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Diffuse bronchiectasis and airflow obstruction in granulomatosis with polyangiitis

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Abstract. Parenchymal lung nodes and diffuse intra-alveolar hemorrhage are the archetypal pulmonary manifestations of Granulomatosis with Polyangiitis (GPA). The occurrence of diffuse bronchiectasis and airflow obstruction during GPA is unusual. We report here 3 patients with GPA who developed diffuse bronchiectasis during follow-up. The airflow obstruction seemed then to evolve independently from the GPA itself and ultimately led to respiratory insufficiency. Bronchiectases promoted the occurrence of opportunistic infections, especially with atypical mycobacteria. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 81-84)*

Key words: bronchiectasis, granulomatosis with polyangiitis, vasculitis, atypical mycobacteria

Introduction

Granulomatosis with Polyangiitis (GPA) is a severe systemic condition characterized by necrotizing small-vessel vasculitis of unknown etiology, usually associated with anti-neutrophil cytoplasmic antibodies (ANCA) with anti- proteinase 3 (PR3) specificity. Severity of the disease mainly results from kidney and lung involvement. Although ANCA-associated vasculitis pulmonary manifestations are pleiotropic and largely described, GPA-associated bronchiectasis was scarcely reported in the literature (1). This complication should not be underestimated, since it may predispose to the development of opportunistic infections, in patients already vulnerable because of immunosuppressive therapies. Here, we report three patients who developed bronchiectasis and airflow obstruction during the course of GPA.

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Methods

Case #1

An 80-year old woman was admitted for fever, cough and dyspnea. Ear, nose and throat (ENT) examination showed chronic dry rhinitis. The chest computed tomography (CT) revealed bilateral cavitary pulmonary nodules. Urinalysis showed moderate proteinuria (0.4 g per day) with glomerular hematuria. Kidney biopsy showed pauci-immune glomerulonephritis and high-titer ANCAs with anti-PR3 specificity (5.3 U/mL, cytoplasmic) were detected, confirming GPA. Corticosteroid therapy in association with oral methotrexate was initiated. Three months later she presented with subacute interstitial pneumonia and low-grade fever; *Mycobacterium avium* was isolated from bronchoalveolar lavage. Methotrexate was discontinued, and antimicrobial therapy including clarithromycin, rifabutin and ethambutol was introduced. GPA relapsed one year later with progression of the pulmonary nodules and rise in ANCA titer, leading to six pulses of intravenous cyclophosphamide permitting disease control. Although she

was non-smoker, pulmonary function tests soon demonstrated beginning airflow obstruction (Table 1) and CT showed diffuse bronchiectasis which gradually worsened. Finally, another relapse occurred two years later. Treatment with rituximab (375 mg/m², 4 weekly infusions and maintenance therapy every 6 months) led to complete remission of GPA at imaging, but had no effect on airway obstruction.

Case #2

A 66-year non-smoker old man with a one-year history of seropositive rheumatoid arthritis was diagnosed with GPA with acute renal failure, cavitary pulmonary nodules, peripheral neuropathy, and positive anti-PR3 ANCA (226 U/mL). Pulmonary function was normal. The dosage of immunoglobulin was normal (8.16 g/L). Remission was obtained with a regimen of 6 pulses of intravenous cyclophosphamide followed by maintenance therapy with mycophenolate and low-dose glucocorticoids. The disease relapsed 2 years later, leading to another course of intravenous cyclophosphamide (9 pulses) then oral cyclophosphamide. At that time, pulmonary function tests demonstrated onset of airflow obstruction. A new relapse of GPA occurred 2 years later. Complete remission of disease was obtained using rituximab, which was continued as maintenance. However, severe airflow obstruction developed, and diffuse bilateral bronchiectases were found on CT. He subsequently presented several pulmonary infections due to *Pseudomonas aeruginosa, Proteus mirabilis* and *Branhamella catarrhalis* that justified long-term therapy with azithromycin.

Case #3

A 75-year old non-smoker woman receiving anticoagulation therapy for atrial flutter presented with diffuse alveolar hemorrhage and acute renal failure with glomerular hematuria and proteinuria. Percutaneous kidney biopsy revealed pauci-immune glomerulonephritis. Anti-PR3 ANCAs with cytoplasmic fluorescence were found at high title (190U/mL, ELISA assay) Nine intravenous pulses of cyclophosphamide were delivered, permitting remission. Rituximab was then administered every 6 months during 2 years as maintenance therapy. Three years after treatment discontinuation, she presented with dyspnea, airflow obstruction at pulmonary function tests, and diffuse bronchiectasis at chest CT (Figure 1). She then presented with several pulmonary infections due to *Pseudomonas aeruginosa. Mycobacterium marseillense* was isolated from endobronchial aspirates, and prolonged antimicrobial therapy was prescribed with clarithromycin, rifampicin and eth-

Table 1. Physiological assessment during follow-up

Follow-up (years)	2007	2008	2009	2010	2011	2012	2013	2014	2015
Patient #1									
FEV1					1.24L 86%	1.06 L 74%	0.94 L 67%	0.88 L 63%	
FEV1/FVC					0.72	0.69	0.66	0.67	
Treatment					MTX	CYC	RTX	RTX	
Patient #2									
FEV1	2.30 L 70%	2.20 L 66%	- -	1.90 L 60%	1.34 L 42%	1.15L 35%	1.50 L 48%	0.90 L 29%	
FEV1/FVC	0.62	0.57	-	0.48	0.42	0.46	0.46	0.57	
Treatment	CYC	MMF	MMF	CYC	CYC	RTX	RTX	RTX	
Patient #3									
FEV1				1.80 L 97%	- -	- -	1.33 L 73%	1.49 L 83%	0.85 L 48%
FEV1/FVC				0.68	-	-	0.65	0.60	0.63
Treatment		CYC	RTX	RTX	RTX	none	none	MTX	MTX

CYC, cyclophosphamide; RTX, rituximab; MMF, Mycophenolate mofetil; FEV, Forced expiratory volume; FVC, Forced Vital Capacity

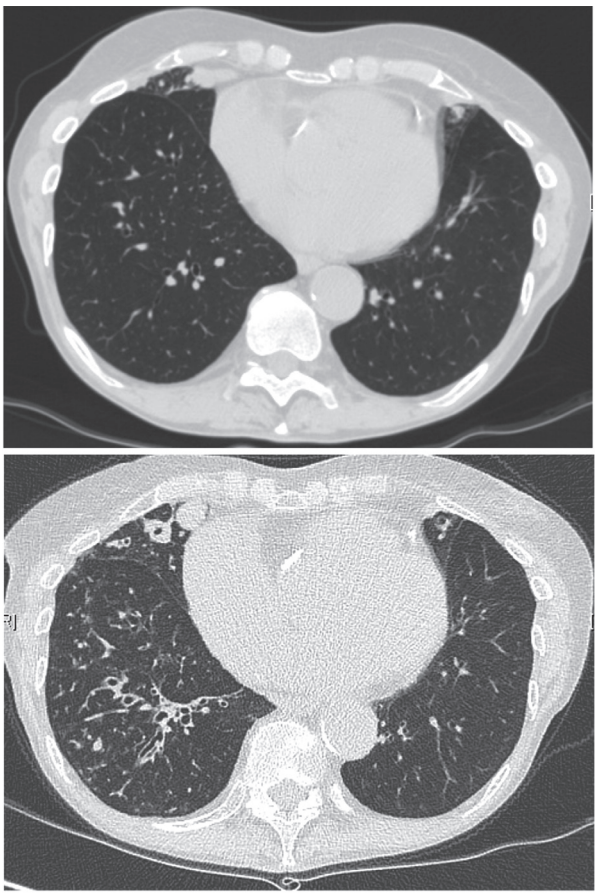

Fig. 1. Chest computed tomography of patient #3 showing bronchiectasis at the end of follow-up, by comparison with initial evaluation.

ambutol. Airflow obstruction progressed to severe chronic obstructive respiratory insufficiency.

Discussion

Pulmonary involvement by GPA includes alveolar hemorrhage and parenchymal lung nodules or masses, single or multiple, which may cavitate. Possible involvement of the proximal bronchi or trachea by GPA comprises inflammation of the bronchial mucosa and wall, which may progress to stenosis of the tracheobronchial tree especially subglottic stenosis, and can lead to life-threatening upper airway obstruction (2). However, longitudinal involvement of the bronchi such as in the present cases, with both proximal bronchiectasis due to involvement of larger bronchi, and airflow obstruction resulting from the involvement of more distal bronchi and bronchioles, is not a well-known complication of GPA.

In the present three cases, bronchiectasis and airflow obstruction developed during the course of GPA (Table 1), especially after the initiation of immunosuppressive therapy, and in all cases worsened independently of the systemic disease which was otherwise controlled by treatment. Although bronchial biopsies were not performed, all the patients were non-smokers and no other cause of bronchial abnormalities and airflow obstruction could be identified. Tracheobronchial inflammation or stenosis of the proximal bronchi was ruled out by CT and fibroscopy. ANCAs were specific for PR3, therefore differing from the possible association of bronchiectasis and bactericidal/permeability-increasing protein (BPI)-ANCAs, which may occasionally improve upon immunosuppressive therapy (3). Interestingly, severe airflow obstruction is also a feature of long-term outcome in patients with eosinophilic granulomatosis with polyangiitis (4), although the pathogenesis generally differs from that of GPA. In the second patient, rheumatoid arthritis may have contributed to the development of bronchiectasis and airflow obstruction, however the chronology is by far more suggestive of a role for GPA.

Along with obstructive lung disease, diffuse bronchiectases were identified in the three cases. In the second case, the severity of the obstructive lung disease was life-threatening and severely impaired the quality of life, although the GPA was in remission. In a recent series, different patterns of air trapping were found in 33% of patients with GPA (5), however only localized bronchiectases were reported and in a minority of patients. In our patients, bronchi were soon colonized with multi-resistant bacteria, notably *P. aeruginosa*, which required prolonged nebulized antimicrobial therapy. Furthermore, two of our patients developed pulmonary infections with Nontuberculous Mycobacteria (NTM) that required long-term antibacterial therapy. To our knowledge, association between GPA and NTM infection has not been reported in the literature. However, NTM infection is a classical complication of cystic fibrosis and non-cystic fibrosis-related bronchiectasis (6-8) suggesting that GPA-associated bronchiectasis may be clinically relevant, infections being a major component of comorbidity and complications in patients treated for systemic vasculitis (9). The im-

munosuppressive therapies used to treat the vasculitis may predispose to opportunistic infections such as NTM. However, little is known about NTM infection susceptibility caused by immunosuppressive agents such as biotherapies. A recent study suggested an increased risk of NTM infection associated with the use of anti-TNFα drugs (10), but no data are available regarding other immunosuppressive regimens. Of note, the first patient we report here was diagnosed with NTM before receiving cyclophosphamide or rituximab, suggesting that NTM may be associated to bronchiectasis and/or GPA rather than immunosuppression.

In conclusion, we report three cases of GPA-associated diffuse bronchiectasis and severe obstructive lung disease, complicated by numerous opportunistic respiratory infections that stirred the prognosis. As the management and the life expectancy of patients with GPA continue to improve, long-term morbidity including bronchiectasis and airflow obstruction may become particularly relevant in the years to come.

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