Atypical carcinoid of the lung: A case report

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ABSTRACT

Hanggoro Tri Rinonce, Toddy Guntersah, Soeripto, J Bras - *Atypical carcinoid of the lung: A case report*

A 30-year old woman came to Dr Sardjito Hospital with chief complain of dyspneu that she had since 1 month before her visit. Clinical examination revealed a dull percussion below. The second intercostal of the left chest. The chest X ray revealed massive pleural effusion in the left chest, could not exclude a mass in left lung. Thoracoscopic biopsy of the left lung mass was done. Macroscopic examination of lung tissue sample revealed fragmented tissue, with volume of 0,25 cc, black colour, and rubbery consistency. The diagnosis of atypical carcinoid with small cell carcinoma as a differential diagnosis was determined based on morphological pattern. Immunohistochemical staining examination showed expression of cytokeratin, CAM5.2, and synaptophysin, but showed negative expression of chromogranin, CD56, and TTF-1. A diagnosis of an atypical carcinoid was confirmed based on the immunohistochemical examination.
A very rare case of atypical carcinoid of the lung in a non-smoker 30-year old woman with morphological diagnostic problem solved by immunohistochemical staining was reported.

Key words: atypical carcinoid of the lung - small cell carcinoma - cytokeratin - CAM5.2 - chromogranin - synaptophysin - CD56 – TTF-1

ABSTRAK

Hanggoro Tri Rinonce, Toddy Guntersah, Soeripto, J Bras - *Karsinoid atipikal pada paru: Laporan kasus*

Seorang wanita berusia 30 tahun datang ke RS. Dr. Sardjito dengan keluhan utama sesak nafas yang sudah diderita sejak 1 bulan sebelum datang ke RS. Pemeriksaan fisik menunjukkan suara perkusi yang pekak dari spatium interkostal kedua ke bawah. Pemeriksaan sinar X dada menunjukkan adanya efusi pleura masif pada dada kiri, kemungkinan adanya massa paru kiri belum dapat disingkirkan. Dilakukan biopsi thorakoskopik. Pemeriksaan makroskopik jaringan paru menunjukkan jaringan pecah belah dengan volume 0,25 cc, berwarna hitam, dan berkonsistensi kenyal. Diagnosis karsinoid atipikal dengan karsinoma sel kecil sebagai diagnosis banding ditetapkan berdasarkan gambaran morfologik. Pemeriksaan immunohistokimia menunjukkan ekspresi sitokeratin, CAM5.2, dan sinaptofisin, tetapi menunjukkan ekspresi negatif kromoganin, CD56, dan TTF-1. Diagnosis karsinoid atipikal dikonfirmasi dengan pengecatan immunohistokimia.
Suatu kasus yang sangat jarang, yaitu karsinoid atipikal paru pada wanita, bukan perokok, dengan permasalahan diagnosis secara morfologi yang dapat dipecahkan dengan pengecatan immunohistokimia dilaporkan.

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INTRODUCTION

Atypical carcinoid of the lung is a neuroendocrine neoplasm with cellular and clinical features intermediate between those of typical carcinoid and small cell undifferentiated carcinoma of the lung.[1] Atypical carcinoids make up about 11% of bronchopulmonary carcinoid tumours.[2] The peak age incidence of 56 years (range 19-75 years) is intermediate between that of typical carcinoid tumour 50 years (range 19-75 years) and small cell carcinoma 62 years (range 30-79 years).[3] Unlike typical carcinoids, atypical carcinoids are associated with a history of cigarette smoking (83%–94% of cases) and occur more often in men (2:1).[4] These neoplasms exhibit a wide range of histologic appearances and are misdiagnosed in up to 50% of cases.[1] Definitive diagnosis of atypical carcinoids is often difficult to determine based on morphological examination on HE staining only. Immunohistochemical staining with cytokeratin, CAM 5.2, chromogranin, synaptophysin, CD56, and TTF-1 antibodies are very helpful to determine definitive diagnosis.

In this article, a very rare case of atypical carcinoid of the lung in a non-smoker 30-year old woman with morphological diagnostic problem, solved by immunohistochemical staining, was reported.

CASE

A 30-year old woman came to Dr Sardjito Hospital in 2007 with chief complaint of dyspneu that she had since 1 month before her visit, accompanied by coughing with thick yellow sputum, sweating, malaise, and decreasing body weight, 6 kg in the last three months. Five days before her visiting, dyspneu got worst, accompanied by fever, coughing with thick yellow sputum, sometimes with bloody sputum.

Clinical examination revealed a dull percussion below the second intercostal of the left chest. Complete blood count revealed increased white blood cell count. Electrolyte levels, liver function test, and kidney function test were within normal limit. The chest X ray revealed massive pleural effusion in the left chest, could not exclude a mass in left lung (FIGURE 1). Chest CT scanning also revealed massive pleural effusion in the left chest, could not exclude a mass in left lung. Chest USG examination revealed a solid superior lobe mass with fibrosis and few localized pleural effusion, an inferior lobe mass without pleural effusion. Abdominal USG examination revealed no abnormality in the liver, spleen, pancreas, gall bladder, and both kidney. Scintigraphy study showed no metastatic lesions in the bone.
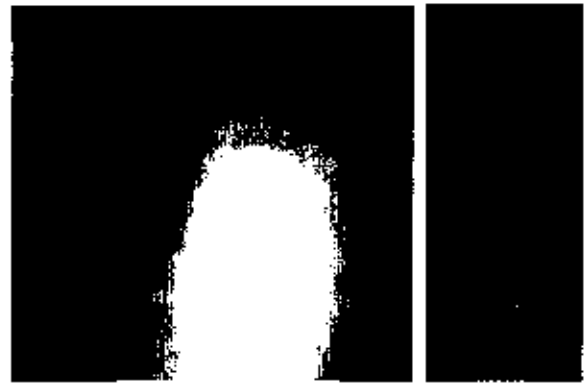

FIGURE 1.The chest X ray revealed massive pleural effusion in the left chest, could not exclude a mass in left lung

Cytological examination of pleural effusion showed many erythrocytes, without malignant cells. Cytological examination of specimen obtained from fine needle aspiration biopsy (FNAB) of a mass in left lung showed many lymphocytes and erythrocytes, without malignant cells. Thoracoscopic biopsy was done.

Macroscopic examination of lung tissue revealed fragmented tissue, with volume of 0.25 cc, brownish black color, and rubbery consistency.

Microscopic examination on HE staining showed cellular and vascular tumor admixed with inflammatory cells particularly lymphocytes (FIGURE 2). The tumor cells were rather small to intermediate in size, varied from polygonal to spindle shape. The amount of cytoplasm varied from rather less to moderate. The nuclei varied from round, oval, to irregular. Chromatin pattern was fine with in a substantial number of nuclei anucleolus. There was a lot of apoptotic activity. There was also punctate necrosis. Mitosis was not found for sure (FIGURE 3). The tumor cells often have relationship with vessel.
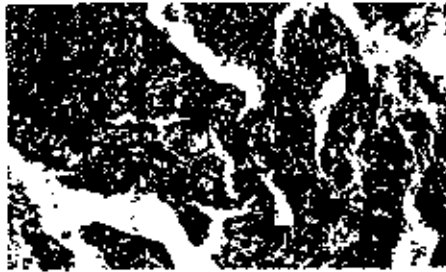
FIGURE 2.Microscopic feature of presented case showed cellular and vascular tumor admixed with inflammatory cells particularly lymphocytes. The black arrows indicate vessels within cellular tumor. The black arrow heads indicate punctate necrosis (HE staining, 100 X).
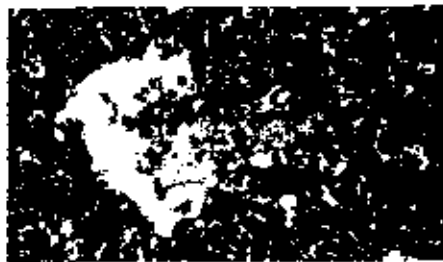

FIGURE 3.Microscopic feature of presented case showed rather small to intermediate tumor cells, varied from polygonal to spindle shape. There was punctate necrosis (black arrows). Mitosis was not found for sure (HE staining, 200 X)

The diagnosis of atypical carcinoid with small cell cacinoma as a differential diagnosis was established based on morphological pattern. A block of paraffin embedded tissue was sent to The Department of Pathology, Amsterdam Medical Center, The Netherlands, for confirmation of the diagnosis and immunohistochemical examination.

Immunohistochemical staining examination showed expression of cytokeratin, CAM5.2, and synaptophysin (FIGURE 4-6), but showed negative expression of chromogranin, CD56, and TTF-1. A diagnosis of an atypical carcinoid was confirmed based on immunohistochemical examination.
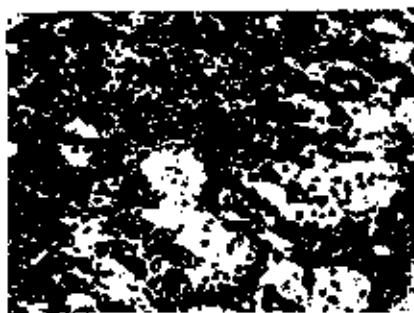

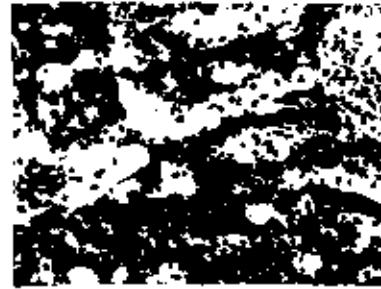FIGURE 4.Positive expression of cytokeratin showed cytoplasmic brown staining (200 X)

FIGURE 5.Positive expression of CAM5.2 showed cytoplasmic brown staining (200 X)

FIGURE 6.Positive expression of synaptophysin showed cytoplasmic brown staining (200 X)

DISCUSSION

Pulmonary carcinoids make up approximately 2 percent of primary lung tumours.[5,6] About 90% of the carcinoid tumours are referred to as typical carcinoid tumours, and are well differentiated with rare mitoses, pleomorphism, and necrosis.[7,8] The remaining 10% are designated atypical carcinoids, and are characterized histologically by increased mitotic activity, nuclear pleomorphism and disorganisation. The peak age incidence of atypical carcinoid tumour 56 years (range 19-75 years) is intermediate between that of typical carcinoid tumour 50 years (range 19-75 years) and small cell carcinoma 62 years (range 30-79 years).[3] Unlike typical carcinoids, atypical carcinoids are associated with a history of cigarette smoking (83%–94% of cases) and occur more often in men (2:1).[4] This presented article reported a case of atypical carcinoid of the lung in a non-smoker 30-year old woman. It was a very rare case.

Most patients with bronchopulmonary carcinoid tumours present with cough, haemoptysis or symptoms referable to the consequences of collapse or pneumonia distal to airway obstruction.[8,9] Sometimes there is wheezing, or even stridor, and

these features have occasionally been mistaken for asthma.[3] Very occasionally, bronchial carcinoids present with metastatic deposits or with a variety of paraneoplastic endocrine syndrome, including Cushing's syndrome, acromegaly, or the carcinoid syndrome.[10-14] This case presented with dyspneu, cough, haemoptysis, and fever related to pneumonia, no Cushing's syndrome, acromegaly, nor carcinoid syndrome. Chest X ray revealed massive pleural effusion in the left chest, could not exclude a mass in left lung

On microscopic examination, carcinoid tumours have a thin fibrous capsule that is often incomplete and also exhibit infiltrative activity.[3] Tumour in the presented case that did not show a thin fibrous capsule might be caused by a small biopsy. Several histological patterns of which may be present in combination, are recognized. Classic patterns consist of mosaic (insular) and trabecular pattern, whereas its variants consist of paraganglioid, adenopapillary, clear cell, oncocytic, melaninogenic, and spindle cell.[15] The pattern may vary within a tumour but to a limited degree histological pattern correlates with site. Central tumour tending to be trabecular and peripheral growths mosaic or spindle cell.[2] Peripheral tumor tends to show a spindle cell pattern in which groups of fusiform cells are separated by a rich network of blood vessels.[2,16,17] The presented case showed cellular tumour consisted of tumour cell with polygonal to spindle shape separated by a rich network of blood vessels considered carcinoid tumour with non-classic pattern, partly spindle type.

Atypical carcinoid tumours are recognized by increased mitotic activity and necrosis being seen in a tumour with the characteristic cellular make-up and trabecular or mosaic architecture of a carcinoid. The necrosis is usually punctate and confined to the centres of cell groups, but it may be more extensive and it may lead to focal dystrophic calcification. The atypical features may not be apparent in small biopsies as they are often focal.[3] Atypical tumours were originally defined as carcinoid that showed any one or a combination of features that included pleomorphism, prominent nucleoli, hyperchromasia, hypercellularity and disorganization, as well as the afore mentioned necrosis and increase mitotic activity[18], but some these additional features are of little prognostic importance. Necrosis and increased mitotic activity are the most

reliable pointers to atypical behaviour.[3] Distinction between typical carcinoid (TC) and atypical carcinoid (AT) is clinically important, because it is based on the number of mitoses, which is the best predictor of prognosis. Also, the presence of necrosis is important. TC is defined as < 2 mitoses per 2 mm^2 with no necrosis, whereas AC is defined as ≥ 2 mitoses but <10 mitoses per 2 mm^2, coagulative necrosis, or both.[19] WHO[20] has proposed criteria for the diagnosis of neuroendocrine tumours (Appendix 1).

Although in the presented case mitosis was not found for sure, diagnosis of TC was excluded because there were necrosis within the tumour. The diagnosis of large cell neuroendocrine carcinoma was also excluded because of the size and nuclear characteristics of the tumour cells did not fit for large cell neuroendocrine carcinoma. The differential diagnosis of small cell carcinoma was also considered. Small cell carcinomas consist of closely packed small or medium-size round or elongated cells, arranged in nests or strands or scattered singly within a scanty stroma.[21,22] The edge of the tumour is ill-defined and lacks a capsule. Extensive necrosis is commonly seen. Mitosis are numerous and the nuclei of adjacent tumor cells characteristically press on one another, a feature termed nuclear moulding, which is especially prominent in cytological specimens.[23] Rosettes of radial arranged tumour cells may be formed and genuine lumina may also be present, sometimes containing a little mucin.[3] In a small biopsy such as in the presented case, distinguishing between atypical carcinoid and small cell carcinoma morphologically is often difficult. Immunohistochemical staining is needed in that case.

The intermediate filaments in the neuro-endocrine cells consist of cytokeratin. Most, but not all, carcinoids express low-molecular-weight keratins.[24] It is especially important to keep the fact that carcinoids can be negative for keratin in mind in the case of spindle cell carcinoids such as the presented case whose histological appearance can suggest a mesenchymal neoplasm to the unwary. Still, aside from vimentin, specific mesenchymal markers are negative and the chromogranin stain is strongly and diffusely positive.[25] The presented case showed expression of cytokeratin and CAM5.2 considered an epithelial origin.

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Immunohistochemical staining should be used to identify markers of neuroendocrine differentiation. Unfortunately, none of the antibodies currently available is totally specific,[26] the best probably being synaptophysin, chromogranin, and CD56.[27-32]. Synaptophysin is a calcium-binding membrane glycoprotein present in synaptic vesicles that is ubiquitously expressed in all neurons and in many endocrine cells. It is currently the most widely used marker for nerve terminals and considered as a valuable marker of neuroendocrine tumours. Synaptophysin immunoreactivity is found both in tumors of neuroectodermal origin and in epithelial neuroendocrine tumours. It has been not detected in non-neuroendocrine cells or their neoplasms, mesenchymal tumors, lymphomas, or melanomas.[25]

Chromogranins are secretory acidic glycoproteins that are found primarily in dense-core neurosecretory granules of neuroendocrine cells. Chromogranins have been used as immunohistochemical markers for normal and neoplastic neuroendocrine cells. Chromogranins are demonstrated in several organs of the diffuse neuroendocrine system, including anterior pituitary, thyroid parafollicular cells, parathyroid chief cells, Kulchitsky cells in the lung, pancreatic islet cells, and intestinal endocrine cells.[25]

CD56 antigen consists of glycoproteins of the neural cell adhesion molecule (NCAM). The antigen has an established history of use in the diagnosis of NK lymphomas, but it is also expressed in a very high percentage (94-100%) of small cell lung carcinomas.[33,34] Therefore, CD56 has been used by some pathologists in a diagnostic panel of antibodies for small cell lung carcinoma.

The presented case showed expression of synaptophysin, but showed negative expression of chromogranin and CD56. Expression of synaptophysin gave an impression that the tumour had neuroendocrine differentiation. Carcinoids express neuroendocrine markers more intensely and diffusely than other neuroendocrine tumours do.[24] That feature can be useful in the differential diagnosis with small cell and large cell neuroendocrine carcinomas, both of which show fewer positive cell and less intense staining. The presented case expressed synaptophysin intensely and diffusely supporting diagnosis of carcinoids

tumours rather than small cell and large cell neuroendocrine carcinomas. The diagnosis of small cell carcinoma also may be excluded by CD56 immunonegativity.

Atypical carcinoids show slightly less extensive and intensive staining for neuroendocrine markers than typical carcinoids do, but not at a level sufficient to be used in distinguishing the two tumours.[25] With the increasing malignancy there is a progressive loss of chromogranin positivity.[35] The presented case showed negative expression of chromogranin that made diagnosis of a typical carcinoid less likely.

Human thyroid transcription factor-1 (TTF-1) is a single polypeptide of 371 amino acids. It is expressed at the onset of lung and thyroid organogenesis and is essential for the normal development of these organs.[36,37] The exclusive expression of TTF-1 in thyroid follicular epithelial cells, pulmonary type II cells, and Clara cells makes it a useful diagnostic epitope to identify adenocarcinomas arising from or expressing differentiation toward these cell types.[25] TTF-1 is frequently present in small cell carcinoma of lung (80-95% of cases), but it is not a specific marker since it is present in non-small cell lung carcinomas (principally adenocarcinoma) as well as in small cell carcinomas from other sites.[39-42] The presented case showed negative of TTF-1 that made the diagnosis of a small cell carcinoma was less likely.

The diagnosis of an atypical carcinoid was determined based on morphological pattern and supported by the result of panel immunohistochemical staining to exclude the differential diagnosis. Determining the definitive diagnosis of neuroendocrine tumour of the lung is very important because each tumour's behaviour is different as listed in Appendix 2.

CONCLUSION

A very rare case of atypical carcinoid of the lung in a non-smoker 30-year old woman with morphological diagnostic problem which can be solved by immunohistochemical staining was reported. Determining the definitive diagnosis of neuroendocrine tumor of the lung is very important because each tumour's behavior is different. Immunohistochemical staining with cytokeratin,

CAM5.2, chromogranin, synaptophysin, CD56, and TTF-1 antibodies were proved useful for definitive diagnosis.

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Appendix 1

WHO Criteria for the Diagnosis of Neuroendocrine Tumors*

Tumor Type	Criteria
Typical carcinoid	Carcinoid morphology and < 2 mitoses/ 2 mm² (10 HPFs), lacking necrosis and ≥0.5 cm
Atypical carcinoid	Carcinoid morphology with 2–10 mitoses/ 2 mm² (10 HPFs) or necrosis (often punctate)
Large cell neuroendocrine carcinoma	Neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae);
	High mitotic rate: ≥10/ 2 mm² (10 HPFs), median of 70/ 2 mm² (10 HPFs);
	Necrosis (often large zones);
	Cytologic features of a NSCLC: large cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/ or frequent nucleoli; some tumors have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm; and
	Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/ or NE granules by electron microscopy
Small cell carcinoma	Small size (generally less than the diameter of three resting lymphocytes);
	Scant cytoplasm;
	Nuclei: finely granular nuclear chromatin, absent or faint nucleoli;
	High mitotic rate: ≥11 mitoses/ 2 mm² (10 HPFs), median of 80/ 2 mm² (10 HPFs); and
	Frequent necrosis often in large zones.

*HPF = high-power field; NSCLC = non-small cell carcinoma; N = neuroendocrine.

Appendix 2

A comparison of behavior among neuroendocrine tumor of lung[3]

Behavior	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell carcinoma
Local invasion	Present	Present	Present	Present
Lymphatic metastases	Occasional	Not Infrequent	Frequent	Usual
Distant metastases	Rare	45-70%	>50%	95-100%
5-year survival rate	95%	60%	27-35%	2%