



## Case report

## “Exercise induced asthma” is not always asthma

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## ABSTRACT

A 25 year old woman was referred to our center for further evaluation of an exercise-induced dyspnea. Moreover, the patient suffered from hoarseness and recurrent sinusitis and otitis.

After initially finding nothing suspicious, a spiro-ergometry was performed. Interestingly, we saw a relevant limitation of the inspiratory flow-volume curve under maximal exercise load. Further evaluation (in particular the bronchoscopy and the resulting biopsies) led us to the final diagnosis of a granulomatosis with polyangiitis.

After 4 weeks of an established therapy regime with prednisone and rituximab the prior detected subglottic stenosis and the inspiratory flow-volume curve limitation could no longer detected.

We describe a rare differential diagnosis of an exercise-induced asthma and we underline the importance of a multimodal therapy concept. We highlight the critical nature of the flow-volume curve in spiro-ergometry under maximal exercise load. We recommend frequent follow-up control visits to monitor the subglottic stenosis.

A 25-year-old Caucasian woman presented with a 3-month history of shortness of breath, wheezing during exercise, hoarseness and post-nasal drip. She had been treated with combined INHALED ICS/LABA (budesonid/formoterol) for several weeks without improvement of these symptoms. She had no known allergies, no family history of asthma or hay fever. The patient suffered from recurrent sinusitis and otitis and reported an increase in dyspnea during her rugby workout. She reported no epistaxis or hemoptysis and denied chest pain or palpitations. She quit smoking in April 2017 (2 pack years). The patient was referred to our hospital because of ongoing symptoms despite an established asthma therapy. The patient was not receiving any other medication.

Physical examination revealed a fully oriented patient with normal vital parameters and normal nutritional condition. Auscultation of the lungs and heart was unremarkable. In particular, no stridor in rest was detected. A correct inhalation technique was observed.

Laboratory examinations are shown in [Table 1](#).

To determine a significant ventilation limitation, a pulmonary function test (PFT) and arterial blood gas analysis (ABGA) were performed. This revealed normal lung volumes, unaffected diffusion capacity and gas exchange and no flow-volume-curve-limitation ([Fig. 1a](#)).

A bronchoprovocation test with methacholine yielded no bronchial hyperactivity.

To further explore the cause of unexplained dyspnea a spiro-ergometry (CPET) was performed. The result showed above average performance (201 Watt, 149% predicted) with a normal maximal oxygen uptake (98% predicted). Besides a normal alveolar-arterial difference (aADO<sub>2</sub>), there were no hints pointing towards a cardiac limitation as the patient had an unremarkable O<sub>2</sub> pulse and a sinus rhythm without alterations of the conduction system. Noteworthy, however, was the finding at the end of the exercise test where the patient developed an evident inspiratory and expiratory stridor. A correlation to the flow-volume-curve during the maximal burden revealed reduced inspiratory and expiratory flows with a typical oval-shaped curve ([Fig. 1b](#)).

A chest x-ray and CT-scan showed sub-pleural masses in the anterior right lobe at the apex and adjacent to the mediastinum, with no pleural effusion and no mediastinal or hilar lymphadenopathy ([Fig. 2](#)).

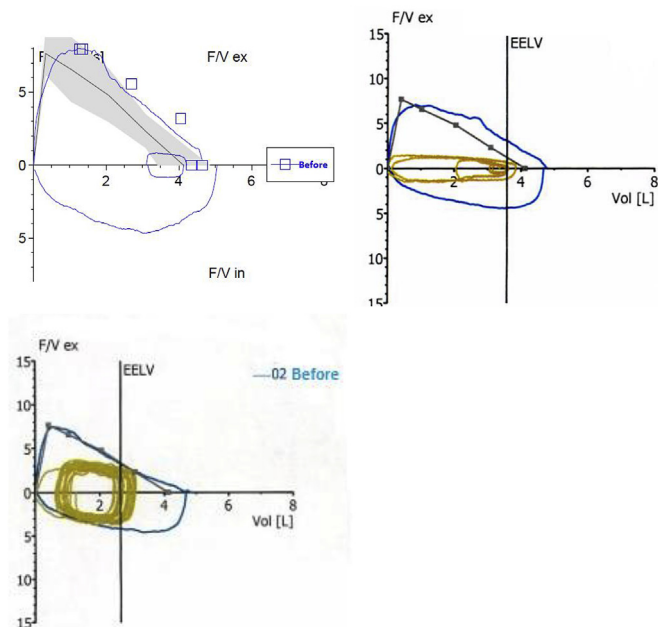
To exclude malignancy, a bronchoscopy was performed revealing a subglottic stenosis ([Fig. 3a](#)). Mucosa biopsies showed basophilic necrosis with epithelioid macrophages and scattered giant cells in the periphery of the necrosis. The adjacent stroma had a mixed inflammation consisting of lymphocytes, plasma cells and some

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**Table 1**  
(Laboratory findings and systemic antibodies).

	Results	Range
Eosinophilic count	$0.918 \times 10^9/l$	[0–0.300] [ $\times 10^9/l$ ]
IgE	128 IU/ml	[ < 100] [IU/mL]
proBNP	26 ng/l	[ < 177] [ng/l]
D-Dimers	< 0.30 $\mu\text{g/ml}$	[ < 0.50] [ $\mu\text{g/ml}$ ]
PR3-ANCA	14 U/ml	[ < 3] [U/mL]
ANCA-titer	1:20	[ < 1:20] [Titer]
Anti-MPO antibodies	< 5 U/ml	[ < 5] [U/mL]
C3c and C4	1.48 and 0.37 g/l	[0.8–1.8] [g/L] and [0.1–0.4] [g/L]



**Fig. 1.** a and b: Four weeks after therapy with a rituximab and a prednisone regime.

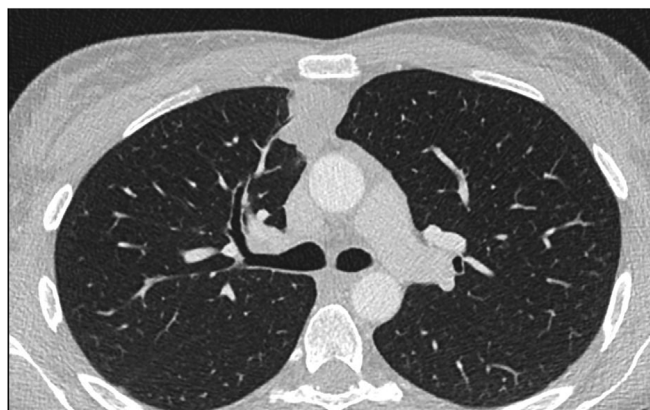
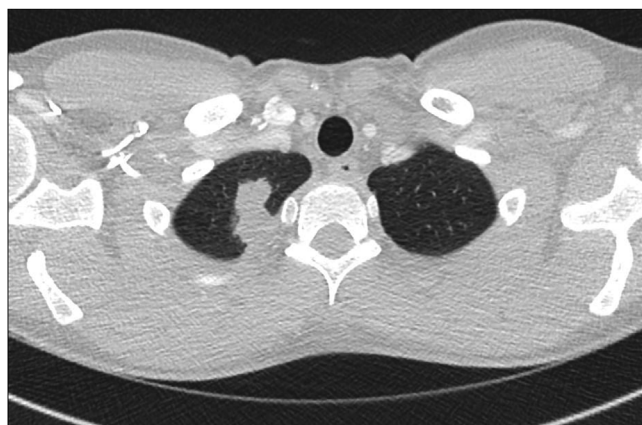
eosinophils. Though the few sampled small vessels had no signs of inflammation, these findings together with the clinical presentation were consistent with granulomatosis with polyangiitis (GPA) (Fig. 4). Special stains for fungi and acid-fast bacteria were negative. Based on the Chapel Hill Consensus Conference Nomenclature of Vasculitides and integrating all findings, we diagnosed GPA. Further findings were diffuse erythema in the bronchi and in the trachea.

Based on the results our working hypothesis was vasculitis, most likely GPA because of the subglottic stenosis.

The results of the systemic antibodies and the complement factors are shown in Table 1.

While evaluating extra-pulmonary manifestations, a kidney involvement with a relevant proteinuria of 1 g daily with glomerular pattern was seen. Active sediment casts could be excluded. A comprehensive otorhinolaryngological examination revealed an otitis media on the left side and a perforation of the septum nasi. A CT-scan of the paranasal sinuses detected a granuloma in the right sinus maxillaris (Fig. 5).

A b-cell-depletion with rituximab and a prednisone regime was established after excluding a relevant immunosuppression, pregnancy or latent mycobacteriosis.



**Fig. 2.** CT-scan.

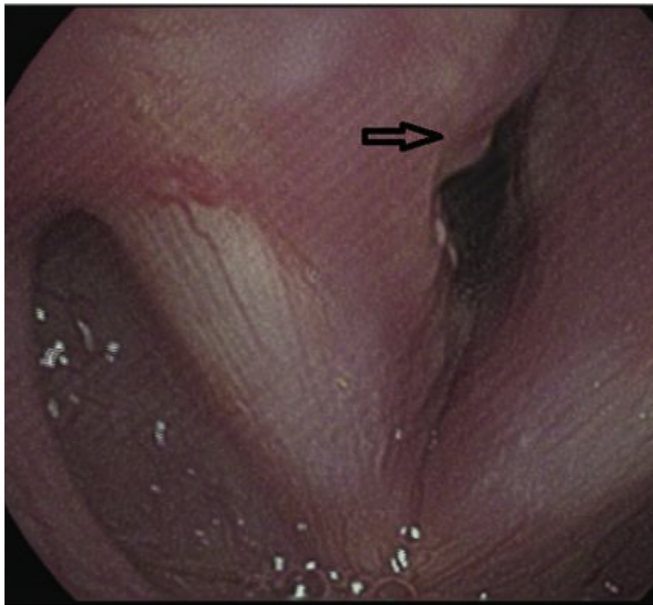
## 1. Discussion

In our case we describe a rare differential diagnosis of asthma in a young woman. The patient did not respond to asthma treatment prescribed by the general practitioner and was therefore referred for further evaluation. Unremarkable test results, i.e. flow-volume-curves at rest, body plethysmography, exhaled nitrogen oxide and a methacholine provocation test, prompted further investigation with spiro-ergometry.

Patients with shortness of breath can present with different types of airflow-volume-curves depending on whether the ventilation limitation is obstructive or restrictive (Fig. 6).

1. Asthmatic patients typically have a complete or partially reversible obstruction (Fig. 6.1). A complete reversibility, which is more prevalent, can be shown by a normalization of the obstruction after bronchodilation ( $FEV_1/FVC > 70\%$ ). A partial reversibility, found less often, can be shown with a persistent obstruction ( $FEV_1/FVC < 70\%$ ) and an improvement of the  $FEV_1$  of more than 120ml and 20% improvement from baseline.
2. Chronic obstructive pulmonary patients typically have an irreversible/fixed obstruction (Fig. 6.2.).
3. A restrictive ventilation limitation is shown with a decreased total lung capacity (TLC) and forced vital capacity (FVC). The  $FEV_1$  is also low because of the reduced lung volume although the  $FEV_1/FVC$  ratio is normal (Fig. 6.3.).

a)



b)

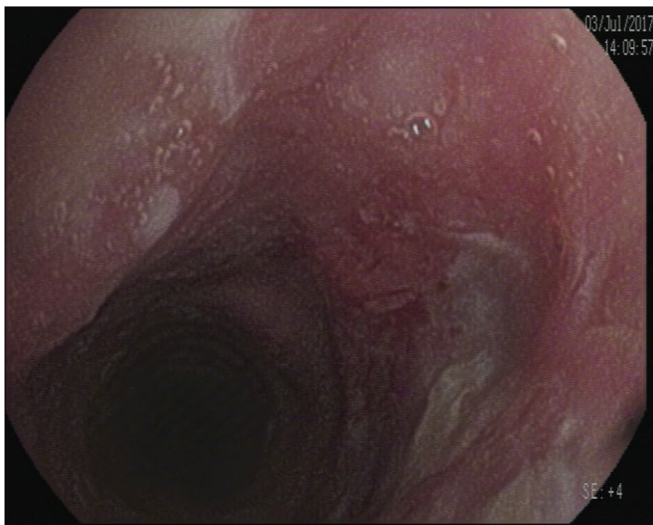


Fig. 3. a and b: Bronchoscopy showing subglottic stenosis.

4. In special cases, such as patients with an extra-thoracic obstruction (e.g. Struma), a horizontal flow-volume limitation is evident in the inspiratory airflow curves (Fig. 6.4.). In our case, we detected not only an inspiratory but also an expiratory flow-volume curve limitation at maximum load during CPET. This was accompanied by auscultatory stridor which was highly suspicious for a tracheal stenosis (Fig. 1a and b).

As shown in our case, it is important to monitor the patient carefully throughout the examination and it is possible to correlate the physical observations with the flow-volume curves retrospectively. This led us to the diagnosis of a GPA.

The etiology of GPA is poorly understood. The histological features include necrotizing granulomatous inflammation with predominant involvement of small vessels [1]. Treatment-associated complications and end-organ damage results in a high rate of mortality [2]. The treatment-associated complications mainly involve antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis of the small-to medium-sized vessels. End-organ damage frequently involves the kidneys and lungs [3].

Multiple nodules and masses (up to 10mm in size) with bilateral distribution and peribronchovascular, angiocentric and subpleural predominance are typical radiological features showing intra-pulmonary involvement. Up to 50% of these nodules cavitate if lesions are greater than 20mm. Moreover, a halo sign, scarring and pleural tags are described. Waxing and waning of these nodules and infiltrates is a typical feature of GPA [4]. Furthermore, in 50% of all cases, ground glass opacities, consolidations and alveolar hemorrhage can occur [5,6].

Airways are involved in 15–55% of all GPA-affected adults. Histologically, the pleura show an unspecific pattern with an acute or chronic fibrinous pleurisy [4]. Although subglottic stenosis is a less common manifestation of GPA, it is related to a higher rate of subglottic airway procedures compared to an idiopathic subglottic stenosis [7–9]. The presence of a subglottic stenosis may result in a potentially life-threatening presentation of GPA, necessitating surgical intervention, tracheostomy [10] and a high rate of restenosis [11]. Tracheal involvement (16–23%) may be segmental or unifocal and may result in a circumferential airway thickening or a total occlusion [12,13].

Untreated GPA has a mortality of about 90% within two years after initial diagnosis [14]. Therefore, a multimodal therapy concept is clearly indicated in patients with GPA and subglottic stenosis. An interdisciplinary therapeutic approach (pneumology, rheumatology, nephrology etc.) is needed to achieve the best long-term outcome for the patient and to guide a lifelong follow-up [15].

The guideline-conformed therapy consists of an initial phase (3–6 months) of combined glucocorticoids with either cyclophosphamide or rituximab [16,17]. Selected patients with severe disease may benefit from the addition of plasma exchange [18]. The use of this highly cytotoxic regime is justified when considering the high mortality of the untreated disease. In the stabilized phase (12–24 months) a combination of glucocorticoids and azathioprine (AZA) or methotrexate (MTX) is a comparable option for sustained remission of GPA [19].

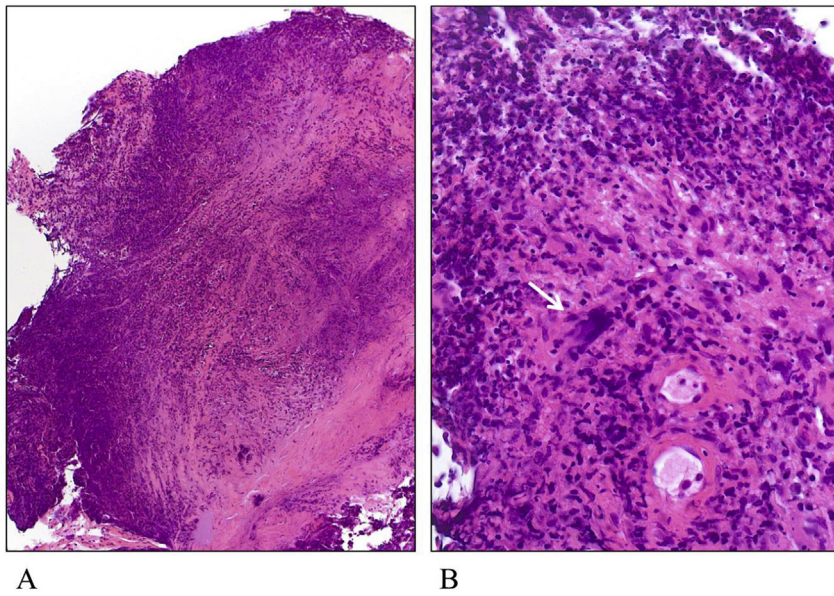
If the subglottic stenosis does not respond to pharmacological treatment, intralesional glucocorticoid injections and tracheal dilatation might be considered to avoid a tracheostomy [20].

In our patient renal involvement with glomerular proteinuria was detected. The glomerular filtration rate, the urine sediment and a sonography of the kidneys were unremarkable, thus frequent controls after onset of therapy were scheduled.

Under the established combined therapy with rituximab and prednisone a follow up with CT-scan, spiro-ergometry and bronchoscopy was performed. During the bronchoscopy, the initial detected subglottic stenosis was longer identifiable (Fig. 3b). As well, the flow-volume curve limitation under maximal exercise load was significantly diminished (see also addendum Fig. 1a and b).

CT-scan should be the choice of diagnosis, surveillance and follow-up.

In conclusion, “asthma”, which does not respond to continuous ICS/LABA inhalation therapy, should be evaluated further for other causes. In the described case the clinical findings and flow-volume curves during maximal exercise load led to the diagnosis of subglottic stenosis. Consequently, an adequate therapy was established timeously.



**Fig. 4.** Subglottic mucosal biopsy with findings consistent with granulomatosis with polyangiitis: Basophilic necrosis (A, HE original magnification 100 $\times$ ) containing abundant nuclear debris (upper part of image B, HE original magnification 400 $\times$ ). The necrosis is bordered by epithelioid histiocytes with the presence of a characteristic giant cell with hyperchromatic, smudged nuclei (arrow). Two small vessels without evidence of vasculitis (lower part of image B). The morphology of the necrosis and the granulomatous inflammation is consistent with granulomatosis with polyangiitis, though a vasculitis was not evident in this biopsy.



**Fig. 5.** CT scan of the paranasal sinuses.

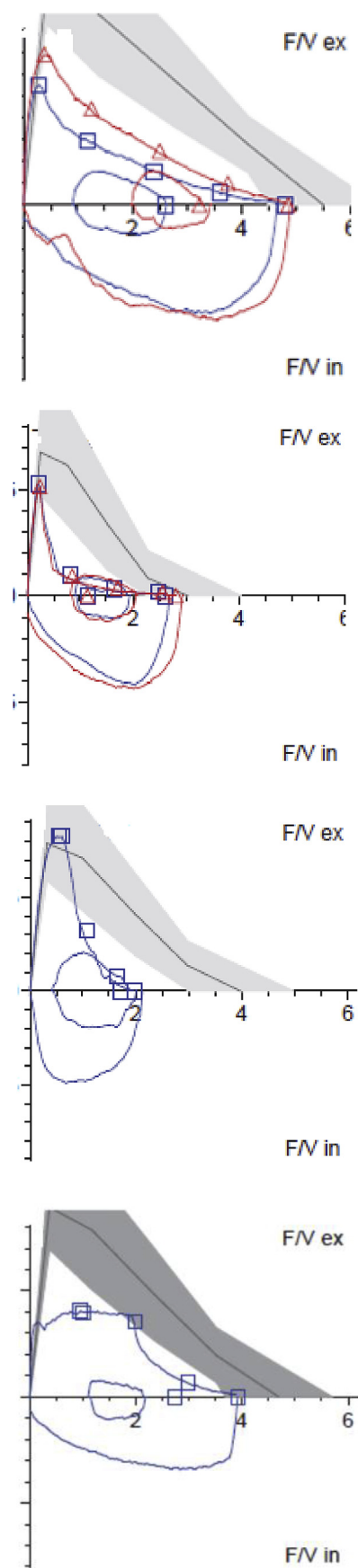


Fig. 6. 6.1 Asthma: 6.2. COPD. 6.3. Restrictive respiratory disorders. 6.4. Extrathoracic obstruction.

## References

- [1] P.M. Lutalo, D.P. D'Cruz, Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis), *J. Autoimmun.* 48–49 (2014) 94–98.
- [2] Z.S. Wallace, N. Lu, E. Miloslavsky, S. Unizony, J.H. Stone, H.K. Choi, Nationwide trends in hospitalizations and in-hospital mortality in granulomatosis with polyangiitis (Wegener's), *Arthritis Care & Res.* 69 (6) (2017) 915–921.
- [3] R. Solans-Laque, G. Fraile, M. Rodriguez-Carballeira, L. Caminal, M.J. Castillo, F. Martinez-Valle, L. Saez, J.J. Rios, X. Solanich, J. Oristrell, et al., Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity, *Medicine* 96 (8) (2017) e6083.
- [4] F. Martinez, J.H. Chung, S.R. Digumarthy, J.P. Kanne, G.F. Abbott, J.A. Shepard, E.J. Mark, A. Sharma, Common and uncommon manifestations of Wegener granulomatosis at chest CT: radiologic-pathologic correlation, *Radiograph. Rev. Publ. Radiol. Soc. North Am., Inc* 32 (1) (2012) 51–69.
- [5] M. Price, M.D. Gilman, B.W. Carter, B.S. Sabloff, M.T. Truong, C.C. Wu, Imaging of eosinophilic lung diseases, *Radiol. Clin.* 54 (6) (2016) 1151–1164.
- [6] J. Vanoli, M. Riva, B. Vergnano, G. D'Andrea, V. L'Imperio, M.R. Pozzi, G. Grassi, Granulomatosis with polyangiitis presenting with diffuse alveolar hemorrhage requiring extracorporeal membrane oxygenation with rapid multiorgan relapse: a case report, *Medicine* 96 (13) (2017) e6024.
- [7] M. Trimarchi, R.A. Sinico, R. Teggi, M. Bussi, U. Specks, P.L. Meroni, Otorhinolaryngological manifestations in granulomatosis with polyangiitis (Wegener's), *Autoimmun. Rev.* 12 (4) (2013) 501–505.
- [8] S.C. Taylor, D.R. Clayburgh, J.T. Rosenbaum, J.S. Schindler, Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis, *JAMA Otolaryngol.– Head & Neck surgery* 139 (1) (2013) 76–81.
- [9] B. Terrier, A. Dechartres, C. Deligny, P. Godmer, P. Charles, G. Hayem, B. Dunogue, M. de Bandt, P. Cohen, X. Puechal, et al., Granulomatosis with polyangiitis according to geographic origin and ethnicity: clinical-biological presentation and outcome in a French population, *Rheumatology* 56 (3) (2017) 445–450.
- [10] J. Fijolek, E. Wiatr, D. Gawryluk, M.M. Martusewicz-Boros, T.M. Orłowski, D. Dziedzic, M. Polubiec-Kownacka, K. Oniszh, R. Langfort, K. Roszkowski-Sliz, Intratracheal dilation-injection technique in the treatment of granulomatosis with polyangiitis patients with subglottic stenosis, *J. Rheumatol.* 43 (11) (2016) 2042–2048.
- [11] M. Martinez Del Pero, D. Jayne, A. Chaudhry, P. Sivasothy, Jani P: long-term outcome of airway stenosis in granulomatosis with polyangiitis (Wegener granulomatosis): an observational study, *JAMA Otolaryngol.– Head & Neck surgery* 140 (11) (2014) 1038–1044.
- [12] T.J. McDonald, H.B. Neel 3rd, R.A. DeRemee, Wegener's granulomatosis of the subglottis and the upper portion of the trachea, *Ann. Otol. Rhinol. Laryngol.* 91 (6 Pt 1) (1982) 588–592.
- [13] T.E. Daum, U. Specks, T.V. Colby, E.S. Edell, M.W. Brutinel, U.B. Prakash, R.A. DeRemee, Tracheobronchial involvement in Wegener's granulomatosis, *Am. J. Respir. Crit. Care Med.* 151 (2 Pt 1) (1995) 522–526.
- [14] J.C. Jennette, R.J. Falk, K. Andrassy, P.A. Bacon, J. Churg, W.L. Gross, E.C. Hagen, G.S. Hoffman, G.G. Hunder, C.G. Kallenberg, et al., Nomenclature of systemic vasculitides. Proposal of an international consensus conference, *Arthritis Rheum.* 37 (2) (1994) 187–192.
- [15] N.P. Jordan, H. Verma, A. Siddiqui, G.A. Morrison, D.P. D'Cruz, Morbidity and mortality associated with subglottic laryngotracheal stenosis in granulomatosis with polyangiitis (Wegener's granulomatosis): a single-centre experience in the United Kingdom, *J. Laryngol. Otol.* 128 (9) (2014) 831–837.
- [16] M. Yates, R.A. Watts, EULAR/ERA-EDTA Recommendations for the Management of ANCA-associated Vasculitis vol. 75, (2016), pp. 1583–1594 (9).
- [17] F. Alberici, D.R. Jayne, Impact of rituximab trials on the treatment of ANCA-associated vasculitis, *Nephrol. Dial. Transplant. : Off. Publ. Eur. Dial. Transplant Ass. - Eur. Renal Ass.* 29 (6) (2014) 1151–1159.
- [18] C.G. Kallenberg, T. Hauser, B-cell therapy in antineutrophil cytoplasmic antibody-associated vasculitis, *Nephrol. Dial. Transplant. : Off. Publ. Eur. Dial. Transplant Ass. - Eur. Renal Ass.* 30 (Suppl 1) (2015) i119–122.
- [19] X. Puechal, C. Pagnoux, E. Perrodeau, M. Hamidou, J.J. Boffa, X. Kyndt, F. Lifermann, T. Papo, D. Merrien, A. Smail, et al., Long-term outcomes among participants in the WEGENT trial of remission-maintenance therapy for granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, *Arthritis Rheumatol.(Hoboken, NJ)* 68 (3) (2016) 690–701.
- [20] C. Comarmond, P. Cacoub, Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment, *Autoimmun. Rev.* 13 (11) (2014) 1121–1125.