

The role of surgery in antineutrophil cytoplasmic antibody–associated vasculitides affecting the nose and sinuses: A systematic review

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Abstract

Background: The ear, nose and throat region has been reported to be one of the commonest sites involved in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis diseases and often precedes the diagnosis of ANCA–associated vasculitis by many months. Although treatment for ANCA–associated vasculitis primarily requires systemic immunosuppressive therapy, there are specific indications for sinonasal surgery during the course of the disease process. The three major roles for surgery in sinonasal vasculitis are to aid diagnosis through biopsy, enable symptom relief and nasal reconstructive surgery consideration when in remission.

Purpose: The aim of this systematic review is to provide an overview of the surgical procedures which can be performed in patients with ANCA–associated vasculitis presenting with sinonasal involvement.

Materials and methods: A systematic literature search was performed for scientific articles on MEDLINE (PubMed Advanced MEDLINE Search) and EMBASE. The search included all articles up to April 2020.

Conclusion: Surgical intervention during the active phase of ANCA–associated vasculitis disease can improve the patient's symptoms and enable histological diagnosis. The surgical decision to manage the nose requires a multidisciplinary approach involving the vasculitis specialist and the ear, nose and throat surgeon. Nasal reconstruction can be performed to restore form and function but only when the disease is in remission so as to maximise success and minimise complications.

Keywords

ANCA-associated vasculitis diseases, antineutrophil cytoplasmic antibody, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, endoscopic sinus surgery, saddle nose deformity, septal perforation, dacryocystorhinostomy

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Introduction

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis diseases (AAV) are multi-system autoimmune disorders, characterised by necrotizing inflammation of small- to medium-sized vessels with the presence of serum antibodies targeting cytoplasmic components of neutrophils. These antibodies specifically target proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA), contributing to cytoplasmic (c-ANCA) and perinuclear (p-ANCA) pattern in indirect immunofluorescence staining, respectively.

The American College of Rheumatology (ACR) in 1990 classified granulomatosis diseases into either granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis

with polyangiitis (EGPA).^{1,2} Instead, definitions for AAV were supplied at the Chapell Hill Consensus Conference in 1994 and later revised in 2012 and comprise GPA, EGPA and microscopic polyangiitis (MPA).³

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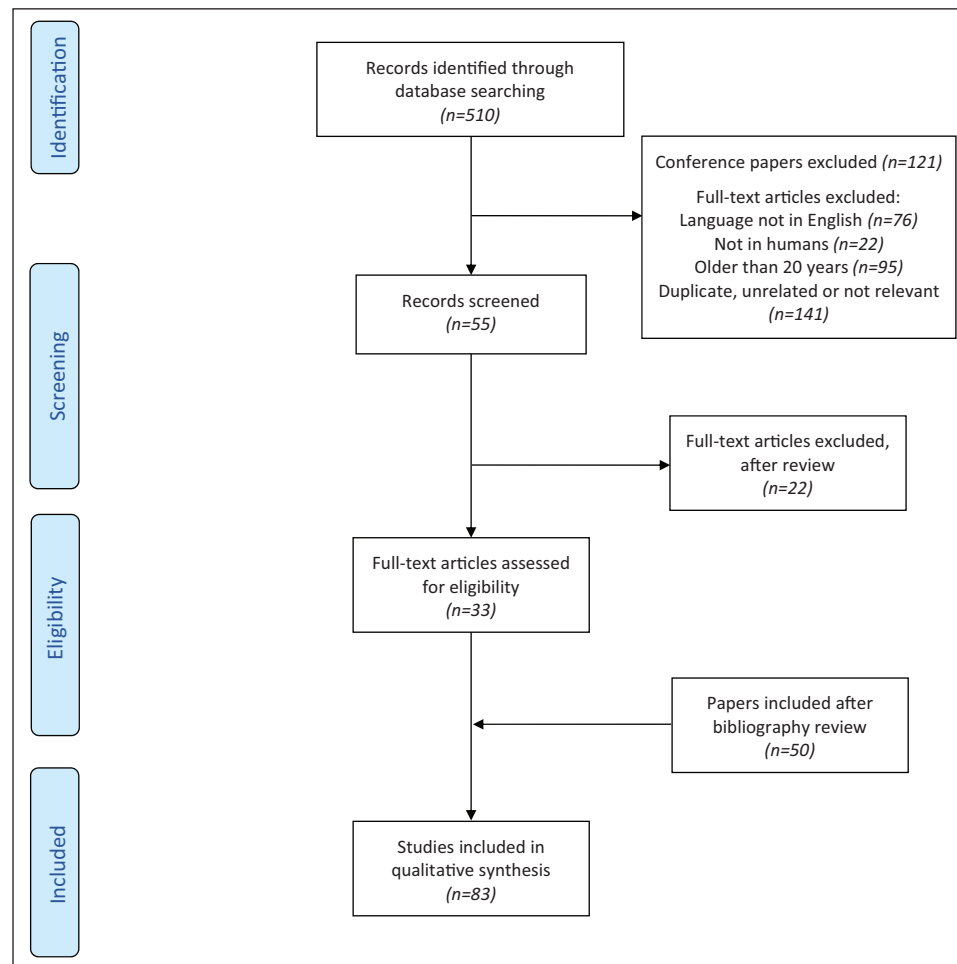


Figure 1. Systematic review flowchart.

Ear, nose and throat (ENT) involvement has been reported to be the second most common site after the lungs and often precedes the diagnosis of AAV by many months.⁴ The nose and paranasal sinuses, in particular, are the most frequently affected sites in the head and neck, with lesions in 64%–80% of the cases. Of importance, the nose has been shown to be the only affected site in about 30% of the GPA patients and hence a high index of suspicion is warranted.⁵ Other ENT manifestations include hearing loss (both conductive and sensorineural), tinnitus and dizziness, otitis media/otomastoiditis, otitis externa and ear drum perforation, laryngeal involvement (e.g. redness and swelling) and subglottic stenosis.^{6–11}

Although the treatment of AAV is primarily systemic, sinonasal surgery may be required to aid diagnosis through biopsy in order to confirm diagnosis and exclude malignancy or invasive fungal disease, to enable nasal symptom relief and to consider nasal reconstructive surgery once the disease is quiescent. Reconstructive surgery must be planned in an appropriate clinical window during which the patient's disease process is in a period of remission.^{5,12,13} A remission state is generally defined as Birmingham Vasculitis Activity Score (BVAS) of 0. The clinical utility of measuring

PR3-ANCA and MPO-ANCA to monitor disease activity is still debated,^{14,15} as levels may change from detectable to undetectable and vice versa in the course of the disease,¹⁶ and have been shown to be unremarkable as prognostic factors.^{15–18}

The aim of this systematic review is to provide an overview of surgical procedures that may be necessary in patients with AAV presenting with sinonasal involvement. Surgical treatment of other ENT sites (i.e. ear and larynx) will not be discussed as that goes beyond the scope of this review.

Material and methods

Literature search and study selection

A systematic literature search was performed for scientific articles on MEDLINE (PubMed Advanced MEDLINE Search) and EMBASE (EMBASE <1980 to 2020 Week 14>, Journals, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to 6 April 2020>). The search included all articles until April 2020 and was performed using the following keywords, also considering previous diseases nomenclature:

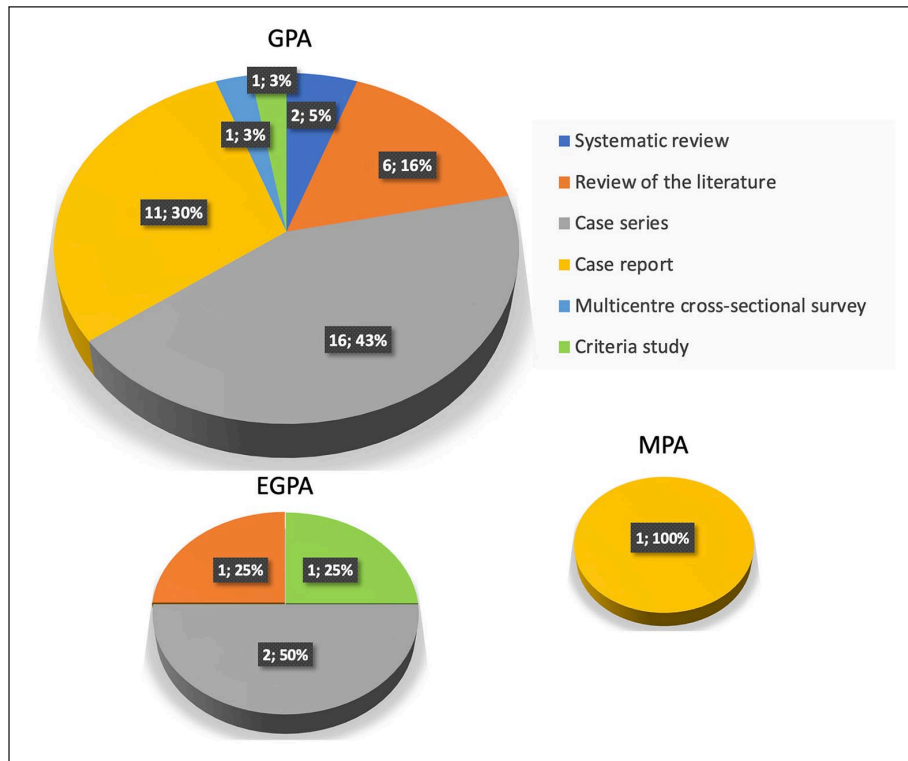


Figure 2. Number and percentage (No.; %) of papers cited related to surgical procedures in relation to study design and AAV disease.

granulomatosis with polyangiitis, Wegener, Churg-Strauss, eosinophilic granulomatosis, microscopic polyangiitis, septal surgery, nose surgery, sinus surgery, nasal surgery, rhinoplasty and dacryocystorhinostomy.

These terms have been later used in combination as follows: (((((((((((((((microscopic polyangiitis) AND septal surgery)) OR ((microscopic polyangiitis) AND nose surgery)) OR ((microscopic polyangiitis) AND sinus surgery)) OR ((microscopic polyangiitis) AND nasal surgery)) OR ((microscopic polyangiitis) AND rhinoplasty)) OR ((microscopic polyangiitis) AND dacryocystorhinostomy)))))) OR (((((((((((((((eosinophilic granulomatosis) AND septal surgery)) OR ((eosinophilic granulomatosis) AND nose surgery)) OR ((eosinophilic granulomatosis) AND sinus surgery)) OR ((eosinophilic granulomatosis) AND nasal surgery)) OR ((eosinophilic granulomatosis) AND rhinoplasty)) OR ((eosinophilic granulomatosis) AND dacryocystorhinostomy)) OR ((Churg-Strauss) AND dacryocystorhinostomy)) OR ((Churg-Strauss) AND sinus surgery)) OR ((Churg-Strauss) AND septal surgery)) OR ((Churg-Strauss) AND nose surgery)) OR ((Churg-Strauss) AND rhinoplasty)) OR ((Churg-Strauss) AND nasal surgery)))))) OR (((((((((((((((granulomatosis with polyangiitis) AND septal surgery)) OR ((granulomatosis with polyangiitis) AND nose surgery)) OR ((granulomatosis with polyangiitis) AND sinus surgery)) OR ((granulomatosis with polyangiitis) AND nasal surgery)) OR ((granulomatosis with polyangiitis) AND rhinoplasty)) OR ((granulomatosis with polyangiitis) AND dacryocystorhinostomy)) OR ((wegener) AND septal surgery)) OR ((wegener) AND nose surgery)) OR ((wegener) AND sinus surgery)) OR

((wegener) AND nasal surgery)) OR ((wegener) AND rhinoplasty)) OR ((wegener) AND dacryocystorhinostomy)).

References of the papers were further screened for relevant articles to reduce any bias linked to the limited range of the year of publication selected or to the key words used in the literature search.

Results

The initial search yielded a total of 510 publications from January 1953 to April 2020. This result was later reduced by applying filters to the database search. Conference abstracts were not considered (n=121) if they were not published as regular articles in MEDLINE/PubMed or EMBASE. We excluded papers not written in English (n=76), not conducted on humans (n=22) and older than 20 years (n=95). After an initial reading of the abstract, articles unrelated or considered not relevant to the topic were excluded (n=141). A total of 55 articles met the selected criteria. A total of 22 papers were excluded after a full-text revision. Further 50 papers were added after bibliography review which helped reducing any bias linked to the limited range of the year of publication selected or to the key words used in the literature search. Finally, 83 papers were considered for the review. Figure 1 shows the flow chart adopted in the systematic review process. Figure 2 shows the breakdown of articles specifically related to surgical procedures.

Table 1 summarises the relevant findings of this systematic review according to main role of surgery, type of surgery and AAV disease.

Table 1. Summary of relevant findings on sinonasal surgical treatments that can be requested in ANCA-associated vasculitis disease.

Main role of surgery	Type of surgery	AAV disease	Study details	Study designs (± sample size)	Summary of findings
Diagnosis	Biopsy	GPA	Leavitt et al., ¹ USA	Criteria study	Historically confirmed evidence of necrosis, granulomatous inflammation and vasculitis in an artery or arteriole is one of the requested criteria according to the 1990 American College of Rheumatology classification criteria for GPA.
			Jennings et al., ¹⁹ UK	Case series of 53 subjects	Patients with negative ANCA and clinical suspicion of GPA should be biopsied. However, negative nasal biopsy does not exclude GPA.
			Gottschlich et al., ²⁰ Germany	Review of the literature	Biopsies frequently fail to establish the diagnosis of GPA.
			Murray and McGarry, ²¹ UK	Case series of 63 subjects	The majority of specimens show findings nonspecific of GPA.
			Pereira et al., ²² Spain	Review of the literature	A negative histopathological result in a nasal biopsy specimen should not exclude vasculitis.
		EGPA	Masi et al., ² USA	Criteria study	Historical proof of vasculitis with extravascular eosinophils represents one of the requested criteria according to the 1990 American College of Rheumatology classification criteria for EGPA.
		MPA	Pagnoux and Wolter, ²³ Canada	Review of the literature	Nasal biopsy of affected tissue can be requested to support diagnosis of EGPA
			Kokan et al., ²⁴ Japan	Case report ^b	Nasal biopsy specimens obtained at surgery may be useful for proving the presence of MPA vasculitis
Symptom relief	Splints insertion	GPA	Sachse and Stoll, ¹² Germany	Review of the literature	Septal buttons are an alternative option of treatment in case of unsuccessful surgical closure of NSP.
			Pereira et al., ²² Spain	Review of the literature	Septal buttons can temporarily close symptomatic NSP and can remain in place for 1 year or more.
			Watson and Barkdull, ²⁵ USA	Review of the literature	Septal buttons can cause several complications (i.e. epistaxis, nasal crusting, intranasal pain, erosion of the NSP edges and eventual enlargement of the defect)
Nasal reconstruction	Septal perforation repair ^a	GPA	Delaney and Kridel, ²⁶ USA	Multicentre cross-sectional survey – 320 respondents	The success rates in closing perforations < 1 cm, 1–2 cm, and > 2 cm were 84%, 64% and 31%, respectively. <i>No information reported with regard to GPA patients.</i>
			Morse et al., ²⁷ USA	Case report ^c – 17 patients (1 GPA patient)	Temporoparietal fascia graft combined with a polydioxanone plate mainly for small NSP.
			Pendolino et al., ²⁸ UK	Case report ^c – 11 patients (1 GPA patient)	A unilateral transpositional/rotational flap utilising lateral nasal wall and inferior turbinate mucosa and a contralateral underlay porcine small intestinal submucosa mesh for big NSP.
	Saddle nose deformity repair	GPA	Coordes et al., ²⁹ Germany	Systematic review – 41 GPA patients	Saddle nose reconstruction in GPA patients with minimal or no local disease is a safe procedure despite an increased rate of revision surgery. Two-dimensional L-shaped strut grafts for saddle nose reconstruction.
			Congdon et al., ³⁰ USA	Case series – 13 patients	Surgery does not appear to either induce a flare-up or accelerate the course of GPA even if they have a higher risk of failure. Costal cartilage grafts are associated with a better transplant success rate (83%) compared with bone grafts.
			Lasso and La Cruz, ³¹ Spain	Case report ^b	Fascia lata graft is a new and good option for nasal reconstruction in patients with GPA.
			Noguchi et al., ³² Japan	Case report ^b	Bilateral nasolabial flaps pedicled on the infraorbital vessels, and costal cartilage grafts for severe nasal deformity caused by GPA.
			Duffy et al., ³³ USA	Case report ^b	External rhinoplasty approach by implantation of a split calvarial bone L-shaped strut.
			Shipchandler et al., ³⁴ USA	Case series – 15 patients	Autologous iliac crest bone for saddle nose deformity.
			Nishiike et al., ³⁵ Japan	Case series – 5 patients	L-shaped rib cartilage graft for restoration of nasal deformity.
			Vogt et al., ³⁶ Germany	Case series – 4 patients	
			Qian and Malata, ³⁷ UK	Case series – 4 patients	
			Sepehr et al., ³⁸ Canada	Case series – 10 patients	Autologous costal cartilage grafts for saddle nose deformity.

(Continued)

Table 1. (Continued)

Main role of surgery	Type of surgery	AAV disease	Study details	Study designs (\pm sample size)	Summary of findings
Management of complications	ESS	GPA	Bennet and Reilly, ³⁹ UK Ezzat et al., ⁴⁰ USA	^a Case report Systematic review – 44 patients	Hyaluronic acid injection to improve cosmesis while awaiting formal nasal reconstruction. Rhinoplasty for saddle nose deformity is a safe and effective procedure in the setting of GPA. L-shaped strut graft appears to be a more robust technique in the setting of GPA. The use of split calvarial bone appears to have a slightly lower complication rate over costal cartilage. The risk of complications decreases with the use of L-shaped struts and increases as the number of individual grafts placed increase.
			Kwame et al., ¹⁶ UK Romo et al., ⁴¹ USA	Case report ^b Case series – 15 patients (No. of GPA patients not reported)	L-shaped rib cartilage graft secured to the glabella and maxillary spine for saddle nose deformity. Composite alloimplant of high-density polyethylene and purified acellular human dermal grafts for major saddle nose deformity.
	Orbital decompression Optic nerve decompression DCR	GPA	Sachse and Stoll, ¹² Germany	Review of the literature	Sinus surgery may be indicated in patients with involvement of the sinuses refractory to systemic treatment. ESS is an effective treatment of CRS in GPA patients.
			Cannady et al., ⁴² USA Nishiike et al., ³⁵ Japan Bacclu et al., ⁴³ Italy	Case series – 13 patients Case report ^b Case series – 29 patients	ESS in EGPA patients should be discouraged considered the good response to medical treatment and early polyp recurrences after surgery.
		GPA	Migliani et al., ⁴⁴ USA Cannady et al., ⁴² USA Nishiike et al., ³⁵ Japan	Case series – 3 patients Case series – 3 patients Case report ^b	Orbital pseudotumour requiring orbital decompression. Optical nerve decompression required for acute visual of vision.
			Cannady et al., ⁴² USA Nishiike et al., ³⁵ Japan Kwan and Rose, ⁴⁵ UK Lee et al., ⁴⁶ USA	Case series – 7 patients Case report ^b Case series – 11 patients Case series – 11 patients	DCR requested for epiphora or dacryocystitis. External DCR surgery safely and effectively treats nasolacrimal duct obstruction.
		GPA	Næser et al., ⁴⁷ Denmark Sweeney et al., ⁴⁸ USA Kwame et al., ¹⁶ UK	Case series – 7 patients Case series – 6 patients Case report ^b	Endoscopic DCR surgery safely and effectively treats nasolacrimal duct obstruction. Pericranial flap reconstruction for chronically discharging medial epicanthal fistulation.

ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; NSP: nasal septal perforation; ESS: endoscopic sinus surgery; CRS: chronic rhinosinusitis; DCR: dacryocystorhinostomy.

^aOnly studies on septal perforation repair in GPA patients have been added to the table.

^bCase report on only one patient.

^cCase series considered as case report as only one GPA patient treated with the described technique.

Nasal biopsy

Histological confirmation of GPA is a classification criterion according to the ACR.¹ A positive histology should demonstrate necrosis, granulomatous inflammation and vasculitis within an artery or arteriole.¹ As the nose and paranasal sinuses are frequently involved in GPA, obtaining an intranasal biopsy is considered the easiest method to obtain histological confirmation. It is important to bear in mind that sinonasal biopsies have a significant false-negative rate¹⁹ with 50% being non-diagnostic.²⁰ In reality, the majority of specimens only demonstrate acute or chronic inflammation which does not help in confirming the diagnosis of GPA.²¹ However, a high index of suspicion needs to remain when in light of a negative histopathological result the clinical picture fits the diagnosis of GPA.⁴⁹

The ACR requires six criteria to be fulfilled to classify EGPA and, also in this case, nasal biopsy with positive histology of the affected tissue is one of them.^{2,23}

While intranasal biopsies are the commonest way to confirm diagnosis in GPA and EGPA, intranasal biopsies from patients with MPA rarely demonstrate the presence of vasculitis³⁰ and consequently is of minimal benefit.

Nasal silastic splints and septal buttons

Nasal silastic splints and septal buttons are silicon prostheses placed inside the nose along the septum to obtain an artificial closure of a nasal septal perforation. They have been shown to improve nasal symptoms associated with active GPA as well as non-active GPA including pain, nasal discharge, crusting and/or whistling.¹² These prosthetic devices are generally well tolerated and can remain in situ for 6–12 months and then replaced if the securing sutures become dislodged or the patient decides to have a trial without splints. Importantly, they can be removed quickly under local anaesthesia if not beneficial. However, they can also be associated with complications such as pain, epistaxis or crusting and very rarely cause an enlargement of the perforation.^{22,25}

Septal perforation repair

Among all autoimmune diseases characterised by sinonasal involvement, GPA seems to be the main cause of septal perforation (48% of all cases of autoimmune disorders).⁴² The aim of surgery is to achieve anatomical integrity of the nasal septum to restore normal nasal function. Numerous techniques have been described including local intranasal flaps, alloplastic material, pericranial flaps, grafting with acellular human dermal allograft and interposition grafting using both synthetic and autologous grafting material.²⁷ However, it must be specified that most of the septal perforation repair techniques described in the literature were on non-AAV patients and a gold-standard technique has not been agreed upon.

The reconstructive surgical approach to septal perforation repair is guided by the surgeon's own experience as well as the dimensions and position of the perforation. Current consensus recommends unilateral or bilateral advancement or rotational septal flaps and have reported success rates of 84% for small perforations, 64% for moderate perforations and 31% for larger perforations measuring more than 2 cm.²⁶ In general, multilayer closure for nasal septal perforation repair has proven to be the most effective technique. Morse et al.²⁷ successfully used temporoparietal fascia autografts in combination with a polydioxanone plate for small perforation repair closures on patients with GPA. In our institution, we have successfully adopted a unilateral transpositional/rotational flap for large perforations. It mobilises a unilateral mucoperichondrial and mucoperiosteal lateral nasal wall and inferior turbinate mucosa rotation flap in conjunction with a contralateral underlay porcine small intestinal submucosa mesh with an interpositional crushed cartilage graft.²⁸

The decision on whether to use the external or internal approach for septal perforation repair equally depends on the surgeon's own experience and size and site of the perforation. We have found that the internal or endonasal approach is associated with less post-operative pain, scarring and aesthetic deformity; however, it provides less exposure compared to an external approach which is, instead, generally recommended when perforations are more than 1 cm in diameter.

To date, septal perforation repairs for EGPA and MPA patients have not been reported upon within the literature.

Saddle nose deformity repair

Nasal deformities can range from loss of dorsal height to a shortened nasal length, with tip deprojection and retraction of the nasolabial angle²⁹ and up to now an optimal repair technique has not been defined. As long as the underlying disease is controlled and in remission, traditionally proven rhinoplasty techniques can safely be applied.¹² It is very important to use a reliable and robust reconstructive technique that is able to deal with a very poor vascular framework secondary to the consequences of vasculitis.⁵⁰ Consequently, the incidence of revision surgery is significantly higher in GPA patients when compared to patients without systemic vasculitis disease.³⁰

As a general rule, the severity of the saddle nose deformity guides the method of reconstruction and can range from isolated dorsal augmentation onlay techniques, to the use of extended spreader graft techniques when length also needs augmenting³¹ and to finally a two-dimensional L-shaped strut technique when length and projection require augmentation.²⁹

The L-shaped strut technique has evolved over time with Noguchi et al.³² and Duffy et al.³³ in 1991 and 1998, respectively, describing a technique using costal cartilage for dorsal and septal support in combination with bilateral

well-vascularized musculomucosal flaps for internal nasal lining. Shipchandler et al.³⁴ described a calvarial bone L-shaped strut technique on four saddle nose deformities using an external rhinoplasty approach which consisted of a dorsal onlay graft and a columella strut fixed together with a titanium screw. Nishiike et al.³⁵ successfully reconstructed one saddle nose using autologous iliac crest bone. Vogt et al.³⁶ used an open rhinoplasty approach for restoration of the nasal framework with an L-shaped rib cartilage graft, reporting no signs of resorption of the rib cartilage grafts despite the immunosuppressive medication in all four patients. Sepehr et al.³⁸ published a series of 10 cases of GPA patients undergoing open rhinoplasty with autologous costal cartilage grafts for reconstruction, with a success rate of 60%. Qian et al.³⁷ performed an open rhinoplasty approach with L-shaped costal cartilage grafts reporting good aesthetic results. Bennett et al.³⁹ described a case of nasal collapse secondary to GPA with unstable disease who benefitted from temporary dermal fillers (hyaluronic acid) while awaiting formal nasal reconstruction. Kwame et al.¹⁶ in 2018 further refined the L-strut technique by harvesting autologous osseocartilaginous costal grafts from the floating ribs. The dorsal onlay osseocartilaginous component was secured to the glabella and the osseocartilaginous strut component was secured to the remnant maxillary spine.¹⁶

Systematic reviews demonstrate that saddle nose reconstruction in GPA patients with minimal or no local disease is a safe procedure and that L-strut grafts appear to be a more robust technique in the setting of GPA.^{29,40} The risk of complication decreases with the use of a L-shaped strut reconstruction technique when compared to reconstruction using multiple smaller grafts.⁴⁰ The L-strut also affords better stability which resists the resultant scarring and contracture caused by surgery, whereas the placement of smaller and less secure grafts does not offer this stability.⁴⁰ However, the debate continues over which technique is the best for nasal reconstruction.^{12,29}

The best graft to use for reconstruction, if autologous (autograft) or non-autologous (allograft) grafts, and in this case, if cartilage or bone, is still matter of discussion. Autografts using costal cartilage and bone are considered to be the first choice for grafting in GPA patients and also confers a strong reconstructive template. On the other hand, the use of allografts (e.g. irradiated bone, cartilage or dura) in reconstruction has been shown to increase the rate of infection and resorption.^{41,51} Moreover, they also require larger amounts of cartilage in order to accommodate for resorption. Congdon et al.³⁰ published a series of 13 cases of GPA patients undergoing reconstructive nasal surgery using costal cartilage (40%), temporoparietal bone (calvarial bone graft, 27%), irradiated rib (7%), irradiated dura (7%), autologous conchal cartilage (7%), iliac crest (7%) and bony septum (7%). They observed that autologous costal cartilage grafts were associated with better transplant success rates (83%)

compared with bone grafts (calvarial bone graft; transplant success rate 75%) and irradiated materials showed complete reabsorption long term.³⁰ Conversely, Ezzat et al.⁴⁰ observed a slightly lower complication rate with calvarial bone grafts (11%) compared with those reconstructed with costal cartilage (19%).

Saddle nose deformity has not been reported in EGPA and MPA patients and this could be related to the fact that nasal manifestations in these two diseases are less destructive when compared to GPA.

Endoscopic sinus surgery

Sinonasal involvement has been reported to be the most commonly affected ENT site in patients with AAV. Patients with GPA are more prone to suffer from sinonasal disorders than those with MPA.⁴ Many patients with GPA present with symptoms and radiological findings that overlap with chronic rhinosinusitis (CRS). However, signs of sinus involvement on computed tomography (CT) or magnetic resonance imaging (MRI) scans do not differentiate between CRS or granulomatous disease.⁵² Conversely, in the chronic stages of the disease, especially after several relapses, the sinuses become filled with scar tissue and the maxillary sinuses frequently become smaller, with progressive ossification of the maxillary bone.⁵²

Endoscopic sinus surgery (ESS) should be reserved for refractory cases unresponsive to maximal medical treatment or those presenting with complications (e.g. mucocoeles).¹² Decompression of the orbit and the optical nerve may become necessary for some patients although data are very limited so far.^{35,42} Surgical orbital decompression should be reserved for patients with orbital inflammation presenting with severe pain, proptosis or optic nerve compression not responding to aggressive medical therapy.^{42,53–55} Furthermore, evidence suggests that sinus surgery for GPA can contribute to additional scarring and lead to protracted sinonasal symptoms.

EGPA presents as a more aggressive form of nasal polyposis with Lund-Mackay scores being reported to be higher than in GPA.¹⁰ Evidence suggests that patients with EGPA respond well to medical treatment and some authors discourage ESS.⁴³ In a recent retrospective review on 424 CRS patients who had undergone ESS with a single surgeon, EGPA patients demonstrated low revision rates when compared to GPA patients.⁴⁴

Dacryocystorhinostomy and other orbital surgeries

Nasolacrimal duct obstruction occurs in 8% of patients with GPA, and epiphora or dacryocystitis may be early signs of duct obstruction.⁵⁵ Epiphora, which represents the most common ophthalmologic finding in patients with GPA, is caused by the direct granulomatous involvement, infection

or compression of the nasolacrimal duct and the lacrimal sac.⁵⁶ It is usually a late manifestation and can present bilaterally.⁵⁷

Orbital pseudotumour is another common finding and represents primary granulation tissue in the retro-orbital area or as a propagation of a sinus lesion.^{42,50} It occurs in 15% of GPA patients during their disease course.⁵⁵ Both external and endoscopic dacryocystorhinostomy (DCR) approaches have been shown to be successful in the management of epiphora and orbital pseudotumor.^{5,45–48,58–60} However, external DCR can lead to wound necrosis and nasocutaneous fistula, endonasal cyst and punctal membrane formation.^{55,61,62} In addition, endoscopic approach offers the advantage to treat a possible coexisting sinonasal disease that, if left untreated, can lead to DCR failure.⁶³ Anecdotally, we previously described a case of a chronically discharging medial epicanthal fistulation into the nose successfully treated with a pericranial flap reconstruction.¹⁶

To our knowledge, neither DCR nor other orbital surgeries have been reported in EGPA and MPA patients.

Discussion

The role of sinonasal surgery in GPA

GPA, previously known as Wegener's granulomatosis, is a systemic inflammatory vasculitis of medium- and small-sized arteries, characterised by necrotizing granulomatous inflammation mostly affecting the respiratory tract with a coexisting glomerulonephritis, but virtually involving all organ systems.⁵⁰ In 80%–95% of the patients, ENT manifestations represent the first symptoms of GPA,⁶⁴ and in some cases, otorhinolaryngological symptoms are the only signs of the disease.⁶⁵ This GPA presentation represents the most frequent type and is termed 'limited GPA'. Limited GPA typically involves only the upper respiratory tract and rarely the skin. It is more recurrent and refractory as well as more likely to affect younger individuals with a female propensity compared to the generalised form.⁶⁵ However, most patients with a limited form will then progress over time into the systemic form. Solely localised GPA accounts for <5% of all cases.^{65,66}

A combination of typical GPA clinical manifestations and positive anti-PR3 c-ANCA antibodies is sufficient to make a diagnosis of GPA and start treatment. However, increasingly the need for a positive biopsy remains central to the diagnostic workup of patients with suspected GPA. This is even more important in scenarios when serologic ANCA testing is non-diagnostic. Consequently, this systematic review supports the importance of nasal biopsy in suspected GPA patients, particularly in those with ANCA negativity and a disease limited to the nose and sinuses, in order to confirm the diagnosis and also exclude other midline destructive disorders. In fact, active GPA can clinically present similarly to other midline destructive disorders such as T cell lymphoma, squamous cell carcinoma or invasive fungal sinusitis. Furthermore, the

clinical and biochemical appearances of limited GPA may be difficult to distinguish from lesions caused by cocaine abuse and the differential diagnosis can be challenging.^{67–72}

In GPA sinonasal involvement usually starts in the septum area supplied by the Kiesselbach plexus and then spreads to the paranasal sinuses.⁵⁶ Active nasal inflammation and the consequent cicatricial process represents one of the major causes of morbidity. Chronic sinonasal involvement may result in CRS, septal perforation, saddle nose deformity and paranasal sinus mucocele formation from chronic outflow tract obstruction. Therefore, surgical procedures focusing on symptom relief as well as nasal reconstruction surgery may be needed during the disease course.

GPA affects the structural integrity and the function of the upper airway tract and affects the ability to breathe, the sense of smell and the barrier function of the nose with consequent bacterial colonisation of the disturbed mucosa. In fact, GPA has been associated with an altered nasal microbial composition, at both the bacterial and fungal levels, which can partially explain the increased tendency to develop CRS.⁷³ Sinonasal involvement impacts significantly on the general quality of life of patients with GPA and it is as significant as that found in the general rhinosinusitis population.⁷⁴ This systematic review confirms the effectiveness of ESS in the treatment of CRS in GPA patients. However, if ESS is employed, mucosal-sparing techniques and preservation of retained structures should be the principle. In cases of limited sinus disease, only the involved site should be addressed, in order to prevent further scarring. Post-operative care plays an important role in these patients, and weekly post-operative debridement, saline or antibiotic irrigations, and culture-directed antibiotics should be the mainstay of treatment.⁷⁵

Anterior septal perforations occur in 33% of GPA cases.⁴² Septal perforation closure in GPA patients has been traditionally a contraindication owing to the chronic course of the disease and multiple flare-ups which may prevent a successful repair.^{56,76} However, with increasing advancement in repair technique, it has been recommended only when the disease is in long-term remission, when the perforation size is less than 2 cm and when healthy nasal mucosa is evident. Septal splints can be considered an option in patients with non-controlled disease or if surgical closure of septal perforation is not feasible.

Saddle nose deformity caused by a combination of a large anterior septal perforation with collapse of the cartilaginous mid-vault has been reported in 33% of GPA patients.^{5,42} This will affect nasal airflow and cause nasal obstruction. The findings of this systematic review confirm that saddle nose reconstruction in GPA patients is generally considered to be a safe procedure albeit with an increased rate of revision. The timing of surgery is extremely important to ensure success and an multidisciplinary team (MDT) discussion with all clinical teams is recommended to ensure the patient's disease is stable and in remission. The best method of reconstruction has been shown to be a self-supporting bony or cartilaginous structure fashioned in a L-shaped design. The

ideal graft is strong costal cartilage/bone in order to support the mid-nasal-third and prevent retraction of the columella.

Ocular and orbital manifestations occur in 50%–60% of GPA patients, and they are often seen in conjunction with or as a result of adjacent sinonasal disease.^{42,77} Our results show that both endoscopic and external DCR are safe techniques in the management of epiphora or dacryocystitis. However, as with other type of surgery on GPA patients, DCR or orbital procedures should be planned when the disease is quiescent and is probably reasonable to undertake if activity is controlled with maintenance therapy.⁵⁹

No general consensus exists on the best time for sinonasal surgery and our systematic review failed to show this. Generally, surgical procedures on the nose should be meticulously planned in GPA patients,⁵⁶ factoring in poor tissue perfusion caused by the vasculitis which can result in a poor wound healing and increased graft resorption. Ideally, reconstructive nasal surgery should be planned once the disease is in a state of complete remission and in the absence of clinical, laboratory and radiologic signs of disease.¹² Some authors further suggest to plan surgery no earlier than 6–12 months following disease stabilisation.¹³ It has been shown that nasal surgery does not induce a flare-up or influence the course of the disease, even if disease severity contributes to the success rates in saddle nose reconstruction, with localised GPA patients reporting an overall higher success rate (88%) when compared to the generalised forms (60%).³⁰

The role of sinonasal surgery in EGPA

EGPA, previously known as Churg-Strauss syndrome, is a systemic small- to medium-sized vasculitis characterised by peripheral blood eosinophilia, bronchial asthma and CRS. EGPA is rarer than GPA⁷⁸ and its pathophysiology still remains partially unknown. Almost 30%–40% of affected patients have been found to show ANCA positivity usually directed against MPO, and most of these present with eosinophilia of more than 10% in peripheral blood.⁷⁹ Moreover, nasal biopsy of affected tissue can be requested to support diagnosis of EGPA.^{2,23}

ENT involvement is a common manifestation in EGPA patients although nasal and sinus lesions are typically not erosive when compared to GPA.²³ Sinonasal manifestations include allergic rhinitis, recurrent rhinosinusitis and nasal polyposis.⁸⁰ Overall, EGPA-related sinonasal morbidity is still significant and is comparable to that of the general rhinosinusitis population.⁸¹ The results of this systematic review advise against ESS as a first-line treatment in EGPA and instead recommends a trial of maximal medication which is often very successful in the initial treatment of nasal polyps.⁴³ In our experience, large cavity ESS (i.e. complete ESS combined with a Draf IIb/III) combined with maximal medical treatment is highly recommended when limited ESS and maximal medical treatment has failed.

To the best of our knowledge, no cases of septal perforations or saddle nose deformities in EGPA patients have been reported.

The role of sinonasal surgery in MPA

MPA is a systemic necrotizing vasculitis affecting small vessels without granulomatous inflammation. ENT involvement has been reported with different percentages ranging from 9% to approximately 40% of MPA patients.^{24,82} The number of reported MPA cases diagnosed by means of nasal biopsy remains exiguous. Crusting may be considered a frequent symptom in MPA patients,⁸³ while CRS with nasal polyps and nasal septal perforations are rarely observed. Our systematic review demonstrated a very low number of publications on sinonasal surgery in MPA patients. Therefore, recommendations cannot be provided.

So far, no cases of septal perforations or saddle nose deformities in MPA patients have been reported.

Limitations

The strategy of the literature search performed (keywords used) and the range of year of publication chosen may have led to an incomplete retrieval of identified research. However, this may have been reduced once we performed a further screening of the references cited in each article. In addition, most of the studies that have been reviewed were related to surgical procedures on GPA patients. This can be a consequence of the more destructive lesions often observed in GPA patients which require more surgical interventions or to the deficiency of works published on this topic in the specific population of EGPA and MPA patients. Moreover, the majority of the articles included in the analysis are case series or reports; therefore, recommendations provided have a low level of evidence being mainly based on expert opinions.

Conclusion

All patients with suspected AAV disease affecting the nose or sinuses require a nasal biopsy to exclude other midline destructive diseases and to confirm diagnosis. All patients should be managed in a multidisciplinary setting and surgery should be tailored to the patient's needs in order to provide symptomatic relief and could include limited ESS and nasal splints. Nasal reconstructive surgery should only be performed when the disease is in remission so as to minimise complications.

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