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Bronchial Carcinoid
Case Report and Review of the Subject

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SUMMARY

Carcinoid tumours are rare entity but carcinoid syndrome is even more uncommon. These tumours arise from neuro-endocrine cells of the fore- mid- and hind-gut and produce a number of substances, the most important is serotonin. Bronchial carcinoid tumours are rare and account for 2.5% of all pulmonary tumours. Two cases of bronchial carcinoid are reported with different presentations and a review of the subject is discussed.

CASE 1

A 45-year-old woman, housewife, mother of three with previous good health, presented to the out patient department with sudden onset of coughing up of fresh blood. She was really concerned about it and on questioning denied any previous such history. There was no history of chronic cough, sputum, fever, weight loss, night sweats or any bleeding disorder either. In the past, she had no significant illnesses and did not undergo any surgical procedures. There was no history of either diabetes mellitus or hypertension etc. No other member of the family had such symptoms and there was no family history of bronchial carcinoma or tuberculosis. However, her mother had bilateral carcinoma of breasts, for which she has had bilateral mastectomy. The patient was on no medications and no significant history of allergies was noted.

On examination, she looked a bit pale, was very anxious but apyrexial. Her pulse was 94 per minute and regular and BP was 135/90 mm of Hg and respiratory rate was 16 per minute. There was no anaemia, jaundice, cyanosis, clubbing or lymphadenopathy. Heart sounds were normal, without added sounds. Her trachea was central and there was good air entry in both sides of the lungs but a fine localized wheeze could be audible over the right upper chest close to sternum. However, there was no fullness of either supraclavicular fossae. Rest of the systemic examination including abdominal, musculoskeletal and neurological examinations were unremarkable.

Investigations showed a Hb of 14.4 g/dl with a heamatocrit of 42.9 %, WCC of 9.3 $\times 10^9$ /l with normal differential count i.e., P 65 % L 30% E 1%, M 4%, platelets were 402 $\times 10^9$/l. Prothrombin time was 13 seconds with a control of 12 seconds. APTT was 34 seconds with control of 35 seconds. Random blood sugar was 98mg/dl, urea was 18 mg/dl and creatinine was 0.7 mg/dl. Her ALT was 87 IU/l, alkaline phosphates was 68 IU/l with a gamma GT of 87 IU/l. Hepatitis B and C serology was negative, ultrasound abdomen showed fatty liver without any hypoechoeic areas. Her HIV test was also negative. Chest X-ray showed right para-tracheal/tracheo-bronchial angle soft tissue density with elevation of lesser fissure however, left lung was clear. (Fig. 1.) Therefore, to see the nature of that density a CT scan of the chest was recommended, which showed an endobronchial mass extending into the main stem bronchus with paratracheal soft tissue density and segmental atelectasis and adjacent patchy consolidation. (Fig. 2). Left lung was clear. Mediastinal, peritracheal and axillary spaces were clear with no significant lymphadenopathy. Left lung was clear. Her pulmonary function tests (spirometry) showed moderate restrictive impairment. Bronchoscopy showed a polypoid tumour filling 2/3 of the lumen of right main

bronchus. Tumour seemed to arise from right upper lobe bronchus. However, the bronchus intermedius and right main bronchus did not appear to be invaded by the tumour.

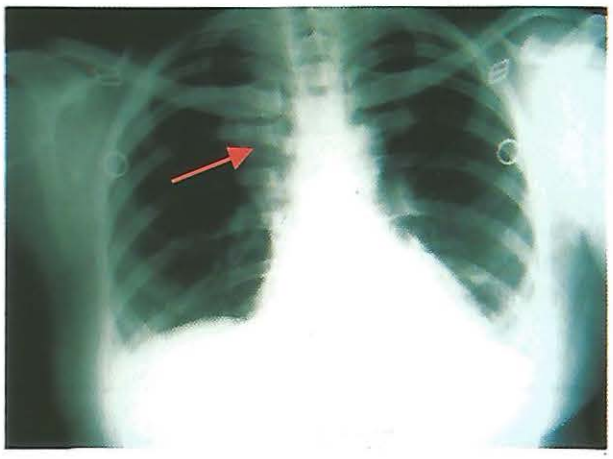

Fig. 1. Right para-tracheal/tracheo-bronchial angle soft tissue density with elevation of lesser fissure.

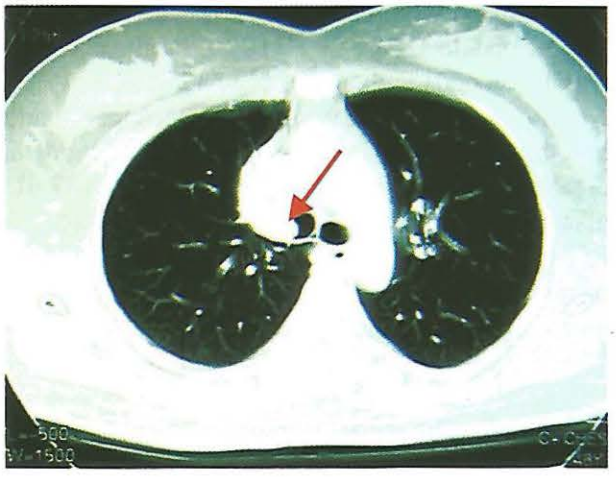

Fig. 2. Endobronchial mass extending into the right main stem bronchus with paratracheal soft tissue density.

It was vascular and bled while taking biopsy. A provisional diagnosis of carcinoid tumour was made at this stage. However, biopsies which were taken were not very conclusive. Bronchial washing did not reveal any AAFB or malignant cells but the polypoid mass seen at bronchoscopy was definitely a tumour. She refused surgery which was advised to her but had a couple of more episodes of haemoptysis and then agreed for surgical intervention. The surgeon resected the tumour and histopathological examination of various parts of resected specimen confirmed the diagnosis of a carcinoid tumour of typical type.

Post-operatively, she stayed in hospital for 7-10 days and made an uneventful recovery. Her urinary 5-HIAA was normal.Three months after her surgery on follow up she remains well and there is no further episode of haemoptysis. Her urinary 5-HIAA remained normal.

CASE-2

A 29-years-old woman, housewife, mother of two attended out patient clinic with a history of upper respiratory tract infection in the form of dry cough, low grade fever and sneezing. There was no history of wheezing or coughing up of blood. No significant past history was present and she was taking some antihistamines and analgesics. Menstrual history was unremarkable and there was no history of allergies either.

On examination, she looked unwell. Temperature was 99.1°F and weight was 63 kg. Her pulse was 94 per minute and regular, BP was 115/80 mm of Hg without postural drop, and respiratory rate was 14/min. Her throat was congested. There was no pallor, cyanosis, clubbing or lymphadenopathy or oedema. Chest was clear and other systemic examination was unremarkable.

Investigations included, Hb of 12.4 g/dl, WCC 8.2×10^9/l with normal differential count, platelets were 312×10^9/L and ESR was 37 mm in 1st hour. Her LFT's and urine examination were unremarkable. Chest X-ray showed small left sided pleural effusion and a rounded well circumscribed opacity in the left lower zone (Figs. 3 and 4.). Repeated sputum examinations were negative for AAFB or malignant cells. Mantoux test was negative as well. An ultrasound of abdomen revealed nothing abnormal in abdomen or in the pelvis. Her symptoms persisted in the form of low grade fever. Pleural aspiration under ultrasound guidance was done which showed a straw coloured fluid with protein of 3.5 g/dl and 340 cells, of which 95% were lymphocytes. A CT scan of the chest showed a soft tissue density mass in the apical

segment of left lower lobe with minimal pleural effusion and calcification. (Fig. 5). It was reported as hamartoma. Another expert opinion on the scan also agreed to a radiological diagnosis of hamartoma rather than a granuloma or malignancy.

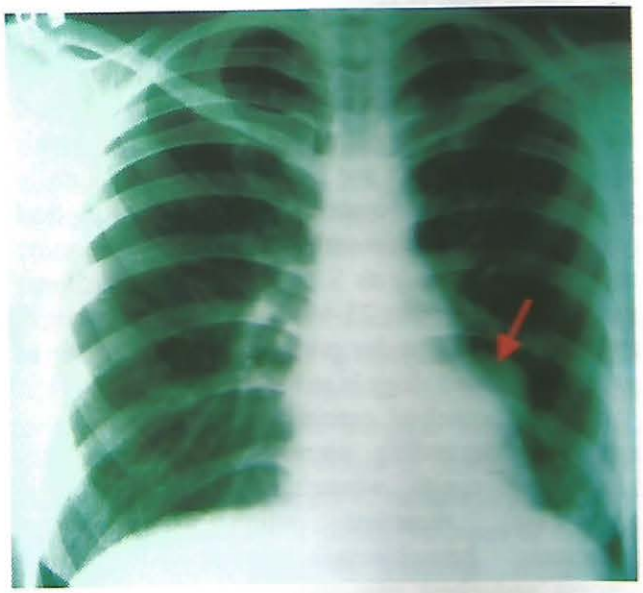

Fig. 3. Rounded well circumscribed opacity in the left lower zone (PA view).

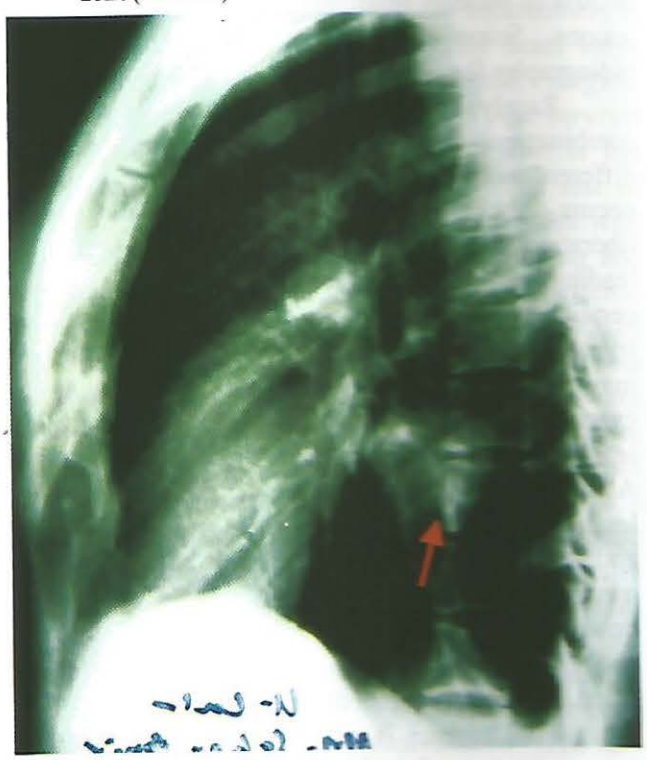

Fig. 4. Rounded well circumscribed opacity in the left lower zone (Lateral view).

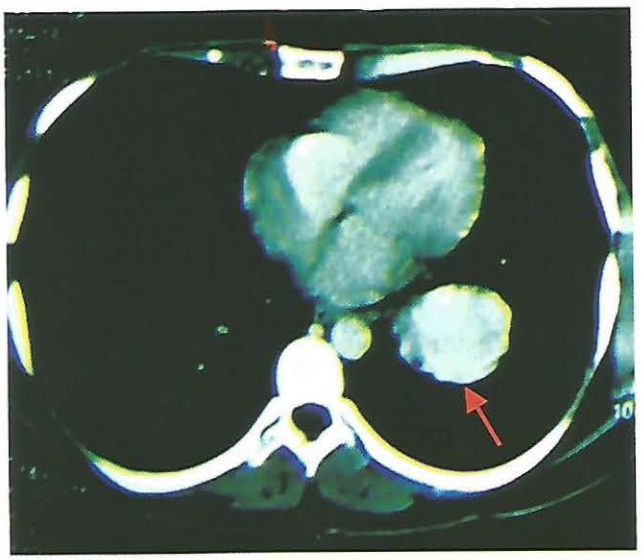

Fig. 5. Soft tissue density mass in the apical segment of left lower lobe.

Over the next few weeks her ESR rose up to 70 mm in 1st hour and in view of the fact of her symptoms of low grade fever, weight loss and results of pleural aspirate, she was started on anti tuberculosis therapy and felt well over the next 6-8 weeks, her temperature settled and her ESR came down to 20 mm in 1st hour. She took anti tuberculosis drugs for 9 months but with ups and downs in her physical condition. After completing the therapy, she again started having fever. A blood count at that time showed an Hb of 9.8 g/dl and an ESR of 131mm in 1st hour with normal differential counts.

A CT scan of chest was repeated which showed a 7.1 × 5.3 cm well marginated soft tissue mass having heterogonous enhancement in the posterior basal segment of left lower lobe with intralobular pulmonary sequestration. She was advised bronchoscopy which showed a polypoid fleshy, bluish tumour obstructing left lower basal segmental bronchus, probably a carcinoid tumour. Biopsies were taken and she was referred to thoracic surgeon who performed left lower lobectomy and lymphadenectomy. Specimens were sent for histopathology which showed a typical carcinoid tumour. Histopathology of serial lymph nodes which were dissected did not show any evidence of tumour. Her urinary 5-HIAA was normal too.

She made an uneventful recovery and was

discharged home. Her Hb was 13 g/dl and ESR was 35 mm in 1st hour and she had no symptoms what so ever. Her urinary 5-HIAA remained normal.

DISCUSSION

Carcinoid tumours were first described over 100 years ago by Lubarsch but Oberndorfor used the term "karzinoide" in 1907.[1] Carcinoid tumours have been reported to be present in wide range of organs but most commonly are found in the lungs, bronchi stomach, ileum, appendix and rectum.

These tumours are most common neuro-endocrine tumours with an incidence of 1.5 per 100,000 population.[2,3] However, in a Swedish study its frequency was calculated on the basis of both surgical and autopsy specimens to be 8.4 cases per 100,000 people.[4] The carcinoid tumours are thought to arise from neuro-endocrine cells which stain with silver stains. A number of hormones and biogenic amines are produced by these tumours which exert their effects and manifest in different symptoms of this tumour – called carcinoid syndrome. Serotonin is the main mediator and results in excretion of 5-hydroxy indole acetic acid (5-HIAA) in the urine, which is a very specific and sensitive marker of carcinoid tumours. Others include histamine, dopamine, substance-P, kallikerin, bradykinin, tachykinin, neurotensin, neuropeptide-K and prostaglandins.

These tumours are classified according to their origin from deficient embryonic division of the gut.[5] Foregut carcinoids originate in the lungs, bronchi or stomach. The mid-gut carcinoid tumours originate from small intestines, appendix and proximal large bowel. The hind-gut carcinoid tumours arise from distal colon and rectum. However, histologically, they are classified in typical and atypical carcinoids. The former are well differentiated and later are undifferentiated.[6] Bronchial carcinoid tumours are uncommon, low grade, slow growing malignant neoplasms, originally called bronchial adenomas, originating from neuro-secretory cells of bronchial mucosa. These tumours account for 2.5% of all pulmonary neoplasms and for 12-15% of carcinoid tumours overall.[7] These tumours are potential to synthesize and secrete peptide hormones and neuroamines particularly adreno-corticotrophic hormone (ACTH), leading to Cushing's syndrome,[8] and growth hormone releasing factor causing acromegaly.[9] Two different types of bronchial carcinoids have been identified.[10] The first, commonest type is typical which is low grade and with a 10 year survival rate approaching up to 90%.[11] They are well defined and smaller than 2.5 cm and located centrally. They are capable of local invasion but rarely metastasize. Atypical carcinoids are more aggressive and are more than 2.5 cm in diameter and are located peripherally. Regional lymph nodes involvement and metastases are more common in as many as 50% of patients and 5 year survival rate is from 25-69%.[12] They can occur at any age without gender preferences and the role of smoking in its etiology is still controversial.

The bronchial carcinoid may lead to many symptoms depending upon the location of the tumour e.g. cough, wheezing, haemoptysis (as in our case), recurrent pulmonary infections, atelectasis, bronchiectasis, pneumonitis, lung abscess and chest pain. Sometimes the patient is asymptomatic. Haemoptysis is common and occurs in 50% of patients reflecting vascular nature of these lesions. Some are found by chance on chest radiography for other reasons.[13]

Rarely, these tumours present with a combination of symptoms due to presence of different amines – the carcinoid syndrome which occurs only in 5% of the patients.[14] This is due to liberation of serotonin in the peripheral circulation leading to uncomfortable flushing precipitated by certain foods, especially alcohol, hot water or tryptophane rich foods. Striking skin colour changes may occur ranging from pallor or erythema to cyanosis. Recurrent diarrhoea with abdominal pain leading to mal-absorption is another striking feature. About 50% of patients develop right sided cardiac lesions in the form of plaques, mitral regurgitation and pulmonary stenosis especially, if there are metastases in the liver as serotonin is not broken down. This causes many side effect mentioned above. Few bronchial carcinoids may lead to left sided cardiac involvement but only up to 10%.

The tumour is diagnosed indirectly by 24 hour excretion of 5-HIAA in urine which is 75% sensitive and 100% specific.[15] Normal excretion is

<10mg/day (10-42 µmol/day). Other biochemical markers include chromogranin-A levels[16] and blood serotonin concentration.[16,17] Epinephrine and pentagastrin provocation tests are used to produce flushing and evaluating patients who describe flushing but have normal or only marginally elevated biochemical markers.[18,19]

The tumour localization is done after biochemical diagnosis of carcinoid syndrome is confirmed. Abdominal CT scanning with contrast,[20] indium-111 octreotide imaging,[21] MRI scans, barium series, endoscopic studies and simple chest X-ray are the techniques currently utilized to localize the tumour.

Once the tumour and its metastases are localized, the carcinoid symptoms are controlled. More than 90% of patients with carcinoid syndrome have metastatic disease. Surgical removal is the treatment of choice and extent of resection depends on the size, site and origin of tumour. The outcome is good if the tumour is <2 cm. In cases of tumours with metastases, surgical outcome is not so promising.[22] Other treatment modalities include radiofrequency ablation, cryoablation and orthoptic linear transplantation. Cardiac valve replacement is advised in patients with symptomatic heart valve involvement.[23] For bronchial carcinoid, surgical resection of tumour is preferred and 5 year survival is 89-92% if tumour is typical and if it is not associated with carcinoid syndrome.[24] The rest of symptoms of carcinoid syndrome can be dealt with octreotide and its analogues. Both short acting and long acting preparation are available.[25] Interferon alpha also induces tumour stabilization is 20-40% of patients and causes its regression as well.[26] The role of chemotherapy is limited. Various agents have been used including 5-fluorouracil, streptozocin, cyclophosphamide and doxorubicin in various combinations but with variable results.[27] Embolization or chemoembolization of hepatic artery is promising modality and response occurs in up to 75% of patients which may last from 1-18 months.[27-28]

Radiation has no role and is not advised as such but occasionally done as a palliation for bone and central nervous system involvement.[29] The role of liver transplantation in the treatment of metastatic carcinoid is still unclear. A small French study showed 5-year survival of 69% patients which were highly selective.[30]

A few words about carcinoid crisis are worth mentioning here which occurs spontaneously or after too much manipulation of the tumour, after chemotherapy and hepatic artery embilizsation particularly in patients with extensive disease.[31] It is characterized by profound flushing, variable blood pressure, bronchoconstriction, arrhythmias, confusion, dehydration and coma. The treatment includes IV fluids and IV octreotide. If not managed properly it can prove fatal.[32]

The prognosis of carcinoid tumor overall is good as they are slow growing tumours and it is in years rather than in months even if there are metastases.[33] The prognosis usually depends on the size of tumour, its site, degree of local invasion, histo-pathological features i.e. typical or atypical and associated structural and functional abnormalities. The prognosis also depends on cardiac valve involvement and level of Ki67 which is a marker of tumour proliferation.[34,35]

These two patients of carcinoid tumour, both females presented with uncommon features. One, with sudden haemoptysis without any prior illness and the other without haemoptysis but with a long protracted illness. Both fortunately had no local or remote complications and both responded very well to surgery i.e. they were cured.

These case reports gives us a lesson that every disease does not present with typical features but some features make these diseases rather "unlikely" therefore delaying the diagnosis of some potentially curable diseases like carcinoid tumours.

In conclusion, the carcinoid tumors are uncommon and carcinoid syndrome is even less common. Early localization of these tumours and resection if possible may cure the patient.

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