Human Pathology (2019) **85**, 168–173

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Human PATHOLOGY

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Original contribution

# Osteoclast-like giant cell–rich carcinomas of the lung: a clinicopathological, immunohistochemical, and molecular study of 3 cases☆

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Received 9 August 2018; revised 24 October 2018; accepted 31 October 2018

**Keywords:**
Lung;
Giant cells;
Osteoclast;
Carcinoma;
Immunohistochemistry

**Summary** Three cases of primary carcinomas of the lung each with an extensive osteoclast-like giant cell component are presented. The patients are 3 men between the ages of 58 and 67 years (average, 62.5 years) who presented with nonspecific symptoms. A history of malignancy, infectious, or granulomatous disease was negative in all the patients. Diagnostic imaging disclosed the presence of a large intrapulmonary mass; in 1 case in the right upper lobe and in 2 cases in the right lower lobe. Surgical resection via lobectomy was performed in the 3 patients. Grossly, the tumors were described as soft, friable intrapulmonary masses, reddish in color, and measuring from 6 to 13 cm in largest diameter. Histologically, the tumors were each characterized by the extensive presence of a multinucleated osteoclast-like giant cell component, which represented approximately 80% of the tumor mass. The osteoclast-like giant cell component was admixed with a sarcomatoid carcinoma in 2 cases and an adenocarcinoma in 1 case. Immunohistochemistry showed that the osteoclast-like giant cells were positive for CD-68, cathepsin K, and histone H3, whereas the carcinoma component was positive for keratin, thyroid transcription factor-1, and histone H3 (patchy). Molecular studies were performed in 2 patients with negative results. Clinical follow-up was obtained in 2 patients; 1 died 14 months after initial diagnosis, whereas 1 remains alive 6 months after initial diagnosis. One patient was lost to follow-up. The current neoplasms represent an unusual type of lung carcinoma that needs highlighting as a separate type from conventional giant cell carcinoma.


## 1. Introduction

Sarcomatoid carcinomas of the lung are unusual neoplasms that represent only a small percentage of all the primary non–small cell carcinomas [1,2]. In more recent publications on the subject, different perspectives have been advanced to triage these tumors in a manner that may provide more meaningful molecular diagnostics. The main concept is to provide a more updated morphologic and immunohistochemical approach to these tumors so that they can be subclassified more appropriately. Therefore, the use of up-to-date immunohistochemical stains for squamous and pneumocytic differentiation is an integral part of the diagnostic tools for these tumors.

In addition, there is another even smaller subset of non–small cell lung carcinomas worth noting—primary giant cell

☆ Disclosure: The authors Drs Lindholm, Kalhor, and Moran state that no grant was received in the writing of this manuscript. In addition, the authors have no conflict of interest to disclose.

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https://doi.org/10.1016/j.humpath.2018.10.030
0046-8177/

**Table** Clinical features of 3 patients with osteoclast-like giant cell–rich carcinomas of the lung

| Case no. | Sex/Age (y) | Symptoms | Location/size | TNM stage | IHC (Ca) | IHC (OGC) | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | M/58 | Cough, shortness of breath | RLL/6.5 cm OGC + SC | T3NOM0 | Pan-keratin Keratin 7 | CD68 Cathepsin K | D/14 mo |
| 2 | M/67 | Chest pain | RUL/13 cm OGC + SC | T4N0M0 | Pan-keratin Keratin 7 | CD68 Cathepsin K | A/6 mo |
| 3 | M/62 | Cough, chest pain | RLL/6 cm OGC + AdenoCa | T3N0M0 | Pan-keratin Keratin 7 TTF1 | CD68 Cathepsin K | N/A |

NOTE. Keratin and keratin 7 positive in the carcinoma component only. CD68 and cathepsin K positive only in the osteoclast giant cell component.
Abbreviations: A, alive; AdenoCa, adenocarcinoma; Ca, carcinoma cells; D, dead; M, male; N/A, not available; OGC, osteoclast giant cells; RLL, right lower lobe; RUL, right upper lobe; SC, sarcomatoid carcinoma.

carcinomas of the lung. If stricter criteria are used for their diagnosis, they should represent less than 1% of all primary non–small cell carcinomas of the lung [3]. However, although the existence of giant cell carcinomas of the lung has been well documented, it is important to highlight that in most of these reports, the giant cells are malignant epithelial cells. Contrary to that concept, the cases herein presented are composed of osteoclast-like giant cells, which are not malignant. Therefore, these particular tumors should not be grouped with giant cell carcinomas. A discussion on this type of tumor and their pitfall in diagnosis is presented.

## 2. Materials and methods

Three cases of osteoclast-like giant cell–rich carcinomas of the lung form the basis of this report. The cases were identified in the files of the Department of Pathology at MD Anderson Cancer Center and the personal files of one of the authors (C. A. M.). Hematoxylin-eosin–stained sections were available in the 3 cases and varied from 8 to 15 tumor sections. The 3 cases were encountered during a review of approximately 110 carcinomas that had been diagnosed as pleomorphic carcinoma, giant cell carcinoma, or sarcomatoid carcinoma. Therefore, the tumors herein reported represented approximately 2% to 3% of these types of primary lung neoplasms and less than 1% of all non–small cell carcinomas of the lung. The histologic criterion for inclusion in this report was for a tumor to have at least 50% of osteoclast-like giant cells in any given non–small cell carcinoma (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, sarcomatoid carcinoma, pleomorphic carcinoma). Tumors containing different types of multinucleated giant cells other than osteoclast-like were not included in this report. Immunohistochemical studies with antibodies targeting cytokeratin AE1/AE3 (1:50; Dako, Carpinteria, CA), keratin 7 (1:300; Dako), p40 (1:2000; Calbiotech, San Diego, CA), thyroid transcription factor-1 (TTF-1) (1:200; Dako);, Napsin A (1:200; Dako);, CD68 (1:50; Dako), human chorionic gonadotropin (HCG; 1:6000; Sigma, St Louis, MO), cathepsin K (1:100, clone 3F9; Cell Marquee, California), histone H3 (1:200, clone 6C36B11; Cell Signaling, California), and G34 W (1:1000, clone RM263; Reb MAB Bioscience, California) were performed with concurrent adequate controls. Clinical follow-up was obtained by reviewing the respective clinical charts. In addition, next-generation sequencing–based analysis for the detection of somatic mutations was performed in 2 cases, whereas fluorescence in situ hybridization analysis for RET, MET, ALK, and ROS1 was performed in 1 case.

This study was performed following the standards of an institutional review board protocol.

## 3. Results

### 3.1. Clinical features

The most important clinical features of these 3 patients are depicted in Table. The patients are 3 men between the ages of 58 and 67 years (average, 62.5 years) who presented with

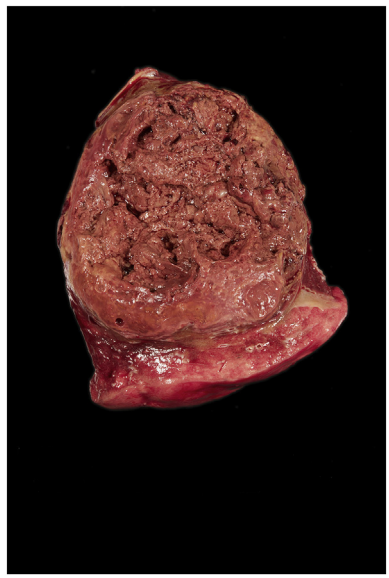

**Fig. 1** Macroscopic view of an osteoclast-like giant cell–rich carcinoma of the lung. The tumor is friable and reddish in color.

nonspecific symptoms of chest pain, shortness of breath, and cough. One patient had a history of tobacco use, whereas in 2 patients, such history was not available. None of the patients had any history of malignancy, tuberculosis, or any other infectious or granulomatous process. Diagnostic imaging showed the presence of an intrapulmonary mass in the right lower lobe in 2 patients and in the right upper lobe in 1 patient. None of the patients received chemotherapy or radiation before the lung resection. Surgical resection was performed in all the cases.

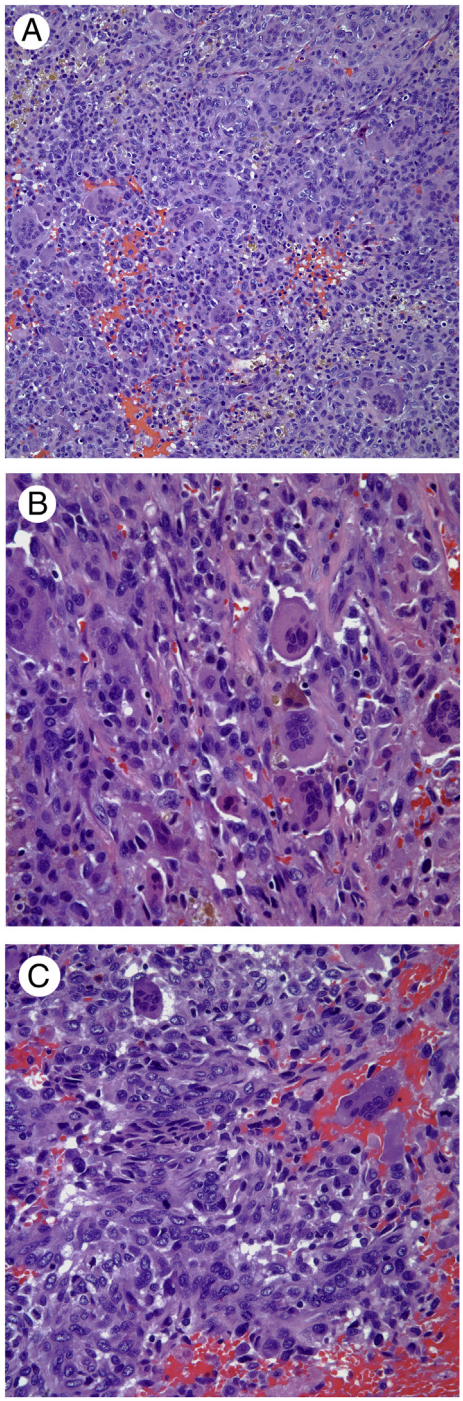


**Fig. 2** A, Low-power view showing extensive presence of osteoclast-like giant cells (hematoxylin and eosin [H&E], original magnification ×10);. B, Higher magnification of the multinucleated giant cells lacking atypia and mitotic activity (H&E, ×20);. C, Higher magnification of the spindle cell component showing atypia and mitotic activity (H&E, ×20).

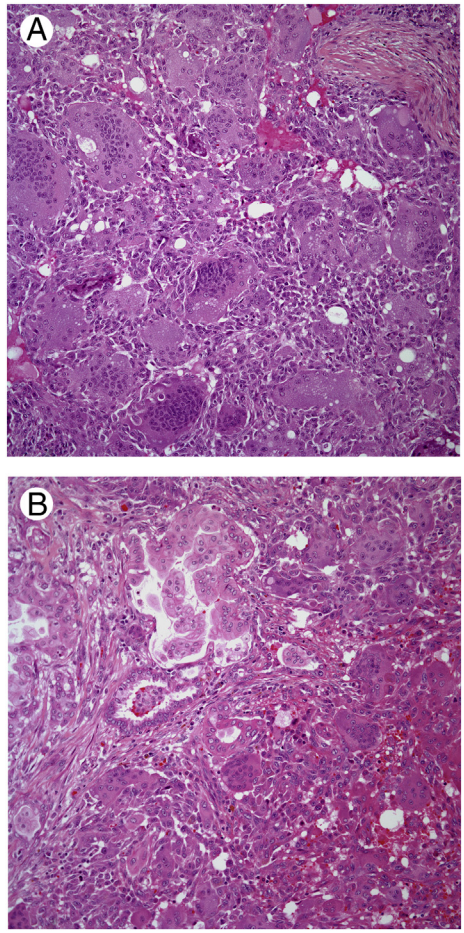


**Fig. 3** A, Low-power view showing a predominant osteoclast-like giant cell component (E;hematoxylin and eosin, original magnification ×10);. B, Focus of adenocarcinoma admixed with osteoclast-like giant cells (E;hematoxylin and eosin, ×20; new illustration).

### 3.2. Pathological features

Grossly, the tumors were described as large, friable, well-demarcated intrapulmonary masses that varied in size from 6 to 13 cm in diameter. The tumors showed a distinct reddish color (Fig. 1).

Histologically, 2 tumors showed similar histopathologic features. The low-power view showed an extensive presence of multinucleated osteoclast-like giant cells characterized by large irregular cells with ample cytoplasm and numerous nuclei. However, these giant cells did not show any evidence of atypia or mitotic activity (Fig. 2). The presence of these osteoclast-like giant cells represented approximately 80% of the tumor mass. In addition, admixed with this multinucleated giant cell component, there was a spindle cell proliferation

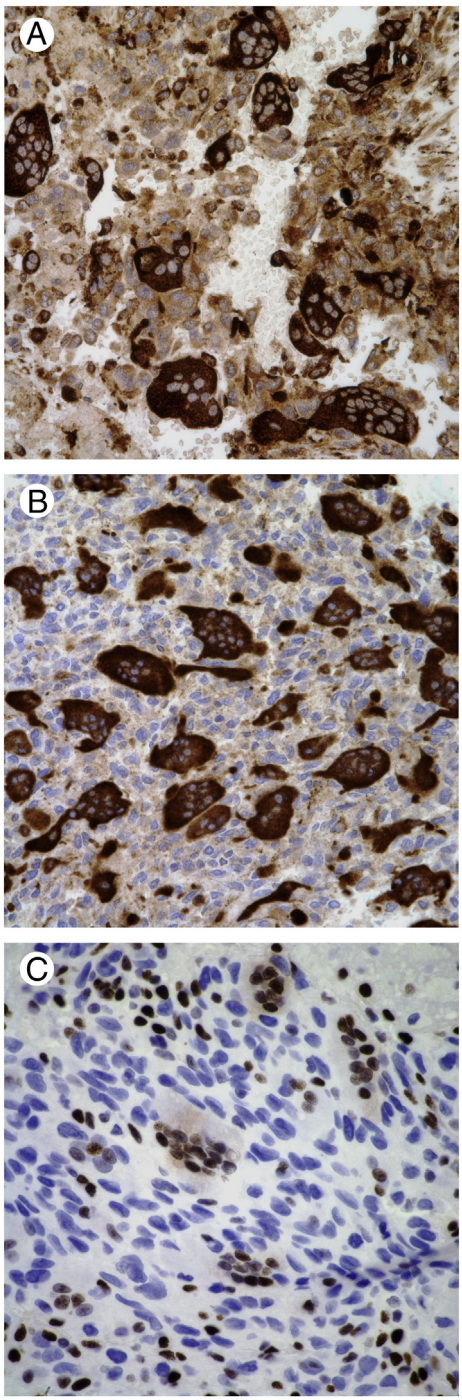


**Fig. 4** A, Immunohistochemical stain for CD68 shows strong positive staining in the osteoclast-like giant cell component (original magnification ×20). B, Cathepsin K also shows strong positive staining in the multinucleated giant cells (×20). C, Histone H3 shows positive staining in the nuclei of the giant cells (×60).

composed of elongated cells with fusiform nuclei and inconspicuous nucleoli showing nuclear atypia and increased mitotic activity. This spindle cell component represented approximately 20% of the tumor mass. In the third case, the osteoclast-like giant cell component showed similar histologic

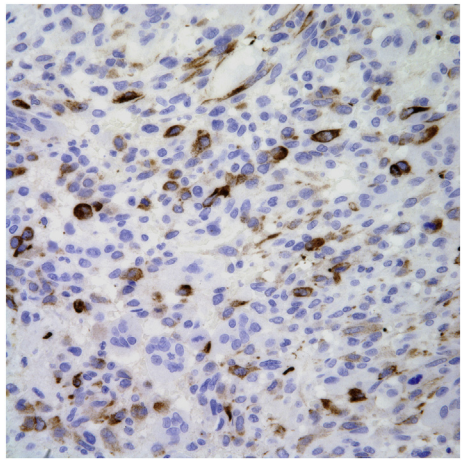

**Fig. 5** Immunohistochemical stain for keratin AE1/AE3 shows positive staining in the spindle cell component (original magnification ×20).

and immunohistochemical features, and also represented approximately 80% of the tumor mass. However, in this case, the osteoclast giant cell component was associated with areas of well-differentiated adenocarcinoma (Fig. 3). Immunohistochemical stains were performed in 3 cases showing the multinucleated giant cells positive for CD68, cathepsin K, and histone H3 (Fig. 4), while negative for G34 W, keratin AE1/AE3, keratin 7, TTF-1, Napsin A, p40, and HCG. On the other hand, the mononuclear spindle cell component showed positive staining for keratin AE1/AE3 (Fig. 5), keratin 7, and histone H3 (patchy), while negative for CD68, cathepsin K, HCG, TTF-1, Napsin A, and p40. The adenocarcinoma component in 1 case showed positive staining for TTF-1 and Napsin A.

Next-generation sequencing for *ALK*, *BRAF*, and *EGFR* were negative in 2 cases. In addition, in 1 case, fluorescence in situ hybridization analysis results for ROS1, RET, and MET were negative.

Pathological staging was determined based on all the clinical and pathological information available, and it was determined as T3N0M0 in 1 patient and as T4N0M0 in 2 patients.

Clinical follow-up information was obtained showing that 1 patient was alive at 6 months after diagnosis, 1 patient died 14 months after diagnosis, and 1 patient was lost to follow-up.

## 4. Discussion

Primary giant cell carcinomas of the lung are rare [3]. We have demonstrated that some of these tumors show 2 different types of giant cells—the syncytiotrophoblastic and the so-called null cell type. The syncytiotrophoblastic multinucleated giant cells show positive staining for keratin and HCG, and in some patients, increased levels of HCG in serum may be detected. The other type of multinucleated giant cells that can be present in giant cell carcinomas of the lung is the so-called null cell type, which consist of multinucleated giant cells that show cellular cannibalism. These latter cells react

only to keratin antibodies by immunohistochemistry. We have also documented that multinucleated giant cells in cases of adenocarcinoma or squamous cell carcinoma may react with TTF-1 and/or p40, respectively. Therefore, based on the reported cases in the literature, there is no doubt that the presence of multinucleated giant cells in these tumors is of the malignant type, thus using the term *giant cell carcinomas*.

Contrary to the different types of multinucleated giant cells associated with the different types of carcinomas, the giant cell component in the cases herein presented is composed of multinucleated giant cells of the osteoclast like, which are not malignant. From the morphologic point of view, the cells do not show any evidence of nuclear atypia or mitotic activity. In addition, the cells do not react with epithelial antibodies (keratins, p40, TTF-1) but do react positively with CD68, cathepsin K, and histone H3. Although similar tumors have been described in the other anatomical areas including the thyroid, and the gynecologic and the genitourinary systems, the existence of these tumors in the lung may be underreported. These tumors may possibly be grouped with other giant cell, pleomorphic, or sarcomatoid carcinomas. Nevertheless, the existence of osteoclast-like giant cell–rich carcinomas of the lung has been previously recorded. However, those reports are essentially in the form of single-case reports or in the context of their presence in association with other lung neoplasms. For instance, Bocklage et al [4] reviewed the presence of osteoclast giant cells infiltrating primary tumors of the lung. The authors reported 6 cases and documented the presence of these giant cells not only in carcinomas but also in sarcomas of the lung in a proportion of 25% to 60%. Judging by the illustrations provided, it is possible that some of the giant cells present were also of the malignant type. In addition, their presence seems to be more scattered, as the authors pointed in their title of "lung tumors infiltrated by osteoclast-like giant cells." Hellstrom and Fisher [5] described 17 cases of giant cell carcinoma of the lung, 1 of which they acknowledged as containing giant cells, which closely resembled osteoclasts. Although this was given the designation of giant cell carcinoma, it is possible that this was actually a case of osteoclast-like giant cell–rich carcinoma. However, it is unclear how abundant the giant cell component was and whether there was a subset of giant cells with more bizarre and nonosteoclast morphology. Nakahashi et al [6] described a case with a prominent component of cells, which seemed consistent with osteoclast giant cells. However, other areas of the tumor showed a sarcomatoid, undifferentiated morphology with atypical giant cells showing pleomorphic, hyperchromatic nuclei. Those cells were considered to be tumor giant cells along with areas of more conventional adenocarcinoma. Thus, it is unlikely that this tumor's classification was that of osteoclast-like giant cell–rich carcinoma of the lung. The cases described by Love and Daroca [7] and Oyasu et al [8] documented the presence of osteoclast giant cells in association with squamous cell carcinomas. Judging by the description and illustrations provided, it is also likely that the giant cell component may have contained, in addition to osteoclast giant cells, the presence of malignant giant cells. Also, it is likely that the osteoclast giant cell component did not represent the main feature of the tumors. It is possible that this component had been scattered throughout the carcinoma. Also, Leung and Morava-Protzner [9] reported a single case in a 58-year-old man with a history of tonsillar carcinoma. The lung carcinoma was interpreted as primary lung carcinoma, which interestingly also showed metastatic disease in peribronchial lymph nodes with similar characteristics including the presence of osteoclast giant cells. However, the author did not state the extent of the osteoclast giant cell component in the lung carcinoma. Dahm [10] also described a similar case in a 59-year-old man, as a non–small cell carcinoma with osteoclast-like giant cells. However, it is not clear from this report whether the main feature of the tumor was the presence of the multinucleated giant cells, or whether the non–small cell carcinoma was infiltrated by osteoclast giant cells, as the cases reported by Bocklage et al [4].

Although there is not a convincing explanation for the occurrence of an osteoclast-like giant cell component in an otherwise conventional carcinoma, it is possible that the presence of this type of multinucleated giant cell may be due to an inflammatory response in the lung. In our cases, the tumors showed areas of necrosis. However, regardless of the underlying mechanism in the development of this response, such tumors should not be classified as giant cell carcinomas, as that denotes the presence of malignant giant cells. These particular neoplasms should be categorized under the more conventional type of primary lung carcinoma (adenocarcinoma, squamous cell carcinoma, sarcomatoid carcinoma) with the addition of the presence of an osteoclast-like giant cell component. Although we have not seen metastatic deposits in these tumors, at least 1 case has been reported in which the metastatic deposit in a lymph node also carried the giant cell component [9].

From the differential diagnostic point of view, the presence of an extensive component of osteoclast-like multinucleated giant cells should alert one to the possibility of metastatic giant cell tumor of bone origin. Also, similar histology may also be seen in metastatic disease from giant cell tumors of soft tissue. In this setting, a good clinical history should aid in the final interpretation. In addition, the use of immunohistochemical stains showing positive staining of the multinucleated giant cells for CD68, cathepsin K, and histone H3, while negative for epithelial markers should also aid in the final interpretation. The most likely pitfall in interpretation of these tumors would be with either giant cell carcinoma or pleomorphic carcinoma [3,11]. In these 2 tumors, the presence of multinucleated giant cells is not of the osteoclast type. On the contrary, the cells are large with prominent, bizarre, enlarged nuclei, which may show prominent nucleoli. Also, those multinucleated giant cells are likely to have negative staining for CD68 and cathepsin K, while showing positive staining for epithelial markers, TTF-1, p40, or HCG, therefore aiding in the final interpretation of the neoplasm.

In short, we have described what we consider an unusual variant of primary lung carcinoma characterized by the presence of extensive multinucleated osteoclast-like giant cells,

which in our opinion represents a distinct subset of primary lung carcinoma. Therefore, attention should be placed on the specific subclassification not only to pursue proper molecular diagnostics but also to accumulate experience into whether the presence of this type of giant cell provides a different prognosis. In our cases, all the patients had large tumors with negative nodal disease. At this time, based on 3 individual cases, it is difficult to draw more meaningful conclusions regarding clinical behavior for this type of carcinoma with an osteoclast-like giant cell–rich component.

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