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An unexpected skin ulcer and soft tissue necrosis after the nonconcurrent combination of proton beam therapy and pazopanib: A case of myxofibrosarcoma

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ABSTRACT

We herein report the case of a patient presenting with myxofibrosarcoma (MFS) who underwent treatment with surgery, proton beam therapy (PBT), and pazopanib. A 64-year-old male was diagnosed with MFS, which ranged from the posterior neck to the shoulder. Surgery was performed as an initial treatment; however, the primary tumor recurred 83 months after the initial treatment. We, therefore, administered PBT. Although most of the recurrent tumor disappeared after PBT, multiple lung metastases were identified 3 months after the completion of PBT. We initiated antiangiogenic treatment with pazopanib. Although long-term survival was achieved with the treatments, the patient suffered from a skin ulcer and soft tissue necrosis and eventually died of general prostration caused by infection, and complicated by pneumonia. Although PBT and pazopanib were effective for treating the local recurrence and lung metastases of MFS, respectively, clinicians must be cognizant of the fact that the combination of high-dose irradiation and angiogenesis inhibitors, even in nonconcurrent cases, can result in a severe skin ulcer and soft tissue necrosis.

1. Introduction

Myxofibrosarcoma (MFS) is a common malignant mesenchymal tumor that occurs in the extremities of older patients [1,2]; however, it rarely appears in the head and neck area [3] or the shoulder [4]. Until Angervall et al. first described MFS as a disease concept [5], it had been classified as myxoid malignant fibrous histiocytoma. In 2002, the World Health Organization also defined it as a distinct entity [6]. We experienced a rare case of MFS ranging from the posterior neck to the shoulder. As particle beam radiation therapy including proton beam therapy (PBT) [7] and pazopanib is generally considered to be effective for soft tissue sarcoma, we performed PBT to treat a locoregional recurrence after surgical resection and administered pazopanib to treat lung metastasis. After treatment, a skin ulcer, necrosis and severe soft tissue necrosis were identified in the supraclavicular fossa. We herein report a valuable case of MFS with emphasis on the treatment modalities.

2. Case report

A 64-year-old male patient was referred to the Department of Otolaryngology-Head and Neck Surgery, Hyogo College of

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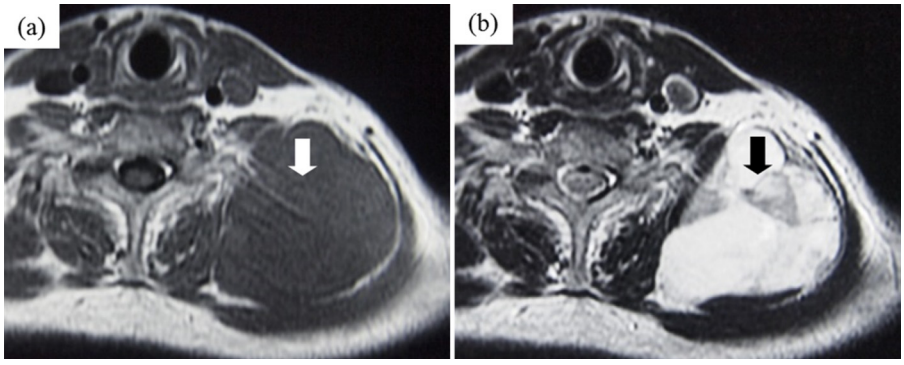

Fig. 1. The neck MRI findings before the initial treatment. (a) T1-weighted imaging and (b) T2-weighted imaging. T1-weighted imaging of the left posterior neck and shoulder showed a smooth and clearly well-demarcated tumor with a low signal intensity (white arrow). T2-weighted imaging showed a high signal intensity (black arrow). No apparent neck lymph node metastases were observed.

Medicine, Japan with a 4-month history of swelling from the left posterior neck to the left shoulder. The patient's condition was complicated with hypertension, hyperlipidemia, and cerebral aneurysm. A 7.5 cm × 7.0 cm, elastic soft, mobile and painless mass was observed underneath the normal skin tissue of the left posterior neck and shoulder at our initial medical examination. The tumor was suspected to be MFS after the first fine needle biopsy. We performed neck magnetic resonance imaging (MRI), which showed a clear tumor border without any invasion of the surrounding tissue (Fig. 1). No apparent neck lymph node metastases were observed. A chest computed tomography (CT) scan and gallium-67 citrate scintigraphy did not reveal distant metastasis.

We performed surgery as the initial treatment and the tumor was successfully resected with negative surgical margins. A postoperative histological examination revealed atypical spindle cells proliferating in myxomatous background, with mitoses and necrosis in solid growth area (Fig. 2). No lipoblasts (a characteristic finding in myxoid liposarcoma) were observed. The tumor was diagnosed as MFS, and classified as grade 3, based on the Fédération Nationale des Centres de Litte Contre le Cancer (FNCLCC) grading system. We judged that no further adjuvant therapy was needed. A positron emission tomography (PET)/CT scan conducted 70 months after the initial surgery showed no evidence of local recurrence or metastasis (Fig. 3a). However, local recurrence appeared unexpectedly on a CT scan at 83 months after the surgery (Fig. 3b).

Although we suggested the patient undergo salvage surgery, he refused it as the amputation of his left arm would have been necessary to achieve the complete resection of the tumor. Instead, PBT with a dose of 70.4 Gy (relative biological effectiveness [RBE][1]) in 32 fractions was performed at Hyogo Ion Beam Medical Center as a curative treatment for the recurrent tumor (Fig. 3c). The inside of the tumor was necrotic after PBT, and the curative effect was considered to be satisfactory (Fig. 3d).

Moderate skin erosion occurred during PBT; however, the symptom steadily improved and only slight pigmentation was observed at 5 months after the therapy. Multiple lung metastases were revealed on a chest CT scan at 90 months after the initial surgery. We administered pazopanib (800 mg/body per day, orally) as a molecular-target drug therapy. After the continuous administration of pazopanib, a change was observed in the cavitation of the patient's lung metastasis, and the size of the lung metastases was reduced. However, radiation dermatitis recurred after the initiation of pazopanib treatment. Eventually, a severe skin ulcer and internal soft tissue necrosis appeared in the supraclavicular fossa at 4 months after the initiation of pazopanib treatment (Fig. 4a). We performed debridement surgery. The necrotic tissue was partially resected around the subclavian artery, but it was almost completely removed in the other parts. An infusion tube and a 5-mm drainage tube were inserted for post-surgical lavage (Fig. 4b). We also conducted a histopathological examination. The examination did not identify any apparent local recurrence.

As post-surgical treatment, we performed lavage while administering a saline solution (500 mL, 3 times daily) through the infusion tube and draining the lavage fluid with a drainage tube, as well as performed continuous administration of pazopanib. Since the progression of soft tissue necrosis was observed after the debridement surgery, we added debridement treatment as needed.

Although we thoroughly and repeatedly provided postoperative irrigation treatment, no sufficient improvement was observed in regard to the skin ulcer or the soft tissue necrosis. The patient eventually died of general prostration caused by infection and complicated by pneumonia at 99 months after the initial surgery. No obvious regrowth of lung metastasis was observed during the follow-up period.

3. Discussion

Surgery is generally chosen as the initial treatment for MFS, and the surgical margin has a significant impact on local recurrence [4,9] and overall survival [9]. MFS is classified in accordance with its pathological characteristics. Although

[1] The proton beam dose is reported in Gy (RBE), which is defined as the physical dose multiplied by the RBE of the protons. For example, 2 Gy (RBE) of PBT is biologically equivalent to 2 Gy of photon radiation therapy. The biological effects of PBT were evaluated *in vitro* and *in vivo*, and the RBE value for the proton irradiation treatment was determined to be 1.1 [8].

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