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Original Article

Solitary fibrous tumor of the thymus with variegated epithelial components

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Abstract: Solitary fibrous tumor is a rare mesenchymal neoplasm, characterized by peculiar histological features composed by the proliferation of spindle cells in "patternless pattern". Although it has been known to sometimes be accompanied by epithelioid cells, the presence of a well-formed epithelial structure is far more rare. We describe herein the case of a 60-year-old female with the radiological finding of a single nodular lesion in the anterior mediastinum. Histopathological examination of the surgically resected specimen led to the diagnosis of solitary fibrous tumor of the thymus with a spectrum of well-formed epithelial components: i) glandular structure, reminiscent of breast or eccrine gland, ii) neural tube-like structure, and iii) clusters of endocrine-like cells. Immunohistochemical analysis revealed that the spindle cells expressed CD34, vimentin, bcl-2 and Stat-6, but not keratin (cytokeratin-AE1/AE3) or epithelial membrane antigen. In contrast, the epithelial components lost expression of most of these marker proteins, including Stat-6, but continued to express vimentin and strongly expressed keratin. Since no relevant past literature was found, the current case could be interpreted as a unique and previously undescribed variant of solitary fibrous tumor comprising conventional spindle cells with a spectrum of well-formed epithelial components. Pathogenesis that may have given rise to these variegated mixtures of spindle cells and epithelial components in a single tumor is also discussed.

Keywords: Solitary fibrous tumor, epithelial component, gland, neural tube, endocrine cells, epithelioid solitary fibrous tumor

Introduction

Solitary fibrous tumor (SFT) is a rare mesenchymal tumor that was first described in the visceral pleura, where it usually arises [1, 2]. However, it has subsequently been described in ubiquitous sites, including the peritoneum, retroperitoneum, mediastinum, meninges and the orbit [3-6]. When located outside the pleura, it is often difficult to make a diagnosis by clinical and radiographical findings, and the diagnosis thus relies solely on the presence of characteristic histopathological features. SFT classically presents with interlacing bundles of spindle cells that have blunt nuclei and are scattered haphazardly among collagenous stroma in variable cellularity. These spindle cells are frequently arranged in "patternless pattern" with hemangiopericytomatous arborizing blood vessels [2, 4, 7]. However, there are occasional descriptions in the literature of epithelioid morphology in SFT [2, 8, 9]. For this group of tumors, the term "epithelioid SFT" has generally been accepted, as SFTs with epithelioid cells that retain the immunohistochemical phenotype of spindle cells, such as the expression of CD34, vimentin and bcl-2. Recently, the pathogenic molecular lesion underlying SFT has been reported to be fusion genes comprised of *NAB2* and *STAT6* [10]. The resultant protein products are detectable by immunohistochemical staining for Stat-6 protein [11]. We, herein, present a case of SFT that showed unique morphology with a spectrum of well-formed epithelial components, and which is quite distinct from the previously described subtypes or variants of SFT. The pathogenesis and the relation between spindle cells and epithelial components are discussed, together with a review of the literature.

Case report

A 60-year-old female was referred to our hospital because of an abnormal shadow on a chest X-ray. Her medical records and family history

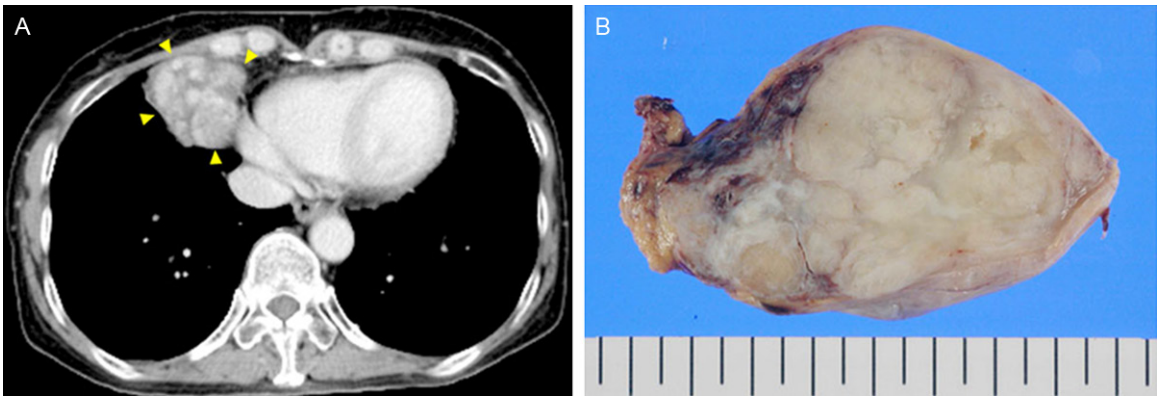

Figure 1. A. Computed tomographic image showing a heterogeneously enhanced, 7-cm mass in the anterior mediastinum, adjacent to the pericardium (arrowheads); B. The gross appearance of a mediastinal tumor, revealing a well-circumscribed and partially encapsulated nodule. The cut surface shows a tan-white and solid appearance.

were unremarkable and she had no history of smoking. She had no complaints of symptoms. Laboratory findings, including tumor markers, were all within the normal ranges. A computed tomography (CT) scan revealed a 7-cm mass on the right side of the pericardium which was heterogeneously enhanced (**Figure 1A**). After selective unilateral ventilation anesthesia with double-lumen endotracheal intubation, the lesion was excised by a video-assisted, right thoracic surgery, with the patient in the lateral decubitus position. At surgery, the tumor was well encapsulated and connected by a peduncle with the mediastinal pleura on the right side of the pericardium. It was not adherent to the lung, diaphragm or phrenic nerve, and thus, could be completely resected with partial resection of the pericardial fat pad near the peduncle. The patient was discharged on postoperative day 6. She returned to daily life with no evidence of recurrence until 10 months postoperatively.

Material and methods

Tissue samples were fixed in 15% formalin, dehydrated by ethanol and embedded in paraffin. Serial sections of 3.5 μm thickness were prepared and used for hematoxylin-eosin and immunohistochemical (IHC) staining. For IHC staining, sections were stained by Autostainer Link 48 (DAKO, Glostrup, Denmark) using the primary antibodies in the dilutions presented in **Table 1**. Pretreatment with heat-induced epitope retrieval was performed using Dako PT Link (Code PT100/PT101) with EnVision™ FLEX Target Retrieval Solution, High pH (pH. 9.0, Code K8004) or Low pH (pH. 6.0, Code K8005).

Results

Macroscopically, the specimen excised from the mediastinum was a well-circumscribed and partially encapsulated tan-white solid mass measuring 7.8×4.7×2.4 cm (**Figure 1B**).

Histologically, the tumor showed a variety of morphology with some areas having features of a benign spindle cell tumor and other areas having diverse patterns of epithelial components. In the spindle cell component, fibroblast-like cells proliferated intermingled with loose or dense collagenous fibers in-between, and the stroma contained remarkable thin-walled vascular structures (**Figure 2A**). By IHC staining, the spindle tumor cells showed positive staining for CD34 (**Figure 2B**), bcl-2 and vimentin, but negative for desmin, α-smooth muscle actin (SMA), S-100 protein, cytokeratin (CK)-AE1/AE3 (CK-AE1/3) as well as all other markers examined (**Table 1**). There were no definitive features suggestive of high grade malignancy, i.e., only very occasional mitoses were identified (up to one per 10 high-power fields [HPFs]), and necrosis was not observed.

In addition to this classical SFT morphology, a spectrum of epithelial components was noted. First, the glandular pattern consisted of a two-cell layer, an inner surface epithelium and outer myoepithelium or basal cells, reminiscent of the ductal component of breast or sebaceous glands (**Figure 3A**). The inner cells stained positive for CK-AE1/3, CK7, epithelial membrane antigen (EMA), S-100, vimentin and focally for CK20 (**Figure 3B-D**), but were negative for CD34, Carcinoembryonic Antigen (CEA), Gross

Table 1. Antibodies used and staining results

Antibody	Source	Clone	pH*	Dilution	Spindle cell	Glandular	Neuroepithelium	Neuroendocrine
CD34	Dako	QBEnd 10	L	1:200	+	-	-	-
Vimentin	Dako	Vim 3B4	H	1:800	+	+	+	+
Bcl-2	Dako	124	H	1:400	+	-	-	-
S-100	Dako	polyclonal	H	ready-to-use	-	+	-	+ focal
a-SMA[1)]	Dako	IA-4	L	1:400	-	-	-	-
Calretinin	Dako	DAK-Calret 1	H	1:100	-	-	-	-
Desmin	Dako	D33	H	ready-to-use	-	-	-	-
Cytokeratin AE1/3	Dako	AE1/AE 3	L	ready-to-use	-	+	+	+
Cytokeratin 5/6	Dako	D5/16 B4	H	1:200	-	+ focal	+ focal	+
Cytokeratin 7	Dako	OV-TL 12/30	L	1:200	-	+	+ focal	+ focal
Cytokeratin 20	Dako	Ks20.8	L	1:160	-	+ focal	+ focal	+ focal
EMA[2)]	Dako	E 29	H	1:800	-	+ focal	-	+ focal
p63	Nichirei	4A4	H	ready-to-use	-	-	-	-
CEA[3)]	Dako	II-7	L	1:800	-	-	-	+
Thyroglobulin	Dako	polyclonal	L	ready-to-use	-	-	-	-
GCDFP-15[4)]	Dako	23A3	H	1:50	-	-	-	-
Calponin	Dako	CALP	H	1:100	-	-	-	-
TTF-1[5)]	Dako	8G7G3/1	H	1:400	-	-	-	-
chromogranin	Dako	polyclonal	H	1:400	-	-	-	+
synaptophysin	Dako	DAK-SYNAP	L	1:50	-	-	+ focal	+
CD56	Leica	1B6	L	1:50	-	-	-	+
NSE[6)]	Dako	BBS/NC/VI-H14	L	1:800	-	-	+ focal	+
CD5	Leica	4C7	L	1:100	-	-	-	-
Stat-6	Santa Cruz	polyclonal	L	1:1000	+	-	-	-
Ki-67	Dako	MIB-1	H	1:40	<1	<1	3~15	<1

Abbreviations: [1)]α-SMA, alpha-Smooth Muscle Actin; [2)]EMA, Epithelial Membrane Antigen; [3)]CEA, Carcinoembryonic Antigen; [4)]GCDFP-15, Gross Cystic Disease Fluid Protein-15; [5)] TTF-1, Thyroid Transcription Factor-1; [6)]NSE, Neuron Specific Enolase; *pH of Target Retrieval Solution. (L, low; H, high).

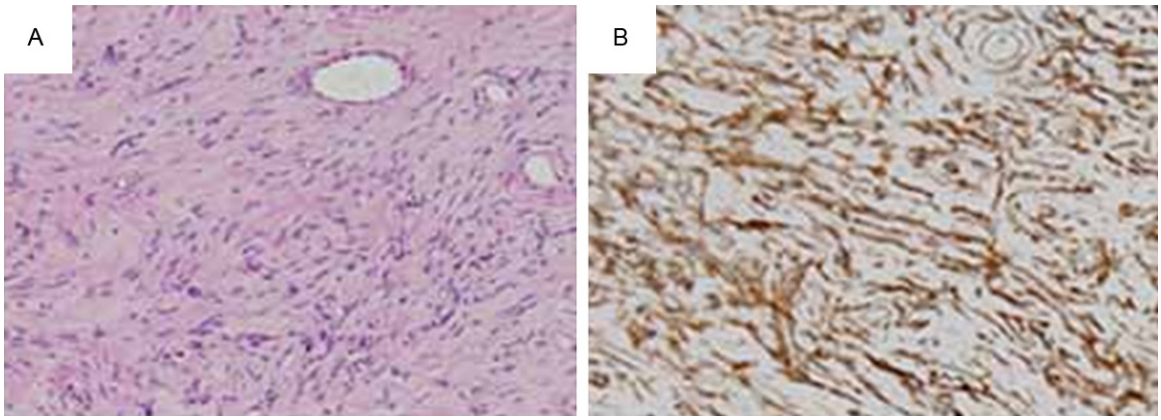

Figure 2. A. Histological features of the tumor, showing uniformly proliferated spindle cells with a scanty cytoplasm and blunt nuclei, intermingled with loose collagenous fibers. Necrosis or mitosis was not observed; B. Immunohistochemical staining of the tumor cells, showing diffuse positive reactivity for CD34. Original magnification, ×200.

Cystic Disease Fluid Protein-15 (GCDFP-15) and thyroglobulin (**Table 1**). Although the outer cells stained positively for CK-5/6, focally for S-100 and vimentin, they were negative for calponin and p63, and thus, definitive myoepithelial differentiation could not be confirmed. However, these overall IHC features still suggest eccrine differentiation. A second component consisted of neural tube-like, or neuroepithelium-like structures, some of which formed multilayered rosettes with central pseudolumen (**Figure 4A**). Those tumor cells stained positive for CK-AE1/3, vimentin and focally positive for neuron-specific enolase (NSE) (**Figure 4B-D**), but were negative for neuroendocrine markers, such as chromogranin, synaptophysin and CD56 (**Table 1**). A third component consisted of solid sheets of polygonal, pale to eosino-

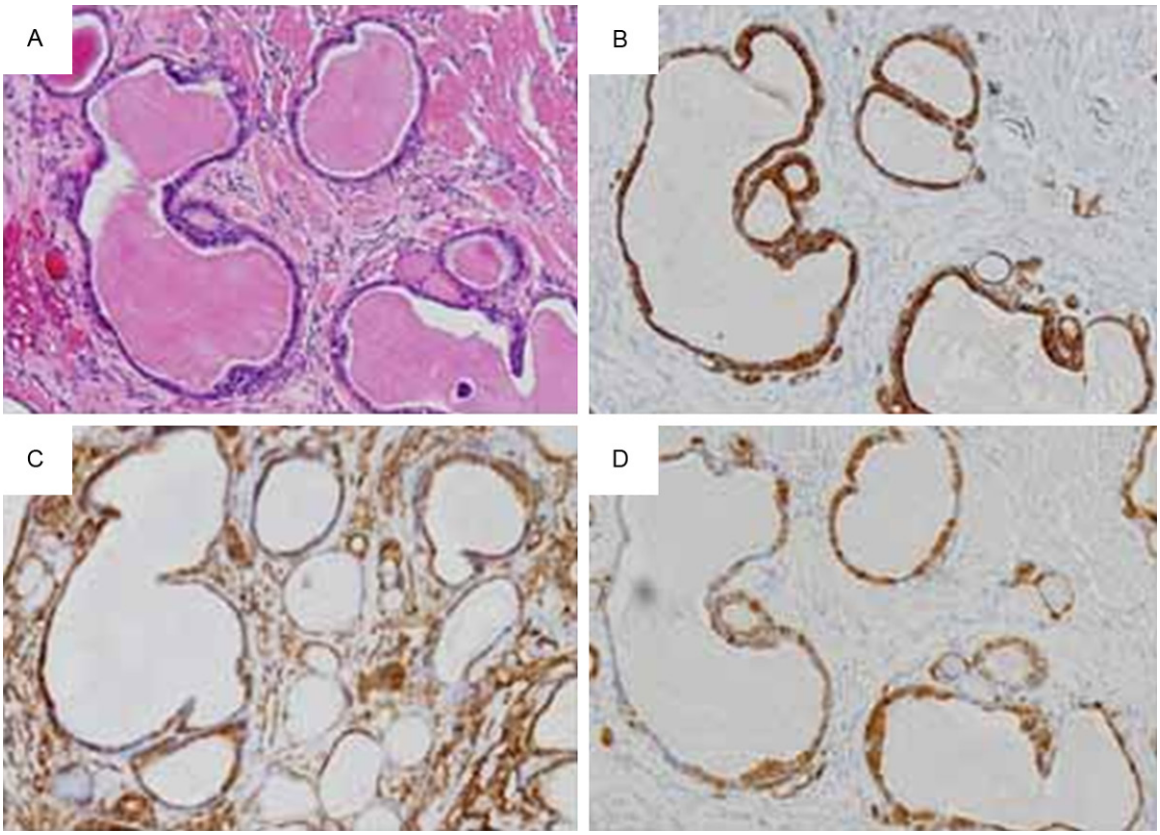

Figure 3. (A) Histological features of the epithelial component of the tumor, showing a glandular pattern composed of two-cell layers. (B-D) Immunohistochemical staining of the tumor cells, showing positive reactivity for cytoleratin-AE1/AE3 (B), vimentin (C) and S-100 (D). Original magnification, ×200.

philic cells, reminiscent of endocrine lineage (**Figure 5A**). These cells stained positive for CK-AE1/3, NSE, CEA, vimentin, EMA as well as chromogranin, synaptophysin and CD56 (**Figure 5B-D**). Moreover, CK7, CK20, S-100 were focally positive in stellate-shaped cells which intervened among polygonal cells. Stat-6, which has recently been described as a specific marker for SFT, was strongly expressed only in the nuclei of spindle cells (**Figure 6**). Ki-67 index was highest, 3 to 12%, in the neural tube-like cells (the second component), but negligible in the glandular (the first component) and the endocrine-like structure (the third component). The epithelial elements showed no positive staining for CD34, bcl-2 or Stat-6, and never merged with the spindle cell element.

The tumor was surrounded by a small amount of thymic tissue at the periphery. Since no tumor was found in any other site, the final pathological diagnosis of "solitary fibrous tumor with epithelial component of the thymus" was made.

Discussion

SFT is recognized nowadays as an established entity whose diagnostic criteria consist of distinct histological features, i.e., the presence of spindle cells commonly expressing CD34, vimentin, and bcl-2 [2]. Furthermore, EMA, α-SMA, S-100 and cytokeratins may be expressed occasionally, but are usually negative [12].

Although SFT was originally described as a tumor consisting purely of spindle cells, rare cases having clusters of epithelioid cells have been sporadically described [2]. More recently in 2003, the term "epithelioid SFT" was proposed for a case of tumor consisting predominantly of epithelioid cells that share the histological and IHC features of both SFT and adenomatoid tumor [8]. Since that time, 24 tumors of "epithelioid SFT", "biphasic SFT" or equivalent lesions in various sites from 19 patients, for which IHC results were well characterized, have been reported [5, 6, 9, 12-19]. However, these reports describe tumors whose epithelioid

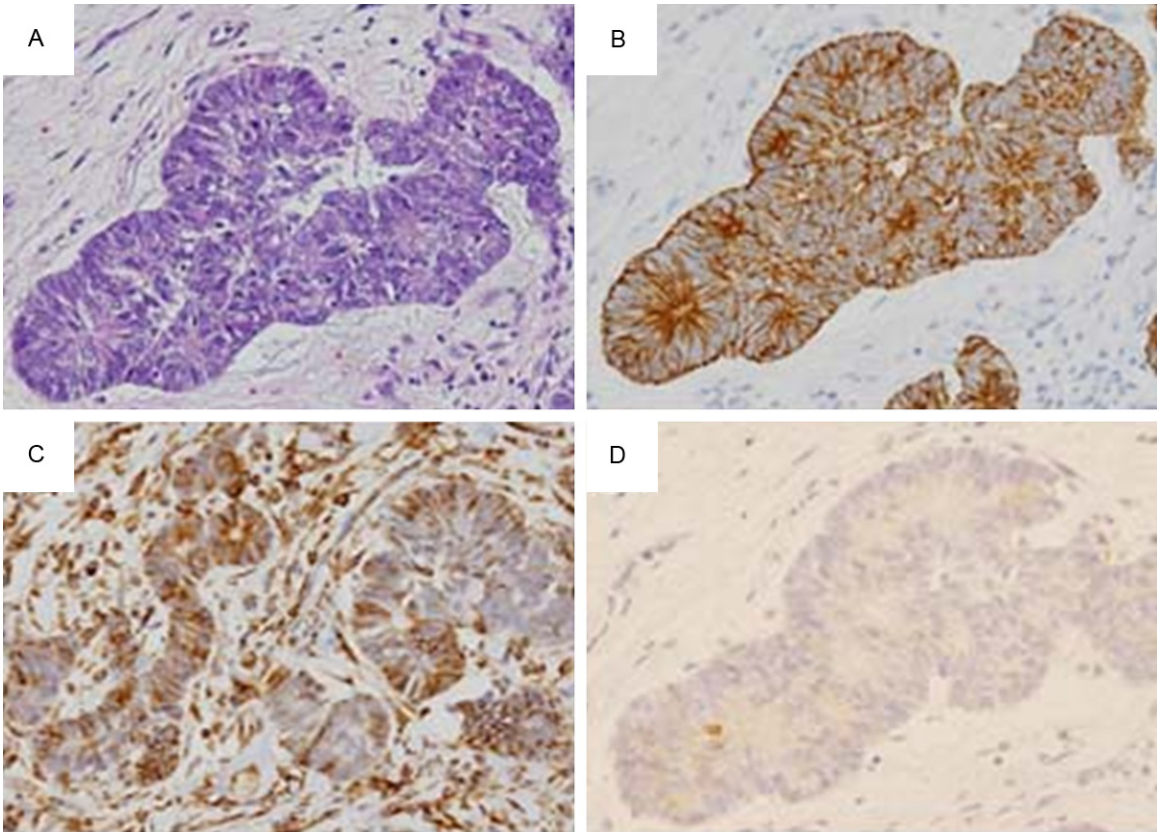

Figure 4. (A) Histological features showing a neural tube-like structure, with an obscure central lumen. (B-D) Immunohistochemical staining revealed positive reactivity for cytoleratin-AE1/AE3 (B), vimentin (C) and focal staining for NSE (D). Original magnification, ×200.

component exhibited solid clusters of polygonal cells, but no definitive forms of differentiated epithelial structure. Moreover, these epithelioid cells mostly retain the phenotype of conventional SFT. In the current case, histology revealed a heterogeneous "tetraphasic" architecture, consisting primarily of conventional spindle cells that were apparently distinct from the epithelial components. In addition, the other components were variable, consisting of gland-like and neural tube-like structures as well as endocrine-like cells. In the glands, the epithelial cells showed diffuse expression of epithelial markers, but also of vimentin and S-100. However, CD34, bcl-2 and calretinin were negative. These IHC profiles are suggestive of the eccrine gland, although they are not completely identical. The second component, i.e. the neural tube-like structure, revealed positive staining for CK-AE1/3, vimentin and focally for NSE, which is not inconsistent with the IHC pattern for neural tubes. The third epithelial component, i.e. sheets of polygonal, pale to eosinophilic cells, stained positive for CK-AE1/3, vi-}mentin, NSE, CEA and S-100 as well as chromogranin, synaptophysin and CD56, suggestive of, but not completely identical to the neuroendocrine cells.

Recently, it has been reported that almost all cases of SFT harbor *NAB2-STAT6* fusion genes and exhibit subsequent Stat-6 overexpression, regardless of the histological features or clinicopathological profiles [10, 11]. The fused *NAB2-STAT6* genes and those protein products are observed almost exclusively in SFTs, except for vary rare cases of meningeal tumors and in 2.5% of other soft tissue tumors [11, 20]. Therefore, IHC detection of Stat-6 has been proposed as a highly sensitive and specific surrogate marker for SFT, and thus would be a useful diagnostic tool [11]. In our case, Stat-6 staining was diffusely observed in the nuclei of the spindle cells, but not in the epithelial cells. Therefore, the epithelial structures could not be interpreted as components of SFT and accord-

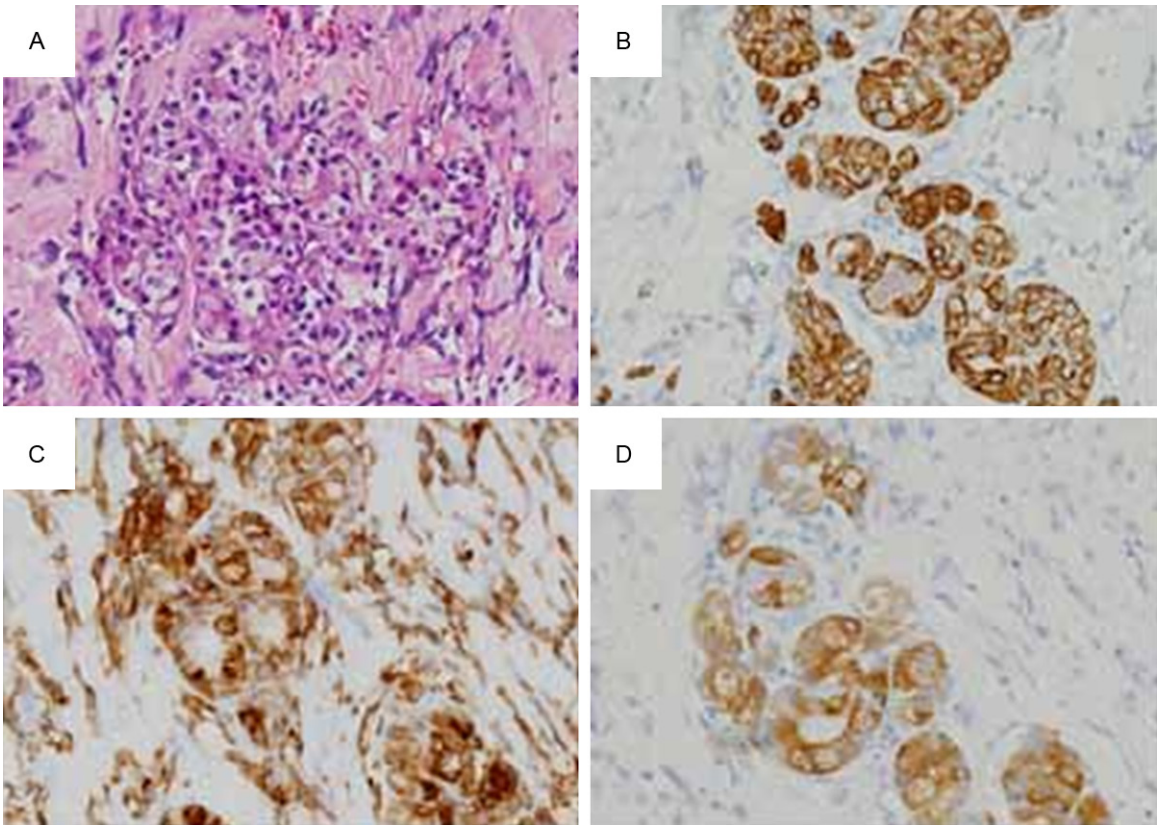

Figure 5. (A) Histological feature showing solid sheets of polygonal, pale to eosinophilic cells, reminiscent of endocrine cells. (B-D) Immunohistochemical staining revealed positive reactivity for cytoleratin-AE1/AE3 (B), vimentin (C) and chromogranin (D). Original magnification, ×200.

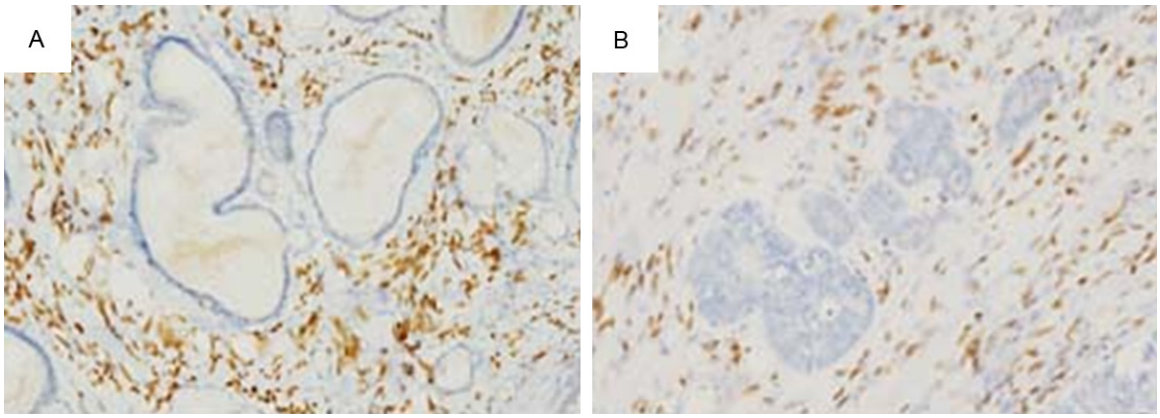

Figure 6. Stat-6 staining. Positive reactivity for Stat-6 was found in the nuclei of spindle cells, but not in epithelial cells of (A) glandular or (B) neural tube-like structures.

ingly, the current case does not fit into the category of epithelioid SFT. We speculate three possibilities for the pathogenesis of this tumor. First, the observed mixture of several epithelial structures is teratomatous components of the thymus and entrapped by SFT. However, this designation does not fit completely due to the lack of a mesodermal component, and its occurrence in association with SFT in older females is quite unusual. Second, these cells may be an epithelial component derived from the thymus that was entrapped in the SFT, and

which has undergone multidirectional differentiation. However, induction of such multidirectional differentiation by SFT has not been documented. And third, this tumor could be SFT with focal, but overt epithelial transdifferentiation in spite of the lack of Stat-6 negativity. As a similar example, in fat-forming SFT, which is a rare subtype, a mixture of Stat-6-negative cells with Stat-6-positive cells was described in a study examining a large series of SFTs by IHC [11]. These Stat-6-negative cells may have derived from the original SFT, but subsequently lost their IHC phenotype. Thus, the epithelial component in the current case may be the result of a pronounced induction of the epithelial phenotype in spindle cells. Consistently, 'primitive desmosomes' were demonstrated ultrastructurally which suggest a minimal degree of epithelial differentiation even in spindle cells of conventional SFTs [21].

Based on the histological features observed in hematoxylin-eosin staining, possible differential diagnosis may be considered, such as i) synovial sarcoma, ii) malignant mesothelioma, iii) ectopic hamartomatous thymoma. Synovial sarcoma could be ruled out based on the expression of CD34 and Stat-6, as well as the complete lack of epithelial marker expression in the spindle cells [5]. Malignant mesothelioma could also be ruled out since positive staining for keratin in spindle cells and calretinin for epithelial cells are commonly observed in this tumor [22]. Ectopic hamartomatous thymoma is rare tumor which exclusively occurs in supraclavicular, pre-, or suprasternal regions in middle-aged male [23]. Although the rare report arising in the soft tissue of the back is found, the spindle cells show keratin expression, but not CD34 in this tumor [23, 24].

Regarding the biological behavior, benign SFTs are more common than malignant ones [6, 18], with the malignant form accounting for 9-22% of the total [25, 26]. Its pathological criteria includes large tumor size (more than 50 mm in diameter), infiltrative margins, high cellularity, nuclear pleomorphism, necrosis and high mitotic index (more than 4/10 HPF) [12, 16, 18, 26]. By these criteria, our case should be interpreted as benign.

In conclusion, a unique case of "SFT with variegated epithelial components of the thymus" was presented.

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Disclosure of conflict of interest

None.

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References

[1] Klemperer PR, CB. Primary neoplasm of the pleura. Arch Pathol 1931; 11: 385-412.
[2] Hanau CA, Miettinen M. Solitary fibrous tumor: histological and immunohistochemical spectrum of benign and malignant variants presenting at different sites. Hum Pathol 1995; 26: 440-9.
[3] Caroli E, Salvati M, Orlando ER, Lenzi J, Santoro A, Giangaspero F. Solitary fibrous tumors of the meninges: report of four cases and literature review. Neurosurg Rev 2004; 27: 246-51.
[4] Bracey TS, Hilton DA, Sulkin T, Smith ME. A meningeal myofibroblastic neoplasm related to solitary fibrous tumour and associated with a malignant neuroblastic element. J Clin Pathol 2010; 63: 180-3.
[5] Warraich I, Dunn DM, Oliver JW. Solitary fibrous tumor of the orbit with epithelioid features. Arch Pathol Lab Med 2006; 130: 1039-41.
[6] Awasthi R, O'Neill JK, Keen CE, Sarsfield PT, Devaraj VS, Stone CA, Smith ME. Biphasic solitary fibrous tumour: a report of two cases with epithelioid features. Virchows Arch 2006; 448: 306-10.
[7] Witkin GB, Rosai J. Solitary fibrous tumor of the mediastinum. A report of 14 cases. Am J Surg Pathol 1989; 13: 547-57.
[8] Marchevsky AM, Varshney D, Fuller C. Mediastinal epithelioid solitary fibrous tumor. Arch Pathol Lab Med 2003; 127: e212-5.

[9] Mourra N, Lewin M, Sautet A, Parc R, Flejou JF. Epithelioid solitary fibrous tumor in the ischioanal fossa. Virchows Arch 2005; 446: 674-6.
[10] Chmielecki J, Crago AM, Rosenberg M, O'Connor R, Walker SR, Ambrogio L, Auclair D, McKenna A, Heinrich MC, Frank DA, Meyerson M. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 2013; 45: 131-2.
[11] Yoshida A, Tsuta K, Ohno M, Yoshida M, Narita Y, Kawai A, Asamura H, Kushima R. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. Am J Surg Pathol 2014; 38: 552-9.
[12] Martorell M, Perez-Valles A, Gozalbo F, Garcia-Garcia JA, Gutierrez J, Gaona J. Solitary fibrous tumor of the thigh with epithelioid features: a case report. Diagn Pathol 2007; 2: 19.
[13] Parrozzani R, Fusetti S, Montesco C, Favero V, Midena E. Biphasic solitary fibrous tumor of the orbit with distant metastases. Int Ophthalmol 2013; 33: 701-5.
[14] Fu J, Zhang R, Zhang H, Bu H, Chen H, Yin X, Zhang Z, Wei B. Epithelioid solitary fibrous tumor of the central nervous system. Clin Neurol Neurosurg 2012; 114: 72-6.
[15] Magro G, Emmanuele C, Lopes M, Vallone G, Greco P. Solitary fibrous tumour of the kidney with sarcomatous overgrowth. Case report and review of the literature. APMIS 2008; 116: 1020-5.
[16] Collini P, Negri T, Barisella M, Palassini E, Tarantino E, Pastorino U, Gronchi A, Stacchiotti S, Pilotti S. High-grade sarcomatous overgrowth in solitary fibrous tumors: a clinicopathologic study of 10 cases. Am J Surg Pathol 2012; 36: 1202-15.
[17] Yan B, Raju GC, Salto-Tellez M. Epithelioid, cytokeratin expressing malignant solitary fibrous tumour of the pleura. Pathology 2008; 40: 98-9.
[18] Mosquera JM, Fletcher CD. Expanding the spectrum of malignant progression in solitary fibrous tumors: a study of 8 cases with a discrete anaplastic component--is this dedifferentiated SFT? Am J Surg Pathol 2009; 33: 1314-21.
[19] Drachenberg CB, Bourquin PM, Cochran LM, Burke KC, Kumar D, White CS, Papadimitriou JC. Fine needle aspiration biopsy of solitary fibrous tumors. Report of two cases with histologic, immunohistochemical and ultrastructural correlation. Acta Cytol 1998; 42: 1003-10.
[20] Schweizer L, Koelsche C, Sahm F, Piro RM, Capper D, Reuss DE, Pusch S, Habel A, Meyer J, Göck T, Jones DT, Mawrin C, Schittenhelm J, Becker A, Heim S, Simon M, Herold-Mende C, Mechtersheimer G, Paulus W, König R, Wiestler OD, Pfister SM, von Deimling A. Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. Acta Neuropathol 2013; 125: 651-8.
[21] Amo-Takyi BK, Gunther K, Peters I, Mittermayer C, Eblenkamp M, Tietze L. Benign solitary fibrous pleural tumour. Evidence of primitive features and complex genomic imbalances, including loss of 20q. APMIS 2001; 109: 601-6.
[22] Ordonez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003; 27: 1031-51.
[23] Fetsch JF, Laskin WB, Michal M, Remotti F, Heffner D, Ellis G, Furlong M, Miettinen M. Ectopic hamartomatous thymoma: a clinicopathologic and immunohistochemical analysis of 21 cases with data supporting reclassification as a branchial anlage mixed tumor. Am J Surg Pathol 2004; 28: 1360-70.
[24] Kazakov DV, Mukensnabl P, Hes O, Michal M. 'Ectopic' ectopic hamartomatous thymoma. Histopathology 2004; 45: 202-4.
[25] Fargen KM, Opalach KJ, Wakefield D, Jacob RP, Yachnis AT, Lister JR. The central nervous system solitary fibrous tumor: a review of clinical, imaging and pathologic findings among all reported cases from 1996 to 2010. Clin Neurol Neurosurg 2011; 113: 703-10.
[26] Gold JS, Antonescu CR, Hajdu C, Ferrone CR, Hussain M, Lewis JJ, Brennan MF, Coit DG. Clinicopathologic correlates of solitary fibrous tumors. Cancer 2002; 94: 1057-68.