

Pulmonary Tumourlets: Case Report and Review of Literature

Swati Agarwal¹, Kumud Gupta¹, Shalini Mullick¹, Aastha Chauhan¹ and R.K. Dewan²

Departments of Pathology¹ and Thoracic Surgery², National Institute of TB and Respiratory Diseases, New Delhi, India

Abstract

We report a case of tumourlets of the lung associated with carcinoid and neuroendocrine cell hyperplasia, found incidentally in a 30-year-old woman, who underwent bullectomy for pneumothorax. These lesions are histologically similar to carcinoid, but differ in molecular pathogenesis about which little is known. Their nature and significance is debated. Here, we point out the importance of histological, clinical, and diagnostic aspects and follow-up to have evidence of eventual malignant evolution. [Indian J Chest Dis Allied Sci 2015;57:235-238]

Key words: Pulmonary tumourlets, Carcinoid, Neuroendocrine hyperplasia, Bullectomy.

Introduction

Pulmonary tumourlets are incidental finding at histopathological examination of lung parenchyma seen particularly in lung scarred by bronchiectasis or other chronic inflammatory process.^{1,2} These are defined as hyperplasia of neuroendocrine cells (NE cells) that are 5mm or less in size.² These share histologic, ultrastructural and immunohistochemical features with carcinoid, but little is known about their exact molecular pathogenesis.^{2,3} As an isolated lesion these are fairly common, but with NE cell hyperplasia these are uncommon.⁴ Recently 11q13.1 region imbalance has been demonstrated in the pathogenesis of pulmonary tumourlets/carcinoids.³ These might represent early or *in situ* small lung cancer.⁵ In this report, we present a rare case of tumourlet associated with carcinoid and neuroendocrine hyperplasia in a patient of pneumothorax who underwent bullectomy.

Case Report

A 30-year-old woman came to our hospital with complaints of left-sided chest pain and reduced appetite for one year. It was not associated with cough, fever, haemoptysis or a past history of tuberculosis. Routine haematological and biochemical investigations and pulmonary function tests were within normal limits. Contrast-enhanced computed tomography (CECT) of chest showed left-sided pleural thickening with encysted pneumothorax (20cm×1.4cm) with plate atelectasis in the left middle zone (Figure 1). There was no evidence of thickening or nodularity in the interstitium. Thoracotomy with left bullectomy was performed. On gross examination, the excised pieces

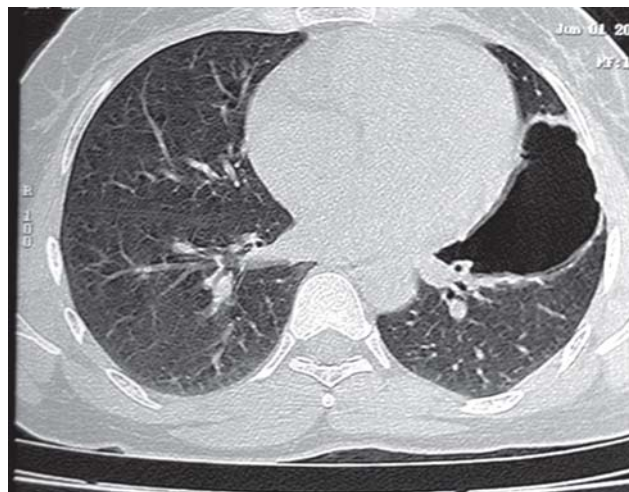


Figure 1. Contrast-enhanced computed tomography of chest showing left-sided pleural thickening with encysted pneumothorax (20cm×1.4cm) with plate atelectasis in the left middle zone.

measured 6cm×2.5cm×1.2cm and 4.5cm×3.5cm×1.2cm (Figure 2). These were greyish black to brown in colour and showed a white circumscribed area measuring 0.8cm in diameter. The microscopic examination revealed pleural tissue covered lung parenchyma lined by respiratory epithelium comprising of multiple clusters/nodular aggregates varying from 2mm to 6mm (Figure 3A). These tumour cells were round to oval with scanty cytoplasm, bland nuclei and speckled chromatin. These cells were positive for CD56, chromogranin (Figure 3 B&C), and synaptophysin and were negative for CD45 and high molecular weight cytokeratin (HMWCK). One of the foci revealed a larger aggregate of similar tumour cells measuring 0.6cm in diameter

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Correspondence and reprint requests: Dr Swati Agarwal, Department of Pathology, National Institute of TB and Respiratory Diseases, Sri Aurobindo Marg, New Delhi-110 030, India; E-mail drswatiagr@yahoo.com



Figure 2. Photograph showing the excised pieces measuring 6cm×2.5cm×1.2cm and 4.5cm×3.5cm×1.2cm. These are greyish black to brown in colour and showed a white circumscribed area measuring 0.8cm in diameter.

(Figure 3D). Cystically dilated bronchi and bronchioles, many of which showed mild chronic inflammation and focal fibrosis. A few of them also

showed scattered single, small clusters and nodules of chromogranin positive cells in the mucosa (Figure 3C). A final diagnosis of multiple tumourlets with neuroendocrine hyperplasia and small carcinoid was made.

Discussion

Pulmonary carcinoid tumourlets are rare, usually discovered incidentally.^{1,6} These are multiple localised regions of NE cell proliferation, measuring <5mm in size located along the airways and found usually in association with pulmonary fibrosis and bronchiectasis.⁷ However, these can occur in the normal lung also.¹ Details of previous major reports of pulmonary tumourlets are presented in the table.^{1,2,5-8,11}

Tumourlets develop from hyperplastic NE cells (Kulchitsky's cell) in the bronchial and bronchiolar mucosa. Some researchers believe that their hyperplasia is a secondary tissue reaction to chronic lung inflammation and fibrosis, while other studies had suggested that this has a primary rather than a secondary role in pulmonary fibrosis.^{1,2,7} It was found that neuropeptides elaborated by hyperplastic NE cells mediate a peribronchiolar fibrosis that ultimately leads to more generalised, symptomatic fibrotic lung disease.^{1,7} Recently, it was found that production of profibrotic growth factor like vascular endothelial growth

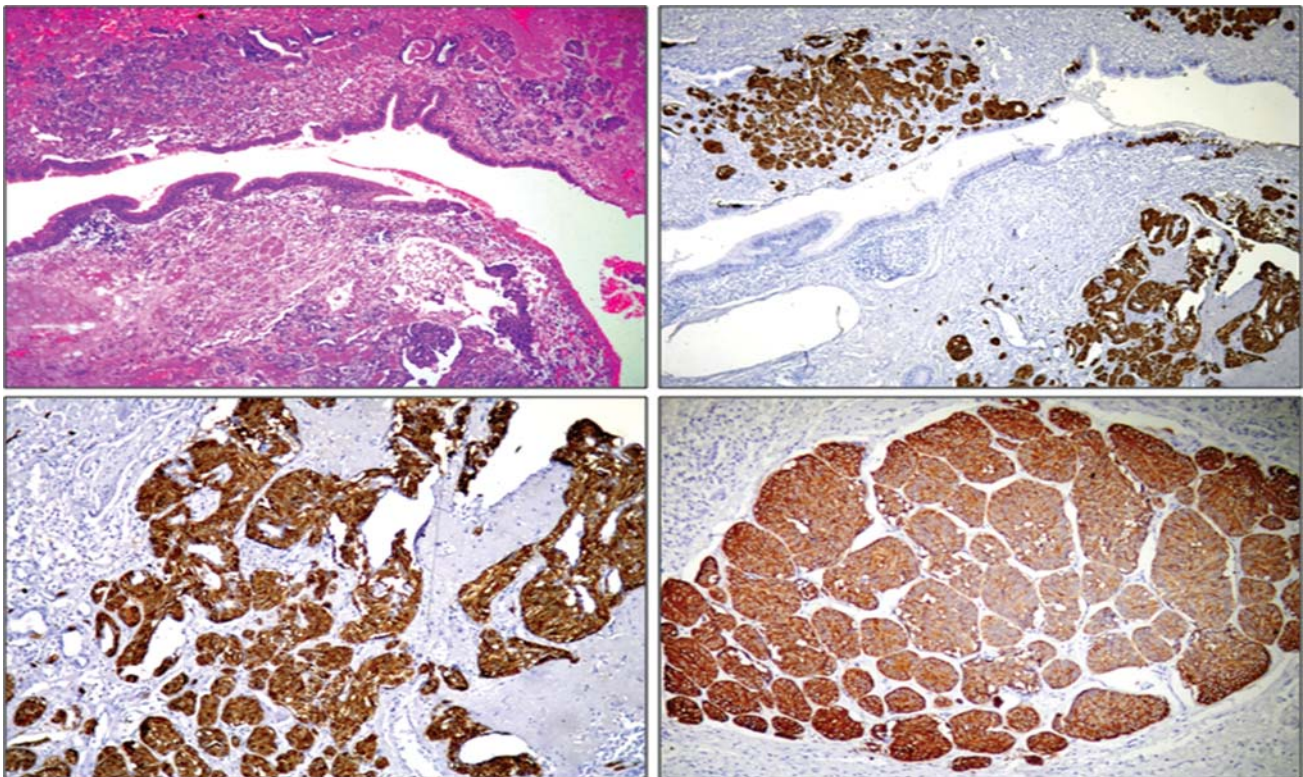


Figure 3: Photomicrograph showing (A) pleural tissue covered lung parenchyma lined by respiratory epithelium. Subepithelial area multiple clusters/nodular aggregates of round to oval cell with granular chromatin varying from 2mm to 6mm (Haematoxylin and Eosin; ×100); (B&C) multiple tumourlets and bronchi showing neuroendocrine hyperplasia (Chromogranin A; ×100); and (D) a carcinoid measuring 0.6cm in diameter (Chromogranin A; ×10).

Table. Major reports of pulmonary tumourlets in the literature

Authors	Case Reports/ Series	Age (years)	Sex	Associated Lesions	Salient Features
Sheerin <i>et al</i> ¹		42	F	Obstructive bronchiolitis Severe air flow limitation	Nodules were found adjacent to pulmonary arterioles and appeared to have obliterated the accompanying bronchioles by inducing fibroblast proliferation and connective tissue deposition
He <i>et al</i> ²		71	F	Invasive lung adenocarcinoma	Strong vascular endothelial growth factor and TGF- β 1 expression seen in the tumourlet showing a possible relationship between tumourlet and pulmonary fibrosis
Klinke <i>et al</i> ³	(n=7)	19-66 (mean=43.5)	M=3 F=4	Bronchiectasis	Described tumourlet as a model for genesis of neuroendocrine lung tumours
Churg and Warnock ⁴	(n=20)	34-91 (mean=68.5)	M=7 F=13	Extensive scarring obliterating normal parenchyma (7) Bronchiectasis (5) Old granuloma (1) Hamartoma (1) Emphysema and chronic bronchitis common to many cases (8) Malignancy (5)	Earliest series to suggest that tumourlets are precursor of carcinoid
Aubry <i>et al</i> ⁵	(n=28)	45-84 (mean=65)	M=2 F=26	Obstrctive lung diseases (11) Pulmonary metastasis (10) Malignancy (7)	Largest series till date Excellent prognosis with minimal morbidity Multiple lesion need to be differentiated from metastatic disease
D'Agati and Perzin ¹¹		38	M	Bronchiectasis, chronic bronchitis and pulmonary fibrosis	

Definition of Abbreviations: M=Male; F=Female; TGF=Tumour growth factor

factor (VEGF) and tumour growth factor (TGF)- β from tumourlets can lead to pulmonary fibrosis.²

Pulmonary tumourlets are generally asymptomatic but there are only a few reported cases where these were symptomatic, commonly with cough and dyspnoea.^{1,8} Although carcinoid tumour has been described as one of the causes of spontaneous pneumothorax, whether tumourlets and NE cell hyperplasia can cause this is unclear.^{8,9}

The nature and significance of tumourlets have been greatly debated. These can occur either as an isolated lesion or less commonly together with diffuse NE cell proliferation.⁴ There are three settings described (chronic lung injury, diffuse idiopathic NE cell hyperplasia and carcinoid) where these can occur together.⁴ In all these settings, NE cell proliferation share morphological, ultrastructural and immunohistochemical properties. The whole spectrum of NE cell hyperplasia, multiple tumourlets and carcinoid, as seen in our case, demonstrate a possible

neoplastic character of pulmonary tumorlets and provide an in sight into histogenesis of neuroendocrine tumours of the lung.^{5,6}

The two processes seems to be likely related with carcinoid tumour evolving from precursor tumourlet lesions.^{3,10} However, the precise mechanism for any such progression is still unclear, but may involve critical genetic alterations causing progressive growth dysregulation. Recently, Finkelstein *et al*³ demonstrated 11q13.1 region imbalance in the pathogenesis of pulmonary tumourlets/carcinoid. This finding provides strong support for the concept of independent *de novo* NE cell proliferation and indicates the pre-neoplastic nature of tumourlets with a potential to develop into carcinoid and even small cell carcinoma.³ Also, occasional reports of metastasis to peribronchial lymphnode further support this.¹¹ Thus, its accurate radiological and pathological identification and correlation is necessary.

Radiologically, these can be detected as multiple

nodular opacities which mimic miliary pattern of metastasis on computed tomography.¹² However, due to their small size and a lack of awareness these often go unreported.¹²

The fact that these mimic metastasis, can cause symptoms and progress to carcinoid, makes the role of pathologist more significant to identify accurately and report when these are even incidental findings in small resections, like bullectomies, lobectomies or resections for other indications. Also, the possibility of diffuse NE cell proliferation in unresected specimen always needs to be considered by pathologist, radiologist and surgeon. As the therapeutic strategy of lung tumourlets is still controversial, a close subsequent follow-up seems to be the best method of choice as done in our case. However, due to their uncertain behaviour and resemblance to carcinoid some authors suggest resection when both tumourlets and carcinoid are seen together.¹³ As the current histogenesis of tumourlets is still unclear, it is important for both pathologist as well as radiologist to identify this distinct yet less commonly described entity, so that their precise biological behaviour as well as prognosis can be defined accurately.

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