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Antemortem Diagnosis of Likely Giant Cell Carcinoma of the Lung by Pleural Fluid Cytology Evaluation

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Background: Sarcomatoid carcinomas (SCs) are poorly differentiated non–small cell lung carcinomas containing components of either sarcomatoid differentiation or true sarcoma. SCs have a poor prognosis; some studies suggest a 6-month survival rate $<$27%.

Case Report: We present a case of the rare entity of SC, likely giant cell carcinoma, that is unique because our patient was older than the mean age at presentation, was female, and had a central lesion.

Conclusion: Clinicians need to be aware of the histologic entities of SCs of the lung because of the aggressive nature of these lesions and because of the need for further studies to determine possible treatment regimens.

Keywords: *Carcinoma–giant cell, carcinoma–non-small-cell lung, carcinoma–renal cell*

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INTRODUCTION

Sarcomatoid carcinomas (SCs) are poorly differentiated non–small cell lung carcinomas (NSCLCs) that contain components of either sarcomatoid differentiation or true sarcoma. SCs comprise 2%-3% of lung cancers, are more common in males and smokers, and present at a mean age of 59 years with no unique signs or symptoms.[1-3] SCs have a poor prognosis; some studies suggest a 6-month survival rate $<$27%.[2,4] SCs are divided into 5 subcategories, one of which is giant cell carcinoma of the lung (GCCL).[5] By definition, GCCL must be composed exclusively of giant tumor cells and can only be diagnosed during excisions or autopsy. SC and GCCL are aggressive tumors that do not respond to any currently known treatment modality.

CASE REPORT

A 75-year-old woman with diabetes, hypertension, chronic kidney disease, and coronary disease presented after several days of dyspnea and weakness. Review of systems revealed weight loss, nonproductive cough, and back pain for 1 month. The patient was a former smoker.

She was admitted to the intensive care unit with acute respiratory failure and hemodynamic collapse. Chest radiography revealed a right-sided pleural effusion and pathologic rib fractures. Computed tomography (CT) of the chest/thorax (Figure 1) noted right lung field and bronchial collapse, pleural effusion, and a 3 $\times$ 1.5 cm left hilar mass. Multiple lytic bone lesions and abnormal foci in the left hepatic lobe and left adrenal gland were concerning for distant metastases. The patient underwent therapeutic and diagnostic thoracentesis. Pleural fluid cytologic examination revealed neoplastic cells consistent with SC, likely giant cell carcinoma.

The pleural fluid specimens contained abundant highly pleomorphic and discohesive tumor giant cells in a neutrophil-rich inflammatory background (Figure 2). Some cells contained a single nucleus, while others contained multiple nuclei or multilobed nuclei of various shapes. Many abnormal mitoses were present (Figure 3). Occasional neutrophil emperipolesis—neutrophils engulfed in the cytoplasm of the tumor cells—was observed (Figure 4). Although there were rare clusters of tumor cells with a swirling pattern reminiscent of squamous pearls, definitive squamous differentiation such as keratinization and intercellular bridges was not seen. The tumor cells were positive for cytokeratin (CK) 7 and negative for mucicarmine, CK20, thyroid transcription factor 1 (TTF-1), p63, and neuroendocrine markers. Calretinin was faintly positive in the cytoplasm and negative in the nuclei.

The patient continued to need ventilatory and vasopressor support. Tissue diagnosis could not be established, and additional imaging studies for staging were unobtainable. She died 4 days after admission. The patient's family declined the request for an autopsy.

DISCUSSION

The term sarcomatoid differentiation refers to malignant epithelial cells that look like malignant mesenchymal cells (eg, spindle-shaped cells or discohesive giant cells). The 2004 World Health Organization classification of lung tumors includes a separate category for SCs, defined as

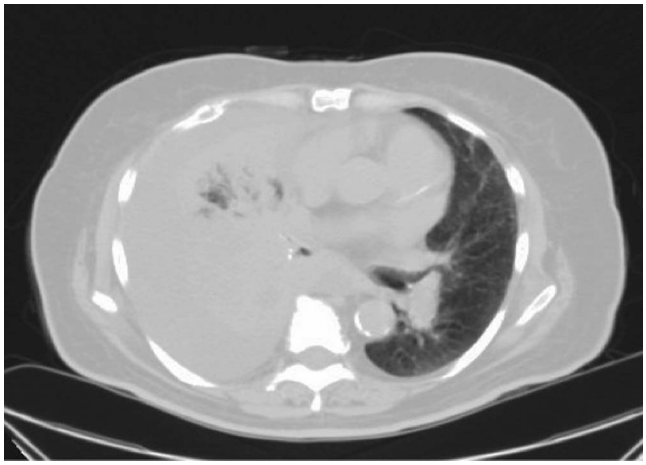

Figure 1. Noncontrast computed tomography scan of the chest shows right lung field and bronchial collapse, pleural effusion, and a 3 × 1.5 cm left hilar mass.

poorly differentiated non–small cell carcinomas that contain a component of either sarcomatoid differentiation or true sarcoma. The SC category is itself divided into 5 subcategories (Table).[5,6] By definition, a giant cell carcinoma must be exclusively composed of giant cells and can only be diagnosed when the entire tumor is examined after surgical resection or autopsy. Because we only had pleural fluid specimens, our patient can be definitively diagnosed with an SC, but no further subclassification is possible.[5]

GCCL is a very rare histologic variant of NSCLC that accounts for 0.1%-0.4% of lung cancers.[1,4,7] GCCL was first described in 1958 and originally classified as a subtype of pleomorphic carcinoma.[4] Given the historical lack of uniformity in the pathologic and other classifications, it is possible that the true incidence of GCCL or pleomorphic carcinoma is not known.[4,8] As a whole, SCs probably comprise 2%-3% of all lung cancers.[2]

SC is more common in males and smokers and generally presents at a mean age of 59.[1-3] SC as a result of exposure to asbestos or other chemicals is uncommon.

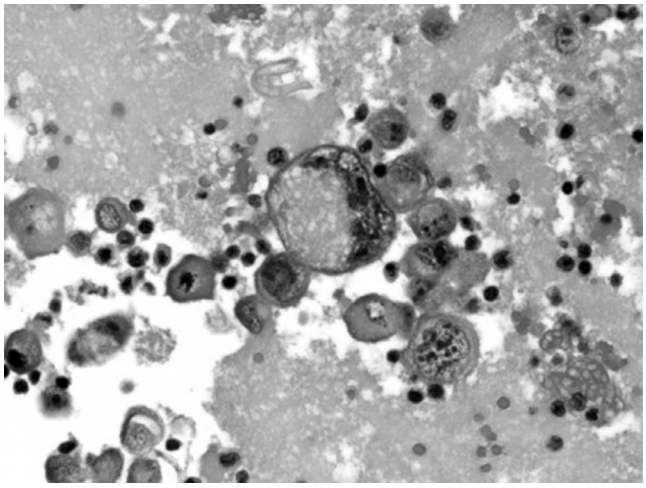

Figure 2. Pleomorphic and discohesive tumor giant cells (cell block hematoxylin and eosin stain 400×).

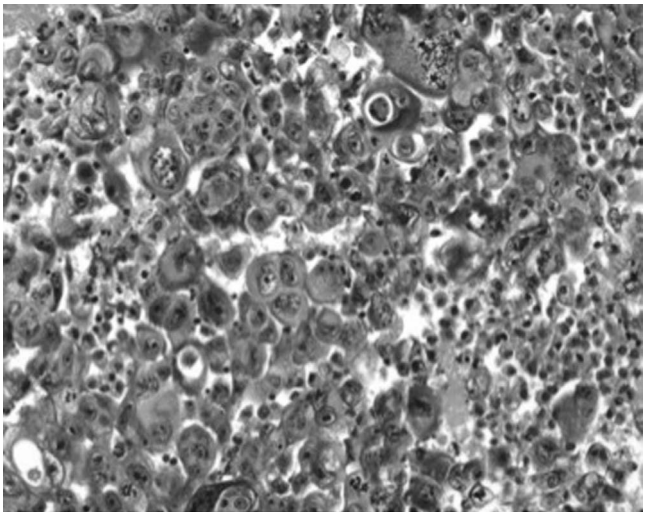

Figure 3. Giant tumor cells in a neutrophil-rich inflammatory background. Note one really abnormal mitosis at the top of the image (cell block hematoxylin and eosin stain, 200×).

No unique signs or symptoms are suggestive of SC; patients may present with cough or hemoptysis or may be asymptomatic.[8,9]

The lesions of SC are either centrally or peripherally located (pleomorphic lesions tend to be more peripherally located) and invade the bronchial tree and parenchyma with necrotic and hemorrhagic lesions.[3,4,8,10] Metastasis is via blood and lymph to sites similar to other NSCLCs (brain, bone, liver, adrenal), but unusual sites in the gastrointestinal tract, kidney, and heart have been reported.[1,8,11] SCs are aggressive tumors with poor overall prognosis (mean survival of 5-19 months), especially GCCL. Some studies suggest a 6-month survival rate <27%.[2,4]

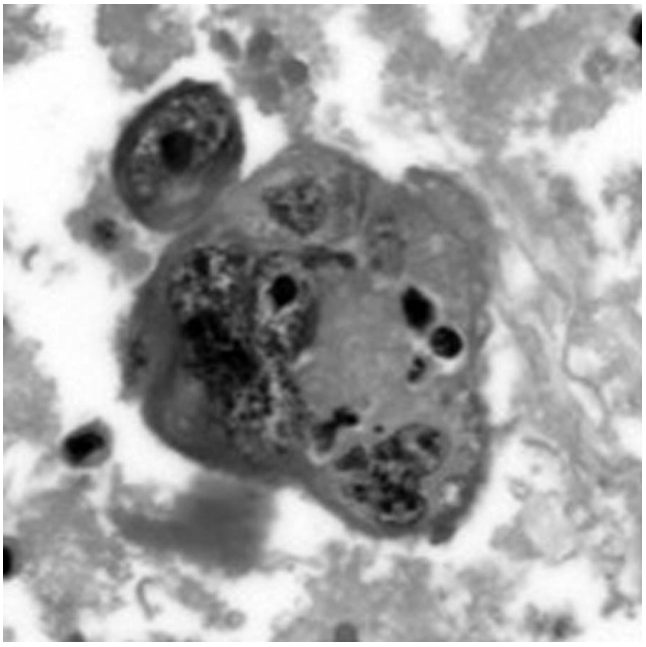

Figure 4. Tumor giant cell with neutrophil emperipolesis (cell block hematoxylin and eosin stain, 400×).

Table. World Health Organization Definitions of Sarcomatoid Carcinoma Subtypes[5]

Sarcomatoid Carcinoma Subcategory	Definition
Pleomorphic carcinoma	A poorly differentiated non–small cell carcinoma (eg, squamous cell carcinoma, adenocarcinoma, or large cell carcinoma) containing spindle cells and/or giant cells or a carcinoma consisting of only spindle and giant cells. The spindle or giant cell component should comprise at least 10% of the tumor.
Spindle cell carcinoma	Non–small cell carcinoma consisting of only spindle-shaped tumor cells. Identical to the spindle cell component of pleomorphic carcinoma.
Giant cell carcinoma	Non–small cell carcinoma composed of highly pleomorphic multinucleated and/or mononucleated giant cells. Identical to the giant cell component of pleomorphic carcinoma.
Carcinosarcoma	Composed of a mixture of carcinoma and true sarcoma, eg, malignant cartilage, bone, or skeletal muscle.
Pulmonary blastoma	Biphasic tumor containing a primitive epithelial component and a primitive mesenchymal stroma.

Diagnosis is made according to light microscopic features, with GCCL exhibiting mononucleated or multinucleated, pleomorphic, variably discohesive tumor cells with abundant eosinophilic cytoplasm often showing leukocyte emperipolesis, phagocytosed anthracotic pigment, or hyaline globules. Clinically, distinguishing between the types of SC is irrelevant in terms of mortality and treatment, but it is important to exclude small cell lung cancer and sarcomatoid features, as these findings would change management. Because of the pathologic challenges in making the diagnosis, often the final diagnosis is made postmortem.[4-7,10,12-16]

Our patient's pleural fluid was composed of a pure population of giant cells that demonstrated the characteristic features of giant cell carcinoma: very large, discohesive, and bizarre-appearing cells; an inflammatory background rich in neutrophils; and neutrophil emperipolesis by the tumor cells.[4-7,10,13-16] The immunophenotype of giant cell carcinoma is nonspecific, but the results for this patient's tumor were consistent with the literature: in a study by Rossi et al, CK7 was positive in 2 of 3 (67%) giant cell carcinomas, TTF-1 was negative in 1 of 3 (33%) giant cell carcinomas, and CK20 was negative in all 3 cases (100%).[13]

Does having a purely giant cell pattern in the pleural fluid indicate that the patient's primary tumor was a giant cell carcinoma, or were the giant cells only a small component of the primary tumor? For this patient, we will never know because the family declined an autopsy. In general, for SCs, does the pleural fluid tend to contain the epithelioid elements, the sarcomatoid elements, or a mixture of both? Unfortunately, we could not find any studies that answer this question. In lymph node metastases, though, the epithelioid component of pleomorphic carcinomas is more likely to metastasize, according to a study by Mochizuki et al.[7] They found that the sarcomatoid component was present in the metastasis in only 5 of 29 cases. Therefore, it is reasonable to assume that a pleomorphic carcinoma would display some epithelioid elements in addition to the sarcomatoid elements when it is present in the pleural fluid. The fact that our patient did not have any epithelioid elements in 2 separate specimens of her pleural fluid suggests that giant cells likely made up a significant proportion of her tumor. Even though we cannot definitively diagnose her with a giant cell carcinoma, the patient's rapid decline suggests that a purely giant cell pattern seen in the pleural fluid may indicate a more aggressive clinical course.

Little information is available about treatment options for these tumors. Most clinicians attempt to treat them with platinum-based chemotherapy, but most studies suggest poor response to chemotherapy in general.[2,4,6,8,17] Survival rates of 800 days have been reported with the use of the second-line agent gefitinib, but these were cases of female patients with epidermal growth factor receptor mutations.[8] Some reports have shown improved survival with surgical resection of early disease, but this outcome is rare, as most cases of GCCL and pleomorphic lung cancers are quite advanced at the time of diagnosis (half of patients present with metastasis at diagnosis).[8,14] Even with surgery, most patients experienced recurrence or death within 16-18 months of surgery.[17] Radiotherapy has no role in the treatment of SC.[4]

CONCLUSION

We presented a case of the rare clinical entity of SC, most likely GCCL. Our case is unique in that our patient was older than the mean age of presentation and was female. Also our patient had a centrally located lesion, whereas most cases of SC are peripherally located. Consistent with prior cases, our patient presented with distant bone, liver, and adrenal metastases and ultimately succumbed to her disease process shortly after the onset of symptoms and diagnosis.

Clinicians need to be aware of the histologic entities of SCs of the lung because of the aggressive nature of these lesions and because of the need for further studies to determine possible treatment regimens.

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REFERENCES

1. Choi HS, Seol H, Heo IY, et al. Fine-needle aspiration cytology of pleomorphic carcinomas of the lung. *Korean J Pathol*. 2012 Dec; 46(6):576-582. doi: 10.4132/KoreanJPathol.2012.46.6.576.
2. Yuki T, Sakuma T, Ohbayashi C, et al. Pleomorphic carcinoma of the lung: a surgical outcome. *J Thorac Cardiovasc Surg*. 2007 Aug;134(2):399-404.
3. Shen XY, Lin ZF, Lin Q, et al. Pulmonary sarcomatoid carcinoma: a case report. *Contemp Oncol (Pozn)*. 2013;17(2):210-213. doi: 10.5114/wo.2013.34375.
4. Krishnamurthy A, Vijayalakshmi N, Majhi U. A fatal case of pure giant cell carcinoma of the lung. *J Cancer Res Ther*. 2011 Jul-Sep;7(3):363-365. doi: 10.4103/0973-1482.87015.
5. *Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. World Health Organization Classification of Tumours*. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, eds. Lyon, France: IARC Press; 2004.
6. Pelosi G, Sonzogni A, De Pas T, et al. Review article: pulmonary sarcomatoid carcinomas: a practical overview. *Int J Surg Pathol*. 2010 Apr;18(2):103-120. doi: 10.1177/1066896908330049.
7. Mochizuki T, Ishii G, Nagai K, et al. Pleomorphic carcinoma of the lung: clinicopathologic characteristics of 70 cases. *Am J Surg Pathol*. 2008 Nov;32(11):1727-1735. doi: 10.1097/PAS.0b013e3181804302.
8. Ito K, Oizumi S, Fukumoto S, et al; Hokkaido Lung Cancer Clinical Study Group. Clinical characteristics of pleomorphic carcinoma of the lung. *Lung Cancer*. 2010 May;68(2):204-210. doi: 10.1016/j.lungcan.2009.06.002.
9. Fishback NF, Travis WD, Moran CA, Guinee DG Jr, McCarthy WF, Koss MN. Pleomorphic (spindle/giant cell) carcinoma of the lung. A clinicopathologic correlation of 78 cases. *Cancer*. 1994 Jun 15;73(12):2936-2945.
10. Laforga JB. Giant cell carcinoma of the lung. Report of a case with cytohistologic and clinical correlation. *Acta Cytol*. 1999 Mar-Apr;43(2):263-267.
11. Rashid S, Rajan D, Jacob R, et al. Colonic metastases from pleomorphic carcinoma of the lung presenting as an ileocecal intussusception. *ISRN Gastroenterol*. 2011;2011:137139. doi: 10.5402/2011/137139.
12. Travis WD. Sarcomatoid neoplasms of the lung and pleura. *Arch Pathol Lab Med*. 2010 Nov;134(11):1645-1658. doi: 10.1043/2010-0086-RAR.1.
13. Rossi G, Cavazza A, Sturm N, et al. Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: a clinicopathologic and immunohistochemical study of 75 cases. *Am J Surg Pathol*. 2003 Mar;27(3):311-324.
14. Alasio TM, Sun W, Yang GC. Giant cell carcinoma of the lung impact of diagnosis and review of cytological features. *Diagn Cytopathol*. 2007 Sep;35(9):555-559.
15. Hiroshima K, Dosaka-Akita H, Usuda K, et al. Cytological characteristics of pulmonary pleomorphic and giant cell carcinomas. *Acta Cytol*. 2011;55(2):173-179. doi: 10.1159/000320860.
16. Gupta N, Srinivasan R, Nijhawan R, Rajwanshi A. Neutrophilic phagocytosis by tumor cells. A feature to consider in the differential diagnosis in fine needle aspiration smears. *Acta Cytol*. 2007 Jan-Feb;51(1):21-24.
17. Bae HM, Min HS, Lee SH, et al. Palliative chemotherapy for pulmonary pleomorphic carcinoma. *Lung Cancer*. 2007 Oct; 58(1):112-115.

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