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Case Report

Infarcted neuroendocrine tumor following endobronchial ultrasound guided fine needle aspiration of a pulmonary nodule: Typical versus atypical carcinoid a pathological diagnostic dilemma

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ABSTRACT

Introduction: Pulmonary Neuroendocrine tumors have been categorized into high, intermediate and low grade. The distinction between low grade typical carcinoid from atypical carcinoid depends on mitotic count and presence of punctate necrosis.
Case presentation: The patient is a 60 year old female with past medical history of diabetes mellitus, hyperlipidemia, gastrointestinal reflux disease and cervical myelopathy. An incidental right upper lobe nodule was discovered during hospitalization for post-total knee arthroplasty sepsis. Follow-up CT and PET scans demonstrated size stability with mild hypermetabolic activity. The tumor was excised by a robotic thoracoscopic right upper lobectomy and mediastinal lymph node dissection. A lobulated, tan-yellow, well demarcated firm mass, measuring $1.2 \times 1 \times 1$ cm was grossly identified. Microscopically, the well circumscribed mass demonstrated near complete infarct-like central necrosis with a peripheral viable cellular rim consisting of nests of tumor cells that stained positively with TTF-1, Synaptophysin, Chromogranin, and CD56; and was negative for calcitonin and monoclonal CEA. The mitotic figure count was negligible and met the WHO criteria for typical carcinoid. The proliferative index (Ki-67) was slightly high at 9.29%.
Discussion: The unusual central necrosis seen in the tumor and the relatively high proliferative index created a pathological diagnostic dilemma discussed in this report.

1. Introduction

The 2015 WHO classification of tumors of the lung, pleura, thymus and heart places pulmonary neuroendocrine tumors within a category of neuroendocrine tumors including small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), and carcinoid tumors [1]. In addition, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) has been proposed as a pre invasive neuroendocrine lesion [1,2]. Tumors within this category are believed to arise from bronchial neuroendocrine stem cells known as Kulchitsky cells [3]. Both SCLC and LCNEC are considered high grade tumors while carcinoid tumors are subdivided into low grade typical carcinoid (TC), and intermediate grade atypical carcinoid (AC) [1]. TC is considered as a well differentiated neuroendocrine tumor with less than 2 mitotic figures per 2 mm^2 or per 10 HPFs along with the absence of necrosis [1]. AC on the other hand, is described as a neuroendocrine tumor with 2–10 mitotic figures per 2 mm^2 or per 10 HPFs, and or foci of usually punctate or comedo-like necrosis [1]. While Ki-67 is included in the differential diagnosis of neuroendocrine tumors in the new WHO classification as up to 5% for typical carcinoids, up to 20% for atypical carcinoids, 40–80% for LCNEC, and 50–100% for SCLC; controversy still exists in the use of a particular cut-off value for Ki-67 proliferative index in differentiating between typical and atypical carcinoids or to predict their prognosis [1,4]. In the present report, near complete infarction of a pulmonary carcinoid following a fine needle aspiration led to significant diagnostic challenges.

2. Case presentation

The patient is a 60 year old female whose past medical history includes diabetes mellitus, hyperlipidemia, hypertension, gastrointestinal reflux disease, and cervical myelopathy. The patient ceased smoking 15 years earlier. She was recently hospitalized for sepsis following a total knee arthroplasty whereupon an incidental nodule was found radiographically in the right upper lobe. The patient underwent endobronchial ultrasound (EBUS) with fine needle aspiration (FNA) of the pulmonary lesion and the cytological evaluation was suggestive of

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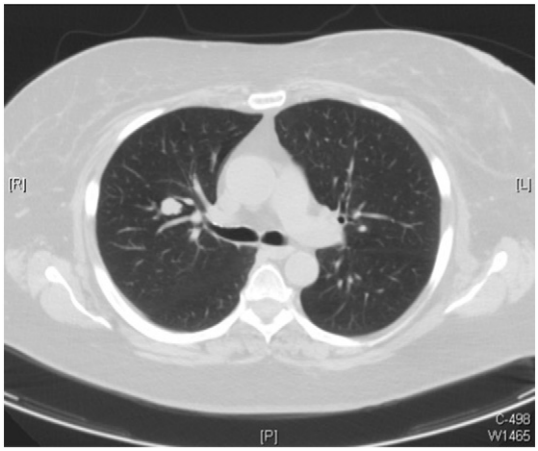

Fig. 1. CT scan of the chest revealing a right upper lobe nodule measuring 13 mm × 12 mm.

carcinoid tumor. Follow up CT and PET scans demonstrated a stable right upper lobe nodule with mild hypermetabolic activity (Fig. 1). Subsequently, a robotic thoracoscopic right upper lobectomy and mediastinal lymph node dissection was performed.

The hilum of the resected upper lobe demonstrated a lobulated, tan-yellow, well demarcated firm mass, measuring 1.2 × 1 × 1 cm, which grossly resembled a caseous granuloma (Fig. 2), located medially at the junction of the anterior and posterior segments. The lesion bore no communication with the nearest airway and was located 0.3 cm from the adjacent pleural surface and approximately 2 cm from the hilar, vascular and bronchial margins. The remainder of the lung parenchyma was unremarkable.

Microscopic examination revealed a well circumscribed mass with near complete infarct-like necrosis and a peripheral viable cellular rim consisting of nests of tumor cells with indistinct cell membranes, small nuclei, and coarsely granular chromatin (Fig. 3, A–D). On closer evaluation, the outlines and necrotic tumor cells could be appreciated within the central area of necrosis (Fig. 3, A, B). Adjacent blood vessels were all patent, without thrombi (Fig. 3, D). The viable rim of tumor cells had a monotonous, uniform appearance (Fig. 3, B—C) with negligible mitotic figures (less than 2 figures per 10 HPF) suggesting the diagnosis of typical carcinoid. Immunohistochemical staining was positive for TTF-1 (Fig. 3, E) and Synaptophysin (Fig. 3, F), CD56 (Fig. 3, G), and Chromogranin, and negative for monoclonal CEA and Calcitonin which confirmed a primary pulmonary neuroendocrine tumor and ruled out the remote possibility of a metastatic medullary thyroid carcinoma. The presence of extensive necrosis, raised concern for an atypical carcinoid.

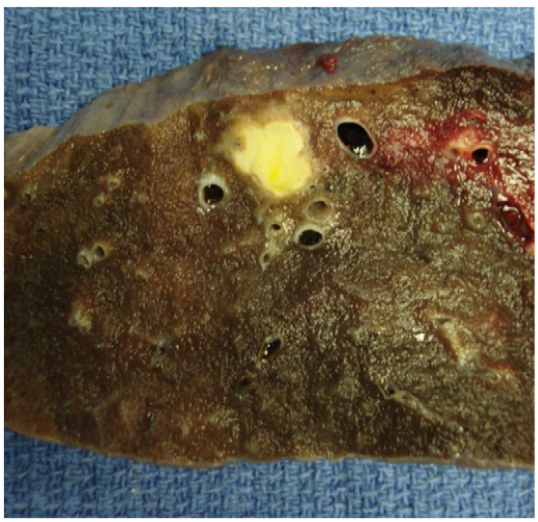

Fig. 2. Gross specimen (right upper lobe) revealing a lobulated, tan yellow, well demarcated firm mass measuring 1.2 × 1.0 × 1.0 cm.

The extensive central necrosis and the low mitotic activity prompted us to perform a Ki-67 proliferative index assessment [4,5,and 6]. Given the extensive central necrosis, assessing Ki-67 proliferative index was very challenging. Intra-lesional reactive inflammatory cells will be expected to infiltrate the neoplasm and should not be counted. We assessed Ki-67 proliferative index by randomly imaging multiple high power fields, in which over 3000 tumor cells were included. We mapped areas of neoplastic epithelial cell nests with the least stromal inflammatory cell infiltrate. This was evaluated using both the H&E and an immunomarker for LCA (CD45, common leukocyte antigen marker) to assure that only tumor cells were counted. We further manually counted the positive nuclear staining for Ki-67 proliferative index. The proliferative index of these different fields yielded a range of 1% to 31%, with an average of 9.29% (Fig. 4).

In addition, focal foreign body giant cells reaction could be appreciated adjacent to the neoplasm and scattered non-necrotizing juxtabronchovascular and interstitial granulomas with mild chronic interstitial inflammation were noted in the remainder of the lung parenchyma. Post obstructive changes in the background lung parenchyma were not appreciated. These microgranulomas were histochemically negative for microorganisms. The Parenchymal, vascular, and bronchial margins demonstrated chronic inflammation, but no tumor was noted. All hilar and mediastinal lymph nodes demonstrated sinus histiocytosis, with no tumor metastasis. The patient is doing well more than a year after her surgery at the time of writing this case report.

3. Discussion

In the present we emphasize three main pathological concepts. To the best of our knowledge, this is the first report discussing the challenging pathological findings of a pulmonary carcinoid tumor with extensive central necrosis following an EBUS-FNA procedure. The unusual central infarct like necrosis seen in the tumor created an interesting diagnostic dilemma. Typical carcinoids, according to the WHO classification do not demonstrate necrosis [1]. Indeed the presence of necrosis in a neuroendocrine tumor of the lung usually indicates a diagnosis of atypical carcinoid or even a higher grade neuroendocrine tumor. The pattern of necrosis in atypical carcinoids is usually characterized as punctate and not extensive infarct- like necrosis. The morphology of the peripheral rim of viable tumor surrounding the central necrosis in our case with fewer than 2 mitotic figures per 10 HPF was paradoxically compatible with typical carcinoid tumor. Lumina of adjacent vasculatures did not demonstrate thrombosis and were patent arguing against a vascular infarct of the tumor. Hence, the central necrosis was considered to be the result of the previous EBUS-FNA procedure. Tumor necrosis is a well recognized complication of needle aspirates and biopsies [7]. Although the WHO classification depends on the two main histopathological features of mitosis and necrosis to differentiate between typical and atypical carcinoids, further categorization is needed and highly recommended [4].

The second significant finding that created additional diagnostic confusion was the proliferative index. The Ki-67 index in our case was slightly elevated at approximately 10%; however, Ki-67 is not the current standard for grading neuroendocrine tumors of the lung [5,6]. In addition, the cut-off value of Ki-67 proliferative index in the WHO 2015 classification in differentiating carcinoid tumors is still undetermined. Despite numerous studies evaluating Ki-67 in typical and atypical carcinoids and focused on the important role of the proliferative index in pulmonary carcinoid classification and prediction of prognosis [5,6]; Walts et al. considered that the cut-off values to differentiate