of EGPA-associated neuropathy with and without ANCA. *Neurology* 2020;94:E1726–37.

6 Holle JU, Gross WL, Holl-Ulrich K, *et al.* Prospective long-term follow-up of patients with localised Wegener's granulomatosis: Does it occur as persistent disease stage? *Ann Rheum Dis* 2010;69:1934–9.

7 Felicetti M, Cazzador D, Padoan R, *et al.* Ear, nose and throat involvement in granulomatosis with polyangiitis: how it presents and how it determines disease severity and long-term outcomes. *Clin Rheumatol* 2018 Apr;37(4):1075-1083.

8 Mukhtyar C, Guillevin L, Cid MC, *et al.* EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009;68:310–7.

9 Yates M, Watts R. ANCA-associated vasculitis. *Clin Med* 2017;17:60–4.

10 Nishi R, Koike H, Ohyama K, *et al.* Association Between IL-5 Levels and the Clinicopathologic Features of Eosinophilic Granulomatosis With Polyangiitis. *Neurology* 2021;96:226–9.

11 Bligny D, Mahr A, Toumelin P Le, *et al.* Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. *Arthritis Rheum* 2004;51:83–91.

12 Rahmattulla C, de Lind van Wijngaarden RAF, Berden AE, *et al.* Renal function and

ear, nose, throat involvement in anti-neutrophil cytoplasmic antibody-associated vasculitis: prospective data from the European Vasculitis Society clinical trials. *Rheumatology (Oxford)* 2015;54:899–907.

13 Hogan SL, Falk RJ, Chin H, *et al.* Predictors of Relapse and Treatment Resistance in Antineutrophil Cytoplasmic Antibody–Associated Small-Vessel Vasculitis. *Ann Intern Med* 2005;143:621.

14 Trimarchi M, Sinico RA, Teggi R, *et al.* Otorhinolaryngological manifestations in granulomatosis with polyangiitis (Wegener's). Autoimmun. Rev. 2013;12:501–5.

15 Comarmond C, Pagnoux C, Khellaf M, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013;65:270–81.

16 Durel C-A, Berthiller J, Caboni S, *et al.* Long-Term Followup of a Multicenter Cohort of 101 Patients With Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss). *Arthritis Care Res (Hoboken)* 2016;68:374–87.

17 Millet A, Pederzoli-Ribeil M, Guillevin L, *et al.* Antineutrophil cytoplasmic antibody-associated vasculitides: Is it time to split up the group? *Ann Rheum Dis* 2013;72:1273–9.

18 Gubbels SP, Barkhuizen A, Hwang PH. Head and neck manifestations of wegener's granulomatosis. Otolaryngol. Clin. North Am. 2003;36:685–705.

19 Rasmussen N. Management of the ear, nose, and throat manifestations of Wegener granulomatosis: An otorhinolaryngologist's perspective. *Curr Opin Rheumatol* 2001;13:3–11.

20 Kwan ASL, Rose GE. Lacrimal drainage surgery in Wegener's granulomatosis. *Br J Ophthalmol* 2000;84:329–31.

21 Kühn D, Hospowsky C, Both M, *et al*. Manifestation of granulomatosis with polyangiitis in head and neck. *Clin Exp Rheumatol*. 2018 Mar-Apr;36 Suppl 111(2):78-84.

22 Holme SS, Moen JM, Kilian K, *et al.* Development of CT-based methods for longitudinal analyses of paranasal sinus osteitis in granulomatosis with polyangiitis. *BMC Med Imaging* 2019;19.

23 Muhle C, Reinhold-Keller E, Richter C, *et al.* MRI of the nasal cavity, the paranasal sinuses and orbits in Wegener's granulomatosis. *Eur Radiol* 1997;7:566–70.

24 Wojciechowska J, Krajewski W, Krajewski P, *et al.* Granulomatosis With Polyangiitis

641 in Otolaryngologist Practice: A Review of Current Knowledge. *Clin Exp*
642 *Otorhinolaryngol* 2016;9:8–13.
643 25 Bacciu A, Bacciu S, Mercante G, *et al.* Ear, nose and throat manifestations of Churg-
644 Strauss syndrome. *Acta Otolaryngol* 2006;126:503–9.
645 26 Olsen KD, Neel HB, Deremee RA, *et al.* Nasal manifestations of allergic
646 granulomatosis and angiitis (Churg-Strauss syndrome). *Otolaryngol - Head Neck Surg*
647 1980;88:85–9.
648 27 Suzuki M, Nakazono A, Morita S, *et al.* Comparison of clinical characteristics of the
649 nasal manifestations of eosinophilic granulomatosis with polyangiitis (EGPA) and
650 eosinophilic chronic rhinosinusitis (ECRS). Allergol. Int. 2021;70:143–4.
651 28 Brescia G, Padoan R, Schiavon F, *et al.* Nasal polyps in eosinophilic granulomatosis
652 with polyangiitis: Structured histopathology and CD105 expression. *Am J Otolaryngol*
653 *- Head Neck Med Surg* 2020;41.
654 29 Contro G, Brescia G, Alessandrini L, *et al.* Neutrophil infiltrates and eosinophil
655 aggregates in chronic rhinosinusitis with nasal polyps and EGPA. *Clin Rheumatol*
656 Published Online First: 2020.
657 30 Brescia G, Schiavon F, Nicolè L, *et al.* No Differences in Nasal Tissue Inflammatory
658 Cells and Adhesion Molecules (iCAM-1 and vCAM-1) Based on the Comparison of
659 EGPA With Eosinophilic Chronic Sinusitis With Polyposis. *Am J Rhinol Allergy*
660 2019;33.
661 31 Rahne T, Clauß F, Plontke SK, *et al.* Prevalence of hearing impairment in patients with
662 rheumatoid arthritis, granulomatosis with polyangiitis (GPA, Wegener's
663 granulomatosis), or systemic lupus erythematosus. *Clin Rheumatol* 2017;36:1501–10.
664 32 Martinez Del Pero M, Walsh M, Luqmani R, *et al.* Long-term damage to the ENT
665 system in Wegener's granulomatosis. *Eur Arch Oto-Rhino-Laryngology*
666 2011;268:733–9.
667 33 Girasoli L, Cazzador D, Padoan R, *et al.* Update on Vertigo in Autoimmune Disorders,
668 from Diagnosis to Treatment. *J Immunol Res* 2018;2018:5072582.
669 34 Nogaki T, Keskin N, Azuma T, *et al.* Quantitative assessment of vestibular
670 otopathology in granulomatosis with polyangitis: A temporal bone study.
671 *Laryngoscope Investig Otolaryngol* 2018;3:473–7.
672 35 Ono N, Niiro H, Ueda A, *et al.* Characteristics of MPO-ANCA-positive
673 granulomatosis with polyangiitis: a retrospective multi-center study in Japan.
674 *Rheumatol Int* 2015;35:555–9.

36 Schirmer JH, Wright MN, Herrmann K, *et al.* Myeloperoxidase-Antineutrophil Cytoplasmic Antibody (ANCA)-Positive Granulomatosis With Polyangiitis (Wegener's) Is a Clinically Distinct Subset of ANCA-Associated Vasculitis: A Retrospective Analysis of 315 Patients From a German Vasculitis Referral Center. *Arthritis Rheumatol (Hoboken, NJ)* 2016;68:2953–63.

37 Ralli M, D'Aguanno V, Di Stadio A, *et al.* Audiovestibular symptoms in systemic autoimmune diseases. J. Immunol. Res. 2018;2018.

38 Seccia V, Fortunato S, Cristofani-Mencacci L, *et al.* Focus on audiologic impairment in eosinophilic granulomatosis with polyangiitis. *Laryngoscope* 2016;126:2792–7.

39 Nakamaru Y, Takagi D, Suzuki M, *et al.* Otologic and rhinologic manifestations of eosinophilic granulomatosis with polyangiitis. *Audiol Neurotol* 2016;21:45–53.

40 Harabuchi Y, Kishibe K, Tateyama K, *et al.* Clinical characteristics, the diagnostic criteria and management recommendation of otitis media with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV) proposed by Japan Otological Society. *Auris Nasus Larynx* 2021;48:2–14.

41 Harabuchi Y, Kishibe K, Tateyama K, *et al.* Clinical features and treatment outcomes of otitis media with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (OMAAV): A retrospective analysis of 235 patients from a nationwide survey in Japan. *Mod Rheumatol* 2017;27:87–94.

42 Girard C, Charles P, Terrier B, *et al.* Tracheobronchial stenoses in granulomatosis with polyangiitis (Wegener's): A Report on 26 Cases. *Med (United States)* 2015;94.

43 Fijolek J, Wiatr E, Gawryluk D, *et al.* Intratracheal dilation-injection technique in the treatment of granulomatosis with polyangiitis patients with subglottic stenosis. *J Rheumatol* 2016;43:2042–8.

44 Seccia V, Cristofani-Mencacci L, Dallan I, *et al.* Eosinophilic granulomatosis with polyangiitis and laryngeal involvement: Review of the literature and a cross-sectional prospective experience. J. Laryngol. Otol. 2018;132:619–23.

45 Del Pero MM, Jayne D, Chaudhry A, *et al.* Long-term outcome of airway stenosis in granulomatosis with polyangiitis (Wegener Granulomatosis): An observational study. *JAMA Otolaryngol - Head Neck Surg* 2014;140:1038–44.

46 Jordan NP, Verma H, Siddiqui A, *et al.* Morbidity and mortality associated with subglottic laryngotracheal stenosis in granulomatosis with polyangiitis (Wegener's granulomatosis): A single-centre experience in the United Kingdom. *J Laryngol Otol* 2014;128:831–7.

47 Quinn KA, Gelbard A, Sibley C, *et al.* Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. *Rheumatol (United Kingdom)* 2019;58:2203–11.
48 Guardiani E, Moghaddas HS, Lesser J, *et al.* Multilevel airway stenosis in patients with granulomatosis with polyangiitis (Wegener's). *Am J Otolaryngol - Head Neck Med Surg* 2015;36:361–3.
49 Terrier B, Dechartres A, Girard C, *et al.* Granulomatosis with polyangiitis: Endoscopic management of tracheobronchial stenosis: Results from a multicentre experience. *Rheumatol (United Kingdom)* 2015;54:1852–7.
50 Alam DS, Rahul S, Raj S, *et al.* Upper airway manifestations of granulomatosis with polyangiitis. *Cleve Clin J Med* 2012;79:16–21.
51 Zycinska K, Wardyn K, Zielonka TM, *et al.* Subglottic and tracheal stenosis due to Wegener's granulomatosis. In: *Advances in Experimental Medicine and Biology*. Springer Science and Business Media, LLC 2013. 221–4.
52 Church AC, Goldsmith K, Sivasothy P. Aspiration and development of subglottic stenosis in patients with Wegeners granulomatosis. *J Laryngol Otol* 2010;124:393–6.
53 Gluth MB, Shinners PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. Laryngoscope. 2003;113:1304–7.
54 Marroquín-Fabián E, Ruiz N, Mena-Zúñiga J, *et al.* Frequency, treatment, evolution, and factors associated with the presence of tracheobronchial stenoses in granulomatosis with polyangiitis. Retrospective analysis of a case series from a single respiratory referral center. *Semin Arthritis Rheum* 2019;48:714–9.
55 Sharma A, Deshmukh S, Dabholkar J. ENT manifestations of Wegeners granulomatosis. *Otolaryngol Pol* 2013;67:257–60.
56 Langford CA, Sneller MC, Hallahan CW, *et al.* Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. *Arthritis Rheum* 1996;39:1754–60.
57 Martinez Del Pero M, Rasmussen N, Chaudhry A, *et al.* Structured clinical assessment of the ear, nose and throat in patients with granulomatosis with polyangiitis (Wegener's). *Eur Arch Otorhinolaryngol* 2013;270:345–54.
58 Taylor SC, Clayburgh DR, Rosenbaum JT, Schindler JS. Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis. *JAMA Otolaryngol Head Neck Surg*. 2013 Jan;139(1):76-81.
59 Nico MMS, Pinto NT, Lourenço SV. From strawberry gingivitis to palatal perforation: The clinicopathological spectrum of oral mucosal lesions in granulomatosis with

743 polyangiitis. *J Oral Pathol Med* 2020;49:443–9.
744 60 Xing X, Zhang T, Wang X. Pediatric Wegener's granulomatosis with oral ulcers and
745 progressive periodontitis: A case report. *Oral Surgery, Oral Med Oral Pathol Oral*
746 *Radiol Endodontology* 2011;112.
747 61 Knight JM, Hayduk MJ, Summerlin DJ, *et al.* 'Strawberry' gingival hyperplasia: A
748 pathognomonic mucocutaneous finding in Wegener granulomatosis. *Arch Dermatol*
749 2000;136:171–3.
750 62 Eufinger H, Machtens E, Akuamoa-Boateng E. Oral manifestations of Wegener's
751 granulomatosis. Review of the literature and report of a case. *Int J Oral Maxillofac*
752 *Surg* 1992;21:50–3.
753 63 Hernández G, Serrano C, Porras L, *et al.* Strawberry-Like Gingival Tumor as the First
754 Clinical Sign of Wegener's Granulomatosis. *J Periodontol* 2008;79:1297–303.
755 64 Hanisch M, Fröhlich LF, Kleinheinz J. Gingival hyperplasia as first sign of recurrence
756 of granulomatosis with polyangiitis (Wegener's granulomatosis): Case report and
757 review of the literature. *BMC Oral Health* 2016;17.
758 65 Trimarchi M, Bondi S, Della Torre E, *et al.* La perforazione del palato differenzia le
759 lesioni destruenti della linea mediana indotte da cocaina dalla granulomatosi con
760 poliangioite. *Acta Otorhinolaryngol Ital* 2017;37:281–5.
761 66 Nelson RE, Hildrew DM, Deblieux T, *et al.* Wegener's Granulomatosis Presenting as a
762 Parapharyngeal Mass. *J Louisiana State Med Soc Off organ Louisiana State Med Soc*
763 2016;168:60–2.
764 67 Lee PY, Adil EA, Irace AL, *et al.* The presentation and management of granulomatosis
765 with polyangiitis (Wegener's Granulomatosis) in the pediatric airway. *Laryngoscope*
766 2017;127:233–40.
767 68 Shenavandeh S, Petramfar P. Three atypical manifestations of granulomatosis with
768 polyangiitis: lateral medullary syndrome, anterior cheek mass and melting scleritis of
769 eye. *Reumatologia* 2017;55:145–50.
770 69 Masuda T, Izumi Y, Takeshita H, *et al.* Granulomatosis with polyangiitis presenting as
771 a choroidal tumor. *Case Rep Rheumatol* 2015;2015:271823.
772 70 Spanuchart I, Zungsontiporn N, O-charoen P, *et al.* Granulomatosis with Polyangiitis:
773 A Case of Nasal Mass, Necrotic Lung, and Normal Kidneys. *Hawai'i J Med public*
774 *Heal a J Asia Pacific Med Public Heal* 2015;74:27–9.
775 71 Coates ML, Martinez Del Pero M. Updates in antineutrophil cytoplasmic antibody
776 (ANCA)-associated vasculitis for the ENT surgeon. Clin. Otolaryngol. 2020;45:316–

777 26.
778 72 Greco A, Marinelli C, Fusconi M, *et al.* Clinic manifestations in granulomatosis with
779 polyangiitis. Int. J. Immunopathol. Pharmacol. 2016;29:151–9.
780 73 Pendolino AL, Unadkat S, Zhang H, *et al.* The role of surgery in antineutrophil
781 cytoplasmic antibody–associated vasculitides affecting the nose and sinuses: A
782 systematic review. *SAGE Open Med* 2020;8:205031212093673.
783 74 Devaney KO, Travis WD, Hoffman G, *et al.* Interpretation of head and neck biopsies
784 in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. *Am J*
785 *Surg Pathol* 1990;14:555–64.
786 75 Seccia V, Baldini C, Latorre M, *et al.* Focus on the involvement of the nose and
787 paranasal sinuses in Eosinophilic Granulomatosis with polyangiitis (Churg-Strauss
788 Syndrome): Nasal cytology reveals infiltration of eosinophils as a very common
789 feature. *Int Arch Allergy Immunol* 2018;175:61–9.
790 76 Vega Villanueva KL, Espinoza LR. Eosinophilic Vasculitis. Curr. Rheumatol. Rep.
791 2020;22.
792 77 D'Anza B, Langford CA, Sindwani R. Sinonasal imaging findings in Granulomatosis
793 with polyangiitis (Wegener granulomatosis): A systematic review. In: *American*
794 *Journal of Rhinology and Allergy*. OceanSide Publications Inc. 2017. 16–21.
795 78 Pagnoux C. Updates in ANCA-associated vasculitis. *Eur J Rheumatol* 2016;3:122–33.
796 79 Carnevale C, Arancibia-Tagle D, Sarría-Echegaray P, *et al.* Head and neck
797 manifestations of granulomatosis with polyangiitis: A Retrospective analysis of 19
798 Patients and Review of the Literature. Int. Arch. Otorhinolaryngol. 2019;23:165–71.
799 80 Hernández-Rodríguez J, Hoffman GS, Koening CL. Surgical interventions and local
800 therapy for Wegener's granulomatosis. *Curr Opin Rheumatol* 2010;22:29–36.
801 81 Erickson VR, Hwang PH. Wegener's granulomatosis: Current trends in diagnosis and
802 management. Curr. Opin. Otolaryngol. Head Neck Surg. 2007;15:170–6.
803 82 Yates M, Watts RA, Bajema IM, *et al.* EULAR/ERA-EDTA recommendations for the
804 management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.
805 83 De Groot K, Rasmussen N, Bacon PA, *et al.* Randomized trial of cyclophosphamide
806 versus methotrexate for induction of remission in early systemic antineutrophil
807 cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:2461–9.
808 84 Puéchal X. Granulomatosis with polyangiitis (Wegener's). Jt. Bone Spine.
809 2020;87:572–8.
810 85 Stegeman CA, Cohen Tervaert JW, de Jong PE, *et al.* Trimethoprim–

Sulfamethoxazole (Co-Trimoxazole) for the Prevention of Relapses of Wegener's Granulomatosis. *N Engl J Med* 1996;335:16–20.

86 Padoan R, Felicetti M, Gatto M, *et al.* Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: a longitudinal observational study. *Clin Exp Rheumatol* 2020;38:188–94.

87 Raffray L, Guillevin L. Rituximab treatment of ANCA-associated vasculitis. Expert Opin. Biol. Ther. 2020;20:899–910.

88 Okada M, Suemori K, Takagi D, *et al.* The treatment outcomes of rituximab for intractable otitis media with ANCA-associated vasculitis. *Auris Nasus Larynx* 2019;46:38–42.

89 Durel C-A, Hot A, Trefond L, *et al.* Orbital mass in ANCA-associated vasculitides: data on clinical, biological, radiological and histological presentation, therapeutic management, and outcome from 59 patients. *Rheumatology (Oxford)* 2019;58:1565–73.

90 Holle JU, Dubrau C, Herlyn K, *et al.* Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. *Ann Rheum Dis* 2012;71:327–33.

91 Aries PM, Hellmich B, Voswinkel J, *et al.* Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006;65:853–8.

92 Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations. *J Rheumatol*. 2008 Oct;35(10):2017-23

93 Pullerits R, Ljevak M, Vikgren J, *et al.* Off-Trial Evaluation of the B cell-Targeting Treatment in the Refractory Cases of Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis: Long-Term Follow-Up from a Single Centre. *Scand J Immunol* 2012;76:411–20.

94 Wechsler ME, Akuthota P, Jayne D, *et al.* Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017;376:1921–32.

95 Ribi C, Cohen P, Pagnoux C, *et al.* Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum* 2008;58:586–94.

96 Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Expert Rev. Clin.

Immunol. 2016;12:1059–67.
97 Cohen P, Pagnoux C, Mahr A, *et al.* Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Care Res* 2007;57:686–93.
98 Nagase H, Ueki S, Fujieda S. The roles of IL-5 and anti-IL-5 treatment in eosinophilic diseases: Asthma, eosinophilic granulomatosis with polyangiitis, and eosinophilic chronic rhinosinusitis. Allergol. Int. 2020;69:178–86.
99 Canzian A, Venhoff N, Urban ML, *et al.* Use of Biologics to Treat Relapsing and/or Refractory Eosinophilic Granulomatosis With Polyangiitis: Data From a European Collaborative Study. *Arthritis Rheumatol* 2020;73.
100 Manka L, Guntur VP, Denson JL, *et al.* Efficacy and Safety of Reslizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA). *Ann Allergy, Asthma Immunol* Published Online First: February 2021.
101 Guntur VP, Manka LA, Denson JL, *et al.* Benralizumab as a Steroid-Sparing Treatment Option in Eosinophilic Granulomatosis with Polyangiitis. *J Allergy Clin Immunol Pract* Published Online First: 2020.
102 Padoan R, Chieco Bianchi F, Marchi MR, *et al.* Benralizumab as a glucocorticoid-sparing treatment option for severe asthma in eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol Pract* 2020;8:3225-3227.e2.
103 Kita H. Eosinophils: Multifaceted biological properties and roles in health and disease. *Immunol Rev* 2011;242:161–77.
104 Laviolette M, Gossage DL, Gauvreau G, *et al.* Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013;132.
105 Bourdin A, Husereau D, Molinari N, *et al.* Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: A systematic review. *Eur Respir J* 2018;52.
106 Hanania NA, Alpan O, Hamilos DL, *et al.* Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial. *Ann Intern Med* 2011;154:573–82.
107 Gevaert P, Omachi TA, Corren J, *et al.* Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020;146:595–605.
108 Goldstein S, Gabriel S, Kianifard F, *et al.* Clinical features of adolescents with chronic idiopathic or spontaneous urticaria: Review of omalizumab clinical trials. In: *Annals of*

Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology 2017. 500–4.

109 Caruso C, Gencarelli G, Gaeta F, *et al.* Efficacy of omalizumab treatment in a man with occupational asthma and eosinophilic granulomatosis with polyangioitis. *Ann Allergy, Asthma Immunol* 2018;120:209–11.

110 Aguirre-Valencia D, Posso-Osorio I, Bravo JC, *et al.* Sequential rituximab and omalizumab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Clin. Rheumatol. 2017;36:2159–62.

111 Detoraki A, Di Capua L, Varricchi G, *et al.* Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: A 36-month follow-up study. *J Asthma* 2016;53:201–6.

112 Jachiet M, Samson M, Cottin V, *et al.* Anti-IgE Monoclonal Antibody (Omalizumab) in Refractory and Relapsing Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss): Data on Seventeen Patients. *Arthritis Rheumatol* 2016;68:2274–82.

113 Winchester DE, Jacob A, Murphy T. Omalizumab for Asthma. *N Engl J Med* 2006;355:1281–2

114 Puéchal X, Rivereau P, Vinchon F. Churg-Strauss syndrome associated with omalizumab. *Eur J Intern Med* 2008;19:364–6.

115 Basta F, Mazzuca C, Nucera E, *et al.* Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review. *Clin Exp Rheumatol*. 2020 Mar-Apr;38 Suppl 124(2):214-220. Epub 2020 Feb 18

116 Groh M, Pagnoux C, Baldini C, *et al.* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015;26:545–53.

117 Akiyama M, Kaneko Y, Takeuchi T. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis: A systematic literature review. Autoimmun. Rev. 2021;20.

118 Casal Moura M, Berti A, Keogh KA, *et al.* Asthma control in eosinophilic granulomatosis with polyangiitis treated with rituximab. *Clin Rheumatol* 2020;39:1581–90.

119 Sattui SE, Lally L. Localized Granulomatous with Polyangiitis (GPA): Varied Clinical Presentations and Update on Treatment. Curr. Allergy Asthma Rep. 2020;20.

120 Holme SS, Moen JM, Kilian K, *et al.* Impact of Paranasal Sinus Surgery in Granulomatosis With Polyangiitis: A Longitudinal Computed Tomography Study.

Laryngoscope 2020;130:E460–8.

121 Unadkat SN, Pendolino AL, Kwame I, *et al.* Nasal reconstructive surgery for vasculitis affecting the nose: our two-centre international experience. *Eur Arch Oto-Rhino-Laryngology* 2020;277:3059–66.

122 Sahyouni R, Moshtaghi O, Abouzari M, *et al.* A Case Series of Granulomatosis With Polyangiitis Primarily Diagnosed by Otological Manifestations. *Ann Otol Rhinol Laryngol* 2019;128:263–6.

123 Srouji IA, Andrews P, Edwards C, *et al.* General and rhinosinusitis-related quality of life in patients with Wegener's granulomatosis. *Laryngoscope* 2006;116:1621–5.

124 Cazzador D, Padoan R, Colangeli R, *et al.* Health-Related Quality of Life in Patients With ANCA-Associated Vasculitis and Sinonasal Involvement: A Single-Center Cross-Sectional Study. *J Clin Rheumatol Pract reports Rheum & Musculoskelet Dis* Published Online First: 2020.

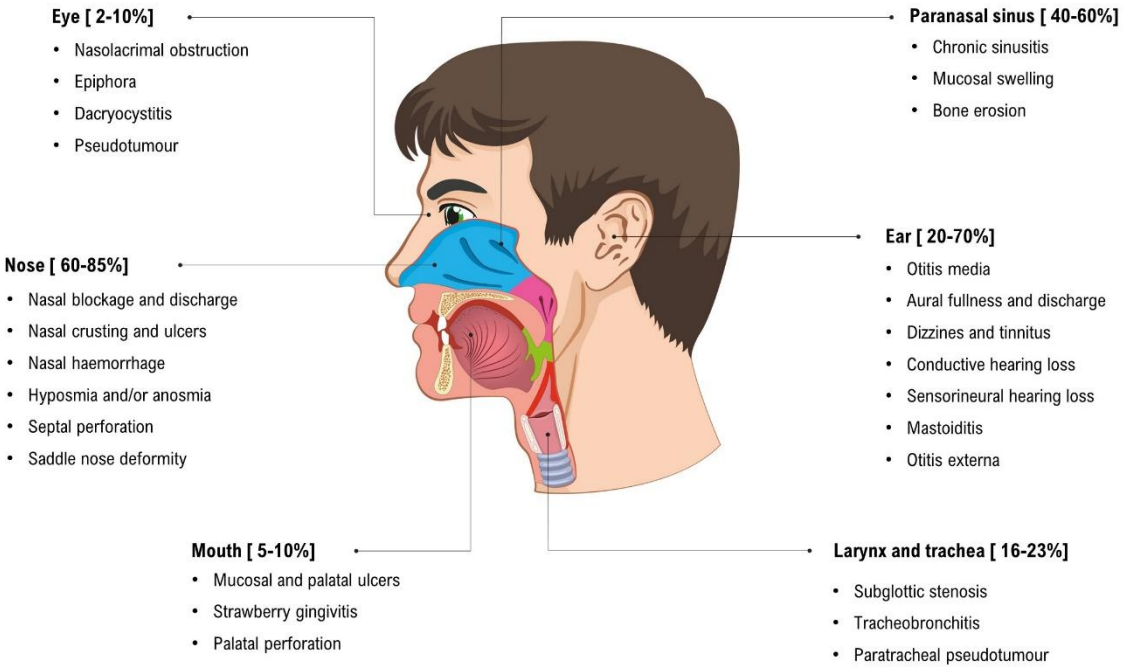

Figure 1. Ear, nose and throat features in granulomatosis with polyangiits according to anatomical region and frequency of involvement.

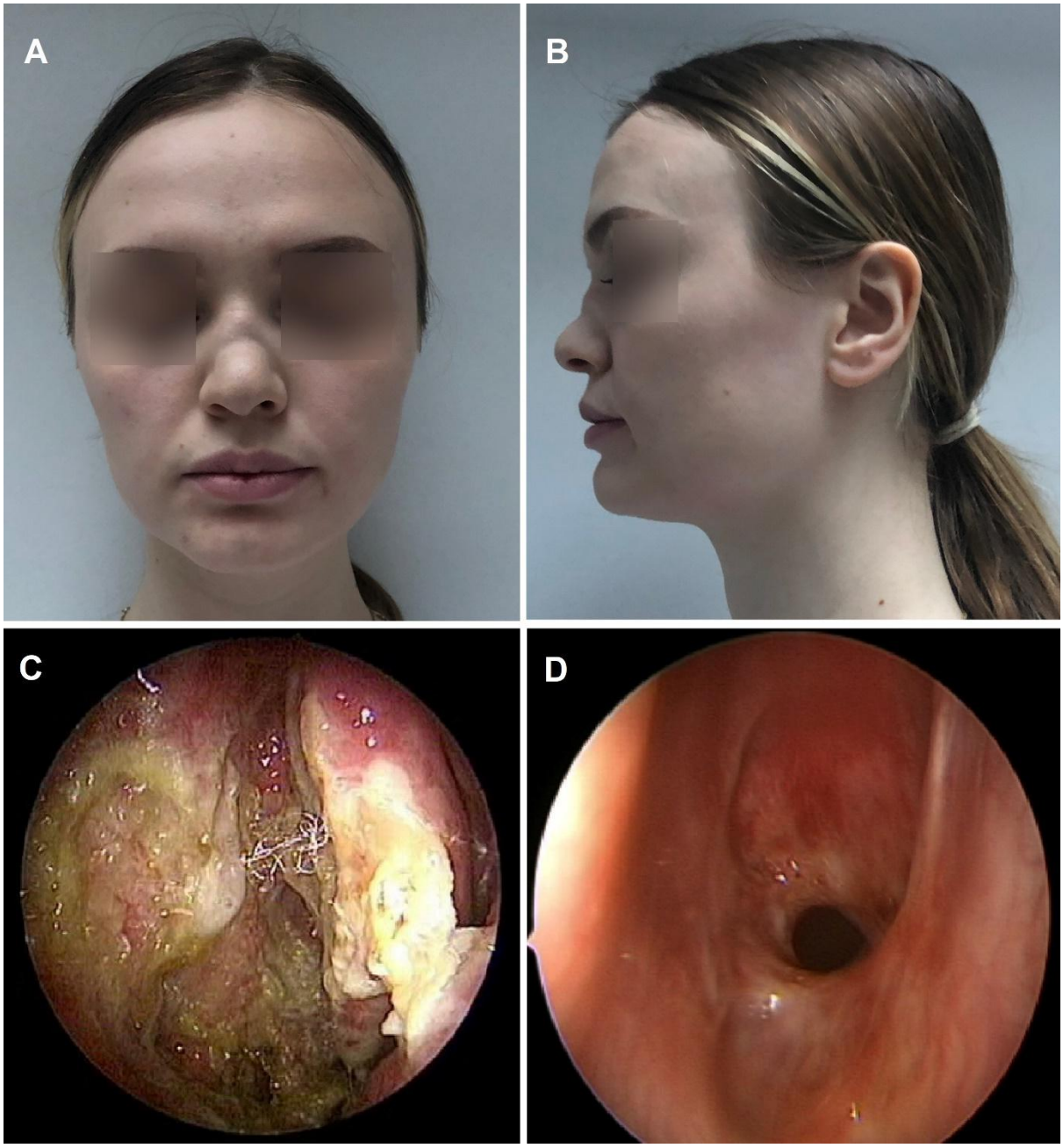

Figure 2. Clinical features of granulomatosis with polyangiits manifestations in the ENT region. Frontal and sagittal view of saddle-nose deformity (A, B). Nasal endoscopy (C) showing subtotal septal perforation, bone erosion of the right middle and inferior turbinates, and diffuse crusting covering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

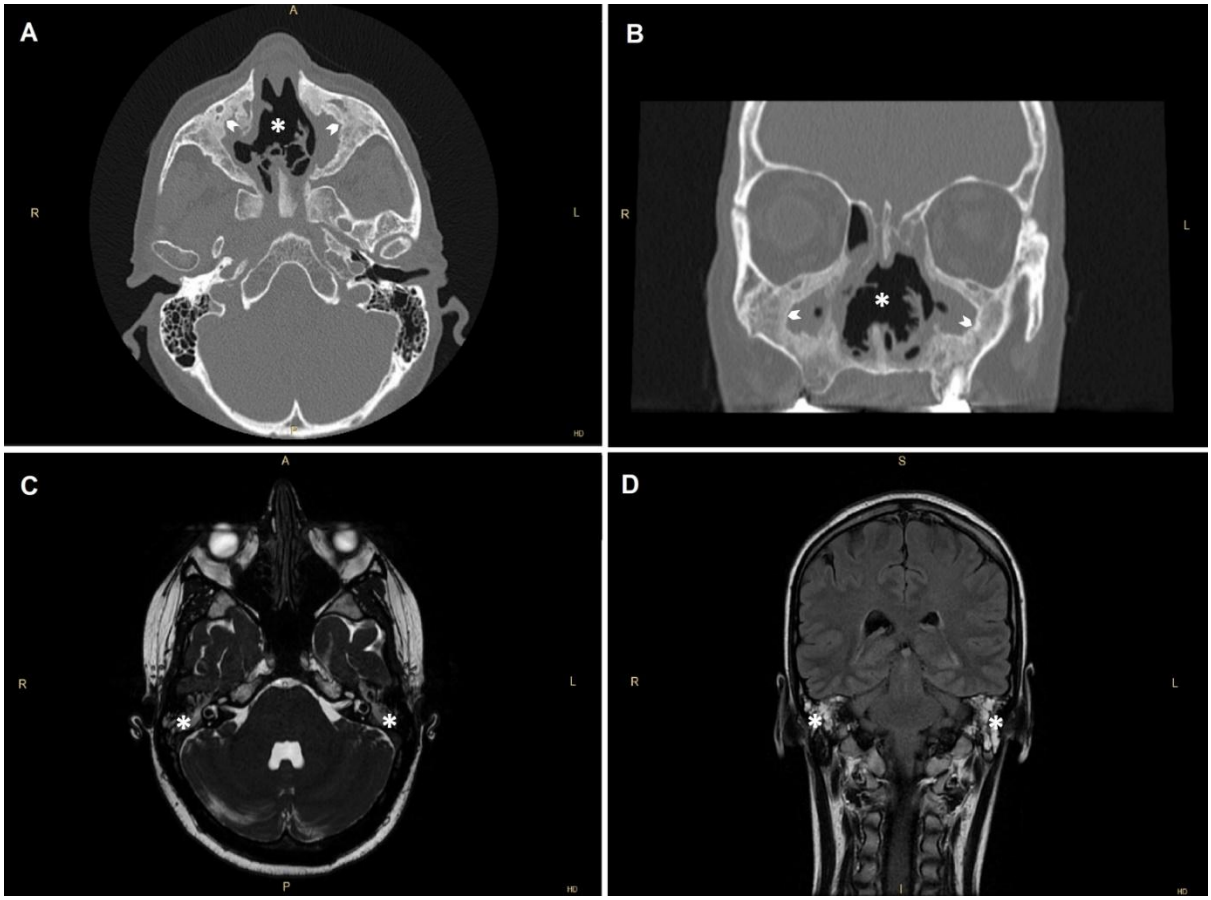

Figure 3. Radiological aspect of chronic rhinosinusitis, anterior septal perforation (asterisks) and maxillary sinus osteitis (arrowhead) in a patient diagnosed with granulomatosis with polyangiitis (CT scan, axial -A- and frontal -B- views). T2-weighted MRI axial scan (C) and Fluid Attenuated Inversion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