Radiology Case Reports 16 (2021) 3029–3033

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Case report

Diffuse panbronchiolitis as parathymic syndrome in a Caucasian man previously treated for thymoma ☆,☆☆

Aldo Carnevale, MD[a], *Elisa Lucioni, MD*[a,*], *Marta Maria Daniele, MD*[b], *Marco Contoli, MD*[b], *Melchiore Giganti, MD*[a], *Brunilda Marku, MD*[b]

[a] *Section of Radiology, Department of Translational Medicine and for Romagna, University of Ferrara, Ferrara, Italy*
[b] *Research Centre on Asthma and COPD, Department of Medical Sciences, University of Ferrara, Ferrara, Italy*

ARTICLE INFO

Article history:
Received 8 June 2021
Revised 8 July 2021
Accepted 10 July 2021
Available online 9 August 2021

Keywords:
Diffuse panbronchiolitis
Thymoma
Sinusitis
CT

ABSTRACT

Diffuse panbronchiolitis (DPB) is a rare disease characterized by bronchiolitis and chronic sinusitis. Being largely restricted to East Asia, its actual incidence in Caucasian patients is probably underestimated. DPB has been described in association with thymic neoplasms, mainly arising as a consequence of immune dysregulation. We present a rare case of DPB diagnosed in a 69-year-old Caucasian man who had undergone surgery for stage 2A thymoma a year before. The patient came to our hospital complaining of exertional dyspnea and productive cough, with a persistent lung consolidation described at chest X-rays. High resolution computed tomography (CT) showed diffuse centrilobular micronodules and solid nodules, tree-in-bud opacities, peripheral consolidations and cylindrical bronchiectasis. Sinus disease was also demonstrated by CT. Analysis of bronchoalveolar lavage showed marked granulocyte inflammation and allowed the isolation of Haemophilus Influenzae. Consequently, the diagnosis of DPB was reached by integrating clinical, and radiological data. Long-term therapy with azithromycin was prescribed, and was found to be effective in controlling symptoms and reducing radiological abnormalities at 6-month clinical and CT follow-up. Confidence with the radiological presentation and clinical significance of DPB is necessary, since the condition is responsive and reversible to long-term macrolide treatment, the effect of which is mainly attributed to an anti-inflammatory, and immunoregulatory action.

☆ Funding: The University of Ferrara supported this work by providing the publication fee.
☆☆ Competing Interests: None.
* Corresponding author.
E-mail address: lucionielisa@gmail.com (E. Lucioni).
https://doi.org/10.1016/j.radcr.2021.07.026

Introduction

Diffuse panbronchiolitis (DPB) is a rare, idiopathic, inflammatory disease characterized by bronchiolitis, and chronic sinusitis. The past literature has emphasized its predominance in East Asia, although case reports and small case series have confirmed, since the late 1980s, that it may affect subjects also in Western countries, albeit rarely [1,2].

The actual incidence of DPB in Caucasian patients is probably underestimated, since many cases might represent *forme fruste* of DPB or limited and/or variant forms [1].

A wide spectrum of parathymic syndromes has been described in association with thymic neoplasms, mainly arising as a consequence of immune dysregulation; among them, some authors have postulated the association of DPB and DPB-like abnormalities with thymic tumors [3].

DPB is now regarded as curable, since the introduction of long-term therapy with low-dose macrolides has remarkably changed the prognosis [4].

We describe a case of a Caucasian patient with a past history of thymoma and a clinical diagnosis of DPB, with a good response to macrolides therapy after thymectomy.

Case description

A 69-year-old Caucasian man, a retired computer scientist, presented to our University Hospital complaining of exertional dyspnoea and productive cough.

The patient was a former smoker (40 pack-years), with atopic familiarity but without any known allergy. His past medical history included ischemic cardiopathy post myocardial infarction treated with percutaneous coronary revascularization, chronic obstructive pulmonary disease (COPD) in treatment with tiotropium bromide and olodaterol, hip prosthetic replacement for osteoarthritis, a past car accident with multiple rib fractures, and subsequent pneumothorax. He was receiving therapy with bisoprolol, aspirin, and doxazosin.

Moreover, the patient reported a surgical intervention of thymectomy for B1-type thymoma (stage 2A) approximately a year before. Shortly afterwards, follow-up chest X-rays (CXR) showed the development of an area of consolidation in the right lung basis with tendency to slow resolution.

At auscultation, the patient's clinical examination revealed diffuse wheezes and rhonchi in both lungs. He reported no fever or weight loss.

Chest computed tomography (CT) performed for further investigation confirmed the presence of an area of lung consolidation in the middle lobe, and showed multiple micronodules and solid nodules distributed in a centrilobular fashion, often extending to small, branching opacities (tree-in-bud pattern) in the middle, inferior lobes as well as in the lingular segments, the superior lobes being relatively spared. Concomitant cylindrical bronchiectasis, smaller peripheral consolidations and enlarged mediastinal lymph nodes were noted (Fig. 1). All the chest abnormalities described were not present in the report of pre-operative CT scan performed for staging.

At the same time, a CT scan of the paranasal sinuses was performed, showing mucosal wall thickening in the maxillary, frontal and sphenoidal sinuses as well as in the ethmoid air cells, suggestive of sinusitis (Fig. 2).

Blood gas analysis revealed hypoxemia (oxygen partial pressure (PaO_2) and percentage saturation (SaO_2) of 64 mm Hg and 94%, respectively). Spirometry was not completed because of a syncopal episode while attempting the procedure.

The patient's routine laboratory findings were unremarkable, except for a serum iron value of 52 mcg/dl. Immunoglobulin levels, rheumatoid factor, and complement factors were normal. Total IgE value was at the upper limits, while Aspergillus Fumigatus specific IgE were negative. No mycobacterial organisms were found in the sputum.

Bronchoscopy showed diffuse stagnation of purulent bronchial secretions, associated with thinning of the bronchial walls. Analysis of bronchoalveolar lavage demonstrated marked granulocyte inflammation. Respiratory bacterial culture from bronchoalveolar lavage allowed the isolation of Haemophilus Influenzae, while the search for Mycobacterium tuberculosis, Pneumocistis jiroveci, Aspergillus fumigatus, and fungal ifae resulted negative.

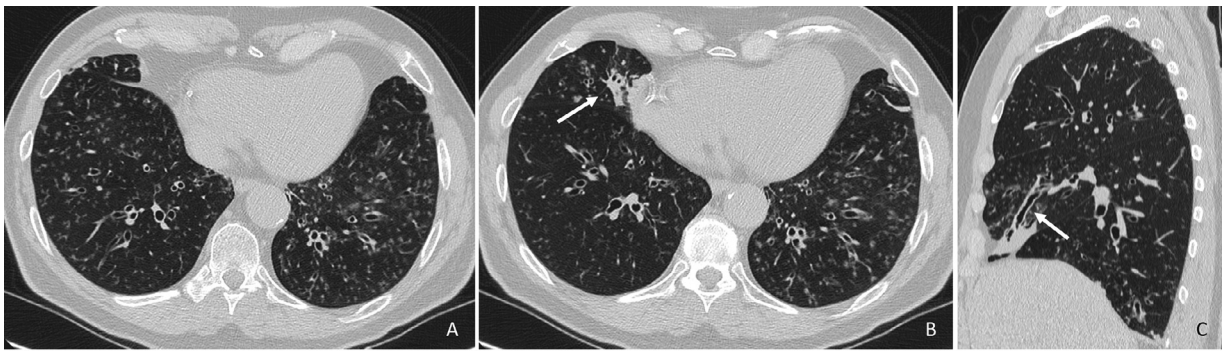

Fig. 1 – Chest high resolution computed tomography (HRCT) demonstrating multiple centrilobular nodules and micronodules through both lung bases (A-B), with a peripheral consolidation in the middle lobe (arrow in B). A cylindrical bronchiectasis is evident in the middle lobe (arrow in C, sagittal plane reformatted image).

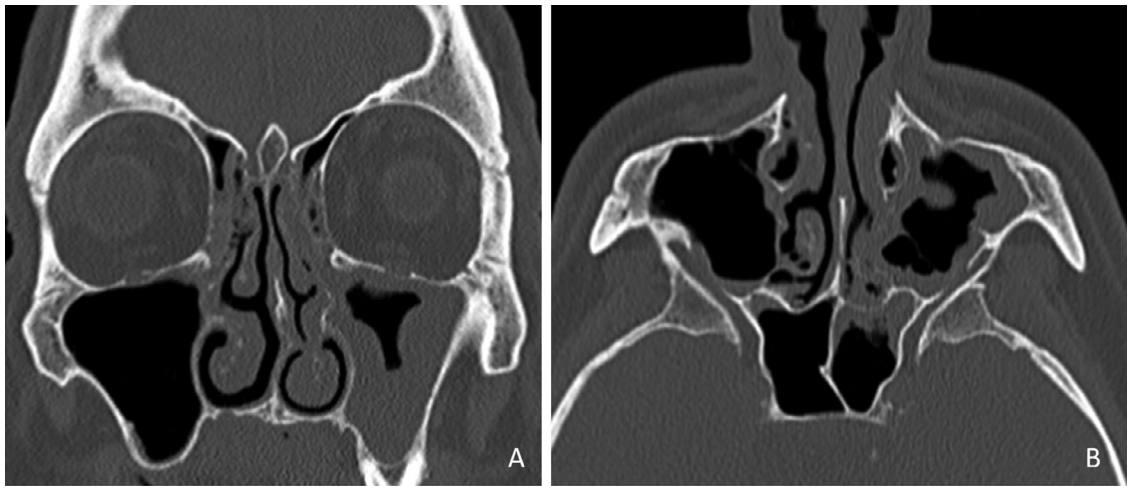

Fig. 2 – Unenhanced computed tomography of the paranasal sinuses showing sinus disease in the ethmoid, maxillary, and sphenoid sinuses (axial and coronal plane in A and B, respectively).

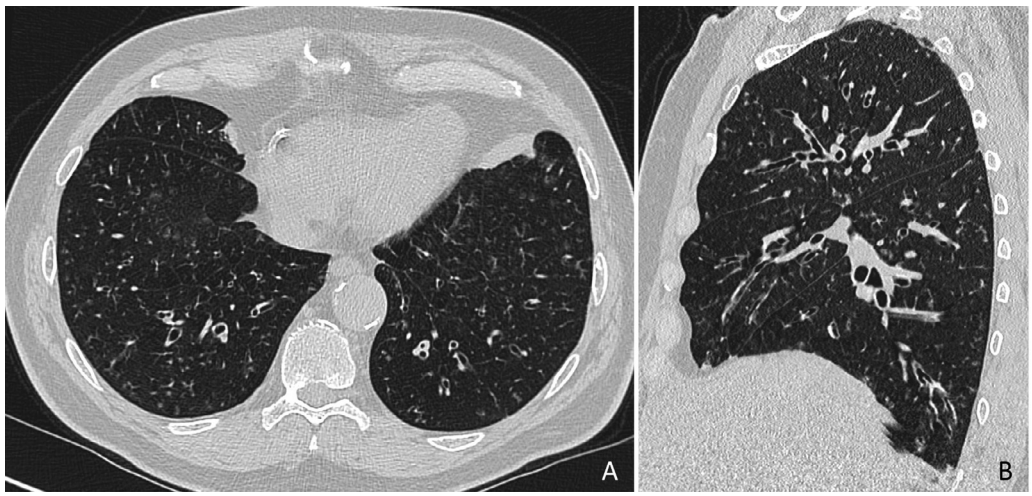

Fig. 3 – HRCT at 6-month follow-up demonstrating a substantial reduction in the extent of lung abnormalities previously seen at the level of lung bases (A) and the resolution of bronchiectasis (B).

Since a diagnosis of DPB was suspected, a long-term treatment with azithromycin 500 mg/die was started.

A follow-up chest CT was performed after 6 months, following the outbreak of COVID-19 pandemic, showing a substantial decrease in number and size of the centrilobular nodules, and a complete resolution of bronchiectasis and consolidations previously noted (Fig. 3). Clinical examination revealed a substantial improvement in symptoms; the patient refused to undergo a spirometry.

Discussion

DBP is an idiopathic inflammatory disease characterized by the association of bronchiolitis and chronic sinusitis. ''Diffuse'' refers to the fact that the lesions are equally distributed in both lungs, while ''Pan'' means that the inflammatory involvement can be found in all layers of the respiratory bronchioles.

The disease is mainly restricted to Japan and East Asia; however, some cases have also been encountered in Western Countries. DPB usually occurs in the second-fifth decade of life, with no remarkable gender predominance. In the majority of patients, no history of cigarette smoking has been reported [1].

The exact pathogenic mechanism underlying DPB is still unknown, but a genetic predisposition seems to contribute to the development of the disease. Indeed, different studies have suggested a major disease susceptibility gene for DPB located between the HLA-A and HLA-B loci. In other studies, patients were found to have polymorphisms in mucin-like gene MUC22, and in mucin gene MUC5B [1,5,6].

Bronchiectasis has been described as a complication of thymic neoplasms. The DPB-like pathologic abnormalities reported in patients with thymoma suggest that bronchiecta-

sis and DPB-like manifestations might result from an abnormal immune attack by lymphocytes or autoantibodies to various target cells or organs, inducing autoimmune manifestations (i.e. parathymic phenomena) [3]. Moreover, bronchiectasis could develop at any stage of thymic neoplasms.

Respiratory symptoms consequent to the bronchial abnormalities may precede the diagnosis of thymic neoplasms, which can be discovered during the diagnostic workup for bronchiectasis [7]. The symptoms may improve after thymectomy and bronchiectasis-related treatment; however, bronchiectasis may also occur after thymectomy, as in the case we have described, suggesting that the abnormal immune response induced by the tumor might persist after surgery [3].

Although DPB can reliably be diagnosed from a histopathology report, as in the case of other lung conditions there are obvious difficulties in obtaining a biopsy due to the invasiveness of the procedure [4,8]. Therefore, there is an increasing diagnostic role of integrated clinical, high resolution CT (HRCT), and lung function data.

Clinical manifestations include a wide range of respiratory symptoms that tend to be progressive over months to years: chronic sinusitis, productive cough, shortness of breath on exertion, and history of wheezing. Physical examination may reveal crackles, wheezes or both.

There are no specific laboratory abnormalities diagnostic for DPB; mild neutrophilia, raised erythrocyte sedimentation rate and elevated levels of C-reactive protein can usually be found. The most characteristic laboratory finding is a persistent elevation of cold agglutinins, even without evidence of Mycoplasma Pneumoniae infection [5].

Sputum cultures have demonstrated the presence of Haemophilus Influenzae in 44% and Pseudomonas Aeruginosa in 22% of patients with DPB. Detection of Pseudomonas Aeruginosa is considered a predictor of a worse prognosis [6].

Pulmonary function tests usually indicate an obstructive defect, which is relatively resistant to bronchodilators; sometimes a mixed obstructive-restrictive pattern may also be seen. The diffusing capacity for carbon monoxide (DL_{CO}) is variably reduced. Hypoxemia and hypercapnia develop in the terminal stages of the disease, often due to *Pseudomonas Aeruginosa* superinfection [1,5].

Plain chest radiographs may initially show non-specific findings such as lung hyperinflation, whereas in advanced cases tram-track or signet ring signs can be found, suggesting bronchiectasis [1]. HRCT scan reveals diffuse parenchymal abnormalities consisting of nodular opacities, often connected to branching linear areas of attenuation (tree in bud), peripheral air trapping, and dilated and wall thickened bronchioles [1,6].

Lung biopsy is not usually necessary in patients that present typical clinical and radiographic features and who live in countries with a high prevalence of DPB. However, in some cases lung biopsy can be obtained in order to confirm the diagnosis. The histologic lesion of DPB is typically seen in respiratory bronchioles, with transmural and peribronchial infiltration by lymphocytes, plasma cells and “foamy” macrophages. The inflammatory infiltrate destroys the bronchiolar epithelium and extends to the surrounding interalveolar septa, but does not usually involve the alveoli [1,6].

The prognosis of untreated DPB has been very poor, as patients develop progressive respiratory failure and cor pulmonale, leading to death within few years. Long-term treatment with macrolides, mainly with erythromycin, has significantly improved the prognosis, increasing the 10-year survival rate up to 90% [1]. Erythromycin therapy is effective in improving symptoms, lung function, and CT findings. The mechanism of action of macrolides include antimicrobial but also anti-inflammatory and immunoregulatory effects [1,4]. The optimal duration of medical treatment is still unknown; therapy is administered for almost 2 years in most patients. Low-dose, long-term azithromycin may be more efficacious in DPB with a reduced side-effect profile compared to erythromycin [4]. Bronchiectasis has been described as a negative predictor of treatment outcome in patients with DPB receiving macrolide therapy [9]. Once treatment is stopped, follow-up is crucial because of the risk of relapse of symptoms and HRCT abnormalities. Indeed, recurrence has been documented even after lung transplantation [1].

In conclusion, DPB is a rare entity in Caucasians, but it may develop in subjects after surgery for thymoma. Although rare, prompt and correct diagnosis of DPB is crucial because it is responsive and reversible to long-term macrolide treatment, the effects of which are beyond those related to antimicrobial properties and attributed to anti-inflammatory and immunoregulatory actions. In our case, azithromycin was effective in attenuating the symptoms and substantially reducing the radiological abnormalities.

Patient consent

Written informed consent was obtained for publication of this case report and any accompanying images.

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