Pleomorphic undifferentiated sarcoma of the mediastinal thymus: A case report and literature review

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Abstract. Pleomorphic undifferentiated sarcoma (PUS) of the mediastinal thymus is a rare type of cancer. In the present case report, a 67-year-old female patient presenting a mediastinal mass for >1 year was assessed for clinical characteristics, histopathological, immunohistochemical expression and gene mutation using fluorescence *in situ* hybridization (FISH), and relevant literature was reviewed. Histological analysis revealed nodular changes of different sizes in the thymus, which consisted of a mixture of pleomorphic and spindle cells. The pleomorphic cells with distinct atypia were giant cells and multinucleated cells with large cell sizes and frequent nuclear divisions. The spindle cells were mild to moderate atypical and arranged in a woven pattern, and nuclear division was rare. Immunohistochemical analysis indicated that vimentin was diffusively expressed in tumor cells. No amplification was found in CDX2 and MDM4 genes using the FISH analysis. In conclusion, mediastinal thymus neoplasm should be considered in the presence of PUS and it is an exclusionary diagnosis based on clinical and pathological examination of the patient.

Introduction

Undifferentiated sarcoma (US) of soft tissue (USST) was considered a malignant fibrous histiocytoma (MFH) until 2013 (1). However, with the development and application of immunohistochemistry (IHC) and molecular genetics, most of these MFH tumors were listed back into other related sarcomas (2); therefore, these tumors were named USST (3) in the fourth edition of World Health Organization (WHO). USST is an exclusionary diagnosis and various other tumor types must be excluded before diagnosis. A total of five subtypes of undifferentiated sarcomas are found in soft tissue, including pleomorphic, small round cell, spindle cell, epithelioid and non-specific sarcomas. Pleomorphic undifferentiated sarcoma (PUS) occurs mostly in middle-aged and elderly individuals, mostly in the soft tissues of limbs, trunk, head, and neck, and only six cases have been reported in the mediastinum (4-9). To the best of our knowledge, this is the first report on the presence of PUS in the mediastinal thymus site (PUSM). The present study analyzed the clinical, pathological, immunohistochemical, molecular and genetic characteristics, and prognosis of a case of PUSM along with an analysis of the relevant literature.

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Case report

CT scans (Optima CT620; GE Healthcare) showed the presence of a mediastinal mass for >1 year in a 67-year-old female patient who was admitted to the First People's Hospital of Xiaoshan District (Hangzhou, China) on August 14, 2022. The patient had no chest pain and palpitation or dyspnea. Physical examination revealed clear consciousness, clear breathing sound in both lungs, no sound of or dry and wet rales, regular heart rhythm, undetectable murmurs and no mass found anywhere else in the body. Enhanced chest CT (Fig. 1) revealed a soft tissue shadow of ~3.8x2.3 cm in size in the anterior mediastinum, with clear boundaries on August 11, 2022, at Shengzhou Hospital of Traditional Chinese Medicine (Zhejiang, China). Uneven progressive enhancement could be seen in the enhanced scan, but no enhancement was observed in some necrotic areas. No enlarged lymph nodes were observed in the hilum and mediastinum, and no pleural effusion was found. Tumor serological findings, such as cancer antigen 125 test, carcinoembryonic antigen α-fetoprotein (third generation) and squamous cell carcinoma-associated antigen, were within the normal range. On August 19, 2022, a thoracoscopic enlarged thymectomy and a thoracoscopic partial pericardiectomy were performed.

A gross pathological examination revealed a pile of sallow soft tissue with a volume of 10x10x4 cm, with an irregular nodule inside. The volume of the nodule was 5x4x3 cm, the boundary was clear, the section was multi-nodular, the size of the nodule was 0.5-1.5 cm, the color was yellowish-grey, the region was mucoid and the texture was tender.

The tissue was fixed with 4% neutral formalin (24 h at 25˚C) and embedded in paraffin, and 4-μm serial sections

were prepared and subjected to H&E staining (Shanghai Regal Biological Technology Development Co., Ltd.; and Sinopharm Chemical Reagent Co., Ltd.) (8 h at 25˚C). Observation using a Leica DM2000 light microscope (Leica Microsystems GmbH) showed that the tumors exhibited nodular changes of varying size in the thymus tissue (Fig. 2A and B), which were composed of mixed pleomorphic and spindle cells. The pleomorphic cells were giant cells and multinucleated cells with large cell size, coarse nuclear chromatin and indistinct nucleoli (Fig. 2C). The pathological nuclear division was frequently observed (20 pcs/10 high-power fields). Spindle cells were arranged in a woven pattern (Fig. 2D), with mild to moderate atypical arrangement and rare nuclear division. A few giant tumor cells were also observed. Lymphocytes, plasma cells and histiocytes infiltrated the interstitium, and mucoid degeneration was observed in the interstitium. Necrotic foci were also observed.

IHC was performed using an EnVision IHC kit (polymer method; cat. no. KIT-0014; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.; OriGene Technologies, Inc.) using primary antibodies obtained from Beijing Zhongshan Jinqiao Biological Co., Ltd. to target the following proteins: Vimentin (working fluid; cat. no. 21031351); cytokeratin (CK)pan (1:200; cat. no. 21061509); epithelial membrane antigen (EMA; 1:100; cat. no. 21020730); CK19 (1:100; cat. no. 20080416); carcinoembryonic antigen (CEA; working fluid; cat. no. 21075911); CD5 (working fluid; cat. no. 2105190593c); terminal deoxynucleotidyl transferase (TdT; working fluid; cat. no. 19082326); S-100 (working fluid; cat. no. 2012240585C8); CD20 (working fluid; cat. no. 21081003); Desmin (1:200; cat. no. 20092713); CD31 (working fluid; cat. no. 21091609); CD34 (1:100; cat. no. 21016826); CD117 (working fluid; cat. no. 2109080632f); STAT6 (working fluid; cat. no. 2101200845a); myoblast determination protein 1 (working fluid; MyoD1; cat. no. 20121719); maltose-binding protein (MBP; working fluid; cat. no. 19082628); cyclin-dependent kinase 4 (CDK4; working fluid; cat. no. 21021952); E3 ubiquitin-protein ligase (MDM2; working fluid; cat. no. 21031850); CD1a (working fluid; cat. no. 19052202); anaplastic lymphoma kinase (ALK; working fluid; cat. no. WP20090101); CD35 (working fluid; cat. no. 20022109); Bcl-2 (working fluid; cat. no. 21092252); p16 (working fluid; cat. no. 2107210673d); Ki-67 proliferation index (1:200; cat. no. 21030436); and CD68 (working fluid; cat. no. 2106290041c). The undyed tissue sections were placed in an oven at 60˚C for 120 min and then dewaxed in xylene (500 ml) three times at 25˚C for 10 min each. The sections were rehydrated by washing in ethanol descendent series (100 and 95% for 3 min, and 85 and 75% for 1 min) and then rinse with distilled water. The sections were placed at 100˚C in EDTA (pH9.0±0.2) buffer (1:50; cat. no. ZLI9069; Beijing Zhongshan Jinqiao Biological Co. Ltd.; OriGene Technologies, Inc.) and the repair solution was used for antigen retrieval for 20 min (hot repair at 100˚C in EDTA 1:50, 2,500 ml liquid for 20 min). Subsequently, sections were washed with distilled water, treated with 3% H_2O_2 (blocking reagent) solution at 25˚C for 10 min to inhibit endogenous peroxidase activity and washed with PBS. Tissue sections were then incubated at room temperature for 40 min with primary antibodies. Following primary incubation, sections were washed three times with PBS for 5 min each time and incubated with Sheep anti-rat/rabbit IgG polymer labeled with HRP (ready-to-use type; cat. no. PV-8000D; Origene Technologies, Inc.) at 25˚C for 15 min. Sections were washed three times with PBS for 5 min each time. Tissues were incubated with 3,3'-diaminobenzidine color development solution (1:50; cat. no. PV-8000D; Beijing Zhongshan Jinqiao Biological Co. Ltd.) at 25˚C for 5-10 min, and then washed with distilled water. Hematoxylin was re-dyed at 25˚C for 1 min, washed in tap water, and then blued in PBS solution. Afterwards, the slide was washed with 75, 85, 95 and 100% ethanol (500 ml each) for 1 min each to remove excess water and facilitate observation under the microscope. Finally, tissue sections were placed in xylene (500 ml) three times for 1 min each and a drop of neutral gum was added to seal. IHC sections were observed under a light microscope (Leica DM2000; Leica Microsystems GmbH) without software analysis.

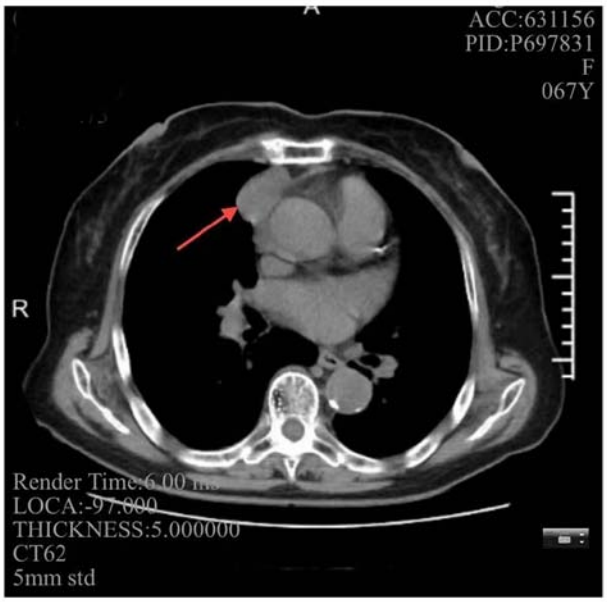

Figure 1. Computed tomography shows a soft tissue shadow ~3.8x2.3 cm in size in the anterior mediastinum with clear boundaries (red arrow).

The results of the immunohistochemical assays showed that the tissue samples were vimentin (Fig. 3A), BcL-2 and P16 positive. Furthermore, the Ki-67 proliferation index was 60% positive (Fig. 3B). By contrast, CKpan (Fig. 3C), EMA, CK19, CEA, CD5, TdT, S-100 (Fig. 3D), CD20, Desmin (Fig. 3E), CD31, CD34 (Fig. 3F), CD117 (Fig. 3G), STAT6, MyoD1, MBP, CDK4, MDM2, CD1a, ALK, CD35 and CD68 (Fig. 3H) staining were negative.

Molecular pathology analysis was performed on 15 paraffin sections and library construction and probe capture were performed. MDM2 (cat. no. 8.03.0015) and CDK4 (cat. no. 8.03.0015) fluorescence *in situ* hybridization (FISH) probe kits were purchased from Amoy Diagnostics Co., Ltd. and the analysis was performed according to the manufacturer's instructions. MDM2 and CDK4 gene-related translocation was detected using a specific two-color separation fracture probe (red probe concentration: 4 ng/μl; green probe concentration: 5 ng/μl). FISH 3.0 (ImstarDx) was used.

For the FISH analysis, the tissue sections were dewaxed three times in xylene at 25˚C for 10 min and subsequently rehydrated

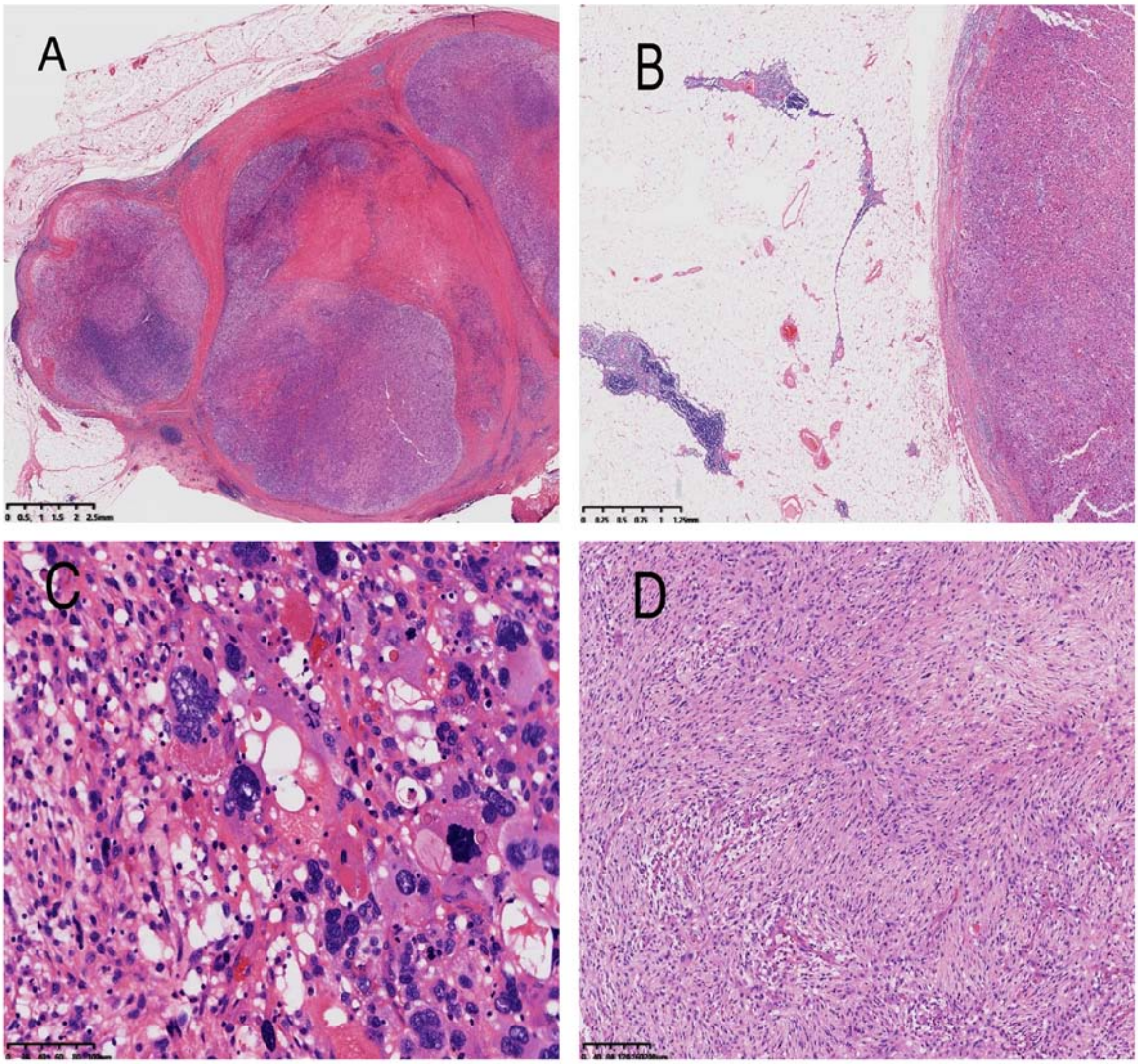

Figure 2. H&E staining of tumor's tissue. (A) Microscopic nodular changes of different sizes in the thymus tissue are shown (scale bar, 2.5 mm). (B) The tumor is located within the thymus tissue (thymus tissue on the left; tumor on the right) (scale bar, 1.25 mm). (C) Pleomorphic cells were giant or multinuclear cells with large cell sizes, coarse nuclear chromatins and indistinct nucleoli (scale bar, 100 μm). (D) Spindle tumor cells are arranged in a woven pattern (scale bar, 200 μm).

in descending ethanol series. Thereafter, the slides (tissue side up) were dipped into the boiling pre-treatment solution (pH 7.0) for 20 min and washed three times in deionized water. The slides were covered working solution [100 μl proteinase K stock solution in 40 ml of 2X saline-sodium citrate (SSC) buffer preheated at 37˚C] and digest for 2-15 min. Working solution (need to completely cover the entire tissue area, about 500 μl is recommended), digest for 2-15 min at 37˚C. After digestion, the slides were immersed in a 2X SSC solution and washed for about 1 min. The slides were gradually dehydrated in ascending ethanol series and let to dry. The *in-situ* hybridization instrument (S500-24; Abbott Medical Optics, Inc.) was set as follows: Denaturation at 85˚C for 5 min, followed by hybridization overnight at 37˚C (12-24 h). Protected from light, the center of the tissue sample was covered with probe solution (10 μl), covered with a coverslip, compressed, sealed and placed in the hybridizer to start the hybridization procedure. Once the hybridization was completed, the slide was soaked into 2X SSC solution at room temperature for 5 min after removing the cover glass. The slide was immersed in a wash solution preheated to 46˚C and washed for 7 min. The slides were gradually dehydrated in ascending ethanol series and then let dry. Protected from light, the nuclei were counterstained by adding 10 μl DAPI (Roche Diagnostics GmbH) at room temperature for 15 min. Stained tissues were observed under a fluorescent microscope (magnification, x100). The tumor area with the highest number of c-Met gene copies was identified and used for analysis. For each sample, 30 nuclei were identified and the intensity of the MDM2 (represented in red) signal from each of them was recorded along with the signal from the centromere-specific probe on chromosome 12 (CSP12; represented in green). These data were used to calculate the ratio MDM2/CSP12. Currently, there is no unified standard for the interpretation of MDM2 FISH results. Nonetheless, the following interpretation standards were adopted as references. MDM2/CSP12 >2.2 or positive cluster of MDM2 signal connections indicated amplification of the MDM2 gene in the sample. MDM2/CSP12 <1.8 indicated that the sample MDM2 gene was not amplified. If 1.88≤ MDM2/CSP122 ≥2.2, 20 more cells were identified and included in the calculation of MDM2/CSP12. CDK4/CSP12 was interpreted similarly.

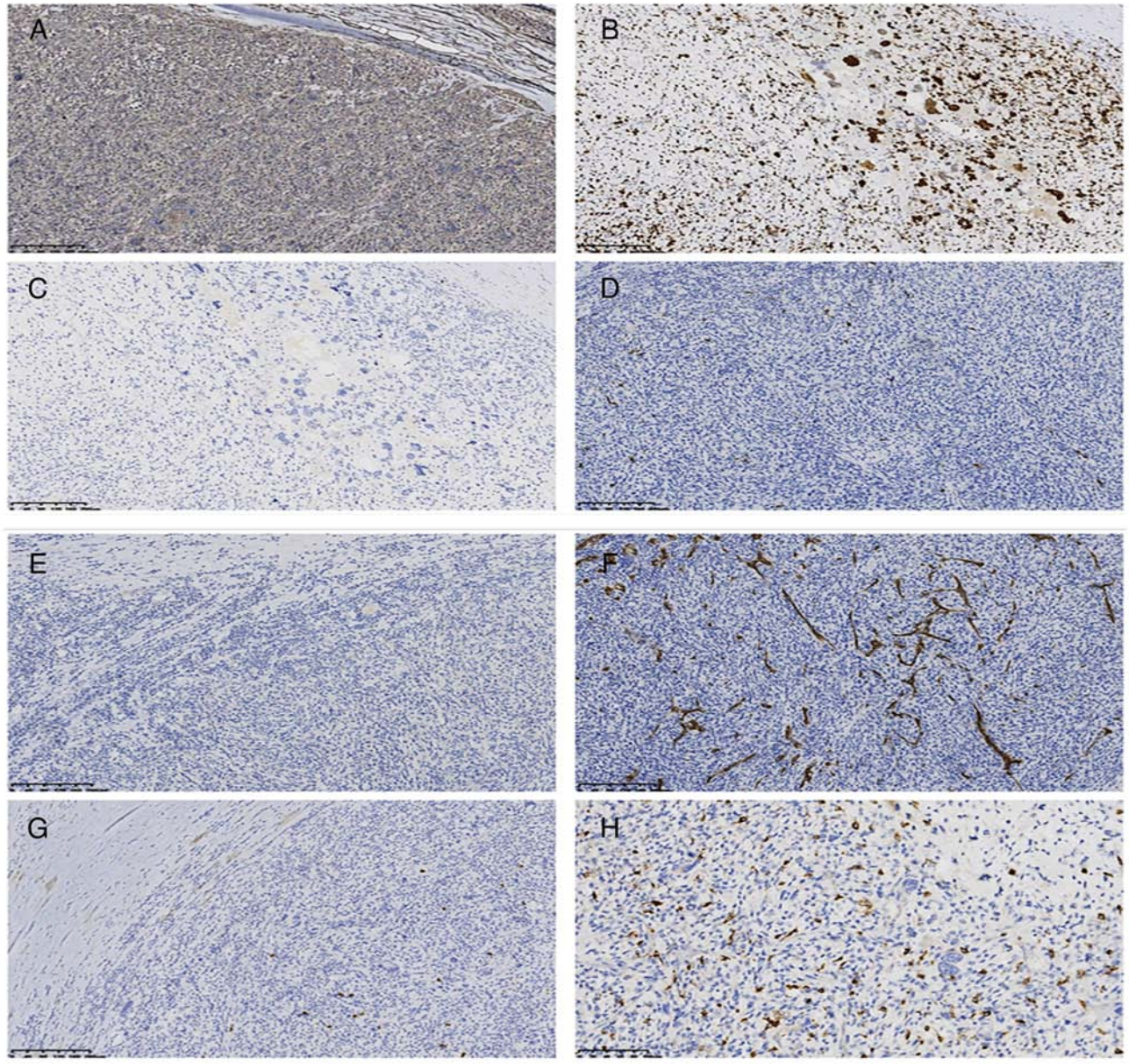

Figure 3. Immunohistochemical staining of tumor's tissue. Tumor cells were positive for (A) Vimentin, (B) Ki-67 (60%), whereas were negative for (C) cytokeratin pan, (D) S-100, (E) Desmin, (F) CD34 and (G) CD117. (H) Histiocytes were positive for CD68, whereas the tumor cells were negative for it. (Scale bar, 100 μm).

The red and green dots in the nucleus indicate gene rearrangement, while the yellow dots indicate no rearrangement. MDM2/CSP12 ratio was 1.18 and CDK4/CSP12 ratio was 1.10. FISH examination revealed that MDM2 (Fig. 4) and CDK4 (Fig. 5) genes were not amplified.

Pathological analysis diagnosed pleomorphic undifferentiated sarcoma of the mediastinal thymus with focal adhesion to the pericardium was observed.

The patient did not receive any treatment after surgery and no recurrence or metastasis was observed at 6-month follow-up.

Discussion

Through immunohistochemical and molecular genetic analyses, soft tissue oncologists have reported that some of the tumors that were classified as malignant fibrous histiocytoma before 2013 should be classified as other sarcomas (2,3). Tumors without specific differentiation or histological, immunohistochemical and genetic characteristics that do not fit in any other category are therefore reclassified as US based on the fourth edition of the WHO classification of tumors of soft tissue and bone (3). A total of five subtypes of the USST present pleomorphism. PUS mostly occurs in middle-aged and elderly individuals, mostly in males and rarely in children. PUS is more common in the soft tissues of limbs, trunk, head and neck. It is mainly a deep and soft tissue mass, which is generally large in volume and can grow rapidly with or without any pain. The specific etiology of PUS is unknown and may be related to genetic aberrations and radiotherapy (10). To the best of our knowledge, only six cases of PUS were previously reported in the mediastinum (4-9) and the present one is the

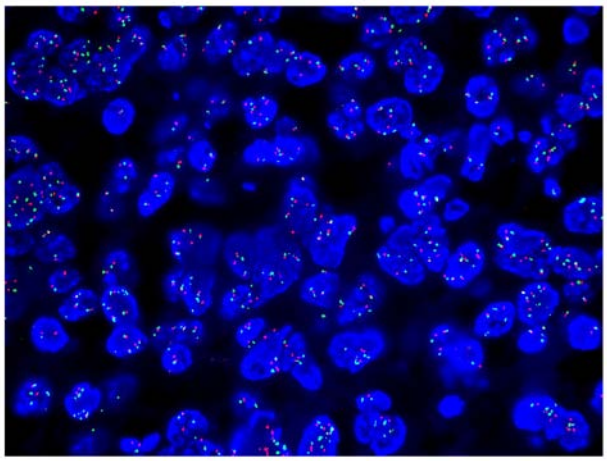

Figure 4. Fluorescence *in situ* hybridization analysis of tumor tissue. MDM2 genes were not amplified (MDM2/CSP12, 1.18). Magnification, x1,000.

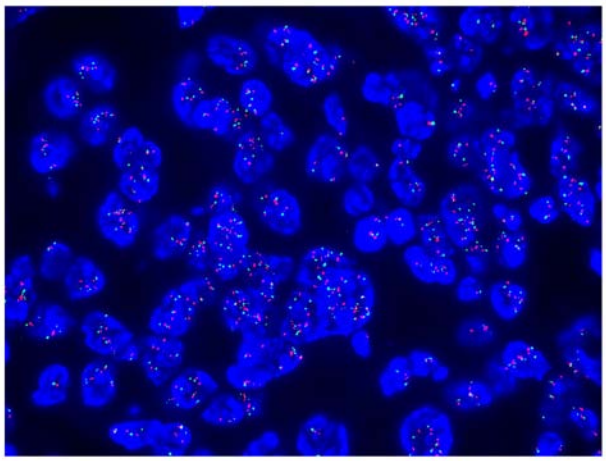

Figure 5. Fluorescence *in situ* hybridization analysis of tumor tissue. CDK4 genes were not amplified (CDK4/CSP12, 1.10). Magnification, x1,000.

first report on PUSM. The present study aimed to report and analyzed this case along with the relevant literature review.

All case reports indicated that the age range of patients with PUSM is 48-82 years, the mean age is 64.3 years and the male-to-female ratio is 1.3:1 (Table I) (4-9). Symptoms of PUSM include dyspnea, cough, shortness of breath and chest tightness. In one previous case (5) and the present case report, tumors were found to be mediastinal masses through physical examination. Serum oncology markers were in the normal range. CT examination showed that five cases were located in the anterior mediastinum, one in the posterior mediastinum and one in the mediastinum. In one case, CT showed very rapid growth in the short term (5). The mass was large, and the maximum diameter was 19 cm (4). An autopsy revealed that the tumor recurred into the pericardium, heart or great vessels (7-9). A physical examination of the present patient revealed that the mass was located in the anterior mediastinum with a clear boundary and irregular nodules with a maximum diameter of 5 cm.

Puncture biopsies frequently indicated sarcomas with uncertain differentiation direction and sarcomatoid thymic carcinoma was suspected (5). One case of a wax block of hydrothorax was misdiagnosed as malignant mesothelioma (9). Histological microscopic analysis revealed no pattern or any specific tissue structure at low magnification, which suggested an undifferentiated malignant tumor. High magnification microscopy showed that the tumor cells were composed of spindle cells and pleomorphic cells with distinct atypia, usually in bundles, woven or storiform patterns. The nuclear division was easy to observe and there may be several types of infiltrating histiocytic cells and foam cells. The observations included interstitial collagen of different degrees, mucoid degeneration, partial bleeding, necrosis and cystic changes. IHC revealed that the tumor was vimentin-positive, indicating that the tumor was only of mesenchymal origin without a clear direction of differentiation. Epithelial, mesenchymal, vascular, muscular, neurological and malignant melanoma biomarkers were negative. High Ki-67 proliferation index expression indicated severe malignancy and only one case expressed WT-1 and NSE protein markers (5). In the present case, the expression of P16 and BCL-2 was also observed. P16, a crucial oncosuppressor gene, specifically binds to CDK4 and inhibits the activity of CDK4, thereby inhibiting cells from entering the S phase from the G1 phase and negatively regulating the cell proliferation cycle controlled by the Rb gene (11). BCL-2 is a member of the apoptosis protein family and can inhibit apoptosis (12). MDM2 gene is a highly amplified oncogene cloned from self-transforming BALB/3T3M cells containing double microbodies. It has the function of a transcription factor and acts as an oncogene when amplified, which can spontaneously lead to tumorigenesis (13). MDM2 and CDK4 gene diagnosis tests are used in the diagnosis and differential diagnosis of liposarcoma (14). The genetic tests cannot confirm the diagnosis of pleomorphic undifferentiated sarcoma, which was not performed in all 6 cases (4-9). In this case, neither MDM2 nor CDK4 gene was amplified. PUS is an exclusive diagnosis and the following tumor types need to be identified: i) Pleomorphic liposarcoma, in which the number of heterogeneous lipoblasts visible in the tumor should be counted, including nuclear hyper staining, deformity, common indentation at the edge, and the focal expression of S-100; ii) pleomorphic leiomyosarcoma, in which some areas of the tumor show marked pleomorphism, however, local areas show classic leiomyosarcoma morphology, along with relative boundary clearance or mutual migration and the immunohistochemical expression of at least one smooth muscle marker; iii) pleomorphic rhabdomyosarcoma in which several heterogeneous eosinophilic polygonal or round cells (rhabdomyoblasts) are found within the tumor, immunohistochemical markers are positive for diffuse desmin and myogenin is present in varying degrees; iv) inflammatory myofibroblastoma, which, at the microscopic level, it is mainly composed of spindle-shaped fibroblasts and myofibroblasts, with several lymphocyte and plasma cell infiltrates in the interstitium, and SMA, desmin and ALK can be found in tumor cells to varying degrees; v) malignant mesothelioma, which is characterized by large tumor cell size, distinct atypia, thick and deeply stained nuclear chromatin, distinct nucleoli and the immunohistochemical expression of calretinin, keratin 5/6, WT-1 and D2-40; vi) thymic sarcomatoid carcinoma, which is a rare tumor and also called carcinosarcoma that histologically presents a tight mix of sarcomatoid and cancerous components, with the cancerous components expressing epithelial markers and the rhabdomyosarcomatoid components being more common and expressing mesenchymal component markers.

The principles of the PUS treatment of the head, neck, trunk and limbs are also applicable to the treatment of the PUS of the

Table I. Clinicopathological data of seven patients with pleomorphic undifferentiated sarcoma in the mediastinal site.

First author/s, years	Sex/age, years	Tumor site	Tumor size, cm)	Immunohistochemistry	Pericardium/ pleural effusion	Therapy	Clinical outcome	Autopsy	(Refs.)
Sun *et al*, 2015	M/59	Post mediastinum	19	Vim (+), Ki-67 (20%+)	Bilateral pleural effusion	Radical operation was performed for recurrence *in situ* after radical operation	The disease recurred *in situ* 7 months after surgery and recovered well 2 months after reoperation	No	(4)
Okuda *et al*, 2015	M/56	Mediastinum	14.5	Vim (+), Ki-67 (54.7% +), WT-1 (+), NSE (+)	NA	Tumor resection + left lung resection; pericardium partial resection + nerve and lymph node resection	Recurrence occurred within 1 month after the operation; recurrent hemorrhage occurred within 3 months; and death occurred within 4 months	NA	(5)
Zhang *et al*, 2019	M/48	Anterior mediastinum	7.8	Vim (+), Ki-67 (40% +)	Pericardial effusion	No	NA	NA	(6)
Nakayama *et al*, 2019	F/82	Mediastinum	NA	NA	Pericardium and pleural effusion	Palliative treatment	Died of right heart failure within 1 month	The tumor surrounded the aorta and pulmonary artery and invaded the pericardial space and myocardium	(7)
Sato *et al*, 2020	F/77	Anterior mediastinum	NA	Vim (+)	Bilateral pleural effusion	Palliative treatment	Died of respiratory failure in 33 days	The tumor infiltrated the heart and major blood vessels	(8)
Matsumoto *et al*, 2021	M/50	Anteri or mediastinum	16	Almost all of the tumor markers were negative	Right pleural effusion	No	Died a few days later	The tumor invaded the pericardium	(9)
Present study	F/67	anterior mediastinum	5	Vim (+), Ki-67 (50%+), BcL-2 (+), P16(+)	No	Thoracoscopic enlarged thymectomy + thoracoscopic partial pericardiectomy	Recurrence or metastasis was not reported at 6-month follow-up	No	-

M, male; F, female; NA, not available.

mediastinum. Complete surgical resection with a negative margin is the preferred treatment strategy, whereas chemotherapy, chemoradiotherapy or high-dose equivalents of radiotherapy are preferred treatment options for unresectable cases (15). Immune checkpoint suppression using pembrolizumab (anti-PD1), nivolumab (anti-PD1) and ipriimar (anti-ctLA4) drugs are currently being studied (16,17). PUSM is large and invades the pericardium, heart, great vessels and lungs, which can cause surgical difficulties or cardiopulmonary failure. It was reported that three patients died after palliative care for up to 33 days (7-9). A total of two patients recurred within 1-7 months of surgery and one died within 4 months (4,5). In the present case, the mass of 5 cm was adherent to the pericardium after surgical resection and no postoperative radiotherapy, chemotherapy or gene-targeting therapy were performed. No recurrence or metastasis was observed during the 6-month follow-up.

In conclusion, PUSM is rare and can only be diagnosed after the exclusion of other tumors in pathological diagnosis. Owing to the large tumor mass at the time of diagnosis, it shows features such as invading heart and lung tissue, high degree of malignancy, easy relapse and cardiopulmonary failure leading to death, thus requiring early detection, diagnosis and treatment. Generally, comprehensive therapy based on surgery should be adopted to treat PUSM. Because patient prognosis is poor in PUSM cases, immunotherapy and targeted therapy may be helpful. Furthermore, due to the small number of cases, more clinical data should be accumulated for in-depth research.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BH and XC drafted the manuscript and conceived the study.HL and LC were responsible for the collection and analysis of case data and literature. JY and XC revised the manuscript and interpreted the data. BH and HL confirm the authenticity of all the raw data.All authors agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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