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Osteosarcomas of the Heart

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We reviewed nine primary cardiac sarcomas with osteosarcomatous differentiation. The patients' ages ranged from 24 to 67 (mean 38 years). All tumors were surgical specimens from the left atrium; many were clinically diagnosed as atypical myxomas. In eight cases complete excisions were attempted, one requiring reconstruction with grafting; one tumor was biopsied only. Two tumors extended into the pulmonary veins. Three patients died within 2 weeks after the initial surgery from postoperative complications; five patients had metastatic disease or died from disease; and one patient was lost to follow-up. Metastatic sites included lungs, thyroid, and skin. In addition to osteosarcoma, four tumors showed chondroid differentiation, three had osteoclastic cells, four had a prominent spindle cell component, and one had myxoid areas. All tumors showed immunohistochemical positivity for vimentin; stains for cytokeratin and desmin were negative. S-100 positivity was demonstrated in chondrosarcomatous areas of one tumor. We conclude that most cardiac osteosarcomas are clinically mistaken for myxomas because of location in the left atrium. They are larger, tend to infiltrate, and are very aggressive neoplasms. Histologically a variety of patterns may be encountered in addition to the osteosarcoma.
Key Words: Osteosarcoma—Heart—Myxoma.

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Extraskeletal osteosarcomas are uncommon, but they have been recognized for decades as examples of the pluripotential differentiation of soft tissue sarcomas (3,19). Osteosarcomas primary in the heart are distinctly rare, and published references are generally restricted to case reports (2,5,6, 9,10,12,15,17,20). Since McAllister and Fenoglio's description of five cases from the second series *Atlas of Tumor Pathology* (AFIP) (11), we have received in consultation nine additional cases from referring pathologists. The purpose of this paper is to describe the clinical and pathological features of these tumors and compare them with previously reported cases.

MATERIALS AND METHODS

A computer search of the AFIP files from 1977 to 1989 produced 81 primary sarcomas of the heart for which slides were available. The slides from these 81 cases were reviewed with specific attention to the presence of osteosarcoma. Osteosarcoma was defined on the basis of hematoxylin-eosin appearance as the presence of enlarged, atypical osteoblast-like cells embedded in homogeneous eosinophilic material resembling osteoid. Mature bone formation alone was not considered diagnostic of osteosarcoma. In every case a primary bone tumor was ruled out by bone scan or skeletal bone series. Nine tumors fulfilled these criteria; paraffin blocks were available on four.

Immunohistochemical stains were performed using commercially available monoclonal antibodies (Table 1) according to methods of Sternberger (18). The avidin-biotin technique was used with reagents from Vectastain Elite kit. Positive and negative controls were run in parallel. For desmin and cytokeratin, sections were mounted on preglued slides (15% white casein) that were predigested in 0.05% Sigma VIII protease for 3 min at 37°C.

TABLE 1. *Immunohistochemical studies*

Antiserum	Dilution	Manufacturer
Cytokeratin AE1/3	1:10	Hybritech
Desmin	1:100	Boehringer-Mannheim
Vimentin	1:100	Boehringer-Mannheim
S-100 protein	1:5120	Dako

RESULTS

Clinical Data (Table 2)

The patient's ages ranged from 24 to 67 years (mean age 38); the sex distribution was 2:1 female to male. The presenting symptom was dyspnea or syncope; in all cases the clinical diagnosis included "myxoma." All tumors were located in the left atrium or on the mitral valve. In three cases, chest x-ray reports were available; all demonstrated cardiomegaly, but in none was calcification mentioned. In three cases, echocardiographic reports were available, and the diagnosis in all three was tumor in the left atrium, atypical for myxoma based on large size, relative immobility, or infiltrative appearance. One tumor was biopsied, considered unresectable; in the remainder of cases, complete excisions were attempted. Three patients died postoperatively; three survived the postoperative period but developed metastasis to the skin, lung, and thyroid, respectively. One patient developed recurrence in 30 months and underwent unsuccessful re-resection with Hancock grafting. This patient received chemotherapy after initial surgery (methotrexate, adriamycin and *cis*-platinum); one other patient received multiagent chemotherapy but died within 2 weeks. All eight patients with follow-up data either developed metastases or died of disease or surgical complications. Of the six patients who died, autopsies were performed on three, with slides available for review on one. Cause of death in each cases was attributed to metastatic sarcoma, primary in the heart.

Histologic and Immunohistochemical Data (Table 3)

By definition, all tumors were spindle cell sarcomas with areas of osteoid. The osteoid ranged from microscopic foci within dense spindle cells to large acellular masses (Fig. 1). All tumors had some foci of atypical osteoid-producing spindle cells occupying lacunar spaces. Two tumors were composed entirely of osteosarcoma. Four tumors had associated chondrosarcoma (Fig. 2), and one metastasis was predominantly chondrosarcoma. Giant cells were prominent in three tumors (Fig. 3), either resembling giant cell tumors or interspersed with osteoid-producing areas. Fibrosarcomatous areas were prominent in four tumors (Fig. 4). Immunohisto-

TABLE 2. *Clinical data*

Case no.	Age	Sex	Site	Presentation	Procedure	Outcome
1	24	M	Left atrium	Syncope	Resection	Died postop
2	43	F	Left atrium	"Myxoma"	Resection	Metastasis in thyroid, 67 months
3	57	F	Left atrium; pulmonary vein	Dyspnea	Resection	Died postop
4	40	F	Left atrium	Pulmonary hypertension	Open biopsy	Lost to follow-up
5	24	F	Left atrium; pulmonary vein		Resection	Died postop
6	67	M	Left atrium	Dyspnea	Resection; reconstruction	Lung metastases DOD 14 months
7	45	M	Left atrium	"Myxoma"	Resection	DOD 11 months with metastasis
8	18	F	Left atrium	Congestive heart failure	Resection	Recurred 30 months; died postop
9	23	F	Mitral valve	Mitral stenosis	Resection	Metastasis to skin

DOD, dead of disease.

TABLE 3. *Histologic and immunohistochemical data*

	Osteosarcoma	Chondrosarcoma	Giant cells	Fibrosarcoma	S100 protein	Desmin	Cytokeratin	Vimentin
1	+	+		+	−	−	−	+
2	+	+						
3	+		+					
4	+			+	−	−	−	+
5	+							
6	+	+						
7	+	+	+	+	+[a]	−	−	+
8	+		+	+	−	−	−	+
9	+							

[a] Positivity limited to chondrosarcomatous areas.

chemical stains demonstrated negative staining for cytokeratin and desmin in four tumors studied, S-100 positivity only in areas of chondrosarcoma, and positivity for vimentin in spindle cell areas in four tumors.

DISCUSSION

Primary cardiac sarcomas can arise in any area of the heart. Angiosarcomas, which are the most common, are usually in the right atrium or ventricle (11). In contrast, all primary osteosarcomas in this report were located in the left atrium or mitral valve, which is the most common site for benign cardiac myxomas (11). Eleven of 14 cases of primary cardiac osteosarcomas that have been retrieved from the literature have also occurred in the left atrium or mitral valve (2,5,6,9–12,15,17,20). Why cardiac osteosarcomas seem to occur most often in the left atrium is not known; in none of our tumors or any in the literature has a transition from myxoma been described. There are no grounds, therefore, to postulate that cardiac osteosarcomas represent malignant transformation in myxomas, which can show osseous metaplasia (10).

Primary cardiac tumors are quite rare (10). The incidence of osteosarcoma in this group of rare lesions is difficult to estimate. In a series of left atrial tumors (6), one of 21 lesions was osteosarcoma; clearly by limiting tumors to the left atrial location, a higher proportion of osteosarcomas will result. Among cases of malignant primary heart tumors sent to us for consultation, nearly 10% showed osteosarcomatous differentiation.

Because of their location, the cardiac osteosarcomas in our study are often clinically mistaken for myxomas, which are more common in the left atrium. In three of our cases, however, echocardiographic findings were atypical, as had already been reported (15). For this reason, we believe that osteosarcoma should be in the differential diagnosis of left atrial tumors that do not have the classic echocardiographic or angiographic findings of myxoma. The extent of calcification can be minimal in these tumors, which explains the lack of calcification noted on fluoroscopy.

Because osteosarcoma of the skeleton can frequently metastasize to the heart (1,4,7,16), it is critical to rule out a metastatic lesion before establishing the diagnosis of primary osteosarcoma. In six of our cases of osteosarcoma metastatic to the heart (unpublished observations), as well as those in the literature (1,4,7,16), the primary tumor was clinically evident before the cardiac metastasis. In our experience with follow-up from 52 cases of fully worked-up nonosteogenic sarcomas of the heart presenting as cardiac masses, only one proved to be a metastasis from a retroperitoneal mass (unpublished observations). Osteosarcomas metastatic to the heart, in contrast to primary cases, are often right-sided (1,4). Therefore, we believe that most cases of cardiac osteosarcomas in the left atrium are primary lesions in the absence of a known primary elsewhere.

The mixture of histologic types seen in addition to osteosarcoma is typical of previously reported cases. Osteoclastoma (2), fibrosarcoma (2,5,12,17), chondrosarcoma (5,12,17), rhabdomyosarcoma (5), angiosarcoma (12), and liposarcoma (17) all have been reported with cardiac osteosarcoma. In our series of nine patients, only two cases were composed entirely of osteosarcoma in the histologic material available for study, and the rest had other components.

The histologic diagnosis of cardiac osteosarcoma is usually straightforward. Occasionally, myxoma with ossification should be considered in the differential diagnosis. Osteosarcomas can have large areas of mature osteoid with acellular lacunae (Fig. 1), but they invariably have cellular spindled areas, unlike myxoma, and lack myxoid features. It is important to note that mature bone formation (osseous

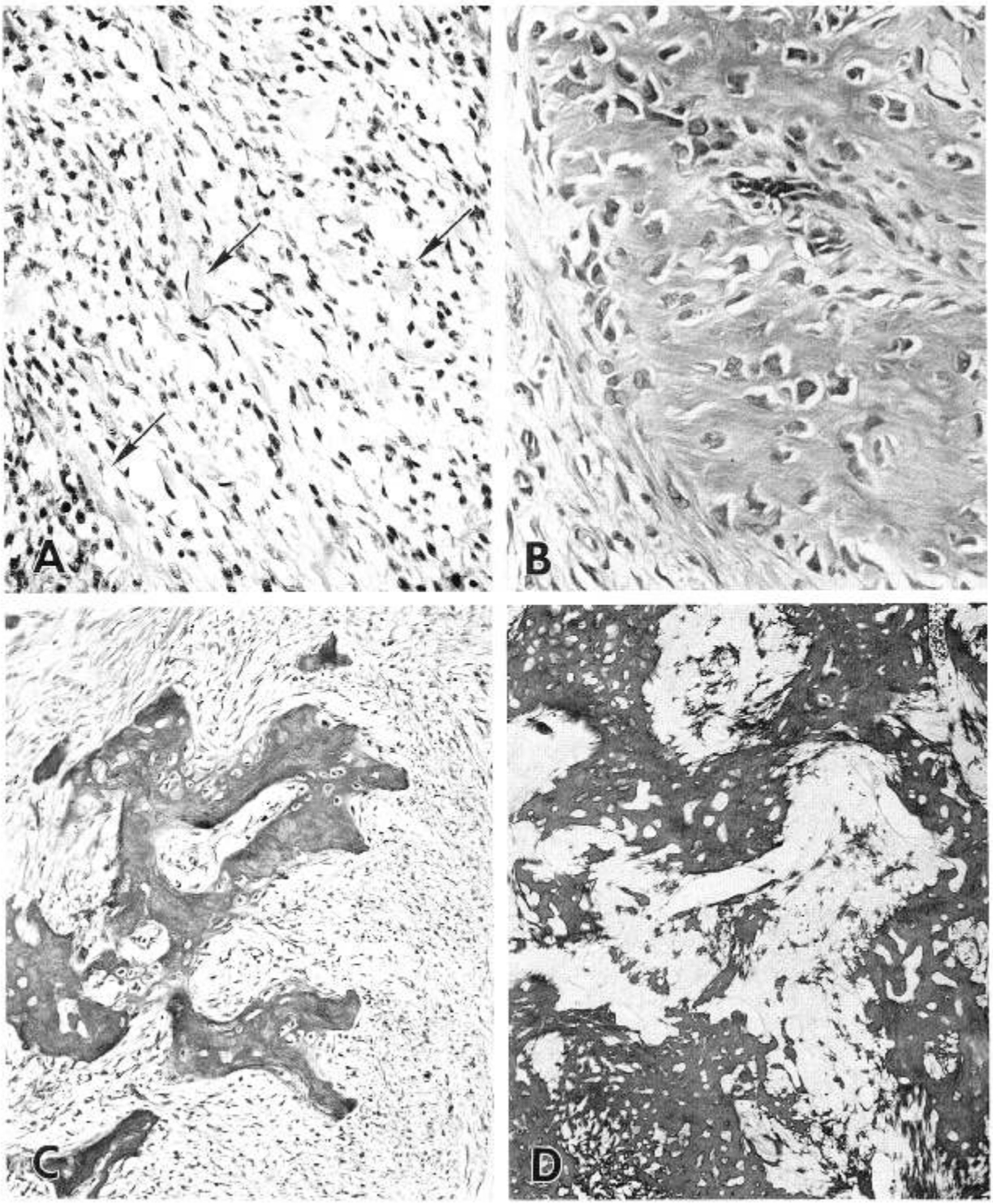

FIG. 1. Spectrum of osteoid in cardiac osteosarcoma. **A:** Minute deposits of osteoid are present (arrows) in an otherwise undifferentiated spindle cell neoplasm. **B:** Atypical osteoblasts are encased in larger masses of osteoid. **C:** Osteoblasts show less atypia, and trabeculae of osteoid are more sharply defined. **D:** Large masses of acellular osteoid are present. Mature bone such as this is not diagnostic of osteosarcoma; however, its presence may indicate adjacent areas of malignant bone formation. All tumors in this series had areas that resemble B or C and that are diagnostic of osteosarcoma.

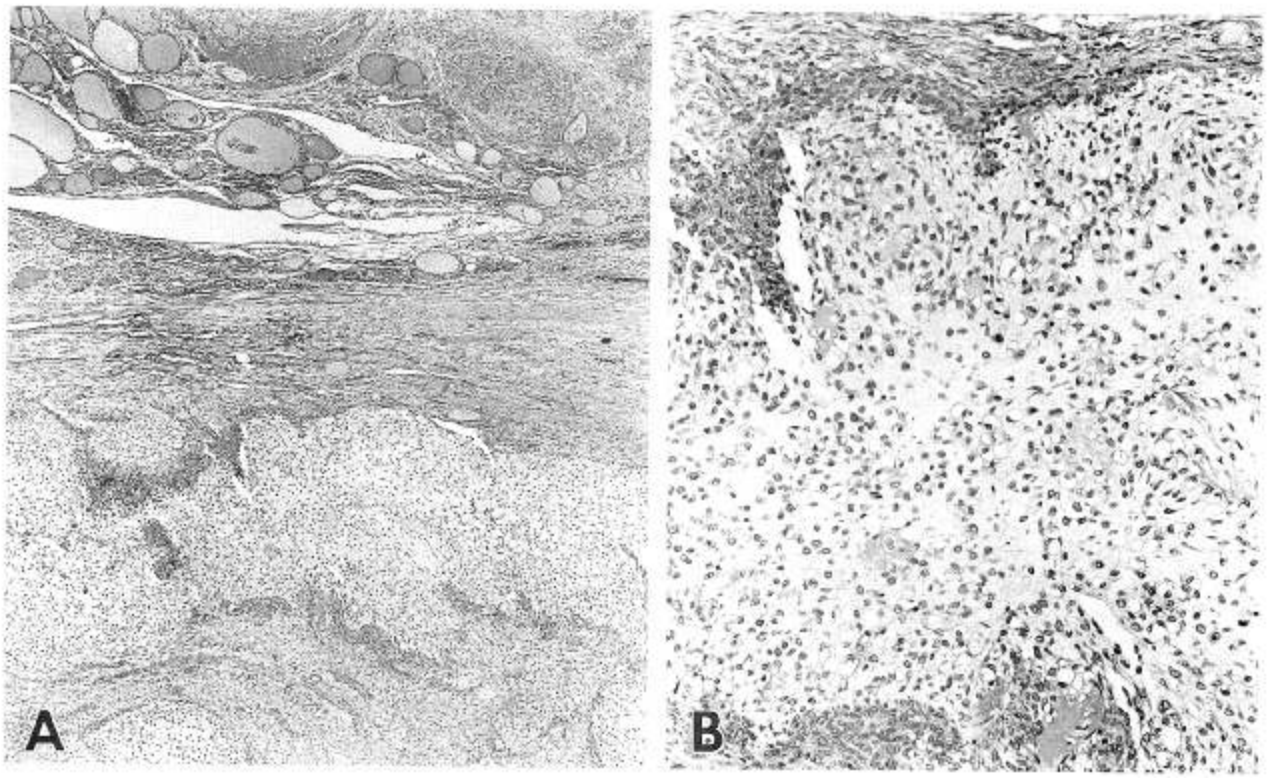

FIG. 2. Metastatic chondrosarcoma, thyroid, **A:** Low-power magnification; **B:** high-power magnification. Primary tumor in myocardium (not shown) was predominantly osteosarcoma. Metastasis developed after initial resection of cardiac lesion. A, ×30; B, ×99.

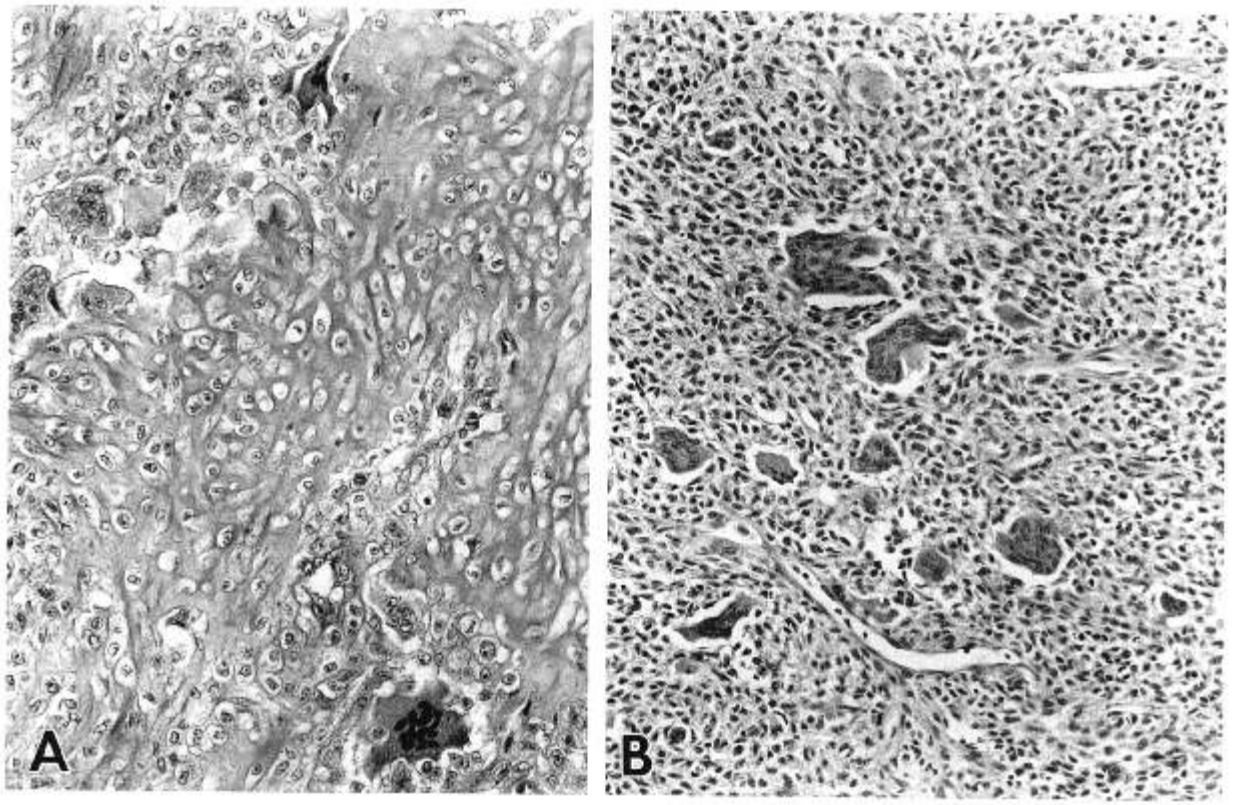

FIG. 3. Osteoclasts in cardiac osteosarcoma. **A:** Osteoclast-like giant cells in area of typical osteosarcoma. **B:** Area resembled giant cell tumor.

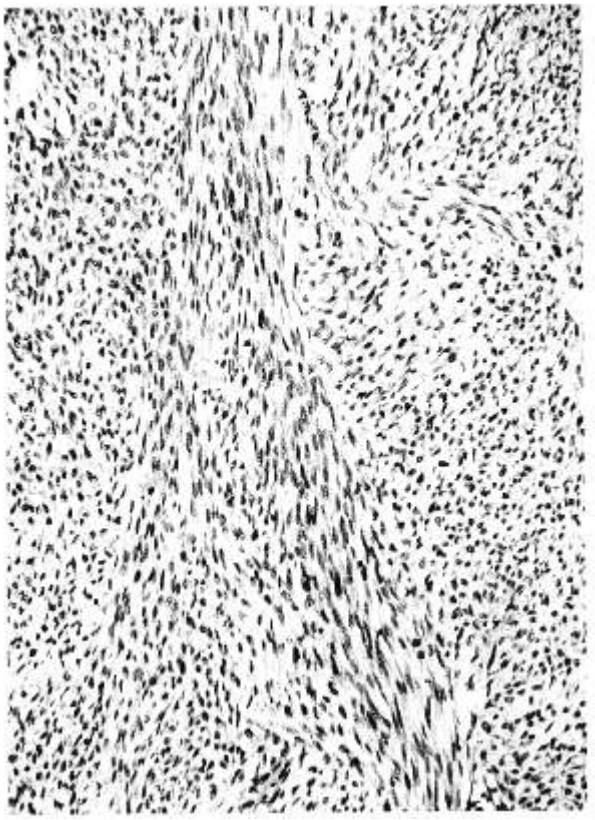

FIG. 4. Fibrosarcomatous area, cardiac osteosarcoma. Fascicular growth of highly cellular spindled sarcoma resembles fibrosarcomas of other soft tissue sites. Other areas (not shown) were osteosarcoma.

metaplasia) occurs in reactive conditions and benign neoplasms, as well as sarcomas without osteosarcomatous differentiation (19). However, any tumor in the left atrium with large amounts of bone in the absence of myxoid features is most likely osteosarcoma. Calcification occurs in up to 10% of myxomas (11), but ossification is uncommon.

The immunohistochemical localization of vimentin in all of our tumors is consistent with data on osteosarcomas of other sites (8,14), as well as the presence of S-100 protein in chondrosarcomas (14). We were unable to demonstrate myosarcomatous or epithelial differentiation in the four tumors studied with desmin and cytokeratin.

The treatment of cardiac tumors remains surgical. Because of tumor infiltration, one of our patients, as well as one previously reported (10), has required intraoperative grafts. In contrast to benign heart tumors, the prognosis for malignant lesions that have been surgically resected remains dismal (13). All patients with surgically resected cardiac osteosarcoma that have been reported have died (10,15,20). In keeping with these findings, all patients in our study either died postoperatively, died of metastases, or have developed metastases. The role of surgical palliation of these lesions remains valid, as two patients in our study died at 30 and 67 months postresection. Therefore, we believe that even if preoperative biopsy demonstrates osteosarcoma, surgery may be indicated for palliation. The role of chemotherapy for these lesions remains to be established; one of our patients lived 30 months before recurrence after receiving triple-agent therapy; an additional previously reported patient developed multiple recurrences after chemotherapy for cardiac osteosarcoma (20).

In conclusion, we have demonstrated that cardiac osteosarcomas are usually found in the left atrium, they can be confused with myxomas clinically, and they have a poor prognosis. Histologically they are quite diverse, and immunohistochemically show similar features as noncardiac osteosarcomas. Palliative surgery may be successful, but metastases are common.

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