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CASE REPORT

Osteoclastoma-like Giant Cell Tumor of the Lung

Zsolt OROSZ,[1] Erika TÓTH,[2] Anna VISKI,[3]

[1]Department of Human and Experimental Tumor Pathology; [2]Department of Molecular Pathology; National Institute of Oncology, Budapest; [3]Department of Pathology, Kaposi Mór Hospital, Kaposvár, Hungary

The main components of an unusual form of lung tumor were osteoclast-like multinucleated giant cells and mononuclear stromal cells. Besides, scattered islands of moderately differentiated squamous cells also appeared. Both the mononuclear and the osteoclast-like giant cells reacted with antibodies against CD68 and vimentin, but did not react with antibodies against cytokeratin, EMA and CEA, or lysozyme and α-1-antitrypsin. The p53 and PCNA antigens were positive only in mononuclear cells and not the osteoclast-like giant cells, suggesting that mononuclear cells represent proliferating elements with histiocytic differentiation while osteoclast-like giant cells are stromal, presumably reactive components of the tumor. (Pathology Oncology Research Vol 2, No1–2, 84–88, 1996)

Key words: osteoclast-like giant cells, giant cell tumor, lung, p53, PCNA

Introduction

Primary extraosseous neoplasms containing osteoclast-like giant cells have been described in many internal organs, the skin and soft tissues (e.g. pancreas,[6,15,18,22,25,26,39,40,41,45,46] liver,[3,29,37] gallbladder,[20] uterus,[8] kidney,[27] ovary,[47] large intestine,[10] larynx,[1] lung,[17,23,28,32,35,37] heart,[9] parotid gland,[5,12] skin,[4] thyroid,[7,11,19,36,43] breast,[13,14,24,31,33,38,44] soft tissue[21,42]). These tumors, apart from the minute epithelial elements, are histologically indistinguishable from the skeletal giant cell tumor, "osteoclastoma". Until now, only six cases of osteoclast-like giant cell tumors of the lung have been reported. Here, we present an additional case, including a detailed immunohistochemistry, with histological signs of malignancy. The vimentin and CD68 reactivity in the mononuclear and the multinucleated cells suggests histiocytic differentiation. Furthermore, since the expression of p53 and PCNA was observed only in the mononuclear cells, these elements can be regarded as the proliferative components of the tumor.

Case Report

A 61-year-old man with known ischemic heart disease was admitted to Kaposi Mór Hospital (Kaposvár, Hungary) for routine examination in 1994. He had diabetes mellitus and rheumatoid arthritis. Routine chest x-ray revealed a mass in the upper lobe of the left lung. Chest CT showed emphysema and fibrosis and a subpleural mass, measuring 4 cm in the 2nd segment of the left upper lobe. A preoperative transthoracic biopsy suggested giant cell carcinoma of the lung. The left upper lobe was resected with hilar lymphadenectomy. A frozen section of mediastinal lymph node confirmed anthracosis without malignancy. A bone scan after surgery revealed abnormalities due to rheumatoid arthritis. Fifteen months after surgery, clinical and X-ray examinations did not reveal any evidence of further neoplastic growth.

Materials and Methods

The specimen was fixed in 10% buffered formalin and embedded in paraffin using standard techniques. Sections were stained with hematoxylin and eosin, periodic acid-Schiff without diastase, and Gömöri's reticulin stains. The same paraffin blocks were utilized for immunohistochemistry.

The panel of mono- and polyclonal antibodies and the results of their reactions are shown in *Table 1*. For development, standard avidin-biotin and peroxidase-antiperoxidase techniques were used.

Macroscopic findings

In the apical region of the resected left upper lobe, the pleura was thick grayish-white. Below, the parenchyma contained a lobulated mass of 6 cm in maximum diameter.

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Correspondence: Zsolt OROSZ, MD; Department of Human and Experimental Tumor Pathology, National Institute of Oncology, 1122 Budapest, Ráth György u. 7-9, Hungary

Table 1. **Immunohistochemical reactions and results**

Antibodies	*Source*	*Osteoclast-like giant cells*	*Mononuclear cells*	*Squamous cells*
Cytokeratin (lu-5)*	BioGenex	–	–	+
EMA*	BioGenex	–	–	+
CEA*	BioGenex	–	–	+
α-1-antitrypsin#	BioGenex	–	–	–
lysozyme#	BioGenex	–	–	–
CD68 (KP1)*	DAKO	+	(focal) +	–
vimentin*	BioGenex	+	+	–
p53 (DO7)*	DAKO	–	+	+
PCNA	DAKO	–	+	(focal) –
LCA*	DAKO	+	–	–
S100#	DAKO	–	–	–

* monoclonal antibody; # polyclonal antibody; EMA - epithelial membrane antigen; CEA - carcinoembryonic antigen; PCNA - proliferating cell nuclear antigen; LCA - leukocyte common antigen

No association with either the lobar or the segmental bronchi was evident. The peribronchial and hilar lymph nodes were anthracotic.

Light microscopy

The tumor was relatively well circumscribed with spotted necrotic areas. The viable part was cellular without forming specific structures and showed a random mixture of mononuclear and osteoclast-like giant cells *(Fig.1A)*. The mononuclear cells were round or angular, occasionally spindle, and had polymorphic nuclei with clumped chromatin, mitoses were numerous. The cytoplasm was eosinophil and relatively narrow with a well-defined cell membrane. The osteoclastic giant cells contained up to 50 vesicular nuclei, bland in appearance each with a single, small amphophilic nucleolus. However, some giant cells had bizarre nuclei. The cytoplasm of the multinucleated giant cells was eosinophilic centrally, amphophilic peripherally and occasionally contained vacuoles or enclosed mononuclear cells. In the peripheral zone of giant cells, there were small, irregular clefts. The tumor was vascularized by sinusoidal blood vessels. No cartilage, osteoid, calcification, or myxoid areas were present.

As part of the tumor, a few, small, solid epithelial nests were found with polygonal cells, resembling squamous epithelium without keratinization *(Fig.1B)*. The nuclear pleomorphism in these areas was moderate.

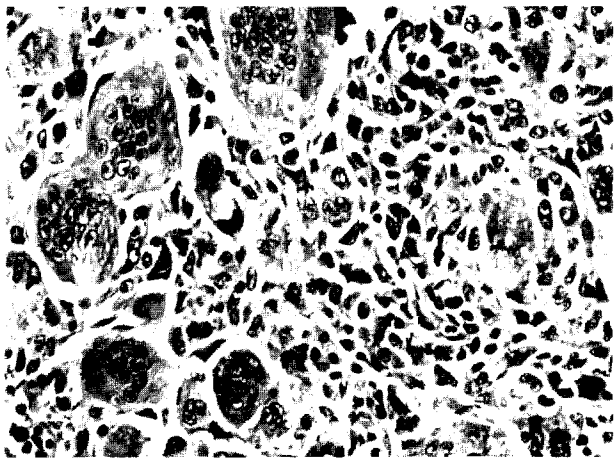

Figure 1 A. Undifferentiated mononuclear stromal cells and characteristic osteoclast-like giant cells

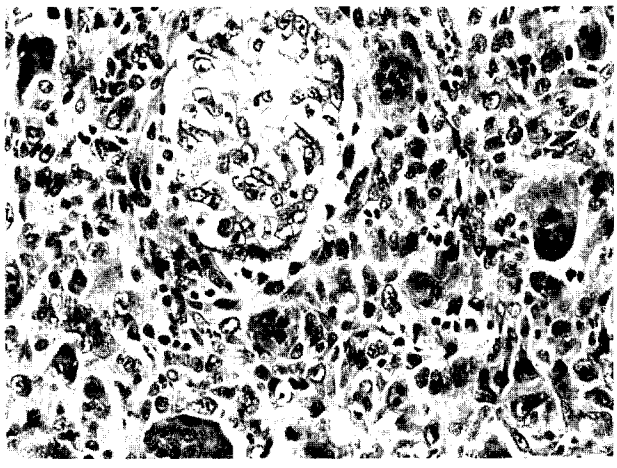

Figure 1 B. Island of malignant squamous epithelial cells surrounded by stromal mononuclear cells and osteoclast-like giant cells

Immunomorphology

The results are summarized in *Table 1*. Three epithelial markers, EMA, CEA and low-molecular-weight cytokeratin showed positive staining within the epithelial islands; however, the mononuclear cells and the multinucleated giant cells were clearly negative *(Fig.2A)*.

Both multinucleated giant cells, and focally, the mononuclear cells were positive for CD68 (KP-1) and vimentin *(Fig.2B)*, while for lysozyme and α-1-antitrypsin they were negative. The mononuclear cells showed positivity with p53 and PCNA *(Fig.3)*. Weak positivity was found with the latter antibodies in the squamous cells.

Discussion

Those tumors which consist of typical osteoclast-type giant cells intimately associated with mononuclear cells are classified under various names including pleomorphic giant cell tumor,[8] sarcomatoid carcinoma,[1] extraosseal osteoclastoma,[4,9] osteoclast-type giant cell tumor,[6] and osteoclastoma-like giant cell tumor.[3,7] We prefer the latter term, which is descriptive and unambiguous, since these neoplasms must be distinguished from the pleomorphic giant cell carcinomas (i.e. in the lung, pancreas and thy-

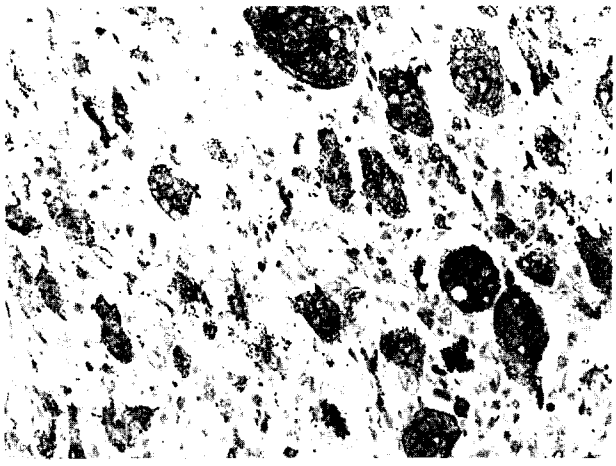

Figure 2 A. Intensive CD 68 positivity within the cytoplasm of osteoclast-like giant cells

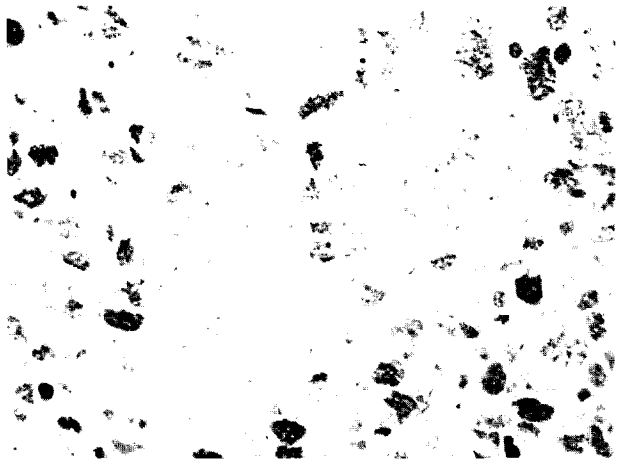

Figure 3. Negative reaction with PCNA in the giant cells but intensive positivity within mononuclear stromal cells

roid gland) in which the giant cell component is clearly malignant and has a different morphology than osteoclasts. The osteoclastoma-like giant cell tumors are found most commonly in the pancreas; but many other sites of parenchymal or soft tissue involvement have been described. So far, other six cases have been described in the lung; the epidemiological data, histological differentiation, bronchial association and metastatic spread of these tumors is summarized with our data are in *Table 2*.

It is important that these osteoclast-like giant cell tumors of the lung should be differentiated from a metastasis of giant cell tumors of the bone which occur occasionally.[30]

The origin and nature of the osteoclastoma-like giant cell tumors are uncertain. The relationship between the mononuclear cells and osteoclast-like giant cells, as well as their connection to the carcinomatous areas observed in some cases, is not clear. When considering immunohistochemical and ultrastructural features of mononuclear cells some authors believe that they are dedifferentiated epithelial elements,[5,32,40,41] while others do not find such evidence and support the mesenchymal origin.[7,12] Our results are partly in agreement with those of Kuroda *et al.*[28] who also found, in a similar but benign lung tumor, that mononuclear cells were positive with CD68 and vimentin; however, we failed to observe positive reactions with lysozyme and α-1-antitrypsin.

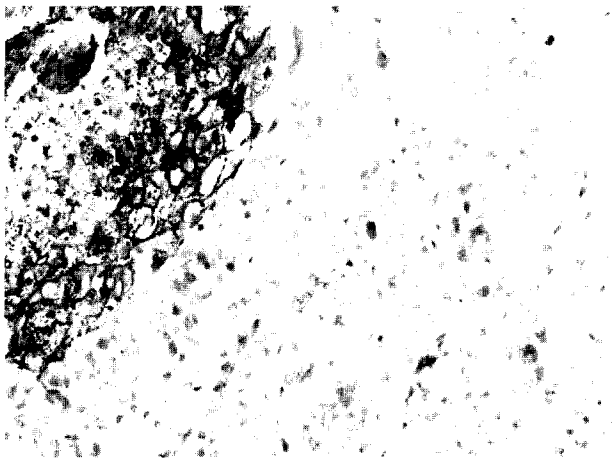

Figure 2 B. Foci of dedifferentiated squamous epithelial cells gave strong reaction for epithelial membrane antigen. All other elements were negative.

***Table 2.* Clinical and morphological characteristics**

Reference	*Age/ sex*	*B**	*Histology*				*Metastases*	*Follow-up*
			sq	*ad*	*sarc*	*gc*		
(17)	42/f	+		–	–	–	–	no data
(23)	40/m	+	–		–	–	–	no data
(28	77/f	–	–	–	–	–	–	autopsy
(32)	60/m	+	+	–	+	–	generalized	6 days
(35)**	?	?	–	+	+	+	?	?
(37)	57/m	–	+	–	+		–	5 years
this case	62/m		+	–	–	+	–	15 months

B* – association with bronchus; sq – squamous; ad – adenoid; sarc – sarcomatoid; gc – bizarre giant cells; ** – only abstract

It seems that extraosseal tumors containing osteoclast-like giant cells cannot be classified as a homogenous group. Based upon the different immunoreactivity of mononuclear cells one can distinguish carcinomas with osteoclast-like giant cells from extraosseal osteoclastoma-like tumors by means of with mesenchymal/histiocytic differentiation. A further question is the origin and nature of the moderately differentiated squamous carcinoma islands mixed with the epithelial marker negative mononuclear cells. There are several options: *a.* All components could have a common origin. In this case, it could be related even to giant cell variant of malignant fibrous histiocytoma which, according to Fletcher,[16] may represent the end stage of poorly differentiated tumors, "horri-

bile dictu" carcinomas. *b.* Lung carcinomas induce atypical histiocytic proliferation which overgrows the primary lesion. *c.* Ostoclastoma-like giant cell tumor could be the cause of squamous metaplasia of the bronchial epithelia. Notably, in our case, there was no connection with the bronchi and the atypical squamous cell islands intermingled with other elements.

The origin of the osteoclast-like giant cells is controversial. In several cases they showed epithelial differentiation,[11,41,43,45] in others they have been interpreted as mesenchymal.[17,15,14,37,44] Athanasou *et al.*[2] suggested that osteoclast-like multinucleated giant cells are a specific type of macrophage, distinct from osteoclast or other types of inflammatory polykaryon. In our case, the multinucleated giant cells were clearly unreactive with epithelial markers, or with lysozyme and α-1-antitrypsin, but showed reactivity with LCA, CD68 and vimentin, supporting mesenchymal and histiocytic differentiation of these cells. Considering the morphology of the osteoclast-like giant cells and the negativity of p53 and PCNA, we think that these cells are non-proliferating, probably reactive, elements of the tumor.

The natural history of tumors containing osteoclast-like giant cells is distinct. Rapid progression and metastatic potential are characteristic of carcinomas containing osteoclast-like giant cells while epithelial marker negative tumors with histiocytic differentiation, especially in the periphery of the lung, seem to have a better prognosis. In the latter group, the histologically benign and malignant counterparts must be distinguished.

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