Case Report

Parosteal Osteosarcoma with Pancreatic Metastasis and Multiple Relapses: A Case Report and Review of the Literature

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Abstract
Osteosarcoma is the most common primary bone cancer in all age groups. Metastasis most commonly occurs with high-grade tumors disseminating to the lungs and other bones. Spread to the pancreas is rare and undocumented in the low-grade subtypes. Additionally, it is uncommon for the disease course of low-grade subtypes to involve multiple relapses. We present a 35-year-old woman with parosteal osteosarcoma who has experienced an atypical metastasis to the pancreas as well as multiple local and pulmonary relapses. The lesion was identified incidentally on routine imaging, and the patient underwent resection. We compare our case to the other reports of pancreatic metastasis in the literature. Despite being especially rare, clinicians ought to be aware of pancreatic metastasis of osteosarcoma. Furthermore, despite parosteal osteosarcoma's less aggressive disease course, it can uncommonly lead to multiple relapses. We present a rare case exemplifying these phenomena in the prognostically favorable histologic subtype of parosteal osteosarcoma.

Introduction

Osteosarcoma is the most common primary bone malignancy in all age groups. The highest risk period for onset coincides with the adolescent growth spurt – 10–14 years old in females and 15–19 years old in males. This suggests an association between rapid bone
growth and malignant transformation [1]. The hypothesis of biologic factors involved in pubertal bone growth playing a role in the pathogenesis is further supported by the metaphysis of long bones being the most common location [2]. The prognostic improvements of multi-agent chemotherapy have made long-term monitoring for recurrence and distant metastasis imperative, which occur in 30–50 and 10–20% of patients, respectively [3–5]. Furthermore, it has been argued improved treatment has caused an increase in extrapulmonary metastasis [6]. Pulmonary metastases are still by far the most frequent (98%), followed by skeletal (37%), pleural (33%), cardiac (20%), renal and hepatic (17%), diaphragmatic (15%), and mediastinal (11%) [7]. Pancreatic metastases are extremely rare [8–11]. We present a case of solitary pancreatic metastasis of multi-recurrent parosteal osteosarcoma.

Case Presentation

A 35-year-old African-American female presented to a community emergency department with painless, progressively enlarging growth of the distal right lower extremity, first noticed by the patient 1 year prior. No other symptoms or physical exam findings were reported, and no history of trauma was given. Computer topography (CT) and magnetic resonance imaging showed a mass consistent with osteosarcoma of the distal tibia with soft tissue invasion (Fig. 1, 2). The emergency department referred the patient to our tertiary care center for further evaluation. Biopsy of the mass revealed low-grade juxtacortical osteosarcoma. Bone scintigraphy and chest CT revealed no evidence of local or distant metastasis. Limb-sparing bone and soft tissue resection of the mass was performed with second-look surgery done due to positive margins, both revealing histopathology consistent with parosteal osteosarcoma. The patient received no chemotherapy at this time. Seventeen months after removal of her primary lesion, surveillance imaging found locally recurrent disease, which was treated by additional limb-sparing bone and soft tissue resection. Pathology of the specimen reveals a 2.5 × 1.2 × 1 cm low-grade juxtacortical osteosarcoma. Three months after her first recurrence, chest CT found 4 calcified pulmonary nodules distributed among all 3 lobes of the right lung. The patient was asymptomatic. She underwent 6 cycles total of chemotherapy as per Children's Oncology Group AOST0331 protocol. A cycle consisted of doxorubicin 37.5 mg/m² and cisplatin 60 mg/m² on days 1 and 2 of weeks 1 and 6, with high-dose methotrexate 12 mg/m² on day 1 and leucovorin rescue on day 2 of weeks 4, 5, 9, and 10. Two cycles of neoadjuvant chemotherapy were administered, followed by wedge resection of pulmonary nodules with negative margins. Subsequently, 4 additional cycles of adjuvant chemotherapy were administered. Twenty months after her last dose, she required a wedge resection of a new pulmonary nodule in the left lower lobe. Three months after resection of the nodule in the left lower lobe, imaging showed recurrence in the same lobe, which was treated with another wedge resection. During the workup for this operation, a calcified mass located in the body of the pancreas, which was not present in remote imaging, first appeared on chest CT but was not noted. Over a 9-month interval, the mass was identified and monitored on surveillance imaging, growing to approximately 3 mm in its largest diameter (Fig. 3). The patient remained asymptomatic and had no prior history of pancreatic disease. Due to the lesion's growth and shared radiologic features with prior pulmonary metastatic findings, resection was recommended, consisting of distal pancreatectomy with splenectomy. Gross inspection of the surgical specimens showed a tan-white 0.3 × 0.3 × 0.3 cm calcified nodule within the pancreas, along with normal resected lymph nodes and spleen. Histopathologic evaluation revealed the lesion was comprised of bland, bony trabeculae consistent with metastatic osteosarcoma with 42 excised lymph nodes all negative for malignancy. Since the removal of her pancreatic metastasis, she has experienced no extrapulmonary disease. She has undergone 4 additional
pulmonary wedge resections and a right tibial revision with allograft implantation for suspected recurrences—only one of the pulmonary resections yielded specimens histopathologically positive for osteosarcoma. Nearly 10 years since initially presenting, she remains healthy without local or distant recurrence for a period of 4 years, continuing to routinely follow-up for surveillance imaging.

**Discussion and Conclusion**

Osteosarcoma is the most common primary bone malignancy in all age groups. Like other sarcomas, the tumor carries high-metastatic potential, usually arising in the lungs, pleurae, and bones. Less typically, the heart, mediastinum, diaphragm, liver, and kidneys may be affected. Parosteal osteosarcoma, the most common form of juxtacortical osteosarcoma, is a subtype characterized by skeletal surface growth of low-grade fibroblastic cells that produce lamellar bone with low potential for relapse and metastasis [12]. The multiple relapses described in our report is uncharacteristic of this variant. In a retrospective cohort study with a median follow-up of 11.2 years, only 2 out of 45 cases of parosteal osteosarcoma without dedifferentiation experienced either local relapse or distant metastasis, which exclusively
arose in the lungs. Additionally, the relapses were isolated for the duration of follow-up in all 4 patients [13]. Our case of parosteal osteosarcoma is particularly unique among the few reports of pancreatic metastasis; none of the cases of pancreatic metastasis found in our literature search reported low-grade primary tumors. Due to its less aggressive disease course, this histologic variant is normally treated with surgery alone with wide negative margins unless cells show dedifferentiation, which our patient’s pathology did not [14]. Despite this favorable histology and standard treatment, she has experienced a rare site of metastasis associated with markedly poor outcomes along with numerous local and pulmonary relapses. It should be noted that at diagnosis she lacked other important indicators of unfavorable prognosis as well, namely metastasis, proximal location, and large tumor size [15].

Pancreatic metastasis is rare regardless of primary malignancy but particularly in osteosarcoma [16]. Searching for prior cases, we identified 12 reported instances in the peer-reviewed literature of English-language publications [8–11]. No instances of pancreatic involvement at initial presentation have been reported, and the pancreas was not the site of the first metastatic recurrence in all except one case [8]. Although some patients present with constitutional or gastrointestinal symptoms, the majority with pancreatic metastases are asymptomatic, which was the case with our patient. The cause of concern in our patient was due to the radiologic features, such as calcification, of the pancreatic lesion. This characteristic is typical of osteosarcoma metastases. However, only 2 of the cases in the literature exhibited calcification and most were indistinguishable from primary cancer on imaging [9]. Cystic masses have also been reported [10, 11]. Most pancreatic metastases are intraparenchymal as seen in our report, but external invasion from typically the duodenum is documented [11]. Regarding posttreatment outcomes of the cases found in the literature, 4 were alive without disease after periods ranging from 6 to over 12 months, 5 died of their disease after 2 weeks to over 16 months, 1 died of unrelated causes after 8 months, and 2 did not disclose outcome status. At the time, this manuscript was submitted for publisher review; our patient is disease-free for over 4 years.

In conclusion, we submit a rare case of pancreatic metastasis of multi-recurrent parosteal osteosarcoma. With multiagent chemotherapy being widely accepted as the standard of care for improving outcomes in osteosarcoma, we anticipate continuing to see occasional reports of unusual recurrences, including pancreatic metastasis. Despite the paucity of gastrointestinal involvement in osteosarcoma, clinicians should be aware of the rare potential for
pancreatic dissemination. Furthermore, our report uniquely exemplifies this possibility even in the prognostically favorable subtype of parosteal osteosarcoma.

**Statement of Ethics**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Daniel Cirotski was the primary writer of the case report. Jyoti Panicker assisted in detailing the patient’s medical history and ensuring the accuracy of the publication.

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