Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia accompanied by airflow obstruction*

Hiperplasia de células neuroendócrinas pulmonares difusas com obstrução ao fluxo aéreo


Abstract
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia with airflow obstruction is a rare form of lung injury. All of the reported cases have been diagnosed by surgical lung biopsy. Only three of the reported cases presented with diffuse interstitial lung opacities on HRCT scans. We report three additional cases of this entity. All of the patients were female and presented with mild-to-moderate airflow obstruction. In the first case, transbrachial biopsy and imaging data were sufficient to make the diagnosis. Although the HRCT scans of all three cases revealed a mosaic pattern, that of the third patient also revealed diffuse interstitial infiltrate. In extremely rare cases, HRCT findings can simulate those seen in other interstitial lung diseases.

Keywords: Neuroendocrine cells; Carcinoid tumor; Bronchiolitis obliterans.

Introduction
Pulmonary neuroendocrine cells are widely distributed within the airway mucosa and play a multifunctional role in pulmonary homeostasis because they produce serotonin and a variety of neuropeptides, such as bombesin. Recent studies suggest that, during lung development, these cells play an important role in sensitivity to oxygen and in the regeneration of the distal lung epithelium. Focal (localized) neuroendocrine cell hyperplasia can be accompanied by various lung diseases, such as COPD, lung abscess, cystic fibrosis and bronchiectasis. Pulmonary neuroendocrine cell hyperplasia can present in various forms. When the proliferation is restricted to the bronchial and bronchiolar epithelium, it is known as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; when the proliferation extends beyond the basal membrane, the foci are designated tumoralrres, which, in turn, can be localized or diffuse; and, finally, when the proliferation forms nodules greater than 5 mm, it is known as a carcinoid tumor.

The first case series of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, involving 6 patients, was conducted by Aguayo...

* Study carried out at the São Paulo Hospital for State Civil Servants, São Paulo, Brazil.
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et al. in 1992. The largest case series, involving 19 patients, was published in 2007. One case report has been published in Brazil.

Some authors use the term neuroendocrine cell bronchiolitis to refer to diffuse idiopathic pulmonary neuroendocrine cell hyperplasia accompanied by functional evidence of airway obstruction, a syndrome that overlaps both clinically and morphologically with bronchiolitis obliterans.

All of the cases reported to date have been diagnosed by open lung biopsy or lobectomy. Chest CT findings of areas of mosaic perfusion are common, suggesting a diagnosis of bronchiolitis.

In the present study, we report three cases, the first of which was diagnosed by transbronchial biopsy and the second and third of which were diagnosed by surgical lung biopsy. The third patient presented with tomographic findings of diffuse interstitial disease, which has been observed in only three reported cases. All of the patients presented with airflow limitation.

**Case report**

**Case 1**

A 49-year-old nonsmoking female, who worked as a teacher, presented with a six-month history of dry cough and mild dyspnea. A routine exercise stress test to monitor arterial hypertension revealed that the patient “got too tired”. She was then submitted to chest X-ray and referred to the Department of Pulmonology of the São Paulo Hospital for State Civil Servants. The patient reported household exposure to birds for three years.

Physical examination revealed that the patient was in good general health and had no apparent respiratory distress, as well as presenting a heart rate of 68 bpm, a respiratory rate of 16 breaths/min and normal vesicular sounds. The rest of the physical examination was normal.

A chest X-ray and an HRCT scan (Figures 1a and 1b, respectively) revealed small nodules of varying sizes accompanied by lobulated areas of air trapping.

A pulmonary function test performed at admission, with lung volumes measured by plethysmography, revealed the following: FVC, 1.68 L (61%); FEV1, 1.15 L (47%); FEV1/FVC ratio, 64%; total lung capacity (TLC), 4.29 L (89%); residual volume (RV), 2.29 L (175%); and specific airway conductance, corrected for pulmonary resistance, 0.076 L/s/cmH₂O/L. After the use of albuterol (400 μg), lung volumes and FEV1 were unaltered. However, specific airway conductance increased to 0.116 L/s/cmH₂O/L. The predicted values were those suggested for the Brazilian population. The functional diagnosis was moderate obstructive lung disease accompanied by air trapping.

Bronchoscopy with transbronchial biopsy was performed (Figure 1c).

The histological findings revealed proliferation of small cells, without atypia, located in the airway walls and forming nodular aggregates that tested positive for epithelial markers (carcinoembryonic antigen and CK7) and neuroendocrine markers (chromogranin and synaptophysin), as determined by immunohistochemistry (Figure 1d). There was concomitant fibrosis, accompanied by focal obliteration of the bronchiolar lumen, as well as mild chronic inflammatory infiltrate and focal bronchiolectasis.

The correlation among clinical, tomographic and histopathological findings allowed the diagnosis of tumorlets accompanied by diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. If the diffuse idiopathic pulmo-

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Figure 1 - In a), chest X-ray revealing bilateral small nodules. In b), HRCT scan of the chest revealing bilateral small nodules. In c), transbronchial biopsy sample revealing proliferation of small cells, without atypia, in nodular aggregates, as well as fibrosis accompanied by focal obliteration of the bronchiolar lumen (H&E; ×100). In d), immunohistochemical positivity for chromogranin in the cells of interest.
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There was no significant variation after bronchodilator use.

The HRCT scan of the chest revealed bilateral small pulmonary nodules, and surgical lung biopsy showed nodules consisting of proliferation of small cells, located in the small airway walls, with strong positivity (brown staining) for neuroendocrine markers (synaptophysin). The histological diagnosis was multiple carcinoid tumors (Figure 2).

The patient developed chronic cough and progressive dyspnea on exertion, together with episodes of bronchospasm. In 2005, another pulmonary function test revealed that FEV1 had decreased to 0.59 L (44%), again without variation after bronchodilator use.

During the follow-up period, the patient was treated with bronchodilators and inhaled corticosteroids.

Case 2

A 76-year-old nonsmoking female presented with a 15-day history of dry cough, dyspnea and fever. The patient had been treated as having bronchial infection and bronchospasm and had presented improvement. She reported weight loss (10 kg) in the last three years. In addition, the patient reported symptoms of gastroesophageal reflux and denied any occupational exposure of interest.

Physical examination revealed that the patient had lost weight and presented an overall reduction in breath sounds, with prolonged expiratory time. An HRCT scan of the chest revealed hyperinflation and multiple pulmonary nodules.

A pulmonary function test performed in 1999 revealed the following: FVC, 1.54 L (59%); FEV1, 0.90 L (49%); FEV1/FVC ratio, 58%; TLC (helium dilution), 4.95 L (110%); and RV, 3.28 L.

During the follow-up period, the patient was treated with bronchodilators and inhaled corticosteroids.

Case 3

A 64-year-old female presented with a ten-year history of dry cough and dyspnea on exertion, both of which had worsened over the last four months. The patient denied any occupational or environmental exposure of interest.

Physical examination revealed that the patient had lost weight and presented an overall reduction in breath sounds, with prolonged expiratory time. An HRCT scan of the chest revealed hyperinflation and multiple pulmonary nodules.

A pulmonary function test performed in 1999 revealed the following: FVC, 1.54 L (59%); FEV1, 0.90 L (49%); FEV1/FVC ratio, 58%; TLC (helium dilution), 4.95 L (110%); and RV, 3.28 L.

The patient was treated with prednisone and an inhaled corticosteroid, having remained clinically and functionally stable for two years after the initial evaluation.

Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is a rare disease. To date, there have been sixty-six reported cases, most of which were included in one of three case series.\(^4,5,12\)

### Figure 2

- **In a) and b), HRCT scan of the chest revealing small nodules with a sparse bilateral distribution.**
- **In c), proliferation of small cells in the walls of the terminal bronchioles (H&E; ×40).**
- **In d), peribronchiolar cell proliferation presenting immunohistochemical positivity for synaptophysin (×40).**
which explains the denomination bronchiolitis obliterans accompanied by neuroendocrine cell hyperplasia. Some authors have postulated that neuroendocrine cell hyperplasia precedes and causes airway fibrosis. Neuroendocrine cells can be observed amid airway fibrosis.

The combination of diffuse idiopathic pulmonary cell hyperplasia and constrictive bronchiolitis is related to the production of neuropeptides, such as bombesin, accompanied by chronic inflammation.

The combination of bronchiolitis and carcinoid tumors is observed with variable frequency. One group of authors evaluated 25 consecutive patients with peripheral carcinoid tumors and found that 19 had neuroendocrine cell hyperplasia in addition to the dominant carcinoid tumor. Of the 25 patients, 8 (32%) had bronchiolitis obliterans lesions accompanied by foci of neuroendocrine cell hyperplasia, and 2 of those 8 patients had airflow obstruction that could not be related to smoking or to any other condition. Another group of authors, in a case series involving 28 patients with multiple carcinoid tumors and tumorlets, found that only 4 had airflow obstruction and that only 1 of those 4 had a profile indicative of diffuse bronchiolitis.

Pathological evaluation of lung tissue obtained by surgical biopsy is the gold standard for the diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, and, to date, all of the reported cases have been diagnosed by open lung biopsy or based on the results of lobectomy for pulmonary nodules. The first case reported here was diagnosed by transbronchial biopsy, after the findings were correlated with the functional profile and the tomography profile. The combination of well-defined nodules and areas of air trapping seen on the HRCT scan of the chest led the attending physician to suspect the diagnosis, since this combination is suggestive of carcinoid tumors accompanied by bronchiolitis. The finding of neuroendocrine cell proliferation in the transbronchial biopsy was considered sufficient to make the diagnosis.

Cough and dyspnea are the most common findings. These symptoms were observed in all three of the cases presented here. In one case series, half of the patients were asymptomatic, and the diagnosis was made based on findings of pulmonary nodules in patients with neoplasms of various types, submitted to a follow-up HRCT scan of the chest.

In spirometry tests, obstructive defects are common and this can lead to confusion with asthma or COPD. Cases of the pseudorestrictive pattern in the spirometry test, similarly to that described in bronchiolitis obliterans, can be observed. Although the disease typically remains stable, in some cases, as in one of our cases, the obstruction can be progressive. Airflow obstruction results from diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, as well as from concomitant bronchiolar fibrosis, which explains the denomination bronchiolitis obliterans accompanied by neuroendocrine cell hyperplasia. Some authors have postulated that neuroendocrine cell hyperplasia precedes and causes airway fibrosis. Neuroendocrine cells can be observed amid airway fibrosis.

In the present study, 2 of the patients were elderly and all were female—findings that are in accordance with those of the three largest published case series. There is no explanation for the predominance of females.

Of the three cases reported here, two were in nonsmokers and one was in a former smoker. Smoking is believed to be unrelated to this condition. In a case series involving 19 patients, 12 had never smoked. In another case series, all of the patients were nonsmokers.

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Chest CT findings of nodules and areas of mosaic perfusion are common and this can raise the suspicion of hypersensitivity pneumonia.

In some cases, only air trapping is revealed, suggesting constrictive bronchiolitis. The
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia is typically indolent and is rarely progressive. In one case series, 83% of the 19 patients studied were alive five years after diagnosis. However, in one case, the patient underwent lung transplantation due to progressive disease.

There is little information regarding treatment. In one case series, 2 of the 6 patients studied underwent chemotherapy, which resulted in no improvement. In one of those two cases, the disease had a rapidly progressive evolution, resulting in death due to respiratory failure. It is recommended that patients be monitored prior to treatment. If pulmonary function worsens, corticosteroid use should be attempted. There are rare reported cases of a clinical and functional response to corticosteroids.

In summary, the present study shows that, although rare, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia should be suspected in cases of airflow obstruction accompanied by multiple pulmonary nodules and areas of air trapping on HRCT scans. Even more rarely, the pattern can be that of diffuse interstitial disease.

References

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