Pulmonary adenocarcinoma with osseous metaplasia: a rare occurrence possibly associated with early stage?

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Abstract: Adenocarcinoma is the most common type of malignant pulmonary tumor, but osseous metaplasia of this tumor is extremely rare. To date, only 21 cases have been reported in the literature worldwide. Here, we report a case of primary pulmonary adenocarcinoma with benign osseous stromal metaplasia in a 60-year-old woman and discuss the pathogenesis of intratumoral ossification and review the relevant literature. We found that pulmonary adenocarcinoma with osseous metaplasia may be more likely to occur in early tumor stages.

Keywords: pulmonary adenocarcinoma, immunohistochemistry, osseous metaplasia

Introduction

Metaplasia is a process in which a differentiated cell type is replaced by another mature differentiated cell type. Although rare, osseous stromal metaplasia has been described in the literature for both benign and malignant neoplasms. Here, we report a unique case of primary pulmonary carcinoma with osseous metaplasia. We believe that this is a case of minimum bone formation (approximately 1.25 mm × 0.85 mm) in a primary pulmonary carcinoma.

Case report

A 60-year-old Chinese woman presented with the symptom of bloody sputum, which she had noticed for 2 weeks. Enhanced computed tomography (CT) showed an irregular abnormal soft tissue mass located in the left upper lobe that was approximately 1.7 cm×0.8 cm in size and obviously enhanced with contrast medium (Figure 1). The CT value in the enhanced arterial phase was approximately 40–60 Hounsfield units, while the venous phase CT value was approximately 72 Hounsfield units. Minimal calcification was not apparent in the tumor. The patient denied any history of gastric carcinoma or digestive symptoms. On the basis of her history and imaging studies, the patient was diagnosed with a malignant pulmonary tumor and underwent lobectomy.

Hematoxylin and eosin-stained sections showed that the alveolar structure had disappeared within the tumor and that the tumor cells were distributed into round or oval glands with a central lumen. There was no mucin in the tumor cell cytoplasm or glandular cavity. The tumor cell nuclei were ovoid and dark-stained, with prominent nucleoli. The mitotic activity was approximately two mitoses per ten high-powered fields. New bone formation was observed at the center of the tumor (approximately...
1.25 mm × 0.85 mm, Figure 2A). The bone island consisted of mature bone tissue and was surrounded by osteoblast cells that were accompanied by proliferating fibroblasts (Figure 2B). No bone marrow cells were present in the bone tissue. Immunohistochemical staining showed that the tumor cells were positive for cytokeratin-7 (Figure 3A) and thyroid transcription factor-1 (Figure 3B), but the metaplastic bone tissue was negative for these factors. However, the tumor cells were negative for caudal-related homeodomain protein 2, which ruled out the possibility of gastrointestinal adenocarcinoma metastasis to the lung, and the Ki-67 labeling index was approximately 35%. An epidermal growth factor receptor exon 19 deletion mutation was found in this patient, but the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase rearrangement was not found. On the basis of histologic and immunohistochemical findings, this tumor was diagnosed as an invasive pulmonary adenocarcinoma with a predominant acinar pattern, accompanied by osseous metaplasia in tiny lesions and without lymphatic metastasis. This diagnosis was based on the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system for standard lung adenocarcinoma.

Discussion

Malignant neoplasms accompanied by osseous metaplasia have been sporadically reported in the kidney, gastrointestinal tract, thyroid, soft tissue, endometrium, bladder, brain, and urachus; however, heterotopic ossification within a primary pulmonary carcinoma is extremely rare. Only 21 cases of pulmonary adenocarcinoma with heterotopic ossification have been previously reported in patients whose ages ranged from 46 to 76 (mean 62.4) years. The male to female ratio in these patients was 11:10, and the tumor sizes ranged from 1.5 cm to 7 cm (mean 3.59 cm). One patient received radiotherapy. Two patients also presented with osteoplastic metastasis. Follow-up information was available for 14 patients and indicated that one patient died after 33 months, while one patient developed a recurrence after 60 months of follow-up. In contrast with patients having conventional lung adenocarcinoma, which usually presents as an advanced cancer, lung adenocarcinoma with osseous metaplasia seems to be more frequent in early-stage disease, given that patients with stage I, II, III, and IV disease accounted for 57.1% (n=12), 14.3% (n=3), 19.0% (n=4), and 4.8% (n=1) of the cases, respectively; staging information was not available for one patient. The stage of the patient presented in this paper was IA, which is consistent with this phenomenon (Table 1).

The mechanism responsible for osseous histogenesis in malignant neoplasms remains obscure. Several studies have documented that osseous metaplasia results from osteoblast metaplasia of pulmonary fibroblasts. Other studies reported abnormally high serum calcium levels (hypercalcemia) in patients with malignant neoplasms; these levels were closely associated with bone formation. However, the serum calcium level was within normal limits in this patient. Most authors report that multipotent stromal stem cells are involved in
the metaplastic process, resulting in bone formation.\textsuperscript{24} Some cytokines such as bone morphogenetic protein 7 promote bone formation by inducing differentiation of pluripotent cells, mesenchymal cells, or fibroblasts into osteoprogenitor cells.\textsuperscript{25} Further, some studies showed that bone formation might occur as a result of local or systemic inflammation. Inflammatory cells, including monocytes and macrophages, produce cytokines such as tumor necrosis factor-alpha and interleukin-1. Tumor necrosis factor-alpha and interleukin-1 are reported to stimulate activated cells to produce transforming growth factor beta and bone morphogenetic protein 7, which act as local cellular regulators of ectopic bone formation.\textsuperscript{26,27}

Osseous histogenesis in malignant neoplasms is a rare and interesting phenomenon, but the prognostic implications of this occurrence are not very clearly described in the literature. Some studies suggest that cerebral ventricle ependymoma with ossification might exhibit more aggressive clinical behavior.\textsuperscript{8} However, ossification has been suggested to be a marker of favorable prognosis in patients with renal cell carcinoma.\textsuperscript{28} Therefore, investigations of the prognosis in patients with pulmonary adenocarcinoma and bone formation remain worthwhile. The lack of evidence of recurrence and metastasis in this patient at a 26-month follow-up indicated that ossification in pulmonary adenocarcinoma might not have adverse prognostic implications, but a longer follow-up period and more case studies are needed to illustrate this rare phenomenon.

**Disclosure**

The authors report no conflicts of interest in this work.

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