Cardiac Chondrosarcoma Producing Parathyroid Hormone-Related Protein

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Chondrosarcoma is a malignant tumor characterized by the formation of cartilage. A case of primary cardiac chondrosarcoma of the left atrium developed in a middle-aged male. The preoperative serum concentrations of C-parathyroid hormone-related protein (PTHrP) and calcium were high (413.2 pmol/L and 12.2 mg/dl, respectively), but normalized after resection of the tumor, which measured 7×5×3.5 cm. The tumor was histopathologically diagnosed as chondrosarcoma, composed of outer atypical chondroid cells and inner pleomorphic and spindle mesenchymal cells mimicking malignant fibrous histiocytoma. Half of the cartilaginous tumor cells and a few pleomorphic cells showed cytoplasmic immunoreactivity for PTHrP. The tumor is a possible example of the functional pleiotropy of chondrosarcoma. (Circ J 2004; 68: 715–718)

Key Words: Chondrosarcoma; Heart; PTHrP

Primary cardiac malignant tumors are rare. Trazelaar et al reported 8 of 106 patients with 110 neoplasms originating in the heart that were treated surgically at the Mayo Clinic. Malignant tumors of the heart are predominantly sarcomas, most commonly angiosarcoma, fibrosarcoma and rhabdomyosarcoma. Primary cardiac chondrosarcoma is extremely rare, and to the best of our knowledge, only 11 cases have been reported in the English literature. C-parathyroid hormone-related protein (PTHrP) was first identified as a factor involved in the humoral hypercalcemia of malignancy. A variety of malignant solid tumors, including bronchial, renal and ovarian carcinomas, have been identified as expressing PTHrP, but there are only 3 reports on chondrosarcomas producing PTHrP, which included development in the bone and there was a high frequency of PTHrP-positive cells, implying that PTHrP might be a protein that is produced by chondrosarcoma cells. We describe a case of cardiac chondrosarcoma in which the immunohistochemical examination of the resected tissue sections and serological analysis suggested that the sarcoma cells might have produced PTHrP.

Case Report

The patient, a 56-year-old male with abdominal pain and diarrhea, was diagnosed with chronic pancreatitis. He did not have cardiovascular or respiratory symptoms. Routine abdominal ultrasonography unintentionally revealed an aberrant mass in the heart and subsequent echocardiography revealed a poorly-demarcated tumor in the left atrium (Fig 1). Magnetic resonance imaging (MRI) showed that the mass had an irregular surface and had progressed into the atrial cavity (Fig 2). General imaging modalities did not show any abnormalities such as tumor or osteolytic lesions, other than in the heart. Preoperative laboratory data showed high concentrations of serum C-PTHrP and calcium (413.2 pmol/L and 12.2 mg/dl, respectively). The patient underwent surgery under the clinical diagnosis of cardiac myxoma. Serum concentrations of C-PTHrP and calcium normalized after surgery. The postoperative course was uneventful and no evidence of tumor recurrence has been noted as of 10 months after the surgery.

Fig 1. Preoperative echocardiogram shows an homogeneous echoic mass (●) in the left atrium, partially connected to the mitral valve.
Methods

Formalin-fixed, paraffin-embedded tissue sections from the resected tumor were immunostained with the antivimentin, α-smooth muscle actin (SMA), desmin, S-100 protein and PTHrP antibodies (Table 1), using a streptavidin-biotin kit (Nichirei Corp, Tokyo, Japan) and the avidin-biotin-peroxidase method. The sections were also incubated with rabbit polyclonal anti-PTHrP antibody at 4°C overnight after incubation with trypsin with CaCl₂ in Tris-HCl buffer, pH 7.6, at 37°C for 30 min. Sections were counterstained with hematoxylin.

To examine the specificity of immunostaining, the primary antibody was replaced by mouse normal IgG at a 1:100 dilution and Tris-buffered saline. Control slides were invariably negative for immunostaining. In addition, sections of the chondrosarcoma with normal serum C-PTHrP were used as a negative control for PTHrP staining. Sections of normal skin served as positive control for the staining.17,20

Pathological Findings

Gross Findings

The tumor, measuring 7×5×3.5 cm,
was located at the back wall of the left atrium and partly adjacent to the endocardium. It was well-circumscribed and elastic hard with a greyish-white irregular surface, lobular growth and a resemblance to the surface of the brain gyri (Fig 3A). Cut surface examination revealed that the outer part was covered with greyish-white myxomatous lesion, whereas the inner part was yellowish and there was a focal, brownish lesion with focal hemorrhage. The border between the inner and outer lesions was indistinct (Fig 3A).

Histologic and Immunohistochemical Findings The tumor was adjacent to the endocardium of the left atrium and had prominent lymphoid cell infiltration. There was no invasion into the muscle layer. The tumor mainly consisted of 2 characteristic lesions: the outer well-differentiated cartilaginous tumor, and the inner spindle and pleomorphic mesenchymal tumor. There were atypical chondroid cells in the outer lesion, of variable cellularity (Fig 3B). The tumor cells showed obvious nuclear atypia, multinuclei and PAS-positive glycogen in the cytoplasm. A few mitoses (Fig 3B) and focal necrosis were also noted. There was neither osteoid or bone formation in any area. In the inner lesion, the tumor was composed of atypical mesenchymal cells, which occasionally showed a bizarre, multinuclear appearance, intermingled with fibroblastic and lymphoid cells. The histology mimicked malignant fibrous histiocytoma (Fig 3C).

The immunohistochemical findings are summarized in Table 1. In the outer cartilaginous lesion, tumor cells showed positive immunoreactivity for vimentin and S-100 protein, but not for ß-SMA or desmin. On the other hand, the inner spindle and pleomorphic tumor cells were positive for vimentin, partially positive for ß-SMA and desmin, but not for S-100 protein. Cytoplasmic PTHrP immunoreactivity was noted in both lesions (Fig 3D). The positive tumor cells were calculated to be approximately 50% of the cartilaginous tumor and less than 10% of the pleomorphic and spindle tumor.

Discussion Primary cardiac chondrosarcoma is extremely rare and is thought to derive from multipotent mesenchymal stem cells that undergo malignant differentiation into cartilage. There are only a few cases of primary cardiac chondrosarcoma, which is considered to originate from the endocardium and progress into the atrial or ventricular cavity. Leung et al reported that chondrosarcoma in the right heart or lung was usually metastatic from another primary lesion. In the present case, there was not another tumor in the right heart or lung, and general imaging modalities, including bone survey, did not reveal any tumors elsewhere in the body. Thus, it is indisputable that the tumor presented here is cardiac in origin. Interestingly, the patient did not show respiratory symptoms, although dyspnea can be a common clinical manifestation in primary and/or metastatic cardiac tumors.

The pathogenesis of the hypercalcemia associated with a malignant tumor has been explained by 2 distinct mechanisms: local osteolytic hypercalcemia (LOH) or humoral hypercalcemia of malignancy (HHM). HHM develops from the endocrine action of humoral factors produced by tumor cells without bone metastasis. PTHrP has been isolated as a major factor responsible for HHM and is known to be produced by various types of tumors. Therefore, serological analysis of PTHrP might be useful in determining the cause of hypercalcemia in patients with malignant tumors. In the present case there was an extremely high preoperative serum concentration of C-PTHrP, which normalized immediately after the surgery, as did the elevated serum calcium concentration. Moreover, there were no osteolytic lesions, confirmed by general imaging modalities. Immunohistochemistry revealed a positive reaction for PTHrP in several types of tumor cells and we believe this indicates that the cardiac chondrosarcoma cells produced bioactive PTHrP, classified clinically as HHM. It is interesting that a few reports have demonstrated the expression of PTHrP in chondrosarcomas including the bone, but cardiac chondrosarcoma has not been previously reported in this regard.

PTHRP is regarded as a mediator of cellular growth and differentiation as well as causing malignancy-induced hypercalcemia. PTHrP regulates the differentiation of chondrocytes and also correlates with tumor progression in cases of chondrosarcoma which might be related to the distribution of the PTHrP immunoreactive tumor cells, the number being higher in the outer cartilaginous lesion than in the inner lesion. Moreover, the tumor cells producing PTHrP might represent the functional pleiotropy of chondrosarcoma.

Surgery is the first choice of therapy for cardiac tumors, not only to make a pathological diagnosis, but also to avoid mass-induced symptoms. Complete resection can, on occasions, be difficult. A variety of primary chondrosarcomas of the bone, including that of the femur and humerus, are low- to intermediate-grade tumors with indolent clinical behavior and show 72.7% of the overall 5-year relative survival rate. In contrast, cardiac chondrosarcoma has a high risk of local recurrence and metastases more frequently and more rapidly than other chondrosarcomas, so it generally has a poor prognosis and survival is measured in weeks or months. These characteristics imply that continuing careful follow-up of the present patient is essential, even without clinical findings of recurrence or metastasis to date. The serum concentrations of C-PTHrP and calcium might be good markers for tumor recurrence or metastasis.

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