# Editorial

# Evaluating the utility of biopsies in tracheobronchial stenosis: an attempt at expanding knowledge on a narrowed issue

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Tracheobronchial stenosis (TBS), which is composed of subglottic stenosis (SGS) and/or endobronchial stenosis (EBS), is among the more feared and yet also less well understood complications of granulomatosis with polyangiitis (GPA). Its manifestations can range from incidentally found lesions on endoscopy to life-threatening airway obstruction and respiratory failure (1, 2). In this issue, Linde *et al*. (3) present a combined literature review and single-centre cohort study that addresses two fundamental questions: what role does histopathology play in evaluating patients with TBS and what is the long-term clinical trajectory of GPA patients affected by this manifestation.

In the single-centre Copenhagen cohort, Linde *et al*. reviewed 67 biopsies from 26 patients with GPA and endobronchoscopic confirmation of TBS. Presence of at least one histopathological feature considered characteristic of GPA, *i.e*. granulomatous inflammation, giant cells, microabscesses, or vasculitis, was identified in only 22% (15/67) of specimens. In an expanded literature review of 296 biopsies from 203 patients across 21 articles, the same frequency of positive biopsies was observed [22%, 64/296]. Notably, biopsy positivity varied by TBS timing: only 1 of 6 biopsies at GPA diagnosis showed characteristic features, *versus* 5 of 10 biopsies from patients developing stenosis later (median 6 years) (3).

For providers that assist in the diagnosis and management of GPA, these results are sobering, yet unfortunately unsurprising. This data suggests that the diagnostic yield of TBS biopsy is overall low, and providers should anticipate the majority of samples to be non-specific or non-diagnostic. Patient and care team discussions should therefore clarify TBS biopsy limitations and guide biopsy site selection and its role in confirming GPA or excluding alternatives.

An important element, unfortunately not included in the report by Linde *et al*., is the number of patients for whom the biopsy from the TBS lesion was the only sample source to evaluate or confirm GPA. This is particularly important because patients with systemic involvement with GPA have been reported to have a 2.6 greater likelihood of obtaining diagnostic GPA airway biopsies compared to those with airway limited disease (4). Among the 27 GPA patients with TBS in the Copenhagen cohort, 41% had skin, 44% lung, and 22% renal manifestations of GPA (3). Kidney and skin biopsies have a substantially higher yield for confirmation of vasculitis with 85–95% of patients with active renal involvement and 68–94% of those with cutaneous manifestations demonstrating histologic features consistent with a diagnosis of vasculitis (5, 6), indicating these locations should be considered before TBS lesions when diagnosis of GPA is in question. The clinical impact and importance of obtaining a characteristic biopsy consistent with GPA in a patient with TBS is much greater when the TBS is the main or sole manifestation of disease, especially in ANCA-negative cases. Therefore, in patients without an established diagnosis of GPA, TBS biopsy can be valuable if no other accessible biopsy sites are available. However, in those with established or clinically certain GPA, TBS biopsy is generally unnecessary unless needed to exclude malignancy, infection, or other causes before initiation or modification of immunosuppression. Furthermore, its role in distinguishing active disease from chronic scar/damage is limited;

therefore, therapeutic decisions should rely on a comprehensive clinical assessment rather than on histopathological findings alone.

Though Linde *et al*.'s Copenhagen cohort and literature review showed similar biopsy positivity rates, their retrospective design lacks detailed biopsy methodology, limiting insights into differences between patients and guidance on best practices. All the biopsies were obtained during a SGS or EBS balloon dilation, however, what remains unknown is the optimal approach of tissue acquisition (*e.g*. snare-forceps, cold-knife excision, cryoprobe, etc.), size and number of samples obtained, decision on location and depth of sampling, visual description of endoscopic findings at the time of biopsy, and timing of biopsy relative to treatment initiation. Although one of the main strengths of this study is that the cohort is from the same tertiary referral centre, given the 27 patients were followed from 1991-2022, it is possible that technology and methodology of performing endoscopic procedures changed over time. For example, laser-wedge excision, which reduces recurrence risk compared to balloon dilation in idiopathic SGS (7), warrants further evaluation and direct comparison in patients with GPA-associated SGS.

One of the greatest strengths of the report by Linde *et al*. is the long-term follow-up of this cohort with median of 17 (0–31) years of observation. A large number of endoscopic dilations were performed, overall, a median of 5 dilations per patient, with one patient having 100 dilations over 21 years of follow-up (3). Stratification based on sex and ANCA specificity did not show a difference in the number of endoscopic procedures during follow-up. Procedure-free intervals were also similar between male and female patients. Comparison between the number of dilations and the interval time between dilations among those with and without characteristic GPA findings on TBS biopsy, however, was not included. In addition, Linde and colleagues could not compare outcomes based on systemic treatment due the retrospective nature of the study, limited sample size and treatment heterogeneity.

The impact of treatment on the TBS lesions in GPA remains an area of limited data and incomplete guidance. While the American College of Rheumatology 2021 guidelines for management of GPA conditionally recommends that patients with actively inflamed TBS tissue are treated with immunosuppression over endoscopic interventions (dilation and intralesional steroids) alone, the supporting evidence for this is of low-quality (8). There are no prospective studies evaluating the outcome of medical management of GPA-associated TBS. Though similarly limited by retrospective evaluation, recent studies have demonstrated endoscopic intervention combined with systemic immunosuppression may lead to improved outcomes with fewer SGS recurrences and longer surgery-free intervals when rituximab, cyclophosphamide, or sirolimus are used concurrently with endoscopic intervention (9-11).

Linde *et al*. present important long-term data on the challenging manifestation of GPA-related TBS, confirming its chronic relapsing nature and low histological diagnostic yield. This data highlights the current knowledge gaps regarding the uncertainty of how to optimise combined systemic and local therapies to reduce procedural burden and preserve airway function. In order to advance the understanding of TBS management, prospective studies incorporating standardised biopsy protocols, uniform histopathologic assessment, defined treatment algorithms and prespecified outcome measurements will be needed.

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