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## Case report

# Recurrent spontaneous pneumothoraxes as a complication of osteosarcoma metastases: a case report <sup>☆</sup>

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## ABSTRACT

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. Osteosarcomas are highly aggressive tumors that historically have had a dismal prognosis. However, the survival rate has improved significantly with the addition of adjuvant and neoadjuvant chemotherapy. Here, we present a case report of a 13-year-old male with a history of a left humeral osteosarcoma whose course was complicated by recurrent sarcoma-related pneumothoraces. Despite recurrent pneumothoraces being a relatively uncommon complication of osteosarcoma, they present a great challenge to providing treatment that optimizes outcomes and quality of life for patients.

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## Introduction

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, of which high-grade intramedullary osteosarcoma, also known as *conventional osteosarcoma*, accounts for 85% of all cases [1]. Osteosarcomas typically arise in the metaphysis of long bones and spread longitudinally within the medullary cavity [1,2]. They are highly aggressive tumors that historically have been accompanied

by a dismal prognosis, with approximately 80% mortality within 2 years despite surgical treatment [3]. In recent years, the addition of neoadjuvant and adjuvant chemotherapy has increased the 5-year survival to approximately 65% in patients without metastatic disease at presentation [1]. However, despite treatment, conventional osteosarcomas continue to have a high metastatic potential, particularly through hematogenous spread to the lungs [1]. Pulmonary metastases are typically peripheral and may be mineralized [4]. Rarely, these metastases can result in chronic pneumothorax [4].

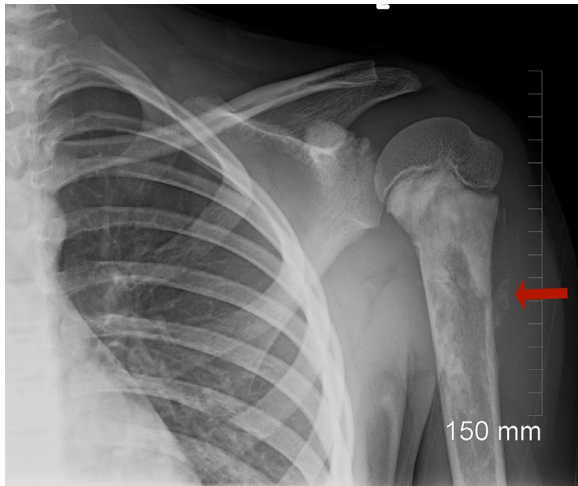
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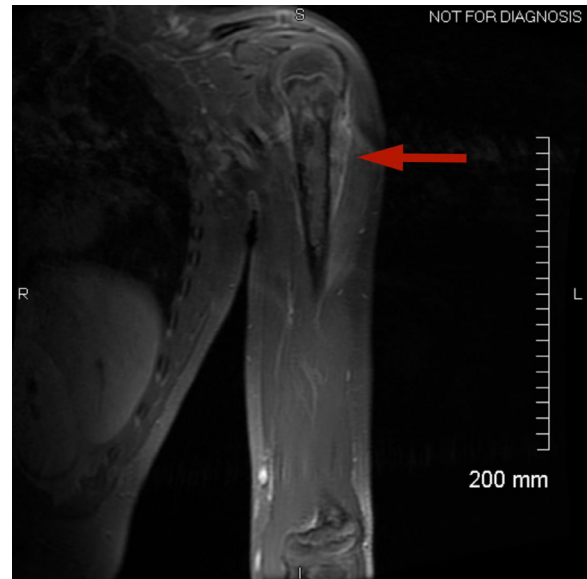
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**Fig. 1 – Shoulder radiograph showing a sclerotic mass in the proximal left humeral diaphysis and metaphysis with a wide-zone of transition and an adjacent soft-tissue mass containing ossification (red arrow) (Color version of figure is available online).**



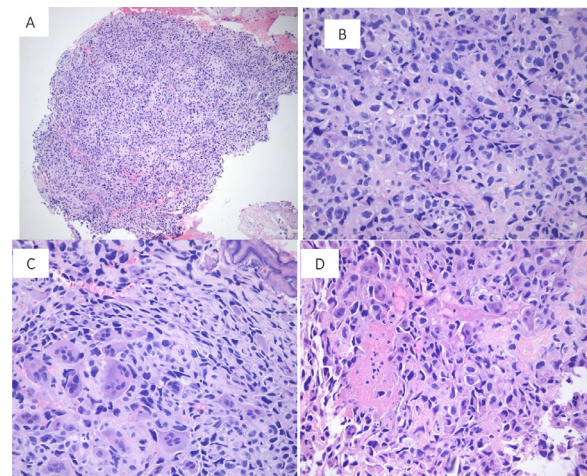
**Fig. 2 – Fat-saturated post contrast T1 weighted MRI image showing an enhancing mass around the proximal humerus (red arrow) (Color version of figure is available online).**

## Case report

A 13-year-old healthy male presented to his primary physician for evaluation of left shoulder pain that started after attempting a layup during a basketball game. On physical examination, his shoulder alignment was normal, and there was no redness, warmth, swelling, or palpable mass. He was neurovascularly intact, and his motor function was preserved. A radiograph demonstrated a blastic lesion in the left proximal humerus extending from the proximal growth plate 7 cm distally along the humeral shaft (Fig. 1). A follow-up MRI demonstrated an aggressive, marrow replacing lesion extending from the physis to the distal fourth of the diaphysis, approximately 5.5 cm proximal to the capitellar and trochlear physes (Fig. 2). There was also evidence of extraosseous spread within the proximal third of the humeral diaphysis and a small enhancing soft tissue nodule concerning for a small pathologic lymph node. Based on these findings, there was concern for osteosarcoma with possible lymphatic metastasis. He therefore underwent open left humeral biopsy; pathology demonstrated conventional high-grade osteosarcoma (Fig. 3).

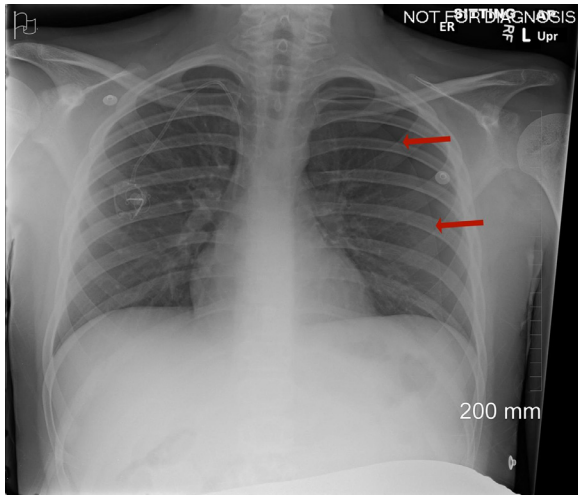
Given the extent of involvement, the patient completed a course of neoadjuvant chemotherapy with doxorubicin prior to proceeding with surgical resection. At that time, a chest CT and bone scan were both negative for metastases. After completion of chemotherapy, he underwent left proximal humerus resection with osteoarticular allograft and open reduction and internal fixation of the left humerus. Pathology demonstrated a 13 cm poorly differentiated osteosarcoma with a 50% treatment response. All margins were negative for osteosarcoma.

After surgical resection of his tumor, the patient continued adjuvant chemotherapy with doxorubicin. Approximately four months later (8months post-diagnosis), he presented to



**Fig. 3 – Low- and high-power histologic images of bone biopsy (A-D). Hematoxylin and eosin (H&E)-stained sections show a hypercellular high-grade sarcoma with admixture of epithelioid, ovoid and plasmacytoid neoplastic cells, increased mitotic activity with atypical mitoses, and scattered clusters of multinucleated, non-neoplastic osteoclast-like giant cells (A-D). Focally, neoplastic, eosinophilic tumor bone formation is present (B), some with coarse and lace-like appearance (C). Rare foci of tumor necrosis are also seen (D).**

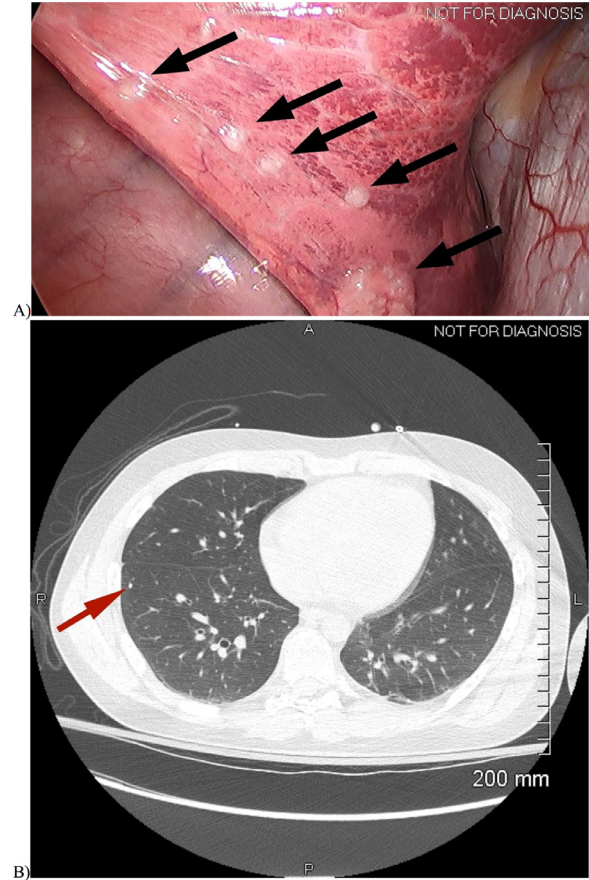
the emergency department with fevers and chills. On evaluation, his temperature was 99.7 F, he was tachycardic in the 120s, tachypneic in the 30s, and his oxygen saturation was in the low 90s on room air. A chest radiograph demonstrated a moderate left-sided pneumothorax (Fig. 4). Due to his history of osteosarcoma, there was a concern that his pneumothorax



**Fig. 4 – Chest radiograph showing a moderate left pneumothorax (red arrows); exam performed 8 months after initial diagnosis (Color version of figure is available online).**

was secondary to metastases. A chest CT demonstrated interval development of five nodules within the right middle and lower lobes with calcifications suspicious for metastatic disease, but no detectable nodules on the left. The patient subsequently underwent bilateral thoracotomies with wedge resections of the right middle and lower lobes and the left lower lobe (Fig. 5); pathologic evaluation confirmed metastatic osteosarcoma in the right and left lower lobes (Fig. 6).

Despite surgical resection of the known pulmonary nodules, the patient continued to present with recurrent left-sided pneumothoraces. He represented with pneumothoraces at 11, 13, and 15 months post-diagnosis (Fig. 7). Each pneumothorax was treated with chest tube placement for 0-2 days; resolution of the pneumothorax was confirmed with chest radiography prior to removal of the chest tubes (Fig. 8). Due to his recurrent pneumothoraces and interval progression and development of pulmonary nodules as demonstrated on a chest CT 15 months post diagnosis (Fig. 9), the patient underwent wedge resections of the left upper lobe and left lower lobe. Although it was originally planned to resect the metastases on the right lung the same day, the patient did not tolerate 1-lung ventilation during the operation, and therefore the right middle lobe lobectomy and wedge resections of the right upper and right lower lobes were performed in a second surgery a few days later. The patient did well following surgery until he again developed spontaneous, left-sided pneumothoraces 19 and 20 months post-diagnosis. These pneumothoraces were again treated with chest tube placements for 0-1 days, and resolution of the pneumothoraces were confirmed with chest radiography prior to removal of the chest tubes. Lastly, he developed a right-sided pleural effusion with a significant number of loculations 24 months post diagnosis. He was briefly admitted and treated with a tunneled pleural drainage catheter and administration of 4 mg of alteplase daily for three days; the catheter remained in place after discharge for continued output monitoring. Although these interventions provided short-

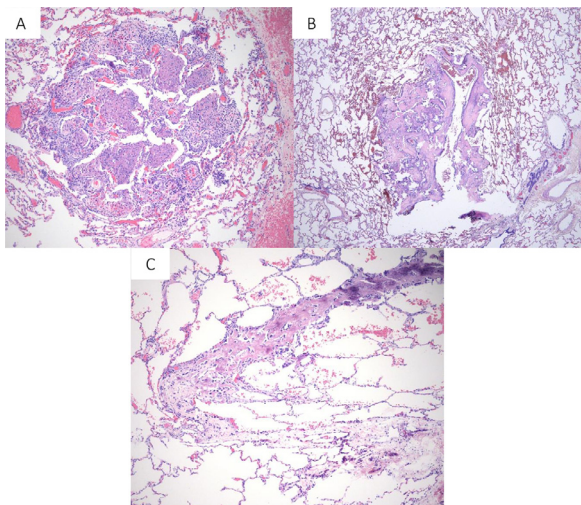


**Fig. 5 – (A) Intraoperative photograph showing subpleural lung nodules, (B) Axial chest CT image showing a tiny calcified nodule in the right lower lobe following evacuation of a left-sided pneumothorax with a pigtail tube. Nodules were occult in the left lung at this time; exam performed 8 months after initial diagnosis.**

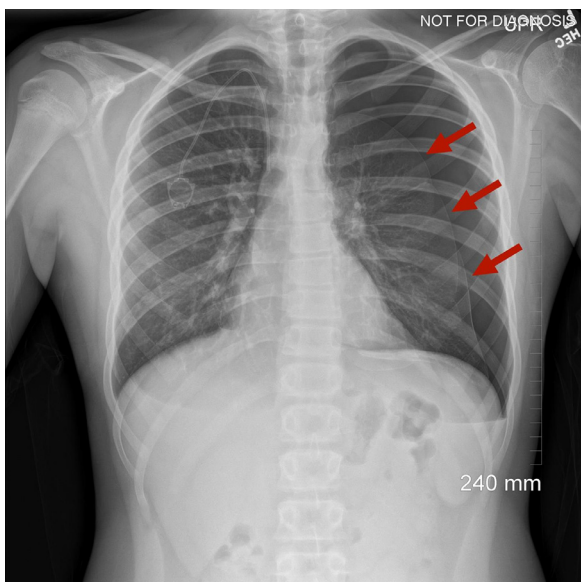
term relief, he continued to have progressive disease. He enrolled in hospice care and ultimately passed away 26 months after initial diagnosis.

## Discussion

Osteosarcoma is a tumor characterized by the production of osteoid by malignant cells. It is the most common nonhematologic primary malignancy of bone. Although onset can occur at any age, osteosarcoma tends to follow a bimodal distribution, with primary high-grade osteosarcoma most commonly presenting in the second decade of life while parosteal osteosarcomas peak in the third and fourth decades of life, and other secondary osteosarcomas occur in older adults ( $\geq$  age 60), typically in the setting of Paget's disease or prior radiation therapy [3-5]. Primary osteosarcomas most often occur at sites of the most rapid bone growth, including the distal femur, the proximal tibia, and the proximal humerus [3]. The presentation of osteosarcoma is very characteristic in nature. The majority of patients present with localized pain, typically

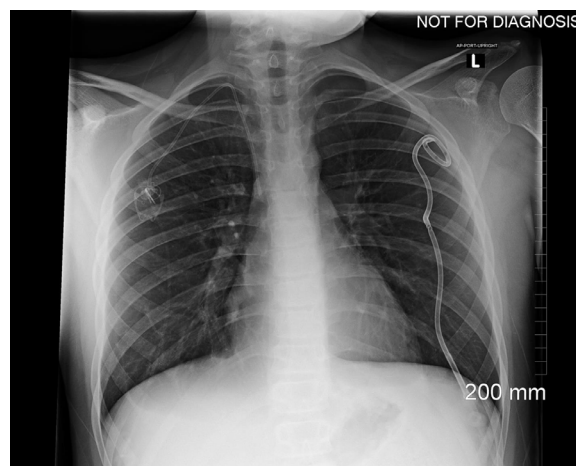


**Fig. 6** – Low- and medium-power histologic images from lung lobe resections with metastatic osteosarcoma (A-C). Hematoxylin and eosin (H&E)-stained sections show foci of metastatic osteosarcoma within the lung parenchyma. Bone matrix and coarse, lace-like neoplastic lamellar bone with primitive, disorganized trabeculae is directly produced by the osteosarcoma.

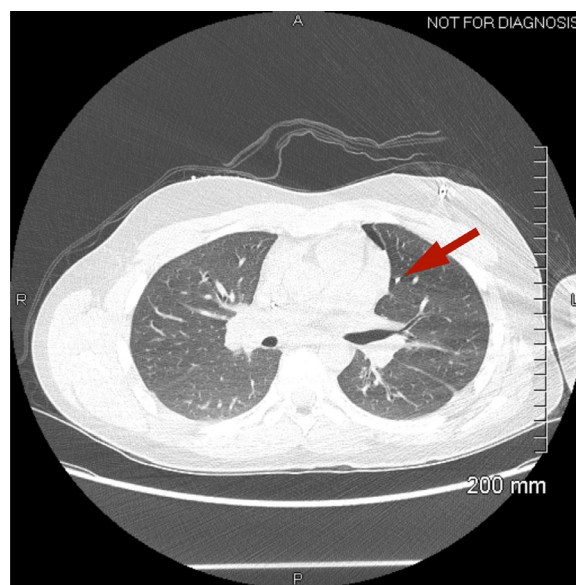


**Fig. 7** – Frontal radiograph showing a moderate left-sided pneumothorax (red arrows); exam performed 13 months after initial diagnosis (Color version of figure is available online).

of several months' duration. Pain frequently begins after an injury, and may wax and wane over time [6]. Pain may initially improve with conservative measures and activity modification, which may distract clinicians against a possible malignancy. However, the pain will tend to worsen with time and become refractory to initial therapies [3]. While night pain would be helpful in identifying a malignancy, only about 25% of pa-



**Fig. 8** – Frontal radiograph showing resolution of the left-sided pneumothorax following anterior pigtail chest tube placement; exam performed 13 months after initial diagnosis.



**Fig. 9** – Axial chest CT image showing a small calcified nodule in the lingula. A tiny residual left-sided pneumothorax is present following chest tube placement; exam performed 15 months after initial diagnosis.

tients experience this phenomenon. Systemic symptoms such as fever, weight loss, and malaise are generally absent [6].

Because patients with osteosarcoma typically present with a musculoskeletal complaint, initial imaging workup will typically consist of a radiograph. It should be noted that many patients will be misdiagnosed with a more common musculoskeletal problem at the initial visit and imaging may not be performed, thus leading to a delay in diagnosis. In some instances, this delay in diagnosis may be substantial. In 1 study, the delay from symptom onset to correct diagnosis was approximately 15 weeks, inclusive of a 6-week pa-

tient delay (time from symptom onset to physician encounter) and a 9-week physician delay (time from patient encounter to correct diagnosis). The most common reason for physician delay included failure to obtain radiographs at the initial visit [3].

Although conventional and secondary osteosarcomas are histologically indistinguishable, the diagnoses of these subtypes are made on the basis of radiographic appearance [7]. On radiography, conventional osteosarcoma typically presents as a metaphyseal lesion. There is a spectrum of radiographic appearances ranging from entirely lytic to entirely sclerotic. Most commonly, the medullary component is lytic with a spectrum of osteoid or chondroid matrix. Osteoid matrix is classically described as ‘cloud-like’ or ‘fluffy’, while chondroid matrix is often described as a rings and arcs pattern [4]. Tumor margins are often ill-defined and can show a lytic permeative or ‘moth-eaten’ appearance, which are features of an aggressive underlying process [4]. Cortical destruction is common, resulting in the development of an eccentric extra-osseous soft-tissue mass, which commonly shows typical osseous amorphous matrix mineralization. The density of the extra-osseous mass is increased by periosteal new bone formation that is frequently complex-perpendicular, spiculated or ‘sunburst’, or lamellated/onion skin or reactive with Codman angles at the margin of the tumor [4]. Although an MRI is not critical to diagnosing osteosarcoma, it is required for surgical staging as it can best define the extent of involvement of the tumor within bone, soft tissues, joints, and neurovascular structures. Additionally, MRI is often utilized to evaluate for the presence of intraosseous skip metastases, a known complication of conventional osteosarcoma. The presence of these skip lesions highlights the importance of covering the entire length of the involved bone and adjacent joints.

The natural history of osteosarcoma is hematogenous spread with subsequent development of pulmonary metastases [4]. Thus, the status of metastatic disease at time of presentation is the most important prognostic factor for osteosarcoma. As a group, patients with metastatic disease have a poor prognosis, with less than 20% long-term survival [3]. Patients with non-pulmonary metastases have an even worse prognosis, with less than 5% long-term survival. Other indicators of poor prognosis include larger tumor size, high lesion grade, poor response to chemotherapy ( $\leq 90\%$  necrosis), and a more proximal lesion location. Historically, patients with high-grade osteosarcoma were treated with immediate wide or radical amputation. Despite this treatment, 80% of patients with apparently isolated disease died of distant metastases. Based on this statistic, it is theorized that, despite a lack of imaging findings, most patients with high-grade osteosarcoma have nondetectable micrometastases at presentation. The goal of adjuvant and neoadjuvant chemotherapy is to treat these micrometastases. Currently, the treatment of high-grade osteosarcoma consists of neoadjuvant chemotherapy followed by surgical resection of the tumor and then adjuvant chemotherapy. Following adjuvant chemotherapy, pulmonary metastases are resected if possible [8].

A well-known but rare manifestation of metastatic lung cancer is a spontaneous pneumothorax [9]. Generally, the incidence of cancer-related spontaneous pneumothorax is small, accounting for less than 1.5% of all spontaneous pneumotho-

rases [10]. However, within cancer-related spontaneous pneumothoraces, the incidence varies by malignancy type. In particular, pneumothoraces appear to be more common in patients with sarcomas, especially osteosarcomas. In 1 study, approximately 11% of patients with osteosarcoma developed a spontaneous pneumothorax [11]. Although the exact mechanism of spontaneous pneumothorax in metastatic osteosarcoma is unknown, several mechanisms have been proposed. In sarcomas and germ cell tumors, spontaneous pneumothoraces are most commonly thought to be induced by necrosis and hemorrhage of pulmonary metastases as a result of chemotherapy. Specifically, it is thought that some peripheral, subpleural nodules are particularly chemosensitive, leading to rapid lysis and necrosis after treatment with chemotherapy. The eventual rupture of these nodules results in leakage of air into the pleural space, producing a pneumothorax [12,13]. Another mechanism that has been proposed includes the use of emetogenic chemotherapy agents. It is believed that, in combination with necrosis of subpleural nodules induced by chemotherapy, the increased intrathoracic pressure produced by emesis leads to rupture of the nodules, producing a pneumothorax [9,13]. Lastly, some authors have proposed that direct extension of metastatic lesions into the pleura or impairment of repair processes produced by some chemotherapy agents (eg Adriamycin, Doxorubicin), may be responsible for spontaneous pneumothoraces in metastatic osteosarcoma [12–14]. As mentioned previously, the current mechanism of spontaneous pneumothorax in patients with pulmonary metastatic osteosarcoma is unknown. It should also be noted that the previously proposed mechanisms are based on observational data, case reports, and review articles [11,14–16]. In fact, in a case report by Bini et al. in 2000, it was noted that only 28 cases of spontaneous pneumothorax as a complication of chemotherapy had previously been described [14].

Despite pneumothorax recurrence being common in osteosarcoma patients who develop a pneumothorax, the optimal management in this patient population is relatively unknown. Several methods have been tried, including chest tubes, pleurodesis, wedge resections, and chemotherapy. However, pneumothoraces still tend to recur [9]. In the future, it will be important to identify which treatment modalities optimize outcomes and quality of life for patients with recurrent pneumothoraces, as the current treatment options appear to provide limited, short-term benefit.

The development of a spontaneous pneumothorax in patients with sarcomas is a poor prognostic indicator with mortality rates of 50% at 4–5 months, 75% at one year, and 91% at 2 years. In particular, osteosarcoma had the lowest 3-month survival rate of the sarcomas, measuring 58% post-pneumothorax. Pneumothorax recurrence is also common in patients with sarcoma-associated pneumothorax and can be seen in almost 1-half of patients. In particular, patients presenting with spontaneous pneumothorax requiring chest tube placement are at a higher risk of recurrence [12]. As mentioned previously, pulmonary metastases may be treated with surgery and chemotherapy. While this method may be beneficial for patients with limited metastatic disease, it may not provide great benefit for patients with recurrent metastases. These patients may develop recurrent pulmonary metas-

tases leading to chronic pneumothorax necessitating frequent chest tube placement and multiple surgical resections.

## Conclusion

This case reviews pneumothorax as a complication of osteosarcoma. Chest tube placement, pleurodesis, wedge resections, and chemotherapy are all treatment options [9,12]. Despite pneumothorax recurrence being common in osteosarcoma patients, the optimal management in this patient population is unknown. In the future, it will be important to identify which treatment modalities optimize outcomes and quality of life for patients with recurrent sarcoma-related pneumothoraces.

## Patient consent

Written informed consent for publication was obtained from the patient.

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