Letter to the Editor

Primary mediastinal extraskeletal osteosarcoma on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT): a case description

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Introduction

Extraskeletal osteosarcoma (ESOS) is a rare malignant soft tissue sarcoma (STS) of mesenchymal origin (1). Primary ESOS in the mediastinum is extremely rare, with only 15 cases reported to date (2). In this article, we present the case of a patient with ESOS originating from the anterior mediastinum who underwent staging ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging and post-operation ^{99m}Tc-methylene diphosphonate (MDP) bone scans to improve the understanding of this disease. We also discuss its clinical and imaging features in combination with those reported in the literature. To the best of our knowledge, this is the first article to report the imaging features of ^{18}F-FDG PET/CT of primary mediastinal ESOS.

Case presentation

All the procedures in this study were performed in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 49-year-old-woman presented to Ruijin Hospital, Shanghai Jiao Tong University School of Medicine complaining of chest tightness (without obvious cause) for 1 month. Her laboratory tests were unremarkable. Except for carbohydrate antigen 125 (41.6 U/mL), her tumor markers (alpha fetoprotein, carcinoembryonic antigen, squamous cell carcinoma associated antigen, cytokeratin 19 fragment, neuron specific enolase, carbohydrate antigen 19-9, carbohydrate antigen 15-3, and carbohydrate antigen 72-4) were not elevated. Electrocardiogram showed sinus tachycardia with ST-T changes. Echocardiography showed moderate-massive pericardial effusion, the slight regurgitation of the mitral and tricuspid valves, and reduced left ventricular function (left ventricular ejection fraction: 47%). Chest CT showed an anterior mediastinum mass with calcification and pericardial effusion. Moreover, the patient's weight had decreased by 8 kg within 20 days.

After symptomatic treatment, the patient's symptoms did not improve significantly. Therefore, in November 2020, ^{18}F-FDG PET/CT was performed at the Third Affiliated Hospital of Soochow University for further diagnosis and staging. The scans showed an anterior mediastinum mass (4.8 cm × 3.0 cm) accompanied by multiple flaky calcification foci, which had intense FDG uptake with a maximum standardized uptake value (SUVmax) of 10.6. It was suspected that the mass had invaded the pericardium. A further scan showed a slightly thickened pericardium with pericardial effusion and FDG uptake with a SUVmax of

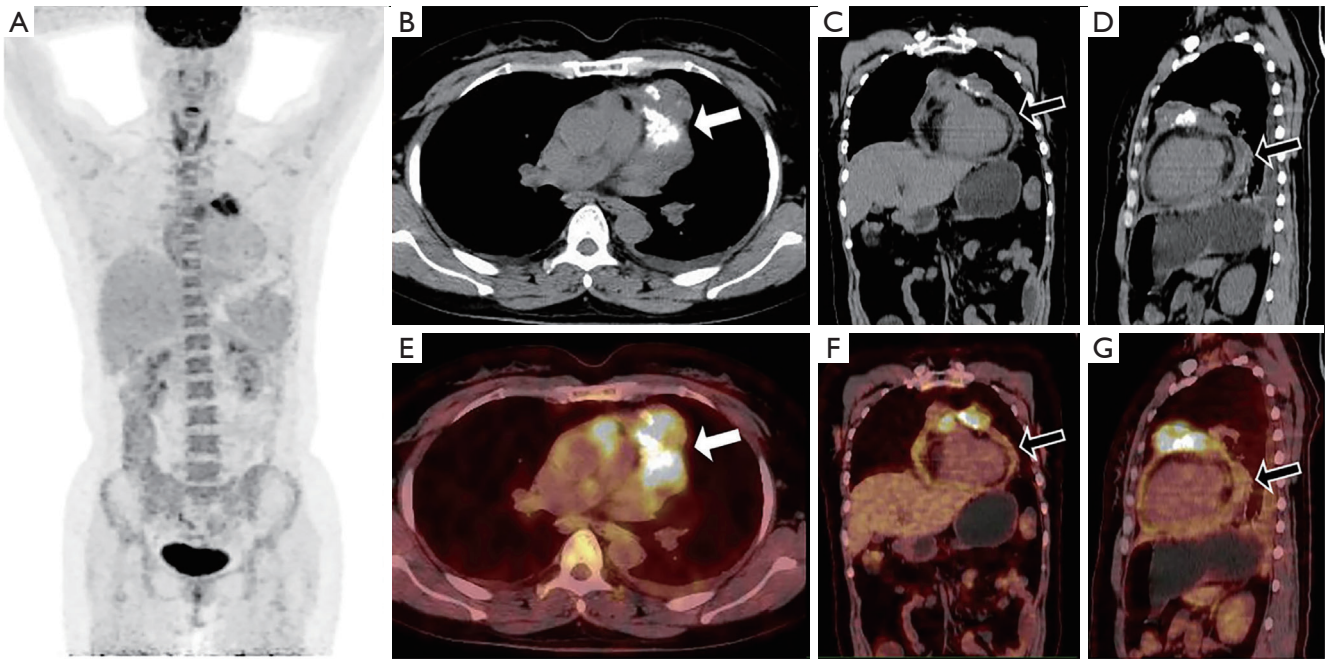

Figure 1 ^{18}F-FDG PET/CT was performed in November 2020. (A) Maximum intensity projection image of PET/CT. (B-D) CT part of PET/CT. (E-G) Fusion image of PET/CT. Staging ^{18}F-FDG PET/CT imaging showed an anterior mediastinum mass with multiple flaky calcification foci, which had intense FDG uptake (SUVmax, 10.6) (white arrows). The mass had also invaded the pericardium. Meanwhile, the pericardium was slightly thickened with pericardial effusion, which had FDG uptake (SUVmax: 4.7) (black arrows). ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; CT, computed tomography; SUVmax, maximum standardized uptake value.

4.7. Multiple lymph nodes were observed in the bilateral clavicle region and mediastinum, of which the largest one had a short diameter of about 0.6 cm, and increased FDG metabolism with a SUVmax of 6.3. Thus, lymph node metastasis could not be excluded (*Figure 1*).

In December 2020, this patient underwent volume reduction surgery due to invasion of the pericardium and left ventricular outflow tract. The excised tumor was 4.0 cm × 3.5 cm × 1.0 cm in size without a complete capsule. The cut surface was grayish white, and the texture was tough. Histologically, the tumor primarily comprised spindle cells with osteogenesis (*Figure 2*). Combined with immunohistochemistry, the pathological diagnosis was anterior mediastinal ESOS. The immunohistochemistry results were as follows: desmin (–), smooth muscle actin (–), myoblast determination protein 1 (–), myogenin (–), special AT-rich sequence-binding protein 2 (+), SRY-box transcription factor 10 (–), beta catenin (+/–), and Ki67 (20–30%+).

In January 2021, ^{99m}Tc-MDP single-photon emission computed tomography/CT (SPECT/CT) showed a mediastinal mass with calcification, and ^{99m}Tc-MDP uptake was observed in the ossification/osteoid-forming regions (*Figure 3*). Subsequently, the patient was treated with a chemotherapy regimen comprising three cycles of doxorubicin and cisplatin. A chest CT re-examination showed a new isodense nodule in the left cardiophrenic angle; thus, anlotinib was added to the treatment regimen. In July 2021 (4 months after the third cycle of chemotherapy), chest contrast-enhanced CT showed that the mediastinal mass was slightly larger than it had been before chemotherapy with increased calcification (or an osteoid matrix), and slight enhancement, accompanied by right ventricle and pulmonary artery compression. Multiple nodular thickening of the pericardium and a nodule in the left cardiophrenic angle suggested metastasis (*Figure 4*). The patient did not subsequently receive further treatment and died in August 2021 (*Figure 5*).

Discussion

ESOS is a rare malignant STS of mesenchymal origin

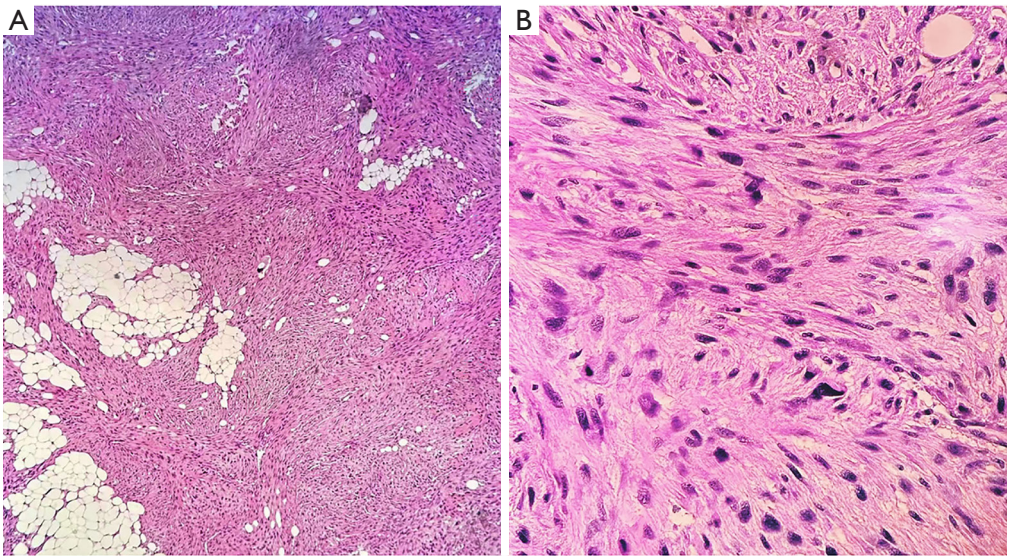

Figure 2 Micrographs revealing the spindle cells and osteogenesis of the tumor. (A) Hematoxylin and eosin staining, 100×. (B) Hematoxylin and eosin staining, 400×.

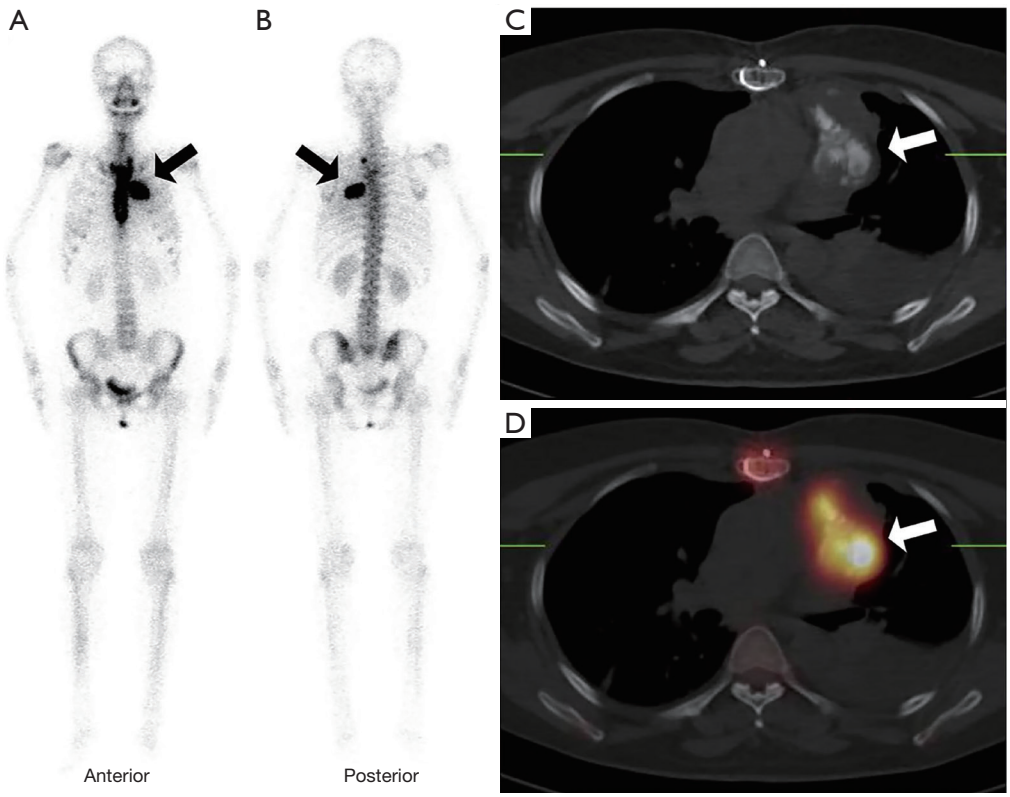

Figure 3 ^{99m}Tc-MDP SPECT/CT obtained 3 weeks after surgery. (A,B) The ^{99m}Tc-MDP whole-body bone scan showed ^{99m}Tc-MDP uptake in the chest (black arrows). (C) CT part of SPECT/CT. (D) Fusion image of SPECT/CT. A mass with calcification was still present in the mediastinum, and ^{99m}Tc-MDP uptake was seen in the ossification/osteoid-forming regions (white arrows). ^{99m}Tc-MDP, ^{99m}Tc-methylene diphosphonate; SPECT/CT, single-photon emission computed tomography/computed tomography; CT, computed tomography.

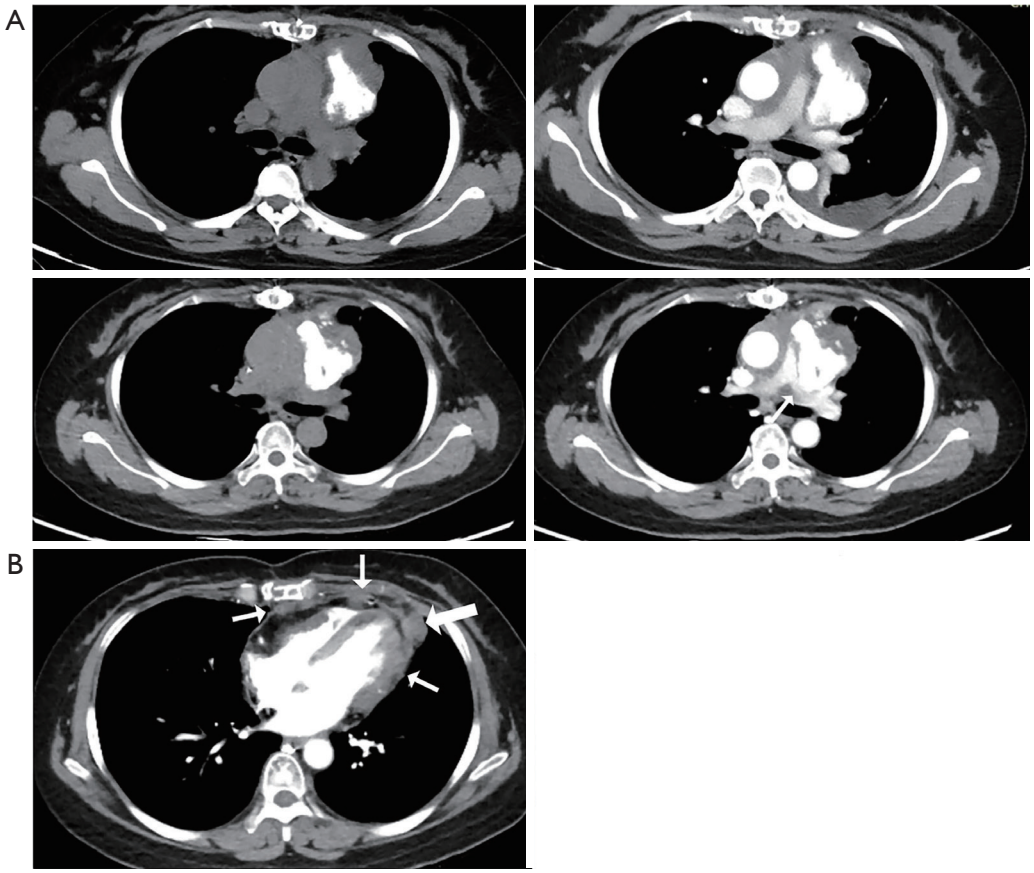

Figure 4 Chest contrast-enhanced CT scans before chemotherapy and at 4 months after the third cycle of chemotherapy. (A) Top row from L to R: contrast-enhanced CT before chemotherapy, second row from L to R: contrast-enhanced CT at 4 months after the third cycle of chemotherapy. The chest contrast-enhanced CT showed that the extent of the mediastinal mass calcification (or osteoid matrix) had increased compared with that before chemotherapy, and a slight enhancement could be seen after the contrast enhancement, with pulmonary artery compression (arrow). (B) The contrast-enhanced CT showed multiple nodular thickening of the pericardium (small arrows) and a nodule in the left cardiophrenic angle (large arrow). CT, computed tomography; L, left; R, right.

that produces osteoid in places other than the bones or periosteum. It accounts for about 1% of all STSs and about 4% of all osteosarcomas (1). Unlike primary osteosarcoma of the bone, ESOS is more commonly found in middle-aged and elderly people; the median age of patients with ESOS is 60.7 years; most studies suggest that ESOS is slightly more common in males than females, and has a male-to-female ratio of 0.8–1.9:1 (3). The majority of ESOSs occur in the lower extremity, followed by the upper extremity, retroperitoneum, and trunk (4). Primary mediastinal ESOS is extremely rare, with only 15 cases reported to date (2). The cause of ESOS remains unknown, but based on the present case and previously reported cases, it may be related to radiation exposure, chemotherapy, trauma, and pulmonary inflammation, such as tuberculosis. The patient in this case had no relevant medical history.

There is no typical clinical presentation for mediastinal ESOS. Most ESOS patients have no symptoms in the early stage, and the initial symptoms, such as cough, dyspnea, or chest pain, are mostly caused by the compression or invasion of peripheral organs. In severe cases, it can present as superior vena cava syndrome (2). The histopathologic features of ESOS are similar to those originating from the skeletal system and include osteoblastic, chondroblast, fibroblastic, telangiectasis, small-cell, and giant-cell types. Most mediastinal ESOSs are high grade; only two low-grade ESOS cases have been reported to date. For a primary ESOS diagnosis, the following criteria must be met

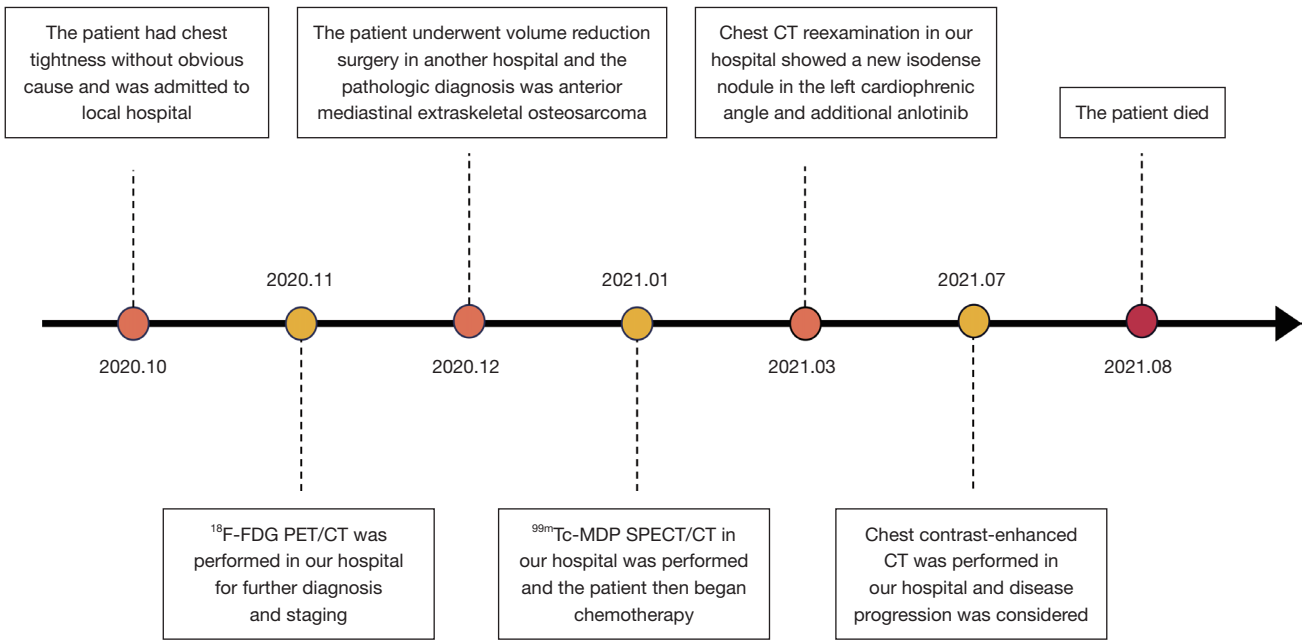

Figure 5 Timeline with relevant data about the onset, diagnosis, and treatment of the patient with primary mediastinal extraskeletal osteosarcoma. ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; ^{99m}Tc-MDP SPECT/CT, ^{99m}Tc-methylene diphosphonate single-photon emission computed tomography/computed tomography; CT, computed tomography.

(3,5): (I) the tumor must occur in the soft tissue without any continuity to the bone or periosteum; (II) the tumor must produce osteoid and/or cartilaginous tissue; and (III) the tumor must have the histological features of osteosarcoma.

On CT, the tumor usually presents as a soft tissue mass with uneven density, and sometimes pseudocapsules can be observed. It can be accompanied by varying degrees of calcification or an osteoid matrix component, and calcification and osteoid matrix formation are characteristic manifestations. Calcification or osteoid matrix formation is present in approximately 50% of primary lesions, and can appear during the course of the disease and increase over time (4). Contrast enhancement of ESOS is heterogeneous and depends on the amount of intra-lesional hemorrhage and necrosis.

The CT findings of this case were similar to those reported previously. On magnetic resonance imaging, the tumor is isointense or hypointense to skeletal muscle on T1-weighted sequences, and isointense to mildly hyperintense relative to skeletal muscle on T2-weighted sequences. The calcification or osteoid matrix may appear as hypointense areas on all pulse sequences. ^{99m}Tc-MDP SPECT/CT demonstrates the uptake of ^{99m}Tc-MDP in the ossification or osteoid matrix component of the primary lesions, but the masses cannot be identified without the ossification or osteoid matrix component. Thus, its role is limited in the evaluation of lymphadenopathy and non-calcified metastasis (6).

^{18}F-FDG PET/CT imaging findings of ESOS have rarely been reported in the literature. It usually manifests as increased FDG metabolism in the mass, but relatively decreased metabolism in the necrotic or hemorrhage areas (4). However, tumor-formed pure ossification lesions may not show high uptake of FDG (7). Images derived from ^{99m}Tc-MDP SPECT/CT and ^{18}F-FDG PET/CT can be complementary. Veselis *et al.* (8) compared the SUVmax between primary osteosarcoma of the bone and ESOS of the lower limbs, and found that ESOS had a narrower range of SUVmax values (5.8–7.1 *vs.* 3.0–15.7). However, the SUVmax of the mediastinal ESOS in this case, paraspinous musculature ESOS (6), and the left lower thigh ESOS (9) were higher than the range reported above. Given the limited number of related cases, further research needs to be conducted.

^{18}F-FDG PET/CT imaging is needed to differentiate mediastinal ESOS from thymoma, teratoma, lymphoma, and chondrosarcoma. Thymoma is the most common primary

anterior mediastinal tumor, mainly occurs in adults, and accounts for about 50% of anterior mediastinal tumors (10). It grows slowly, and it is mostly benign, but it is potentially invasive and easily infiltrates surrounding tissues and organs. A CT scan will show a mass in the anterior mediastinum, closely attached to the pericardium and large vessels, which may be accompanied by calcification, hemorrhage, necrosis, or cystic change. Invasive thymoma can be implanted along the pleura and pericardium, and FDG metabolism is increased to varying degrees, making it difficult to distinguish from ESOS. However, the incidence of thymoma calcification is lower than that of ESOS. In teratoma, the composition is mixed, and fatty components are key to distinguishing it. In lymphoma, multiple enlarged lymph nodes are scattered or fused with increased FDG metabolism, and while calcification and hemorrhage are rare, multiple infiltration of the body is common. Chondrosarcoma presents as a soft tissue mass with dense clustered or blocky calcification. ^{18}F-FDG PET/CT may also show hypermetabolism, which is difficult to identify. The SUVmax of FDG depends not only on the cancer type but also on the cell density, which is also known for intimal sarcoma (11). If the imaging differential diagnosis is challenging, pathology and immunohistochemistry are necessary to confirm the diagnosis.

Surgical treatment is the preferred treatment for focal ESOS. When detecting mediastinal ESOS, it is often difficult to completely resect the tumor due to its large size and unclear boundaries with the surrounding vessels, nerves, or other tissues. In the case of inadequate surgery, metastasis and local recurrence are extremely common in ESOS, and the literature reports that the recurrence rate of ESOS is more than 75% (1). Radiotherapy can improve the overall survival of patients with incomplete resection (12), and particle beam radiotherapy is more effective (2). However, ESOS is less sensitive to chemotherapy, and there is controversy as to whether conventional or adjuvant chemotherapy should be administered after ESOS surgery (1,13-15).

Anlotinib, a multi-target tyrosine kinase inhibitor, has been shown to be effective in treating refractory STS and osteosarcoma (16,17). The combination of anlotinib and epirubicin followed by anlotinib maintenance as a first-line treatment showed promising efficacy with a favorable safety profile in the treatment of advanced STS (18). The five-year overall survival rate of ESOS patients is only 47%, and when the disease metastasizes, the median survival period is only 8 months (3). Mediastinal ESOS has a worse prognosis, with a median survival time of 4 (1.3–6.7) months (19).

In the present case, the tumor involved the pericardium and had invaded the left ventricular outflow tract, which could not be completely resected. After surgery, the patient received three cycles of chemotherapy and targeted therapy. Six months after surgery, the size of the tumor had increased, the right ventricle and pulmonary artery were compressed or invaded, and the pericardium and cardiophrenic angle showed metastasis. The survival time of this patient was only 8 months, which is similar to that reported in the literature.

For ESOS patients, nuclear medicine imaging has important application value. As a whole-body examination technology that integrates anatomical and functional images, ^{18}F-FDG PET/CT can be used for the differential diagnosis of primary osteosarcoma with distant metastasis and ESOS, and to determine the scope, location, and number of lesions. In addition, the level of FDG uptake in the lesion can provide information on tumor viability, which can be used to develop accurate radiotherapy targets for ESOS patients, and also help to evaluate the therapeutic effects of radiotherapy, chemotherapy, or targeted therapy. As a type of osteogenic tumor, in ESOS, the concentration of the ^{99m}Tc-MDP imaging agent is increased in the osteogenic active area of the lesion. Consequently, ^{99m}Tc-MDP SPECT/CT can also be used for the differential diagnosis of primary and metastatic lesions, staging, and efficacy evaluation at a low cost. Due to the rarity of mediastinal ESOS, further research is needed to determine the clinical value of PET/CT. Nonetheless, PET/CT imaging still has the potential to become the most effective non-invasive method for evaluating ESOS.

Conclusions

In summary, primary mediastinal ESOS is a rare malignant STS of mesenchymal origin with no specific clinical manifestations, and has a high recurrence rate and poor prognosis. Early diagnosis and treatment can improve the survival of patients with ESOS. ^{18}F-FDG PET/CT plays an important role in the diagnosis of mediastinal ESOS, especially in the differential diagnosis of ESOS and primary osteosarcoma with extraosseous metastasis, clinical staging, and efficacy evaluation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-467/coif). All authors report this work was supported by the Changzhou Science and Technology Program (grant No. CJ20220228). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this article and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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