Case Report

Intranuclear Pseudo-inclusions and Grooves in Fine Needle Aspiration Cytology of Pulmonary Carcinoid Tumor

Maral Mokhtari MD•[1], Perikala Vijayananda Kumar MD[1]

Abstract

Cytologic findings of pulmonary carcinoid have been well described. We report new cytological findings in a case of carcinoid tumor. The patient is a 36-year-old man presenting with hemoptysis of about six months in duration. Chest CT scans showed a well-defined round polypoid lesion measuring 1 × 1 cm within the right upper lobe of the bronchus with hyperinflation of the right upper lobe. Trans-bronchial fine needle aspiration and biopsy were done. Cytologic smears showed isolated and loose clusters of uniform round to spindle shape cells with round centrally located nuclei, fine granular (salt and pepper) chromatin and pale cytoplasm. Intranuclear pseudo-inclusions and grooves were seen in some tumor cells. No mitotic figures or necrosis were evident. A cytological diagnosis of carcinoid tumor was made and histopathologic examination and subsequent immunohistochemical study confirmed the diagnosis. Carcinoid tumor may be reliably diagnosed on fine needle aspiration cytology smears. Intranuclear pseudo-inclusions and grooves may be evident in tumor cells.

Keywords: Carcinoid tumor, fine needle aspiration, intra nuclear pseudo inclusion, intra nuclear groove, lung

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Introduction

Neuroendocrine tumors of the lung arise from Kulchitsky cells dispersed through bronchial mucosa. Based on the World Health Organization (WHO) classification, these tumors are categorized into four groups, including typical carcinoid (TC), atypical carcinoid, small cell lung carcinoma (SCLC), and large cell neuroendocrine carcinoma.[1–3]

TC comprises less than 5% of primary pulmonary tumors.[1,2] It affects mainly adults with no sex predilection.[1,3] Mostly, they present with a slowly growing and polypoid tumor within the major bronchus (central type). They may also occur at the peripheral area of the lung (peripheral carcinoid).[1]

The most common clinical presentation is hemoptysis (due to rich vascularity of the tumors and their location within the major bronchus), fever, cough, pulmonary infections caused by obstruction of bronchial tree, wheezing and chest pain.

Patients may rarely develop symptoms related to ectopic hormone production by the tumor.[1–4]

Fine needle aspiration (FNA) cytology, especially trans-bronchial FNA, has become a useful tool in diagnosing pulmonary tumors.[2] Cytological findings of carcinoid tumor have been well described.[4–7] Here, we report a case of carcinoid tumor with rare cytological findings.

Case Reports

The patient is a 36-year-old man who referred to Faghihi Hospital, affiliated with the Shiraz University of Medical Sciences with complaint of on-off hemoptysis of about six months in duration. He denied any constitutional symptoms like fever, sweating and weight loss, recurrent pneumonia, allergic disorders, bleeding diathesis and anticoagulant drug consumption. On physical examination, he had stable vital signs. Chest percussion revealed a hyperresonance area at the right upper lobe and end expiratory wheeze was heard on auscultation. Other examination findings were unremarkable. Frontal chest X-ray showed hyperinflation of the right upper lobe. Chest computed tomography (CT) scan revealed hyperinflation of the right upper lobe with accentuation during expiration. There was a polypoid round lesion arising from the right upper lobe of the bronchus measuring about 1×1 centimeter (cm). After contrast injection, the lesion was homogeneously enhanced. On bronchoscopic examination, there was a small polypoid nodule within the right upper lobe bronchus. Trans-bronchial FNA and subsequent biopsy were performed. The cytologic material was sprayed on glass slides and stained with Wright-Giemsa and Papanicolaou method.

Results

Cytological smears showed isolated and loose clusters of monomorphic round to spindle shape cells with centrally located nuclei and pale staining cytoplasm. The chromatin pattern was finely granular (salt and pepper) (Figure 1). There were also intra-nuclear pseudo-inclusions and grooves (Figures 2 and 3). No mitotic figures or necrosis were evident.

A cytological diagnosis of carcinoid tumor was made. Histopathological examination of the corresponding biopsy showed a hypervascular tumor with papillary configuration consisting of sheets of uniform cells with centrally located round nuclei and pale cytoplasm (Figure 4). The chromatin was finely stippled. No pleomorphism, mitotic figures and necrosis were seen. Immunohistochemical study revealed reactivity for Chromogranin, Synaptophysin, Thyroid transcription Factor-1 with Ki-67 immunolabling about 2%, thus confirming the diagnosis of TC (Figure 5A and 5B).

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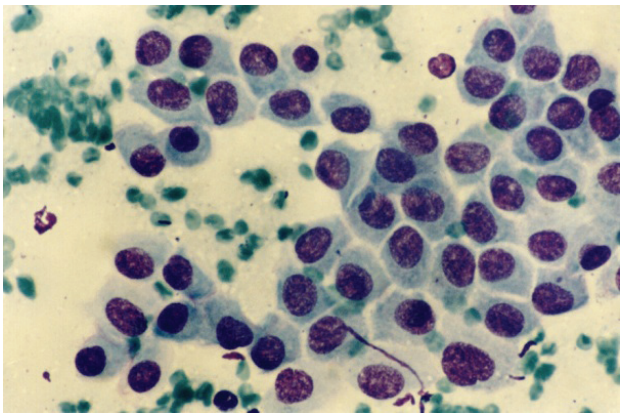


Figure 1. Cytological smears showed isolated and loose clusters of monomorphic round cells with centrally located nuclei and fine chromatin pattern, Wright-Giemsa, Oil immersion.

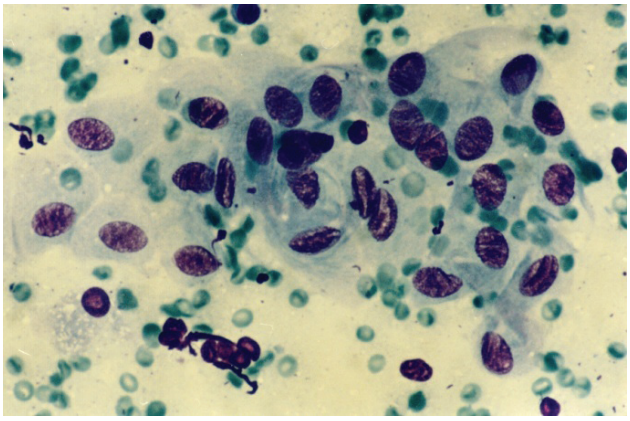


Figure 2. Aggregate of round and spindle shape cells. Intranuclear grooves are evident in tumor cells, Wright-Giemsa, Oil immersion.

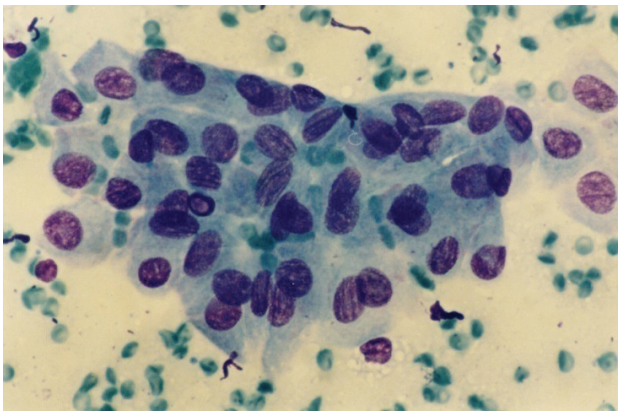


Figure 3. Cluster of tumor cells. Intranuclear pseudoinclusion and nuclear grooves are evident in tumor cells, Wright-Giemsa, Oil immersion.

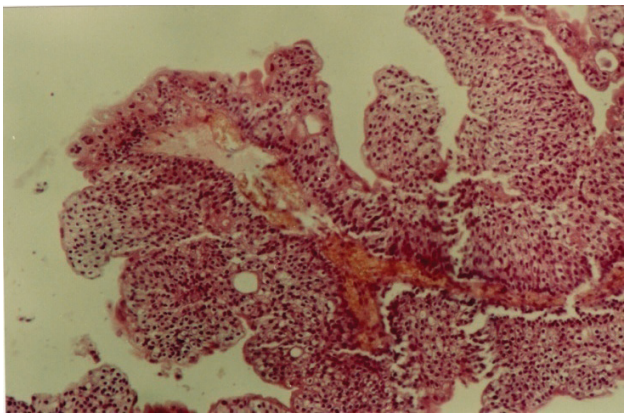
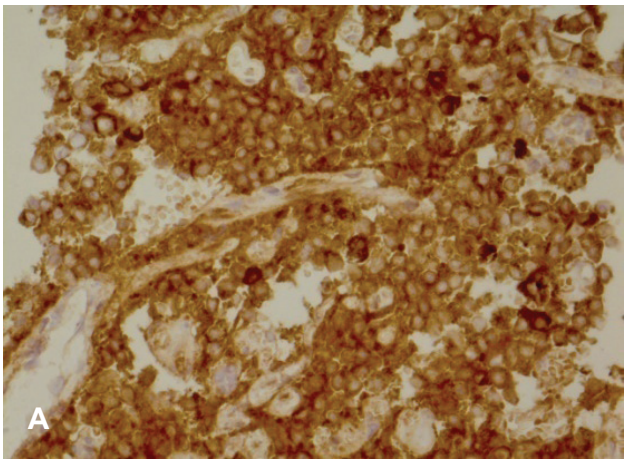


Figure 4. Histological examination showed sheets of uniform round cells with centrally located nuclei and papillary configuration, Hematoxylin and Eosin, x200.



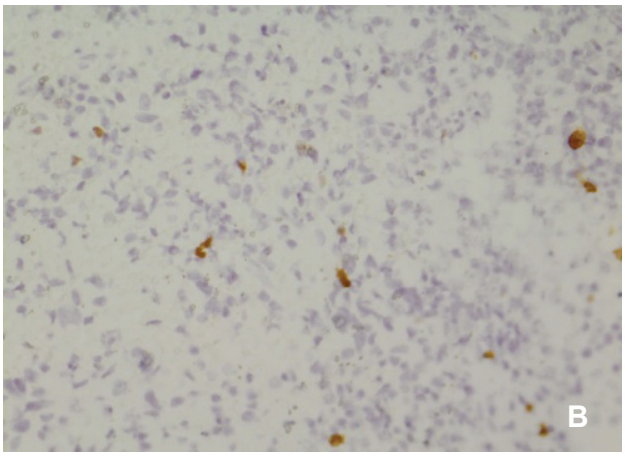


Figure 5. Immunohistochemical study. **A)** immunoreactivity for Chromogranin. **B)** Ki-67 labeling is about 2%.

Discussion

TC is a rare primary pulmonary tumor belonging to low grade spectrum of neuroendocrine tumors of the lung with slow growth rate and low possibility of metastasis.[2,4,8]

Cytological specimens obtained by variable methods, such as bronchial wash and brush and FNA, are valuable samples for diagnosis of a variety of pulmonary lesions.[4] Cytological findings of carcinoid tumor have been well described. The smears consist of isolated and loose aggregates of uniform round, spindle or plasmocytoid cells attaching to vascular wall, streaming pattern of vessels, small nucleoli and fine granular chromatin pattern. Mitosis and necrosis are uncommon in TC.[2–6] In addition to these findings, we describe intra-nuclear pseudo-inclusions and grooves in cytological smears of carcinoid tumor. Intra-nuclear pseudo-inclusion has been described in some neuroendocrine tumors such

as paraganglioma, pituitary adenoma and pheochromocytoma, papillary thyroid carcinoma, melanoma, hepatocellular carcinoma and meningioma.[9] Intra-nuclear groove is also noted in other pulmonary and non-pulmonary tumors. Sugar tumor of the lung is an example. Cytomorphologically, this tumor shows clusters of epitheloid and spindle shape cells with round to oval nuclei, smooth nuclear membrane, clear cytoplasm and occasional intranuclear groove.[10]

The classical cytology may be not evident in carcinoid tumor, so these tumors may be mistaken with other pulmonary lesions.

Carcinoid tumor may be erroneously diagnosed as SCLC. This tumor is considered a high-grade malignant lesion of neuroendocrine tumor family. On cytologic grounds, SCLC has pleomorphic tumor cells with scant cytoplasm, tumor clusters, nuclear molding, nuclear hyperchromasia, frequent mitotic figures and areas of necrosis.[2,5,6] Some carcinoid tumors may have cellular crowding and overlapping, pleomorphism, coarse chromatin pattern and irregular nuclear membrane.[2] These changes are mainly caused by poorly preserved specimens and suboptimal fixation.[6] The features in favor of carcinoid tumor versus SCLC are less cohesive clusters, absence of significant pleomorphism, mitosis and necrosis.[2,5,7] In ambiguous cases, Ki-67 immunolabling index may be of great help in differentiating these tumors. Carcinoid tumor has significantly lower ki-67 index than SCLC.[2]

Another cytological mimicker of carcinoid tumor is well-differentiated adenocarcinoma.[2,5,6,8] They form cohesive clusters of relatively uniform columnar cells with round to oval nuclei containing macronucleoli. The chromatin is usually pushed toward the nuclear membrane. In bronchoalveolar carcinoma, tumor cells may be bland looking.[10] Carcinoid tumor may show rosette formation resembling glandular like structures or contain columnar shape cells.[5,6] Helpful diagnostic features of adenocarcinoma are presence of three-dimensional clusters, macronucleoli, mitosis and necrosis.[2,4,5]

Carcinoid tumor should be differentiated from metastatic tumors. As previously noted, intra-nuclear pseudo-inclusion can be identified in malignant melanoma. Features in favor of melanoma are large discohesive cells with pleomorphism, intra-nuclear pseudoinclusion, and melanin pigments.[10] Papillary carcinoma of the thyroid also comes in differential diagnosis of carcinoid tumor. In its classic form, papillary carcinoma of the thyroid shows sheets of tumor cells with focal nuclear crowding and overlapping, irregular nuclear contours, intra-nuclear cytoplasmic inclusions and nuclear grooves.[11] Lack of significant nuclear atypia, prominent nucleoli and nuclear overlapping helps to differentiate carcinoid tumor from its metastatic mimickers.

Nowadays, with advent of neoadjuvent chemotherapies and different targeted therapies in management of lung cancers, it is crucial to correctly diagnose the subtype pulmonary tumors. The cytologic differentiation of carcinoid tumor from other tumors is of clinical consequence. Resection of the tumor is the mainstay of treatment in TC with no need to perform additional treatments while management of TC mimickers may be completely different.[2,3]

In summary, carcinoid tumor may be reliably diagnosed on FNA smears. Intra-nuclear pseudo-inclusions and grooves may be evident in tumor cells. Demonstration of fine granular chromatin pattern (salt and pepper) and absence of macronucleoli, mitosis and necrosis are helpful cytological findings to differentiate carcinoid tumor from its malignant mimickers.

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