A Case of Angiosarcoma of the Breast

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This is a case report of a 20-year-old woman who had primary angiosarcoma of the left breast, with metastases to the spleen and ovary. Eight months after detecting a mass in her breast, she underwent mastectomy with biopsy of the ipsilateral axillary lymph nodes, splenectomy and bilateral oophorectomy. Five months after the operation, the patient succumbed to lung metastases. Angiosarcoma of the breast is a rare condition with a poor prognosis, and there are no established chemotherapeutic regimens as yet. Immunohistochemical staining for endoglin, known to be expressed mainly on the surface of endothelial cells, was positive. This suggests the possibility of treating angiosarcoma with anti-endoglin monoclonal antibodies.

Key words: angiosarcoma – breast – endoglin

INTRODUCTION

Angiosarcoma of the breast is an uncommon, extremely hostile neoplasm of vascular origin. Two hundred and nineteen cases have been described (1) since the first case reported by Schmidt (2) in 1887. The frequency of this rare tumor is 0.04% of primary mammary tumors (3) and approximately 8% of mammary sarcomas (4). Several reports have been published with different names for this malignant condition, such as hemangioendothelioma (5), haemangioblastoma (6), haemangiosarcoma (7,8), haemangiosarcoma (3), and metastasizing angioma (9–11). This neoplasm carries a very poor prognosis, with a five-year survival of 8–50% (12). Metastases derived from mammary angiosarcomas have been reported in lung, skin, liver, bone, CNS, spleen, ovary, lymph nodes and heart (13,14). We report herein the history of a 20-year-old woman who suffered from mammary angiosarcoma with metastases to the ovary and spleen.

CASE REPORT

CLINICAL HISTORY

The patient was a 20-year-old, unmarried, nulliparous woman with a chief complaint of left breast enlargement of nine months duration at the time she was admitted to the Tokai University Hospital. She was admitted to our hospital on September 28, 1989.

On physical examination, a hard, contracted-muscle mass was located in the left breast which measured 16 × 12 cm and was accompanied by ulceration and necrotic changes in the overlying skin. Tumor markers such as CEA, CA15-3, α-fetoprotein and CA19-9 were all within normal limits. In hormonal studies, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were within normal limits.

An abdominal echogram elucidated a low echoic mass which measured 8.3 × 7.8 cm in the upper pole of the spleen with a heterogeneous internal echo. Heterogeneous masses in both ovaries, measuring 15.7 × 12.6 × 10.0 and 8.0 × 7.8 × 5.7 cm, were suggestive of metastases. Thoracic computed tomography revealed a huge mass in the left breast with cystic components partly invading the underlying major pectoral muscle, but without invasion into the thorax.

On October 3, 1989, an incisional biopsy of the mass in the left breast was performed. Many dilated capillaries were found, including an irregular network of vasculature with proliferation of cells, suggestive of an angiogenic tumor, the cells of which were immunohistochemically weakly positive for factor VIII. On October 12, 1989, bilateral oophorectomy, hysterectomy, splenectomy, biopsy of intraabdominal lymph nodes and the liver, and subsequent left mastectomy with biopsy of the axillary lymph nodes accompanied by mammary reconstruction using a latissimus dorsi flap were performed. The patient was discharged on November 16, 1989. Multiple lung, liver and bone metastases were detected approximately three months after her operation. She eventually succumbed from respiratory failure caused by prominent pulmonary metastases, complicated by severe pneumonia, five months after her operation.

PATHOLOGIC FINDINGS

For light-microscopy and immunohistochemistry, surgical resected tissues were fixed in 20% buffered formalin solution and embedded in paraffin using routine procedures. Dewaxed paraffin sections were stained with hematoxylin and eosin, argyrophilic...
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Figure 1. The cut surface of the resected specimen of the breast appears dark red and contains massive coagula.

stains. Additional sections were stained with a rabbit polyclonal antibody to human von Willebrand Factor (×200, Dakopatts) using the avidin-biotin immunoperoxidase complex (ABC) method, and a murine monoclonal antibody to human endoglin (×160, Cosmo Bio Inc., Tokyo, Japan).

Grossly, the breast tumor measured 16×12×10 cm in the greatest dimension. The cut surface of the tumor was ill-defined, without a capsule, and appeared spongy due to the numerous dilated vascular spaces filled with blood clots (Fig. 1 NO TAG). The right ovary measured 14×11×6 cm, the left ovary 7.5×6.5×3 cm, due to invasion by the tumor. The spleen weighed 320 g, including the metastatic lesion, and measured 8×7×5 cm in its upper portion.

Microscopic examination of the mammary tumor demonstrated a marked proliferation of atypical capillaries and endothelial cells (Fig. 2). Necrotic foci with marked hemorrhage and proliferation of polygonally-shaped atypical endothelial cells were seen. Other sections showed an invasive proliferation of irregular, various-sized, vascular channels with massive hemorrhage and necrosis. The endothelial cells had scanty cytoplasm with spindle-shaped or round nuclei and showed either a papillary or solid growth pattern. Mitotic figures were often observed. The vascular channels, which were clearly demonstrated (Fig. 2), were accompanied by highly atypical and prominent endothelial cell proliferation.

The atypical cells were immunohistochemically positive for factor VIII related antigen, using a rabbit anti-human von Willebrand Factor (Fig. 2). These cells were also positive for desmin (×50, Dakopatts), vimentin (×20, Dakopatts) and actin (×400, Amersham), but negative for keratin (×500, Dakopatts) and estrogen receptor (Dainabot). Vascular invasion of the tumor was a common finding. Sections of the spleen and ovary showed massive metastatic deposits of angiosarcoma resembling those in the breast. Electron microscopy revealed Weibel–Palade bodies in tumor cells of the breast, which generally characterize vascular endothelial cells (Fig. 3).

Immunohistochemically, endoglin was detected on the surface of tumor cells (Fig. 4).

Figure 2. A, Histologic preparation shows that neoplastic endothelial cells demonstrate solid growth, occasional mitotic figures and sporadic protruding growth into the vascular lumen; B, vascular network was clearly observed by argyrophilic staining; C, indirect immunoperoxidase staining for factor VIII-related antigen shows the endothelial nature of the neoplastic cells.

Using the dextran-coated-charcoal (DCC) assay (15), the estrogen and progesterone receptors of the resected tumor tested negative.
**DISCUSSION**

Angiosarcoma of the breast occurs during the third and fourth decade of life (16), in contrast with mammary carcinoma which generally arises later. This malignant tumor occurs primarily in young women, with 6–12% of the cases found during pregnancy (13,14), implying a hormonal effect. However, reported cases with positive estrogen receptors are so rare that the hormonal dependency of angiosarcoma is still unresolved (17). Estrogen and progesterone receptors of the tumor in our case were negative, as previously mentioned.

In the cases reported to date, the tumor manifested as a painless and rather quickly enlarging, palpable mass without tenderness. In most cases, the tumor size was >4 cm in diameter. A few patients with tumors <4 cm at diagnosis had a better survival rate (18). Another report indicated that gross tumor size did not correlate with survival (19). Our patient succumbed to extensive metastases to the lungs, liver, and bones 7 months after the initial diagnosis. Her first symptom was enlargement of the left breast, without pain or tenderness. The tumor size at discovery had reached 16 cm in diameter.

Preoperative diagnosis of angiosarcoma of the breast, by aspiration cytology and biopsy, are often difficult. Chen et al. (13) reported that the false negative rate of biopsy was 37%. The differential diagnosis of this rare malignancy includes benign hemangioma, cystosarcoma phyllodes, stromal sarcoma, metaplastic carcinoma, squamous cell carcinoma with sarcomatoid features, myoepithelioma, fibromatosis, fibrosarcoma, liposarcoma and reactive spindle cell proliferative lesions. Ultrastructural examination can reveal the vascular nature of angiosarcoma and demonstrate the existence of Weibel–Palade bodies and pinocytic vesicles. In our case, the Weibel–Palade bodies were recognized by electron microscopic examination. Immunostaining for factor VIII related antigen is helpful for the diagnosis of angiosarcoma of the breast (20). An incisional biopsy in this case revealed the widespread angiogenesis very clearly by means of immunohistochemistry for factor VIII.

The sites of metastases in our patient were the ovary and spleen. A primary splenic malignant neoplasm is uncommon. In 1982, Wick et al. (21) reviewed 92 cases of primary splenic angiosarcoma, including 6 of their own. Sondenaa et al. (22) surveyed the metastatic sites of previously reported cases, and found that the liver was the most common site, followed by lung, lymph node, skeleton, bone marrow and, less frequently, ovary, kidney, omentum,
adrenal gland, stomach, pancreas, peritoneum, esophagus and skin. To our knowledge, metastases to the breast have not been reported. Primary ovarian angiosarcoma is an extremely rare tumor. Patel et al. (23) reviewed 5 cases of primary ovarian angiosarcoma. Among the 5 cases, no metastases to the breast were noted. In our case, it is strongly suggested that the breast was not secondarily involved from the ovary or spleen, but was the primary site of the tumor.

Chen et al. (13) reviewed the metastatic sites of primary angiosarcoma of the breast and showed that the lung, skin and subcutaneous tissue, bone, liver, brain and ovary were the most common sites, in order of frequency. Angiosarcoma of the breast tends to metastasize hematogenously to the lungs, similar to other soft part sarcomas. It often metastasizes to bones, skin and the contralateral breast, which are not frequently involved by other types of sarcoma (14). Axillary lymph node metastases only numbered three among the previously reported cases (18,23,24).

The histologic features of angiosarcoma of the breast are classified into three groups (6). Group I angiosarcoma shows dilated, sinusoid-like vessels surrounding a duct in the breast. The vessels are lined by a single layer of relatively flat endothelial cells. Mitotic figures are not present and almost never identified in Group I tumors. Group II shows numerous small buds or tufts of endothelial cells projecting into the vascular lumen and papillary growth of endothelial cells. Group III shows a focus of growth of spindle and polygonal cells. Necrosis and blood lakes were present only in Group III tumors. The resected specimen from our patient’s mammary tumor demonstrated marked proliferation of atypical capillaries and endothelial cells. Necrotic foci with marked hemorrhage and the proliferation of atypical, polygonally-shaped endothelial cells were seen. These features are compatible with those of Group III, and the clinical course was extremely rapid. According to a report concerning 19 patients with primary mammary angiosarcoma (25), relapses occurred in none of eight in Group I, two of four in Group II and four of seven in Group III. Other attempts to correlate histologic features with clinical behavior were made in a series of 10 cases where an unfavorable prognosis was related to a high mitotic count (26).

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Recently, an approach to attacking a proliferative endothelium has been extensively investigated. It was demonstrated that rapidly proliferating tumor endothelial cells were susceptible to immunotoxins in experimental models (28,29). Close interactions between endothelial cells and the blood stream appears to make the vasculature a practical target for tumor therapy. Specific antibodies conjugated with efficient cytotoxins (e.g. ricin) or radioactive isotopes could be used to target the tumor vessels (30). Endoglin is an antigen, identified originally by a monoclonal antibody produced against a pre-B leukemic cell line (31). Thorpe et al. (32) suggested that the antibody, which was directed against the endoglin molecule, was a promising agent in the vascular targeting approach, since this molecule was overexpressed on tumor-associated endothelial cells, not on normal endothelial cells. As previously mentioned, angiosarcoma has a poor prognosis and is refractory to systemic chemotherapy. Monoclonal antibodies with affinity to antigens in the tumor vasculature such as endoglin could be applicable in the therapy of this vicious neoplasm.

References

