

CASE REPORT

A case report of primary breast angiosarcoma with fatal pulmonary hemorrhage due to thrombocytopenia

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Primary angiosarcomas of the breast are rare malignancy that account for fewer than 0.04% of all malignant breast tumors. The prognosis is poor. Surgery is the first line of treatment for angiosarcoma. Adjuvant chemotherapy and radiotherapy have been tried, but their efficacy remains controversial. Here we present the case of a 47-year-old woman with a palpable left breast mass that was diagnosed as a primary angiosarcoma. The patient underwent modified radical mastectomy with adjuvant chemotherapy and radiotherapy. Postoperatively, eighteen months later, the angiosarcoma recurred. The patient returned complaining of dyspnea and hemoptysis and was found to have a large pleural effusion. She developed a gradual onset of thrombocytopenia that persisted despite platelet transfusions. Finally, the patient died of respiratory failure secondary to pulmonary hemorrhage.

Key Words: Angiosarcoma, Breast neoplasms, Thrombocytopenia

INTRODUCTION

Angiosarcoma is a malignant neoplasm of endothelial cells that begins in the lining of the blood vessel wall. Although angiosarcoma of the breast is a rare entity, the breast is a favorable site for it [1]. Breast angiosarcomas may be categorized as primary or secondary angiosarcoma.

Primary angiosarcoma arises within the breast parenchyma, the overlying skin, and subcutaneous tissue. In contrast, secondary angiosarcoma of the breast is commonly associated with radiation therapy in patients who have undergone breast-conserving surgery for another

type of primary neoplasm of the breast. These secondary angiosarcomas occur several years after the initial treatment, are often associated with lymphedema, and involve the skin. Primary angiosarcomas account for fewer than 0.04% of all malignant breast neoplasms, and tend to occur in younger patients with no prior history of malignancy [1,2].

The prognosis is poor for patients with primary angiosarcomas as compared with invasive ductal carcinomas. Angiosarcomas are highly aggressive vascular and soft tissue malignancies. Angiogenesis, believed to be strongly influenced by vascular endothelial growth factor (VEGF), is crucial in the pathogenesis of these tumors. The histo-

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logic grade of primary angiosarcoma of the breast plays an important role in the prediction of outcomes [3,4]. Because high-grade primary breast sarcomas behave like extremity sarcomas, some authors have advocated using the same treatment protocol: surgical resection followed by adjuvant chemotherapy and radiotherapy [5]. Because of its rarity, the clinical course of primary breast angiosarcoma remains unclear, although metastases involving lung, liver, and other organs have been reported.

Here we present the clinical course of a 47-year-old female with primary angiosarcoma of the breast which showed recurrence to the chest wall and fatal lung complication with the review of literature.

CASE REPORT

A 47-year-old female presented with a lump in the left breast in September 2009. She had no history of pain or nipple discharge. There was no significant past medical history.

Sonography demonstrated an irregular, spiculated, 1.7 cm hypoechoic nodule in the upper inner quadrant of the left breast, accompanied by skin thickening and edematous change (Fig. 1). A core needle biopsy identified an atypical angiomatous lesion, and the diagnosis of angiosarcoma was confirmed by positive results for factor VIII-related antigen and CD34. Because the patient had no history of previous radiation therapy or surgery, we classi-

fied the tumor as a primary angiosarcoma.

On dynamic magnetic resonance imaging (MRI), the mass exhibited early rapid enhancement with plateau. The MRI also detected lymph node enlargement in the left axilla (Fig. 1).

A positron emission tomography (PET)/computed tomography (CT) scan confirmed an area increased fluorodeoxyglucose uptake in the upper inner quadrant of the affected breast with faint uptake by the lymph nodes in the left axilla, but no other metastatic lesions were found.

The patient underwent a modified radical mastectomy in October 2009. Grossly, there is a 3.0 × 1.5 × 1.4 cm sized ill defined dark brown hemorrhagic spongy mass in the upper outer quadrant of breast. Microscopically, the mass composed of epithelioid areas, spindle areas and necrosis. The epithelioid areas are made up of large rounded cells of high nuclear grade which are arranged in sheets or rudimentary vascular channels (Fig. 2A). The spindle areas show vasoformative growth with complex anastomosing channels (Fig. 2B). These neoplastic channels are irregular in shape, freely intercommunicating with one another in a sinusoidal fashion. The mass shows high mitotic count (14/10 HPF), high nuclear grade and necrosis, the diagnosis is angiosarcoma, grade 3 in World Health Organization classification. There is no lymph node metastasis. On immunohistochemical staining, the tumor was negative for estrogen receptor, progesterone receptor and HER2. The tumor was positive for VEGFR-2 and CD-34 (Fig. 2C).

The patient was treated with adjuvant chemotherapy of

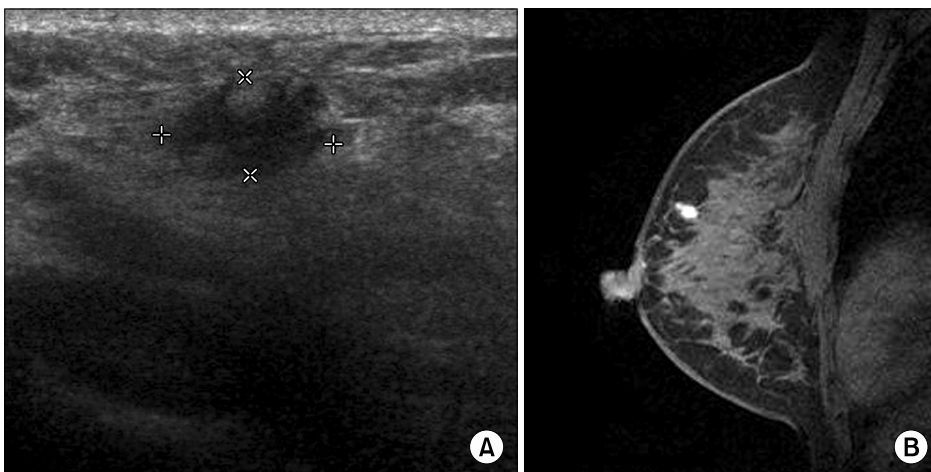


Fig. 1. Sonography and magnetic resonance imaging revealed irregular spiculated mass in left breast.

doxorubicin (60 mg/m^2) and ifosfamide ($5,000 \text{ mg/m}^2$) every 3 weeks for six cycles from November 2009 until February 2010.

Following this, the patient underwent radiation therapy on the left chest wall with 50 Gy for 5.5 weeks. CT, and

bone scan were normal. A biopsy was done in the left axilla. Histological diagnosis was lymphangioendothelioma, which was benign. We decided on follow-up 6 months later due to the possibility of local recurrence.

In January 2011, the patient returned complaining of

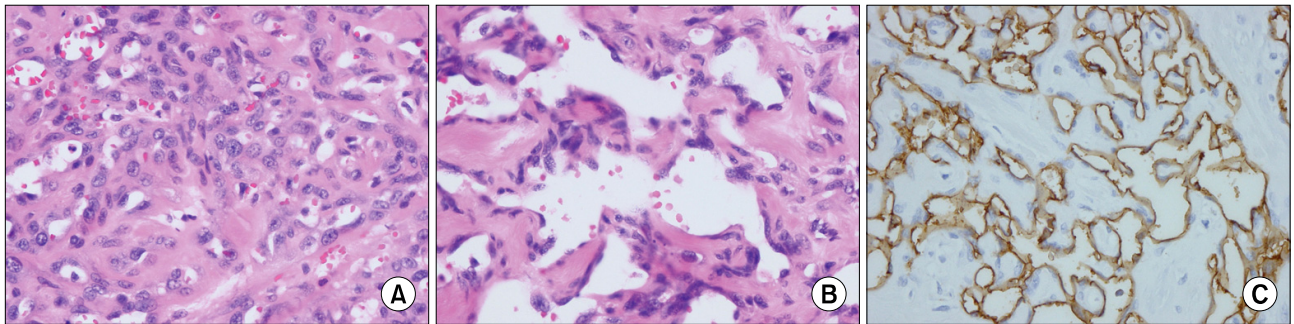


Fig. 2. (A) Epithelioid areas of angiosarcoma (H&E, $\times 400$). (B) Spindle vasoformative growth areas of angiosarcoma (H&E, $\times 400$). (C) CD34 immunohistochemical staining results shows diffuse strong positive in tumor cells ($\times 400$).

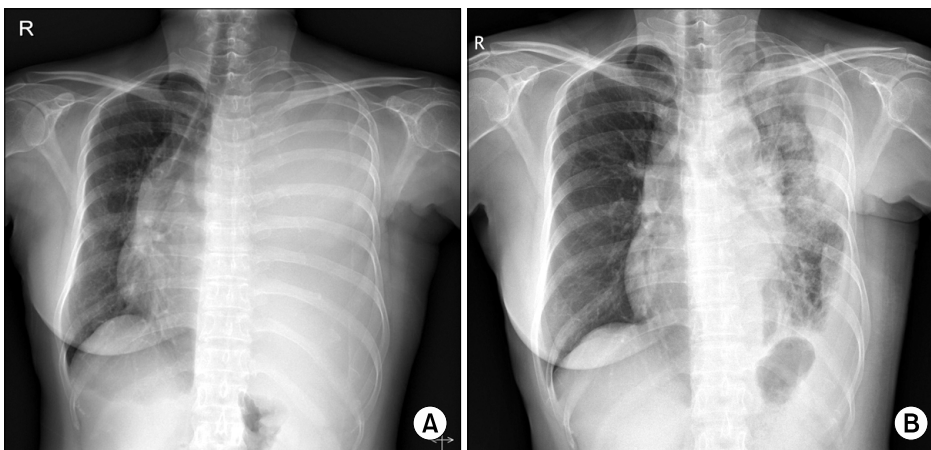


Fig. 3. (A) Chest X-ray showed large amount of pleural effusion in left side and mediastinal shifting to right side. (B) Chest X-ray showed decreased amount of pleural effusion in left side.

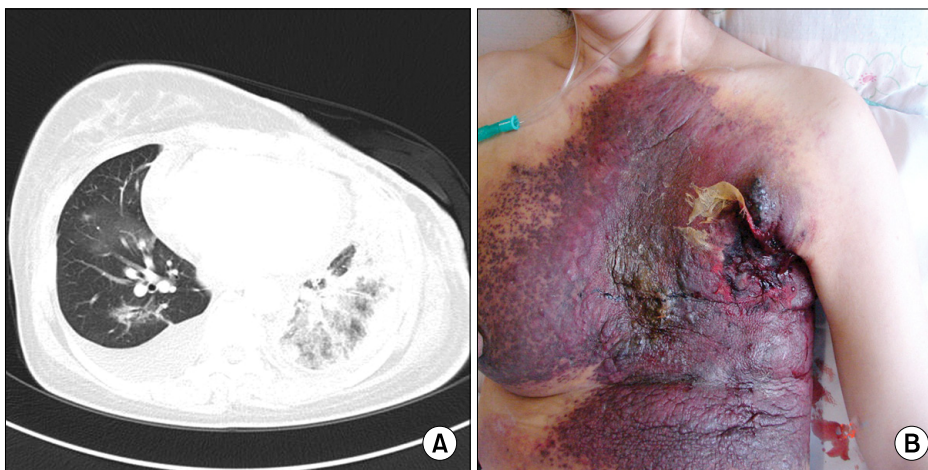


Fig. 4. (A) Chest computed tomography showed pulmonary hemorrhage in left side and pleural effusion in right side. (B) Recurrent angiosarcoma was observed in left chest wall.

dyspnea that had started 1 week prior. A chest X-ray showed a large pleural effusion in the left side (Fig. 3A). Chest CT verified a massive pleural effusion with complete atelectasis in the left lung. A chest tube was placed to drain the effusion and 3,600 mL of dark, sanguineous fluid was emptied. Pleural biopsy and fluid cytology were done. On histological examination, there was no definite malignant lesion but a marked proliferation of vascular endothelial cells, which was thought to be a reactive change.

During this admission, the patient's initial platelet count was normal, but she developed a gradual onset of thrombocytopenia that persisted until discharge (2 months later) despite platelet transfusions. Effusion decreased gradually and chest tube was removed, but the patient's condition was not yet improved (Fig. 3B). She left the hospital arbitrarily.

The patient presented again with dyspnea and hemoptysis in April 2011. Chest X-ray and CT showed pulmonary hemorrhage in the left side and pleural effusion in the right side (Fig. 4A). A chest tube was placed to drain the effusion and sanguineous output was noted. The patient was anemic and again remained thrombocytopenic in spite of transfusion. The skin lesion had been observed in left chest wall (Fig. 4B). Biopsy was done and histological examination established the diagnosis of recurrent grade 3 angiosarcoma. Persistent hemoptysis and pleural effusion were not improved.

After diagnosis of recurrent angiosarcoma, we tried combination treatment with bevacizumab and paclitaxel with informed consent. After the first treatment, the patient's respiratory symptoms improved, but after five days, her respiratory status again deteriorated. The patient died of respiratory failure secondary to pulmonary hemorrhage.

DISCUSSION

Angiosarcomas are rare malignant tumors that arise from vascular endothelial cells. In general, they develop in the soft tissue and skin. Patients with primary angiosarcoma of the breast present with a palpable mass. There are no

typical radiologic characteristics in mammography or sonography. MRI will reveal a heterogeneous mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images due to the vascular endothelial origin of the tumor [6].

Immunohistochemical stains for factor VIII-related antigen and CD34 are helpful to confirm the diagnosis of angiosarcoma. In this case, on initial core needle biopsy, immunohistochemical examinations were positive for the expression of factor VIII-related antigen and confirmed the diagnosis of angiosarcoma.

Primary angiosarcomas of the breast are classified into three grades [4]. Grade 1 (low grade) tumors consist of vascular channels invading the breast fat and parenchyma with little or no endothelial proliferation. Grade 2 (intermediate grade) tumors contain solid neoplastic vascular growth and papillary endothelial components. Grade 3 (high-grade) tumors present as sarcomatous growths with necrosis and hemorrhage. In the case presented here, breast and skin biopsies were consistent with grade 3 primary angiosarcoma.

The clinical course for this patient was very difficult due to the recurrence of tumor and complicated by an intractable thrombocytopenia. There are two hypotheses that may explain this thrombocytopenia. The first is that it was due to antiplatelet antibody. The second is that it may have resulted from antitumoral consumption of platelets. This platelet consumption may have been due to defective synthesis of prostaglandin I_2 by neovascular endothelium or to the release of a platelet aggregating substance by tumor cells [7]. Endothelial cells express several kinds of cell adhesion molecules, including ICAM-1, VCAM-1, and PECAM-1 [8], but in this case, we were not able to evaluate for these molecules. Such an evaluation may have been useful to confirm that the patient's thrombocytopenia was due to the angiosarcoma.

Uncontrolled Thrombocytopenia in this case is similar with the consumptive coagulopathy seen in Kasabach-Meritt syndrome, which is characterized by platelet sequestration and consumption of clotting factors within the vascular bed of giant angiomas naevi [9]. The widespread skin lesion, which was diagnosed as angiosarcoma had been observed in the left chest wall. So, we deemed

that the uncontrolled thrombocytopenia was caused by persistent platelet consumption in the large skin lesion.

In high-grade angiosarcoma, the current treatment modalities are surgery followed by adjuvant chemotherapy and radiotherapy. Doxorubicin-based chemotherapy has been the mainstay of treatment for high-grade soft tissue sarcomas, and while adjuvant chemotherapy is recommended for grade 3 tumors, little benefit has been reported for grade 1 or grade 2 tumors [4].

Bevacizumab is a humanized monoclonal immunoglobulin G1 antibody that targets VEGF, prevents binding of VEGF to receptors on vascular endothelial cells, and blocks tumor angiogenesis. It has demonstrated efficacy as a first line treatment of metastatic breast cancer, especially in combination with paclitaxel and docetaxel. Phase II trials evaluating the efficacy bevacizumab with paclitaxel for angiosarcoma are currently under way [10]. On the basis of this trial, we tried bevacizumab treatment after informed consent.

The prognosis is poor in patients with primary breast angiosarcoma compared with other types of breast carcinoma and is dependent on tumor grade. Disease-free survival 5 years after initial treatment is 76% with grade 1 tumors and falls to 15% with grade 3 tumors. Disease recurrence is more than 15 years with grade 1 tumors, but in patients with grade 3 tumors, the time to recurrence averages 15 months [4]. In this case, the patient had a grade 3 tumor and the time to disease recurrence was about 18 months.

Metastases occur most frequently to the lung, bone, liver, and chest wall [1]. Although not confirmed by biopsy, this patient had evidence of metastasis to the lung. She developed dyspnea, hemoptysis, and episodes of pleural hemorrhage beginning about 18 months after initial treatment and persisting until death. The hemoptysis is considered to have been caused by alveolar hemorrhage secondary to the suspected pulmonary metastasis, rather than spontaneous bleeding secondary to the thrombocytopenia. We suggest the patient died due to uncontrolled bleeding stemming from the alveolar hemorrhage.

Because primary angiosarcoma of the breast is so aggressive and rare, there is currently no consensus data for standard treatment or clinical course. We have detailed our experience with a primary breast angiosarcoma that failed to respond to multimodality treatment of surgical resection and adjuvant chemotherapy and radiotherapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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