Bronchocentric granulomatosis in rheumatoid arthritis: case report and literature review

Pitsilka DA, Kampolis CF, Rontogianni D, Zisis C, Loukeri AA, Vlachoyiannopoulos PG

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

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. Overall, the pathogenesis of BcG remains uncertain. It is suggested that BcG is one of the limited ways in which bronchi and bronchioles respond to a variety of different types of stimuli. In asthmatic patients, BcG probably results from a hypersensitivity reaction to inhaled fungi and has been associated with allergic bronchopulmonary aspergillosis (ABPA). The causative agent of hypersensitivity response in non-asthmatic patients with BcG is obscure. 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. 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 negative. 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 cavitary 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).
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 disease. The wide spectrum of pulmonary diseases in patients with RA includes conditions 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.

BcG should be considered not as a disease, but as a descriptive pathological diagnosis, 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>
<thead>
<tr>
<th>Reference First author Year</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>RA activity</th>
<th>RA duration</th>
<th>RA Treatment</th>
<th>RF</th>
<th>CRP/ESR</th>
<th>Presenting symptoms Duration</th>
<th>Radiology findings</th>
<th>Treatment for BCG</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellens SO 1983</td>
<td>Female</td>
<td>49</td>
<td>Active polyarthritis</td>
<td>4 years</td>
<td>None</td>
<td>(-)</td>
<td>---/70</td>
<td>Cough Fever 6 weeks Dyspnea Acute</td>
<td>Multiple, bilateral, round densities (2-3.5 cm)</td>
<td>Surgical excision + Steroids</td>
<td>Clinical improvement, Radiographic stability, Frequent relapses on tapering</td>
</tr>
<tr>
<td>Bonafede RP 1987</td>
<td>Female</td>
<td>41</td>
<td>Active symmetric polyarthritis</td>
<td>10 years</td>
<td>None</td>
<td>(+)</td>
<td>---/97</td>
<td>Cough Hemoptysis Fever Dyspnea 2 years</td>
<td>Multiple, bilateral, solid + cavitary nodules (2.5-3.5 cm)</td>
<td>Surgical excision + Steroids</td>
<td>Clinical + radiographic improvement, Remission</td>
</tr>
<tr>
<td>Berendsen HH 1985</td>
<td>Male</td>
<td>58</td>
<td>Active polyarthritis</td>
<td>0 years</td>
<td>Steroids</td>
<td>(+)</td>
<td>---/145</td>
<td>Cough Hemoptysis Chest pain Dyspnea Acute</td>
<td>Multiple, bilateral nodules</td>
<td>Surgical excision + steroids</td>
<td>Clinical + radiographic improvement, Remission</td>
</tr>
<tr>
<td>Neff K 2010</td>
<td>Female</td>
<td>43</td>
<td>Inactive</td>
<td>6 years</td>
<td>Hydroxychloroquine</td>
<td>NR</td>
<td>252/--</td>
<td>Recurrent lower respiratory infections</td>
<td>Multiple, bilateral, pulmonary cavities + Bronchiectases + &quot;tree-in-bud&quot; lesions</td>
<td>Surgical excision + steroids + antifungal agents + abatacept</td>
<td>Clinical + radiographic improvement, Radiographic stability after Abatacept</td>
</tr>
<tr>
<td>Bes C 2012</td>
<td>Female</td>
<td>49</td>
<td>Inactive</td>
<td>16 years</td>
<td>Leflunomide</td>
<td>(+)</td>
<td>WNL</td>
<td>None</td>
<td>Solitary pulmonary nodule (2 cm)</td>
<td>Unilateral Lower lung fields</td>
<td>Surgical Excision</td>
</tr>
<tr>
<td>Our case</td>
<td>Female</td>
<td>69</td>
<td>Inactive</td>
<td>16 years</td>
<td>Leflunomide Low dose Steroids</td>
<td>(+)</td>
<td>120 /100</td>
<td>Cough Fever Fatigue 2 months</td>
<td>Solitary Cavity 5cm</td>
<td>Unilateral lower lobe Surgical excision</td>
<td>Remission</td>
</tr>
</tbody>
</table>

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)\textsuperscript{13–15}, autoimmune diseases (RA, Wegener’s granulomatosis, ankylosing spondylitis)\textsuperscript{3,5,8–11,16,17}, chronic granulomatous disease, bronchogenic carcinoma, glomerulonephritis, red cell aplasia, diabetes insulin and scleritis\textsuperscript{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)\textsuperscript{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\textsuperscript{23,24}. Cavitation of solid lesions is less frequent\textsuperscript{25}. BcG diagnosis cannot be established solely on the basis of radiographic features and open-lung biopsy is usually required\textsuperscript{25}.

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 inconsistent\textsuperscript{7}. 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\textsuperscript{2,3}. 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\textsuperscript{2,5,8,10}. Although surgical resection as monotherapy may be curative in some patients\textsuperscript{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\textsuperscript{13,15}. 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 bilaterally\textsuperscript{13,6–10} with a predilection for middle and/or lower lung fields\textsuperscript{5,8,6,11}. After surgical resection, two-thirds of patients (n=4) received systemic steroids\textsuperscript{5,8–10} with an initial daily dosage of prednisone ranging between 40 and 100 mg/day. One of them had frequent recurrences on steroid tapering\textsuperscript{6}, while, in another case, abatacept was successfully administered after the failure of conventional medical or surgical treatment\textsuperscript{9}.

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.

CORRESPONDENCE TO
Christos F Kampolis
Department of Pathophysiology
Athens University Medical School and “Laiko” General Hospital
75 M. Asias str.
1527, Athens, Greece
E-mail: chkamp77@gmail.com

REFERENCES
4. Clee MD, Lamb D, Clark RA. Bronchocentric granulomatosis:...


