A Case of Biphasic Sarcoma with Lung and Breast Metastasis Responding to Pazopanib

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INTRODUCTION

Soft tissue sarcomas represent a rare, heterogeneous group of malignant tumors originating from mesenchymal tissue that contribute an estimated frequency of 1% to all adult malignancies [1]. The following case report describes a unique case of a young woman of Hmong ethnicity manifesting with a recurrent biphasic pleomorphic soft tissue sarcoma with multifocal metastatic disease compounded by underlying a Li-Fraumeni syndrome. This case represents the first report of successful treatment of a breast metastasis in a patient with multi-focal metastasis and a complex medical history, treated successfully with pazopanib as a second line treatment following failure of other chemotherapeutic approaches.

CASE PRESENTATION

A 31-year-old female of Hmong origin initially presented with persistent pain in her leg sustained from an injury. The patient had a family history of cancer: her mother died of cervical cancer; a sister was in remission from a lymphoma; and another sister had been diagnosed with cervical cancer. The patient was initially diagnosed on imaging with a 6.3 x 4.7 x 6.3 cm peripherally enhancing lesion in the distal left femur. Biopsy revealed an intermediate grade spindle cell sarcoma indicative of leiomyosarcoma. Subsequently, the patient underwent left femoral distal resection of the knee with rotating hinge knee placement. The pathology report revealed the presence of a biphasic sarcoma with high grade spindle cells and osteoclast-type giant cell-rich pleomorphic components and negative soft tissue margins.

Local recurrence of the tumor in the femur occurred less than a year later, manifesting as a 4x4x2 cm soft tissue mass. Metastatic workup further revealed the presence of bilateral pulmonary nodules. The patient received six, 5-week cycles of treatment with adriamycin, cisplatin, and high dose methotrexate to treat her initial presentation of the osteosarcoma with pathology showing biphasic sarcoma. After the progression of her disease, she was treated with four cycles of gemcitabine/docetaxel, which she completed one month after undergoing video-assisted thorascopic surgery of the left lower-lobe pulmonary lobectomy. Pathology reports indicated a similar high grade sarcoma with positive bronchial margins.

The patient further underwent left hip disarticulation due to her pain and swelling and lack of disease control following treatment with adriamycin, high dose cisplatin, and high dose methotrexate. This treatment was supported by pathology reports indicating presence of a high grade sarcoma with negative margins. The patient was further diagnosed with papillary thyroid cancer in 2012, for which she did not undergo specific treatment.
Several months later in the same year, the patient detected a mass in her left breast. Imaging and breast biopsy revealed a high metastatic grade osteosarcoma with similar pathological features. Follow-up computed tomography (CT) chest imaging revealed advancement of bilateral multifocal disease with cavitation and air fluid level in the mass occurring in the left upper lobe. Positron emission tomography (PET)/CT scan confirmed increased metabolic activity of the lung lesion and breast mass. Gemcitabine and cisplatin were given for four cycles. On follow up visits, thickening and enhancement extending into the pectoralis major muscle revealed progression of the breast mass that was measured at 12.4 x 9.2 x 13.8 cm (see Figures 1 and 2). The patient was considered a poor candidate for other treatment options; therefore, treatment with pazopanib, a second line treatment for soft tissue sarcoma approved by the Food and Drug Administration (FDA), was selected as a viable option for palliation. Surprisingly, the treatment response was positive, with the patient reporting decreased tenderness and distention. The mass had decreased in size to 8.7 x 4.0 x 10.7 cm when last evaluated.

Prior to her treatment with pazopanib, the patient had reported worsening of headaches, blurred vision, and episodes of numbness and weakness. Magnetic resonance imaging (MRI) of the brain revealed a left cerebellar peduncle lesion within the superior vermis and extending slightly to the left cerebellum, potentially indicating brain metastases or presence of glioma. In light of these new findings, her prior history of thyroid cancer, and the progressive metastatic leiomyosarcoma diagnosis, genetic sequencing of the TP53 gene was ordered. This confirmed that the patient was heterogeneous for a causal mutation of the TP53 gene associated with Li-Fraumeni syndrome, confirming the diagnosis.

**DISCUSSION**

This case describes a young woman with multifocal metastatic events of a recurrent biphasic pleomorphic soft tissue sarcoma compounded by underlying Li-Fraumeni syndrome. The patient’s frequent recurrences of metastatic disease originated from the left femur, which was eventually amputated above the knee. Metastatic disease occurring in the lung and breast ensued. The patient was also found to have cancer of the thyroid and was diagnosed with a brain tumor. Additionally, the patient’s pedigree indicated a strong family history of cancer, indicating strong contribution for heritable underpinnings and increased risk of carcinogenesis.

Given this background, the patient was genetically evaluated via TP53 gene sequencing and was found to be heterozygous for a missense mutation defined as c.818G>A, resulting in an amino acid substitution (Arg273His). This variant has been associated with causation for Li-Fraumeni syndrome and was confirmed to be pathogenic in functional studies [2]. Li-Fraumeni syndrome is a very rare syndrome associated with increased susceptibility to cancer with an autosomal dominant transmission mode. TP53 gene function includes DNA repair initiation or activation of apoptotic pathways in response to DNA damage [3]. Five other variants identified during sequencing of the TP53 gene did not appear to be associated with pathology [4]. These data are in keeping with a potential for a genetic basis for cancer susceptibility given the patient’s family history, wherein multiple members of her immediate family were impacted by cancer diagnoses.

Treatment options leading up to placing her on pazopanib was limited for this patient. The patient was not a candidate for further surgical management, since she could not be rendered disease-free from an oncological perspective. Despite her case history, the patient remained high-functioning, so that palliative surgical approaches were not indicated. Further, the patient exhibited some delays in wound healing. Radiation was not recommended, because of the multifocal, extensive nature of her disease that could increase toxicities over a wide field. Additional treatment with the initial regimen was not considered beneficial, since safe administration of adriamycin was not possible with the escalation of dosing that would be required. The option of pazopanib, FDA-approved for metastatic soft tissue sarcoma, was recommended as a palliative approach to ease the discomfort associated with breast metastasis. Pazopanib is a multikinase inhibitor. The patient responded well to this interventional approach, with a decrease in the size and extent of the breast tumor. Thus, this is the first case report of successful treatment of a patient presenting with underlying Li-Fraumeni syndrome and biphasic, pleomorphic, metastatic soft tissue sarcoma treated with pazopanib. A recent report in the literature suggests that pazopanib may have enhanced efficacy in combination with valproate [5].

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**Figure 1** Picture of left breast with bandage.

**Figure 2** Picture of the left breast showing the metastases.
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