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Case Report

Atypical Carcinoid Tumours of Lung - Analyzing the Diagnostic Challenges and its Substantial Impact on Prognosis: A Case Report with Review of Literature

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Abstract

Neuroendocrine tumours arise from NE cells, show a diverse behavior and most commonly originate in gastrointestinal tract and bronchopulmonary system. According to the latest 2015 classification of WHO, they are divided into well differentiated (typical carcinoids), intermediate-grade (atypical carcinoids) and poorly differentiated (large cell neuroendocrine carcinoma and small cell carcinoma).

Carcinoid tumours of lung (including typical and atypical) are distinct entity of lung however, the incidence is increasing but still the awareness among the clinicians and pathologists is quite low due to its rarity. Patients normally present with varied history and nonspecific symptoms. Computed tomography is the gold standard investigation and surgical resection is the best treatment. Histopathological examination along with immunohistochemistry is mandatory for categorization of the neuroendocrine tumours.

Pulmonary carcinoids are usually asymptomatic and non-functional, still it is important to identify and classify typical from atypical carcinoids as both of them have different treatment options and prognosis. Herein, we are presenting a case of atypical carcinoid of lung which presented with the chief complain of dry cough for 2 weeks along with review of literature.

Keywords: *Carcinoid; Neuroendocrine Tumour; Organoid; Necrosis; Mitosis*

Introduction

Neuroendocrine tumours of the lung comprise a heterogeneous group in which low grade typical carcinoid, intermediate grade atypical carcinoid and high grade tumours, namely small cell carcinoma and large cell neuroendocrine carcinoma, have been placed together. Atypical carcinoid is a moderately differentiated tumour, which usually presents in the third decade [1]. On histopathological evaluation, it demonstrates an organoid pattern with either mitosis (2 - 10 per 2 mm^2 of viable tumour) or focal necrosis. It is separated from typical carcinoid and small cell/large cell neuroendocrine carcinoma based on the architectural pattern, presence or absence of necrosis and mitotic activity [2].

Case Report

A 32 year old male presented with the chief complains of weight loss since 4 months along with dry cough for 2 weeks. The computed tomography (CT) scan of the chest revealed ill-defined soft tissue attenuation in the left superior hilar region, measuring 3.6 x 3.7 cm, with extension to right apical and main bronchus (Figure 1A and 1B). The lesion was described as possibly mitotic in nature on radiological study. The patient was planned for bronchoscopy. During the procedure, a fleshy glistening growth was identified from which multiple biopsies were taken.

The histopathological examination demonstrated a tumour with cells arranged in an organoid and trabecular pattern with fine vascular stroma in between (Figure 2A and 2B). The tumour cells display mild to moderate pleomorphism. They are polygonal in shape having round to oval nuclei with finely granular chromatin, inconspicuous nucleoli and moderate amount of eosinophilic cytoplasm (Figure 2C and 2D). Occasional oncocytic cells were also present. The stroma was highly vascularized with presence of thin walled blood vessels intervening between the tumour cells. There were no foci of necrosis seen. Based on the architectural pattern and morphology of the tumour cells, a provisional diagnosis of neuroendocrine tumour versus glomus tumour was considered and immunohistochemical examination was done. The tumour was strongly positive for Pan-CK (Figure 3A), diffusely positive for chromogranin (Figure 3B) while it was negative for SMA and CD34 (Figure 3D and 3E) The intervening thin walled vessels, which served as the internal control, were positive for CD34 and SMA. The Ki-67 index counted in areas of hotspots in the tumour was 4 - 5% (Figure 3C) Therefore, a final diagnosis of atypical carcinoid was made.

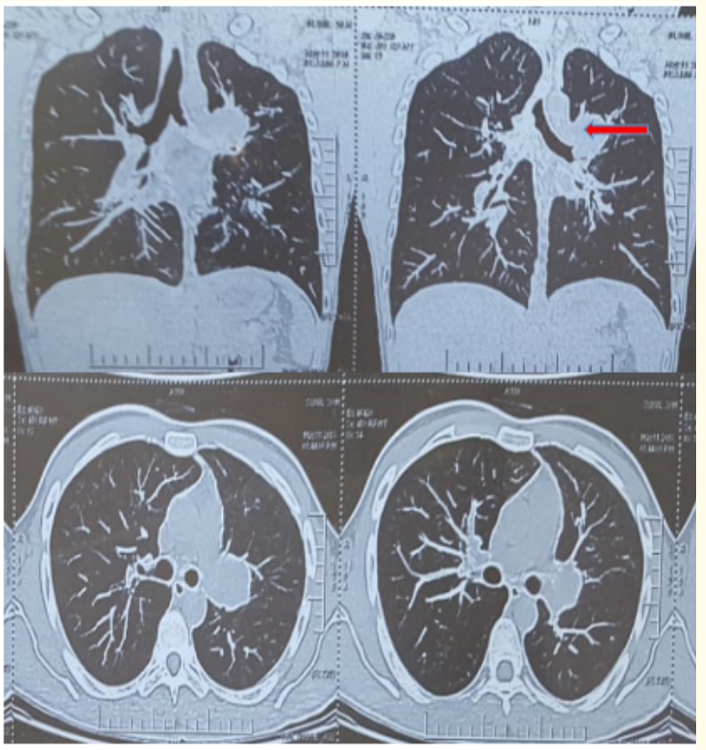

Figure 1A and 1B: *Computed tomography shows ill-defined soft tissue attenuation in the left superior hilar region 3.6 x 3.7 cm in size.*

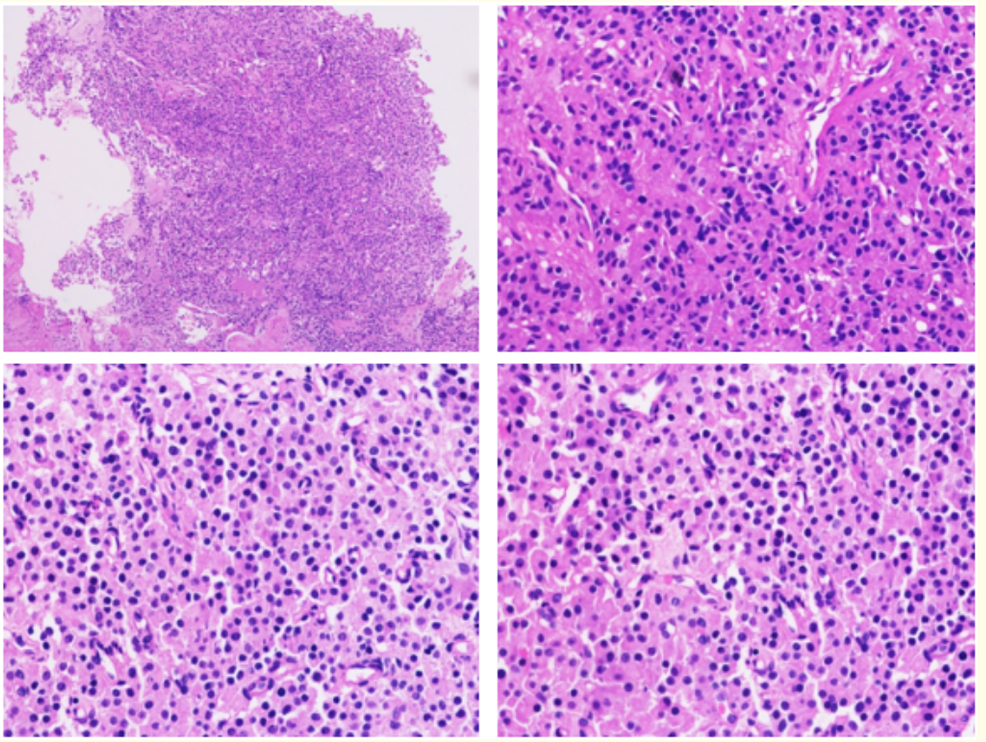

Figure 2: *Histomorphological findings in the present case. 2A: Low power view (100X) showing well organised tumour arranged in organoid pattern with highly vascularised stroma. 2B: High power view (400X) showing tumour cells arranged in an organoid and trabecular pattern with intervening thin walled blood vessels. 2C: Tumour cells display mild to moderate pleomorphism, are polygonal in shape having round to oval nuclei with finely granular chromatin, inconspicuous nucleoli and moderate amount of eosinophilic cytoplasm (400X). 2D: Occasional tumour cells show oncocytic changes (400X).*

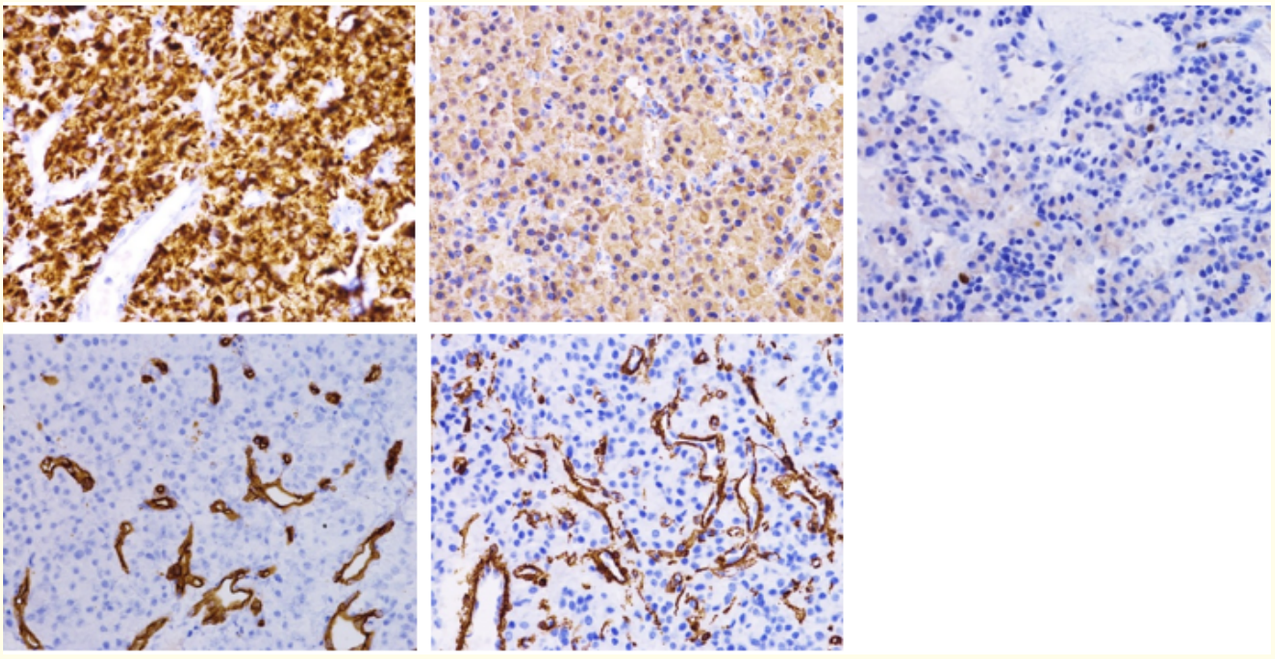

Figure 3: *IHC panel in the present case. Figure 3A: Pan-CK showing strong positivity (400X). Figure 3B: Chromogranin showing diffuse positivity (400X). Figure 3C: Ki-67 index of 4 - 5% (400X). Figure 3D: CD 34 showing positive staining only in the endothelium of blood vessels (400X). Figure 3E: SMA showing positive staining only in the endothelium of blood vessels (400X).*

The patient was taken up for surgery for resection of the lesion and is being kept on follow-up with no adverse event reported till date.

Discussion

Neuroendocrine tumours are a group of malignancies, which arise from the neuroendocrine cells in the body. They are most commonly observed in the small intestine, rectum and lungs. In the lungs, the neuroendocrine cells occur as single cells or as neuroepithelial bodies [3].

In the WHO 2004 classification of lung tumours, carcinoids including both typical as well as atypical, were placed in a separate group and considered as a different entity from the large cell neuroendocrine tumour and small cell lung carcinoma [4,5]. However again in the WHO 2015 classification of lung tumours, these four variants were reclassified under one single category named as neuroendocrine tumours. The recent classification categorizes the four variants based on architecture, morphologic features, necrosis and mitotic activity [2].

Again the method for mitotic count estimation has also undergone modulation from the 2004 to 2015 classification. Earlier, mitosis was counted per 10 high power fields. In the latest guidelines, mitosis is estimated per 2 mm2 of viable tumour tissue [2,4].

Typical carcinoid is a low-grade well differentiated tumour with neuroendocrine morphology, less than 2 mitoses per 2 mm^2 of viable tumour and an absence of necrosis. Atypical carcinoid is an intermediate grade tumour, which shows 2 - 10 mitoses per 2 mm^2 of viable tumour or presence of focal necrosis along with neuroendocrine morphology. Small cell carcinoma and large cell neuroendocrine carcinoma constitute the higher end of the spectrum and show > 10 mitoses per 2 mm^2 of viable tumour along with areas of extensive necrosis [2]. The well differentiated tumours show an organoid pattern with festoons, ribbons and nests while the high grade tumours are arranged in solid sheets or trabecular pattern [6,7]. The clinicopathological features of the whole spectrum of neuroendocrine tumours had been enumerated and discussed in table 1.

Most of the neuroendocrine tumours of lung are asymptomatic, however the patient in our study was symptomatic and presented with dry cough and history of weight loss. The result was similar to the cases studied by Thomas., *et al*, Amirthan., *et al,* Descovich and Pathak., *et al*. Moreover their patients also presented with dyspnoea and hemoptysis. Majority of the low to intermediate grade tumours

	TC	AC	LCNEC	SCLC
Mean age	40 - 50	50 - 60	68	50 - 70
M:F	1:1	1:1	4:1	1:1
% of total number of lung cancer	1-2%	0.1-0.2%	1.6-3%	15-20%
Clinical presentation	Cough and hemoptysis	Cough and hemoptysis	Mostly smokers Nonspecific symptoms	Hoarseness, vocal cord paralysis
Most common location	Central	Peripheral	Peripheral	Central
Mitoses per 2 mm^2	< 2	2-10	> 10	> 10
Necrosis	Absent	Focal	Extensive	Extensive
IHC	Chromogranin, synaptophysin, CD57 and CD56 - Strong positivity Cytokeratin (80%) KI67 Moderate positivity TTF-1 Moderate positivity	Chromogranin, synaptophysin, CD57 and CD56 - Patchy positivity Cytokeratin (80%) KI67 Strong positivity TTF-1 Strong positivity	CD 56, chromogranin, synaptophysin, TTF-1 (50 %)	CD56, chromogranin, synaptophysin, TTF-1 (90 %)

Table 1: *Clinco-pathological discussion of neuroendocrine tumours of lung.*

have a central location in the lobar bronchi [8]. Thomas., *et al*. conducted a retrospective study on 25 cases of pulmonary carcinoid and concluded that the most common location for these tumours was the right main bronchus [9]. Ichiki., *et al*. studied 11 cases of pulmonary carcinoids and found atypical carcinoids to be peripheral nodules [10]. These centrally located tumours generally present with cough and dyspnea while the peripherally located tumours are asymptomatic [11]. In our study, the tumour was placed peripherally. Usually neuroendocrine tumours of the lungs are non-functional; only less than 2% of tumours present with carcinoid syndrome due to secretion of serotonin. However, neuroendocrine tumours of the gastrointestinal tract present with carcinoid syndrome in about 10% cases [12,13].

The well differentiated tumours present at a younger age group and are not associated with smoking. In contrast, the poorly differentiated tumours are seen in the 6th to 7th decade and show a strong association with smoking [1]. Thomas., *et al*. concluded a female to male ratio of 0.8 to 1 for carcinoid tumours [9].

Carcinoid tumours of lung are rare tumours with a prevalence of 1% out of all the lung malignancies [10].

In table 2 and 3, we compared the clinico-pathological ad immunohistochemical parameters of our case with other studies.

Sn no	Name of the authors	No of cases	M:F	Most common clinical presentation	Location (Central/ peripheral)	Microscopy (Typical/ Atypical)
1.	Thomas., *et al*. (2008)	25	1:0.8	Hemoptysis and cough	23 (97%)/2 (3%)	22 (88%)/03 (12%)
2.	Ichiki., *et al*. (2012)	11	1.2:1	Hemoptysis and cough	4 (36%)/7 (63.6)	6 (55%)/5 (45%)
3.	Fing., *et al*. (2000)	142	1:1.6	Obstructive pneumonitis, atelectasis, pleuritic pain and dyspnea	68%/32%	128 (90.1%)/14 (9.8%)
4.	Amirthan., *et al*. (2017)	10	1.5:1	Cough, and hemoptysis	3 (30%)/7 (70%)	5 (50%)/5 (50%)
5.	Descovich (2000)	35	1:1.6	Cough and hemoptysis	29 (82.8%)/6 (17.2%)	30 (85.7%)/5 (14.3%)
6.	Pathak., *et al*. (2014)	01	Male	Cough, expectoration and hemoptysis	Peripheral	Typical carcinoid
7.	Our case	01	Male	Dry cough with loss of weight	Peripheral	Atypical carcinoid

Table 2: *Comparison of clinicopathological parameters of our case with other studies.*

The association with diffuse idiopathic neuroendocrine cell hyperplasia is seen in the low to intermediate grade tumours, while the high grade lesions show no such association [14].

Sn no	Name of authors	Chromogranin	Pan-Ck	Ki67 index
1.	Thomas., *et al*. (2008)	10/16 (61.8%)	5/15 (33.3%)	-
2.	Amirthan., *et al*. (2017)	10/10 (100%)	-	-
3.	Pathak., *et al*.(2014)	+ve	-	-
4.	Our case	+ve	+ve	4 - 5%

Table 3: *Comparison of immunohistochemical parameters of our case with other studies.*

The current WHO guidelines recommend the usage of immunohistochemistry to confirm the diagnosis by using the following pan neuroendocrine markers, namely synaptophysin, chromogranin A and CD 56. In high grade tumours, there is decreased positivity of chromogranin A; hence it should be assessed at higher magnification (40x) to avoid missing a faint positivity and to prevent misclassification [2]. Synaptophysin positivity is retained in the poorly differentiated lesions. Human achaete-scute homolog 1 (Hash1) is a new marker which is seen in high grade tumours, though it is lost by the lower end of the spectrum [15]. Ki-67 immunohistochemistry, which is used to classify these tumours, is assessed in the hotspots with highest staining [2].

The molecular profile of the atypical and typical carcinoid includes mutations involving ARID1A, SMARC1, while RB1 and TP53 are rare. The high grade tumours show a higher somatic mutation rate than the lower end of the spectrum with TP53, RB1 CREBBP and MLL mutations [16-18].

The NCCN guidelines for workup of neuroendocrine tumours includes histopathological identification and grading along with a CT scan, bronchoscopy, somatostatin scintigraphy and biochemical evaluation, if indicated [19].

The treatment guidelines are based on the extent of the disease. For localized typical and atypical carcinoids, surgical resection is the treatment of choice with a 5-year survival of 90% and 70%, respectively. NCCN guidelines does not recommend use of adjuvant therapy in localized carcinoid tumours, while it is advocated in the poorly differentiated lesions and in advanced typical as well as atypical carcinoid tumours. In cases with symptoms of carcinoid syndrome, somatostatin analogs like octreotide and lanreotide are advocated [19-21].

Conclusion

The differentiation of atypical carcinoid from other high grade neuroendocrine carcinomas is of utmost importance as the latter have a poorer prognosis and requires adjuvant therapy. It is also important to differentiate it from typical carcinoid as atypical carcinoid shows an aggressive behavior, higher frequency of lymph node and distant metastasis as well as lower 5-year survival rate.

It is also mandatory for the histopathological sections to be thin to identify the salt and pepper chromatin of the neuroendocrine tumours hence avoiding misdiagnosis.

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