

Case Report

Primary sclerosing rhabdomyosarcoma of the mediastinum with pulmonary and vascular invasion in an elderly patient: a case report and literature review

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Abstract: Herein, we report a clinical case involving a 67-year-old male patient who complained of head and neck pain lasting for 3 days. Subsequently, an enhanced computed tomography (CT) scan was performed on the patient's chest cavity, showing fused masses in the middle and upper mediastinal regions as well as the right hilar area. The CT images also showed that the mass surrounded the vena cava, brachiocephalic trunk, and brachiocephalic vein; and a tumor thrombus could be seen in the vena cava. Multiple enlarged lymph nodes were observed in the bilateral supraclavicular fossae, suspected to be malignant, and they had fused into clusters. Additionally, based on the imaging diagnosis and the pathologic examination results of the biopsy specimens, the patient was ultimately diagnosed with sclerosing rhabdomyosarcoma. The immunohistochemical (IHC) test results were positive for desmin (a protein marker for muscle cells), myoD1 (a muscle differentiation factor), and Ki-67 (a nuclear proliferation antigen, with a positive rate of approximately 85%). Myogenin, smooth muscle actin (SMA), and S-100 protein were negative. This case confirmed the value of morphology and IHC for differential diagnosis and disease assessment of sclerosing rhabdomyosarcoma, and gave a reference basis for diagnosis and treatment by clinical doctors.

Keywords: Rhabdomyosarcoma, sclerosing rhabdomyosarcoma, pathological examination, spindle-cell, MyoD1

Introduction

Sclerosing rhabdomyosarcoma (SRMS) is an independent rhabdomyosarcoma subtype established by the World Health Organization (WHO) classification of soft tissue tumors. Distinct from classic subtypes including embryonal, alveolar, and pleomorphic rhabdomyosarcoma, it possesses unique morphology and biological properties. As a rare clinical entity, SRMS accounts for 3%-10% of all rhabdomyosarcoma cases and is susceptible to missed diagnosis or misdiagnosis due to its specific morphologic features and limited clinical recognition [1, 2]. Characterized by extensive deposition of sclerotic and hyalinized collagen fibers in the tumor stroma, SRMS typically presents with sparsely distributed, nested or cord-like tumor cells, showing distinct pathologic differences

from other rhabdomyosarcoma subtypes [3]. SRMS exhibits high heterogeneity in clinical phenotype, molecular profile, and prognostic outcome, with no fixed pattern of disease progression. It affects children, adolescents, and adults with obvious age-stratified distribution characteristics. Patients of different age groups vary significantly in clinical symptoms, tumor invasiveness, and recurrence. This greatly hinders clinical diagnosis, treatment, and prognostic evaluation. Accordingly, SRMS is a key and challenging research focus in the precise classification and individualized therapy of rhabdomyosarcoma.

Case report

A 67-year-old man sought medical attention at our hospital due to localized swelling in the

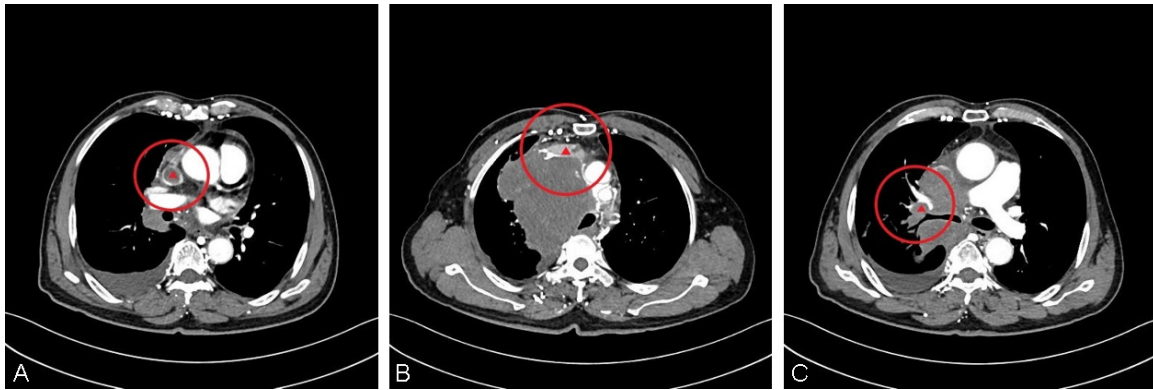


Figure 1. Chest contrast-enhanced CT scan showing multiple lesions (A,B,C). (A) The tumor has infiltrated and encircled the superior vena cava with a tumor embolus inside (red circle). (B) The tumor has invaded brachiocephalic vein (red circle). (C) Invasion of the pulmonary artery was noted (red circle).

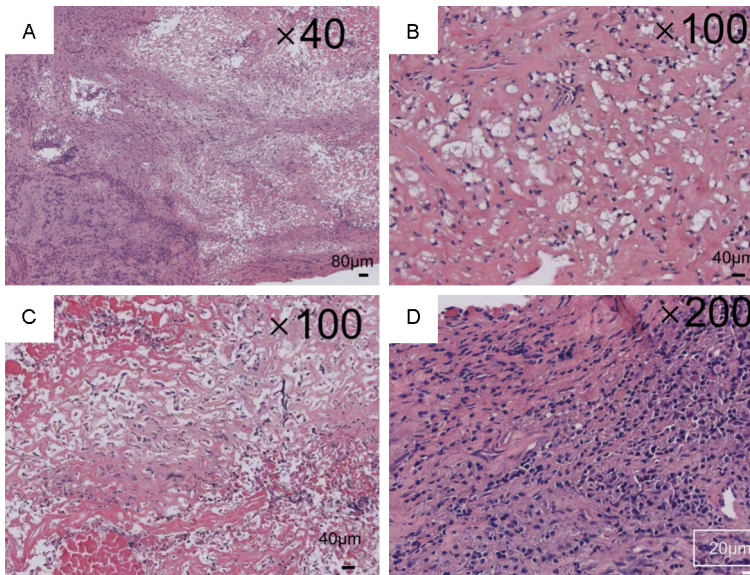


Figure 2. Hematoxylin and eosin (H&E) staining of tissue sections at different magnifications. A. Low-power view ($\times 40$) showing the overall tissue architecture of spindle-shaped, ovoid, and small round cells within a prominent hyalinizing matrix, resembling osteoid tissue ($\times 40$). B. Chondroid tumor cells are visible in the stroma ($\times 100$). C. Pseudovascular arrangement of tumor cells (or chondroid-like matrix) ($\times 100$). D. High-power view ($\times 200$) revealing a dense small round cell and spindle cell proliferation. Bar = 80 μ m (A), Bar = 40 μ m (B, C), 20 μ m (D).

head and neck area for 3 days. Contrast-enhanced computed tomography (CT) of the chest was carried out on the chest, detecting a fused mass in the middle-upper mediastinum and right hilar region, measuring approximately 12.4 cm $\times$ 9.1 cm $\times$ 7.7 cm. Additional findings included enlargement of the right pulmonary hilum with blurred margins, poor demarcation of the major mediastinal blood vessels, and multiple filling defects in the superior vena

cava. Further CT examination revealed that the mass surrounded the superior vena cava (**Figure 1A**), the brachiocephalic artery, and brachiocephalic vein (**Figure 1B**), and invaded the pulmonary artery (**Figure 1C**). A tumor thrombus was also detected in the superior vena cava (**Figure 1A**). Additionally, multiple suspiciously malignant enlarged lymph nodes were observed in the bilateral supraclavicular fossae, and they had fused into clusters. The initial imaging diagnosis was paratracheal lung cancer with metastasis to the supraclavicular fossae and cervical lymph nodes. The radiologic differential diagnoses included germ cell tumor and mediastinal sarcoma. A biopsy was recommended for further confirmation.

Tumor specimens were obtained from the supraclavicular fossa, where the lesion was suspected to be a lymph node metastasis of lung cancer. Three tissue samples (0.1-0.3 cm in diameter) were grayish-red.

Histological examination revealed a mixture of spindle-shaped, ovoid and round cell proliferation within a markedly hyalinized stromal matrix (**Figure 2A**), with no normal lymph node structure identified. In some areas, these cells often

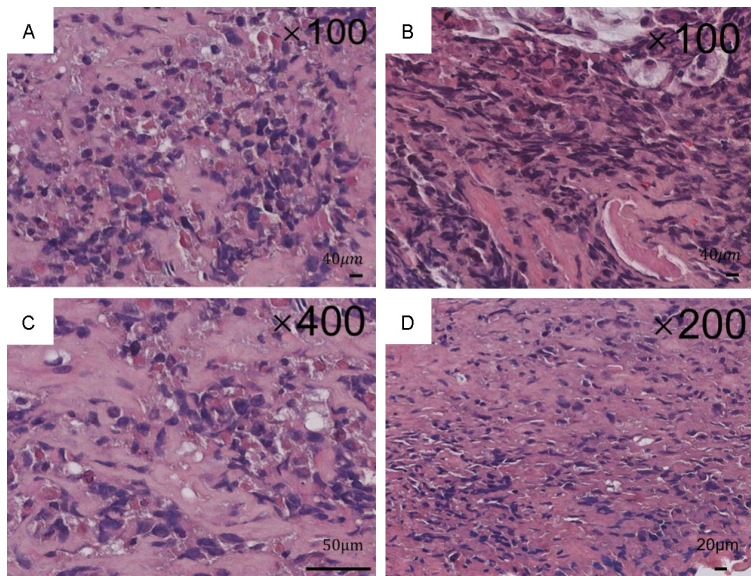


Figure 3. Histopathologic features of spindle cell rhabdomyosarcoma, H&E stain. A. Tumor cells exhibited eosinophilic cytoplasm and enlarged, atypical nuclei, including large round tumor cells and tumor giant cells, resembling typical rhabdomyoblasts with hyperchromatic nuclei. Frequent mitotic figures were observed, along with intracytoplasmic vacuoles containing PAS-positive glycogen ($\times 100$). B. The tumor was composed of densely packed, poorly differentiated spindle cells arranged in a tadpole-like pattern, interspersed with primitive small round cells. Rhabdomyoblastic differentiation was evident, as evidenced by enlarged nuclei and intracytoplasmic vacuoles ($\times 100$). C. At high magnification, tumor cells showed marked atypia, frequent intracytoplasmic vacuoles, hyperchromatic and condensed nuclei, and a high nuclear/cytoplasmic ratio. The cytoplasm was eosinophilic, consistent with a high-grade malignant morphology. D. Strap cells with elongated eosinophilic cytoplasm and a tapered nucleus, consistent with rhabdomyoblastic differentiation in sclerosing rhabdomyosarcoma ($\times 200$). Bar = 40 μ m (A, B), Bar = 50 μ m (C), 20 μ m (D).

mimicked osteoid or chondroid tissue (**Figure 2B**). Localized intercellular stroma and a pseudovascular arrangement of tumor cells were noted (**Figure 2C**). At $\times 200$ magnification, in cell-dense areas resembling ERMS, a differential diagnosis of round cell tumors should be considered. This tumor can also be easily misdiagnosed as small cell lung carcinoma (**Figure 2D**). Round and polygonal tumor cells of moderate size were observed, with the cytoplasm showing a significant eosinophilic change, similar to that of typical rhabdomyoblasts. These cells exhibited hyperchromatic nuclei and frequent mitotic figures, and were easily identified based on their distinct morphologic features (**Figure 3A**). In other areas, the tumor was composed of poorly differentiated spindle cells (resembling tadpoles) interspersed with primitive small round cells, and striated muscle cell differentiation was observed (**Figure 3B**). In

scattered tumor cells, the nuclei were enlarged, and eosinophilic vacuoles were detected (**Figure 3C**). Frequent strap cells and cross-striations were easily visible in the spindle tumour cells within the tumor-bearing area (**Figure 3D**).

On immunohistochemical (IHC) analysis, the neoplastic cells showed strong positive staining for Ki-67 (85%+) (**Figure 4A**), diffuse expression of desmin (**Figure 4B**) and myoglobin (**Figure 4D**), and focal positive staining for myoD1 (**Figure 4C**). In contrast, the tumor cells were completely negative for myogenin (**Figure 4E**) and smooth muscle actin (SMA) (**Figure 4F**), as well as for cytokeratin (CK), epithelial membrane antigen (EMA), anaplastic lymphoma kinase (ALK), and S-100 protein. Based on its morphologic and immunophenotypic features, this mass was diagnosed as RMS, further classified as the sclerosing variant RMS (SRMS).

MDM2 *in situ* hybridization was performed, and a negative result was obtained, which excluded intimal sarcoma with rhabdomyoblastic differentiation.

Given that the tumor had invaded the lungs and major blood vessels, surgical resection was not feasible. Accordingly, a conservative treatment plan was initiated in the clinic to maximize the patient's survival time. Subsequently, intervention measures such as adjuvant chemotherapy, routine follow-up, and traditional Chinese medicine (TCM) treatment were implemented. Unfortunately, two months after the diagnosis, the patient passed away due to complications of a sudden cardiac arrest.

Discussion

Clinical-molecular subgroups of sclerosing rhabdomyosarcoma (SRMS), can exhibit dis-

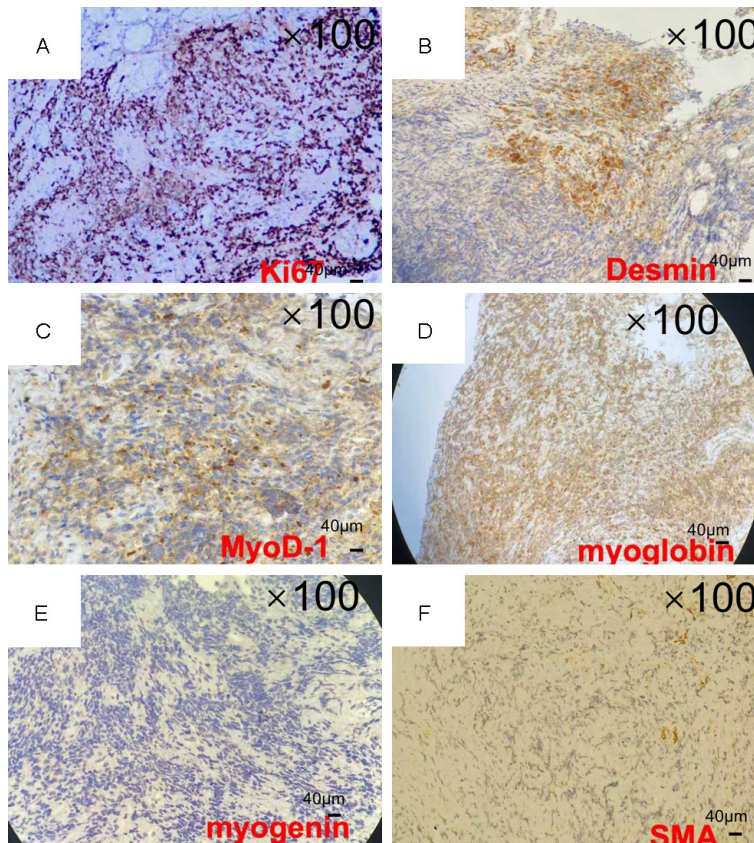


Figure 4. Immunohistochemical staining of spindle cell rhabdomyosarcoma ($\times 100$, scale bar = 40 μm). A. The Ki-67 proliferation index was approximately 85% ($\times 100$). B. Focal positive expression of desmin ($\times 100$). C. Focal positive staining for MyoD1 ($\times 100$). D. Diffuse positive staining for myoglobin ($\times 100$). E. Negative expression of myogenin ($\times 100$). F. Negative expression of SMA ($\times 100$). Bar = 40 μm .

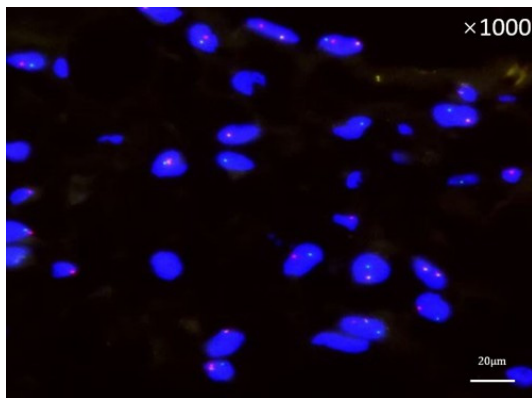


Figure 5. MDM2 *in situ* hybridization (ISH) result. MDM2 ISH performed on the tumor cells showed no evidence of gene amplification, with two distinct, balanced red and green signals observed in most nuclei. The negative MDM2 result excluded the diagnosis of intimal sarcoma with rhabdomyoblastic differentiation (Fluorescence ISH; original magnification, $\times 1000$).

tinct prognoses and tumour molecular pathogenesis across different age groups. Poorer survival in adult versus pediatric patients is a well recognized feature across the broad spectrum of rhabdomyosarcoma [4]. With a growing volume of reported cases of SRMS in adults, it has become evident that this prognostic disparity also holds true for this specific subtype [3].

Congenital/infant fusion-driven subtype (0-1 year): Affecting neonates and infants, this subtype may be detected prenatally on obstetric ultrasound. The male-to-female ratio is approximately 1:1. Predilection sites include the chest wall, lumbodorsal region, subcutaneous extremities, and perineum; retroperitoneal involvement is extremely rare. Molecular features comprise VGLL2-NCOA2 and TEAD1: NCOA2 fusions, without MYOD1 mutations. It follows an indolent biological behavior, mostly presenting as localized disease. The recurrence rate after complete surgical resection is less than 17%, conferring the most favorable prognosis among SRMS subgroups [5].

Paediatric/adolescent MYOD1-mutant subtype (1-18 years): Tumors arise predominantly in paratesticular sites and soft tissues of the head and neck. Prognosis is intermediate; local recurrence is common, whereas distant metastasis is uncommon [6].

Adult-onset SRMS (≥ 18 years, a research hotspot in the last three years): Predominant locations are the retroperitoneum, deep soft tissues of extremities, and intra-osseous ribs. Retroperitoneal SRMS represents the most aggressive phenotype. A meta-analysis of a global cohort of 403 patients demonstrated 100% local recurrence for retroperitoneal cases, with a 2-year overall survival (OS) of merely 40%. At the molecular level, the hotspot

MYOD1 p.L122R mutation accounts for 95.5% of cases, frequently accompanied by concurrent PIK3CA co-mutations. Clinically, these tumors present as large masses invading adjacent organs; distant metastases (lung, bone, lymph nodes) occur in 30.5% of patients, and disease-specific mortality reaches 34.7% [3].

Rare fusion-positive subtype FUS: TFCEP2 (adolescents and adults): Most tumors arise primarily in bone (ribs, jaw bones), displaying a mixed epithelioid-sclerosing morphology. The clinical course is highly aggressive, with early lymph-node metastasis and a median overall survival of only 4-6 months [7].

These lesions, with copious intercellular stroma rich in hyalinized osteoid-like or chondroid-like matrix, morphologically exhibit substantial overlap with osteosarcoma and chondrosarcoma, thereby increasing the difficulty of differential diagnosis [8]. Cells resembling rhabdomyoblasts, ranging from small to medium in size, with round or polygonal contours were identified, and these cells were characterized by scant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli [9]. Although the pleomorphic subtype predominates in this age group, we did not observe wreath-like rhabdomyoblasts in this particular case, thus ruling out pleomorphic rhabdomyosarcoma (PRMS).

To the best of our understanding, this represents the first reported and verified case of sclerosing rhabdomyosarcoma (SRMS) with concurrent involvement of the mediastinum and lungs. Clinically, the suspected lymph node metastasis of lung cancer was actually a mass formed by SRMS through hematogenous metastasis. We conclude that the head and neck region and lungs are typical metastatic locations for visceral sclerosing rhabdomyosarcoma, possibly owing to the abundant vascular supply in these areas.

The key alternatives considered in the differential diagnoses of SRMS in this case included small cell lung cancer and other small round tumors, such as Ewing's sarcoma, small round cell tumor promoting connective tissue proliferation, osteosarcoma, chondrosarcoma, synovial sarcoma, leiomyosarcoma, and angiosarcoma. Intimal sarcoma with rhabdomyoblastic differentiation should be excluded. (The MDM2 fluorescence in situ hybridization (FISH) result of this case was negative) (Figure 5).

Literature studies indicate that the MyoD1⁺, Myogenin⁻ immunophenotype typically denotes low tumor cell differentiation and high malignancy. For instance, MyoD1-mutant SRMS shows diffuse expression of desmin and MyoD1 with focal myogenin staining or totally myogenin⁻, and this subtype is highly aggressive. In contrast, the MyoD1⁺, myogenin⁺ pattern is associated with relatively higher differentiation and lower malignancy [10]. According to diagnostic consensus established over the past three-year period regarding immunohistochemical marker profiles: 1. Myogenic markers: Diffuse strong nuclear MYOD1 positivity is seen in 92% of cases, superior to myogenin, which shows only focal positivity in 42% of cases. Desmin is generally diffusely positive [3].

Accessory markers: Focal positivity for α -SMA, CD56, and ALK can be observed in partial cases.

Key negative markers for differential diagnosis: S-100, CD34, MUC4, BCOR, NKX2.2, and MDM2 are consistently negative, which helps exclude fibrosarcoma, neurogenic neoplasms, extraskelatal osteosarcoma, and endometrial sarcoma with rhabdomyoblastic differentiation [11].

In previously reported cases of rhabdomyosarcoma, the Ki-67 proliferation index lies between 10% and 60%; in contrast, this particular case exhibited a Ki-67 index as high as 85%, which was already the highest value reported in the literature so far. This indicates that the tumor is highly aggressive and its clinical malignant progression is relatively rapid.

Recent three-year clinical-molecular investigations have advanced risk-stratification for sclerosing rhabdomyosarcoma (SRMS) by incorporating age, primary location, molecular features, and metastatic status [3, 12]. Low-risk disease is defined as localized superficial extremity SRMS in patients aged 0-1 years with VGLL2-NCOA2-family fusions, with 5-year OS over 80% [13]. Intermediate-risk SRMS refers to localized MYOD1-mutant tumors in children and adolescents (1-18 years) arising within paratesticular or head-and-neck soft tissues, characterised by frequent local recurrence yet rare distant spread [6]. High-risk features include adult age (≥ 18 years), retroperitoneal or intra-osseous primaries, combined MYOD1 plus PIK3CA mutations, FUS: TFCEP2 fusion, and initial met-

astatic presentation, associated with 5-year OS below 40% [3, 7]. Across all subgroups, MYOD1 p.L122R mutation, positive surgical margins, retroperitoneal origin, Ki-67 index >30%, and distant metastasis represent consistent adverse prognostic markers for SRMS [3, 7, 12].

Evidence from the past three-years has established molecular subtyping as the practical diagnostic gold standard for sclerosing rhabdomyosarcoma (SRMS), superseding conventional morphology-only classification, as endorsed by the WHO classification and Chinese Pediatric Oncology Group (PPOG) sarcoma panel for guiding therapeutic decisions and risk assessment [13, 14].

The congenital-infantile fusion-driven subgroup is defined by VGLL2-NCOA2-family fusions. The fusion oncoprotein blocks myogenic differentiation and confers indolent biological behavior [5]. Clinically, complete surgical resection alone may be sufficient, so intensive chemotherapy can be avoided to prevent overtreatment. NCOA2 break-apart FISH and targeted RNA-seq are feasible routine detection modalities [2].

The MYOD1-mutant subgroup affects predominantly children older than 1 year and high-risk adults, characterized by a MYOD1 p.L122R hotspot variant. Recent mechanistic work demonstrated that this mutation reprograms stem-cell signaling and activates non-canonical ROR2/WNT cascades, directly conferring chemo- and radio-resistance [15]. Concurrent PIK3CA alteration further activates the IGF2-PI3K axis to boost tumor proliferation and metastatic potential [16]. Single-cell sequencing uncovered three intratumoral sub-populations (stem-progenitor, proliferative transitional and poorly-differentiated cells), identifying IGF2 as a core autocrine oncogenic driver [17].

The second fusion-driven subgroup harbors FUS: TFCP2 rearrangement, which frequently arises within bone and exhibits highly aggressive clinical behaviour, including early lymph-node dissemination and refractoriness to conventional chemotherapy [8]. Concomitant homozygous CDKN2A/B deletion is recurrent in this subtype, providing a pre-clinical rationale for CDK4/6-inhibitor-based therapy [7, 18].

Rare mutation-/fusion-negative SRMS occupies an intermediate prognostic position between fusion-driven and MYOD1-mutant cohorts [3].

Conclusion

We present the first confirmed case of primary mediastinal sclerosing rhabdomyosarcoma (SRMS) with pulmonary and vascular invasion, expanding understanding of this rare adult subtype. Histologically, its hyalinized stroma and overlap with osteosarcoma/chondrosarcoma make immunohistochemistry (MyoD1, Desmin, myoglobin) critical for differential diagnosis, while the MyoD1⁺/Myogenin⁻ profile and 85% Ki-67 index reflect high aggressiveness. Clinically, this case confirms the lungs as a major metastatic site for visceral SRMS, requiring thorough imaging in suspected cases.

Without molecular testing, the immunoprofile and rapid progression strongly suggest MyoD1-mutant SRMS (linked to poor outcome), emphasizing the value of molecular assays (e.g., FISH, gene sequencing) for diagnosis and treatment. A potential COVID-19 vaccine-tumor link remains unproven and needs further research. Overall, this case reinforces SRMS as a distinct entity, highlighting multidisciplinary management to optimize outcome for patients with this aggressive malignancy.

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The signed publication consent form is retained in the patient's medical records and is available for review upon request.

Disclosure of conflict of interest

None.

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