Case Report

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Locally advanced malignant solitary fibrous tumour successfully treated with conversion chemotherapy, operation and postoperative radiotherapy: a case report

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Abstract

Preoperative diagnosis of solitary fibrous tumour (SFT) may not provide a complete tumour picture and may be inaccurate. There is no standard treatment for locally advanced or metastasised malignant SFT (MSFT). Here, the case of a 17-year-old male patient with final pathology diagnosis of MSFT is reported. Preoperative biopsy pathology results suggested an Ewing sarcoma that was positive for CD99 antigen, vimentin, friend leukaemia integration 1 transcription factor, apoptosis regulator Bcl-2, and synaptophysin; and negative for CD34 antigen, S-100 protein (S-100), smooth muscle antigen, cytokeratin, and Wilms tumour 1 associated protein. The Ki67 positive rate was 8%, so the patient initially received eight cycles of conversion chemotherapy (vincristine, etoposide, ifosfamide and pirarubicin for one cycle, and vincristine, doxorubicin, and cyclophosphamide/ifosfamide and etoposide for 7 cycles in total). The tumour shrunk significantly and was surgically removed. The final pathology diagnosis was MSFT that was positive for CD99 and signal transducer and activator of transcription 6, and negative for CD34, tumour protein 63, S-100, desmin, and epithelial membrane antigen. Fluorescence in situ hybridization showed no gene translocation in EWS RNA binding protein 1, SS18 subunit of BAF chromatin remodelling complex or FUS RNA binding protein. The patient finally accepted adjuvant radiotherapy of 5600 cGy. Disease-free survival has been $>$ 1 year, with no recurrence or metastasis detected to date. MSFT is rare and treatment for locally advanced or metastatic MSFT remains controversial. The efficacy of the present therapeutic strategy requires further research.

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Introduction

Solitary fibrous tumour (SFT) is a rare, slow-growing mesenchymal neoplasm considered to be of fibroblastic origin, and believed by some scholars to originate from CD34 antigen-positive dendritic stromal cells.[1] SFT may occur in any anatomical location, with the most reported being the thorax, particularly the pleura.[2] Even so, SFT is rare and accounts for less than 5% of all pleural tumours, and the incidence is reported to be less than 0.1/ 100 000/ year.[3,4] Most SFTs are thought to be benign, while about 10–20% are reported to be malignant (MSFT),[5,6] however, it remains difficult to strictly distinguish MSFT from benign SFT. There is no difference in incidence rates between male and female patients, and SFT mostly occurs in those aged 50–70 years, with only a small number of cases in younger patients.[3,7,8]

The aetiology of SFT is still unknown, while some molecular changes are thought to be related to tumour progression, such as changes to NGFI-A binding protein 2 (*NAB2*)-signal transducer and activator of transcription 6 (*STAT6*) fusion and tumour protein 53 (TP53).[9,10] Preoperative diagnosis, such as imaging examination and even biopsy can be inaccurate.[11] Surgery is the best treatment option, serving as both a diagnostic and therapeutic procedure, and postoperative pathology remains the gold standard for diagnosis.[12] The role of preoperative and postoperative treatments are still unclear, including those involving patients with locally advanced or metastatic SFT.[1,3,6]

Here, the case of a patient with a locally advanced MSFT (final pathological diagnosis after surgery), who was treated with conversion chemotherapy using doxorubicin and ifosfamide-based regimens and achieved significant tumour shrinkage, giving the chance of radical surgery followed by adjuvant radiotherapy, is reported. This treatment strategy has not been reported previously, and has proved to be successful to date, with the patient remaining in good health at the time of reporting.

Case report

Ethics approval was not deemed necessary for this case report and no research protocol was applied for. Written informed consent was obtained from the patient and his parents for all the treatments used, and verbal informed consent was obtained for publication of this report.

In March 2018, a 17-year-old male presented at Dazhou Central Hospital, Dazhou, Sichuan, China, with a painless tumour on the chest wall, with no personal or family history of previous tumour diagnosis or treatment. Computed tomography (CT) and magnetic resonance imaging (MRI) showed a massive soft tissue occupation of almost all of the left thorax with bone destruction of the fourth left rib. The tumour size was $15.5 \times 15.5 \times 16$ cm (Figure 1). The first puncture biopsy

conducted at Dazhou Central Hospital didn't find a tumour, and showed only a few lymphocytes. The pathology of the second biopsy at the same hospital suggested an Ewing sarcoma, and immunohistochemical staining showed that the tissue was positive for CD99 antigen, vimentin, friend leukaemia integration 1 transcription factor, apoptosis regulator Bcl-2 (Bcl-2), and synaptophysin; and negative for CD34, S-100 protein (S-100), smooth muscle antigen (SMA), cytokeratin, and Wilms tumour 1 associated protein. The Ki67 positive rate was about 8%. The thoracic surgeon assessed that the lesion could not be completely removed, and as chemotherapy is standard for Ewing sarcoma, the patient received an immediate first single cycle of standard dose chemotherapy (2 mg vincristine [day 1], 0.1 g etoposide [day 1–5], 2 g ifosfamide [day 1–4], and 80 mg pirarubicin [day 1]) at Dazhou Central Hospital.

Following treatment with one chemotherapy cycle, the patient was admitted to the Cancer Centre of West China Hospital, Sichuan University, Chengdu, China. A pathologist experienced in sarcomas (CC) in the Cancer Centre of West China Hospital verified the pathological results and also suggested an Ewing sarcoma. Subsequently, fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG PET)/CT was recommended to the patient, but he refused for financial reasons. After a multidisciplinary discussion and serious consideration, treatment comprising 2 mg vincristine (day 1), 120 mg doxorubicin (day 1) plus 2 g cyclophosphamide (day 1)/ 3 g ifosfamide (day 1–5) plus 150 mg etoposide (day 1–5), every 3 weeks (VDC/IE) was chosen as the chemotherapy regimen. The pathology result of bone marrow puncture before chemotherapy was normal. As a result, the patient received another seven cycles of standard dose chemotherapy (VDC/IE) at West China Hospital, providing eight cycles in total with no obvious adverse events and drug reduction before surgery. The last cycle was delivered in January 2019. Due to the patient's strong request, he underwent a third puncture biopsy of the tumour between the 5th and 6th cycle of chemotherapy. The pathology result was undifferentiated sarcoma, Fédération nationale des centres de lutte contre le cancer (FNCLCC) grade: level 3; the tumour was positive for CD99, cyclin D1, and myc proto-oncogene protein; and negative for CD34, S-100, and SMA; the Ki67 positive rate was about 10–15%; and the results of fluorescence in situ hybridization (FISH) showed no BCL6 corepressor (*BCOR*) or capicua transcriptional repressor (*CIC*) gene translocation.

As the tumour shrunk significantly after chemotherapy (partial response [PR] shown by CT according to Response Evaluation Criteria in Solid Tumours [RECIST 1.1]; Figure 1), his tumour was surgically removed in March 2019, by wedge resection of the left superior lobe. Grossly, the tumour was a grey-brown cystic solid with a size of $13.6 \times 10.6 \times 4.2$ cm. The final pathology result was MSFT, with post-treatment change, FNCLCC grade: level 2, and the tumour was positive for CD99 and STAT6 (Figure 2); and negative for CD34, tumour protein 63 (P63), S-100, desmin, and epithelial membrane antigen (EMA). The results of FISH showed no gene translocation, either in EWS RNA binding protein 1 (*EWSR1*), SS18 subunit of BAF chromatin remodelling complex (*SS18*) or FUS RNA binding protein (*FUS*). The patient accepted adjuvant radiotherapy after surgery (5600 cGy in 28 fractions of 200 cGy each), which began in May 2019 and ended in July 2019. Following radiotherapy, he underwent regular follow-ups. More than 1 year later, the patient remains in good health with

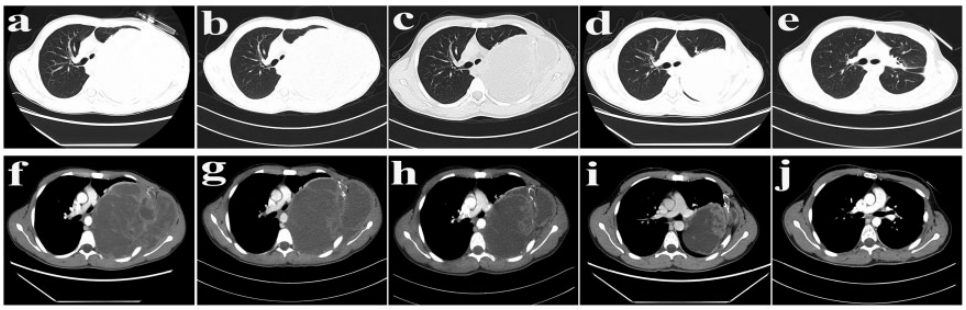

Figure 1. Computed tomography scan of the chest conducted at West China Hospital, Sichuan University, showing: (a and f) the tumour before chemotherapy; (b and g) the tumour after the second cycle of chemotherapy; (c and h) the tumour after the fifth cycle of chemotherapy; (d and i) the tumour after all cycles of conversion chemotherapy; and (e and j) disappearance of the cancer following surgery. Panel a–e shows the lung windows, and f–j shows the mediastinal windows.

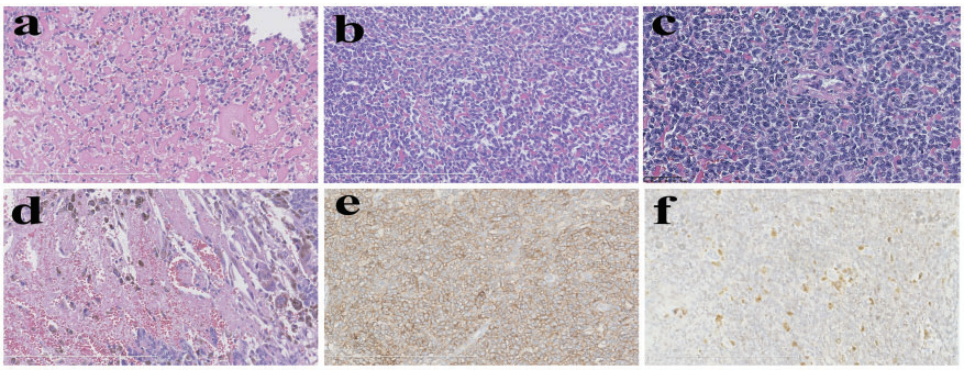

Figure 2. Representative final pathology images of the haematoxylin and eosin-, and immunohistochemically-stained malignant solitary fibrous tumour, showing: (a) sparse area with intratumoral haemorrhage and collagenous stroma (original magnification, × 200); (b) dense area (original magnification, × 200); (c) marked atypia and mitotic cells (original magnification, × 400); (d) necrosis and haemorrhage (original magnification, × 200); (e) positive staining for CD99 (original magnification, × 200); and (f) positive staining for signal transducer and activator of transcription 6 (original magnification, × 200).

no recurrence or metastasis shown by CT and MRI.

Discussion

Solitary fibrous tumour is a very rare mesenchymal neoplasm rich in blood vessels, with no difference in the incidence between males and females. SFT is mostly diagnosed in those aged 50–70 years, and only a small number of cases occur in younger patients.[7,8] The patient described in the present case was relatively young, at 17 years-of-age when diagnosed. Some researchers divide SFT into three categories: benign SFT, malignant SFT, and dedifferentiated SFT.[13,14] Most SFTs are benign, but MSFT, which accounts for 10–20% of all SFTs, has a higher recurrence and metastatic rate, and relatively poor survival.[5,6]

Tumour sizes larger than 10 cm appear to be malignant, and the tumour size in the present case was larger than 10 cm, both before and after the conversion chemotherapy, indicating a malignant tumour. Although 18F-FDG PET/CT may be helpful in diagnosing MSFT, its diagnostic utility remains debatable due to its imperfect sensitivity.[15] The criteria in some countries for distinguishing MSFT is as follows: (1) high cellularity and mitotic activity (mitotic index: >4 mitotic figures in 10 high power fields); (2) pleomorphism; (3) haemorrhage; and (4) necrosis.[6] The present case was consistent with these criteria, as can be partly observed in Figure 2.

More than half of MSFT cases are symptomatic and the clinical symptoms depend on factors such as tumour location, size, and whether they invade adjacent organs. Lesions in the chest may cause respiratory symptoms, such as cough and chest pain.[16] The male patient in the present case was admitted with a painless chest wall mass, as the tumour was large and pressed on the chest wall. Less than 5% of SFT is accompanied by hypoglycaemia, which is caused by tumoral production of insulin-like growth factor II,[17] but this was not observed in the present case.

Malignant SFT is composed of a type of spindle cell originating from fibroblasts, and needs to be distinguished from sarcomas that are full of spindle cells.[18] Preoperative biopsy can only obtain a small portion of tumour tissue, while MSFT is a very heterogeneous tumour, and may comprise myxoid degeneration, haemorrhage, and necrotic tissue. Thus, preoperative diagnosis may not always provide a complete picture of the tumour and may be inaccurate.[11] For example, a previously published report showed that the accuracy of CT-guided transthoracic fine needle aspiration biopsy (FNAB) ranges in levels below 50%.[4] The patient in the present case had four pathology results. The first puncture biopsy in the local hospital failed to find a tumour; the pathology of the second biopsy suggested an Ewing sarcoma; the third puncture biopsy between the 5th and 6th cycle of chemotherapy showed an undifferentiated sarcoma; and the final pathology result following surgery showed MSFT. Thus, it is rather difficult to understand that these pathology results could be interpreted as precise preoperative diagnoses.

Microscopic morphological diagnosis by haematoxylin and eosin (H&E) staining and immunostaining are both essential for diagnosing SFT, and immunohistochemistry is the most helpful. SFTs are NAB2-STAT6 fusion-associated neoplasms and nuclear staining of STAT6 is specific for SFT.[9] SFT is often positive for STAT6, CD99, CD34, Bcl-2, and TP53; and negative for S-100, SMA, and EMA; and the Ki67 positive rate is often week, but is higher in the malignant lesions.[19] The final pathology results in the present case supported the diagnosis of MSFT, as H&E-stained images of the tumour showed sparse and dense areas, intratumoral haemorrhage, collagenous stroma, and the tumour cells showed marked atypia, mitosis, and necrosis, which are seldom observed in the benign tumours; while immunostaining showed that the tissue was positive for STAT6 (in the nucleus) and CD99 (Figure 2); and negative for CD34, P63, S-100, desmin, and EMA. The positive STAT6 result highly indicated an SFT. Approximately 5–10% of SFTs are negative for CD34,[7] and most of these are MSFT, in other words, a negative CD34 result may be suggestive of a malignant SFT, as in the present case. FISH showed no gene translocation, either in *EWSR1, SS18* or *FUS*, whose gene fusions are traditionally regarded as pathognomonic for diagnosis of Ewing sarcoma, synovial sarcoma and myxoid/round cell liposarcoma, respectively.[20–22]

The best treatment option for MSFT is surgical resection with enough margin, and

this is also the most important key factor in survival.[12] There is no standard treatment for locally advanced or metastasised SFT, including preoperative or postoperative treatment.[1,3,6] Many drugs and regimens have been reported to be effective in SFT, such as doxorubicin-, ifosfamide- or gemcitabine-based regimens, and dacarbazine, and trabectedin amongst others, but these treatments might not be very effective in achieving tumour shrinkage, and may rarely achieve PR,[3,23] as was observed in the present case (Figure 1). Neoadjuvant or conversion chemotherapy is controversial, even regarding whether it should be done, as preoperative accurate diagnosis is relatively difficult.[1,3,6] In the present case, the tumour was closely bound to the surrounding tissues and the pathology of preoperative biopsy suggested an Ewing sarcoma. After multidisciplinary discussion, the patient finally accepted conversion chemotherapy comprising VDC/IE, and eight cycles of conversion chemotherapy were given in total. The tumour shrunk significantly (PR), which gave the patient the chance to undergo surgery.

As mentioned above, postoperative treatment, including postoperative radiotherapy is also controversial.[6] In fact, radiotherapy has conventionally been used in those with high risk of recurrence, such as MSFT, large tumour size (more than 10 cm), apparently fast-growing tumours or narrow margins.[6] The doses of postoperative radiotherapy reported in the literature usually range from 45–60 Gy.[6] In the present case, the tumour was up to $13.6 \times 10.6 \times 4.2$ cm, even after significant shrinkage, plus the tumour was tightly bound to normal tissues. Coupled with the patient's intent-to-treat, postoperative radiotherapy (5600 cGy in 28 fractions) was finally administered.

All of the described treatments have proven effective in the present young male patient with MSFT, and he remains in good health at the time of reporting, with no recurrence or metastasis, however, according to previous reports, recurrence or metastatic lesions may develop very late after surgery and long-term follow-up is recommended.[6,24] Thus, efficacy of the therapeutic treatment regimen reported in the present case requires more time to be confirmed. Regardless, the present case may provide an alternative therapeutic choice for patients with locally advanced MSFT.

In conclusion, the present report describes the case of a 17-year-old male patient with locally advanced MSFT (final pathological diagnosis after surgery) who was successfully treated with conversion chemotherapy of doxorubicin and ifosfamide-based regimens, followed by surgery combined with adjuvant radiotherapy. The efficacy of this previously unreported therapeutic strategy for such patients requires further research.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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