Angiosarcoma of the Heart: Case Report and Review of the Literature

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Abstract. *Background: Primary angiosarcoma of the heart is an extremely rare malignant disease. Patients and Methods: A 32-year-old female with primary angiosarcoma of the heart at an advanced stage with lung and bone metastases is presented. The tumor showed extensive expression of c-erb-B_2 and a moderate expression of c-kit. Chemotherapy (cisplatin, epirubicin and ifosfamide) was administered. Herceptin as well as glivec were added to the above combination. Results: There was a good partial response and the lung deposits almost disappeared. The duration of response was 6 months. Conclusion: This case of angiosarcoma of the heart is presented because of the extreme rarity of this disease, and its responsiveness to chemotherapy in combination with imatinib and herceptin.*

Primary tumors of the heart are rare entities with an autopsy-defined incidence of 0.2% (1); one quarter of these are benign tumors. The most frequent malignant cardiac tumors are sarcomas, with patients having a median survival of 6 months (2). Angiosarcoma of the heart constitutes 2% of primary cardiac neoplasms (including benign tumors) and it is the most common primary malignant cardiac tumor (3). More often it develops in the right ventricle, especially arising from the right atrium, and less often from the pericardium (4). These tumors may be asymptomatic over a long period of time and when the symptoms appear, the disease is already advanced. The main clinical signs are pulmonary hypertension, haemopericardium, cardiac tamponade and pulmonary embolism (5).

The present study presents a case of primary cardiac angiosarcoma and a review of the literature.

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Case report

A 32-year-old woman was admitted to hospital because of a 10-day fever, shortness of breath and pain in the left shoulder which radiated to the left arm. The ECG demonstrated sinus tachycardia with a pulse rate of 140 bpm which was persistent and not related to the high fever. She was clinically immobilized and any effort increased breathlessness. A transesophageal echocardiography was performed and showed a tumor 4.6x2 cm in the right ventricle. Computed tomography (CT) of the chest showed multiple metastatic nodules in both lungs and an osteolytic lesion with a soft-tissue mass attached to it, at the right first rib. A biopsy of this mass was performed. The histopathology showed angiosarcoma (malignant epithelioid hemangioendothelioma). At that time, CT of the abdomen and brain and a bone scan were negative with respect to the spread of the disease.

Chemotherapy (epirubicin 75 mg/m^2 on day 1, cisplatin 80 mg/m^2 on day 1 and ifosfamide 2 gr/m^2 per day on days 1, 2 and 3, plus uromitexan 800 mg x 2 on days 1, 2 and 3) was administered. A histological specimen was examined for gene expression (particularly c-kit and c-erb-B_2). Both were expressed, but c-erb-B_2 in particular, was highly expressed. Trastuzumab (herceptin) 150 mg once weekly and imatinib (glivec 400 mg tablet) were added to the treatment.

Patient follow-up. Within a short period of time, (4-6 weeks) the patient showed clinical improvement which was confirmed by a CT scan of the chest in the 8th week after the beginning of treatment. There was a good objective partial response and a highly improved clinical benefit (quality of life). The patient no longer required the administration of oxygen; the esophageal echogram, as well as the CT scan of the chest (both examined by experienced radiologists before treatment and one month and 6 months post treatment) showed a reduction in the size of the cardiac mass and the lung metastases had almost disappeared. The duration of response was 6 months; this

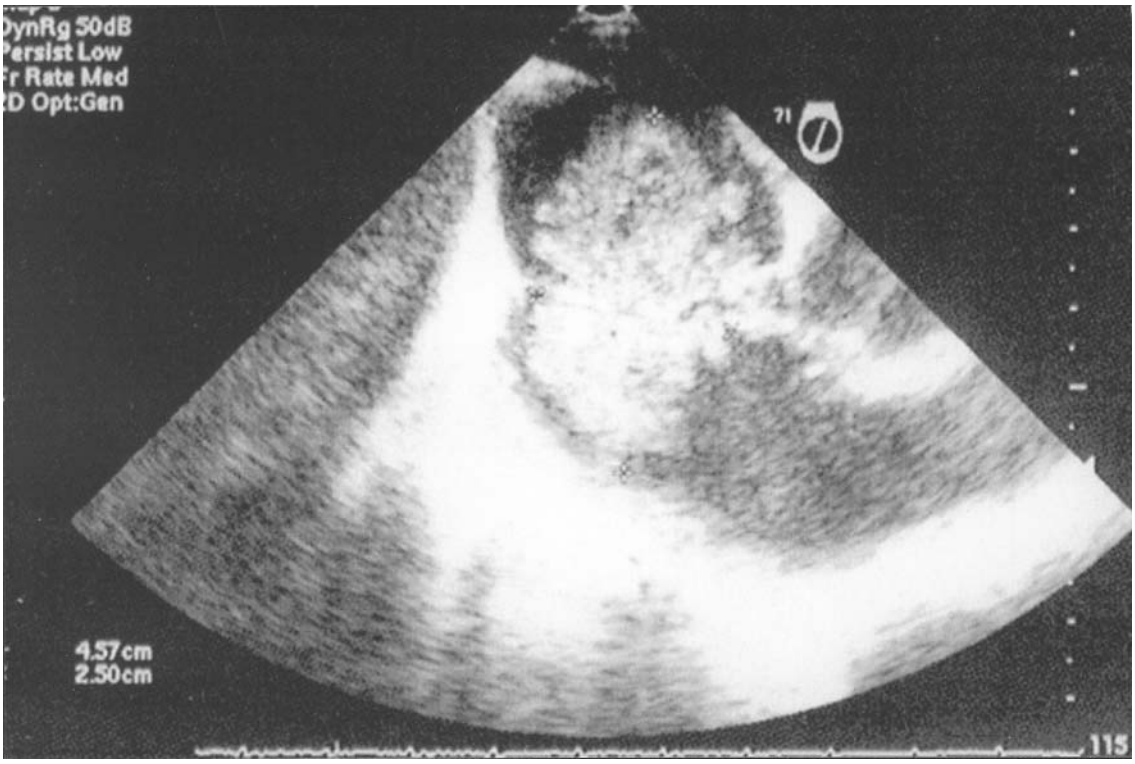

Figure 1. *Trans-esophageal ultrasound. Mass of 4.6 x 2 cm attached to the right ventricle wall.*

was followed by a deterioration expressed by bone pain, dyspnea and central nervous system symptomatology. The patient presented with hemiparesis, headache and blurred vision. The bone scan revealed multiple bone metastases. Magnetic resonance tomography (MRI) showed multiple signs of brain metastases, mainly in the right parietal lobe. CT of the chest showed a recurrence of metastatic disease with numerous nodules in the lungs. Despite supportive treatment, within a few weeks the patient failed to recover and died 7 months post diagnosis.

Histological and radiological images are shown in Figures 1-6.

Review of the literature. Angiosarcoma is a rare, malignant neoplasm characterized by the rapid proliferation of the undifferentiated malignant cells which originate from the vascular endothelium. The tumor is characterized by the configuration of vessel channels. This is an aggressive neoplasm with a tendency for local relapse and a high rate of metastases. There are approximately 60 new cases per year in the United States and the annual incidence is approximately 2-3 per population of 100,0000 (4). The worldwide incidence is also low. This neoplasm can occur in any organ of the body but it more frequently occurs on the skin and soft tissues (5).

The aetiology of angiosarcoma is unknown. Chronic lymphedema is the most common pathogenic preceding condition. Chronic lymphedema may appear after radiation therapy in mastectomized patients (Stewart-Treves syndrome [STS], a rare, extremely malignant and rapidly-progressing tumor – angiosarcoma developing in lymphostasis of an arm after radical mastectomy for cancer) (6) or after radical inguinal lymphadenectomy for metastatic melanoma (Kettles syndrome, a lymphoma-associated angiosarcoma which occurs in the leg of patients as a consequence of radical inguinal lymphadenectomy for metastases from malignant melanoma) (2). Chronic idiopathic or traumatic lymphedemas have also been pathogenetically related (5). Other aetiological factors are radiation (post radiotherapy sarcoma), the existence of a foreign body, environmental carcinogens and pre-existing benign conditions such as chronic osteomyelitis in cases of angiosarcoma of the bone (2).

Angiosarcoma is classified according to the TNM system. The pathological classification is graded as moderate or low differentiation. Locally advanced angiosarcoma is stage IIB. The histological diagnosis of angiosarcoma is often difficult and immunohistochemical examination for several cellular markers is often needed to

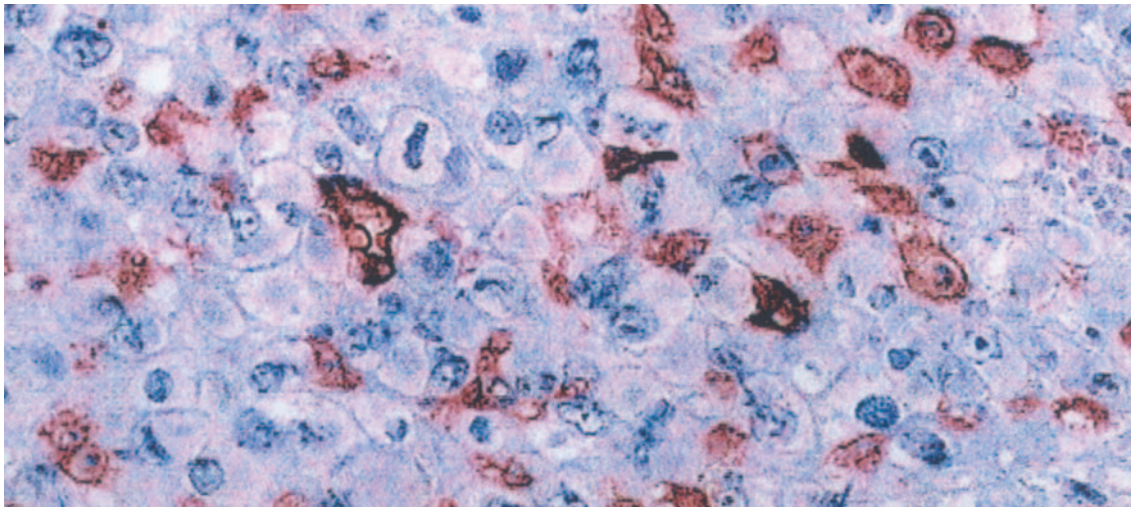

Figure 2. *Immunohistochemistry showing positive expression of CD34 indicating the angiogenic origin of the neoplasm.*

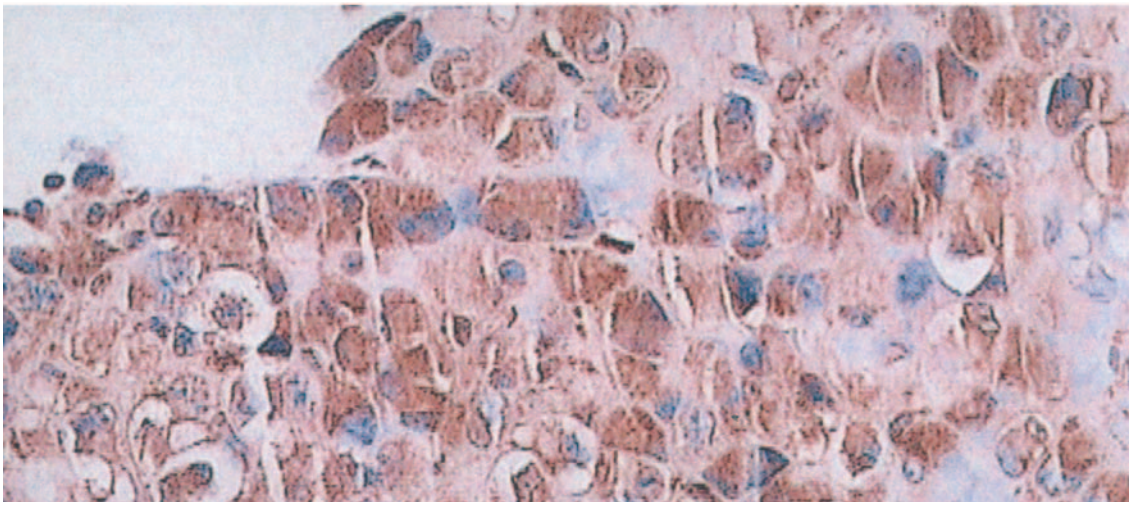

Figure 3. *Histological specimen showing the extensive expression of the c-erbB_2 gene.*

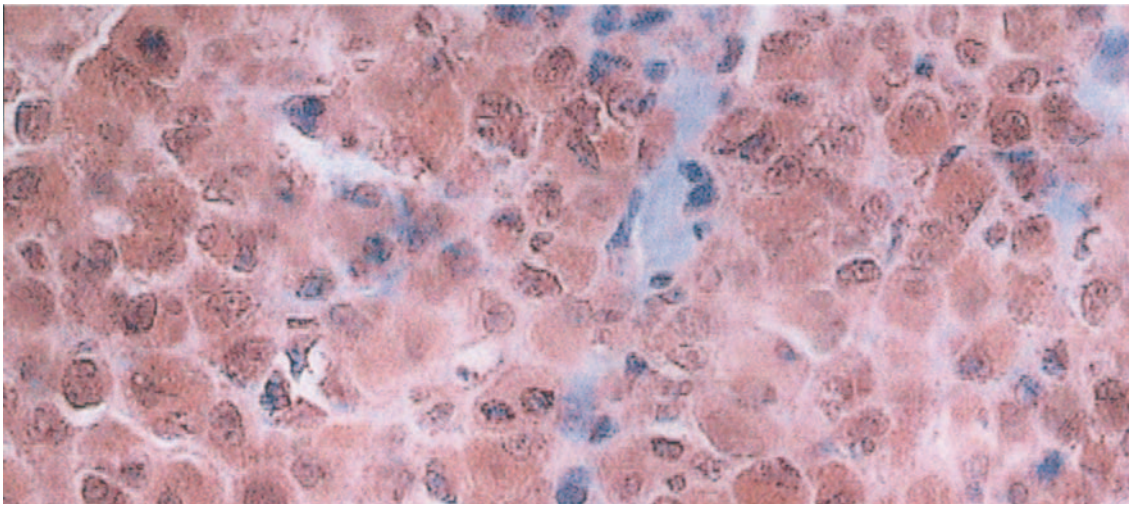

Figure 4. *Histological specimen showing moderate expression of c-kit (CD117).*

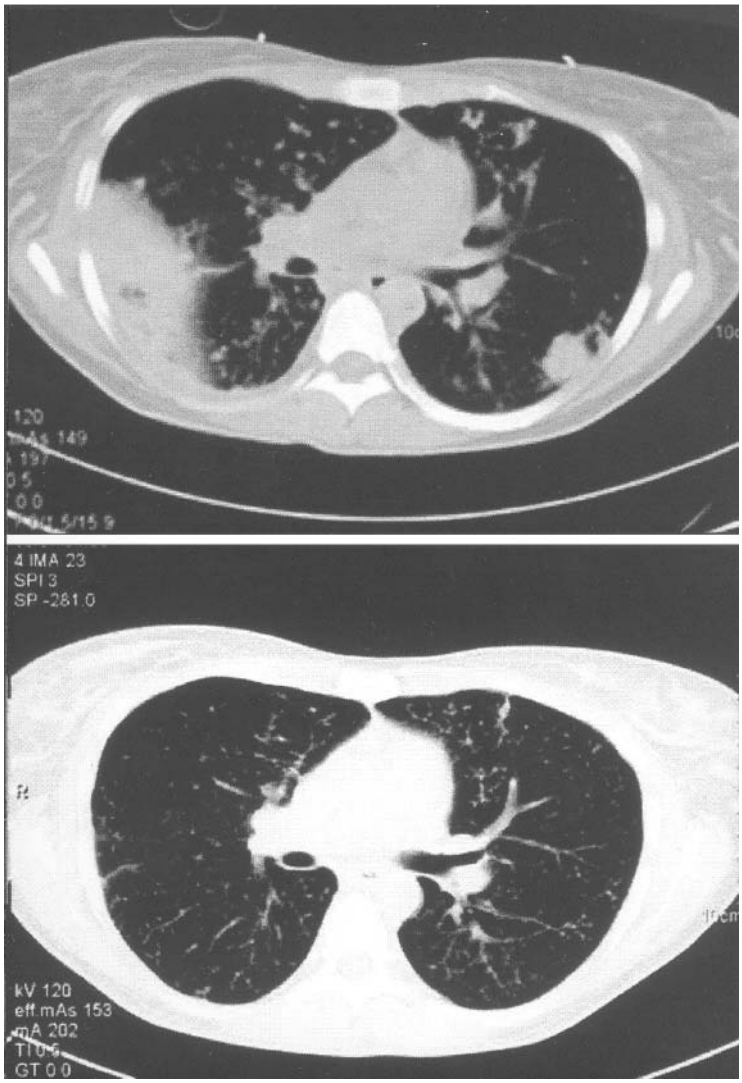

Figure 5. *CT scan of the lungs showing the response of the disease a) before treatment and b) after treatment.*

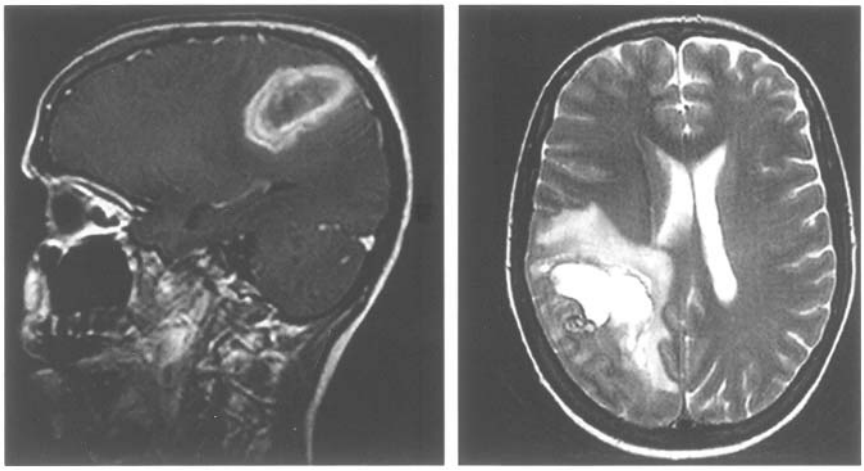

Figure 6. *MRI of the brain showing metastatic lesions.*

confirm the diagnosis. The detection of CD34 determines the endothelial origin of the malignant cells (7).

Angiosarcoma belongs to the category of sarcomas with no specific genetic alterations but several karyotype detachments and the addition of chromosomal material have been described as well in osteosarcomas, malignant fibrous histiocytomas, non-myxoid liposarcoma and leiomyosarcoma (7). The molecular pathogenesis of these genetic lesions seems to be related to pathways of deactivation of the oncosuppressive gene *p53*, *via* the molecular expression of retinoblastoma oncogenes (7). The expression of MDM2 and CDK4 constitutes a frequent finding in the majority of soft-tissue sarcomas (6). The absence of specific mutations and the usually poor expression of certain oncogenes, on the one hand, limit the possibility of molecular classification and, on the other hand, the hope of therapeutic intervention using targeting therapy with monoclonal antibodies (8). However, a frequent expression of the oncogenes *EGFR* and c-erb-B_2 has been detected in several sarcomas irrespective of the histological subtype and the degree of malignancy (9).

Treatment. The main therapeutic method in early-stage (localized) angiosarcomas, is the combination of surgical excision and radiotherapy (10). Surgical management is the treatment of choice and radiotherapy is performed afterwards as adjuvant treatment. If surgery cannot be radical, then radiotherapy is performed before the operation, aiming for the downstaging of the disease to an operable stage. The role of chemotherapy as adjuvant treatment is debatable. Comparative studies on sarcomas to date have shown that although adjuvant chemotherapy does not lead to an increase in survival, it does however, increase the duration of disease-free survival (11). Case reports in the literature have indicated that surgical excision of angiosarcoma of the heart leads to up to 5 years or longer survival (10).

Among other surgical therapeutic methods, heart transplantation has been suggested (12), but many moral and social dilemmas are involved (13). Generally, the median survival from the time of the diagnosis of cardiac angiosarcoma is less than one year (14). Chemotherapy functions as palliative treatment and may improve the quality of life and prolong survival. It does not appear to affect an increase in survival, even though no randomized trials have been performed in metastatic sarcomas with or without chemotherapy (15). With regard to chemo-resistant metastatic sarcomas (including angiosarcoma), another opinion has been expressed: as long as the patient is asymptomatic, it is better to avoid chemotherapy (16). As with the majority of sarcomas, the most eligible cytotoxic agents are doxorubicin and ifosfamide. Cyclophosphamide, vincristine, dactinomycin and etoposide have also been administered (15). Taxanes have also rendered satisfactory results (17). The possibility of adding molecular therapeutic factors (monoclonal antibodies) depends on the expression or not of oncogenes in the malignant cells. In the past few years, emphasis has also been placed on the important expression of vascular endothelial growth factor as a tumor marker in the serum of sarcoma patients (18). The successful administration of anti-angiogenetic factors (bevacizumab) in other tumors indicates that there may be possible therapeutic benefit in sarcomas as well (19). In the case of our patient presented here, the expression of c-erb-B_2 was impressively high, while c-kit expression was moderate. The expression of c-kit in angiosarcomas appears increased and related to the stem cell factor (20). The simultaneous administration of herceptin and imatinib (glivec) with chemotherapy might have assisted clinical improvement and tumor reduction in our patient (21).

Primary angiosarcoma of the heart is a very rare and aggressive disease. In the early stages it can only be treated by surgery which may lead to a long survival.

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