

# Extraskelatal Myxoid Chondrosarcoma-like Features in Metastasizing Lung Adenocarcinoma: Unique Morphological Changes after Chemo-radiotherapy

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## Abstract

Lung cancer closely resembling Extraskelatal Myxoid Chondrosarcoma (EMC), called “primary pulmonary myxoid sarcoma (PPMS),” is an extremely rare tumor. This report is presented here of a unique case showing EMC-like changes only in metastases from conventional lung adenocarcinoma in an 81-year-old man. After lung tumor resection and chemo-radiotherapy, he underwent the resection of right adrenal metastasis composed of carcinomatous and EMC-like components. There were multifocal transitions between these components. He was treated with additional chemo-radiotherapy for newly developed liver and brain metastases, but he died 3.3 years after the initial surgery. Autopsy revealed EMC-like tumors, with or without minute adenocarcinomatous components, extensively involving widespread organs. Reverse transcription-polymerase chain reaction did not detect *EWSR1-CREB1* fusion in the primary tumor or metastases. These features indicated that the current tumor was different from PPMS characterized by *EWSR1-CREB1* fusion. We concluded that such EMC-like features represent morphological changes of metastatic lung adenocarcinoma. We believe that this possible occurrence should be recognized for accurate diagnosis of metastatic lung carcinoma.

**Keywords:** Chemo-radiotherapy; Extraskelatal Myxoid Chondrosarcoma; *EWSR1-CREB1*; Lung; Adenocarcinoma

## Introduction

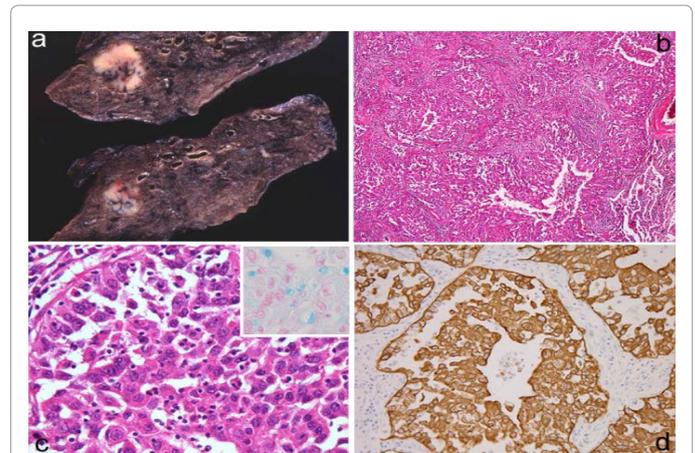
Extraskelatal Myxoid Chondrosarcoma (EMC) is an uncommon soft-tissue tumor usually originating in the deep tissues [1]. Primary lung cancers resembling EMC have been rarely reported as “primary pulmonary myxoid sarcoma (PPMS)” [2,3]. Recently, we encountered a unique autopsy case of lung carcinoma showing EMC-like features only in metastases after chemo-radiotherapy. To our knowledge, such EMC-like changes have not been mentioned previously in metastases of lung carcinoma, although therapy-induced myxomatous or colloid-like changes have been reported in some other site cancers [4,5]. We herein described this case to expand our knowledge of morphological changes in metastasizing lung carcinoma.

## Case Report

An 81-year-old man underwent the left upper lobectomy for a 2 cm-sized lung tumor. Before the lobectomy, the whole-body examination using X-ray computed tomography (CT) scan and bone scintiscan could not reveal any metastases, and the removed tumor was classified as Stage IA (pT1N0cM0). The patient did not receive additional chemo-radiotherapy, and was followed up with laboratory examination of serum tumor markers and chest radiologic examination. About 1.5 years later, abdominal X-ray CT scan was performed for his progressive weight loss in a year, and revealed a right adrenal metastasis. He was treated with local radiotherapy and chemotherapy using gemcitabine, vinorelbine, and tegafur. Because of its progressive increase 1.2 years after the beginning of chemo-radiotherapy, the right adrenalectomy was performed. Thereafter, for newly developed liver and brain metastases, he received additional chemotherapy using gemcitabine, vinorelbine, and paclitaxel, and radiotherapy for brain metastasis. However, he died 3.3 years after the initial surgery.

The well-demarcated primary lung tumor showed features of poorly differentiated adenocarcinoma (histological grade 3) composed of nested polygonal cells occasionally showing papillary or mucin-positive glandular features (Figure 1). Sarcomatous features were not

identified. The surgically removed right adrenal metastasis included adenocarcinomatous components and myxoid areas (Figure 2a).



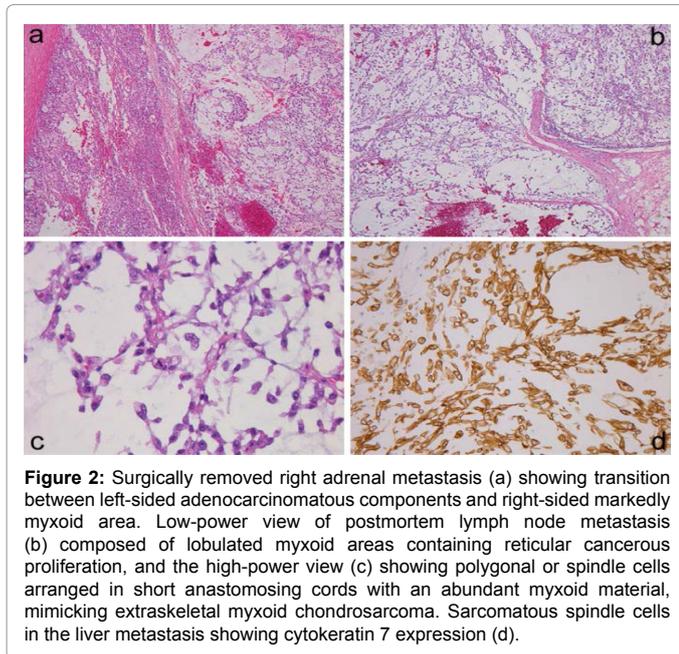
**Figure 1:** Primary lung adenocarcinoma (a) showing a well demarcated nodule. Low-power view (b) showing nested and vague papillary cancerous growth and high-power view (c) demonstrating polygonal cancer cells (c) with alcian blue+ lumina (c, inset). Primary carcinoma cells expressing strong positivity for cytokeratin 7 (d).

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The latter consisted of faintly eosinophilic spindle or polygonal cells proliferating in a fascicular or reticular fashion, mimicking EMC. There were multifocal transitions between these carcinomatous and sarcomatous components. Autopsy revealed EMC-like tumors extensively involving both lungs, liver, peritoneum, left adrenal gland, brain, and generalized lymph nodes (Figures 2c and 2d). Minute concomitant adenocarcinomatous features were found focally in these myxoid tumors.

Adenocarcinomatous components in both the primary tumor and metastases were diffusely positive for pan-cytokeratin (pan-CK), CK7 (Figure 1d), epithelial membrane antigen (EMA), focally positive for carcinoembryonic antigen (CEA), Napsin A, and vimentin, but were negative for CK20, thyroid transcription factor-1 (TTF-1), S-100 protein, CD34, desmin, smooth muscle actin (SMA), or HMB-45. EMC-like components in both the right adrenal metastasis and postmortem metastases were focally positive for pan-CK, CK7 (Figure 2d), EMA, and vimentin, but were negative for CEA, Napsin A, TTF-1, SMA, S-100 protein, or CD34. Reverse transcription-polymerase chain reaction (RT-PCR) using the formalin-fixed, paraffin-embedded tissues (the primers and PCR conditions used were described elsewhere [6]) did not detect *EWSR1-CREB1* and *EWSR1-ATF1* fusions in the primary tumor, surgically removed right adrenal metastasis, or postmortem liver myxoid tumor.

## Discussion

In this case, there were distinct transitions between adenocarcinomatous components and EMC-like features chiefly in right adrenal metastasis and focally in postmortem specimens. These findings suggested that EMC-like features represent secondary changes of pulmonary adenocarcinoma. In addition, in the primary lung tumor before chemo-radiotherapy, EMC-like features were not identified. These findings raised a possibility that such therapy may play a role in EMC-like changes of metastases. Previous reports have described therapy-induced histological alterations, such as necro-inflammatory response in non-small lung carcinoma [7], massive myxomatous

response in prostatic and rectal adenocarcinomas [4,5], clear cell carcinoma-like features in ovarian carcinoma [8], and granulosa cell tumor-like pattern in ovarian sex cord tumor with annular tubules [9]. However, therapy-induced EMC-like changes have not been mentioned previously in lung or other site carcinoma. Moreover, in the current case, the histology of metastatic sites before chemo-radiotherapy was unknown. Widespread metastatic lesions without radiotherapy also showed EMC-like changes. Hence, the current study could not determine whether EMC-like changes in this case were a chemo-radiotherapy-induced condition or a simply manifestation of metastases themselves.

Primary lung tumors resembling EMC include PPMS [2,3], pulmonary angiomatoid fibrous histiocytoma (AFH) [10], and pulmonary microcysticfibromyxoma [11]. PPMS is a rare tumor of uncertain differentiation, characterized by EMC-like histology and *EWSR1-CREB1* fusion [2,3], and this entity would encompass “low-grade pulmonary myxoid sarcoma” [12] and “primary pulmonary EMC” [13]. The currently presented primary and secondary tumors showed pan-CK/CK7+ and no *EWSR1-CREB1* fusion, which could rule out a diagnosis of PPMS. Similarly, CK+ in the current case is distinctively different from no CK expression in pulmonary AFH and microcysticfibromyxoma [10,11]. No *EWSR1-ATF1* fusion in the present case can rule out a diagnosis of AFH [10]. Lung myoepithelioma with extensive myxoid changes may be another differential diagnosis of this case. However, most cases of myoepithelioma were S-100 protein+ and/or SMA+ [3,14], whereas such expressions were not observed in the current case. Hence, the present case would represent no myoepithelial differentiation in primary or secondary lesions.

Thus, EMC-like changes can occur in metastasizing lung adenocarcinoma. Consideration of this possible occurrence would be useful for accurate diagnosis and therapeutic management of patients with lung carcinoma, although it may be a rare phenomenon.

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