Multidisciplinary treatment in pulmonary metastasis of a mesorectal angiosarcoma achieving complete remission

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To the Editor: Angiosarcoma (AS) is a rare and highly malignant mesenchymal tumor that accounts for 2% of adult soft tissue sarcomas. The prognosis of AS is poor due to the high rate of metastasis and reoccurrence. According to a retrospective study by Lahat *et al* and Fayette *et al*,[1,2] 31 of 121 (19%) patients had metastases upon initial diagnosis, and 90 (74%) had relapse and progression. The median survival of AS was 3.4 years, declining to 10 months in patients with metastasis. To attempt to improve AS treatment outcomes, a multimodality approach is advocated, including surgical resection combined with radiation, chemotherapy, immunotherapy, and/or anti-angiogenetic therapy. Herein, we present a man who previously underwent resection of a mesorectal-derived intermediate hemangioendothelioma (HAE) and developed pulmonary metastasis of AS within a year. The history is remarkable because of (1) the rare primary location: only 2 cases were mesenteric-related; (2) the uncharacteristic clinical course: the primary diagnosis of intermediate hemangioendothelioma later progressed to pulmonary metastatic AS; and (3) a successful series of multidisciplinary therapeutic procedures, especially selective arterial infusion (SAI) chemotherapy before metastases resection.

A 26-year-old man presented to the Department of Gerontology, the Second Xiangya Hospital, complaining of increasing anterior sacral pain and altered defecation habits for nearly 3 months. Physical examination revealed a hard and inflexible tumor in the right and anterior to the rectum, 4 cm to the dentate line. Magnetic resonance imaging (MRI) showed a tumor volume of $6.0 \times 5.5 \times 5.0$ cm with a capsule close to the right seminal vesicle. The mass also compressed the rectum and prostate [Figure 1A–1C]. A positron emission tomography and computed tomography (PET-CT) showed high glucose metabolism in the right pelvic cavity with invasion to the right spermatophore and rectum [Figure 1D]. No obvious abnormality was detected in a chest X-ray [Figure 1E] and colonoscopy examination. Diagnostic aspiration guided by ultrasonography presented with characteristics of the mesenchymal tissue-derived borderline tumor. After a multidisciplinary consultation, we decided to operate immediately. Prior to surgery, sperm was retrieved to preserve in case the spermatophore and sperm ducts are involved during resection. The tumor R0 resection was successfully performed. The tumor was approximately $5.5 \times 4.5 \times 4.3$ cm and was mesorectum-derived with adhesion to the rectum [Figure 1F]. The procedure was an extra-low Dixon surgery.

Microscopically, the tumor had a fibrous capsule, exhibited substantial hemorrhage and necrosis, and was mainly filled with hyperplastic spindle cells with a partial vascular-lumen-like structure. Immunohistochemistry (IHC) revealed that the tumor cells were CD31 (++), CD34 (+), and Ki-67 (50%), and a few exhibited heteromorphism. All of the pathological evidence indicated a diagnosis of intermediate HAE (T2N0M0). No other specific postoperative treatment was administered. The patient had phase I incision healing before hospital discharge.

One year later, the patient returned to the hospital with cough, chest pain, and hemoptysis for 2 weeks. A chest CT showed nodules in the middle lobe of the right lung and the lower lobe of the bilateral lungs with pleural effusion [Figure 1J], with enhanced glucose metabolism in positron emission tomography-computed tomography (PET-CT) scan. A magnetic resonance imaging (MRI) showed no recurrence in the primary location and no other metastatic signs. For neo-adjuvant chemotherapy, we conducted SAI

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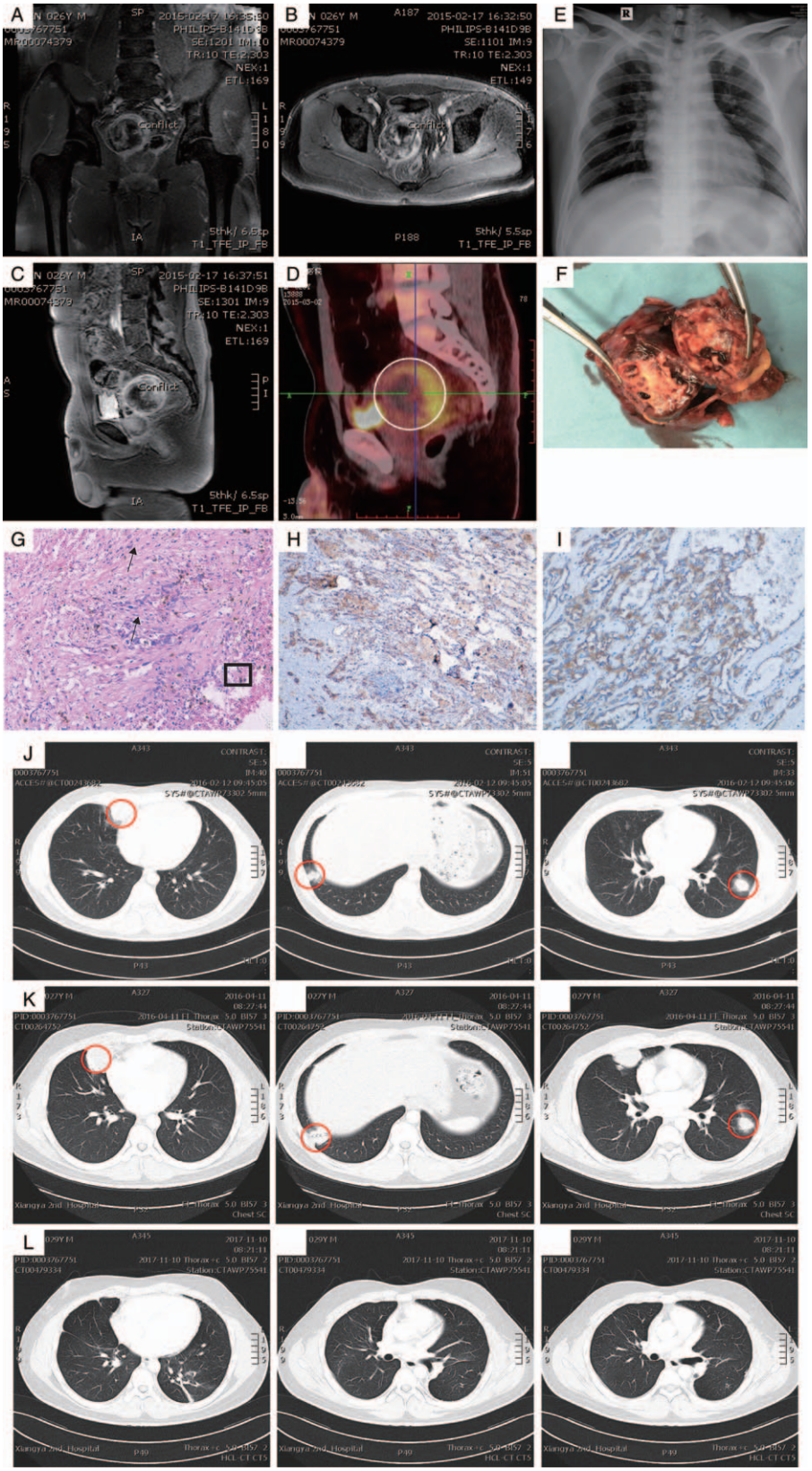

Figure 1: Representative image of the patient. (A–C) Magnetic resonance imaging (MRI) of the abdomen and pelvis showed a mass compressing the rectum and prostate with clear boundaries. (D) Positron emission tomography-computed tomography (PET-CT) showed enhancing glucose metabolism (white circle) in the right pelvic cavity with invasion to the right spermatophore and rectum (E) No obvious abnormality could be seen in the chest X-ray. (F) The tumor was enclosed within a capsule and showed cystic changes and necrotic areas. (G) Metastatic lesion pathology showed vasoformative lesions (cap arrow) and multiple necrotic areas (rectangle) (hematoxylin-eosin stain, original magnification ×100). (H–I) Immunohistochemical staining for the endothelial markers CD31 and CD34 was positive (brown area) in accordance with the endothelial origin (original magnification ×100). (J) Three unequally sized and ground glass margined nodules (red circle) are seen in the peripheral regions of both lungs. (K) The nodules' margins (red circle) were sharpened after 2 cycles of selective arterial infusion (SAI) chemotherapy. (L) No obvious recurrence and new metastasis was seen in re-examination during 19 months post-surgery.

therapy, infusing 200 mg of carboplatin and 100 mg of paclitaxel into the metastases by the right internal thoracic artery and bilateral bronchi artery, which were verified as the main vascularization of the metastases. After 2 rounds of chemotherapy, all of the metastases had decreased inflammation areas and clear margins according to the CT results [Figure 1K]. The patient underwent metastases resection in both lungs at 4-week intervals, during which time the third round of SAI was administered to the metastasis in the left lung. The pathological diagnosis was AS (right middle and left metastases) [Figure 1G–1I] and HAE (right lower metastasis) with CD31 (+), F8 (+), CD34 (+), Ki-67 (40%), P53 (8%+), and epithelial growth factor receptor (EGFR) (+).

The left metastasis and adjacent normal pulmonary tissue were sent for whole-genome sequencing and RNA. The analysis showed no targeted therapy-related somatic mutations were found in this patient. However, annotation analysis suggested that this patient might be sensitive to anthracyclines and ifosfamide with relatively low toxicities. Consequently, 3 g of ifosfamide plus 20 mg of pegylated liposomal doxorubicin were administered for three rounds postoperatively.

At present, the patient is in a stable clinical condition with no complaints. He had a CT scan in both his chest and abdomen in November 2017 [Figure 1K] with no signs of re-occurrence and fathered a child in April 2018.

As reported by Weiss *et al*[3] HAEs are vascular neoplasms with borderline biological behavior, intermediate between entirely benign hemangiomas and highly malignant ASs. Some authors hypothesized that HAE is an intermediate state of endothelial dedifferentiation. As in the case, HAE and AS both can be seen in pulmonary metastases, demonstrating that these two pathological types may be associated.

As proposed by Buehler *et al*[4] cases with metastases at presentation, visceral/deep soft tissue tumor location, tumor size >5 cm, tumor necrosis, and the absence of surgical excision are adverse predictors of survival. Accordingly, although the R0 excision could be done in the first step, 1 year later pulmonary metastasis occurred.

Current treatments for AS include surgery, wide-field radiotherapy, and reportedly electrochemotherapy or chemotherapy as adjuvant treatment. For localized AS, surgical resection is the only curative approach. Some authors proposed that the addition of radiation or chemotherapy in an adjuvant setting may improve local control and long-term survival. For patients with non-cutaneous AS, combination chemotherapy with doxorubicin and ifosfamide is preferred, which could be substituted by gemcitabine and docetaxel for patients with cardiac dysfunction. Additionally, based on studies demonstrating the overexpression of vascular endothelial growth factor and receptors in AS, the response of anti-vascular endothelial growth factor (VEGF) targeted drugs such as bevacizumab, sorafenib, and pazopanib were assessed via clinical trials and demonstrated modest VEGF antagonism.

For advanced or metastatic AS, systemic therapy is the mainstay of treatment. However, surgery is still a radical approach whenever feasible. Almost all studies reported that the complete resection of metastatic disease is critical for long-time survival. In soft tissue sarcomas, the 5-year survival rates are reportedly 18% to 44% after pulmonary metastasectomy (PM). The most important favorable prognostic factor after PM is the complete resection of metastases even when there are two or more. Selective arterial infusion (SAI) has been studied for decades. SAI, a new method of neoadjuvant chemotherapy, can achieve high concentrations in tumors, secondary anti-cancer effects, and lower systemic side effects.[5] As in the present case, we maintained the metastases in the stable condition through SAI and PM without recurrence. The patient's chest pain and hemoptysis were significantly relieved 3 to 4 days after SAI.

In conclusion, AS is a rare and highly malignant mesenchymal tumor with various manifestations. Under the background of prevalent neo-adjuvant chemotherapy, SAI and PM can be combined for better outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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