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Giant Cell Carcinoma of Lung with Aberrant Cytoplasmic Localization of P63 Protein

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Abstract- Giant Cell Carcinoma is a rare, aggressive type of lung malignancy and very few cases have been extensively studied and reported to date. Because of its rare occurrence, this neoplasm is often not included in the classifications of usual lung cancers. It is considered by some as a variant of undifferentiated large cell carcinoma. Giant cells have, however, been found to occur in different types of lung cancers and their presence in any histologic type is associated with a significantly worse outcome. We present a non-smoking female who was diagnosed with lung adenocarcinoma composed of many giant cells showing cytoplasmic expression of p63 protein. Admitting imaging studies revealed metastases to liver, lymph nodes and the pelvic region. Due to the rarity of this cancer, the diagnosis as well as therapeutic and prognostic features of giant cell carcinoma is often overlooked. This neoplasm has been shown to have dismal response to chemotherapy when compared to other non-small cell lung carcinomas. Cytoplasmic localization of p63, only rarely described, is also associated with poor patient survival.

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I. CASE PRESENTATION

A 59 year-old non-smoking female presented to the Emergency Department with worsening fever of one day duration reaching up to 102°F associated with hemoptysis, mild shortness of breath and hematochezia. She complained of upper abdominal and epigastric pain, which was worse with coughing, dull, burning and radiating to the back. She also complained of nausea but denied vomiting, diarrhea, and melena.

Physical examination revealed a well-developed, well-nourished female in no acute distress. The patient's vital signs were as follows: temperature, 99°F, pulse of 103/minute, blood pressure of 110/79 mmHg, respiratory rate of 18/minute and O₂ saturation of 97% on room air. On auscultation of the chest, there were diminished breath sounds throughout the left lung field. Right lung was clear to auscultation. There were no other significant abnormal findings on further physical examination.

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Significant laboratory findings included leukocytosis of $15.0 \times 10^3/\mu\text{L}$ with band neutrophils of 31%, hemoglobin of 9.3 g/dL and albumin of 1.5 g/dL. The latter finding was later attributed to a colonoscopically diagnosed inflammatory bowel disease (IBD). Chest X-ray showed a consolidation at the left lung base and an infiltrate in the left mid-lung.

The clinical impression on admission was, "post-obstructive pneumonia likely secondary to a lung mass and anemia of chronic disease."

Upon admission, the patient received 2 units of packed red blood cells and was started on antibiotics for suspected pneumonia and on metronidazole for her colitis, which started to improve her hematochezia.

High resolution CT of the chest with contrast showed a large left pneumothorax and a left lower lobe cavitary lesion with fluid level and surrounding infiltration (figure 1) "of uncertain etiology, possibly carcinoma or infectious process such as tuberculosis". A subsequent abdominal CT revealed multiple lesions in the liver and a complex lesion in the left pelvis measuring 3.4 x 3.6 cm, which was considered to represent a necrotic lymph node or left adnexal mass. There was diffuse thickening of the wall of the distal descending and sigmoid colon, suggestive of IBD.



Figure 1 : CT of the chest (with contrast) showed prominent cavitory lesion in the left lower lobe of lung, possibly a neoplasm or granulomatous disease

Core needle biopsies of the lung lesion showed irregular cords and sheets of loosely cohesive malignant neoplastic cells with markedly pleomorphic bizarre nuclei, prominent nucleoli, and abundant faintly eosinophilic cytoplasm (figures 2 and 3). The scant supporting stroma was sprinkled with moderate numbers of mononuclear inflammatory cells accompanied by occasional eosinophils. There were extensive areas of tumor necrosis.

The neoplastic cells showed an immunohistochemical staining pattern characteristic of primary lung adenocarcinomas, i.e. positive for CEA(p), CK7 (figure 4), TTF-1 (figure 5), and focally for napsin-A (figure 6). There was nonspecific weakly positive staining for Hepar-1 and focally weak positive staining for S-100. The neoplastic cells stained negative for CK-5/6, CK 20, GCDFP - 15, GPC - 3, ALK - 1, B - HCG,

chromogranin, PAX-8, AFP, and p63 (nuclear). The latter, essential in the differentiation of stratified squamous epithelia, is a common nuclear marker used in the diagnosis of squamous cell carcinomas. There was however aberrant strong p63 cytoplasmic expression by the tumor cells (figure 7) of our patient.

The immunohistochemical pattern and the light microscopic features described supported the diagnosis of poorly differentiated adenocarcinoma, large cell (pleomorphic giant cell) type. Molecular analysis of EGFR mutation was negative and FISH analysis of ALK gene showed no evidence of gene re-arrangement. However, 20% of the cells showed 1 or more additional fusion signals for ALK DNA sequence located at the 2p; likely representing an aneuploidy population with extra copies of chromosome 2/2p ALK region.

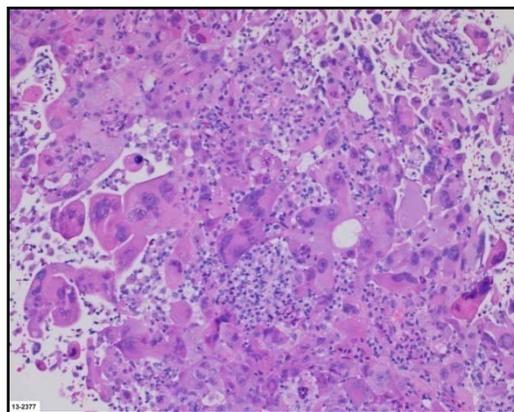


Figure 3 : Higher power of the lesion shows many malignant neoplastic giant cells

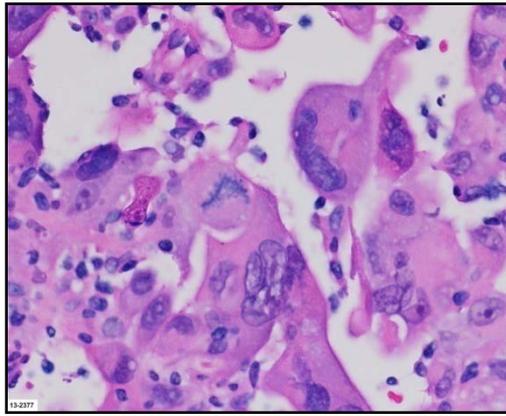


Figure 4 : Immunohistochemical stain for cytokeratin-7 (CK-7) shows characteristic cytoplasmic staining

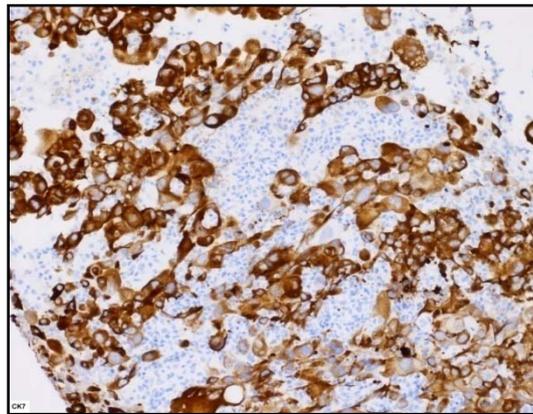


Figure 5 : Thyroid transcription factor-1 (TTF-1): positive nuclear staining, a sensitive marker for primary adenocarcinomas of lung

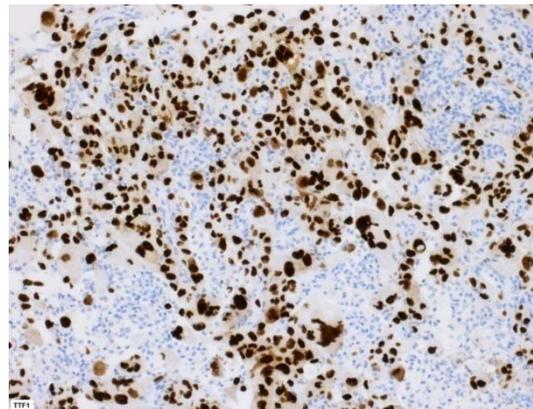


Figure 6 : Napsin A: focal positive cytoplasmic staining, a specific marker for primary adenocarcinomas of lung



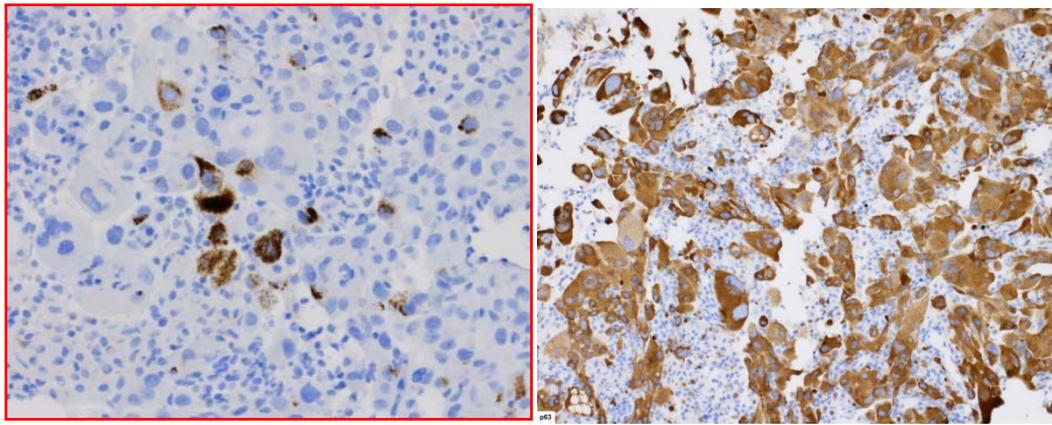


Figure 7 : Aberrant cytoplasmic staining of the neoplastic cells by p63

Due to the advanced stage of her metastatic lung cancer involving the liver, lymph nodes and pelvic area, oncology recommendation offered only supportive and palliative follow-up chemotherapy on an outpatient basis. However, before discharge, the patient expressed interest in hospice, although she would still follow up with oncology regarding the prognosis of her metastatic carcinoma. The patient was treated with IV Albumin during the course of her hospitalization for hypoalbuminemia and was started on mesalamine for her colitis before being discharged on prednisone.

II. DISCUSSION

Large cell carcinomas are peripherally located tumors, which are defined as poorly differentiated carcinomas of the lung composed of larger malignant neoplastic cells without histomorphologic evidence of squamous, glandular, or neuroendocrine differentiation¹. These tumors usually consist of sheets of large malignant cells, often with associated necrosis. Four variants of undifferentiated large cell carcinoma have been described: giant cell carcinoma, lymphoepithelioma-like carcinoma, large cell neuroendocrine carcinoma and non-small cell carcinoma with neuroendocrine features⁹.

The term giant cell carcinoma is restricted to tumors in which multinucleated giant cells (greater than 40 microns) make up at least 10 percent of the neoplastic population¹. The tumor cells alternate with mononuclear forms in a solid fashion, usually with a heavy neutrophilic infiltration and peripheral leukocytosis. This tumor comprises 1-5% of all lung cancers⁴. Most tumors are quite extensive at diagnosis. The presence of tumor giant cells in any histologic type is significantly associated with a worse outcome.

Giant tumor cells have been found to occur in different types of primary lung cancers as well as primary sarcomas, pleural mesotheliomas, pulmonary choriocarcinomas and metastatic tumors. Giant cells can also be found in many lung tumors after irradiation.

Immunohistochemical staining profile and clinical history are helpful in these differential diagnostic considerations. Other helpful features, cited by some authors, include the presence of neutrophils and large pleomorphic phagocytic cells engulfing the neutrophils⁴.

There has been mixed opinions in the literature as to whether giant cell carcinoma is an entity unto itself or a dedifferentiated adenocarcinoma. Addis et al., suggested that giant cell carcinoma arises by a process of dedifferentiation with eventual loss of epithelial markers showing unique ultrastructural features that support a diagnosis of giant cell carcinoma as a separate entity⁵.

Wang et al. described several features specific to giant cell carcinoma in their study. Giant cell carcinomas were characterized by concentric whorls of fine fibrils. There was an abundance of mitochondria recorded, which may represent the high degree of activity of giant tumor cells. The tumor cells in giant cell carcinoma lack the well developed Golgi apparatus as seen in usual types of adenocarcinomas. Also, they lack dense bodies, usually seen in bronchioloalveolar carcinomas. The cytoplasmic fibrils, frequently associated with desmosomes in squamous cell carcinomas, are found in lesser quantity in giant cell carcinomas⁶. On the other hand, Attanoos et al.² suggested that giant cell carcinoma of the lung does not appear to be a distinct entity, instead, a morphological phenotype expressed by a heterogeneous set of tumors. They suggested that the term *Giant Cell Carcinoma* should not be used for any carcinoma with an abundance of giant tumor cells, instead, terms such as "pleomorphic" or "anaplastic" describe tumors that have no specific differentiation pattern but display a variety of morphological features such as giant cell formation, clear cells or spindle cells.

Nevertheless, carcinomas of the lung with giant cells are characterized as having a more aggressive course compared to the common types of non-smoker associated lung carcinomas. Multiple ribosomes, poorly developed Golgi apparatus, and the poor aggregation

of the endoplasmic reticulum are characteristics of the rapidly advancing nature of these tumors. These tumors characteristically present with early distant metastases, short survival times, and worse overall outcomes⁴.

There have been several studies on the efficacy of surgical resection and chemotherapy for advanced pleomorphic carcinomas. Yuki et al.⁸ followed patients with pulmonary pleomorphic carcinoma who had undergone early surgical resection. Patients without lymph node metastases, pN0, frequently manifested vascular invasion supporting the aggressive nature of the tumor. The five year overall survival rate and the disease free survival was 39.2% and 47.1% respectively. Patients with pN1/N2 disease had a significantly worse outcome than patients with pN0 disease. The recurrence within 6 months after resection was found in 50% of patient and the median survival time after initial relapse was 2.6 months. Hong et al.⁷ reported on the clinical course of patients undergoing palliative chemotherapy with advanced pulmonary pleomorphic carcinoma. The median overall survival time from the initiation of the chemotherapy was eight months with the median follow-up of 26 months.

Lung adenocarcinomas with giant cell features are aggressive tumors which have not been found to be responsive to surgical resection or chemotherapy due to the early advance stage of these tumors at presentation. Our patient presented in an advanced stage with early metastasis to the liver, lymph nodes and the pelvic area and was thus not a suitable candidate for surgical resection and chemotherapy. Furthermore, aberrant cytoplasmic localization of p63, evident in our patient, was reported in one study to represent an unfavorable prognostic feature associated with poor patient survival in lung adenocarcinomas¹⁰. Additionally, absence of EGFR mutation and ALK gene re-arrangement precluded any attempt at targeted therapeutic regimens. There has been limited research on the pathogenesis of adenocarcinomas with giant cell features due to its rarity. Future studies should further investigate and evaluate the molecular pathogenesis of these tumors in order to gain insight regarding an approach to development of efficacious targeted treatment modalities.

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