Bronchocentric granulomatosis: Clinical course illustrated by serial computerized tomography of the chest

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Bronchocentric granulomatosis is a pathological process characterized by granulomatous inflammation in conducting airways. A case of bronchocentric granulomatosis of unknown etiology in a previously well 24-year-old female is reported. The variable and often fluctuating course of this entity and its response to corticosteroids is demonstrated by serial computerized tomography of the chest. The pathology, etiology and therapy of bronchocentric granulomatosis is reviewed.

Key Words: *Bronchi, Bronchocentric granulomatosis, Computerized tomography, Idiopathic*

Granulomatose bronchocentrique: Évolution clinique illustrée par tomodensitométrie thoracique en série

RÉSUMÉ : La granulomatose bronchocentrique est un processus pathologique caractérisé par une inflammation granulomateuse des conduits aériens. Un cas de granulomatose bronchocentrique d'étiologie inconnue chez une femme de 24 ans auparavant en bonne santé est signalé. L'évolution de cette maladie souvent variable et incertaine, et sa réponse aux corticostéroïdes, est démontrée par tomodensitométrie thoracique en série. La pathologie, l'étiologie et le traitement de la granulomatose bronchocentrique sont examinés.

BRONCHOCENTRIC GRANULOMATOSIS (BCG) REPRESENTS a nonspecific response to various forms of airway injury (1,2). It is important to exclude an infectious cause in all patients and fungal colonization in asthmatic pa-

tients. The radiographic appearance of BCG is diverse and no pattern appears to be pathognomonic. Features on plain chest radiographs do not consistently correlate with disease presentation (3). To our knowledge the appearance of BCG on

computerized tomography (CT) of the chest has not been described.

We report a patient with BCG for which no cause could be identified. CT of the chest was used to follow her clinical course and guide therapeutic decisions.

As the result of our experience with this patient we believe that CT may be a useful tool to follow the course of this pathological process.

CASE REPORT

A 24-year-old female was referred for assessment of fluctuating fatigue, low grade fever, anorexia and nonproductive cough associated with fleeting alveolar opacities over the previous six months. There was no history of hemoptysis. She was treated intermittently with oral antibiotics for presumed infection without obvious benefit. She was previously well and had no personal or family history of asthma. She had no exposure to animals or occupational agents. She was a nonsmoker and had no human immunodeficiency virus risk factors. Apart from intermittent use of antibiotics over the previous months, she was taking no medication at the time of assessment. Her physical examination was normal. Her white blood cell count was elevated ($17.0 \times 10^9/L$) with a prominent neutrophilia ($13.6 \times 10^9/L$) without eosinophilia and her hemoglobin was 95 g/L with normal red blood cell indices. The sedimentation rate was elevated to 43 mm/h. Urinalysis was normal. Chest radiograph revealed bilateral, patchy, basilar airspace disease (Figure 1). There was no evidence of airflow obstruction, and her diffusing capacity, corrected for hemoglobin, was normal. A CT scan of the chest demonstrated impressive basilar nodules some of which had cavitated (Figure 1). Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage were noncontributory including cultures for fungi and bacteria. Open lung biopsy showed airway centred ulcerative disease associated with acute neutrophil-dominant inflammation admixed with a definite granulomatous component (Figure 2). There was no evidence of a primary vasculitis. Eosinophils were present but did not predominate. Periodic-acid Schiff, Ziehl-Neelson and silver methenamine stains as well as culture of tissue did not reveal any pathogens. These features were indicative of BCG. A search for an etiology was unrewarding. The patient had no history of asthma and serum immunoglobulin E and aspergillus precipitins were not elevated. Rheumatoid factor, antinuclear antibodies, complement studies and antineutrophil cytoplasmic antibodies (ANCA) were negative.

During convalescence from surgery all of her symptoms improved without specific therapy. A follow-up CT scan one month later demonstrated that the parenchymal opacities were resolving and no areas of cavitation could be identified (Figure 3). Five months later she complained of right-sided pleuritic chest pain in the region of her surgery. A chest radiograph performed at this time appeared unchanged from her postoperative examinations. A limited high resolution CT examination through the region of her pain was performed. Owing to a change in scan technique (1.5 mm versus 10 mm collimation) and patient positioning, subsequent CT scan

Figure 1 (Top) Roentgenogram demonstrating patchy bibasilar airspace disease. A computerized tomographic scan using 10 mm collimation revealed large nodules scattered throughout both lungs (middle), some of which had cavitated (bottom) (arrow)

levels were not identical to those obtained previously. However, a section obtained at approximately the same level as the initial study (Figure 3) and accompanying cuts did demonstrate recurrence of the lung nodules. Therapy consisting of daily prednisone 40 mg orally was initiated.

Her symptoms subsequently improved over two weeks. Prednisone was decreased slowly over one-and-a-half months

Figure 2) Photomicrograph showing an inflamed bronchial wall. The lumen (L) contains neutrophilic exudate and the airway lining is replaced by epithelioid histiocytes, some multinucleated. Organism stains were negative (hematoxylin and eosin x78)

to 15 mg/day and she remained asymptomatic. A subsequent limited high resolution CT scan through her chest showed that the parenchymal opacities had again decreased in size (Figure 3). Over the ensuing 18 months, attempts to taper steroids further were met with a return of symptoms and densities on limited CT scanning. Routine chest radiography failed to demonstrate new parenchymal abnormalities during flares in her illness. At this time, three years after her initial presentation, we have successfully discontinued her prednisone. Her latest limited CT scan was free from nodular disease.

DISCUSSION

Liebow (4) characterized BCG as a necrotizing granulomatous inflammation centred on peripheral airways. He included BCG with the classification of four forms of angitis: classical Wegener's granulomatosis; limited Wegener's; lymphomatoid granulomatosis; and necrotizing sarcoid granulomatosis. However, BCG differs from these other diseases as it is not primarily angiocentric and does not involve extrapulmonary sites. Katzenstein and colleagues (5) reviewed BCG and identified two groups of patients based on clinical and pathological findings in 23 patients. The first comprised asthmatics in whom peripheral eosinophilia and a sensitivity to aspergillus were observed. On examination of lung sections the lesions exhibited tissue eosinophilia in addition to granulomatous inflammation. Scattered fungal hyphae could often be seen in the intraluminal exudate. In this group of patients BCG appears to represent a form of allergic bronchopulmonary aspergillosis and to be an inflammatory response to inhaled antigen (5). The second and larger group comprised nonasthmatic patients.

Eosinophilia was absent and the airway-centred infiltrates were predominantly neutrophilic. Proximal obstruction with sustained inflammation and distention of distal airways was commonly observed, and this pathological appearance has been postulated to be a requirement for the development of BCG (1). In this regard, BCG likely represents the lung's

Figure 3) High resolution (1.5 mm collimation) CT scans of the chest. One month after an open lung biopsy improvement in the lung nodules was seen (top). Five months later a repeat limited CT (middle) showed that the nodules had returned. During therapy with prednisone the nodules again disappeared (bottom)

limited inflammatory response to a wide variety of injurious agents. As emphasized by Myers and Katzenstein (6), in this group of patients infectious causes need to be carefully excluded by appropriate cultures and tissue stains. In one study of solitary necrotizing granulomas of the lung, 27% of patients with tuberculosis had bronchocentric granulomas identified (7). In addition to tuberculosis, BCG has been

reported in patients with histoplasmosis, aspergillosis and echinococcus infection (6,8,9). BCG may also occur in patients with seropositive and seronegative arthropathies (10-12).

To add to the difficulty, BCG may be confused with Wegener's granulomatosis. Reports of Wegener's granulomatosis demonstrating a relative 'bronchocentric' distribution that predominated over the associated angiitis have been described (13). Thus, the presence of primary vascular involvement needs to be sought and the presence of ANCA excluded. Patients in whom no cause including infection could be identified have been reported and represented 25% of Katzenstein and co-worker's patient population.

Our patient had no evidence of asthma or demonstrable sensitivity to aspergillus. Despite appropriate staining and culturing of lung tissue and bronchoalveolar lavage samples, no infectious etiology could be identified. Furthermore she had no clinical or serological evidence of a collagen vascular disease nor evidence histologically to support the diagnosis of 'bronchocentric' Wegener's. Thus our patient appears to have BCG of undefined etiology.

A variety of radiographic appearances have been described in BCG (3). Multiple, or more commonly solitary mass lesions, cavitating masses, alveolar filling and reticulo-nodular patterns are reported. Scattered nodules resembling metastasis have been seen in up to 35% of cases (3,4). An upper lobe distribution appears to predominate. Hilar lymph node enlargement is infrequent. Hence, no radiographic pattern appears to be specific for any etiology. We are unaware of any description of the use of CT in diagnosing or following patients with BCG. In this patient, the initial CT appearance was dramatic and disproportionate to the radiographic appearance and her symptoms. Subsequent flares in her illness were not accompanied by any notable changes in her chest radiograph. CT scanning, however, was useful in demonstrating regions of new parenchymal disease. The superiority

of CT to plain radiography has been described in a variety of diffuse lung diseases. Mathieson et al (14) demonstrated that, in the setting of diffuse interstitial lung disease, radiologists' level of diagnostic confidence and accuracy was significantly greater for CT compared with chest radiography. CT scanning may also aid in defining the course and prognosis of diffuse lung disease. In one study examining CT appearances before and after therapy in patients with sarcoidosis, ground-glass, nodular, and interlobular septal thickening correlated with potentially reversible disease, while cystic airspaces and architectural distortion correlated with progressive or irreversible disease (15). In the present patient CT assisted in making therapeutic decisions and in following her response to therapy. Importantly, we were able to reduce the amount of radiation exposure by limiting CT imaging to small regions of the chest and using 1.5 mm collimation scans as opposed to 10 mm collimation scans. In this regard CT scanning may be a more useful tool than chest radiography for assessing activity of this pathologic entity.

This patient also highlights the variable course and response to treatment in patients with BCG of unknown etiology. These patients often have spontaneous remissions lasting months to years, making assessments of response to therapy difficult. We are confident that the corticosteroids administered following her second flare were responsible for her clinical and radiographic improvement. We base this assumption on the observation that a return in her symptoms and parenchymal densities paralleled attempts to decrease her dose of prednisone. In addition to corticosteroids, cyclophosphamide, azathioprine and surgery (for single mass lesions) have been reported as being successful in cases where infectious causes have been reliably excluded (5,16). There are no prospective interventional studies for idiopathic BCG and therapeutic claims are limited to case reports. We suggest that CT scanning may represent a useful tool for the care of patients with BCG.

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