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Idiopathic subglottic stenosis – a familial association and review of practice

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Main Article

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Abstract

Objective. Idiopathic subglottic stenosis describes subglottic stenosis where no inflammatory, traumatic, iatrogenic or other causative aetiology can be identified. The present study aimed to outline our institution's experience of patients diagnosed with idiopathic subglottic stenosis and describe a very rarely reported familial association.

Methods. A retrospective review was conducted of prospectively maintained medical records from 2011 to 2020. Patient clinical, radiological and intra-operative data were reviewed to assess for defined endpoints.

Results. Ten patients with idiopathic subglottic stenosis were identified in this series. One familial pairing was identified, with two sisters presenting with the condition. Successful treatment with carbon dioxide laser and dilatation was achieved in most cases.

Conclusion. Idiopathic subglottic stenosis represents a rare, clinically challenging pathology. Management with endoscopic laser and balloon dilatation is an effective treatment. This paper highlights a very rare familial association, and describes our experience in treating idiopathic subglottic stenosis.

Introduction

Idiopathic subglottic stenosis is a rare condition, with an estimated incidence of around 0.2 per 100 000 population.[1] Idiopathic subglottic stenosis results in progressive narrowing from the subglottis to the first tracheal ring, where no other inflammatory, iatrogenic or traumatic cause can be identified, leading to progressive airway narrowing manifesting as dyspnoea and stridor. The condition occurs almost exclusively in young, Caucasian patients.[1–3] In a recent multi-institutional series of 479 patients with idiopathic subglottic stenosis by Gelbard *et al.*, the mean age at presentation was 49.9 years, with a 98.3 per cent female preponderance, and the majority of patients were Caucasian (97.3 per cent).[2]

Known causes for subglottic stenosis include prolonged endotracheal intubation, tracheostomy, inhalational or chemical burns, and trauma.[4] Specific investigation is required to rule out other inflammatory causes, including granulomatosis with polyangiitis, Behçet's disease and sarcoidosis.

Familial association is very rare, with a recent study reporting a 2.5 per cent familial rate,[5] and a single additional case reporting on two pairs of sisters with idiopathic subglottic stenosis.[6]

Idiopathic subglottic stenosis treatments range from conservative approaches, to endoscopic and open surgical methods. Endoscopic dilatation alone can lead to a high rate of recurrence,[7] with more recent approaches also involving radial incisions performed with an endoscopic laser,[8] and occasionally the adjuvant injection of mitomycin C, an anti-neoplastic agent.[4,9]

Mitomycin C is an antibiotic derived from *Streptomyces caespitosus* that has anti-fibrotic and anti-neoplastic properties, and has been shown to block fibroblast activity and thus reduce scar formation. Although its use has been popular in the past, debates exist over its role and safety profile, including unknown pharmacokinetics in local applications. This has led more recently to a preference for intralesional steroids.[10]

The present study aimed to outline our institution's experience with the diagnosis and treatment of idiopathic subglottic stenosis, and describe a case of an exceedingly rare familial association of idiopathic subglottic stenosis.

Materials and methods

A retrospective review of prospectively maintained medical records from 2011 to 2020 was conducted with institutional review board approval. Patients with idiopathic subglottic stenosis were identified, and their medical records were accessed for: age; gender; presenting complaint; medical history; medications history; medical, radiological and pathological investigation findings; surgical procedural records; and laryngoscopy records. Medical history was assessed in particular for a history of endotracheal intubation, tracheostomy, gastroesophageal reflux disease and smoking.

Only adult patients were included. Patients with identifiable causative factors were excluded. Ten patients met the final inclusion criteria. Only patients with symptomatic disease manifesting as dyspnoea on exertion or rest, or stridor were included.

Following referral, patients were assessed with out-patient flexible laryngoscopy to confirm diagnosis of subglottic stenosis. All patients underwent microlaryngoscopy and biopsy to rule out malignant or granulomatous aetiology. Consultation was sought from relevant disciplines to further investigate for potential causative aetiologies, such as granulomatosis with polyangiitis, Behçet's disease and sarcoidosis. Patients typically underwent further laboratory assessment, with evaluation of: full blood count, erythrocyte sedimentation rate, antineutrophil cytoplasmic antibodies targeting proteinase 3 (c-ANCA) and myeloperoxidase (p-ANCA), antinuclear antibodies, and rheumatoid factor.

Symptomatic patients were given the option of surgical intervention. All patients were jet-ventilated for the duration of the procedure; this anaesthetic technique involves oxygen delivery via a high-pressure jet ventilator into the open airway, allowing for ventilation and oxygenation without the use of an endotracheal tube. Surgical treatment was completed with laser incision of subglottic stenosis and balloon dilatation, followed by steroid injection. A carbon dioxide laser was utilised, with laser energy delivered via Swiftlase apparatus, for char-free ablation, to make three radial incisions at 12 o'clock, 4 o'clock and 7 o'clock positions prior to balloon dilatation. Sequential balloon dilatations involving progressively larger balloons were performed under direct visualisation using Boston Scientific CRE™ Fixed Wire Balloon Dilators; the outer balloon diameters were 12–18 mm, with a maximal pressure of 7–8 atmospheres, according to manufacturer's guidelines. Dilatation was performed for 2 minutes, unless oxygen saturations dropped below 92 per cent. Patients remained as in-patients overnight for airway observations, and were usually discharged the day after.

All patients were reassessed with out-patient flexible laryngoscopy post-operatively, initially at 3 months, and every 6–12 months thereafter.

Results

A total of 10 patients were identified from 2011 to 2020 with a diagnosis of idiopathic subglottic stenosis (Table 1). Mean age was 51.2 years, with a range of 20–65 years. One patient was male. All patients were Caucasian, Northern European in ethnicity. Four patients (40 per cent) had a history of other co-morbidities, though none were contributory to their history of idiopathic subglottic stenosis. All patients were investigated for other potential subglottic stenosis aetiologies, with none found in our patient cohort.

The presenting complaint in all cases was mild exertional dyspnoea, with stridor only present in a single patient. The most common Cotton–Myer grade was II, ranging from I to III. Two patients underwent radiological assessment, with patient one demonstrating a representative appearance of subglottic stenosis on imaging. All patients underwent biopsy prior to dilatation, with no cases of malignancy or granulomatous disease change identified.

All but two patients underwent laser incision and balloon dilatation with steroid injection, with the remaining two patients undergoing just balloon dilatation and steroid injection because of difficulty with access. The most common length of stay in hospital was 1 day. Five patients (50 per cent) required repeat dilatation procedures. No patients required open surgery. No surgery-related complications were reported.

A familial association was identified within the patient cohort, with two sisters both being diagnosed with idiopathic subglottic stenosis (patients two and three) (Table 1). Their ages were 51 and 53 years. Both presented with mild dyspnoea. Neither patient had any medical co-morbidities or history of endotracheal intubation. No known previous family history in preceding generations could be identified. Both patients underwent microlaryngeal laser incision and balloon dilatation with steroid injection, with a complete symptomatic response. One of the patients required a single repeat dilatation procedure, while the second sister remains symptom free.

Discussion

The present study, with a level of evidence of 4, outlines the experience of a large, Northern European tertiary referral centre regarding the treatment of idiopathic subglottic stenosis. It also highlights a very rarely described familial association of idiopathic subglottic stenosis. We demonstrate similar demographic findings to other studies, with the patients affected typically being female, middle-aged and Caucasian.[1–3] Symptoms within the group were mild overall; however, all patients opted for intervention to treat their idiopathic subglottic stenosis. Within the present cohort, the repeat procedure rate was 50 per cent, slightly lower than in previously reported cohorts.[1] A single treatment modality, laser incision and balloon dilatation, was used for the initial treatment in most cases, meaning no comparison can be made between the efficacy of this technique versus others.

Half of the patients required a repeat procedure, of which two patients initially had a balloon dilatation only, in light of the soft-appearing nature of the stenotic segment.

Our study highlights a familial association of idiopathic subglottic stenosis, with two sisters diagnosed with the condition. To our knowledge, only two papers have reported on a familial association in idiopathic subglottic stenosis.[5,6] A recent study by Drake *et al.* reported a familial association rate of 2.5 per cent amongst a cohort of 810 patients in a multi-centre observational study. They found only three sibling pairs, while the majority were parent–child pairings. They found a non-Mendelian inheritance pattern, with anticipation present in 84 per cent of their cases, meaning that disease presented earlier in subsequent generations. With no other causative aetiology or intubation history, it may be reasonable to hypothesise that a genetic preponderance could give rise to idiopathic subglottic stenosis in these patients. To date, no genetic cause for idiopathic subglottic stenosis has been identified, though genetics may offer further insights into the condition in future. Although the demographic characteristics of the sisters in the present study and their Cotton–Myer staging were similar, one patient required repeat endoscopic treatment, while the second sister remains symptom free.

Some authors have suggested an association between idiopathic subglottic stenosis and gastroesophageal reflux disease, highlighting resolution with proton pump inhibitor therapy.[11] Idiopathic subglottic stenosis associated with gastroesophageal reflux disease may, however, represent a separate pathological subgroup. Given the clear female preponderance of the condition, it has also been suggested that a hormonal cause may underlie idiopathic subglottic stenosis, with previous studies demonstrating alterations in oestrogen receptors in affected

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Table 1. Patient demographic and treatment-related data

Pt. no.	Sex	Age (years)	Cotton–Myer grade*	Past medical history	Hospital stay (days)	Repeat dilatation?	Open surgery?
1	F	57	II	Diabetes mellitus	2	Yes	–
2	F	51	I	–	1	Yes	–
3	F	53	I	–	2	–	–
4	M	63	II	Hypertension	1	–	–
5	F	65	I	Ischaemic heart disease, endometriosis	2	–	–
6	F	48	II	–	4	Yes	–
7	F	60	II	–	1	–	–
8	F	42	II	–	1	Yes	–
9	F	20	II	–	1	–	–
10	F	53	III	Asthma, transient ischaemic attack	2	Yes	–

*Subglottic stenosis grade. Pt. no. = patient number; F = female; M = male

patients.[12–14] Misdiagnosis as idiopathic subglottic stenosis, or failure to identify the true causative pathology (such as inflammatory, rheumatological conditions), have also been suggested as the reasons for the diagnosis in some cases. In our series, all patients underwent extensive investigation and multidisciplinary specialist assessment prior to a diagnosis of idiopathic subglottic stenosis.

- Idiopathic subglottic stenosis is a rare condition, resulting in progressive subglottis narrowing, without inflammatory, iatrogenic or traumatic cause
- Progressive airway narrowing can manifest as dyspnoea or stridor
- This condition occurs almost exclusively in young, Caucasian women
- Treatment can range from conservative approaches, to endoscopic and open surgical methods
- A familial association is exceedingly rare, and is described here; this highlights a possible genetic preponderance

Abundant fibroblasts, disordered subepithelial extracellular matrix deposition, and activation of interleukin 17A have been identified on pathological samples in idiopathic subglottic stenosis patients; however, the specificity of these findings to idiopathic subglottic stenosis, and potential related therapeutic applications, have not been fully investigated.[15]

Treatment with laser incision and balloon dilatation with steroid injection has been described in a number of series, both for subglottic stenosis with a known cause and idiopathic subglottic stenosis. The technique is favoured in our unit given its relatively low morbidity and high treatment success rates. The principle limitation of the technique is stenosis recurrence post-treatment. Our unit did not require the use of mitomycin C or open surgical techniques for this cohort, though these are described in the literature.[4]

This study is limited because of its retrospective nature and small patient number. The rarity of this condition makes it more challenging to assemble larger patient groups, though collaborative databases could address this in future.

Conclusion

Idiopathic subglottic stenosis represents a rare, clinically challenging pathology. We highlight a very rare familial association, with two sisters affected in our cohort. We advocate a combination of laser incision and balloon dilatation in the management of idiopathic subglottic stenosis.

Competing interests. None declared

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