Successful treatment of refractory tracheal stenosis complicating anti-neutrophil cytoplasm antibody-associated vasculitis with sirolimus

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Summary

Laryngotracheal granulomatous inflammation is a clinical entity that may complicate either localized or systemic disorders. It can result in life-threatening airway compromise, requiring urgent medical or surgical intervention. We report the case of a patient presenting with recurrent tracheal stenosis secondary to anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, refractory to conventional treatments. Despite multiple endoscopic dilatations and surgical resection of tracheal rings, disease control remained suboptimal. Introduction of sirolimus led to a sustained improvement of the stenotic lesion, as demonstrated by clinical and instrumental assessment. Sirolimus may be considered a valuable therapeutic option for severe subglottic inflammatory manifestations in ANCA-associated vasculitis.

Introduction

Subglottic stenosis of the laryngotracheal region is a consequence of inflammatory processes occurring in the upper airways. This condition may present as an isolated primary disorder or as a secondary complication of systemic diseases (1). In rheumatology, subglottic stenosis is most commonly associated with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, such as granulomatosis with polyangiitis (GPA) and eosinophilic GPA, as well as with IgG4-related disease, particularly in pediatric patients, where it may represent the initial manifestation of the diseases (2-4). Other conditions linked to subglottic stenosis include inflammatory bowel diseases, such as Crohn's disease (5), and sarcoidosis (1). Regardless of the underlying cause, clinical manifestations include cough, stridor, dyspnea, exertional intolerance, obstructive sleep apnea, and, rarely, life-threatening airway obstruction (1, 6). Diagnosis requires endoscopic assessment with biopsies combined with laboratory investigations, including infectious serologies, inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), complete blood count, autoantibody screening, serum angiotensin-converting enzyme, urinary calcium, and lysozyme levels. Therapeutic endoscopic interventions include balloon dilatation, laser ablation, mucosal-sparing surgery, and local injection of glucocorticoids (GC) or mitomycin C, as well as stent placement (1, 7). Surgical management mainly consists of resecting the stenotic tract with subsequent end-to-end anastomosis or tracheostomy (1). Systemic treatments include GC, conventional synthetic disease-modifying anti-rheumatic drugs, *i.e.*, cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate, as well as biologic agents including rituximab (RTX), and targeted therapies like avacopan (6, 8).

Case Report

We report the case of a 33-year-old woman with recurrent tracheal stenosis secondary to GPA. The disease onset dated back to 2018 and was characterized by recurrent episodes of rhinosinusitis and otitis media. Laboratory tests revealed elevated perinuclear ANCA (p-ANCA) levels (418.7 U/L) by indirect immunofluorescence and anti-myeloperoxidase (MPO) antibodies >100 U/L by enzyme-linked immunosorbent assay. Serology for cytoplasmic ANCA (c-ANCA), anti-proteinase 3 (PR3), anti-nuclear antibodies, extractable nuclear antigen antibodies, rheumatoid factor, anti-citrullinated peptide antibodies, and anti-double-stranded DNA was negative. Infectious etiologies were excluded. A head computed tomography scan showed thickening of the nasal mucosa with marked deviation of the nasal septum. High-resolution computed tomography of the chest revealed no pulmonary involvement. Broncho-alveolar lavage was negative for infectious pathogens and showed no significant inflammatory cellularity. Hence, a diagnosis of ANCA-associated vasculitis, with predominant involvement of the upper tract airways, was made. Although the serological profile was atypical for GPA, characterized by p-ANCA/MPO positivity rather than c-ANCA/PR3, this phenotype has been reported in approximately 20% of GPA patients and is thought to represent a distinct clinical subset (9-11). Shortly after diagnosis, the patient developed a severe tracheal stenosis. Initial treatment relied on endoscopic balloon dilatation coupled with intravenous methylprednisolone pulses (500 mg/day for 3 days), followed by oral prednisone (1 mg/kg/day), and subcutaneous methotrexate (15 mg/week). In February 2019, due to a life-threatening recurrence of the stenosis, a surgical resection of four tracheal rings with primary end-to-end anastomosis was performed. Histopathological analysis of the resected tissue demonstrated the presence of acute inflammation on a chronic background with granulomas and neutrophil infil-

tration. In April 2023, a new relapse of stenosis occurred. The patient was treated with a combination of avacopan (60 mg/day) and RTX (1000 mg at day 0 and 14), replacing previous ineffective treatment. Avacopan was discontinued in June 2023 due to secondary failure, while RTX was continued as maintenance therapy. In August 2023, sirolimus was introduced at 2 mg/day in combination with RTX (1000 mg every 6 months) and low-dose GC (prednisone, 2.5 mg/day). Sirolimous blood level was regularly monitored, maintaining a therapeutic range of 5-9 ng/mL. The last endoscopic procedure, performed in September 2024, showed no new lesions. The residual tracheal stenosis remained stable with a luminal diameter of 9 mm, which allowed regular breathing (Figure 1). Radiological follow-up by computed tomography confirmed improvement and stability of the airway narrowing (Figure 2).

Discussion

Subglottic stenosis has been described in MPO-positive GPA patients (10, 11); to date, the experience with sirolimus to treat this complication is limited to a few case reports and small series. Poo *et al.* reported a case series of 6 patients with subglottic stenosis, 5 secondary to GPA and one to IgG4-related disease, who were treated with sirolimus. Of these, 4 patients continued long-term treatment, achieving GC discontinuation and a significant reduction in the frequency of endoscopic interventions (12). Samtani *et al*. described the case of a 13-year-old girl with upper airway obstruction due to idiopathic granulomatous inflammation of the glottis and supraglottis, unrelated to infectious or rheumatic diseases, that required continuous positive airway pressure (CPAP) for severe respiratory impairment. The patient showed inadequate response to both local and systemic GC, endoscopic procedures, and immunosuppressive drugs, such as mycophenolate mofetil and adalimumab. Ultimately, sirolimus was introduced with endoscopic reduction of edema, improvement in exercise tolerance, and resolution of sleep apnea, with consequent CPAP discontinuation (13).

The rationale for using sirolimus in the case of subglottic stenosis is supported by i*n vitro* studies that revealed a double anti-fibrotic effect. Indeed, sirolimus has been shown to reduce fibroblast proliferation and collagen production (14) and to inhibit T helper-17 cells expressing *mTOR*, preventing further activation of fibroblasts (15). Thus, sirolimus may exert both anti-fibrotic and anti-inflammatory effects, potentially interfering with key pathogenic processes causing the development and progression of subglottic stenosis.

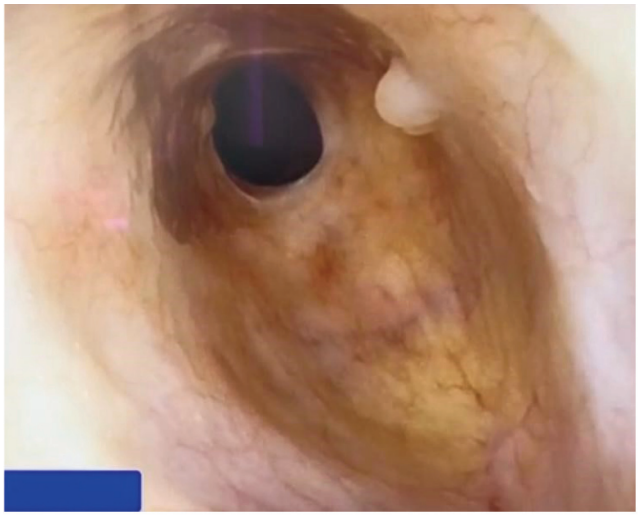

Figure 1. Image from the rhinofibroscopic evaluation performed after 12 months of treatment with sirolimus that showed stable subglottic stenosis in the absence of new lesions.

Conclusions

The management of GPA-associated subglottic stenosis remains challenging, often requiring a combination of systemic and local therapeutic approaches that need further research to be optimized. Systemic immunosuppressive treatments are usually necessary to control active disease. In this regard, GC plus cyclophosphamide or RTX may induce clinical remission, particularly in cases of generalized vasculitic involvement (6, 16). Notably, RTX appears to reduce the risk of relapse compared to other agents (17, 18). Among alternative therapies, leflunomide has shown some efficacy in improving airway stenosis, while evidence on azathioprine, methotrexate, and mycophenolate mofetil remains limited (17).

Local interventions, such as endoscopic balloon dilatation with intra-lesional GC injection and topical mitomycin C, stand out as first-line options for subglottic stenosis management. In refractory cases, marked by extensive fibrosis, open transcervical surgery remains the definitive treatment, and tracheostomy may be necessary in life-threatening situations (19). Nevertheless, the current evidence is primarily anecdotal, based on isolated case reports and small series, and no consensus exists on a preferred treatment strat-

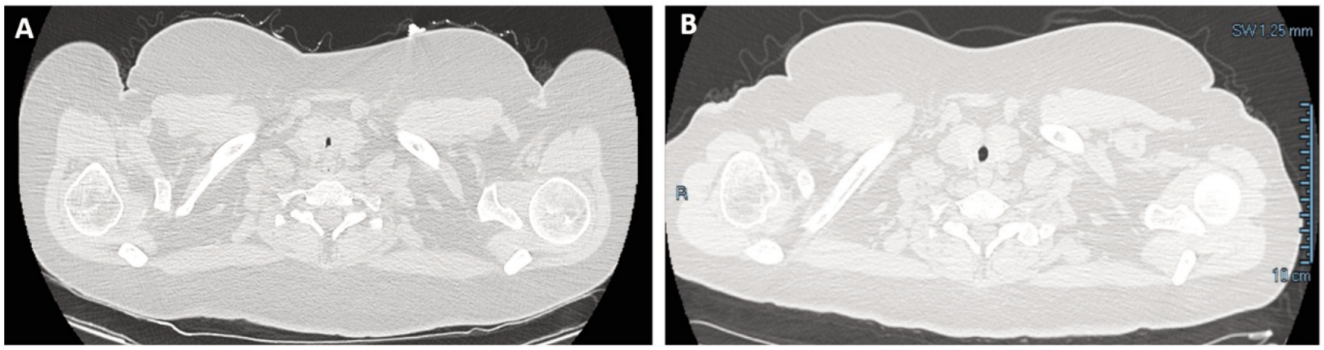

Figure 2. Subglottic stenosis is evidenced in the computed tomography scan performed in 2022 (**A**) and after treatment in 2024 (**B**).

egy. In this context, sirolimus emerges as a promising therapeutic option, warranting further investigation, in the management of GPA-related subglottic stenosis.

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