L25. Medical treatment of subglottic stenosis in granulomatosis with polyangiitis (Wegener’s)

Subglottic stenosis (SGS) has been noted to develop in 12–23% of patients with granulomatosis with polyangiitis (GPA, Wegener’s) [1–3], and may be more common among children and young adults with GPA [1] although this has not been seen in all series [4]. SGS is a feared complication since it can be life-threatening and frequently is associated with considerable morbidity, with up to 40-50% of patients historically requiring tracheostomy at least temporarily [5,6]. The region at risk is narrow and is located 1.5–2 cm below the true vocal cords and above the trachea [7]. This region is at a junction of two microcirculatory beds, which is thought to make the subglottis particularly susceptible to permanent damage and scarring [6–8], but other factors such as turbulent airflow, exposure to gastric contents, and a complete ring of cartilage at this level are also potential factors [6], and whether the “watershed” microvascular anatomy also predisposes to the initial development of inflammation or limits the delivery of blood-borne drugs is uncertain.

Over the past 10 years, local therapies for SGS have risen to the forefront, as reviewed elsewhere in this issue of The Quarterly Medical Review and previously [9], and somewhat different strategies have been developed at different centers [1,6,7,10]. This review will focus on the extremely limited data regarding the effectiveness, or lack thereof, of medical therapy.

Active inflammation versus scarring in subglottic stenosis

One major difficulty in interpreting the literature on immune-suppressive therapy for SGS is the fact that in the largest series, evidence for active GPA is lacking in many cases, and methods for reporting that evidence have differed. For example, in 20 of 27 cases reported by Gluth et al., the endoscopic appearance was that of scar tissue rather than active inflammation, and only four of 16 biopsies (among all 27 patients) showed granulomatous inflammation [6]. It was not reported whether any cases that appeared normal on exam showed inflammation on biopsy, or vice versa. Similarly, among 26 patients examined repeatedly by the same otolaryngologist and reported by Langford et al., endoscopic examination revealed active inflammation 42 times and scarring without inflammation 169 times [1]. In this study, however, endoscopic appearance clearly did not correlate perfectly with biopsy results: 4/76 biopsies from 18 patients whose tracheas appeared normal on endoscopy showed both granulomatous inflammation and vasculitis, compared to 1/31 biopsies from 13 patients whose tracheas appeared inflamed. Many additional biopsies in this study (93/140, 66%) showed acute and chronic inflammation that might or might not represent active GPA, but these data were not stratified by endoscopic appearance [1].

Thus, it appears likely that many cases of SGS represent scarring from prior damage, but on the other hand, absence of inflammation on endoscopy underestimates the prevalence of active GPA, and biopsy may improve detection of inflammation but not be specific for active GPA. Fortunately, local therapies appear to work in both settings [1,9,10]. However, uncertainty about the presence of active GPA makes the interpretation of reports about medical treatment of SGS challenging.

Systemic medical therapy for subglottic stenosis

With that caveat, it is probably still appropriate to conclude that SGS is less responsive to systemic immune-suppressive therapy than are most other manifestations of GPA. A summary of early case reports concluded tentatively that treatment led to better outcomes than no treatment [11], and a recent review estimated the response to systemic treatment at 20–26% [9]. Most strikingly, half of the cases (21/43) reported by Langford et al., occurred during immune-suppressive therapy (usually cyclophosphamide, prednisone, or both), and half of the cases (21/43, not necessarily the same ones) occurred without evidence of active GPA in other organ systems [1]. Even if many of these cases simply represented scarring from prior damage, at least some of them must have represented recurrent GPA, clinically limited to the subglottis, despite treatment. In other reports, the presence of active GPA in a few such cases of relapse limited to the subglottis was proved by biopsy [12,13].

To the extent that systemic therapy is helpful, the possibility of differential benefit of different drugs cannot be determined from the literature. Results related to SGS have not been reported in any of the large clinical trials published in the past 10 years. One early report suggested that glucocorticoids alone produced only transient improvement whereas addition of cyclophosphamide led to remission, although outcomes, in the era before local therapy, were still poor [14]. Most other reports of successful medical treatment have also involved cyclophosphamide plus glucocorticoids, since that was standard of care for all cases of severe GPA at the time [1,11] and was often being used in such cases to control severe disease in other organ systems [1]. However, isolated reports of response to glucocorticoids alone also exist [9,15]. Data specifically pertaining to use of methotrexate or azathioprine in treating or controlling SGS are very limited and often involve cases in which local therapy was also used [16–18]. Reports of GPA flares limited to the subglottis have been reported in patients who were receiving these drugs or mycophenolate for maintenance therapy [1,13,17]. Rituximab has become widely used since the publication of the major series on SGS, but only a few cases regarding its use in SGS have been published. Most of these cases have been
reported amidst many other cases of GPA refractory to standard therapy in other organ systems, so data on severity of SGS, endoscopic appearance, biopsy results, and concomitant use of local treatment are lacking. Aries reported two patients with SGS treated with rituximab without an increase in glucocorticoids, one of whom went in remission and one of whom had no response [19]. See et al. reported one patient treated successfully with rituximab plus glucocorticoids [20]. Pullerits et al. reported three patients with SGS treated with rituximab, one of whom improved and two of whom did not [21]. Eustaquio et al. reported successful use of rituximab in three pediatric patients with SGS, but since local therapies and surgery were also employed in these complicated cases, the benefit attributable to rituximab is difficult to discern [22]. Overall, the response of SGS to rituximab does not seem to be impressive, but since that statement can be made about older therapies, rituximab can probably be added to the list of agents that probably work in some patients with SGS. Finally, because chemical damage from gastric contents could lead to further damage and scarring in SGS, some authors have advocated use of proton-pump inhibitors and other measures to control gastroesophageal reflux as adjunctive therapy [6,16].

Conclusion

Because local therapy has proved to be more beneficial than systemic therapy for SGS in GPA, a search for systemic regimens with better efficacy specifically in treating SGS may not be an important priority. However, as more new medications and regimens are identified that are effective for treating GPA in general, it will be helpful to have data published regarding induction and particularly maintenance of remission in the subglottis to assist physicians in the management of this particularly challenging problem.

Disclosure of interest: the author declares that he has no conflicts of interest concerning this article.

References


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Available online 26 February 2013

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http://dx.doi.org/10.1016/j.lpm.2013.01.025