

Bronchopulmonary Carcinoid: A Case Report and Brief Review

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A 45 years old female presented with mild persistent nonproductive cough since past one year, and shortness of breath (SOB) with recently detected hypertension and diabetes since 3 months. The patient also mentioned hot flushes since last one month. She remained on home quarantine without oxygen support for COVID-19 in the year 2020. She was advised anti-TB in 2021 which she stopped due to intolerance. All routine investigations were essentially normal except RBS 160 mg/dl and HbA1C which was 8.5%. She was regularly taking antihypertensive and anti-diabetic drugs. Chest x-ray revealed left cardiac silhouette due to collapse of lingular segment, which was confirmed with CECT thorax. BAL, brush cytology and biopsy were carried out with fiberoptic bronchoscopy, revealing a smooth polypoid mass obstructing the lingular segmental bronchus. Histopathology reported it as a typical carcinoid. The case was referred for surgical intervention. There was a delay in diagnosis in this case, as there was past history of COVID-19 infection and was misinterpreted as its sequelae; wrong diagnosis and empirical treatment for tuberculosis and the association of diabetes and systemic hypertension makes this case worthy for presentation.

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Introduction

The bronchopulmonary carcinoid tumor (BCT) is a very rare and low malignant tumor that mostly behaves benignly. The BCTs were formerly known as bronchial adenomas, a term no longer used as they are neither glandular nor all benign as rarely it may grow rapidly and behave much more aggressively. It was first described in the late 19th century by Lubarsch, who observed multiple tumors in the small bowel in an autopsy specimen. Later on, German pathologist Siegfried Oberndorfer gave the term *karzinoide*, or carcinoma-like. Gosset and Masson later described the endocrine-related properties in 1914 and Hamperl in 1937.¹ The BCTs develop from Kulchitsky cells found within the bronchial mucosa and the cartilage of airways, specifically the epithelium.² The Enterochromaffin (EC) cells or "Kulchitsky cells" are a type of enteroendocrine and neuroendocrine cells present in the epithelial lining within the lumen of the digestive tract and the respiratory tract that releases typical peptide hormones and neuro amines, which secrete, ACTH,

somatostatin, and bradykinin into the central circulation.^{2,3} Carcinoid syndrome was first recognized in 1954 as a clinical entity,³ including symptoms like flushing, pain abdomen etc.

The BCT is sub-classified by World Health Organization/The International Association for the Study of Lung Cancer (WHO/IASLC) on the basis of histology with the presence or absence of tumor suppression marker. The typical carcinoid is well differentiated (less than 2 mitosis/2 mm² and no necrosis) and found in about 90% cases. The other one is atypical carcinoid with increased mitosis (2–10 mitosis/2 mm² and known to have abnormalities in p53, BCL2, or BAX genes) with confirmed necrosis.^{2,4} The pulmonary tumorlet so-called "microscopic carcinoid tumor" is also known to occur in association with fibrous tuberculous lesions and the differential diagnosis became difficult between tumorlet and carcinoid. Thus a tumorlet nodule greater than 5 mm may be considered a small carcinoid tumor⁵ while the BCTs may exhibit neuroendocrine function. The atypical variant of BCT is more aggressive and tends to invade nearby structures. In 15% of cases metastasize

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usually to mediastinal lymph nodes and to the liver, other rare sites which could be bone, adrenal glands, or brain.¹ The most common site for carcinoid tumor is GI system and among all carcinoids, only 10% are found as bronchopulmonary, of which, 75% arise in the lobar bronchi, while 10% in main stem bronchi and rest of 15% arise from the periphery of the lung.² The BCTs are highly vascular, polypoid masses and are about <3–4 cm in size, and are likely to obstruct the bronchi. However, a symptom free incidental detection is up to 25 to 40%¹

The overall incidence of carcinoid tumors is estimated to be 1 to 2 cases per 100,000 in the United States.¹ The average age remained 40 to 50 years without sex predilection.⁶ The typical carcinoids have the best prognosis with a survival rate of 10 year in 80% as against 5 years with atypical carcinoids. However, it is reported that 5 years survival rate is reported to fall from 80 to 60% if metastases exist. The clinical presentation of BCTs is variable and most of them are asymptomatic and detected on evaluation for some other reason. However, persistent cough and or hemoptysis remained the major reasons for seeking medical consultation. The differential diagnosis of BCTs is vast, may be divided into various malignant and benign etiologies. The former includes adenocarcinoma, squamous cell, large cell and small cell carcinoma. The benign tumor can also be differentiated in sub-group infectious granulomatous lesions such as histoplasmosis, coccidioidomycosis, tuberculosis, cryptococcosis, and blastomycosis. The benign tumors such as bronchial hamartomas, lipomas, fibroma, neurofibroma, leiomyoma, and angiomas are the other differential diagnosis. Vascular etiologies such as arteriovenous malformation, pulmonary varix, and pulmonary infarct also need to be considered. The inflammatory origins such as granulomatosis with polyangiitis, rheumatoid nodule, or sarcoidosis, should also be considered while other etiologies like the round atelectasis, intrapulmonary lymph nodes, loculated fluid, mucoid impaction, and aspirated foreign body, etc.² should be ruled out.

Clinical presentation of the carcinoid syndrome may include the endocrinal manifestations due to the release of corticotropins resulting in Cushing's syndrome or GH-releasing hormone resulting in acromegaly, and release of serotonin etc.¹ The site/location, size, type and metastasis status of a tumor could be determined by different imaging modalities i.e. Chest X-ray (CXR), CT Scans etc and the ultimate pathological diagnosis be established by procuring biopsy which is an important

part of management of BCTs. The Carcinoid tumors have poor response to adjuvant chemo and radiotherapy thus a complete resection of the tumor with regional lymph nodes remains the mainstay of treatment⁴

Case Report

A 45 years old female came with mild persistent nonproductive cough for last one year, and shortness of breath (SOB) with recently detected hypertension and diabetes in the past 3 months. She started gaining weight and experienced hot flushes in last one month. She had an old chest X-ray which had been reported to be normal. There was a past history of COVID-19 (in 2020) for which she was in home isolation without oxygen support. She had also been treated with anti-tuberculosis drugs in 2021 as a smear negative x-ray positive case but the patient stopped treatment due to intolerance. Her BMI was 24, BP 140/70 mm Hg, pulse 84/minute, SpO2 96% at room air, afebrile and Icterus/ Pallor/ Cyanosis/ JVP/ Lymph nodes/ Clubbing/ Edema were all absent. All routine investigations (Hb, TLC, DLC, Platelets, ESR, CRP, Liver, Renal, coagulation profile) were unremarkable with RBS 160mg/dl and HbA1C 8.5% (Type 2 diabetes mellitus). Her repeat chest X-Ray (Figure 1) showed the cardiac silhouette with the collapse of lingular segment of the left upper lobe; hence CECT thorax was done. This was followed by fiberoptic bronchoscopy (Figure 2), which revealed a mass fully occluding the lumen of lingular segment. The biopsy of the mass and Broncho-Alveolar Lavage (BAL) were performed for histopathological evaluation. Fluid cytology was essentially normal, while the HPE of biopsy material revealed it as a case of Typical Carcinoid (Figure 3 a-c). The patient was referred to a higher centre for evaluation by Positron emission tomography FDG-PET scan and consideration for surgical intervention/ resection.

Discussion

The central location of the typical carcinoid is the commonest (> 80%) presentation among BCT, has also been found in our case. These tumors have low grade of malignancy and are comparatively found in the relatively younger age of 40 to 50 years.¹ They also mimic other chronic lung diseases like tuberculosis and need to be considered in the differential diagnosis of cases with lung lesions and carcinoid symptoms.⁷ The main symptoms in our case were a nonproductive persistent cough with breathlessness. The clinically respiratory examination was unremarkable. The most common presentation



Figure 1: Chest X-ray show cardiac silhouette with lingular segment of upper lobe



Figure 2: Lingular segment opening obstructed by the mass: Biopsy & BAL Fluid collected



Figure 3: a, b & c Section shows nests and clusters of monomorphic medium sized cells with moderate amount of eosinophilic cytoplasm with regular normochromic nuclei. No mitotic figures or necrosis could be identified

usually reported are hemoptysis (25–50%), recurrent infection and wheezing; although about 25–40% do not have symptoms in the early stage.^{1,2} Smita Pathak *et al.* reported hemoptysis with expectoration of carcinoid mass in hospitalized patients during several bouts of coughing, which was a rare event.⁶ These tumors are highly vascular and most likely to bleed profusely on touch and at times become difficult for biopsy,⁵ but the Esubalew Taddese Mindaye *et al.* mentioned a very low of <1%, incidence of serious bleeding during the bronchoscopic biopsy.⁴ Our case also remained uneventful during fiberoptic

bronchoscopy. At many occasions, diagnosis is made more than a year after presentation and is more likely to be misdiagnosed as PTB.⁷ Our patient was diagnosed in the recent past as diabetic with hypertensive, and she also complained of hot flushes during night which supported the carcinoid syndrome; however, biochemical investigation could not be carried out in the present case. The 24 hours urine measurement of elevated serotonin metabolite, 5-HIAA (5 hydroxy indole acetic acid of normal range 2–8 mg/24 hours) but is found in only 50% cases. The Chromogranin-A (CGA), is a 49-kD protein, which is also a tumor marker present in the neurosecretory vesicles of neuroendocrine tumor cells is more reliable.¹ Gauri S. Kulkarni *et al.* also mentioned that incidental detection of pulmonary carcinoids are a common occurrence (25–39% of overall cases), and among these, the carcinoid syndrome occurs in only about 2%.¹

The chest radiographs alone may reveal abnormalities in about 75–90% of cases, and the central lesions are seen as hilar/perihilar mass with or without atelectasis while peripheral carcinoids may present as solitary pulmonary nodule (SPN).³ A homogenous increased opacities with volume loss may also be found on radiographs.² The left cardiac silhouette due to atelectasis of lingular segment was found on CXR in our case. The middle lobe and lingular segments are more vulnerable to be blocked due to acute/sharp turn and small caliber of the bronchus. The other imaging modalities, i.e. contrast enhance computer tomography (CECT) or MRI of thorax, may most precisely locate the mass site, size contour, calcification, etc., to narrow the diagnosis. In the present case no mediastinum lymph node enlargement was found while trans-bronchial needle aspiration (TBNA), endo-bronchial Ultrasound (EBUS) guided biopsy and PET-CT can detect mediastinal or elsewhere metastasis (the later one is not available in our institution). Smita Pathak *et al.* mentioned that the bronchial mucosa overlying carcinoid tumors is frequently intact or may show squamous metaplasia. Therefore, examination of sputum (exfoliation cytology) is frequently negative and only brushings or FNAC of the lesion may succeed in procuring a large number of malignant cells.⁶ However, bronchial lavage & brush cytology were negative in our case, while the tumor biopsy was reported a typical carcinoid tumor.

Surgical resection is the mainstay of treatment for patients with no evidence of systemic metastasis. The outcome of typical carcinoid tumors even with lymph node metastasis, is excellent with complete resection, but a patient with larger tumor requires cautious

follow-up postoperatively as the chance of recurrence is relatively higher.⁴ Katarzyna Drożdż *et al.* stressed about conservative lung resection with bronchoplasty for bronchial carcinoid as a safe procedure with low morbidity and good long-term survival.⁸ Hyfaa Mashaal *et al.* reviewed 98 cases (during 2014-2018) with a resolution of neuroendocrine-specific symptoms in all the patients who underwent surgical resection.² Tumors confined to main bronchus are treated by sleeve resection and circumferential resection. Complete excision is usually possible; other tumors may require lobectomy or pneumonectomy. The patients with typical bronchial carcinoids have an excellent prognosis, with 5, 10, and 15 year survivals of 92.4, 88.3, and 76.4% respectively.³ In stage IV a surgical resection alone is not sufficient; these patients may require radiological intervention to reduce the size of the tumor. The use of somatostatin analogs in these procedures reduce the neurosecretory activity and mass size or stabilizes tumor growth which may help in symptomatic relief.² Clinical trials with the intent to improve the medical management with the Cabozantinib vs. placebo and the use of Ipilimumab and Nivolumab are in the pipeline. Association of diabetes is well documented with carcinoid, especially with gastrointestinal involvement.^{9,10}

Conclusions

broncho pulmonary carcinoid is a rare, slow-growing neuroendocrine tumor (behaves like a benign tumor), often bleeding on touch during the procedure and is mostly situated centrally. These are most likely to be missed or have a delayed diagnosis if attention is not given to the associated presentation of carcinoid syndrome and other neuroendocrinal manifestations. Hence due

consideration has to be given in the differential diagnosis. Surgical intervention/resection are still a mainstay of management with reasonable good outcomes even in the case with atypical carcinoid having metastasis. The association of diabetes with pancreatic carcinoid has sporadic presentations, while the presence of systemic hypertension could not be explained with the BCT.

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