

A thoracic SMARCA4-deficient undifferentiated tumor: A case report

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Abstract. Thoracic SWI/SNF-related BAF chromatin remodeling complex subunit ATPase 4 (SMARCA4)-deficient undifferentiated tumor (SMARCA4-UT) is a newly recognized, high-grade malignant neoplasm that is rare in clinical practice. There is no standardized or clearly defined treatment protocol for SMARCA4-UT in clinical guidelines. The current study reports the case of a 54-year-old male patient who presented with a 2-month history of an intermittent productive cough. Bronchoscopy demonstrated a neoplasm in the anterior segment of the right upper lobe bronchus, which almost obstructed the lumen, with a hyper-vascular surface, suggestive of a right upper lobe carcinoma. Histopathological examination confirmed a poorly differentiated carcinoma. Immunohistochemical analysis demonstrated a SMARCA4 gene mutation in exon 4, classifying the tumor as SMARCA4-deficient undifferentiated lung carcinoma. The patient developed superior vena cava syndrome (SVCS), requiring emergent percutaneous stent placement. Treatment also included computed tomography-guided cryoablation and radiofrequency ablation (RFA), alongside targeted molecular therapy with crizotinib. Despite aggressive multimodal therapy, the patient succumbed to tumor thrombosis at 1 month post-treatment. Overall, SMARCA4-UT is rare and diagnostically challenging, lacking standardized treatment guidelines. In clinical practice, cryoablation with argon-helium and RFA may provide palliative benefits by alleviating tumor burden and

improving quality of life. Endovascular intervention provides a rapid and effective approach to alleviate tumor-induced SVCS. However, subsequent anticoagulation and antineoplastic therapies require further investigation to determine their efficacy in the management of such cases.

Introduction

Thoracic SWI/SNF-related BAF chromatin remodeling complex subunit ATPase 4-deficient undifferentiated tumor (SMARCA4-UT) is a newly recognized, high-grade malignant neoplasm introduced in the 5th edition of the World Health Organization Classification of Thoracic Tumors in May 2021 (1). The characteristic feature of this tumor is the inactivation of the SMARCA4 gene, and the cancer primarily involves the mediastinum and lung parenchyma in adult patients. The tumor tissue morphology is undifferentiated or striated muscle cell-like, and the patients are usually young to middle-aged male smokers (2). The SMARCA4 gene, located on chromosome 19q13, encodes the BRG1 protein (a key component of the SWI/SNF chromatin remodeling complex with tumor suppressor functions). BRG1 protein is defined as a central ATPase subunit of the SWI/SNF complex that is crucial for development, cellular pluripotency and has non-redundant roles in mammals, with mutations linked to various tumors. The abnormal expression of BRG1 is associated with the occurrence of various tumors, involving multiple anatomical sites and organs, such as SMARCA4-deficient thoracic sarcoma, colorectal cancer, small-cell carcinoma of the ovary hypercalcemic type and endometrial stromal sarcomas (3). SMARCA4-UT, as a recently reclassified entity under the category of 'other pulmonary epithelial tumors', has been reported in <100 cases globally as of 2021 (4). Clinically, SMARCA4-UTs typically present as bulky mediastinal masses, with secondary involvement in the pleural surfaces and pulmonary parenchyma (3). These masses may compress or even penetrate adjacent organs, leading to complications such as superior vena cava syndrome (SVCS), atelectasis, spinal cord compression and esophageal infiltration (5). The specific manifestations are closely associated with disease progression, with common symptoms including dyspnea, chest pain, fatigue, dysphagia and weight loss (6). Studies have shown that most patients ultimately succumb to local

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Abbreviations: SMARCA4-UT, thoracic SWI/SNF-related BAF chromatin remodeling complex subunit ATPase 4-deficient undifferentiated tumor; SVCS, superior vena cava syndrome; CT, computed tomography; RFA, radiofrequency ablation

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tumor complications (3). The diagnosis of SMARCA4-UT requires an integrated approach, including clinical manifestations, imaging studies, pathological features and molecular profiling (3). Currently, there are no standardized treatment guidelines for this disease, and conventional treatments such as chemotherapy, radiotherapy and surgical intervention have shown limited efficacy (5). SMARCA4-UTs are rarely reported. The current study reports the case of a patient who presented to the Department of Pulmonology in Dongzhimen Hospital (Beijing, China) in April 2024, with the clinical course of this case and the diagnostic and therapeutic considerations recorded and discussed in detail for clinical reference. The present study is reported in accordance with the Case Report Guidelines (7).

Case report

A 54-year-old man with a long-term smoking history of >30 years was admitted to Dongzhimen Hospital (Beijing, China) in April 2024 with the chief complaint of an intermittent cough and sputum production for >2 months. Preliminary assessments, including positron emission tomography-computed tomography (PET-CT, bronchoscopy and histopathological analysis, were conducted at other hospitals prior to this current hospitalization. PET-CT imaging revealed a hypermetabolic mass in the right upper lobe, suggestive of a primary lung malignancy, accompanied by obstructive atelectasis, pneumonia and lymph node metastases in station 4R mediastinal and right hilar regions, with the possible involvement of station 2R lymph nodes. The largest lesion, measuring ~11.3x9.2x8.0 cm, appeared to be a merged mass. Scattered small nodules and patchy opacities were observed in the posterior segments of both lower lobes, with the most prominent nodule measuring 0.6x0.4 cm, which raised suspicion of metastatic tumors, although no significant metabolic abnormality was noted. Bronchoscopy revealed a highly vascularized neoplasm nearly occluding the lumen of the anterior segmental bronchus of the right upper lobe, which was suspected to be primary lung carcinoma. Histopathological analysis confirmed a poorly differentiated carcinoma, with subsequent consultation identifying an adenocarcinoma component, leading to a diagnosis of pulmonary adenocarcinoma. The hematoxylin and eosin-stained image of the carcinoma is shown in Fig. 1. Radiotherapy was recommended as a treatment option; however, the patient and their family declined immediate intervention.

Upon admission to Dongzhimen Hospital, the patient presented with an aggravated cough with the production of white sputum occasionally streaked with blood, accompanied by facial edema. A physical examination revealed lymphadenopathy, a barrel chest deformity and diminished breath sounds over the right upper lung. Despite symptomatic treatment, including intravenous piperacillin sodium and sulbactam sodium every 8 h for 7 days, oral carbocysteine and intravenous furosemide (10 mg) every day, the patient's clinical condition showed no notable improvement. After a comprehensive evaluation, the acute presentation in this patient [with SVCS classified as type II and a Kishi score of 4 points (8,9)] was considered to be due to malignant compression or direct tumor invasion, manifesting as SVCS. For malignant SVCS,

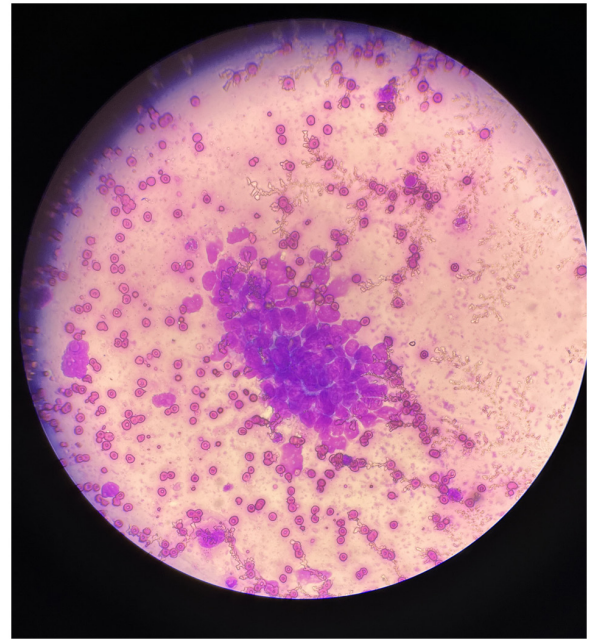


Figure 1. Hematoxylin and eosin staining of the carcinoma. Samples were stained and analyzed using the Diff-Quik staining method. The staining solution contains the acidic dye eosin and the basic dye methylene blue. The specific procedure was as follows: Diff-Quik A solution, Diff-Quik B solution, phosphate-buffered saline (PBS) and distilled water were respectively placed in covered glass staining jars; slides were sequentially immersed in Diff-Quik A solution (10-30 sec), rinsed in PBS and drained, then immersed in Diff-Quik B solution (20-40 sec), and finally washed with distilled water, blotted with absorbent paper and wiped to remove residual liquid from the edges of the slides. Staining was performed at room temperature (20-25°C), with a total staining time of 30-70 sec. Observation was carried out under a light microscope at x40 magnification.

stent placement was considered as a first-line therapy to rapidly alleviate the symptoms and relieve the obstruction. Subsequently, percutaneous transvenous stent placement in the SVC and bronchial infusion chemotherapy (30 mg cisplatin in 50 ml normal saline administered by intravenous push) were performed under digital subtraction angiography. The procedure revealed extrinsic compression-type stenosis of the SVC, with a 4-cm segment of narrowing located extrapericardially. A stent was successfully placed in the SVC, resulting in restored venous patency with stent stability. The procedure was well tolerated, and no discomfort was reported. Postoperatively, the patient continued to receive anti-infective with intravenous levofloxacin sodium chloride once daily, antitussive treatment with oral carbocysteine, and anticoagulant therapy (administered for ~1 week) with subcutaneous low-molecular-weight heparin calcium every 12 h. The follow-up chest CT scans are shown in Fig. 2.

Following symptomatic improvement, the patient underwent CT-guided argon-helium cryoablation for targeted therapy of the left lung lesion, along with a percutaneous transthoracic lung biopsy. During the procedure, three grayish-brown pathological tissue samples were obtained via coaxial needle puncture biopsy and sent for pathology. The operation was completed without complications, and postoperative management included antibiotics, expectorants/cough suppressants and anticoagulant therapies as aforementioned. The postoperative chest CT scans are shown in Fig. 3. The

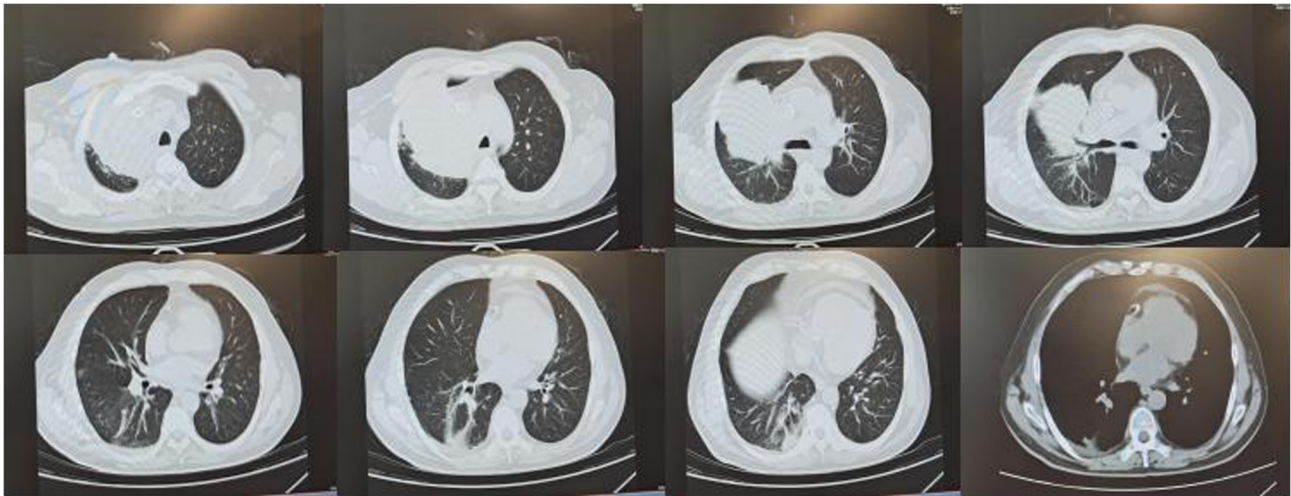


Figure 2. Chest computed tomography performed at Dongzhimen Hospital in April 2024. Occupation of the upper lobe of the right lung with mediastinal lymph node metastasis, and invasion of the main trunk of the right pulmonary artery; Multiple small nodules in both lungs, leading to the consideration of possible lung metastases; Chronic inflammation in the lower lobe of the right lung; Right superior vena cava stenting; Small amount of pericardial effusion and arteriosclerosis; Right pleural effusion.

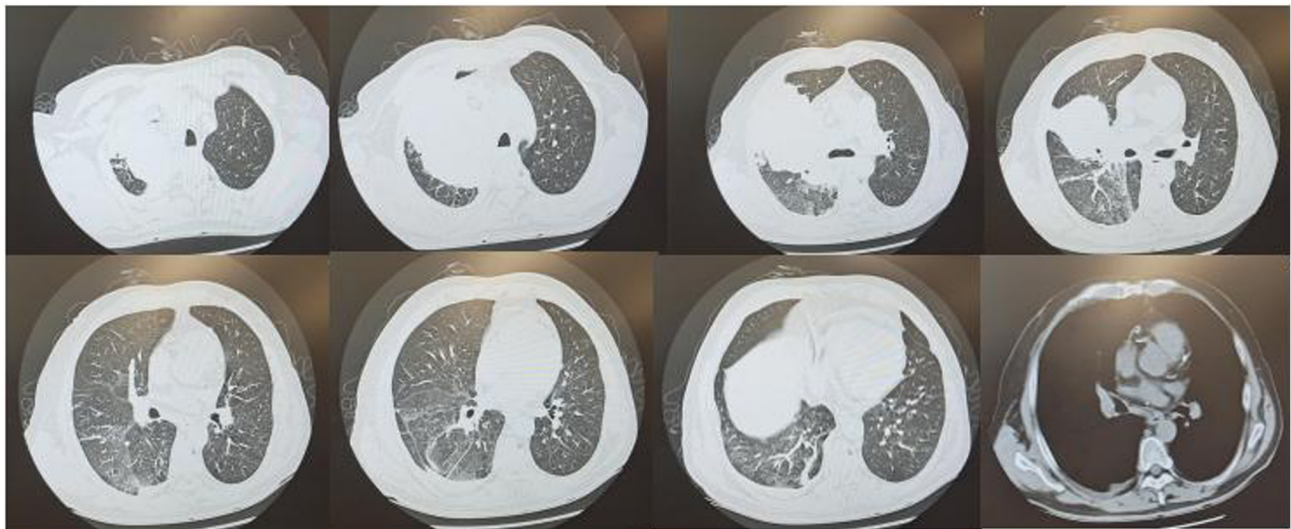


Figure 3. Chest computed tomography performed at Dongzhimen Hospital in April 2024 (9 days after the previous scans shown in Fig. 2). Occupation of the upper lobe of the right lung with mediastinal lymph node metastasis; Multiple small nodules in both lungs, leading to the consideration of possible lung metastasis; Chronic inflammation in the lower lobe of the right lung; Right superior vena cava stenting; Small amount of pericardial effusion and arteriosclerosis; Right pleural effusion.

pathology report received back from the Cancer Hospital Chinese Academy of Medical Science (Beijing, China) revealed a ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) gene translocation (rare fusion, unknown activity, with a recommendation for RNA-next generation sequencing for precise characterization) alongside a SMARCA4 exon 4 mutation, confirmed through immunohistochemistry and DNA sequencing (data not shown), thereby definitively establishing the diagnosis of SMARCA4-UT in April 2024.

Follow-up chest CT scans in May 2024 (Fig. 4) indicated the following compared with the previous scan in April 2024: i) The mass in the right upper lobe of the lung with mediastinal lymph node metastasis showed no significant change; ii) multiple small nodules in both lungs, suspected to be pulmonary metastases, were slightly increased in size;

iii) chronic inflammation was present in the right lower lobe of the lung; iv) post-procedure status of the right SVC stent (the stent was properly positioned and patent); v) minimal pericardial effusion; vi) arteriosclerosis; and vii) right-sided pleural effusion. Currently, there are no standardized and definitive treatment guidelines for SMARCA4-UT. Based on the patient's chest CT imaging findings and pathology report, CT-guided radiofrequency ablation (RFA) was performed during hospitalization in May 2024. After the procedure, the patient was administered targeted chemotherapy with 250 mg oral crizotinib once daily for >1 month. No significant adverse reactions were observed after the medication, and the patient's symptoms improved, leading to discharge.

Following the patient's discharge, ongoing surveillance was maintained to monitor any alterations in the condition.

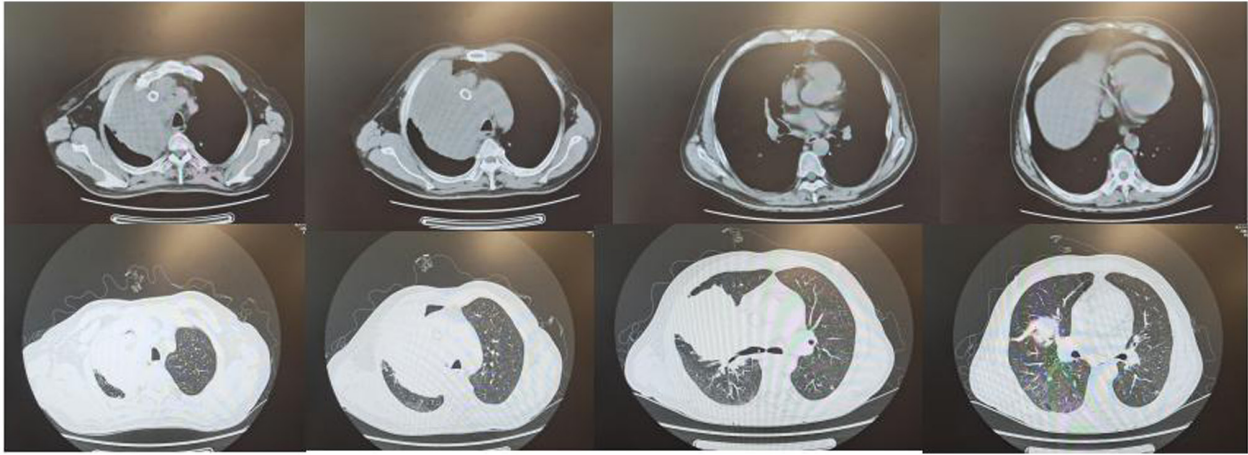


Figure 4. Chest computed tomography performed at Dongzhimen Hospital in May 2024. In comparison with the images captured in April 2024, the current images revealed occupation of the upper lobe of the right lung and metastasis of the mediastinal lymph node, with no obvious changes from before; multiple small nodules in both lungs, leading to the consideration of possible lung metastases, with a slight increase in size than before; chronic inflammation in the lower lobe of the right lung; right superior vena cava stenting; a small amount of pericardial effusion and arteriosclerosis; and right pleural effusion.

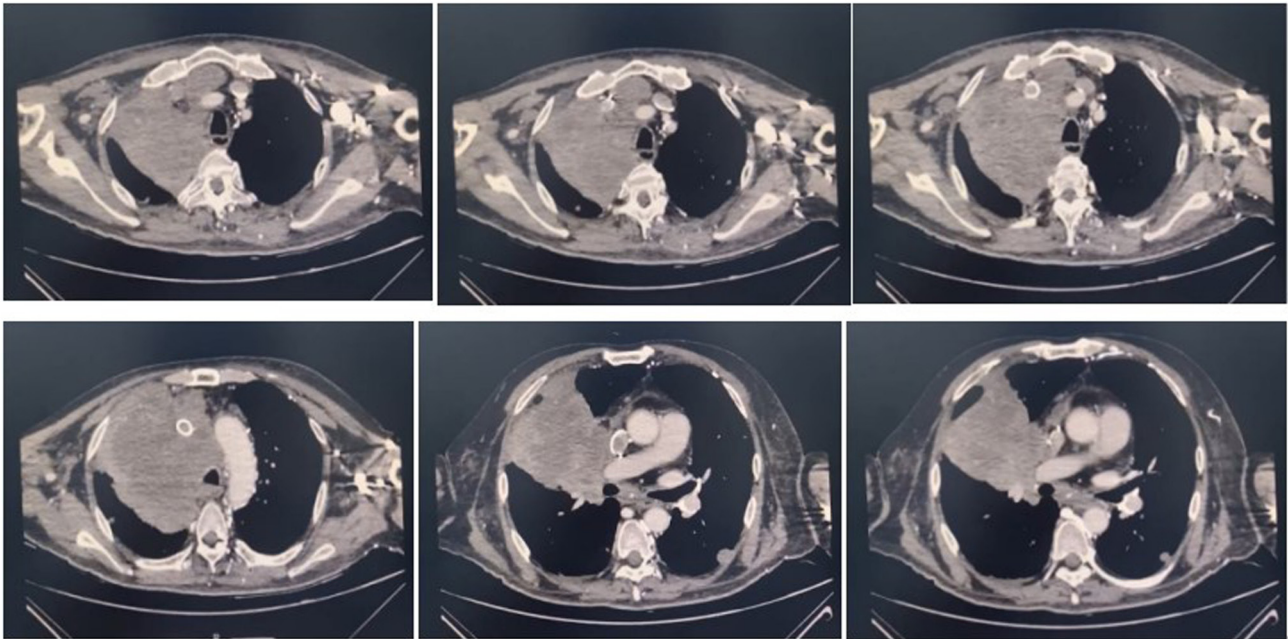


Figure 5. Enhanced neck and chest computed tomography performed at Hulunbeir City People's Hospital in June 2024. In comparison with the images captured in May 2024, the current images revealed occupation of the upper right hilar area, with no significant interval change in size, leading to the consideration of a malignant lesion with obstructive changes and mediastinum invasion. Multiple nodules were present in both lungs, roughly the same as before, and metastases were considered. The mediastinum, bilateral subclavian and axillary lymph nodes were enlarged with uneven density, and metastasis was considered. After the superior vena cava stent, filling defect images were seen in the lymph nodes, as well as a tumor thrombus.

In May 2024, results from fluorescence *in situ* hybridization examinations (data not shown) performed in Cancer Hospital Chinese Academy of Medical Science indicated the absence of ALK (2p23) chromosomal translocations (ALK-negative), ROS1 (6q22) chromosomal translocations (ROS1-negative) and CMET gene amplification. The germline susceptibility gene analysis revealed no pathogenic mutations in the BRCA1, BRCA2, MLH1 or MSH2 genes. Furthermore, the comprehensive assessment of common tumor-associated gene fusions and translocations via RNA sequencing conducted in May 2024 did not identify any significant rearrangements involving the following genes: SS18, EWSR1, CIC, BCOR, FUS,

FOXO1, FOXO4, NCOA1, NCOA2, NUTM2A, NUTM2B, ALK, ROS1, RET, NTRK, STAT6, PDGFB, DDIT3, TFE3, CAMTA1, GLI1, NR4A3, USP6 and GRM1. In light of the patient's recurrent negative findings for ROS1 chromosomal translocations in May 2024, the efficacy of crizotinib for targeted chemotherapy was deemed negligible. The patient was advised to consider a combination of immunotherapy and chemotherapy, which they declined.

At 1 month post-discharge, the patient relapsed with severe dyspnea and orthopnea; they presented at Hulunbeir City People's Hospital for evaluation, where comprehensive laboratory tests and contrast-enhanced CT were completed

(Fig. 5) in June 2024. The cumulative evidence pointed to a high probability of tumor thrombus formation, which occurred ~2 months after endovascular stent placement. Despite urgent medical attention, including emergency interventions, the patient's condition deteriorated without effective treatment, resulting in a fatal outcome in July 2024.

Discussion

SMARCA4-UT represents an exceptionally rare variant of thoracic neoplasms. Characterized by its highly invasive nature, this tumor type presents across a broad age range of 28 to 90 years (5). SMARCA4-UT lacks specific clinical manifestations and is associated with a high risk of postoperative recurrence (10). The tumor has been demonstrated to show resistance to radiotherapeutic modalities and exhibits a suboptimal response to conventional chemotherapy, resulting in a poor prognosis, with a median survival time of 4 to 7 months (5). In the diagnostic realm, histopathology remains the gold standard for the definitive diagnosis of SMARCA4-UT (3). Research suggests that the classification of a tumor as SMARCA4-UT is warranted when BRG1 immunohistochemical staining is negative, irrespective of the presence of SMARCA4 gene mutations (11). In terms of therapeutic strategies, there is currently no standardized therapeutic regimen. According to current guidelines (12), SMARCA4-UTs typically exhibit resistance to cytotoxic chemotherapeutic regimens, which has led to an increased focus on identifying targets for targeted therapy and evaluating the efficacy of immunotherapeutic approaches (13). Studies have demonstrated that the use of immune checkpoint inhibitors, either alone or in combination with chemotherapy, as well as the conversion to surgical treatment following immunotherapy, can prolong the median overall survival time of patients affected by SMARCA4-UT (14-18).

For patients with bulky SMARCA4-UTs, a treatment sequence of argon-helium cryoablation followed by RFA has been employed to reduce the tumor burden and prolong the survival time (19). Cryoablation, guided by CT, is a safe, minimally invasive technique that selectively induces tumor cell death with less procedural pain and tissue damage (20). While RFA exhibits broader treatment coverage compared with cryoablation, it is associated with higher procedural pain levels (21). The combination of cryoablation and RFA has been shown to inhibit tumor growth, and cryoablation is preferred for tumors near the visceral pleura due to its superior pain control and patient tolerability profile (22,23).

In the current study, the patient's initial presentation was SVCS. After 2 months, stent thrombosis occurred, which was highly suggestive of tumor thrombus formation, although venous thrombosis could not be ruled out. The brief duration of anticoagulant therapy (~1 week) following stent implantation, without subsequent sustained anticoagulation, may have been one of the factors contributing to this complication. Currently, the selection of anticoagulation regimens after stent implantation in patients with cancer remains controversial and is supported by limited clinical evidence. This case underscores the complexity of integrated management involving interventional, anticoagulant and antineoplastic therapies. SVCS is commonly secondary to malignant tumor

compression or invasion, and treatment modalities include radiotherapy, chemotherapy, surgical intervention and endovascular stenting (8,24). Endovascular stenting is favored for its simplicity, minimal invasiveness and rapid efficacy; its high success rate, low incidence of restenosis and associated low recurrence rate have established it as a first-line treatment (25-27). In the present patient, based on symptoms, signs, SVCS classification (8) and the Kishi score (9), endovascular stenting was deemed appropriate. Following stent implantation, the choice and timing of anticoagulant therapy remain controversial (8), with its benefits and safety requiring further validation, while cancer-related factors are the primary determinants of prognosis (28). Tumor cell-induced thrombosis is one of the main causes of death in patients with cancer (29-31). In terms of antineoplastic treatment, the 2024 edition of the Chinese Society of Clinical Oncology non-small cell lung cancer (NSCLC) guidelines recommends targeted drugs such as crizotinib for first-line treatment in patients with NSCLC and ROS1 fusion mutations (32). However, the present patient's ROS1-negative status suggested limited benefit from targeted therapy, resulting in challenging tumor control and a poor prognosis.

The present study has certain limitations. The SMARCA4 immunohistochemistry assays and ROS1 gene DNA sequencing were performed by a collaborating hospital. Owing to restrictions imposed by the hospital's medical ethics regulations and data governance policies, the original immunohistochemistry images and raw DNA sequencing data could not be shared with the research team in the present study. As a result, these data could not be deposited in a public repository, and corresponding accession numbers are unavailable. It should be noted that these constraints may affect the transparency and reproducibility of the study findings. Constrained by the rapid progression of the patient's condition, the long-term survival benefits of relevant treatment regimens are difficult to accurately assess. Furthermore, the formulation of treatment strategies (such as the selection of targeted agents) was substantially influenced by the patient's individual condition and the family's treatment preferences. The implementation of interventional and ablation therapies was dynamically adjusted based on the patient's real-time status and tolerance. Therefore, the extrapolation and generalizability of the clinical efficacy of the current treatment protocols require validation through further studies. Future research should explore the potential of immunotherapies or novel targeted agents in the management of SMARCA4-UT, providing robust evidence to optimize clinical treatment strategies.

In summary, SMARCA4-UT is a recently reported, rare type of pulmonary malignancy, which is challenging to diagnose and treat. The application of argon-helium targeted therapy and RFA extended the survival period of the current patient to ~5 months and improved the quality of life for the present patient. It is worth noting that the median overall survival time of SMARCA4-UT is generally 4-7 months (33). Whether other targeted drug therapies and immunotherapy combinations can increase the survival rate of patients requires further exploration.

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Availability of data and materials

The data generated in the present study are not publicly available due to reasons of sensitivity and medical ethics regulations and data governance policies, but may be requested from the corresponding author.

Authors' contributions

XW, MC, MW, CB, LZ, HZ, HW and BY participated in the conception and design of the study. XW wrote the manuscript, and BY revised and reviewed the manuscript. All authors have read and approved the final manuscript. XW and BY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethical review and approval were waived for this study due to the retrospective study design. Appropriate informed consent was obtained from the patient prior to starting the project. The Declaration of Helsinki was respected in all steps.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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