Case Report

Severe hypoglycemia and finger clubbing in a patient with a BRCA1 mutation in a solitary fibrous tumor: a case report

Wei Guo[1], Ying Ji[1], Lei Guo[2], Shunan Che[3], Qilin Huai[4], Kun Yang[1], Fengwei Tan[1], Qi Xue[1], Shugeng Gao[1], Jie He[1]

[1]Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [3]Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [4]Department of Graduate School, Zunyi Medical University, Zunyi, China

Correspondence to: Jie He; Shugeng Gao; Qi Xue. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Panjiayuannanli No. 17, Chaoyang District, Beijing 100021, China. Email: prof.jiehe@gmail.com; gaoshugeng@vip.sina.com; xueqi@cicams.ac.cn.

Abstract: Solitary fibrous tumors (SFTs) are rare tumors that stem from mesenchymal cells of submesothelial tissues belonging to the pleura. They can occur in many places such as the spinal canal, intracranial, neck, kidney, liver, pelvis, limbs and other places, most commonly in the chest and abdomen. Pleural SFTs are one of the most common types, and are common in middle-aged people. Pleural SFTs can have an insidious expression, such that the illness can progress for years before diagnosis. SFTs can induce paraneoplastic syndromes, such as reactive hypoglycemia [Doege-Potter syndrome (DPS)] or hypertrophic osteoarthropathy [Pierre-Marie-Bamberger syndrome (PMBS)]. In this article, we report a case study of a 51-year-old man with pleural SFTs. Preoperative imaging examinations, including chest X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), showed a huge mass in the right thoracic cavity, compressing surrounding tissues and organs and may invade other tissues. In addition, he suffers from severe hypoglycemia and finger clubbing, and has successfully undergone a complete resection, and now attends regular follow-up appointments. The paraneoplastic syndromes have resolved, and no recurrence has been found. Importantly, we used next-generation sequencing (NGS) to explore the molecular characteristics of the patient's pathological tissue at the DNA level and mRNA level, and found that breast cancer gene 1 (BRAC1) mutations may be an important pathogenic factor.

Keywords: Solitary fibrous tumor (SFT); Doege-Potter syndrome (DPS); Pierre-Marie-Bamberger syndrome (PMBS); NAB2-STAT6 fusion; case report

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Introduction

Solitary fibrous tumors (SFTs) are rare tumors that originate in mesenchymal tissues, and account for only 2% of all soft tissue tumors (1,2). Despite widespread reports of SFTs in various parts of the body, they typically occur in the pleura (3). Clinically, most pleural SFTs have a slow growth rate. Due to a lack of obvious symptoms, they are often only detected accidently on chest radiographs. However, in some instances, pleural SFTs may manifest with compressive symptoms or, exceptionally, with paraneoplastic syndromes, such as reactive hypoglycemia [Doege-Potter syndrome (DPS)] or hypertrophic osteoarthropathy [Pierre-Marie-Bamberger syndrome (PMBS)] (3-5). The surgical resection of pleural SFTs is the most effective treatment for primary tumors and prevents the recurrence of DPS and PMBS (6,7).

Here, we describe an occurrence of DPS and PMBS

Table 1 Summary of the laboratory tests results of the case

Serum concentration	Pre-operation value	Post-operation value	Reference range
Glucose, mmol/L	2.04	4.41	3.61–5.11
Potasium, mmol/L	2.67	4.01	3.5–5.5
Insulin, uIU/mL	<0.2	3.41	2.6–24.9
C-peptide, ng/mL	0.07	–	0.78–1.89
GH, ng/mL	0.15	–	0.03–2.47
Direct renin, mU/L	9.5	–	2.8–39.9
Aldosterone, ng/dL	1.9	–	3.0–23.6
Cortisol, μg/dL	11.16	–	4.4–19.9
ACTH, pg/mL	37.98	–	7.2–63.3
IGF I, ng/mL	108	–	87–283
IGF II, μg/dL	1,228.71	347.82	–

C-peptide, GH, direct renin, aldosterone, cortisol, ACTH, and IGFI were not measured after operation. GH, growth hormone; ACTH, adrenocorticotropic hormone; IGF I, insulin-like growth factor I; IGF II, insulin-like growth factor II.

with a huge pleural SFT in an adult Chinese man. After radical resection of the causative tumor, the paraneoplastic symptoms disappeared quickly. In comparison with other literature reports, this case featured a huge tumor with DPS and PMBS. Additionally, the breast cancer gene 1 (*BRAC1*) mutation was detected in this case using next-generation sequencing (NGS). We present the following case in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-914).

Case presentation

A healthy 51-year-old male presented to our hospital with a recurrent 2-month episode and symptoms history of severe hypoglycemia, including diaphoresis, tremor, anxiety, and loss of consciousness. A chest X-ray and computed tomography (CT) scan of his thorax at another hospital revealed a pleural mass in the patient's right thoracic cavity. There were no pulmonary complaints. No dramatic findings were observed on the physical examination other than finger clubbing and diminished breath sounds in the right middle and lower lobes of the lung. Laboratory tests, including peripheral blood examinations and tumor biomarkers, were within normal range, except that the level of blood potassium was 2.67 mmol/L. Despite marked hypoglycemia (1.4 mmol/L), the serum insulin level did not reach 0.2 mIU/mL (normal range, 2.6–24.9 mIU/mL), the C-peptide level reached 0.07 ng/mL (normal range, 0.78–1.89 ng/mL), the serum insulin-like growth factor-II (IGF-II) level reached 1,228.71 mg/dL, and the IGF-I level reached 108 ng/mL (see *Table 1*).

Repeated chest X-rays showed a huge mass in the right thoracic cavity (see *Figure 1A,B*). The thoracic CT scan revealed a mass with an unclear boundary that was compressing the right atrium, right pulmonary artery, and right superior pulmonary vein. The great heart vessel was also deviated to the left. Additionally, the right lung's middle lobe and lower lobe was compressed and inflated, and the local lung field near the mass was consolidated (see *Figure 1C,D*). The mass presented with high-degree intensity in T2-weighted image magnetic resonance imaging (MRI), and showed a heterogeneous signal increase on the dynamic MRI; however, there was no obvious enhancement in the necrosis area (see *Figure 1E,F*). Bone emission CT scans and MRI of the brain were unremarkable. From the preoperative image findings, we suspected that the tumor might have invaded other organs, including the lung, right atrium, right pulmonary artery, right superior pulmonary vein, and great heart vessel. A CT scan-guided transthoracic puncture biopsy was performed on the patient, and a microscopic examination of the specimen revealed spindle tumor cells. The tumor cells were slightly atypical, and the soft tissue tumors had low-grade malignancy.

Next a, right posterolateral open thoracotomy was performed. We chose the left lateral position, and made a right posterolateral sixth intercostal incision into the chest.

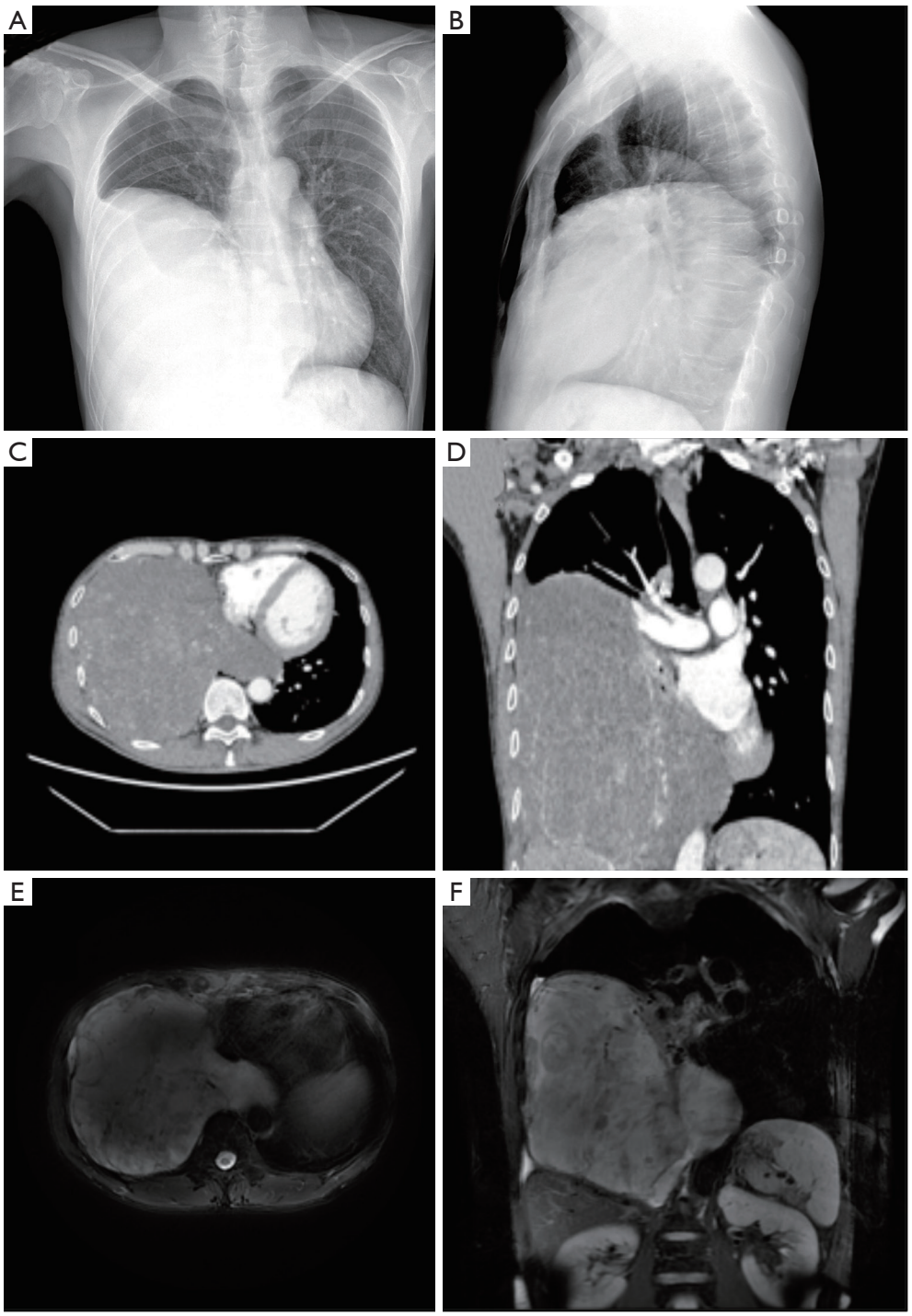

Figure 1 Imaging examination of patients with pleural solitary fibrous tumor (SFT). (A,B) A chest X-ray showed a huge mass in the right thoracic cavity; (C,D) thoracic computed tomography (CT) scan of the SFT; (E,F) magnetic resonance imaging (MRI) of the SFT.

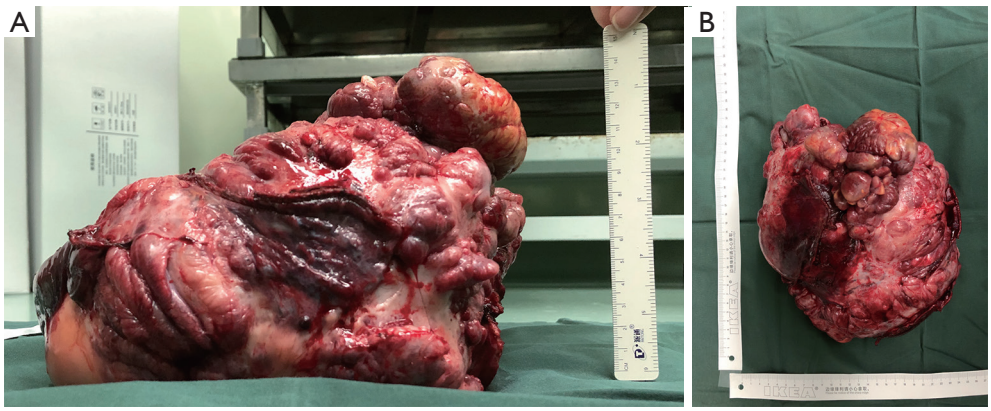

Figure 2 Macroscopic findings of resected tumor: the tumor measured approximately 22×22×11 cm^3.

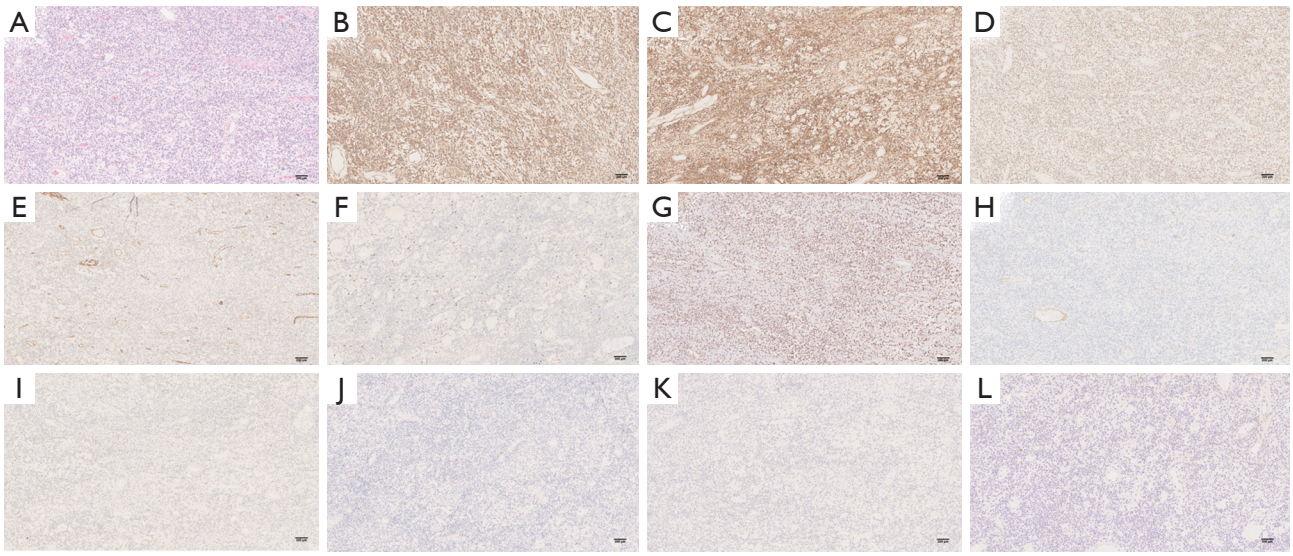

Figure 3 Histopathological findings showing spindle cells arranged in an organization lacking an obvious pattern. Hematoxylin-eosin (HE) staining (A) and immunohistochemistry of vimentin (B), bcl-2 (C), STAT6 (D), CD34 (E), Ki-67 (15%) (F), IGF-2 (G), SMA (H), desmin (I), S-100 (J), calretinin (K) and AE1/AE3 (L).

The length of the wound was approximately 30 cm. There were a small number of adhesions in the thoracic cavity. The tumor, which stemmed out of the anterior mediastinum, was in the accompanying right lung and diagram, and there was phrenic nerve invasion. A percentage of the lower lobe of the right lung, a proportion of the diagram, and the phrenic nerve were resected. The tumor, which measured 22×22×11 cm^3 in size and weighed 3,500 g, was encapsulated (see *Figure 2*). Histologic assessment of a lung biopsy specimen revealed a tumor composed of simple spindle-shaped cells with no obvious nuclear pleomorphism (less than 4 mitotic figures per 10 high-power fields). Necrosis was not observed. The immunohistochemical findings were as follows: vimentin (+), Bcl-2 (+), STAT6 (+), CD34 (+), IGF-II (+), SMA (–), desmin (–), S-100 (–), calretinin (–), AE1/AE3 (–), and Ki-67 labeling index 15% (see *Figure 3*). A pathology report confirmed the diagnosis of a malignant SFT.

NGS of the tissue of the SFT revealed a mutation in the *BRCA1* (p.Q1458*) gene at the DNA level, and NAB2-STAT6 fusion at the messenger RNA (mRNA) level (see *Figure 4*).

The patient's postoperative serum glucose levels

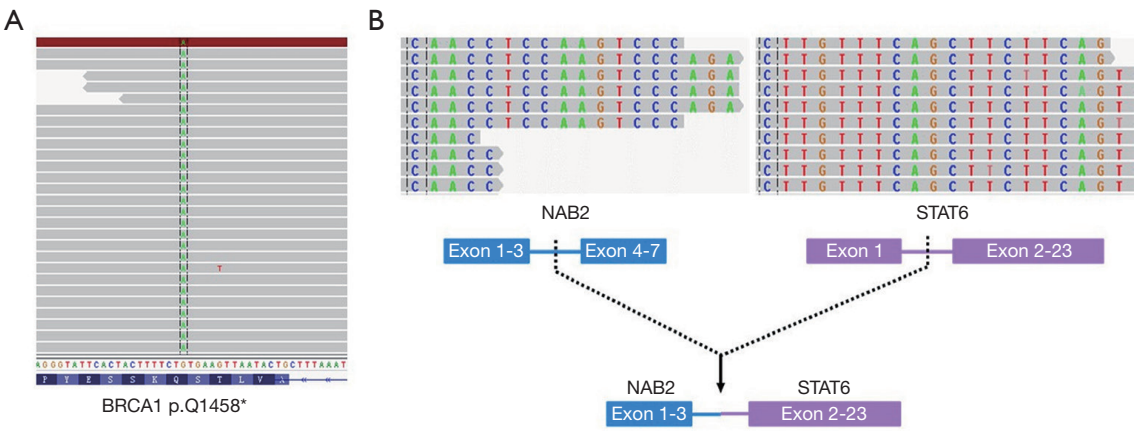

Figure 4 Next-generation sequencing (NGS) detected the breast cancer gene 1 (BRCA1) germline mutation and NAB2-STAT6 fusion transcripts of the intrathoracic solitary fibrous tumors (SFTs). NGS reads in the BRCA1 germline mutation and NAB2-STAT6 fusion breakpoint regions are visualized using the Integrated Genomics Viewer (Broad Institute, Cambridge, MA, United States).

normalized, and he experienced no hypoglycemic episodes. Additionally, the patient's serum IGF-II levels decreased from 1,228.71 to 347.82 mg/dL. After the operation, the case was submitted to a multidisciplinary team for discussion. The experts agreed with the approach adopted (i.e., that the tumor be removed completely), and that no additional adjuvant treatment was needed at present. The patient was followed up once every 4 months for the first 2 years and then, every 6 months for the next 3–5 years. The digital clubbing resolved within 3 months. No episodes of hypoglycemia occurred, and no recurrence or other signs of metastasis were found based on the CT examinations during the 1.5 year follow-up period.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Discussion

Pleural SFT is an uncommon primary tumor originating from the mesenchymal layer of the parietal or visceral pleura (3). The assessed age-standardized incidence ratio (World Standard Population) for pleural SFT is 2.8 per 100,00 cases (8). There is no gender predominance, and it peaks among patients aged 50–70 years old, but has been reported in patients of all ages (3,9,10). Most SFTs are benign (11). In relation to malignant SFTs, Penel *et al.* reported that they are hypercellular and display at least focal moderate-to-severe nuclear atypia. Malignant SFTs often have infiltrative margins with surrounding tissues, a high mitotic count (≥4 mitoses per 10 high-power fields), and display cellular pleomorphism and tumor necrosis (11).

The clinical presentation of a SFT is of an asymptomatic slow growing mass that usually presents as an incidental finding on a radiological scan. When a tumor becomes large enough, the patient may present with local symptoms due to compression, such as vague chest pain, dyspnea, or a cough (9,12). It has been reported that nearly a quarter of pleural SFTs are commonly associated with paraneoplastic syndromes (4,9,13). Hypertrophic pulmonary osteoarthropathy (HPO), also referred to as PMBS, was first described by Bamberger in 1889, who described painful, digital clubbing; arthralgia; the swelling of the wrists, knees, ankle or elbows; and dermal hypertrophy (14-16). It has been reported that up to 22% of SFT patients have PMBS (9). The cause of HPO is not clearly understood. It has been posited that HPO may result from the following 3 pathophysiological causes: abnormal vascularization, hypoxia, and chronic inflammation, which all presumably give rise to a terminal common pathway involved in the vascular endothelial growth factor (16). In general, the HPO symptoms are effectively mitigated after the tumor is removed often within a few days but might reappear if the tumor recurs.

Reactive hypoglycemia, which was first described in 1930 by Doege and Potter independently, is connected with pleural SFTs in nearly 4% of cases (5,9). Clinical manifestations of hypoglycemia consist of a number of

symptoms, including diaphoresis, tremors, anxiety, and a loss of consciousness. Hypoglycemia is 2–3 times more common in women than men, and more common in right-sided pleural SFTs located in the right hemithorax (12). Previous reports have shown that large pleural SFTs (>20 cm) are often accompanied by hypoglycemia (4). The present case study involved a male patient suffering from a right-sided tumor. Hypoglycemia is thought to be the result of secretions of the precursor to insulin, such as factor-II (pro-IGF-II) (17). Pro-IGF-II can activate the insulin receptor, thus increasing peripheral glucose uptake and inhibiting hepatic gluconeogenesis, which results in hypoglycemia (17). A high IGF-II:IGF-I ratio is viewed as a surrogate marker of hypoglycemia. A ratio of 3:1 normally indicates hypoglycemia The IGF-II:IGF-I ratio is viewed as a surrogate marker with a high IGF-II concentration, in which 3:1 is the rate under normal consideration (18). In the present case, the patient's preoperative serum IGF-II level was 1,228.71 μg/dL, but his serum IGF-I level was only 108 ng/mL. Additionally, it is worth noting that high IGF-II may reduce the level of blood potassium in the short term (19). In this case, our patient presented with hypokalemia based on potassium concentrations of 2.67 mmol/L. After surgery, his blood potassium level returned to normal. However, the mechanism underlying these findings remains unclear.

Imaging characteristics are important diagnostic tools. Both CT scanning and MRI are very effective at showing the size and location of tumors, the invasion of surrounding structures, and aid in surgical planning. CT scans of pleural SFTs typically show smooth, well-defined borders, and a homogenous mass with the same density as muscle. Mediastinum and lung parenchyma are often displaced under pressure (2,9,20). A malignant SFT of the pleura usually has unclear boundaries, adhesion with or invasion of the surrounding tissues, uneven density, calcification, and pleural effusion (20). MRI can also be a useful alternative, as MRI usually shows multinodular tumors of low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images (7). Positron emission tomography-CT (PET-CT) usually shows low 18F-deoxyglucose uptake in the intrathoracic mass, but has limited diagnostic value for malignant pleural SFT patients (21,22).

Pathological diagnosis is the gold standard for diagnosing pleural SFTs. The histopathological character of SFT indicates the existence of sparse and dense areas under the separation of fibrous stroma, and the mutual existence of hemangiopericytoma branching vessels (23). Standards of malignancy, as identified by England *et al.*, include high cellularity and mitotic activity (over 4 mitotic figures for every 10 in a high-power field), pleomorphism, hemorrhage, and necrosis (12). De Perrot and other researchers have reported that malignant SFTs of the pleura have a high cellularity based on crowding and overlapping of nuclei, cellular pleomorphism, a high mitotic count, necrosis, and stromal/vascular invasion (19). In the present case, while some of the preoperative features of the tumor indicated a latent malignancy, the histologic analysis confirmed that the tumor was benign. Immunohistochemical analyses play an indispensable role in distinguishing pleural SFTs from other pleural tumors, such as mesothelioma, sarcoma, and other similar neoplasms. Pleural SFTs are positively correlated with vimentin, Bcl-2, CD34, and STAT6, but are negatively correlated with AE1/AE3, synaptophysin, S-100, and calretinin (7). In some cases, it has been suggested that in addition to CD34 and bcl-2, IGF-II should also be used as a marker for the postoperative differential diagnosis (24).

In addition, a gene analysis based on NGS might reveal the mutation features of pleural SFTs (25). Recently, an intrachromosomal gene fusion (a NAB2-STAT6 fusion) was identified as the defining driving genetic event of SFT, and different fusion types were correlated with tumor histology and behavior. Due to the proximity of NAB2 and STAT6 on chromosome 12, this fusion is difficult to identify by fluorescence in-situ hybridization (26). In a clinicopathologic study conducted by Tai *et al.*, the NAB2-STAT6 fusion was found in 34 of 52 cases (27). These studies have shown that *NAB2-STAT6* gene fusion is the most prominent and well-adopted genomic hallmark of pleural SFTs. Additionally, given the nuclear entry of STAT6 driven by the *NAB2-STAT6* gene fusion, several studies have reported the high sensitivity and specificity of STAT6 nuclear expression for SFTs (28-31). This is the first case to report germline *BRCA1* functional mutation in pleural SFTs. *BRCA1* is a tumor-suppressor gene that encodes a protein involved in DNA repair. Kang *et al.* suggested that the *BRCA1* p.Q1458* mutation changes the glutamine residue in reference to the sequence to stop-gained codon protein truncation (32). Abbas *et al.* suggested that the Q1458* mutation changes of *BRCA1* are highly pathogenic in breast cancer patients (33). Genetic testing for *BRCA1* p.Q1458* could be helpful in the diagnosis and treatment of cancer. However, in our case, the patient had no family history of cancer, including breast cancer.

A complete resection with wide margins of adjacent tissues is recommended for the treatment of pleural SFTs (12). Thoracotomy has been employed as therapy for

those who suffer from a large tumor or expansive adhesions. Following the complete resection of the tumor, the deformed lung tissue may expand, and the paraneoplastic syndromes usually disappear (32). To date, findings on the effects of adjunctive therapy, including chemotherapy, radiation, and embolization, have been controversial (7).

The surgical removal of pleural SFTs usually produces satisfactory results, including a 5-year disease-free survival rate of approximately 80%. However, the recurrence rate of malignant SFTs of the pleura has been reported to be 63%, even after complete resection (34). Tapias *et al.* developed a scoring system to predict the recurrence of SFTs of the pleura after resection, including parietal pleural origin (*vs.* visceral/intrapulmonary origin), sessile morphology (*vs.* pedunculated morphology), a size larger than 10 cm (*vs.* a size smaller than 10 cm), hypercellularity, the presence of necrosis or hemorrhage, and the number of mitoses (per 10 in a high-power field) (35). This system partially overlaps with the diagnosis criteria of malignancy, but it emphasizes predictive value. A long-term follow-up period is mandatory due to the risk of recurrence of SFTs. The survival outcomes revealed that the 5-year recurrence-free survival and overall survival (OS) rates of benign patients were both 100%; however, the 5-year relapse-free survival (RFS) and OS rates of malignant patients were 58.3% and 66.7%, respectively (3). Malignant SFT recurrence has been reported 17 years after surgical resection (3,36). Thus, a postoperative follow-up period with CT is recommended every 3–6 months for 2 years and annually thereafter. For malignant tumors with a high risk of recurrence, a closer clinical follow-up approach is recommended.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-914

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-914). The authors have no 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 studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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