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Mini Review

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Reconstructive Flaps After Salvage Nasopharyngectomy

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ABSTRACT

Importance: The emergence of new technologies for early diagnosis of recurrent nasopharyngeal cancer and new techniques of endoscopic nasopharyngectomy increase the incidence of salvage nasopharyngectomy and pose the question of the ideal flap for reconstruction of this defect.

Objectives: A review of the literature to identify the flaps used in nasopharyngeal reconstruction and their advantages and disadvantages, characteristics, and outcomes.

Methods: We reviewed the literature available in the English language to identify the various flaps used, their indications and surgical technique, complications and outcomes.

Results: Multiple flaps have been used. Local mucosal flaps such as the posterior pedicled middle turbinate mucoperiosteal flap, the posterior pedicled Nasal Septal Flap (NSF) and Floor mucoperiosteum flap (FF), pedicled flaps such as the extended glabellar fascial cutaneous flap, the Haddad-Bassagasteguy flap, the temporoparietal fascial flap and the pericranial flap and free flaps such as the radial forearm and vastus lateralis flap have been described. These flaps are used depending on the specific defect characteristics and tissue available for reconstruction. The advantages and disadvantages of these flaps are discussed.

Conclusion: No single flap is ideal for all cases. The choice of flap will have to be tailored according to the patient, the defect created, consistent with oncologic principles, donor site availability and surgeon preference. A working knowledge of available flaps is essential to provide coverage of the skull base to avoid vascular and infectious complications.

KEYWORDS: Nasopharyngeal flap; Salvage nasopharyngectomy; Nasopharyngeal cancer.

ABBREVIATIONS: NSF: Nasal Septal Flap; FF: Floor mucoperiosteum flap; HBF: Haddad-Bassagasteguy Flap; TPF: Temporoparietal fascial flap; ALT: Anterolateral thigh free flap.

INTRODUCTION

Nasopharyngeal cancer differs from other head and neck tumors in that it occurs predominantly in a younger age group and is unrelated to tobacco or alcohol exposure.¹ It is a radiosensitive tumor and the primary treatment is radiotherapy or chemoradiotherapy. Surgery is reserved for persistent or recurrent tumors after the initial therapy. The emergence of significant anatomic and technical advances coupled with improvements in instrumentation has facilitated the exposure and resection of nasopharyngeal pathology which in turn has increased the incidence of salvage nasopharyngectomy. Such resections often necessitate skull base reconstruction for defect coverage and to promote healing (especially in the setting of radiation therapy). As such, it is of utmost importance for the surgeon to consider all reconstructive options in order to choose a flap individualized for the patient. Materials for reconstruction include pedicled nasoseptal flaps, turbinate flaps, endoscopic regional flaps from extranasal sources as well as free flaps. Choices should be guided by the location and size of the defect, presence of intraoperative cerebrospinal fluid leak after resection, and history of radiation or previous sinonasal surgery.

METHODS

A review of the published literature was undertaken to collate the data available on reconstructive techniques employed after nasopharyngectomy. A search strategy on PubMed was designed to include articles with keywords middle turbinate mucoperiosteal flap, the posterior pedicled Nasal Septal Flap (NSF), Haddad-Bassagasteguy Flap (HBF), Temporoparietal fascial flap (TPF), pericranial flap, free flap, and nasopharyngectomy/salvage nasopharyngectomy.

RESULTS

Six case series, one retrospective chart review, and two literature reviews were included in this review (Table 1). Reconstructive methods specifically following salvage nasopharyngectomy have not been well studied therefore it is not surprising that there are no randomized controlled studies or systematic reviews regarding the subject. Table 2 lists various pedicled flaps used successfully in reconstruction after nasopharyngectomy.

DISCUSSION

In 2006, the hadad-bassagasteguy flap (HBF) was first described. The advances in instrumentation and imaging and better anatomic understanding of transnasal endoscopic approaches called for an endonasal technique in skull base reconstruction.

The HBF is a neurovascular pedicled flap of the nasal septal mucoperiosteum and perichondrium based on the nasoseptal artery, a branch of the posterior septal artery and the terminal branch of the internal maxillary artery (Figure 1). In the first description of the technique, it was used on 44 patients with a variety of pathologies including Cerebrospinal fluid (CSF) leaks, meningoencephaloceles, clival chordomas, esthesioneuroblastoma, craniopharyngioma, meningiomas, and pituitary tumors. Complications included postoperative CSF leaks in two patients and a posterior nosebleed in one patient.²

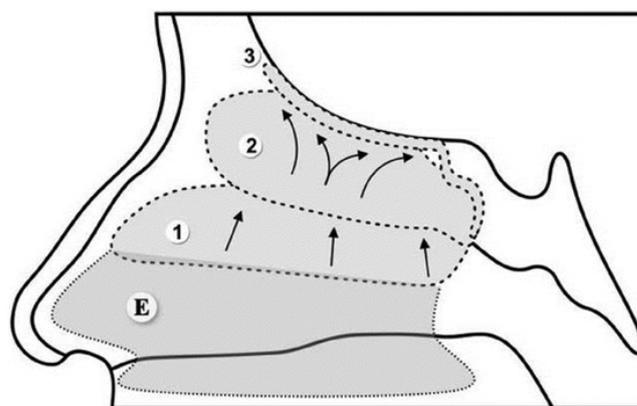


Figure 1: Drawing of the septum illustrating the septal incisions and possible modifications. Reproduced from Hadad et al². A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap.

Study	Year	Type of Study	Study Focus
Zanation	2011	Review	Skull Base Reconstruction
Kim	2013	Review	Pedicled Extranasal Flaps
Chan	2012	Case Series	Recurrent NPC
Rohaizam	2009	Case Series	Endoscopic Nasopharyngectomy
Bridger	2005	Case Series	Salvage Nasopharyngectomy
Chen	2012	Case Series	Middle Turbinate Flap
Chan	2011	Case Series	Nasopharyngectomy
Hadad	2006	Retrospective chart review	Nasoseptal Flap
Khoo	2001	Case series	Nasopharyngectomy, free flap

Table 1: Six case series, one retrospective chart review, and two literature reviews were included in this review.

Vascular Flap	Pedicle	Advantages
Nasoseptal flap	Posterior septal a. from sphenopalatine a.	Ideal for all skull base reconstruction
Inferior turbinate flap	Inferior turbinate a.	Good for small clival defects
Middle turbinate flap	Middle turbinate artery	Good for small ACF
Pericranial flap	Supraorbital and supratrochlear arteries	Hearty flap, versatile dimensions
Temporoparietal Fascia flap	Superficial temporal artery	Usually from non-irradiated field
Palatal flap	Greater palatine artery	Long pedicle
Facial buccinator flap	Facial artery	Good for ACF, no facial incision
Occipital galeopericranial flap	Occipital artery	Long pedicle, good for posterior lesions, Usually from non-irradiated field

Table 2: Lists various pedicled flaps used successfully in reconstruction after nasopharyngectomy.

A 2009 case series by Rohaizam et al employs this technique after endoscopic resection of locally recurrent nasopharyngeal carcinoma. They describe their experience of six patients with rT1N0M0 nasopharyngeal carcinoma. All patients had tumor recurrence after completion of primary irradiation. All six patients had negative margins after endoscopic nasopharyngectomy; HBF was used for reconstruction. Two patients had flap necrosis three to five weeks post operatively and one patient had flap necrosis at four weeks with subsequent osteoradionecrosis at 41 weeks after surgery. The authors state that the procedure is contraindicated when there is exposure of the carotid artery. Complications of procedure include flap necrosis, bleeding, nasal congestion and crusting, neck stiffness, and wound infection.³

Chen and his colleagues describe a posteriorly pedicled Middle Turbinate Flap (MTF) for resurfacing the nasopharynx after endoscopic nasopharyngectomy followed by resurfacing with an ipsilateral MTF. Of the 18 patients, 83.3% achieved functional recovery. In three patients, the flap failed to cover the entirety of the defect. Surgical technique involves making two parallel incisions on both sides of the middle turbinate following the sagittal plane and a vertical incision anteriorly connecting the two parallel incisions (Figure 2). The mucoperiosteal flap is raised posteriorly until the posterior pedicle to avoid injury to the MT artery and then it can be rotated to cover the nasopharyngeal defect.⁴ The MTF is safe and minimally invasive for reconstruction after endoscopic nasopharyngectomy; however, the disadvantage of this technique is that it often is not large enough to cover entire nasopharyngeal defect.⁴

Patel and his colleagues recently published their experience with secondary flaps in endoscopic endonasal skull base surgery.⁵ These flaps are useful in situations when there is invasion of tumor into the nasal septum or when prior surgery or

radiation has disrupted its vascular supply. At their institution, the endoscopic assisted pericranial flap was utilized for cases of sinonasal cancer with intradural involvement. The pericranial flap is pedicled on the deep branches of the supraorbital and supratrochlear vessels. Advantages of this flap are its ease of dissection, low risk of operative complications, length and radioreistance. No flap failures occurred in their series of 16 patients. The tunneled temporoparietal flap was used for defects in the clivus or nasopharynx. No flap failures occurred in this group of patients. Potential operative complications of this flap are donor site alopecia, facial nerve transection, and internal maxillary artery injury.

Intranasal flaps in Patel's review included the inferior turbinate flap, the middle turbinate flap, and the anterior lateral nasal wall flap.⁵ The inferior turbinate flap is a mucoperiosteal flap which is based on the inferior turbinate artery best utilized for clival or sellar defects. Its main pitfall is the potential disruption of the nasolacrimal duct. Additionally, a fat bolster is recommended for defects >1 cm due to its limited bulk. There were no flap failures in their series of three patients. Patel and his colleagues also describe the anterior lateral nasal wall flap which is an inferior turbinate flap with extension of the mucoperiosteal dissection to the lateral nasal wall and floor. It is based on branches of the anterior ethmoid and facial arteries. Its advantages are the its robust blood supply and large surface area. Potential pitfalls are disruption of the nasolacrimal duct and difficult dissection of the inferior turbinate mucoperiosteum.⁵

Khoo and colleagues have described their experience with open nasopharyngectomy with maxillary swing approach with radial forearm free flap reconstruction for recurrent nasopharyngeal carcinoma.⁶ The advantages of a free flap for this purpose is that it can facilitate the healing process and minimize the risk of infection, osteoradionecrosis, and carotid rupture. The

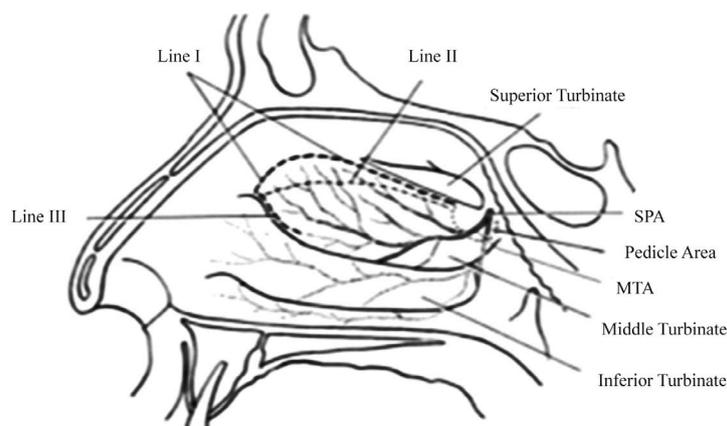


Figure 2: Diagram to outline the procedure for posterior pedicled middle turbinate mucoperiosteal flap. Reproduced from Chen et al.⁴. A posteriorly pedicled middle turbinate mucoperiosteal flap resurfacing nasopharynx after endoscopic nasopharyngectomy for recurrent nasopharyngeal carcinoma.

radial forearm free flap is harvested with little donor site morbidity; it provides adequate flap size to resurface the entire surgical defect; its thinness and pliability facilitates contouring and inseting of the flap; the flap may be harvested with a long vascular pedicle. The maxillary swing approach allows for good access for inseting of the radial forearm free flap. Pearls to ensure a successful reconstruction include suturing the inferior margin flap to the cut edge of the posterior wall of the oropharynx to ensure stability, ipsilaterally it should cover the internal carotid artery, laterally the flap should be sutured to the lateral nasal wall or pterygoid muscles if a wide resection has been performed.⁶ Other free flaps that have been used successfully are the Anterolateral thigh free flap (ALT), the rectus abdominis muscle flap, and the posterial tibial fasciocutaneous flap. In Chan's series of 22 patients, all patients were reconstructed with one of these flaps and there were no cases of flap failure.⁷ The advantage of free flaps is their reliability, versatility, and ability to be harvested simultaneously with the resection using a two-team approach to reduce operative time.⁸⁻¹⁰

CONCLUSION

Surgical salvage after residual or recurrent nasopharyngeal carcinoma has been shown to achieve better control than re-irradiation. Reconstruction is necessary after resection for defect coverage and promotion of healing to prevent carotid artery blow out and osteoradionecrosis. No single flap is ideal for all cases. The choice of flap will have to be tailored according to the patient, the defect created, consistent with oncologic principles, donor site availability and surgeon preference. A working knowledge of available flaps is essential to provide coverage of the skull base to avoid catastrophic vascular and infectious complications.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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An Unusual Entity of Sarcoidosis: Acute Parotitis

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ABSTRACT

Sarcoidosis is a rare systemic granulomatous disease of unknown etiology that may affect many organ and system, mainly lungs. This disease is rare in children. Sarcoidosis is staging contingent on posterior-anterior chest x-ray. Stage 3 rarely occurs. In generally, sarcoidosis in children is diagnosed by extrapulmonary organ involvement. We presented hereby a rare case of sarcoidosis stage 3 diagnosed in a child patient with acute parotitis and reviewed the relevant literature.

KEY WORDS: Sarcoidosis; Acute parotitis; Staging; Child; Granulomatous; Chest x-ray.

INTRODUCTION

Sarcoidosis is a rare systemic granulomatous disease of unknown etiology that may affect many organs and system, mainly lungs and rarely affects child.¹ The diagnosis of sarcoidosis is more difficult because of its rarity and the similarity to other several granulomatous diseases.^{2,3} There are four stages in sarcoidosis based on the extent of lung involvement. These stages are: stage 0 (normal); stage I (Bilateral Hilar Adenopathy (BHL) without pulmonary infiltrates); stage II (BHL plus pulmonary infiltrates); stage III (parenchymal infiltrates without BHL) and stage IV (irreversible scarring and distortion). Stage I and stage II are the most common types of presentation.^{3,4} Hereby, we report a rare case of sarcoidosis stage 3 diagnosed in a child patient with acute parotitis and reviewed the relevant literature.

CASE REPORT

A 12-year-old male presented with a 3-day history of painful, tenderness, swelling on right preauricular and submandibular area. The patient's history was clear from trauma, frequent infection and mumps. Tenderness and hyperemia of the skin on preauricular and submandibular area was observed. Further, otolaryngological and systemic examinations were unremarkable. Complete Blood Count (CBC), biochemistry, C-reactive protein (CRP) and coagulometer tests were applied. The patient's White Blood Count (WBC) 15,000 /mm³ (N:4,000-11,000/mm³), CRP:15,2 mg/dl (N:0-1.0 mg/dl), amylase 128 mg/dl (N:10-100 mg/dl). All other laboratory test results were unremarkable. The ultrasonography on neck revealed the presence of servical multiple tender, elliptic configuration lymphadenopathy with mild pallor that the largest of measuring approximately 30×17 mm. The patient was diagnosed with acute parotitis. We prescribed amoxicillin-clavulanic acid (40 mg/kg/day) 2×1 for two weeks. We reassessed the patient after medical therapy. The treatment regimen applied was prolonged with two weeks because of persisting of patient's complaints. Even though, the persisting of patient's complaints was observed, so patient was evaluated in more details. Vasculitis panel, including Anti-nuclear antibody (ANA), Antineutrophil cytoplasmic antibody (c-ANCA), perinuclear neutrophil antibodies (p-ANCA), Radio frequency (RF), chest x-ray and tuberculosis skin test Purified Protein Derivative (PPD) were applied. Vasculitis panel was within normal limits and his tuberculosis skin test revealed the presence of a skin reaction of 4 mm. There was no family history of tuberculosis. Chest x-ray revealed the presence of ground

glass view on superior segment of the right lung. (Figure 1) High Resolution Computer Tomography (HRCT) was applied to evaluate lung parenchyma and it revealed the presence of patchy, ground glass view and air trapping with no enlarged hilar lymph nodes and a normal mediastinal silhouette on superior segment superior and apical segment of the right lung. (Figure 2) Fine needle aspiration biopsy was performed from servical lymphanopathy. Biopsy revealed the presence of non-necrotising epithelioid cell granulomas with giant cells. The patient was suspect of granulamatous diseases especially sarcoidosis. Angiotensin Converting Enzyme (ACE) was 128.7 U/L (normal: 8-52 U/L). Based on these findings, sarcoidosis stage 3 was diagnosed and the patient was prescribed oral prednisolone 2 mg/kg/day. The severity of his symptoms decreased following treatment and he was symptom-free at his 2-year follow-up and prednisolone dose was reduced to 2 mg/day. His medical therapy including prednisolone is still proceeding.

and system, is characterized by a variable clinic presentation and course.^{1,2} Even though it occurs more frequently at 20-40 years, it can occur at any age. It relatively occurs rare in childhood.³ In pediatric population, sarcoidosis is usually characterized by two clinic presentation. One of them, it is characterized by triad of rash, arthritis and eye involvement, occurs frequently in young children. Other clinic presentation, older children present with involvement of the lungs, lymph nodes and eyes as adult.^{3,4}

Sarcoidosis may often affect lungs more than 90% of patients, sometimes with symptoms or asymptomatic radiographic abnormalities.^{1,2} The radiographic abnormalities consist of bilateral hilar adenopathy, diffuse or local pulmonary infiltrates, irreversible scarring and distortion. However, clinic presentations and radiographic findings can be not similar. The chest x-ray was categorized into four stages by Scadding, but these stages are not necessarily denote the severity or progression of disease.³ According these stages, normal chest x-ray is stage 0, bilateral hilar adenopathy, often with right paratracheal adenopathy, without pulmonary infiltrates is stage 1, bilateral hilar adenopathy with parenchymal infiltration is stage 2, parenchymal infiltration without hilar adenopathy is stage 3 and advanced parenchymal disease demonstrating fibrosis is stage 4.^{3,4} The most common of these stages are stage 1 and 2.⁴ In our case, stage 3 lung involvement, is rarely reported in literature was determined according to these staging.

Sarcoidosis can affect minor and major salivary glands, mainly parotid gland, approximately 6% of patients.⁵⁻⁸ Parotid gland affecting cause variable clinic presentation between acute parotitis and diffuse parotid enlargement due to chronic inflammation. It can cause sicca like-symptom in patients. In our case, acute parotitis was determined but there were no any sicca like-symptoms as extrapulmonary involvement. In literature, this clinic presentation was reported in rare.¹

Sarcoidosis is diagnosed by a correlation between clinical and radiographic findings supported by histopathological examination. However, there are no specific laboratory tests for diagnosis of sarcoidosis but some abnormalities in laboratory tests can be determined such as elevated erythrocyte sedimentation rate and other acute phase reactants, anemia, leukopenia and hypergammaglobulinemia.¹⁻³ Even though serum ACE levels are elevated in more 40% patients with sarcoidosis, the value of a serum ACE level for diagnosis of sarcoidosis remains limited.^{1,9} In our case, abnormalities in laboratory tests were elevated ACE and acute phase reactants.

The differential diagnosis of sarcoidosis consist of granulamatous disease such as tuberculosis, lymphoma, parasitic infections.^{3,4,10}

The treatment of sarcoidosis depends on its severity but typically includes prednisolone and other immunosuppressive drugs, especially methotrexate. However, medical therapy is not mandated for sarcoidosis because of regression spontaneously.^{3,6,8} In our case, patient was treated by prednisolone 2 mg/

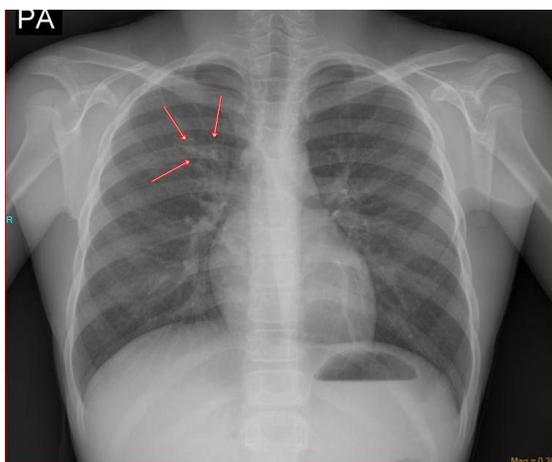


Figure 1: Chest X-ray showing the presence of ground glass view on superior segment of the right lung (red arrows).

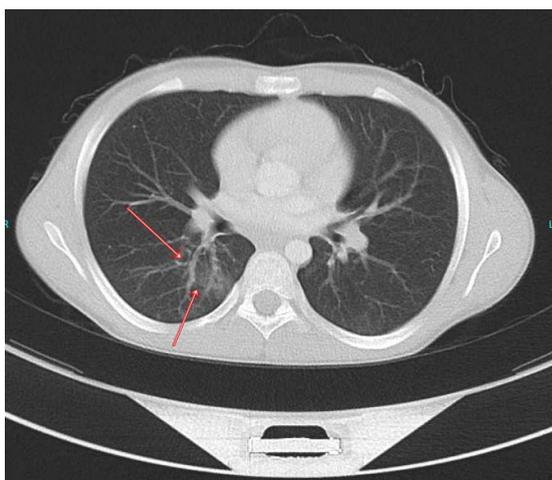


Figure 2: Axial view of HRCT image showing the presence of patchy, ground glass view and air trapping with no enlarged hilar lymph nodes and a normal mediastinal silhouette on superior segment superior and apical segment of the right lung. (red arrows).

DISCUSSION

Sarcoidosis is a rare autoimmune systemic granulamatous disease of unknown etiology that may effect many organ

kg/day in a 2 years and the severity of his symptoms decreased following treatment, prednisolone dose was reduced to 2 mg/day.

CONCLUSION

Sarcoidosis should be considered in the differential diagnosis of patients with acute parotitis in children. A high degree of clinical suspicion is needed to determine this rare potential etiology. Because patients with sarcoidosis can present with many different manifestations affecting multiple systems, the otolaryngologist must be aware of sarcoidosis and its rare presentations.

CONSENT

Written informed consent was obtained from the patient described in this case.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

FINANCIAL DISCLOSURE

The authors declare that this case has received no financial support.

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Research

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Prospective Study of Upper Esophageal Sphincter Assist Device for Treating Extraesophageal Reflux

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ABSTRACT

Background: Extraesophageal reflux (EER) is a heterogeneous disease, caused by the regurgitation of gastroduodenal contents into the larynx. The Upper Esophageal Sphincter (UES) Assist Device is a novel medical device designed to prevent gastroduodenal reflux into the laryngopharynx.

Objective: A multicenter prospective study assessing safety and effectiveness of the UES Assist Device in patients with EER.

Methods: Patients with Reflux Symptom Index (RSI) >13 were enrolled. The device was fit and adjusted to at least 20 mmHg applied external cricoid pressure. The primary effectiveness end-point was reduction in RSI at 4-weeks compared to baseline. 36-Item Short Form Health Survey or SF-36[®] Health Survey (SF-36), patient and physician satisfaction, and Functional Outcomes of Sleep Questionnaire (FOSQ) were secondary end-points. Safety was based on reported adverse reactions.

Results: Eighty-nine of 95 patients completed the study [mean(Standard Deviation (SD)) age=48.8(+/-13.7); mean(SD) Body Mass Index (BMI)=25.5(+/-4.2); 69.5% female, 81.1% Caucasian]. Most common troublesome symptoms included chronic cough (21.3%) and excess mucus/post nasal drip (20.2%). There was a significant ($p<0.0001$) reduction in median (Intelligence Quotient (IQ)) RSI at 2- and 4-weeks [12.5(8.0-20.0) and 10.0(5.8-16.5), respectively] compared to baseline [25.6(21.0-30.0)]. Eighty-two percent (82%) reported improvement greater than 25% with 30.1% having an improvement of 75% or more. 84.7% of patients and 95.2% of providers reported satisfaction. Adverse events were generally mild and transient with no withdrawals due to adverse events.

Conclusion: The UES Assist Device is a safe and effective for the treatment of extraesophageal symptoms and may be an alternative for the many patients that do not respond to Proton Pump Inhibitors (PPI) therapy.

KEYWORDS: GERD; Reflux; Extraesophageal reflux (EER); Laryngopharyngeal reflux (LPR).

ABBREVIATIONS: EER: Extraesophageal reflux; UES: Upper Esophageal Sphincter; RSI: Reflux Symptom Index; FOSQ: Functional Outcomes of Sleep Questionnaire; SD: Standard Deviation; IQ: Intelligence Quotient; PPI: Proton Pump Inhibitors; UES: Upper Esophageal Sphincter; IRB: Institutional Review Board; CPAP: Continuous Positive Airway Pressure; ICD: Implanted Cardioverter Defibrillator; ITT: Intent to treat; QoL: Quality-of-Life; ANOVA: Analysis of Variance; SAS: Statistical Analysis System; BMI: Body Mass Index.

INTRODUCTION

Extraesophageal reflux (EER) disease represents a wide spectrum of manifestations, mainly related with the upper and the lower respiratory system, such as laryngitis, asthma, chronic obstructive pulmonary disease, cough, hoarseness, postnasal drip disease-sinusitis, otitis media, recurrent pneumonia and laryngeal cancer.^{1,2} Evaluation and management of EER is often resource intensive with significant economic burden. In the US, the cost of caring for this group of patients exceeds \$50 billion.³ The main driver of this cost is the use of Proton Pump Inhibitors (PPI's), which are often over-utilized and in many, do not result in symptomatic improvement. PPI therapy results in reduction of gastric acidity but does not affect reflux of weakly acidic or non-acidic material. Studies have shown that in many patients with EER, incompetence of the Upper Esophageal Sphincter (UES) plays an important role in allowing reflux of gastric content into the pharynx.^{4,5}

The Upper Esophageal Sphincter (UES) Assist Device is a novel medical device designed to prevent the reflux of gastric contents into the laryngopharynx.⁶ It is a non-pharmacologic non-surgical medical device worn while sleeping and applies a standardized external pressure to the cricoid cartilage in order to decrease retrograde reflux of gastroduodenal contents (Figure

1). Physiologic studies with this device have shown that application of 20-30 mmHg cricoid pressure by an external UES Assist Device, significantly increases the UES intraluminal pressure and prevents pharyngeal reflux induced by esophageal slow liquid infusion.⁶

Outside initial important physiologic tests, there are currently no clinical data regarding the efficacy and safety of the UES Assist Device in patients with EER. Thus, the aim of this multi-center prospective cohort study was to employ validated tools to evaluate clinical benefit and safety of the UES Assist Device in patients with chronic EER symptoms.

METHODS

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Each investigational site obtained Institutional Review Board (IRB) approval prior to initiating the study.

Study Population

The study was a non-randomized, prospective, open label trial of 95 patients at 5 investigational sites in the United States to assess the safety and effectiveness of the Reza Band[®]



Figure 1A: Overview of the UES Assist Device. Cushion is placed at the patient's cricoid with the Comfort Band attached to the frame body, by a magnetic Clasp. Physician fit the patient according to pressure required and patient comfort, by adjusting the Comfort Band. Patient is allowed some adjustment to the pressure, using the Comfort Dial.



Figure 1B: UES Assist Device positioned at the cricoid on a patient while sleeping.



Figure 1C: The UES Assist Device is fit by the physician, using the External Manometer connected by a luer lock to the Pressure Sensor. As the UES Assist Device is adjusted, the pressure being applied in mmHg, is displayed in real time. Once the device fitting has been completed, the Pressure Sensor is disconnected, as each Pressure Sensor is a one-time use component.

Upper Esophageal Sphincter (UES) Assist Device for the treatment of esophagopharyngeal reflux with extra-esophageal symptoms (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing). The study population consisted of subjects that were 18 years of age or older, clinically diagnosed with esophagopharyngeal reflux with extra-esophageal symptoms and had a Reflux Symptom Index (RSI)⁷ score >13. Patients were excluded if they were currently receiving treatment for sleep apnea with Continuous Positive Airway Pressure (CPAP), were female and of child bearing potential and is not using an acceptable method of birth control, or was pregnant or breast feeding, had undergone previous head or neck surgery or radiation, had been diagnosed with carotid artery disease, thyroid disease, or history of cerebral vascular disease, was suspected of esophageal or nasopharyngeal cancer, had either a pacemaker or Implanted Cardioverter Defibrillator (ICD) or had undergone Nissen Fundoplication.

Protocol and Study Design

As part of the inclusion requirement, and prior to being fit with the UES Assist Device by the investigator, patients completed the RSI. All subjects had to achieve a RSI score of >13 to be included in the study. Patient demographics and medical history were obtained, including procedural history, relating to the condition over the last 2 years. Once fitted with the device (Figure 1A), patients were instructed as to how to apply the device, and to wear it when sleeping at home (Figure 1B). The fitting process included the UES Assist Device being set to apply external cricoid pressure to above 20 mmHg (Figure 1C). Patients were required to complete a diary and return it to the investigator at the follow-up visits. RSI, SF-36, and Functional Outcomes of Sleep Questionnaire (FOSQ)⁸ were measured at baseline, 2- and 4-weeks post-enrollment. The patient and physician satisfaction scores were measured at 4-weeks post-enrollment. The investigator documented all adverse events as noted in the diary, as well as upon examination for both the 2 and 4 week visit. Reduction in RSI comparing baseline to post intervention was the study primary endpoint and reductions in SF-36, FOSQ and patient and physician satisfaction scores were the secondary endpoints. Intent to treat (ITT) analysis conducted post intervention.

pH testing was not employed in this study since the sensitivity of pH monitoring is about 50% in the proximal esophagus and 40% in the hypopharynx in detecting true reflux events. Patients were diagnosed with esophagopharyngeal reflux based on laryngeal exam and symptom presentation, had been poorly responsive to PPI therapy, and had continued on pursuing treatment for their condition.

Investigators and patients were asked about their satisfaction with the UES Assist Device at the conclusion of the study based on a 7-point Likert Scale (1=extremely satisfied; 2=very satisfied; 3=satisfied; 4=somewhat satisfied; 5=dissatisfied; 6=very dissatisfied; 7=extremely dissatisfied). The FOSQ is a self-reported measure designed to assess the impact of

disorders of excessive sleepiness on multiple activities of everyday living that includes areas of physical, mental and social functioning. The SF-36 is a multidimensional, health-related, Quality-of-Life (QoL) questionnaire, which measures 8 health related parameters (physical function, social function, physical role, emotional role, mental health, energy, pain, general health perceptions). Each parameter is scored from 0 to 100. The SF-36 also includes a list of 18 self-reported chronic conditions.

Statistical Analysis

Sample size was based on the primary efficacy variable, which was defined as the percent reduction in RSI from Baseline to Week 4. For this efficacy variable it was assumed that the study would be successful if the mean percent reduction of the RSI score when comparing the baseline to the final measure, is significantly greater than 25%. This criterion was based on the average placebo response of placebo-controlled trials using the RSI.^{9,10} Assuming that the UES Assist Device has a 35% reduction in the RSI score, using a power of 80%, and a one-sided significance level of 0.05, it was determined that 85 subjects were required for the study. Allowing for slight departure in the assumptions, and allowing for some subjects having no post-baseline efficacy assessments, up to 100 subjects would be recruited for the study.

Baseline demographic and medical history data were obtained and summarized for all subjects treated. The primary efficacy variable is the percent reduction in total the RSI score when comparing baseline measures to week 4 measures. The mean percent change was compared to the hypothesized response of 25% using a one-sample t-test. A *p*-value of <0.05 was considered significant, with regard to demonstrating efficacy. Subjects who did not complete the study but who had at least one post-baseline efficacy assessment had their four-week assessment imputed by using the last post-baseline assessment. No other special data handling algorithms were used for imputing missing data. Subgroup analysis were conducted including study site, pre-existing comorbidities, gender, race, smoking status, alcohol consumption, Body Mass Index (BMI) group, age range group, applied pressure range group, and most troublesome RSI symptom reported by the subjects at baseline. For subgroups that formed two outcomes (i.e., gender) the subgroups were compared using a two-sample t-test. Subgroups that formed more than two outcomes (i.e., race) the subgroups were compared using an Analysis of Variance (ANOVA).

Safety was based on reported adverse reactions. These events were summarized overall, by severity, and by relationship to the device. If subjects reported the same event several times, the worst reported case of the event was used for the purpose of analysis of severity, and the most related event was used for the purpose of analysis of relationship to the UES Assist Device. The incidence of site reactions, including laryngospasm, choking, pain, cough and hoarseness, is summarized, including the exact 95% confidence intervals.

Continuous data were summarized that included the number of observations analyzed, the mean, the standard deviation, the median, the minimum, and the maximum. Categorical data were described by the number and percent of subjects for each outcome. Statistical significance was declared if the two-sided *p*-value was <0.05. No correction for multiple testing was performed. Data were summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for continuous variables (e.g., age) and counts and percent for discrete variables (e.g., success vs. failure). Statistical Analysis System (SAS) statistical software, version 9.2, was used for all data analyses. All analysis were performed on data points stored in SAS in the primary datasets (containing data derived directly from Case Report Forms) or on secondary data points stored in temporary datasets created from SAS scripts performing functions on the primary datasets.

RESULTS

Demographics

Ninety-five (95) subjects with esophagopharyngeal reflux with extra-esophageal symptoms (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing), were treated with the UES Assist Device (69.5% female; 81.1% Caucasian; 48.8(±13.1) mean age; 25.5(±4.2) Body Mass Index) (Table 1). There was no significant difference among demographic parameters across the investigational sites. Table 2 outlines the distribution for RSI components by study site and overall. The most common symptom complaints included: troublesome or annoying cough (21.3%), excess mucous or post nasal drip (20.2%), throat clearing (13.5%), hoarseness (9%) and heartburn (9%).

	Site 1	Site 2	Site 3	Site 4	Site 5	All
	N=44	N=22	N=14	N=1	N=14	N = 95
AGE (Years)						
Mean	47.0	51.5	43.9	68.0	53.6	48.8
Standard deviation	13.1	15.8	10.8	N/A	13.0	13.7
<i>p</i> -Value						0.13
BMI						
Mean	24.8	27.3	23.4	25.8	27.0	25.5
Standard deviation	3.5	4.1	3.6	N/A	5.6	4.2
<i>p</i> -Value						0.06
GENDER						
Female	65.9%	77.3%	71.4%	0.0%	71.4%	69.5%
Male	34.1%	22.7%	28.6%	100.0%	28.6%	30.5%
<i>p</i> -Value						0.13
RACE						
African American	4.5%	9.1%	0.0%	0.0%	0.0%	4.2%
Caucasian	75.0%	81.8%	78.6%	100.0%	100.0%	81.1%
Hispanic	5.0%	0.0%	21.4%	0.0%	0.0%	8.4%
Asian	0.0%	4.5%	0.0%	0.0%	0.0%	1.1%
Other	2.3%	0.0%	0.0%	0.0%	0.0%	1.1%
Not reported	6.8%	4.5%	0.0%	0.0%	0.0%	4.2%
<i>p</i> -Value						0.53

Table 1: Patient demographics by study site and overall.

Most Troublesome RSI	Site 1 N=42(n%)	Site 2 N=21(n%)	Site 3 N=12(n%)	Site 4 N=1(n%)	Site 5 N=13(n%)	All Sites N=89(n%)
Q1 – Hoarseness	3(7.1)	1(4.8)	1(8.3)	1(100.0)	2(15.4)	8(9.0)
Q2 – Clearing throat	7(16.7)	4(19.0)	1(8.3)	0(0.0)	0(0.0)	12(13.5)
Q3 – Excess mucus/post nasal drip	9(21.4)	3(14.3)	4(33.3)	0(0.0)	2(15.4)	18(20.2)
Q4 – Difficulty swallowing	1(2.4)	1(4.8)	0(0.0)	0(0.0)	1(7.7)	3(3.4)
Q5 – Coughing after eating/lying down	1(2.4)	1(4.8)	0(0.0)	0(0.0)	1(7.7)	3(3.4)
Q6 – Breathing difficulties	3(7.1)	2(9.5)	1(8.3)	0(0.0)	0(0.0)	6(6.7)
Q7 – Troublesome or annoying cough	6(14.3)	7(33.3)	3(25.0)	0(0.0)	3(23.1)	19(21.3)
Q8 – Lump in throat	4(9.5)	0(0.0)	1(8.3)	0(0.0)	2(15.4)	7(7.9)
Q9 – Heartburn	4(9.5)	1(4.8)	1(8.3)	0(0.0)	2(15.4)	8(9.0)
Invalid [†]	4(9.5)	1(4.9)	0(0.0)	0(0.0)	0(0.0)	5(5.6)

[†]3 patients cited 2 most troublesome RSI symptoms. These responses were classified as an invalid.

Table 2: Reflux symptom index (RSI) component distribution by study site and overall.

Primary Effectiveness Endpoint

The median (IQ) RSI score for the study population at baseline was 25.6(21.0-30.0). Median (IQ) RSI scores at the 2- and 4-weeks post study enrollment were significantly (<0.0001) improved; 12.5(8.0-20.0) and 10.0(5.8-16.5), respectively (Table 3) (Figure 2). Thirty percent (30%) of participants reported >75% improvement in their RSI while 82% had >25% improvement. The severity of the baseline RSI score did not impact the percentile improvement of the 4-week RSI score ($p=0.11$) (Table 4). Demographic variables were not predictors of the RSI outcome. The most improved symptom component of RSI (Table 5) included heartburn (78%), difficulty swallowing (64%), cough after eating (63%) and hoarseness (62%). The best predictor of success among all RSI components was the presence of heartburn, chest pain, indigestion, or stomach acid coming up.

Baseline RSI	% Improvement
13-15	45%
16-20	61%
21-25	52%
26-30	58%
31-35	48%
>35	32%
<i>p</i> -Value	0.11

Table 4: Percentage RSI improvement as a function of baseline RSI score. Improvement in RSI occurred at all baseline levels.

	Reflux Symptom Index		<i>p</i> -Value
	Median	Interquartile (25%-75%)	
Baseline	25.6	21.0-30.0	
2 nd Week	12.5	8.0-20.0	<0.0001
4 th Week	10.0	5.8-16.5	<0.0001

Table 3: Reflux Symptom Index (RSI) at baseline and post UES Assist Device at 2- and 4-weeks.

Secondary Effectiveness Endpoints

Investigators rated their satisfaction as Satisfied, Very Satisfied or Extremely Satisfied 91.7% of the time. There were no reports of the investigators being Very Dissatisfied or Extremely Dissatisfied. The investigator satisfaction was not significantly different across the study sites ($p=0.26$). Similar to the investigator satisfaction reporting, the majority of patients also reported that they were satisfied to some degree (75.4%). The patient satisfaction results were also found not to be different across the investigational sites ($p=0.10$).

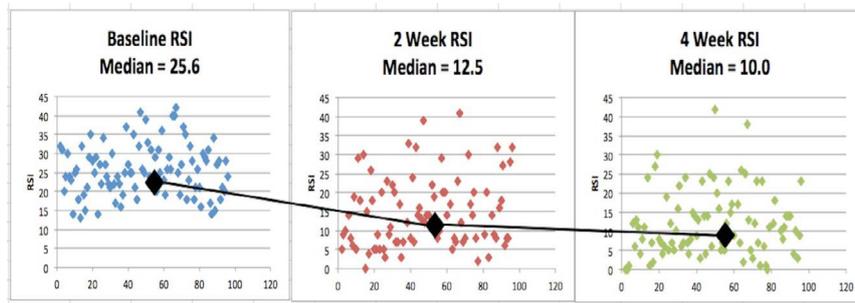


Figure 2: Median reflux symptom index (RSI) for the study population at baseline and at 2- and 4- weeks. There was a significant ($p<0.0001$) reduction of the RSI as compared to baseline.

Most Troublesome Symptom	Mean RSI % Improvement
Hoarseness	62.7
Throat clearing	50.2
Post nasal Drip	45.6
Difficulty swallowing	64.2
Coughing after eating/lying down	63.1
Breathing difficulties	42.5
Troublesome/annoying cough	57.6
Lump in throat	49.2
Heartburn	78.1

Table 5: Reflux symptom index (RSI) improvement as a function of individual reported symptoms.

There was no difference in mean (SD) or median (IQ) FOSQ scores at 2-weeks ($p=0.5$) and 4-weeks (0.15), when compared to baseline. Similarly, there was no difference in the mean (+SD) overall SF-36 scores comparing the baseline [115.5(+6.8)] to 4-weeks [116.0(+7.3)] post study enrollment ($p=0.46$).

Primary safety endpoint: The safety of the UES Assist Device was evaluated by assessing the incidence, type, duration and severity of adverse events observed in all subjects. The reported adverse events were generally mild, short in duration, not related to the device and were typically related to the subjects becoming accustomed to the wearing the device (Table 6). The primary reports included soreness, hoarseness, mild skin reaction and a

transient choking sensation. There was one report of laryngospasm. It is important to note that the success of all the categories of adverse events were consistent with overall population. There were no deaths in the study and none of the subjects withdrew from the study due to an adverse event.

DISCUSSION

This is the first report on the effectiveness and safety of a novel UES Assist Device in patients presenting with suspected extraesophageal reflux symptoms. This multicenter study found that the UES Assist Device, when worn for 2-4 weeks at night, resulted in the significant reduction in RSI score among patients

Event	N	Mean Duration in Days (Range)	Mean RSI % Improvement
Soreness	8	6.8(0-32)	38.4%
Laryngospasm	1	0.0(0-0)	86.2%
Transient choking sensation	10	7.6(0-32)	55.3%
Hoarseness	9	2.0(0-7)	46.7%
Skin reaction	9	1.0(0-8)	51.8%

Table 6: Device safety data by complaint, duration and RSI improvement.

with extraesophageal symptoms. There was high degree of satisfaction by both providers and patients and the device use was safe. Among the participants, 30% reported >75% improvement in their RSI, and over 80% had more than 25% improvement.

The question of why an externally applied device, such as UES Assist Device, would result in improvement of extraesophageal symptoms must be addressed based on pathophysiologic mechanisms suspected in patients with extraesophageal reflux symptoms. The two proposed mechanisms include the reflux and reflex hypotheses. The latter operates on the principal that embryologically, the esophagus and bronchial tree share similar origin and neural innervation *via* the vagus nerve. With reflux, acidification of the distal esophagus can stimulate acid-sensitive receptors, which can lead to extraesophageal symptoms.¹¹ The reflux hypothesis refers to direct retrograde reflux of gastric (acid and pepsin) and duodenal (bile acids and pancreatic enzyme trypsin) into the esophagus with subsequent aspiration into the lungs; or even higher up in the setting of dental erosions or laryngitis.¹² This leads to direct mucosal injury by gastroduodenal contents leading to extraesophageal symptoms. For example, direct aspiration into lung tissue causes chronic inflammation, which can lead to impaired gas exchange and airway obstruction.^{13,14} In addition, exogenous exposure of larynx to gastroduodenal ingredients can result in significant laryngeal inflammation¹⁵ that may lead to chronic throat symptoms.

An important component of the reflux theory is the incompetence of the UES not preventing the passage of esophageal refluxate into the pharynx.^{4,5} For example, Szczesniak et al⁴ studied 11 patients with extraesophageal reflux symptoms with documented abnormal pH parameters, and found that all reflux of acid into the hypopharynx was associated with relaxation of UES, classified as transient, in 91% of subjects. The authors concluded that UES relaxation is the essential permissive mechanism involved in regurgitation of gastroduodenal contents into the hypopharynx. The same group also showed that in 14 patients with posterior laryngitis, the threshold for esophageal distention induced UES relaxation, was reduced compared to 21 healthy volunteers.⁵ They suggested that up-regulation of the UES relaxation response might be an important pathophysiologic mechanism in reflux laryngitis.

An essential mechanism involved in exposure of the larynx to gastroduodenal contents, is the pressure generated by the volume of refluxate. Intraesophageal pressure increases during a reflux event, which eventually leads to relaxation of UES and subsequent reflux into the larynx. However, the pressure generated within the esophagus is often less than 20 mmHg.¹⁶ Thus, could an externally applied pressure of 20-30 mmHg on the cricoid cartilage prevent relaxation of UES and prevent laryngeal exposure to esophageal contents? This question was addressed in a recent physiologic study by Shaker et al in 14 patients with extraesophageal symptoms and 12 healthy volunteers.⁶ The authors reported that slow esophageal liquid infusion resulted in UES incompetence with subsequent laryngeal reflux

events. However, reflux events were significantly reduced by application of a sustained predetermined externally applied cricoid pressure between 20-30 mmHg. The utility of cricoid pressure has been previously recognized in several other settings; for example, cricoid pressure has been used in acute life threatening situations to prevent aspiration of gastric content, and during ventilator assistance of cardiopulmonary resuscitation to prevent air-induced gastric distention.^{17,18} Thus, externally applied pressure on the UES may prevent reflux which might reduce patients symptoms. However, no prior study had systematically addressed the impact of this therapy in a large group of patients with laryngeal symptoms. Therefore, our data are unique and provide impetus for continued evaluation of this alternative therapy in this difficult to treat group of patients.

The strengths of our study includes the large sample size multi-institution nature of the trial, employing validated questionnaires to assess impact on patient symptoms, quality of life as well as sleep and in-depth evaluation for possible unexpected side effects to ensure safety of the employed device. Limitations might include the uncontrolled and non-randomized nature of the study. However, plans are in place to address these limitations with in future trials. Overall, our findings are unique and provide alternative treatment options for patients with suspected extraesophageal reflux based on physiologically confirmed mechanisms. The UES Assist Device resulted in significant symptom improvement within 2-weeks which was sustained for the duration of the study at 4-weeks.

In conclusion, our study showed that the UES Assist Device is a safe and effective non-invasive method for the treatment of extraesophageal symptoms. Given the poor response to PPI therapy in many such patients this device may serve as a potential alternative for this difficult to treat group of patients. Future controlled studies will further validate the importance of this device in this group of difficult to treat patient population.

CONSENT

The subjects provided written permission for publication of case details. The Informed Consent document that was reviewed and approved by the IRB, and signed by all subjects prior to enrolling into the study.

FINANCIAL DISCLOSURES

Dr. Silvers has provided scientific input regarding study design under a consultant agreement for Somna Therapeutics who markets the device used in this study.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

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A Case of Huge Intradermal Melanocytic Nevus of the External Auditory Canal Orifice

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ABSTRACT

The intradermal Melanocytic Nevus (MN) is usually referred to as the nevomelanocytic nevi and is composed of nevus cells. Although intradermal nevi are common benign pigmented skin tumors, their occurrence within the External Auditory Canal (EAC) is uncommon. Recently the author experienced a case of huge intradermal MN which almost completely obstructed EAC orifice without accompanying conductive hearing loss in a 42-year-old female patient. It originated in the inferior wall of cartilaginous portion of left EAC. It was treated by en bloc excision without skin graft by transcanal approach. Here, we report a case of huge intradermal MN arising in the EAC with review of literatures.

KEYWORDS: Melanocytic nevus; External auditory canal, Tumors.

ABBREVIATIONS: MN: Melanocytic Nevus; EAC: External Auditory Canal; HMB-45: Human Melanoma Black-45; MRI: Magnetic Resonance Imaging; MRA: Magnetic Resonance Angiography.

INTRODUCTION

This article reports a case of huge intradermal Melanocytic Nevus (MN) of the External Auditory Canal (EAC) orifice. A nevus is a benign melanocytic neoplasm and is the most common type of skin tumor.¹ The intradermal MN is usually referred to as the nevomelanocytic nevi and is composed of nevus cells. Although intradermal nevi are common benign pigmented skin tumors, their occurrence within the external auditory canal is uncommon.² There are 20 reported cases of MN in the EAC in the English-language literature thus far.³⁻⁵ Recently the author experienced a case of huge intradermal MN which almost completely obstructed EAC orifice without accompanying conductive hearing loss in a 42-year-old female patient. It originated in the inferior wall of cartilaginous portion of left EAC. It was treated by en bloc excision without skin graft by transcanal approach.

CASE REPORT

A 42-year-old woman presented with 10-year history of a slow-growing mass in the right external auditory canal (EAC) orifice associated with cosmetic discomfort. She denied any previous medical history and reported having no hearing impairment. Physical examination revealed a protruding mass covered with gray desquamated keratin arising from the inferior wall of the cartilaginous portion of EAC (Figure 1A). It showed a 10 mm sized dark brownish, dome-shaped, pedunculated hair-bearing mass with a mammilated surface which causes almost complete closure of the EAC. During the palpation with forceps, it was firm, non-tender mass nearly completely occupying the most lateral part of the EAC (Figure 1B). The otoscopic and audiologic examination revealed normal tympanic membrane and hearing level. There were three fungating skin lesions with similar character on the right posterior neck area (Figure 2). However, there were no abnormal findings on the superior portion of the trunk. Although, the

lesions were completely asymptomatic, she underwent excision for aesthetic reason only. During the pre-operative evaluation, dermatopathologist's opinion helped to exclude the possibility of malignancy such as naevoid melanoma, and confirmed that the mass appears to be a benign intradermal nevus. High-resolution computed tomography of the temporal bone demonstrated normal middle ear cavity and mastoid pneumatization. To exclude the possibilities of vascular tumor, internal auditory canal Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) were performed. Pre-operative imaging showed about 6×9×9 mm sized mass with high signal, oval in appearance, with heterogeneous enhancement in the right external auditory canal orifice after gadolinium administration without any evidence of temporal bone destruction or abnormalities in the middle ear and mastoid (Figure 3). In the report of magnetic resonance angiography, hemangioma was suspected because of the progressive enhancement in the dynamic scan study and prolonged contrast enhancement with slow filling, but, nonetheless, the embolization of the feeding vessel seemed not to be required because of the small size. Under local anesthesia, complete tumor excision was performed *via* transcanal approach. An elliptical incision was made around the base of the mass with adequate margins under otomicroscope. The lesion was confined to the cartilaginous EAC and completely removed. A deep margin was

taken to the level of the perichondrium. The author did not perform the frozen section exam during the excision because there was no evidence of bone destruction on pre-operative images and intraoperative finding showed well-demarcated mass covered with normal overlying skin. The skin on the base was cauterized to control bleeding and applied with antibiotic ointment. And the patient asked three masses with similar features on her right posterior neck to be removed simultaneously during the operation. Following surgical excision, the patient experienced an uneventful recovery. Cutaneous wound healing occurred with complete re-epithelialization of the EAC skin defects by regular dressing (Figure 4). Histologic analysis revealed melanocytes arranged in round to ovoid nests or clusters located completely within the upper dermis, the intradermal type (Figure 5A). The nevus cells are strong positive for S-100 immunohistochemical stain, and they are focal positive for HMB (Human melanoma black)-45, and positive in less than 1% for Ki-67 which is cellular marker for proliferation (Figure 5B). At the 2-year follow-up after operation, there was no sign of recurrence.

DISCUSSION

MN is the most common benign skin tumor which is composed of nevus cell. It may be found anywhere on the skin,

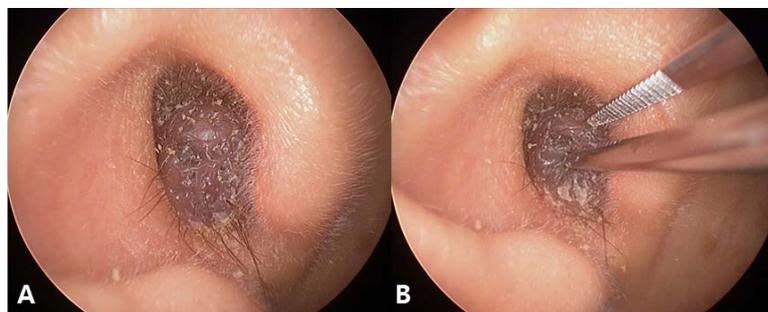


Figure 1: Otoscopic view showing the dome-shaped hair bearing lesion covered with gray crusts on the inferior wall of the right EAC(A). Palpation with Bayonet forceps. Firm, non-tender mass nearly completely occupying the most lateral part of the EAC(B).



Figure 2: There were three fungating mass lesions with similar character on the right posterior neck area. Small image in the bottom left corner of the figure is a distant view.

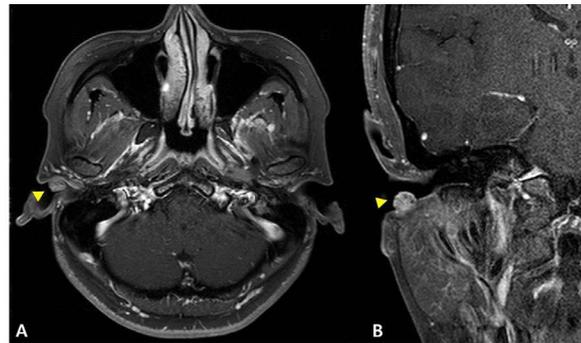


Figure 3: Pre-operative axial (A) and coronal (B) Magnetic Resonance Imaging (MRI) shows about 6×9×9 mm sized mass (yellow arrowheads) with high signal, oval in appearance, with heterogeneous enhancement in the right external auditory canal orifice after gadolinium administration.



Figure 4: The picture shows external auditory canal is healing well without wound problem 2 weeks after excision.

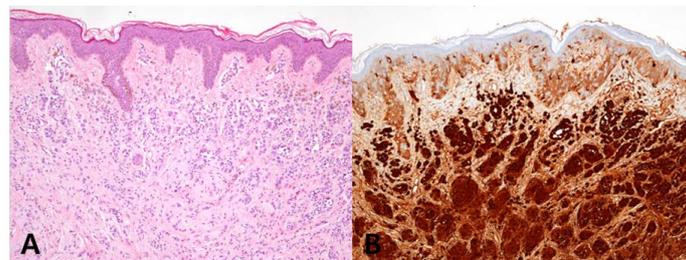


Figure 5: Histopathologic findings. The upper dermis contains nests and cords of nevus cells which have uniform round and oval nuclei with finely dispersed chromatin and delicate nuclear membrane (Hematoxylin and eosin; original magnification×100) (A). The nevus cells are strong positive for S-100 immunohistochemical stain (original magnification×100). And they are focal positive for HMB-45 and positive in less than 1% for Ki-67 (B).

but its presence in the EAC is very uncommon.²

Histologically, MN is recognized by the presence of nevus cells, which, although they are melanocytes, differ from ordinary melanocytes by being arranged at least partially in cluster or nests and has been classified into three subtypes depending on the distribution of the melanocytes. A collection of nevomelanocytes located along the junction of the epidermis and the underlying dermis or remain in contact with the lower epidermis can be classified as a junctional nevus, situated in the upper dermis only and no longer contact the epidermis as intradermal nevus, and a mixture which display the features of both junctional and intradermal proliferation in both areas as a compound nevus.² In

this case, the result was an intradermal MN. Most papillomatous lesions and almost all dome-shaped and pedunculated lesions represent intradermal MN.³

The nevus evolved by a process of nevus cells from the epidermis “dropping down” into the dermis. MN in adults is primarily of the intradermal type, and MN in children is primarily of the junctional type.⁴

Some authors asserts that overexposure to ultraviolet light from the sun may play a role in the skin damage that can lead to melanoma and the formation of acquired MN.⁶ And the number of moles a person has was found to have a correlation

with telomere length which may be of significance in the ageing process.⁷

The common clinical manifestations of MN of the EAC have been reported to include frequent itching, ear fullness, foreign body sensation, conductive hearing loss, otalgia and excessive accumulation of wax with difficulty in cleaning,^{5,8} but most cases were asymptomatic and were found incidentally. In this case, although it was a completely asymptomatic, she removed the lesion for aesthetic purpose only.

MN in EAC has the tiny risk of transformation into cutaneous melanoma. However, the author recommends that MN in EAC be treated as soon as possible to prevent progression to more advanced-staged EAC cholesteatoma. It is also believed to be important to obtain pathological confirmation of all nevus looking masses within the EAC by excisional biopsy when a nevus becomes symptomatic or when all of its features cannot be observed.¹ It is known that complete scalpel excision of all clinically atypical nevi permits the histological assessment of the entire lesion and spares the patient the need for further surgical intervention.⁹

Clinical and histologic differential diagnosis include benign lesions such as lentigo, viral wart, seborrheic keratosis, dysplastic nevus, inflammatory polyp, encephaloceles and squamous papilloma and other malignant lesions such as squamous cell carcinoma, malignant melanoma, basal cell carcinoma.^{2,3,10} Unlike melanomas that progress over time, MN enlarges to a point, stabilize, and then involute.²

MN should be considered to be early diagnosed and to be managed with early complete surgical resection for aesthetic, functional and preventive purposes. Because MN in EAC has the possibility of developing into an EAC cholesteatomas, especially when it is large enough to obstruct the lumen of the EAC and the tiny risk of transformation of any single melanocytic nevus into cutaneous melanoma. As a matter of course, the treatment of choice of a symptomatic pigmented nevus in the EAC is complete excision. The possibility of malignancy should be excluded all the time.¹ Occasionally, to avoid postsurgical scar contracture, the auditory canal could be covered with split-thickness skin graft. The prognosis of MN is substantially favorable; however, the risk of progression to malignancy in benign melanocytic lesions was recently studied in a meta-analysis,¹¹ which revealed a 2% incidence for melanoma, especially for congenital nevi >40 cm located on the trunk.¹²

CONSENT

The author has received written informed consent from the patient described in this case report.

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Systematic Review

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A Review of the Role of the Endoscopic Sinus Surgery in the Management of Sinusitis Complicated by Extradural Vs. Subdural Brain Abscesses

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ABSTRACT

Objective: To review the literature comparing management of extradural and subdural complications of acute sinusitis and the role of the rhinologist in managing these complications.

Patient Population: Adult and pediatric patients presenting with acute sinusitis complicated by brain abscesses.

Intervention: Role of Endoscopic Sinus Surgery (ESS) in managing patients with sinusitis complicated by brain abscesses.

Methods: Papers from 1960-2015 discussing subdural and extradural complications of acute sinusitis and the role of sinus surgery.

Conclusions: The results suggest an aggressive approach to sinusitis complicated by subdural collections with a select role for conservative management in treatment of extradural collections.

KEYWORDS: Patients; Sinusitis; Rhinosinusitis; Sinus surgery.

ABBREVIATIONS: ESS: Endoscopic Sinus Surgery; EMBASE: Excerpta Medica dataBASE; MEDLINE: Medical Literature Analysis and Retrieval System Online; ARS: American Rhinologic Society.

INTRODUCTION

Rhinosinusitis ranks among one of the most common ailments in the United States, with the prevalence of chronic sinusitis estimated at 1 in 8 individuals.¹ While serious intracranial complications of sinusitis are uncommon due to their decreased incidence in the antibiotic era, approximately 0.5 to 24 percent of hospitalized individuals with rhinosinusitis will progress to develop intracranial complications.² About 3 to 17 percent of patients hospitalized with acute sinusitis will develop intracranial complications.³ Neurological consequences such as epidural abscess, subdural abscess, intracerebral abscess, meningitis, and venous sinus thrombosis, can be life-threatening if left untreated.

While prior studies have illustrated the necessity of neurosurgical drainage of subdural abscesses, the role of Endoscopic Sinus Surgery (ESS) in conjunction with the neurosurgical procedure has not been clearly defined.³ Furthermore, it is unclear whether there is any difference in management for a subdural or extradural abscess with respect to sinus drainage. We aim to review the role of ESS in sinusitis complicated by intracranial complications looking at disease free outcomes and patient complications. The results of this study will delineate the role of ESS for sinusitis complicated by extradural and subdural collections and will provide insights for the role of sinus drainage in conjunction with medical management and neurosurgical intervention.

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MATERIALS AND METHODS

We reviewed the literature from 1960-2015 by performing Pubmed, Excerpta Medica dataBASE (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Cochrane searches using the search terms “intracranial”, “sinusitis”, “complications”, “abscess”, “extradural”, “epidural”, “subdural”, and various combinations of the terms.

Randomized Control Trials (RCTs), experimental studies without randomization, and observational studies with and without control groups examining the role of ESS in neurologic complications of acute sinusitis, in both adults and pediatric patients, were included in the study. Patients with no other source of intracranial infection besides the sinuses were also included. Case reports, non-full text articles, and studies

written in a language other than English were excluded.

RESULTS

A total of 18 papers were identified that met our inclusion criteria, which included 320 patients. Table 1 summarizes the demographic data in these studies. Of these patients, there were 94 extradural abscesses and 156 subdural abscesses (Table 2). Generally, all patients regardless of whether they had an extradural or subdural abscess underwent surgical intervention. Gallagher et al performed a case series of 15 patients with suppurative intracranial complications of sinusitis in which all patients underwent sinus procedures. They argue that sinus drainage is necessary in conjunction with a neurosurgical procedure for adequate treatment regardless of the type of abscess, given that the sinuses are the original source of infection.¹⁷ Many of the papers did not stratify the type of surgical proce-

Study Authors	Year of Publication	Country	Study Design	Data Collection	Sample Size	Study Groups	Interventions
Leong et al ⁹	2011	USA	Case series	Chart review	14	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Hicks et al ²	2011	USA	Case series	Chart review	13	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Kwang et al ¹⁰	2002	Singapore	Case series	Chart review	7	Pediatric patients undergoing drainage of sinuses and intracranial collections	Medical treatment, ESS, craniotomy
Sommer et al ¹¹	2011	Canada	Case reports	Case reports	4	Adults undergoing trans-nasal endoscopic drainage of sinuses and intracranial abscess	Medical treatment, ESS, craniotomy
Del Gaudio et al ⁴	2010	USA	Case series	Chart review	23	Adults with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Kombogiorgas et al ¹²	2007	UK	Case series	Chart review	11	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Germiller et al ¹³	2006	USA	Case series	Chart review	25	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Glickstein et al ¹⁴	2006	USA	Case series	Chart review	21	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Heran et al ⁸	2003	USA	Case series	Chart review	8	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Younis et al ¹	2002	USA	Case series	Chart review	39	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Albu et al ¹⁵	2001	Romania	Case series	Chart review	16	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Fenton et al ¹⁶	1999	Ireland	Case series	Chart review	16	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Gallagher et al ¹⁷	1998	USA	Case series	Chart review	15	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Giannoni et al ¹⁸	1998	USA	Case series	Chart review	10	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Altman et al ¹⁹	1997	USA	Case series	Chart review	7	Adolescent patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Giannoni et al ²⁰	1997	USA	Case series	Chart review	203	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Clayman et al ⁷	1991	USA	Case series	Chart review	24	Adult patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy
Patel et al ⁶	2015	UK	Case series	Chart review	27	Pediatric patients with sinusitis and intracranial complications	Medical treatment, ESS, craniotomy

Table 1: Author information.

Total Sample Size	483
Average age	17.18
Percent Male	75
Percent Female	25
Number of Subdural Abscesses	156
Number of Extradural Abscesses	94

Table 2: Demographic data.

ture based on whether the patient had a subdural or extradural abscess. Of the studies that stratified the type of surgical procedure, Del Gaudio et al published a paper in which all 8 patients with extradural abscesses underwent ESS yet they still required subsequent craniotomy.⁴ Based on their results, they found that smaller intracranial abscess (<1 cm) without focal neurologic deficits could be managed with intravenous antibiotics and serial imaging while those greater than 1 cm necessitated early neurosurgical intervention.

A paper by Jones suggested that failure to perform ESS at early stages was associated with the need for additional craniotomies.⁵ In this study, 77 percent of patients with intracranial collections underwent ESS, including frontal sinusotomy and ethmoidectomy.⁵ Of the remaining patients, all underwent craniotomy with an additional 33 percent requiring future sinus drainage. Similarly, Clayman et al illustrated a direct correlation between surgical delay and increased length of hospitalization.⁷ Albu et al found similar findings in their study and suggested that complications were associated with a delay between diagnosis and urgent surgical treatment as well as by the presence of subdural abscess.¹⁵

Studies on patients in the pediatric population had similar findings. Patel et al in their study on pediatric sinusitis suggested that early ESS was associated with a faster recovery and shorter length of stay.⁶ The only three patients in their study who did not undergo ESS had frontal sinus cranializations that negated the need for sinus surgery. Ong et al also found similar findings in their case series on seven pediatric patients with suppurative intracranial complications of sinusitis. All patients underwent sinus surgery in conjunction with early neurosurgical drainage with the exception of one patient, who underwent frontal sinus trephination. While some patients required additional craniotomies, there were no mortalities in the study.³ Another case series on intracranial complications of sinusitis in children and adolescents by Germiller et al illustrated that nearly all underwent sinus drainage with the exception of one who developed meningitis that was successfully treated medically and two others who received external frontal sinus trephination. Of these patients, there was a 4 percent mortality rate and 8 percent morbidity rate that included patients with residual, long-term neurological deficits.¹³ Other case series such as the one by Leong et al, Glickstein et al, and Gianonni et al also supported an aggressive medical and surgical approach.^{9,14,18}

However, conservative management may be an option

for extradural collections. A 2002 review by Heran illustrated that small epidural abscesses could be conservatively managed given adequate sinus drainage, intravenous antibiotics, and minimal extradural effect.⁸ Of the eight patients, six underwent sinus drainage, most commonly of the frontal, ethmoid, and sphenoid sinuses. Four of these six patients also underwent a neurosurgical procedure for drainage of intracranial abscess. More equivocal was the indications for neurosurgical drainage. They suggested that neurosurgical intervention should be reserved for those patients with focal neurologic signs, evidence of intradural extension, or if adequate sinus drainage and appropriate bacteriologic cultures were unable to be achieved. Gallagher et al also cited the controversy with regards to neurosurgical management of these complications, particularly with regards to subdural empyema. Craniotomy has often been the treatment of choice but they suggest an alternative approach using aspiration with the aid of CT to localize the precise site of the collection.¹⁷ Thus, ESS is suggested the first line of treatment with an option for watchful waiting for neurosurgical drainage.

DISCUSSION

In the vast majority of cases complicated by either extradural or subdural abscesses, ESS is necessary in conjunction with a neurosurgical procedure to address the source of infection. ESS carries a fairly low morbidity but can be more complicated in the setting of acute rhinosinusitis with active bleeding and inflammation. Medical management alone of sinusitis complicated by intracranial infection has been associated with an increased rate of complications and prolonged hospital stay. However, endoscopic drainage of the sinuses may be avoided in cases where cranialization of the frontal sinuses by neurosurgery negates the need for further rhinologic procedures.⁶ Based on our literature review, management of subdural and extradural complications generally requires IV antibiotics, ESS and craniotomy to address the source of infection with a selective option for ESS and antibiotics alone for small (<3 cm) extradural abscesses.⁷

CONCLUSIONS

In this review article, we summarize the literature regarding management of sinusitis complicated by extradural *versus* subdural complications. While the majority of these cases require ESS as well as a neurosurgical procedure, good coordination is necessary between the otolaryngologist and the neurosurgeon as well as infectious disease specialists to provide optimal management of sinusitis with intracranial complications.⁹

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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