A case of subglottic and diffuse tracheal stenoses appearing responsive to macrolide therapy

James G Sanders, Marie-Françoise Jean-Louis

Abstract

We present an atypical case of subglottic stenosis with diffuse tracheal stenoses in a child responsive only to steroid and azithromycin (AZI) therapy. A 12-year-old boy presented with acute biphasic stridor on the background of an 18-month history of progressive shortness of breath, decreased exercise tolerance and snoring. Subsequent laryngoscopy and bronchoscopy revealed granulation tissue in the subglottic area, two circumferential stenoses of the trachea and a number of fibrous bands at the carina and at the aperture if the right main bronchus were seen. A battery of serological and histological investigations did not reveal a specific aetiology. In the acute phase this patient only responded to steroid therapy. In the medium term, repeat laryngoscopies were performed with sharp division of stenotic bands and balloon dilatation.

The patient’s condition was unresponsive to non-steroidal anti-inflammatory agents, multiple first-line antibiotics, and surgical treatment of the tracheal lesions. However definitive treatment was found with the macrolide antibiotic AZI used for its anti-inflammatory properties.

This highly unusual case of diffuse tracheal stenoses in a child proved to be a management challenge. Definitive treatment was found with the use of AZI. From our literature search this appears to be the first reported case of AZI successfully treating subglottic and tracheal stenoses.

Paediatric subglottic stenosis (SGS) is a condition that can be idiopathic or acquired. There are only a few conditions that can cause diffuse stenoses throughout the trachea and bronchi. We present an atypical case of SGS with diffuse tracheal stenoses in a child responsive only to steroid and azithromycin (AZI) therapy.

The evaluation and treatment of the patient with paediatric SGS is challenging as it has many recognised aetiologies. It consists of a narrowing of the subglottic airway at the level of the cricoid cartilage that forms a complete non-expandable ring, in contrast to the trachea, which has an expandable posterior membranous wall. The acquired form of this condition is the most common in children and has been linked to trauma, infection, allergy, neoplastic lesions, autoimmune and vasculitic conditions, and irritant reactions.

Diffuse tracheal stenoses associated with SGS is a much more rare condition often associated with diffuse tracheal injury or a systemic cause including endotracheal infection, hypersensitivity, autoimmune conditions and severe acid reflux. The signs of subglottic and tracheal airway obstruction are related to the severity of the obstruction. They can be classified as acute and chronic.
Case report

Patient Y, a very fit 12-year-old boy who is a keen rugby player, presented first to the Ear Nose and Throat (ENT) Service in 2002 with symptomatic adenoid hypertrophy for which he had a laryngeal mask airway adenoidectomy. In July 2009 he had an uneventful tonsillectomy and revision adenoidectomy, using an age-appropriate endotracheal tube, for symptoms of recurrent tonsillitis and sleep disordered breathing.

On the 11 March 2010, 8 months later, patient Y presented acutely with dyspnoea, biphasic stridor and intercostal recession on a background of 5–6 months of limited exercise tolerance, noisy breathing and very prolonged feeding time at meals.

Flexible nasolaryngoscopy showed a very inflamed larynx and acutely inflamed subglottic stenosis with a pinhole lumen (Myers-Cotton grade III, see Table 1). After observation in the Intensive Care Unit and treatment with IV augmentin, IV steroids, nebulised adrenaline and saline for 48 hours, his stenosis improved to a Myers-Cotton grade I. At day 5 from his initial presentation he was discharged on a reducing dose of prednisone started at 60 mg daily.

Table 1. Myers and Cotton grading for circumferential SGS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lumen obstruction</th>
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<tr>
<td>I</td>
<td>0–50 %</td>
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<tr>
<td>II</td>
<td>51–70 %</td>
</tr>
<tr>
<td>III</td>
<td>71–99 %</td>
</tr>
<tr>
<td>IV</td>
<td>100 %</td>
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</table>

After stopping prednisone the previous week, patient Y represented acutely with increasing stridor, a hoarse voice and dyspnoea 19 days after his initial presentation. A subglottic narrowing with a 8 mm lumen was seen. He was booked for a semi-urgent laryngoscopy under GA, however he deteriorated on the day of his surgery (day 26) with PA and lateral neck radiographs showing a narrow tracheal lumen confirmed by nasolaryngoscopy to be 4 mm (Myers and Cotton grade III). He was recommenced on high dose IV dexamethasone but failed to improve.

A formal GA laryngobronchoscopy and upper GI endoscopy (see Figure 1–2, Table 2) was postponed until day 34, as he was too unstable to proceed without a very significant risk of requiring an emergent tracheostomy. Histology revealed posterior subglottic epithelial inflammatory infiltrate and intraepithelial eosinophilic infiltrate and inflamed respiratory mucosa at the inferior tracheal band.

Tissue and bronchial lavage cultures were negative for all organisms. His symptoms were considered stable after his airway improved to a 9–10 mm lumen and he was discharged 35 days from his initial presentation on prednisone 60 mg daily, empirical omeprazole 20 mg bd and erythromycin 400 mg qds for 1 week.
During his admissions, an extensive battery of radiological, microbiological, histological and serological investigations was performed. MRI showed subglottic soft tissue thickening but no vascular abnormality or other involvement of the bronchopulmonary system.

Positive results included a non-significantly raised serum IgE (774) and an ANA titre of 1280, not considered significant in the absence of other antibodies. Specific serum IgE demonstrated house dust mite and mild mixed grass allergy.
Over the next 20 days his symptoms remained stable but his subglottic narrowing failed to improve to its original capacity on maximum dose prednisone (60 mg daily) and omeprazole 30 mg bd. His weight gain was now 4.5 kg (increase of 11%), due to steroid therapy. AZI 500 mg 3 times weekly was started 55 days after his initial presentation.

Within 2–3 days Patient Y’s airway improved to 9–10 mm and his steroid therapy was gradually weaned. As an adjunctive therapy balloon dilatation\(^1,2\) and intralesional steroid injections were performed at day 61 along with oesophageal biopies which excluded eosinophilic oesophagitis.

Balloon dilatation was repeated on one further occasion a month on. He remained stable on no steroids and AZI alone for 112 days before it was finally stopped. His weight peaked at 15 kg heavier (increase of 37.5%) before regressing. When omeprazole was stopped, laryngeal and subglottic erythema returned but resolved with restarting treatment.

### Table 2. Theatre visits

<table>
<thead>
<tr>
<th>Days from presentation</th>
<th>Procedures under GA</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>+ 34 days</td>
<td>Laryngobronchoscopy and upper GI endoscopy</td>
<td>–General tracheal inflammation, two main bands of circumferential stenosis in upper and mid trachea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–Right tracheal bronchus at level of carina, adhesions at the carina. Normal oesophagus.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–Biopsies of trachea and subglottis showed intraepithelial eosinophilic infiltrate</td>
</tr>
<tr>
<td>+ 47 days</td>
<td>Procedure postponed: flexible laryngoscopy only (Figure 3)</td>
<td>Severe SGS causing increased risk of emergent tracheostomy and increased anaesthetic risks</td>
</tr>
<tr>
<td>+ 55 days</td>
<td>Commencement of azithromycin 500 mg 3 times weekly</td>
<td></td>
</tr>
<tr>
<td>+ 61 days</td>
<td>Laryngobronchoscopy, subglottic balloon dilatation and oesophageal biopies</td>
<td>–Improved SGS in comparison to clinic at +55 days and decreased oedema and erythema, Myers-Cotton I.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–Balloon dilatation performed with intralesional steroid injection</td>
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</table>

After being off treatment for 4 months, patient Y has returned to all his normal activities including rugby, and has lost a substantial amount of weight following cessation of his steroid therapy. His SGS remains minimal. He suffers laryngopharyngeal reflux currently controlled on omeprazole; dyspepsia was not a symptom at his original presentation. A final diagnosis of non-autoimmune idiopathic subglottic stenosis was made.

**Discussion—azithromycin and inflammation**

AZI, a macrolide, has its antibiotic effect by binding to the 50S ribosomal subunit of susceptible microorganisms, it also blocks dissociation of peptidyl tRNA from ribosomes subsequently causing RNA-dependent protein arrest.
It has been proposed that AZI, used in sub-antibiotic doses, also has an immunoregulatory effect by decreasing mucous production, chemotaxis, expression of cellular adherence molecules, and cytokine production. An autoimmune cause was considered early on given Patient Y’s positive ANA and serum IgE, however these were not deemed significant and the oesophageal biopsies excluded eosinophilic oesophagitis. Intubation injury from his previous adenotonsillecomy was excluded due to the diffuse nature of tracheal involvement. AZI was considered for its anti-inflammatory properties often described for the treatment of cystic fibrosis, and reported in pharmacology literature. Prior to the AZI therapy patient Y relapsed at each attempt to wean him off the prednisone. It was cautiously decreased from the 60 mg dose over 77 days. Balloon dilatation was used as an adjunct and it was felt that maximum disease control came from the AZI.

There have been reports of macrolide antibiotics being used in SGS in patients suffering from Chlamydia pneumoniae. We believe this is the first case of idiopathic SGS and diffuse tracheal stenoses, aggravated by laryngopharyngeal reflux, to be successfully managed with the macrolide AZI. It was used in sub-antibiotic dosing, specifically as an anti-inflammatory agent.

Laryngopharyngeal reflux was not the causative factor as 20 days of therapy with a proton-pump inhibitor failed to improve his symptoms. The risk of becoming steroid dependant has been described and in this case AZI has proved beneficial in reducing this risk.

Competing interests: Nil.

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