Pulmonary Carcinoid Tumorlets: A Rare Cause of Chronic Intractable Cough

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Abstract Chronic cough is a common presenting complaint in pulmonary clinics. We present a patient who had undergone extensive work up for chronic intractable cough that was finally diagnosed as diffuse pulmonary carcinoid tumorlets. Pulmonary tumorlet is an incidental finding at histopathologic examination of lung parenchyma that is often located adjacent to bronchogenic tumors or carcinoid tumors or particularly in lung scarred by bronchiectasis or other chronic inflammatory processes. Tumorlets are usually smaller than 5 mm in diameter and are multiple. Tumorlets are composed of small uniform cells that appear cytologically benign; they tend to form compact aggregates or nests and may grow into the mucosa of the airways. Also, tumorlets, like carcinoids, contain neurosecretory granules and have distinctive electron microscopic and immunohistochemical findings. Our case is a 61 year old Caucasian female, non-smoker, was followed in pulmonary clinic because of chronic dry cough which was associated with dyspnea and wheezing. Normal physical examination except for occasional wheezes. Pulmonary function test showed restrictive pattern, FEV1 75%, FEV1/FVC 88% and TLC 67% of predicted. High resolution chest CT had shown multiple non-calcified well circumscribed pulmonary nodules scattered throughout the lungs, the largest 5 mm. She had been treated as a case of asthma. Inhaled bronchodilators and corticosteroids partially improved her symptoms. Later her cough had become intractable with worsening exertional dyspnea. Otolaryngology evaluation and EGD had been inconclusive. Bronchoscopy with bronchoalveolar lavage and multiple transbronchial biopsies came with normal results. VATS biopsy showed multiple small nodules less than 1 cm in the right upper, middle, and lower lobes, predominantly peripheral lesions. The lesions were found to represent carcinoid tumorlets. Usually the lesions are asymptomatic and discovered incidentally on CT scan and can be confused with metastases, however they can present with chronic cough or dyspnea.

Keywords: carcinoid tumorlets, Chronic Cough, pulmonary tumorlets, neuroendocrine tumors

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1. Introduction

Pulmonary Carcinoid Tumorlets (PCT) are rare, benign and usually constitute incidental findings on Computed Tomography (CT) scan or histopathologic examination. They arise from focal proliferation of bronchial and bronchiolar neuroendocrine Kulitschisky cells. They often coexist with diffuse bronchiectasis, emphysema and interstitial fibrosis. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), tumors, and carcinoids are distinct entities that share a common initial event - the neuroendocrine cell proliferation. Unlike diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, the proliferation of neuroendocrine cells in tumorlets extends beyond the basement membrane. Additionally, as opposed to scattered proliferation of cells in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, hyperplastic cells organize to form nests of less than 5 mm in tumorlets. These nests of hyperplastic cells manifest as nodules on CT scans. Tumorlets can be asymptomatic or present with various respiratory symptoms like cough, dyspnea or wheezing.

2. Case Presentation

We present a 61-year-old Caucasian female, non-smoker, with no past exposure to allergens, irritants, noxious gases or chemicals who was followed in pulmonary clinic for chronic dry cough of 2 years duration that was associated with wheezing and dyspnea mainly on exertion. She denied any phlegm production, fever, chills, weight changes, chest pain, palpitations or gastroesophageal reflux symptoms. She only took over the counter multivitamins and reported no drug or food allergies. Physical examination showed normal vital signs. Chest examination revealed occasional wheezes on auscultation. Cardiovascular examination revealed normal S1 S2 with no murmurs or added sounds and no peripheral
edema. Abdominal examination revealed no distention or shifting dullness. Pulmonary function test showed a restrictive pattern, with FEV1 75%, FEV1/FVC 88% and TLC 67% of predicted. High resolution chest CT revealed multiple non-calcified, well circumscribed pulmonary nodules scattered throughout the lungs, with the largest 5 mm (Figure 1). She had been treated as a case of asthma with inhaled bronchodilators and corticosteroids both of which partially improved her symptoms. Over the next months of follow up she reported no significant improvement and her cough had become intractable with worsening exertional dyspnea. Referral to otolaryngology evaluation and esophagogastroduodenoscopy was inconclusive. Bronchoscopy with bronchoalveolar lavage and multiple transbronchial biopsies returned with normal results. Decision was to proceed with Video-assisted thoracoscopic surgery (VATS) biopsy which showed multiple small nodules less than 1 cm in the right upper, middle, and lower lobes, predominantly in the periphery. Pathological studies were found to represent carcinoid tumorlets. The immunohistochemical stains were positive for CD 56, chromogranin, synaptophysin, TTF1 and CK7 (Figure 2).

3. Discussion

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), carcinoid tumorlet and typical carcinoid (TC) are distinct subsets of neuroendocrine tumors which share morphologic, ultrastructural, immunohistochemical and molecular characteristics. DIPNECH is defined as a generalized proliferation of scattered single cells, small nodules, or linear proliferations of pulmonary neuroendocrine cells (PNCs) within the bronchial epithelium. The proliferation of PNCs may extend beyond the basement membrane into the peribronchial tissue, forming cell nests that are called tumorlets or carcinoids according to their diameter. Morphologically, tumorlets are identical to typical carcinoids but smaller in size (≤ 0.5 cm). Size is currently the only criteria discriminating tumorlets from typical carcinoids. Tumorlets develop from Kulchitsky cells, which are hyperplastic neuroendocrine cells in the bronchial and bronchiolar mucosa. It has been postulated that these hyperplastic cells secrete neuropeptides that can elicit a peribronchiolar fibrotic reaction leading to fibrotic lung disease.

Pulmonary carcinoid tumorlets (PCTs) usually are incidental findings at autopsy or in pulmonary tissues surgically excised for other reasons. The relationship between pulmonary tumorlets and carcinoid tumors has not been definitively established. It has been suggested that carcinoids can evolve from tumorlets. Tumorlets are substantially more common than carcinoid tumors, and most do not progress beyond the tumorlet stage. These nests of hyperplastic cells manifest as nodules on computed tomography (CT) scans. PCTs often occur in conditions of chronic lung damage, such as in the context of pulmonary fibrosis, chronic or granulomatous inflammation, bronchiectasis, and giant cell pneumonia. In most instances, neuroendocrine cell hyperplasia and tumorlets are regarded largely as secondary tissue reactions. Tumorlets are also associated with areas of scarring, bronchiectasis, and emphysema and are often associated with carcinoid and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Extremely rare cases of tumorlets with atypia and regional lymph node metastases have been reported. Patients with pulmonary tumorlets are relatively asymptomatic or present with cough, dyspnea, hemoptysis and recurrent pulmonary infections. Pulmonary function test results for most patients are either normal or mildly abnormal. Radiologically, tumorlets present as small pulmonary nodules and mosaic attenuation secondary to air trapping on CT.

Pathologists should also be aware that multiple tumorlets may mimic a miliary pattern of metastasis. This issue was highlighted in a study by Darvishian et al, in which a group of patients with breast cancer was suspected of having multiple pulmonary metastases by CT scans, but subsequent pathologic examination revealed multiple carcinoid tumorlets. Although usually not a diagnostic challenge, tumorlets should be distinguished from minute meningothelioid nodules (the so-called chemodectoma-like bodies)—a common lesion of no clinical significance with similarly bland cytologic features and frequent multiplicity. The distinguishing
features of minute meningotheioid nodules are perivenular location with stellatelike extension into alveolar walls, whorls and intranuclear inclusions similar to meningioma, and the lack of associated fibrosis. Unlike tumorlets, minute meningotheioid nodules do not stain positive for neuroendocrine markers or cytokeratins.

Clinically, there is a female preponderance and pulmonary tumorlets are generally encountered in patients between 60 and 70 years old. Carcinoid tumorlets are of typical carcinoid tumor cell type, rarely metastasize, and have an overall good prognosis.

4. Conclusion

Carcinoid tumorlets are rarely considered in the diagnosis of chronic cough and documentation of this phenomenon in the literature is extremely sparse. This diagnosis would be very difficult to make prior to lung biopsy. Carcinoid tumorlets are typical carcinoid tumor cell type, rarely metastasize, and have an overall good prognosis.

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