Case Report
Primary cardiac osteosarcoma with recurrent episodes and unusual patterns of metastatic spread
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Abstract
Primary osteosarcoma of the heart is an extremely rare entity. In this report, we describe a case of primary osteosarcoma of the heart that recurred and metastasized. The patient is a 50-year-old woman who presented with an abrupt onset of dyspnea, dizziness, and palpitations. Echocardiography results showed a left atrial tumor that was resected and had histological features of high-grade osteosarcoma. The patient was treated with adjuvant chemotherapy. The tumor recurred in the same location 4 years later and was resected. Three years later, the patient presented with a 4-cm polypoid mass in the stomach that was consistent with metastatic osteosarcoma. One year later, the patient presented with recurrent high-grade sarcoma in the soft tissue of the left chest wall. We herein present the spectrum of histological findings and molecular genotyping data. © 2008 Elsevier Inc. All rights reserved.

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1. Introduction
Primary cardiac neoplasms are rare and less common than metastatic lesions of the heart. Autopsy series have reported ranges between 0.001% and 0.03% [1–5]. Rapid advances in diagnostic modalities including the use of noninvasive echocardiography modalities have improved the ability to diagnose cardiac neoplasms [2].

The majority of the primary cardiac tumors are benign and include entities such as myxoma, lipoma, papillary fibroelastoma, and rhabdomyoma. Malignant primary cardiac tumors include angiosarcomas, fibrosarcomas, osteosarcomas, and rhabdomyosarcomas [2–4,6–11]. A recent series described 21 cases, of which 17 involved adults and 4 were pediatric cases. There were 16 myxomas (76%), 2 rhabdomyomas (10%), 1 fibroma (5%), 1 angiosarcoma (5%), and 1 synovial sarcoma (5%) [11]. Similarly, Odim et al. [12] described 29 patients with primary cardiac neoplasms. Of the 29 patients, 26 had benign tumors while only 3 had malignant ones.

Extraosseous osteosarcomas are rare with less than 400 reported cases, with the lower extremity soft tissue being one of the frequent sites [13]. Primary cardiac osteosarcomas are extremely rare, comprising 3–9% of all cardiac sarcomas [3,4,7]. Because of their location in the left atrium, osteosarcomas tend to be present with signs and symptoms of congestive heart failure and thromboembolism [4]. Imaging studies such as CT and MR are valuable tools in characterizing the location of the tumor [3,4,7]. Histologically, a variety of growth and cellular patterns may be encountered in addition to the osteosarcoma. Cardiac osteosarcomas are aggressive neoplasms with a poor prognosis and limited surgical options [3,4,7,11]. We report this case because of its rarity and the unusually long survival despite distant metastasis.

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2. Report of a case

This 50-year-old woman presented with a 6-week history of dyspnea on exertion, paroxysmal nocturnal dyspnea, dizziness, and palpitations and had both a diastolic and a systolic murmur. An echocardiogram showed a large, smooth, irregularly shaped echodense mass in the left atrium that appeared adherent to the interatrial septum. There was also a large cystic portion of the mass that directly extended to the anterior leaflet of the mitral valve during diastole. The mass was noted to prolapse through the valve and obstructed a large portion of the left atrium. The atrial mass was resected and the atrium was reconstructed. Further evaluation revealed a 6.0-cm multilobulated mass with cystic changes. Histological examination showed a high-grade osteosarcoma (see Section 3). The patient was treated with cisplatin, Adriamycin, and high-dose methotrexate.

Four years after the initial surgery, the patient presented with acute onset of palpitations and atrial fibrillations. Echocardiogram findings reported a recurrence of possible sarcoma. The patient underwent a resection of the left atrial tumor, left arteriectomy, and creation of bovine pericardial left atrium. Pathology revealed recurrent osteosarcoma.

The patient did well for 3 years, following the second resection, at which time she presented with abdominal pain of 2 to 3 weeks’ duration. An upper endoscopy revealed a 4.0-cm polypoid gastric mass that was resected endoscopically. Pathology was consistent with metastatic sarcoma (see Section 3).

One year following the resection of the gastric mass, the patient presented with chest pain. A 6.0-cm chest wall mass was found. CT-guided biopsy of this mass showed metastatic sarcoma. The patient underwent left chest wall resection and reconstruction. A metastatic workup including a bone scan, MRI of the brain, and CT scan of the chest and abdomen resulted in negative results. Currently, the patient has no evidence of tumor 4 months after the chest wall mass resection.

3. Pathological findings

3.1. Primary occurrence, left atrium (Year 0)

Grossly, the specimen consisted of a 5.0-cm irregular, pink–gray, rubbery mass with a 2.5-cm cystic area. The entire tumor was submitted for microscopic evaluation. Histomorphologically, foci of malignant osteoid formed by sarcomatous cells were present. Foci of malignant cartilage were also noted (Fig. 1). Much of the tumor resembled myxoid malignant fibrous histiocytoma. Mitotic activity was brisk (Fig. 2).

Fig. 1. Primary occurrence, left atrium. Histological section illustrating the primary high-grade osteosarcoma with heterogeneous sarcomatous elements including osteoid and chondroid elements (hematoxylin–eosin, original magnification ×100).

Fig. 2. Primary occurrence, left atrium. A predominant portion of the primary tumor resembled myxoid malignant fibrous histiocytoma with myxoid background and scattered osteoid and chondroid elements (hematoxylin–eosin, original magnification ×200).

Fig. 3. Recurrent left atrial tumor (Year 4). Histological sections showed high-grade sarcoma with the involvement of the endocardium (hematoxylin–eosin, original magnification ×40).
3.2. Recurrent left atrial tumor (Year 4)

Grossly, the specimen consisted of a 9.5-cm portion of the atrium with a smooth, tan–white surface, with a tan–white, well-circumscribed 2.6-cm nodule projecting from the inner surface. Histological sections showed a spindle cell sarcoma directly forming malignant osteoid and involved the endocardium (Fig. 3) and the pulmonary vein.

3.3. Polypoid gastric mass (Year 7)

Grossly, the tumor formed a 4.0-cm polypoid mass confined to the submucosa (Fig. 4). Morphologically, the tumor was composed of plump spindle cells arranged haphazardly and focally forming vague interlacing fascicles. The tumor had an edematous stroma. No malignant cartilage or osteoid was identified (Fig. 5). Because of the unusual presentation, the possibility of a second primary tumor was considered, and microdissection genotyping of the primary and the metastatic tumor was performed (see Section 4).

Immunohistochemical stains were performed. The tumor cells displayed cytoplasmic positivity for vimentin and WT1. Smooth muscle actin was focally positive within some of the cells. The tumor cells were negative for C-kit, CD34, HHF35, and pancytokeratin.

3.4. Chest wall mass (Year 9)

Grossly, the specimen included three ribs and adjacent soft tissue. The tumor was centrally located, round, well circumscribed, and 6.0 cm in greatest dimensions. The cut surface of the tumor was heterogeneous with areas of white–blue gray, firm to rubbery parenchyma with cystic and hemorrhagic areas. Microscopic evaluation showed a high-grade sarcoma involving the chest wall and adjacent subpleural soft tissue and ribs. The constituent cells were spindled and pleomorphic with myxoid and edematous background. No malignant osteoid elements was identified, although in some compact areas, there was presence of dense collagen (Fig. 6). Immunostains were performed on the tumor, and they revealed the neoplastic cells to be weakly positive for osteonectin and negative for osteocalcin, cytokeratin, and actin.

4. Molecular studies

4.1. Microdissection genotyping

The primary cardiac tumor and the recurrent cardiac and gastric tumors were further characterized by microdissection genotyping, as previously described [14]. Briefly, serial 4-μm histological sections were used. As a control, nonneoplastic heart tissue from the patient was also
analyzed. Three tissue targets were microdissected by hand under stereoscopic observation using the Zeiss SZ-40 stereomicroscope (Zeiss SZ-40, Thornwood, NY) and were collected in 50 μl of 10 mM Tris–hydrogen chloride, pH 7.5. Following microdissection, sections were stained with hematoxylin–eosin to confirm accuracy of tissue sampling. Microdissected tissue samples were digested overnight with 10 mg/ml (μmol/ml) proteinase K and then boiled for 10 min to inactivate the enzyme.

A broad panel of 15 tumor suppressor genes (1p) was selected for microdissection-based genotyping (Table 1). Tumor suppressor genes located at these informative sites include OGG1, APC, p16/MTS1, and PTEN. Nucleic acid amplification by PCR was performed according to the manufacturer’s instructions (GeneAmp Kit, Perkin-Elmer Cetus, Norwalk, CT). P33-labeled deoxyadenosine triphosphate was used as the report molecule in the PCR reaction, which was carried out for 36 cycles (95°C denaturation, 55°C annealing, 72°C polymerization). Amplification primers were based on flanking sequences situated adjacent to the microsatellite of interest.

The pattern of allelic losses or allelic imbalances was essentially similar in the primary and recurrent tumor, indicating a single neoplasm. These concordant markers involved 1p36, 9p22, 10q23, 17q22, and 22q13. Additional allelic losses, indicating clonal evolution, were also identified, involving 3p26, 9q22, and 17p13 in the gastric metastasis.

4.2. Cytogenetic analysis

Routine karyotype analysis of the tissue cultures derived from the chest wall revealed 14 cells with a normal female chromosome complement. Only 1 cell had a haploid karyotype. Each cell had the following chromosome patterns: 47, XX,+8; 47, XX, +mar; 46, XXt(1;9)(p10;q10), −11, +mar; 46, XX, t(3;17)(p21;q25).

5. Discussion

We report this case of primary cardiac osteosarcoma because of the spectrum of pathological findings starting from the initial resection to the occurrence of metastatic disease 9 years later. Interestingly, the osteoid differentiation was not histologically apparent in the metastatic disease presentation in the stomach and chest wall. This case of primary cardiac osteosarcoma of the left atrium is unusual because of the pattern of recurrences and the length of survival. Although the possibility of a second primary tumor was considered in the stomach tumor, the pattern of allelic losses involving chromosomes 1, 9, 10, 17, and 22 was similar in the primary and the metastatic tumors. Karyotypic analysis of the left chest wall tumor revealed random changes in cells that showed structural abnormalities of chromosomes 1, 3, 9, and 17. The latter differences may reflect a karyotypic evolution in the metastatic site. To our knowledge, this type of presentation and the pattern of recurrence and spread have not been previously described for primary cardiac osteosarcomas.

Primary cardiac neoplasms are rare, affect patients of all ages, and have a reported prevalence in autopsy series of 0.001–0.03% [4]. Patients with primary cardiac neoplasia present with a spectrum of symptoms, most commonly cardiovascular. In the series of 29 patients described by Odim et al. [12], 6 of the patients presented with thromboembolism, 8 with congestive heart failure symptoms, and 3 with chest discomfort. Five were asymptomatic or the neoplasm was an incidental finding.

In a large series of cases (n=71) reported by Perchinsky et al. [2], 57 of 71 cases (80%) were benign while the remaining 14 (20%) were malignant. Seventy-two percent of the masses were located in the left atrium. Forty-three percent of tumors in the right atrium were malignant (6 of 14) compared with only 14% in the left atrium (7 of 51). Complete resection was possible for 50 of 52 benign atrial tumors (96%) but for only 5 of 14 malignant tumors (36%). The authors concluded that the majority of left atrial tumors were benign, including myxoma, hamartoma, neurofibroma, and papillary fibroelastoma, whereas up to one half of tumors found in the right atrium were malignant. The malignant tumors included rhabdomyosarcoma, fibrosarcoma, leiomyosarcoma, myxosarcoma, synovial sarcoma, and angiosarcoma [2].

Primary cardiac osteosarcomas are often aggressive with a very poor prognosis. The overall survival of the patients with primary cardiac osteosarcoma is poor. In a large series (n=25) reported by Larrieu et al. [15], all patients with malignant lesions (n=6) died from recurrence 6 to 13 months postoperatively, while only 3 patients in the benign group (n=25) died of unrelated causes. Marvasti et al. [16] described a patient with primary osteogenic sarcoma of the left atrium. The operative procedure required excision of the posterior atrial wall and...
portions of the left pulmonary veins. The patient survived the operation but subsequently was found to have distant metastasis. He died 7 months after the operation.

The treatment strategy for the primary osteosarcomas is dependent on the origin and extension of the tumor into the surrounding structures. Of the nine primary cardiac sarcomas with osteosarcomatous differentiation, many were clinically diagnosed as “atypical” myxomas. Complete excisions were attempted in eight cases, with one requiring reconstruction with grafting. Two tumors extended into the pulmonary veins. Three patients died within 2 weeks after the initial surgery from postoperative complications, while five patients had metastatic disease or died from disease. Metastatic sites included the lungs, thyroid, and skin [7]. Ahmad et al. [13] described clinicopathological features of 60 cases of extraosseous osteosarcomas and their response to treatment and long-term outcome. Twenty-seven patients were treated with doxorubicin-based chemotherapy. For the subset of 30 patients with localized disease, the 5-year disease-specific survival rate was 46% (95% CI=26–80%). The authors concluded that extraosseous osteosarcomas should be considered clinically and therapeutically distinct from osseous osteosarcoma [13].

In summary, this case illustrates a rare case of primary osteosarcoma of the heart presenting at an advanced stage as a large cystic mass of the left atrium and clinically mimicking a myxoma. The long survival may be due to surgical resection of primary and metastatic disease with the addition of chemotherapy.

References
