also useful and we frequently make use of them for such cases, although as demonstrated in this and other series [7], they are not entirely reliable due to false positives, and their results should be considered carefully in light of other clinical and radiological findings.

The gold standard remains tissue confirmation from the suspicious mass. However, the sensitivity in the context of the extensive fibrotic and/or necrotic changes from the high-dose SBRT is not entirely known, and in the case of patient B, pathological confirmation of recurrence only occurred after a total of 11 passes had been taken over three separate biopsy attempts. The procedure itself may be relatively contraindicated in patients with poor pulmonary status. As a result, careful consideration should go into the selection and planning of such procedures.

We have demonstrated that local failures following SBRT may be successfully and safely salvaged, particularly in the case of isolated local failures. Two recent reports from Japan demonstrated surgical salvage in patients who were initially medically operable but had refused surgery up-front [8, 9]. Our series demonstrates that surgical salvage may also be feasible in selected patients that were initially considered medically inoperable. Our experience would suggest that the optimal surgical approach for these patients should remain thoracotomy as opposed to video-assisted thoracoscopic surgery. The challenge remains in identifying those patients who truly have local failure in a timely manner. Careful patient selection combined with surgical expertise allows for successful salvage with minimal morbidity. Once again, close and regular follow-up as well as close cooperation between the appropriate medical disciplines is emphasised.

**Z. Allibhai*, B.C.J. Cho*, M. Taremi#, S. Atallah*, A. Hope*, D. Hwang¶, S. Keshavjee+, M. Tsao¶, K. Yasufuku+, S-W. Kim* and A. Bezjak***

*Dept of Radiation Oncology, Princess Margaret Hospital, ¶Dept of Pathology, and, +Division of Thoracic Surgery, Toronto General Hospital, Toronto, and #Dept of Radiation Oncology, Stronach Regional Cancer Centre, Newmarket, ON, Canada.

**Correspondence:** Z. Allibhai, Dept of Radiation Oncology, Princess Margaret Hospital, 620 University Avenue, Toronto, ON, M5G 2M9, Canada. E-mail: zishan.allibhai@gmail.com

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# Tracheobronchial amyloidosis: evidence for local B-cell clonal expansion

*To the Editors:*

Amyloidosis is characterised by the deposition of insoluble protein fibrils in organs and tissues, which leads to organ dysfunction. Amyloidosis is classified according to the composition and localisation of fibrils. The most frequent amyloidosis is immunoglobulin (Ig)-light-chain (AL) amyloidosis. In systemic AL amyloidosis, the fibrils are derived from circulating monoclonal light chains that are usually produced by intramedullary clonal plasma cells. Localised AL amyloidosis is most often identified in upper respiratory, urogenital and gastrointestinal tracts, in the skin and in the orbit. In such

circumstances, the amyloidogenic light chains are produced by a subtle clone of lymphoplasma cells localised near the amyloid deposits [1]. Characterising the associated clonal cells is often not possible because of their low number.

Tracheobronchial amyloidosis is a rare form of localised amyloidosis [1, 2]. To our knowledge, local B-cell clonal expansion has never been consistently demonstrated in tracheobronchial amyloidosis. We present the first case of tracheobronchial amyloidosis with molecular demonstration of localised tracheobronchial B-cell clonal proliferation and the results of targeted B-cell therapy with rituximab.

A 41-yr-old female complained of persistent cough and expectoration for 1 yr. She was a 10-pack-yr active smoker. The physical examination was unremarkable. Lung function tests revealed an obstructive pattern, with a forced expiratory volume in 1 s of 1,880 mL (66%) and vital capacity of 3,420 mL (102%) without reversibility. Thorax computed tomography (CT) revealed a thickening of the trachea and primary bronchi without sparing the posterior tracheal wall (fig. 1a). Bronchoscopy confirmed a diffuse infiltration of the mucosa from the beginning of the trachea to the beginning of the tertiary bronchi, without sparing the posterior wall (fig. 1b). A search for pathogens gave negative results. Tracheal biopsies showed abundant submucosal deposits of an amorphous, mildly eosinophilic material without detectable lymphoproliferation (fig. 1c). The material was stained with Congo red (fig. 1d) and produced green birefringence under polarised light. Immunofluorescence of frozen biopsies was positive for lambda light chain antibody (fig. 1d, insert) but not kappa, IgA or IgM.

B-cell clonality analysis of the bronchial biopsy was performed by PCR according to the European BIOMED-2 technique [3]. Briefly, the diversity of heavy chain CDR3 lengths was analysed with 100 ng DNA for each FR1-JH and FR2-JH PCR. The amplified products were run on an ABI Prism 3100 Genetic analyser (Applied Biosystems, Foster City, CA, USA). Results were analysed by use of Genscan (Applied Biosystems). A dominant B-cell clone was documented in one of the two tested fragments. B-cell clonality analysis could not be interpreted from the bone marrow.

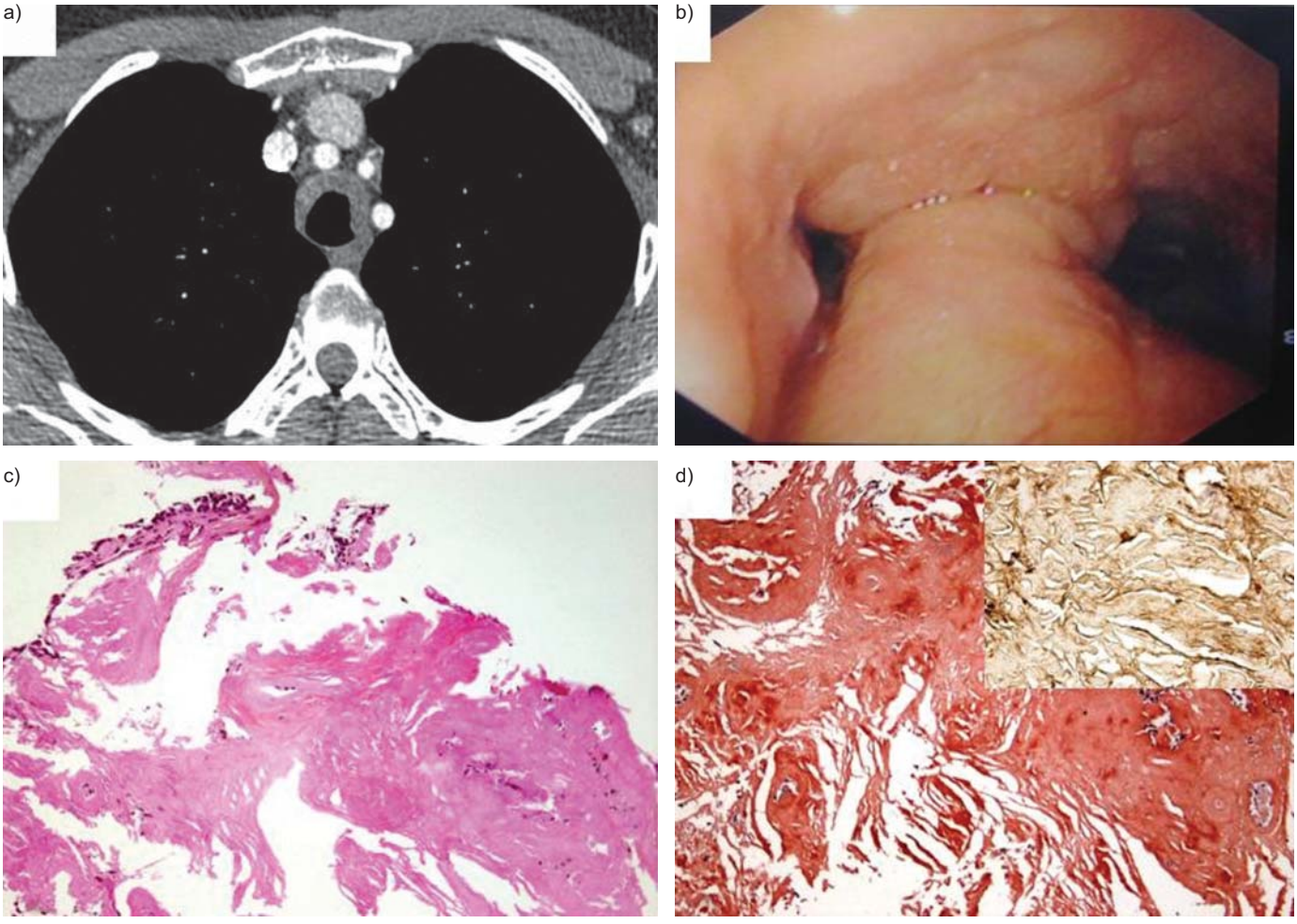


**FIGURE 1.** a) Chest computed tomography scan showing wall thickening of the trachea in a 41-yr-old female with persistent cough and expectoration. b) Endoscopic view of the carina showing wall thickening of the trachea and carina. c) Haematoxylin and eosin staining of bronchial biopsies showing abundant submucosal deposits of an amorphous, mildly eosinophilic material. d) Congo red staining of bronchial biopsies confirmed amyloidosis that was positive for lambda light chain on immunofluorescence staining of frozen biopsies (insert).

Routine biological tests, including serum protein electrophoresis, gave normal results. Serum and urine immunoelectrophoresis did not reveal monoclonal Ig. Peripheral blood lymphocyte phenotyping was normal and B-cell repertoire was polyclonal. Bone marrow, labial salivary gland, rectum and abdominal fat-pad biopsies did not reveal amyloidosis or lymphoproliferation. Echocardiography results were normal. A diagnosis of tracheobronchial amyloidosis, AL type, was given.

Because the pulmonary obstruction was not severe, local endobronchial treatment was not necessary. After discussion and informed consent by the patient, treatment with rituximab was agreed. Rituximab was administered in February 2009 as an intravenous infusion of 375 $mg \cdot m^{-2} \cdot week^{-1}$ for 4 weeks, with maintenance therapy after 1 yr (375 $mg \cdot m^{-2}$ in February 2010 and every 3 months until November 2010). Inhaled corticosteroids and bronchodilators were given. Rituximab was well tolerated. The cough was ameliorated, and the patient presented only one exacerbation with worsening of cough and expectoration requiring oral antibiotics. CT, pulmonary function tests and bronchoscopy evaluation at 12 and 24 months after rituximab infusion showed stable disease. Repeated analysis of tracheal biopsies revealed a persistent B-cell clone after 12 months.

Our report is the first molecular demonstration of the presence of a local B-cell clone in tracheobronchial amyloidosis and the first evaluation of the efficacy of B-cell-targeted therapy with rituximab, an anti-CD20 monoclonal antibody, for the disease.

Tracheobronchial amyloidosis is an uncommon diagnosis [1]. The disorder has been associated with tracheobronchopathia osteoplastica, which is characterised by calcified or cartilaginous submucosal nodules within the airways [4]. Tracheobronchial amyloidosis typically presents after the fifth decade of life, with dyspnoea, cough and, occasionally, haemoptysis. Narrowing of the airways can cause distal atelectasis or recurrent pneumonia. Symptomatic tracheobronchial amyloidosis is usually localised. However, its course is not necessarily benign: three out of seven patients followed by HUI *et al*. [5] died of respiratory failure or secondary pneumonia, three out of four patients followed at the Mayo Clinic died within 79 months of diagnosis [6] and two out of 13 patients with follow-up data died with respiratory problems in the series by CAPIZZI *et al*. [2].

Tracheobronchial amyloidosis is usually of the AL type [1], without evidence of other amyloidosis localisation, detectable lymphoma or monoclonal gammapathy, although some exceptions have been reported [2]. Detection of a B-cell clone in localised amyloidosis has been difficult. In our patient, the lymphoproliferation was not detectable by histopathology and required molecular biology techniques for detection. Moreover only one of our two tracheal samples showed the clonal cell population, which suggests that the number of cells is limited in the samples studied. We could study one other patient with AL-type tracheobronchial amyloidosis but could not demonstrate a dominant B-cell clonal population by PCR in a fresh, frozen tracheal biopsy. Analysis of stored, fixed, nonfrozen biopsies in two more patients gave no interpretable results. If molecular analysis is to be performed, we suggest analysing two or more frozen biopsies, obtained at different sites.

Therapy for tracheobronchial amyloidosis lacks consensus. However, systemic chemotherapy is commonly accepted for systemic AL amyloidosis [7] and local intervention for its localised forms [1]. Endobronchial management of tracheobronchial amyloidosis is preferred for symptomatic patients, with laser desobstruction and stenting if needed.

The association of an aetiological treatment targeting the B-cell population responsible for the continuing deposit of amyloid fibrils remains up for discussion. External beam radiation to the tracheobronchial tree, probably targeting monoclonal plasma cells, has been effective for tracheobronchial amyloidosis [8]; however, the improvement may be modest, and the long-term side-effects of radiation might be a concern [9]. Because we detected a monoclonal B-cell, we considered that the patient had low-grade lymphoma that could be treated with rituximab alone. Rituximab has been investigated as a first-line therapy for low-grade lymphoma. However, in our case, the B-cell clone was still detectable in bronchial biopsies 1 yr after rituximab treatment, which suggests that rituximab alone could not clear the monoclonal B-cell population. Clonality analysis demonstrated a clonal B-cell proliferation but did not determine the stage of differentiation. Amyloidosis may be related to plasma cell proliferation and plasma cells do not express CD20, which could explain the persistence of positive clonality after rituximab therapy. Furthermore, the clone surrounded by a large amount of amyloidosis may be inaccessible to intravenous rituximab therapy.

Therapy for tracheobronchial amyloidosis remains to be established. Future treatments could combine endobronchial management of complications with an aetiological therapy targeting the B-cell clone, as well as antibodies to the serum amyloid P component to increase the clearance of the insoluble protein fibrils [10].

We report herein for the first time an association between tracheobronchial amyloidosis and a local B-cell clonal proliferation without any other localisation of amyloidosis or clonal proliferation. This case confirms data on the pathophysiology of localised amyloidosis and highlights the need for specific evaluation of therapy to treat the disease.

**R. Borie*,#, C. Danel¶, V. Molinier-Frenkel+,§, G. Prevotf, G. Deslee**, M.P. Debray##, M.H. Delfau-Larue+,§ and B. Crestani*,#,¶¶**

*Service de Pneumologie A, Centre de Compétence Maladies Rares Pulmonaires, ¶Service d'Anatomopathologie, and, ##Service de Radiologie, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, #INSERM, U700, ¶¶Université Paris Diderot, Faculté de Médecine, Paris, +Laboratoire d'Immunologie Biologique, Centre Hospitalier Henri Mondor, Assistance Publique-Hôpitaux de Paris, §INSERM U955, UPEC, UFR de Médecine, Creteil, fService de Pneumologie-Allergologie, Clinique des Voies Respiratoires, Hôpital Larrey, Toulouse, and **Service des Maladies Respiratoires et Allergiques, INSERM U903, Hopital Maison Blanche, Centre Hospitalier Universitaire de Reims, Reims, France.

**Correspondence:** R. Borie, Service de Pneumologie A, Hôpital Bichat, 46 rue Henri Huchard, 75877 Paris Cedex 18, France. E-mail: raphael.borie@bch.aphp.fr

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# Curing HIV-associated pulmonary arterial hypertension

*To the Editors:*

Pulmonary arterial hypertension (PAH) results from chronic obstruction of small pulmonary arteries, leading to right ventricular failure and ultimately death. PAH is a severe complication, known to be related to HIV infection [1]. The frequency of PAH in HIV patients is strikingly higher than in the general population and the fourth-leading cause of PAH in the French registry [2]. The incidence of PAH related to HIV (PAH-HIV) has not decreased over time, despite efficient anti-retroviral therapy (ART) [3].

Since its description in 1987, PAH-HIV has been well characterised and multiple therapeutic strategies have been proposed, but no full recovery has yet been published. Here, we report a complete recovery from PAH in two HIV patients with a sustained and fully reversible PAH after a 4-yr discontinuation of bosentan.

Two females, a 36-yr-old with African origins and a 46-yr-old Caucasian intravenous drug abuser received ART 1 month and 25 yrs, respectively after the onset of HIV infection. Normal CD4+ cell count and undetectable HIV viral load were obtained rapidly (fig. 1). Other causes of PAH were ruled out.

For the first patient, bosentan was introduced 12 months after HIV diagnosis. After 5 yrs of persistent haemodynamics and normalisation of functional parameters, bosentan was withdrawn. 4 yrs after discontinuation, the patient remained asymptomatic with normal haemodynamics. For the second patient, bosentan was introduced 5 months after ART. Because of rapid normalisation of functional class and haemodynamic parameters, bosentan was withdrawn only 1 yr later. 2 yrs after bosentan discontinuation, the patient remained asymptomatic with normal haemodynamics.

While haemodynamic normalisation after bosentan has been described previously [1], there is a lack of data on long-term evaluation after specific therapy discontinuation. These patients are the first two cases with PAH-HIV and without other comorbidity in whom long-term vasodilator has been successfully withdrawn for 4 and 2 yrs, respectively.

Haemodynamic normalisation and long-term benefit in bosentan-treated PAH-HIV patients has recently been described, but not yet with full recovery [1] Considering that a complete recovery is a persistent remission over years, even after weaning from specific PAH treatment, there has been, to our knowledge, no description of cured PAH-HIV.

Inflammation may be one underlying mechanism of PAH, so according to the guidelines, we used ART, considering it may be beneficial when associated with another specific PAH treatment [4]. We continued ART therapy even after specific PAH treatment discontinuation and until this day.

As described for experimental inflammatory PAH [5] and other inflammation-related PAHs [6–9], PAH-HIV is more likely to reverse and cure. Consequently, we suggest that pulmonary vasodilators may be cautiously withdrawn in PAH-HIV patients when they fulfil two conditions: a 1-yr haemodynamic normalisation and controlled HIV disease. However, due to lack of data, we recommend long-term close monitoring, with serial systematic haemodynamic catheterisation after bosentan withdrawal.