

Bronchocentric granulomatosis in rheumatoid arthritis: case report and literature review

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ABSTRACT

Bronchocentric granulomatosis (BcG) is characterized by granulomatous destruction of bronchial or bronchiolar walls and adjacent parenchyma, with debris and exudates filling the airway lumen. Approximately 50% of total cases have been associated with asthma and allergic bronchopulmonary aspergillosis, while it has been rarely reported in the context of rheumatoid arthritis (RA). We describe the case of a 69-year-old female RA patient with BcG presenting as a solitary cavitary pulmonary mass. In addition, we conducted a literature review about the clinical and imaging features of BcG in RA patients.

A chronically immunosuppressed 69-year-old female patient with a 16-year history of RA presented with constitutional symptoms (low-grade fever, excessive sweating and malaise) and a sizeable cavitary lung lesion. Open lung biopsy was performed and histopathological findings were consistent with the diagnosis of BcG. Other seven cases of BcG have been previously reported in the context of RA, with clinical and laboratory characteristics described in five of them. Overall, pulmonary nodules or masses were the most frequent imaging finding of BcG, while no clear relationship with disease activity or previous treatment modalities could be established. Surgical resection followed by administration of oral steroids was effective for achieving complete remission of symptoms and radiological stability in most cases.

Keywords: Pulmonary cavity; Rheumatoid arthritis; Bronchus; Asthma

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INTRODUCTION

Originally described by Liebow in 1973, bronchocentric granulomatosis (BcG) is an unusual form of granulomatosis characterized by granulomatous destruction of bronchial or bronchiolar walls and adjacent parenchyma, with debris and exudates filling the airway lumen^{1,2}. Overall, the pathogenesis of BcG remains uncertain³. It is suggested that BcG is one of the limited ways in which bronchi and bronchioles respond to a variety of different types of stimuli⁴. In asthmatic patients, BcG probably results from a hypersensitivity reaction to inhaled fungi and has been associated with allergic bronchopulmonary aspergillosis (ABPA)⁵. The causative agent of hypersensitivity response in non-asthmatic patients with BcG is obscure⁶. The histological appearance differs between asthmatic and non-asthmatic patients: in the former, it is characterized by abundant tissue eosinophilia, while, in the latter, tissue infiltration is primarily neutrophilic^{2,5}. We herein report the case of a middle-aged woman with rheumatoid arthritis (RA) and BcG presenting as a sizeable pulmonary cavity, and subsequently, review all relevant cases previously reported in the English literature.

CASE PRESENTATION

A 69-year-old female patient, non-smoker, with a 16-year history of RA treated with leflunomide and low dose methylprednisolone (4 mg/day), presented with low-grade fever, non-productive cough, excessive sweating, fatigue and malaise during the last two months, with no other accompanying symptoms, namely dyspnea or chest pain. She had no active arthritis and the Clinical Disease Activity Index (CDAI) score was 2 (inactive RA). She had received empirical antibiotic therapy (clarithromycin and amoxicillin) without improvement of her symptoms. On admission, she had fever (38.3 C) and mid and end-inspiratory crackles at

the right lower lung field. Physical examination of the heart, abdomen, joints and nervous system was unremarkable.

A chest CT scan was performed and revealed mild pulmonary fibrosis in the upper, mid and lower zones of bilateral lung fields and a 5-cm thick-walled pulmonary cavity in the right lower lobe (Figure 1, Panels a and b). In addition, the patient had mild normochromic normocytic anemia (Hb: 11.3 g/dl), significantly raised serum levels of inflammatory markers (C-reactive protein was 120 mg/L and erythrocyte sedimentation rate was 100 mm/hour) and positive rheumatoid factor (RF) and anticitrullinated peptide antibodies (anti-CCPs). On the other hand, antinuclear and antineutrophil cytoplasmic antibodies, assays for the detection of human immunodeficiency virus infection, Mantoux tuberculin skin test and interferon-gamma release assays (IGRA) were all negative. Bronchoscopy with bronchoalveolar lavage (BAL) was subsequently performed. Bronchial mucosa had a normal macroscopic appearance. BAL fluid staining and cultures for bacteria, mycobacteria or fungi, and nuclear amplification assays for *M. tuberculosis* were also nega-

tive. No malignant cells were found in the cytological analysis. Neutrophils were moderately increased (40%) and lymphocytes were mildly elevated (13%) on BAL differential cell count.

In order to establish a definite diagnosis, on the basis of a high pre-operative clinical suspicion of bronchocentric carcinoma, an open-lung procedure with right lower lobectomy was performed. Histological examination was consistent with a diagnosis of BcG (Figure 2, Panels a to c). In particular, the epithelium of large-sized bronchi was focally replaced by an inflammatory granulomatous tissue and bronchiolar lumen was filled with fibrinopurulent exudates and necrotic debris. Chronic inflammatory infiltration, mainly consisting of lymphocytes, plasma cells, polymorphonuclear leukocytes, “foamy” cells and fibroblasts, also extended into interstitial space and alveolar lumens, thus forming foci of organizing pneumonia. A thorough examination of the resected lobe excluded the presence of pulmonary vasculitis, fungal hyphae, malignancy or tissue infiltration by eosinophils. Besides surgical excision, no additional treatment was given, including corticosteroids.

Two years after surgical excision of the cavitory le-

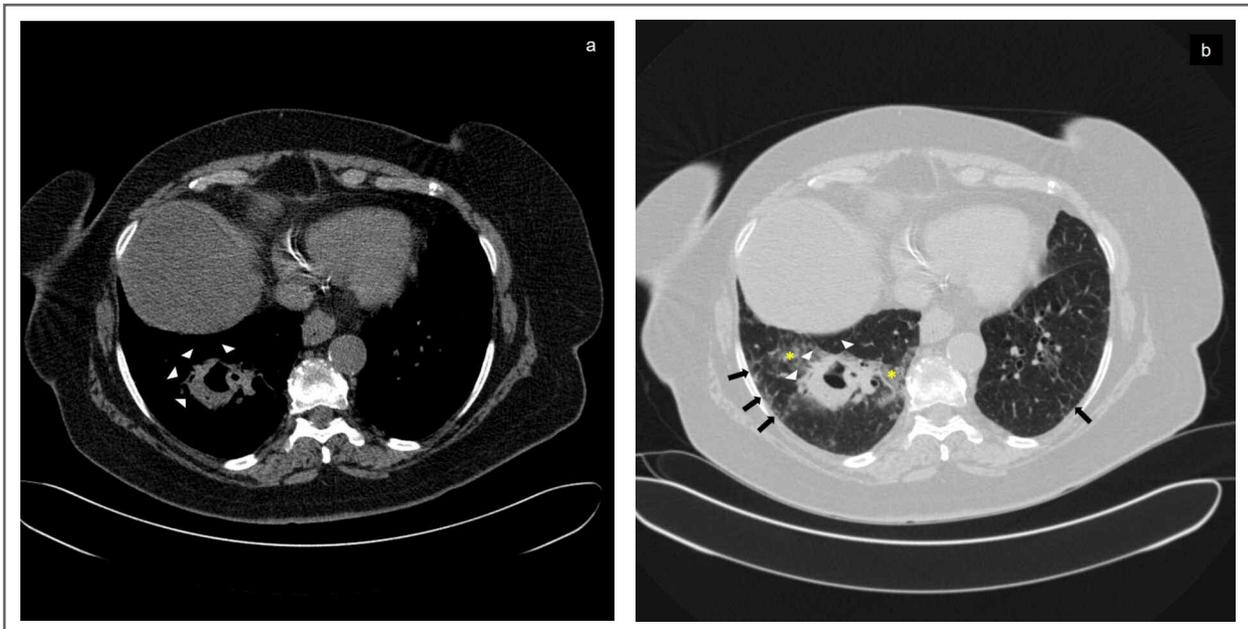


FIGURE 1. Bronchocentric granulomatosis presenting as a thick-walled cavity.

The major finding of chest computed tomography (CT) scan was a 5-cm thick walled cavity in the right lower lobe (Panels a + b). The lesion had well-defined margins with areas of spiculation (see white arrowheads, Panels a + b), was adjacent to subsegmental bronchi and was surrounded by patchy ground glass opacities (see yellow asterisks) (Panel b). Small areas of bilateral septal thickening and/or ground glass attenuation restricted to the subpleural regions of the lower lung fields (see black arrows) were also visible on lung window and were indicative of mild interstitial lung disease (Panel b).

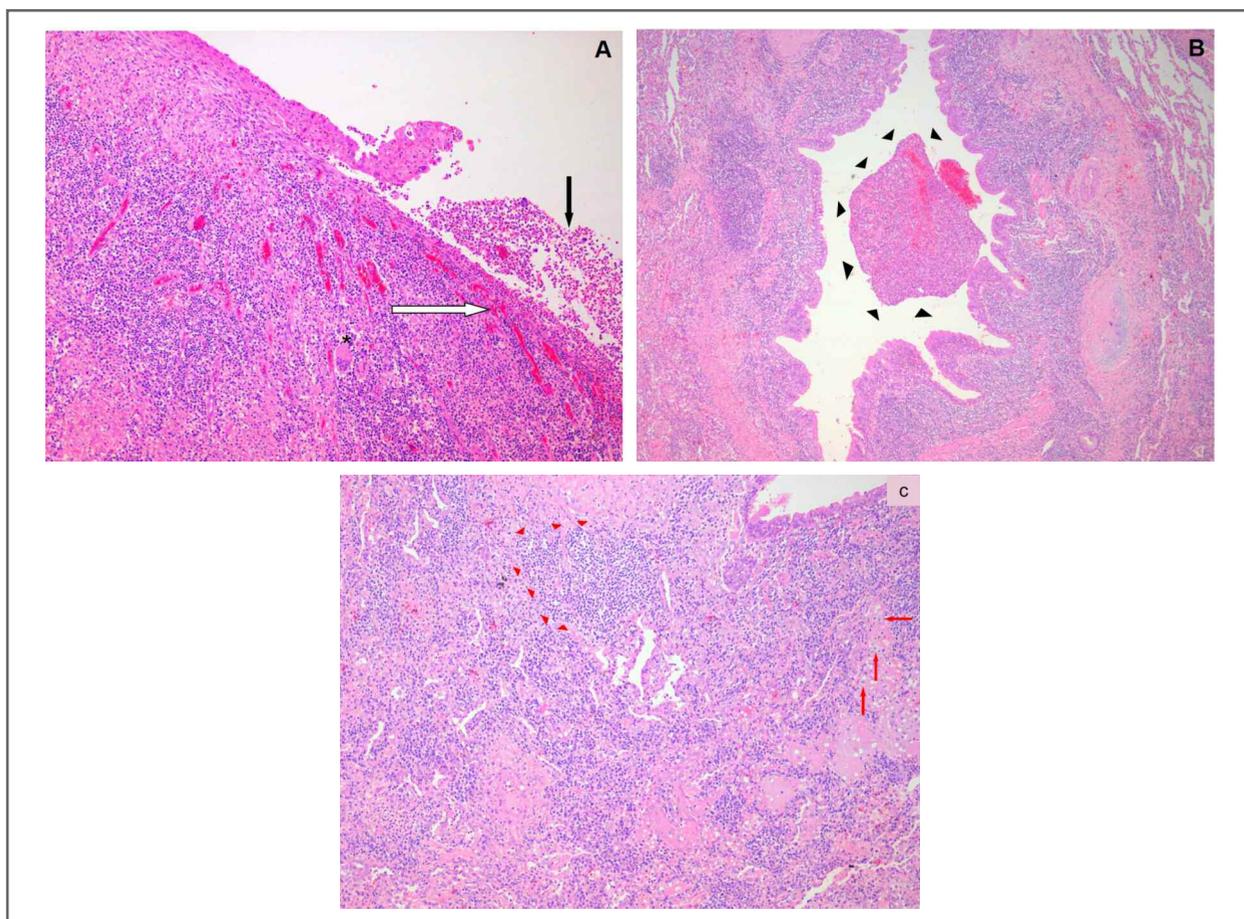


FIGURE 2. Major histopathological findings in bronchocentric granulomatosis (BcG).

The epithelium of medium- and large-sized bronchi has been focally replaced by granulomatous tissue (white arrow) with scarce multinucleated giant cells (asterisc). In addition, the bronchial lumen is filled with necrotic debris (black arrow) [Panel a, Hematoxylin & Eosin (H-E) stain (x100)]. Granulation tissue apparently arising from respiratory epithelium damage of central airways extends to the lumen of more peripheral ones (black arrowheads) [Panel b, H-E stain (x50)]. Chronic inflammatory infiltration by lymphocytes (red arrowheads), plasma cells, polymorphonuclear leukocytes, “foamy” cells (red arrows) and fibroblasts also extends into surrounding lung parenchyma (interstitial space and alveoli) [Panel c, H-E stain (x10)].

sion, the patient remained asymptomatic, complete blood count and inflammatory markers had normalized and follow-up CT scan showed stable postoperative fibrotic changes.

DISCUSSION

Pulmonary involvement is among the most common extra-articular manifestations in RA and, along with cardiovascular disease and infections, is one of the leading causes of morbidity and mortality, affecting the course of the disease⁷. The wide spectrum of pulmonary diseases in patients with RA includes condi-

tions that affect the parenchyma (infections, interstitial lung disease, rheumatoid nodules, drug toxicity, malignancy), pleura (pleural thickening and effusions), airways (bronchiectasis, bronchiolitis) or vasculature (rheumatoid vasculitis). BcG is a granulomatous lung disease of unknown cause, usually associated with allergic bronchopulmonary aspergillosis (ABPA) and asthma, but its occurrence in the context of RA has been rarely reported in the literature^{3,5,8-11}.

BcG should be considered not as a disease, but as a descriptive pathological diagnosis¹², which has been associated with two different clinical forms. About 50% of all reported cases of BcG are associated with asthma and ABPA (*asthmatic form*). The *non-asthmatic form* of

TABLE I. CLINICAL, LABORATORY AND IMAGING FINDINGS IN BCG ASSOCIATED WITH RA

Reference First author Year	Gender	Age (yrs)	RA activity	RA duration	RA Treatment	RF	CRP/ ESR	Presenting symptoms Duration	Radiology findings			
									Pattern (Size)	Distribution	Treatment for BCG	Outcome
Hellems SO 1983	Female	49	Active polyarthritits	4 years	None	(-)	--/70	Cough Fever 6 weeks Dyspnea Acute	Multiple, bilateral, round densities (2-5.5 cm)	Bilateral middle + lower fields	Surgical excision + Steroids	<ul style="list-style-type: none"> Clinical improvement Radiographic stability Frequent relapses on tapering
Bonafede RP 1987	Female	41	Active symmetric polyarthritits Easy fatigue	10 years	None	(+)	--/97	Cough Hemoptysis Fever Dyspnea 2 years	Multiple, bilateral, solid + cavitary nodules (2.5-3.5 cm)	Bilateral middle + lower fields	Surgical excision + steroids	<ul style="list-style-type: none"> Clinical + radiographic improvement Remission
Berendsen HH 1985	Male	58	Active polyarthritits	0 years	Steroids	(+)	--/145	Cough Hemoptysis Chest pain Dyspnea Acute	Multiple, bilateral nodules	Bilateral middle + lower lung fields	Surgical excision + steroids	<ul style="list-style-type: none"> Clinical + radiographic improvement Remission
Neff K 2010	Female	43	Inactive	6 years	Hydroxy- chloroquine	NR	252/--	Recurrent lower respiratory infections	Multiple, bilateral, pulmonary cavities + Bronchie- ctases + "tree-in-bud" lesions	Bilateral Upper lung fields	Surgical excision + steroids + antifungal agents + abatacept	<ul style="list-style-type: none"> Clinical + radiographic improvement Radiographic stability after Abatacept
Bes C 2012	Female	49	Inactive	16 years	Leflunomide	(+)	WNL	None	Solitary pulmonary nodule (2 cm)	Unilateral Lower lung fields	Surgical Excision	Remission
Our case	Female	69	Inactive	16 years	Leflunomide Low dose Steroids	(+)	120	/100	Cough Fever Fatigue 2 months	Solitary Cavity 5cm	Unilateral lower lobe Surgical excision	Remission

BcG: Bronchocentric granulomatosis, RA: Rheumatoid arthritis, RF: Rheumatoid factor, (+): positive, (-): negative, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NR: Not reported, WNL: Within normal limits

BcG is usually idiopathic, but associations with pulmonary infections (mycobacterial, fungal, echinococcal, viral)¹³⁻¹⁵, autoimmune diseases (RA, Wegener's granulomatosis, ankylosing spondylitis)^{3,5,8-11,16,17}, chronic granulomatous disease, bronchogenic carcinoma, glomerulonephritis, red cell aplasia, diabetes insipidus and scleritis^{6,18-22} have been reported. In our patient, RA was not complicated by scleritis. In addition, although Mantoux tuberculin skin test and IGRA may be false negative in immunocompromised patients, BAL fluid staining and cultures for *M. tuberculosis* were also negative in our patient.

Patients with the *asthmatic* form, which is associated with eosinophilia, tend to be younger (9 to 50 years old) and mainly complain of respiratory symptoms such as cough, dyspnea, haemoptysis, wheeze and pleuritic pain. In the *non-asthmatic* form, patients are relatively older (with a range of 32 to 76 years) and prevailing symptoms are usually non-specific (malaise, fatigue, fever)^{4,5,17}. BcG radiographic findings are similar for *asthmatic* and *non-asthmatic* patients. A wide variety of radiographic appearances have been described, but they have consistently been divided into two main patterns: mass-like lesions/ nodules or focal areas of consolidation which are usually confined to a single lobe with a predilection for the upper lobes^{23,24}. Cavitation of solid lesions is less frequent²⁵. BcG diagnosis cannot be established solely on the basis of radiographic features and open-lung biopsy is usually required²³.

Smoking, advanced age, high-titer anti-CCPs, high-titer RF and family history of RA are among the most widely recognized risk factors for RA-associated interstitial lung disease, while data regarding the role of male gender are inconsistent⁷. Our patient was elderly, but, although RF and anti-CCPs were positive, their titers were not high (RF: 37 IU/ml, normal value <20, and anti-CCPs: 31 U/ml, normal value <17). Thus, the limited radiological extent and the clinically insignificant manifestations of interstitial lung disease in our elderly female patient could partially be attributed to the presence of low-titers of RF and anti-CCPs.

Treatment of underlying or associated condition is effective in most patients with BcG. In cases without an obvious cause, many patients improve without medical treatment^{2,5}. Glucocorticoids are a mainstay treatment for asthmatic patients, and, in a small number of BcG with recurrent or persistent disease, long-term therapy may be required^{12,5,8,19}. Although surgical resection as monotherapy may be curative in some patients^{2,11}, there are no definite predictive factors of a

successful outcome.

Other seven cases of RA-associated BcG have been reported so far in the English literature, with clinical and laboratory characteristics described in five of them, as presented in Table I. The majority of patients were middle-aged (range: 41-69 years) women with a relatively long history of RA (at least 4 years), and 50% (n=3) had active polyarthritis on the diagnosis of BcG^{3,8,9}. Recurrent fever, chronic cough with or without hemoptysis and acute or chronic dyspnea were the main presenting respiratory symptoms. Solid or cavitated pulmonary nodules or masses (2-5.5 cm in size) was the usual radiographic pattern of BcG in RA patients. In most cases, they were multiple and bilateral^{3,8-10} with a predilection for middle and/or lower lung fields^{3,8,9,11}. After surgical resection, two-thirds of patients (n=4) received systemic steroids^{3,8-10}, with an initial daily dosage of prednisone ranging between 40 and 100 mg/day. One of them had frequent recurrences on steroid tapering⁸, while, in another case, abatacept was successfully administered after the failure of conventional medical or surgical treatment¹⁰.

In conclusion, BcG seems to be a rare pulmonary manifestation among patients with RA, whose differential diagnosis from cavitary lesions of another origin may be challenging. The exact pathogenetic mechanism remains elusive, since a causal relationship with a particular antigen, RA disease activity or the use of specific disease-modifying agents could not be substantiated in the few cases published. The radiologic and clinical manifestations of BcG are non-specific and the diagnosis is almost impossible to be established without surgical lung biopsy. Most patients usually have a favorable prognosis after surgical excision of the pulmonary lesion.

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REFERENCES

1. Liebow AA. The J. Burns Amberson lecture--pulmonary angitis and granulomatosis. *Am Rev Respir Dis* 1973; 108: 1-18.
2. Koss MN, Robinson RG, Hochholzer L. Bronchocentric granulomatosis. *Hum Pathol* 1981; 12: 632-638.
3. Berendsen HH, Hofstee N, Kapsenberg PD, van Reesema DR, Klein JJ. Bronchocentric granulomatosis associated with seropositive polyarthritis. *Thorax* 1985; 40: 396-397.
4. Clee MD, Lamb D, Clark RA. Bronchocentric granulomatosis:

- a review and thoughts on pathogenesis. *Br J Dis Chest* 1983; 77: 227–234.
5. Katzenstein AL, Liebow AA, Friedman PJ. Bronchocentric granulomatosis, mucoid impaction, and hypersensitivity reactions to fungi. *Am Rev Respir Dis* 1975; 111: 497–537.
 6. Martínez-López MA, Peña JM, Quiralte J, Fernández MC, González JJ, Patrón M, et al. Bronchocentric granulomatosis associated with pure red cell aplasia and lymphadenopathy. *Thorax* 1992; 47: 131–133.
 7. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. *Rheum Dis Clin North Am* 2015; 41: 225–236.
 8. Hellems SO, Kanner RE, Renzetti AD. Bronchocentric granulomatosis associated with rheumatoid arthritis. *Chest* 1983; 83: 831–832.
 9. Bonafede RP, Benatar SR. Bronchocentric granulomatosis and rheumatoid arthritis. *Br J Dis Chest* 1987; 81: 197–201.
 10. Neff K, Stack J, Harney S, Henry M. The use of abatacept in debilitating cavitating lung disease associated with rheumatoid arthritis, bronchocentric granulomatosis and aspergillosis. *Thorax* 2010; 65: 545–546.
 11. Bes C, Kılıçgün A, Talay F, Yılmaz F, Soy M. Bronchocentric granulomatosis in a patient with rheumatoid arthritis. *Rheumatol Int* 2012; 32: 3261–3263.
 12. Myers JL. Bronchocentric granulomatosis. Disease or diagnosis? *Chest* 1989; 96: 3–4.
 13. Tazelaar HD, Baird AM, Mill M, Grimes MM, Schulman LL, Smith CR. Bronchocentric mycosis occurring in transplant recipients. *Chest* 1989; 96: 92–95.
 14. Myers JL, Katzenstein AL. Granulomatous infection mimicking bronchocentric granulomatosis. *Am J Surg Pathol* 1986; 10: 317–322.
 15. Den Hertog RW, Wagenaar SS, Wastermann CJ. Bronchocentric granulomatosis and pulmonary echinococcosis. *Am Rev Respir Dis* 1982; 126: 344–347.
 16. Yousem SA. Bronchocentric injury in Wegener's granulomatosis: a report of five cases. *Hum Pathol* 1991; 22: 535–540.
 17. Rohatgi PK, Turrisi BC. Bronchocentric granulomatosis and ankylosing spondylitis. *Thorax* 1984; 39: 317–318.
 18. Molyaner Y, Geerts WH, Chamberlain DW, Heyworth PG, Noack D, Rae J, et al. Underlying chronic granulomatous disease in a patient with bronchocentric granulomatosis. *Thorax* 2003; 58: 1096–1098.
 19. Rossi GP, Pavan E, Chiesura-Corona M, Rea F, Poletti A, Pessina AC. Bronchocentric granulomatosis and central diabetes insipidus successfully treated with corticosteroids. *Eur Respir J* 1994; 7: 1893–8.
 20. Wiedemann HP, Bensingler RE, Hudson LD. Bronchocentric granulomatosis with eye involvement. *Am Rev Respir Dis* 1982; 126: 347–50.
 21. Warren J, Pitchenik AE, Saldana MJ. Bronchocentric granulomatosis with glomerulonephritis. *Chest* 1985; 87: 832–4.
 22. Houser SL, Mark EJ. Bronchocentric granulomatosis with mucus impaction due to bronchogenic carcinoma. An association with clinical relevance. *Arch Pathol Lab Med* 2000; 124: 1168–71.
 23. Bain GA, Flower CD. Pulmonary eosinophilia. *Eur J Radiol* 1996; 23: 3–8.
 24. Ward S, Heyneman LE, Flint JD, Leung AN, Kazerooni EA, Müller NL. Bronchocentric granulomatosis: computed tomographic findings in five patients. *Clin Radiol* 2000; 55: 296–300.
 25. Robinson RG, Wehunt WD, Tsou E, Koss MN, Hochholzer L. Bronchocentric granulomatosis: roentgenographic manifestations. *Am Rev Respir Dis* 1982; 125: 751–756.