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Successful treatment of antineutrophil cytoplasmic antibody-associated bronchiectasis with immunosuppressive therapy

To the Editor:

The underlying mechanisms of bronchiectasis are poorly understood and the cause remains unknown in half of the patients [1]. Whether bronchiectasis is the direct consequence of pathogen aggression or of an abnormal immune response remains unresolved [2–4]. We report here the first case of a patient with bronchiectasis improved by an immunosuppressive regimen.

In 2010, a 27-year-old male nonsmoker was referred by his oncologist to our respiratory department (Hôpital Foch, Suresnes, France) for recurrent haemoptysis associated with anaemia at 90 $g \cdot L^{-1}$ and abnormal chest computed tomography (CT) scan.

He first sought medical advice in our hospital in 2008 for a testicular stage I nonseminomatous germ cell tumour. Despite the PT2 stage of the tumour (with vascular emboli) and the pure carcinoma histology, he declined to receive adjuvant chemotherapy and chose an active surveillance policy. This implied repeated CT scans and follow-up visits. The cancer was in complete remission in 2010.

He reported several episodes of cough and spitting, all considered as minor infections, even before the orchiectomy, but pulmonary symptoms continued to worsen. He had no other symptoms, was in very good shape otherwise, with a performance status of 0, a weight of 80 kg and height of 180 cm.

While the 2008 chest CT scan only exhibited bi-basilar micronodules, the chest CT scan performed in 2010 revealed bi-apical ground-glass opacities with a crazy paving pattern with interlobular septal

thickening (fig. 1a) and bilateral cylindrical bronchiectasis with thickening of the bronchial wall, which appeared on lung bases (fig. 1a). The bronchoalveolar lavage (BAL), obtained during a fibreoptic bronchoscopy, exhibited a bloody fluid. Analysis showed a cellular count of 500 000 cells·mL^{-1}, with 14% neutrophils and 84% macrophages. The Golde score was calculated at 176, confirming the diagnosis of diffuse alveolar haemorrhage (DAH). Microbiological tests remained negative. Perinuclear antineutrophil cytoplasmic antibodies (ANCA) were identified at a titre of 1/640 UI by immunofluorescence, with specificity against both myeloperoxidase (MPO) and bactericidal/permeability-increasing protein (BPI) on ELISA tests (ORGENTEC Diagnostika GmbH, Mainz, Germany). No extrathoracic manifestation was identified; hence, a diagnosis of a probable lung-limited microscopic polyangiitis was retained. No additional cause of bronchiectasis was detected: sinus CT scan, serum IgG, IgA, IgM, IgG subclasses, IgE, α_1-antitrypsin, anti-cyclic citrullinated peptide antibodies, rheumatoid factor, *Aspergillus* precipitins, and antibodies against HIV or hepatitis C virus were undetectable or within normal values.

Prednisone (started at 1 mg·kg^{-1}·day^{-1}, then progressively withdrawn) and rituximab (375 mg·m^{-2} weekly for 4 weeks) were started in October 2010 (fig. 1). 2 months later, recurrence of haemoptysis occurred, with DAH confirmed on BAL and CT scan, despite an ongoing corticosteroid therapy of 12.5 mg·day^{-1} (fig. 1c). Intravenous immunoglobulins 2 g·kg^{-1} monthly were administered for 6 months. Both haemoptysis and radiological opacities disappeared and serological tests for ANCA became negative on immunofluorescence and ELISA. As shown in figure 1d, bronchiectasis disappeared on the chest CT scan. In July 2011, despite maintenance treatment with 7 mg·day^{-1} of prednisone and 500 mg of rituximab every 6 months, a first relapse occurred with haemoptysis recurrence, new radiological opacities on CT scan (fig. 1d) and intra-alveolar haemorrhage on BAL fluid analysis. ANCA testing was positive by fluorescence, but MPO-ANCA was not detected whereas BPI-ANCA was found by ELISA testing. Prednisone was increased to 80 mg·day^{-1} and eight infusions of cyclophosphamide (0.6 g·m^{-2} at 3-week intervals) were administered. A second remission was obtained, with simultaneous disappearance of cough, haemoptysis and radiological opacities. As depicted in figure 1d, bronchiectasis reversed on the CT scan concomitantly with BPI-ANCA disappearance.

This remission lasted for 16 months with a maintenance treatment including mycophenolate mofetil (1000 mg twice daily) and prednisone 10 mg·day^{-1}. A second relapse occurred, with coughing and haemoptysis with DAH. A thoracic CT scan showed the recurrence of bronchiectasis in the same location as previously. The ANCA titre rose to 1/640 by immunofluorescence with BPI-ANCA (but not MPO) on ELISA testing. Cyclophosphamide (1 g in one pulse) combined with rituximab (1 g on day 1 and on day 15) was started. A third remission was obtained, with complete disappearance of both bronchiectasis on thoracic CT scan and BPI-ANCA on ELISA assay, and is still ongoing after a follow-up period of 2 years with a maintenance treatment of rituximab at 500 mg every 6 months and prednisone 5 mg·day^{-1}. The patient received cotrimoxazole 800 mg three times per week to prevent opportunistic infections. No respiratory infectious complications occurred during follow-up. The nonseminomatous germ cell tumour remained in complete remission.

We report here the first case of a patient whose bronchiectasis was reversed while using solely an immunosuppressive regimen to treat alveolar haemorrhage associated with ANCA. This led us to reflect on the underlying pathophysiological mechanisms leading to bronchiectasis.

While some authors have reported vasculitis onset in patients with previously known chronic suppurative bronchiectasis, none had described bronchiectasis emerging and vanishing simultaneously with both ANCA-associated vasculitis onset and BPI-ANCA titre [5, 6]. BPI-ANCA positivity in chronic suppurative bronchiectasis, especially in cystic fibrosis, has been previously highlighted [7–9]. In cystic fibrosis, the presence of BPI-ANCA is associated with poorer respiratory functional evolution and linked to *Pseudomonas aeruginosa* presence in sputum [7, 10]. Hence, BPI-ANCA production is usually thought to be the consequence of an intensive immune stimulation due to the chronic suppurative disease, but not as the cause of bronchiectasis. Conversely, our reported case seems to favour the role of an immune mechanism *versus* that of a pathogen-driven lesion in the establishment of bronchiectasis, since no pulmonary infection had been identified on BAL and no anti-infectious treatment had been given together with the immunosuppressive therapy. The immunosuppressive regimen, which mainly targeted ANCA production, allowed BPI-ANCA disappearance three times, always associated with bronchiectasis disappearance. Similarly, the reappearance of BPI-ANCA was each time, three times in a row, followed by that of the bronchiectasis.

A relationship between the ANCA-associated vasculitis and the testicular cancer of our patient could be evoked. ANCA-associated vasculitis onset is known to be a possible paraneoplastic manifestation and germ cell tumours have already been associated with vasculitis [11]. Moreover, symptoms can precede the diagnosis of the germ cell tumour then progress irrespective of the neoplastic disease [11–14]. However, most cancer-associated vasculitis is articular and cutaneous.

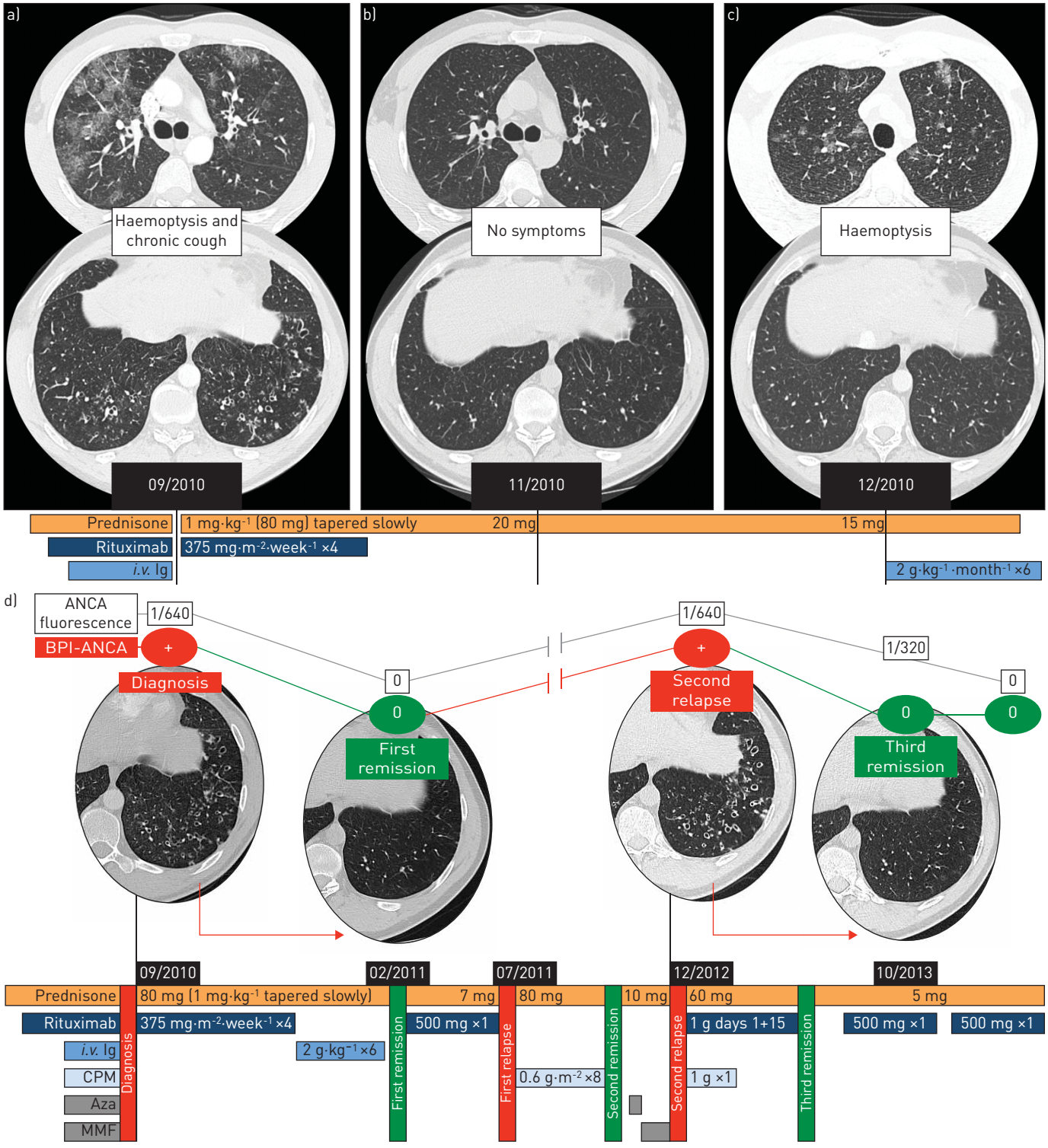

FIGURE 1 Effectiveness of oral corticosteroids and rituximab on bronchiectasis disappearance. a) The computed tomography (CT) scan before antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis treatment showed bilateral apical ground-glass opacities (apical image; top) with bi-basal bronchiectasis (basal image; bottom). b) Bronchiectasis rapidly disappeared after administration of corticosteroid therapy associated with rituximab, as demonstrated on the basal (bottom) image of the second CT scan performed 2 months later. c) After 3 months, the patient exhibited haemoptysis and alveolar haemorrhage on the apical image (top), without resurgence of bronchiectasis on the basal image (bottom) or bactericidal/permeability-increasing protein (BPI)-ANCAs, when corticosteroids were stepped down to 15 mg·day^{-1}. Intravenous immunoglobulins were administered, allowing first remission. d) Summary of the therapeutic course and the multiple relapses, focusing on the first and third remissions and highlighting the resurgence of bronchiectasis following BPI-ANCA testing positive. The bronchial wall thickness disappeared in all places, whereas the enlargement of the bronchi often disappeared, but persisted in a few areas. CPM: cyclophosphamide; Aza: azathioprine; MMF: mycophenolate mofetil.

In conclusion, this report suggests that an autoimmune mechanism may be involved in the establishment of bronchiectasis and that BPI-ANCA could be an actor in bronchiectasis development rather than a marker of chronic infection. Moreover, this case outlines that bronchiectasis, which is usually considered as a sequel, could be a dynamic process with potential reversibility [2]. To date, guidelines suggest performing ANCA testing in bronchiectasis evaluation only if clinically relevant (*i.e.* looking for associated vasculitis), mainly because no therapeutic modification is expected in other cases [1, 15]. We think that this report should lead to further evaluation of the practice of looking for ANCA in immunofluorescence and BPI-ANCA on ELISA test in patients with non-cystic diffuse bronchiectasis. Indeed, it could help to identify patients in whom administration of immunosuppressive regimens could help to avoid definitive bronchial damage, as in other bronchial diseases with immune hyperresponsiveness, such as allergic bronchopulmonary aspergillosis.

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Could ANCA testing in bronchiectasis help to identify patients who would benefit from immunosuppressive regimens? http://ow.ly/L7Nat

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