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Case Report

A sarcomatoid localized malignant mesothelioma with ostesarcomatous elements

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1. Introduction

A sarcomatoid tumor located in the pleura is difficult to diagnose because there are many possible conditions, such as malignant mesothelioma and soft tissue sarcomas, that must be considered in the differential diagnosis. From the location of the tumor, the first consideration might be sarcomatoid malignant mesothelioma. If the patient has a history of asbestos exposure or shows characteristic thick pleura, the diagnosis of malignant mesothelioma is straightforward. However, if the patient has no history of asbestos exposure and shows a localized mass, making the correct diagnosis is a challenge.

We encountered a case of a solitary osteogenic sarcomatous tumor located in the pleura in a patient with no history of asbestos exposure. It was difficult to make the diagnosis, and we herein discuss the differential diagnosis of this tumor, focusing on sarcomatoid localized malignant mesothelioma (LMM) with osteosarcomatous elements and extraskeletal osteosarcoma of the pleura.

1.1. Case report

A 70-year-old woman was evaluated for a nodule in the right lower lobe of the lung on chest X-ray at her regular checkup. She was a "never smoker" and had never been exposed to asbestos. Her physical examination, blood biochemistry test results, and complete blood counts were normal and no pleural effusion was seen. High-resolution computed tomography (CT) of the chest showed an irregularly shaped, 7-cm-diameter mass of the right lower lung. Positron emission tomography-CT showed no evidence of any other primary site outside of the right lung. Since transbronchial lung biopsy specimens showed a few atypical short spindle cells with osteoid material, this lesion was considered a malignant tumor, but the final diagnosis was not confirmed because of the small number of tumor cells included in the biopsy materials. Based on the biopsy diagnosis of a malignant tumor, a right lower lobectomy of the lung was performed. After the lobectomy, chemotherapy with Cisplatin and Adriamycin was performed, however the patient developed a tumor in the right pleura that grew rapidly and occupied the right chest cavity. The patient died of respiratory failure 11 months after the lobectomy.

1.2. Pathology

On gross examination, the specimen of the right lobectomy showed a white colored, 65 × 45 × 35 mm^3, firm, localized mass located in the right lower parietal pleural and sub-pleural regions (Fig. 1), with no attachment between the tumor and ribs. Histopathologically, the tumor was pushing the pleural elastic plate, with invasion into the lung parenchyma (Fig. 2 A and B), and the major part of the tumor showed proliferation of atypical short spindle cells producing coarse lace-like neoplastic bone similar to conventional osteosarcoma of the bone (Fig. 2 C). Near the pleural area, focal proliferation of atypical round cells similar to mesothelial cells was seen (Fig. 2D). On immunohistochemistry, the tumor cells were diffusely positive for vimentin in both osteosarcomatous and mesothelial-like cells, focally positive for AE1/AE3 (Fig. 2E) and pan-cytokeratin (panCK), and weakly positive for calretinin (Fig. 2F) and D2-40 only in mesothelial-like cells. The osteosarcomatous area showed weak, focally positive staining for AE1/AE3 and panCK, and negative staining for mesothelial markers. All tumor cells were negative for S-100, alpha smooth muscle actin, cytokeratin 7, epithelial membrane antigen, and thyroid transcription factor 1. Additional immunohistochemistry for special AT-rich sequence-binding protein 2 (SATB2) as a marker of osteoblastic differentiation was performed. Nuclear SATB2 immunoreactivity was detected only in osteosarcomatous elements (Fig. 2G), and it was negative in mesothelial-like atypical round cells in this tumor (Fig. 2H).

Thus, a diagnosis of sarcomatoid LMM with osteosarcomatous elements was suggested based on the findings mentioned above, especially the tumor location, the focal proliferation of atypical round cells similar to mesothelial cells adjacent to the pleura, and the positive staining for cytokeratins (AE1/AE3 and pan CK) and mesothelial markers (calretinin and D2-40), even though the latter was weak.

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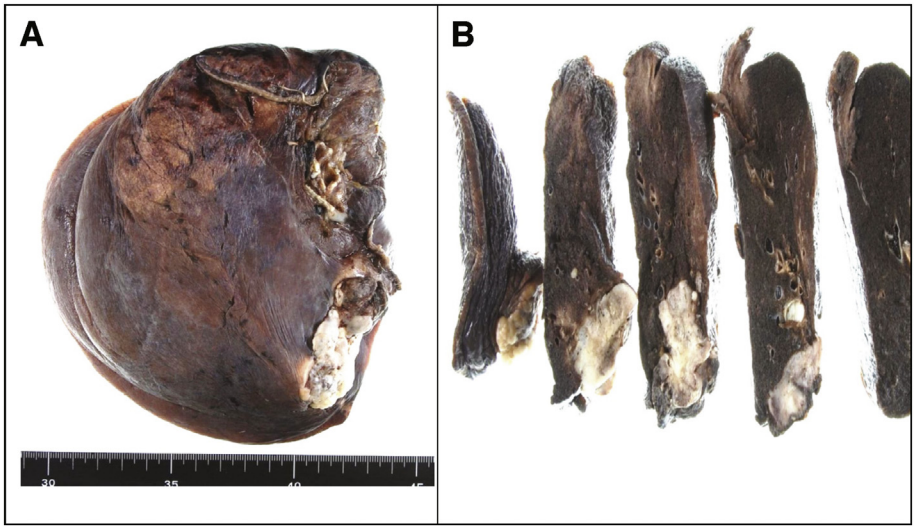

Fig. 1. Grossly, the tumor is a white-colored, 65 × 45 × 35 mm^3, firm mass located in the right lower pleural region (A,B).

2. Discussion

The differential diagnosis of sarcomatoid tumor of the pleura is often challenging. In the present case, a well circumscribed mass was found abutting the pleura, and the tumor cells showed prominent production of coarse lace-like neoplastic bone similar to conventional osteosarcoma of the bone. In the differential diagnosis, two conditions were considered: a sarcomatoid LMM with osteosarcomatous elements, and an extraskeletal osteosarcoma of the pleura.

Malignant mesotheliomas are classified into two categories, diffuse malignant mesothelioma (DMM) and localized malignant mesothelioma (LMM). Most malignant mesotheliomas are DMMs, which proliferate diffusely along the pleura. In contrast, LMMs are rare and appear as distinctly localized nodular lesions without diffuse pleural spread [1]. Historically, the term “LMM” was used not only for “true” LMM, but also for a variety of pleural tumors, including benign fibrous tumors or DMMs, until Crotty et al. first described six true cases of LMM in 1994 [2]. LMM has been classified as a separate disease entity since the 2004 World Health Organization (WHO) classification. Over 50 cases have been reported in the English literature since Crotty's report [1, 3, 4]. According to three large series of LMMs, the mean age at diagnosis was around 60 years [2, 5, 6]. Most LMMs arise from the pleura, and a few arise from the peritoneum [5]. Unlike DMMs, about 62% of LMMs had no history of asbestos exposure in a review of 52 reported cases [3]; thus, the relationship between asbestos exposure and the tumorigenesis of LMM is unclear [2, 3, 5–7]. Similar to DMM, LMM has three histological subtypes: epithelial, biphasic, and sarcomatoid. Although calretinin, D2-40, Wilms tumor 1, and cytokeratin are useful markers of LMM, the sarcomatoid type is often negative for these mesothelial markers [8, 9]. In reported sarcomatoid LMM cases, the diagnosis was confirmed based on tumor location and focal positivity for mesothelial markers or cytokeratins on immunohistochemistry [5, 10]. Interest in the diagnostic applications of p16/CDKN2A deletion in sarcomatoid DMM has increased recent years [11]. However, it was not possible in the present case to analyze p16/CDKN2A deletion by fluorescence in situ hybridization because the DNA in the tissues of paraffin sections was damaged due to decalcification of osteoid material (data not shown).

In contrast, over 60 case reports of extraskeletal osteosarcoma arising from the pleura have been reported in the English literature [12–16]. Vimentin is positive, and S-100, alpha-SMA, EMA, and CK are positive in various ratios, but they are not specific. The diagnosis in most reports was based on a localized mass of the pleura that consisted of pleomorphic spindle cells with osteogenesis in a similar histologic pattern to that of conventional osteosarcoma of the bone, and many reports did not mention examinations for mesothelial markers. Because focal immunoreactivity for CK and negative immunoreactivity for mesothelial markers could be seen in both pleural extraskeletal osteosarcoma and sarcomatoid LMM, the current study with immunohistochemistry could not distinguish between them.

Mesothelial cells have potential plasticity of differentiation including to osteoblasts [17], which is consistent with the fact that heterologous elements in DMM are often recognized, and osteosarcomatous elements are the most frequent [18]. However, an LMM case with heterologous elements has not yet been reported. In the report of a series of 27 cases of DMM with heterologous elements, the authors suggested that the criteria for osteosarcomatous elements in malignant mesothelioma should mirror those applied for primary osteosarcoma of bone and soft tissue. They also suggested that a pleural localized mass lesion reported as a malignant pleural mesenchymoma with heterologous differentiation might be a case of LMM with heterologous differentiation. Some reported cases of primary extraskeletal osteosarcoma of the pleura had a history of asbestos exposure [19] or suspected occupational asbestos exposure [16],with no mention of positivity of mesothelial markers.

Recently, SATB2 was reported as a novel marker of osteoblastic differentiation in bone and soft tissue tumors, especially in cases of skeletal/extraskeletal osteosarcoma [20]. In addition, SATB2 immunopositivity was also reported in heterologous osteosarcomatous components of gynecologic tract carcinosarcomas [21]. Similarly, the present case showed positivity for SATB2, and mesothelial-like atypical round cells were negative, which suggested that this tumor was partially associated with osteoblastic differentiation.

Thus, there are no evidence-based criteria for completely distinguishing between sarcomatoid LMM with osteosarcomatous elements and extraskeletal osteosarcoma of the pleura. Some authors have suggested that sarcoma-like tumors arising from the pleura should be considered mesothelial in origin, because true mesenchymal sarcomas arising from the pleura are extremely rare [18, 22].

Taking all of these together, this tumor was considered a sarcomatoid LMM with osteosarcomatous elements based on the tumor location, focal proliferation of mesothelial-like tumor cells and focal positivity for a mesothelial marker and cytokeratins, in addition to the background of a pleural tumor. Further analysis of the nature of mesothelial cells with potential plasticity of differentiation including osteogenesis should be established to elucidate the tumor origin and the mechanism of tumorigenesis.