

Case Report

Misdiagnosed Case of Bronchial Carcinoid Presenting with Refractory Dyspnoea and Wheeze: A Rare Case Report and Review of Literature

Avradip SANTRA, Pravati DUTTA, Sudarsan POTHAL, Rekha MANJHI

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Department of Pulmonary Medicine, Veer Surendra Sai Medical College and Hospital, P.O. +P.S. Burla, Odisha, India, Pin-768017

Abstract

A 59-year-old male smoker presented with persistent wheezing and occasional coughing that had been ongoing for two years and had been unsuccessfully treated with an inhalational β_2 agonist, an anticholinergic and an inhalational steroid in the last year. On clinical examination, a left-sided wheeze was detected. The initial chest X-ray was normal. A computed tomography (CT) scan of thorax demonstrated a mass lesion in the left main bronchus. On subsequent bronchoscopy, an endobronchial polypoid mass was detected in the left main bronchus, completely occluding the bronchial lumen. A biopsy taken from the mass revealed features of bronchial carcinoid. Bronchial carcinoid can present uncommonly with wheezes, resulting in misdiagnosis as bronchial asthma or chronic obstructive pulmonary disease (COPD). If an asthma or COPD patient does not respond to conventional therapy, a CT scan and subsequent bronchoscopy is warranted.

Keywords: asthma, bronchoscopy, carcinoid tumour, neuroendocrine tumors

Introduction

A bronchial carcinoid is an uncommon tumour of the respiratory system, although it is the commonest benign tumour of tracheobronchial tree. This neuroendocrine tumour usually presents with haemoptysis and cough, but can sometimes present in an unusual manner with refractory wheezing and breathlessness. Patients with such symptoms are often wrongly treated for bronchial asthma or chronic obstructive pulmonary disease (COPD) for a long time before the actual diagnosis is established. Here, we report such a case of bronchial carcinoid which was initially misdiagnosed and treated for obstructive airway disease (OAD) prior to the final diagnosis.

Case report

In March 2012, a 59-year-old male patient, a school teacher by profession, was admitted to the pulmonary medicine ward with complaints of gradually progressive dyspnoea with occasional cough and scanty mucoid expectoration over two years. The dyspnoea was initially exertional and associated with wheezing, but it was occurring even at rest prior to admission. There was no history of haemoptysis, chest pain, fever or palpitation. The patient also complained of anorexia, although

there was no loss of weight. He also denied any history of rhinorrhoea, sneezing or atopy. He had been a smoker for the last 35 years, having four to five cigarettes a day, but he was a non-drinker.

The patient had been diagnosed with COPD on the basis of his symptoms one year previously, and was put on inhalational formoterol and budesonide (800 μ g/day), along with inhalational tiotropium, at that time. He was on regular medication and denied any non-compliance with the therapy. However, although he was never hospitalised, his symptoms continued to progress. There was no history of hypertension, diabetes, cardiac disorder or any other co-morbid illness. Bowel and bladder habits were normal, although sleep was disturbed due to shortness of breath.

On clinical examination, the patient was found to be of thin built and to have pallor. However, cyanosis, icterus, oedema, clubbing, and lymphadenopathy were all absent. Jugular venous pressure (JVP) was normal. There was tachypnoea and tachycardia with a SpO_2 of 93% in room air. Blood pressure (BP) was 136/88 and temperature was 97.8 °F. Auscultation of the chest revealed diminished vesicular breath sound and wheeze on the left hemithorax.

Initial spirometry demonstrated a restrictive

pattern with a post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) value of 77.19, FVC of 1.822 L (55% of predicted) and FEV₁ of 1.402 L (53% of predicted) with a poor bronchodilator reversibility. The patient was put on nebulisation of levosalbutamol and ipratropium along with systemic corticosteroid, but the response was inadequate.

A complete blood count (CBC) showed haemoglobin 10.9 gram/dL, total white cell count of 16 000/mm³ with neutrophils at 87%. Other routine blood investigation and urine routine/microscopic examination (RE/ME) were within normal limit except for a raised C-reactive protein (CRP) and hypoalbuminaemia. Electrocardiogram revealed a right axis deviation with first-degree heart block without any ischemic changes.

The initial chest X-ray (Figure 1) was normal. Ultrasonography of the thorax and abdomen revealed no abnormality. A computed tomography (CT) scan of the thorax was performed; this revealed a near-complete cut off of the left main bronchus due to an intraluminal soft tissue mass (Figure 2) without any evidence of lymphadenopathy. No pulmonary infiltrate or pleural effusion was noted.

A flexible bronchoscopy of the left main bronchus was carried out. As a result, a smooth, reddish-yellow polypoidal mass was found occluding whole lumen and a biopsy was taken (Figure 3 and 4). Histology showed the presence of uniform polygonal cells with finely granular chromatin in round nuclei and a moderate amount of eosinophilic cytoplasm without any nuclear atypia, mitosis or necrosis (Figure 5).

Immunohistochemistry indicated neuroendocrine differentiation of tumour cells with cytoplasmic positivity of cytokeratin, chromogranin A and synaptophysin. Thus, a diagnosis of a typical carcinoid tumour was established. The patient was subsequently referred to thoracic surgeons and a bronchial sleeve resection was performed; his symptoms were well controlled with inhalational formoterol and budesonide (400 µg/day) during fifteen post-operative days in the hospital.

Discussion

Pulmonary carcinoid tumours are the most frequently encountered benign tumours of the tracheobronchial tree, and constitute 2–5% of all lung cancers (1). Mueller (1882) first described the carcinoid type of bronchial adenoma found at necropsy on a young woman who had suffered

from haemoptysis and a chronic productive cough (2). Carcinoids may develop in many locations in the body, but most often, they are found in



Figure 1: Chest X-ray apparently normal.



Figure 2: Computed Tomography (CT) scan of thorax showing a soft tissue mass occluding the left main bronchus with comparatively hyperinflated left lung.

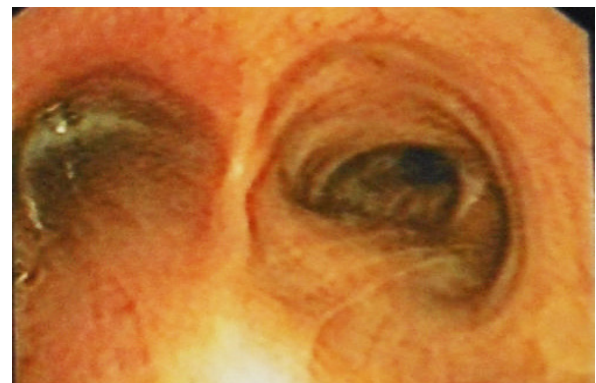


Figure 3: Fibreoptic bronchoscopy showing narrowed left main bronchus distal to carina.

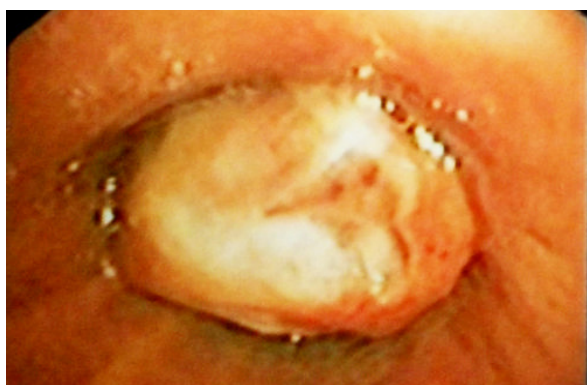


Figure 4: Fibreoptic bronchoscopy showing smooth polypoid mass in left main bronchus.

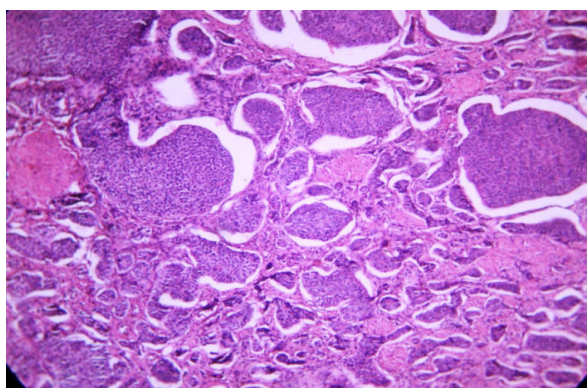


Figure 5: Photomicrograph shows solid nests of monotonous appearing cells with small, round nuclei; moderate amount of finely granular cytoplasm & fine nucleoli. (Hematoxylin & eosin; 100× magnification).

the small intestine (26%), respiratory system (25%) and appendix (19%) (3), although some researchers found nearly 90% of carcinoids to be located in GI tract (4).

Bronchial carcinoids belong to the neuroendocrine tumour group arising from the amine precursor uptake decarboxylation (APUD) system and share the same neuroectodermal cell of origin, the so-called neuroendocrine (Kulchitsky) cell with small cell carcinoma of the lung. The enterochromaffin cells synthesise and secrete neuroendocrine peptides into the central circulation, and their ability to synthesise serotonin from dietary tryptophan is suggested to be pathognomonic of carcinoids (5).

Hypoproteinaemia results from tryptophan depletion, which is an essential amino acid

needed for the synthesis of serotonin, proteins, and nicotinic acid. As a result, nicotinic acid production, which normally uses approximately 99% of tryptophan, may be reduced. This alteration of tryptophan metabolism results in hypoalbuminaemia, decreased protein synthesis and pellagra-like symptoms (e.g. dermatitis, dementia and diarrhoea) (6). This feature of hypoalbuminaemia was noted in our patient as well.

Typical and atypical carcinoids are subgroups of neuroendocrine tumours that are determined as low-grade and intermediate-grade tumours, respectively, according to biological aggressiveness. About 90% of carcinoid tumours are well differentiated with rare mitoses, pleomorphism and necrosis (7). These are referred to as 'typical' carcinoid tumours, as described originally by Hamperl (8). The remaining 10% are characterised histologically by increased mitotic activity, nuclear pleomorphism and disorganisation; these lesions are designated as 'atypical' carcinoids. They tend to have a higher rate of metastasis and are larger at the time of diagnosis. This division has a strict extrapolation to survival rates: In the case of typical pulmonary carcinoids, the five-year survival rate is over 90%, whereas in atypical cases, it is within the range of 40–60% (9).

It was documented many years ago that typical carcinoids, atypical carcinoids, and small cell undifferentiated lung cancers belong to same family of APUDomas arising from bronchopulmonary Kulchitsky cells. Therefore, Paladugu et al. (10) suggested calling them Kulchitsky cell carcinomas (KCCs) to reflect the overlap among these cancers. They called typical carcinoids KCC-I, atypical carcinoids KCC-II and small cell cancers as KCC-III.

Aetiologically, no association has been found between carcinoids and cigarette smoking, ambient radiation or exposure to other known carcinogens (7), although a recent study described a possible association between atypical carcinoids and smoking (11). Mean age at presentation of patients with typical carcinoids is in the fifth decade, while atypical carcinoid presents a decade later in life. It is more common in women than men. Our patient, however, was a male smoker who presented with typical carcinoid in the sixth decade of life.

Symptoms of pulmonary carcinoids depend on the location of the tumour. Central tumours (located mostly in the right lung) mostly present with haemoptysis (caused by high vascularisation), recurrent lower respiratory tract infections

and cough, although they can sometimes present with dyspnoea, wheezing or chest pain. Peripheral tumours are mostly asymptomatic. Typical carcinoid syndrome, characterised by flushing, palpitations, wheezing and right-sided valvular heart disease, is extremely uncommon with pulmonary carcinoid. There is usually a time gap from the onset of symptoms until diagnosis, and patients are often misdiagnosed with asthma or COPD, as occurred in the above case, which featured with wheezing and was treated unsuccessfully for COPD. Diagnosis in our case was further delayed, as this patient had no haemoptysis in spite of having a centrally located tumour.

When a patient presents with refractory asthma or COPD, other causes of non-response to therapy like upper respiratory tract causes (rhinitis, nasal polyps, sinusitis, post-nasal drip), gastro-oesophageal reflux disease, allergic bronchopulmonary aspergillosis (ABPA), airway malignancy, chronic pulmonary infection (especially tuberculosis), cardiac disorders and carcinoid tumour must be considered.

Radiographic findings are similar among patients with typical and atypical carcinoids, and depend largely on tumour location (12). Most carcinoids appear as circumscribed, centrally located lesions with a diameter of 2–5 cm (13,14). Given the central location of the lesions, associated radiographic findings of post-obstructive pneumonia or mucus plugging are common. Peripherally located lesions occur in approximately one-third of cases, and generally are of < 3 cm in diameter (14). Endobronchial lesions may also cause distal air trapping, unilateral hyperlucent lung and segmental or lobar atelectasis, although chest X-ray can sometimes appear normal, as occurred in our case. CT or magnetic resonance imaging is more sensitive than X-ray, especially when it comes to detecting lymph node metastases.

Fibre-optic bronchoscopy easily detects centrally located, polypoidal, smooth, cherry-red tumours, and biopsy can be obtained in this way. A school of physicians does not support taking bronchoscopic biopsy due to the chance of bleeding, but most recent studies, as well as the British Thoracic Society, refer to it as a safe procedure. Endobronchial brushings and washings are generally non-diagnostic because the bronchial epithelium overlying the tumour is typically normal (15).

On light microscopy, bronchial carcinoids consist of small, polyhedral cells with small round or oval nuclei. The arrangement of the cells is

regular and consists of ribbons, nests, sheets or spindling structures separated by a fibrovascular stroma.

Fluoro-deoxyglucose-Positron Emission Tomography (FDG-PET) may be somewhat more useful than previously reported, although its sensitivity is still marginal, at 75%. Somatostatin receptor scintigraphy (SRS) is useful for the evaluation of neuroendocrine tumours due to the high expression of somatostatin receptors on these tumours. However, while more sensitive than FDG-PET imaging, SRS lacks specificity because other tumours and inflammatory conditions may give positive results (15). Thus, neither FDG-PET nor SRS is currently recommended for routine evaluation of a suspected carcinoid tumour.

Both typical and atypical bronchial carcinoids may be found to express the neuroendocrine markers by immunohistochemistry (chromogranin A, synaptophysin and non-specific enolase), and may also express somatostatin receptors. Plasma chromogranin A is the most frequently elevated hormone (94%), and thus appears to be the most sensitive tumour marker in patients with metastatic bronchial carcinoids. A higher level of chromogranin A is correlated with tumour burden.

Surgery is the therapy of choice for carcinoid tumours, with parenchyma-sparing procedures recommended for typical carcinoids (12). Surgical procedures include pneumonectomy, bilobectomy, lobectomy, segmentectomy, sleeve resection, and wedge resection. The aim is to remove the primary tumour and affected lymph nodes radically, keeping as much of the lung parenchyma as possible. Endoscopic laser resection also has a role, and this can be performed with a rigid or flexible bronchoscope. Many experts prefer a rigid bronchoscope because the open tube allows the laser fibre, suction catheters, and forceps to be used simultaneously. Ventilation and excessive bleeding can be easily controlled, and the bronchoscope can perform dilatation and mechanical resection, thus shortening procedure times (16). Because of the many disadvantages of the rigid bronchoscope like need for general anaesthesia and more chance of complications, however, most pulmonologists prefer a flexible bronchoscope for laser photoresection.

If complete surgical resection cannot be accomplished, or if metastatic disease is present, chemotherapy and radiation therapy provide a little hope for cure. Metastatic or locally advanced carcinoids display very poor responsiveness to a variety of chemotherapeutic regimens similar to those utilised for treatment of small cell lung

carcinoma, with a median overall survival of 20 months (17). Biotherapy with α and γ interferon, octreotide, and lanreotide are mainly being attempted for symptomatic relief.

Conclusion

Finally we can conclude that 'all wheezes are not asthma' and more particularly when wheezes are localised. The possibility of a bronchial obstruction should be kept in mind when a provisionally diagnosed case of refractory asthma or COPD is dealt with and this warrants further investigation to confirm the diagnosis.

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Conflict of interest

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Final approval of the article: PD

Correspondence

Dr Avradip Santra
MD (Pulmonary Medicine)
Department of Pulmonary Medicine
V.S.S. Medical College and Hospital
P.O.+P.S.-Burla
Odisha, India. Pin-768017
Tel: 099 3725 5125
Fax: 916 63243 0768
Email: avradipsantra@gmail.com

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