



Adenofibromatous Solitary Fibrous Tumor: An Unusual Morphologic Variant Occurring in the Sinonasal Tract

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Abstract

Background Solitary fibrous tumor can exhibit a broad morphologic spectrum, such as presence of epithelioid tumor cells, adipose cells and multinucleated giant cells. This report describes an unusual morphologic variant characterized by adenofibromatous features, all occurring in the sinonasal region.

Methods Four cases of the adenofibromatous variant of solitary fibrous tumor were retrieved from the surgical pathology and consultation files in Queen Elizabeth Hospital, Hong Kong. Histologic examination, immunohistochemical study and reverse-transcription polymerase chain reaction (RT-PCR) were performed.

Results The patients were adults who presented with an obstructive mass of the nasal septum, nasal cavity or nasolacrimal sac. Histologic examination showed a circumscribed biphasic tumor with intermingling of glandular structures and spindle cells, reminiscent of mammary fibroadenoma. Bland-looking spindle cells formed short, irregularly oriented fascicles, admixed with variable amount of collagen fibers. The glandular component comprised ducts and seromucinous acini with a lobular architecture, indicating that it represented exuberant hyperplasia of indigenous glands rather than part of the neoplastic process. Demonstration of CD34 and STAT6 immunoreactivity in the spindle cells and *NAB2::STAT6* gene fusion by polymerase chain reaction supports the diagnosis of solitary fibrous tumor.

Conclusion This study reports four cases of sinonasal solitary fibrous tumor with adenofibromatous features, furthermore expanding the morphologic spectrum of this tumor.

Keywords Adenofibromatous variant · Solitary fibrous tumor · Sinonasal tumor · STAT6

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Introduction

Solitary fibrous tumor is a mesenchymal tumor that has now been recognized in almost every anatomic site since its original description as a pleural tumor in 1931 by Klemperer and Rabin [1, 2]. Upon the theme of circumscribed growth, alternating hypercellular and hypocellular foci, patternless proliferation of spindle cells, collagenous stroma and pericytomatous blood vessels, the morphologic spectrum of this tumor type has expanded from the classical form (solitary fibrous tumor) and hypercellular form (so-called hemangiopericytoma) to encompass the epithelioid variant (with a component of epithelioid cells arranged in solid sheets) [3], fat-forming variant (with interspersed mature adipocytes) and giant cell-rich variant (formerly known as giant cell angiofibroma, with multinucleated cells which sometimes line pseudovascular spaces) [4, 5]. The distinctive genetic alteration of this tumor is inversion on chromosome 12q13 resulting in *NAB2::STAT6* gene fusion, leading

to overexpression of the C-terminal portion of *STAT6* [6, 7]. We herein describe an unusual morphologic variant of solitary fibrous tumor occurring in the sinonasal tract, characterized by biphasic morphology due to presence of a prominent adenomatoid component.

Materials and Methods

Four cases of the adenofibromatous variant of solitary fibrous tumor were studied, including two (cases 1 and 3) retrieved from the surgical pathology files of Queen Elizabeth Hospital, Hong Kong and two from the consultation files of the authors. Clinical and follow-up information were obtained from the hospital records or the referring pathologists. Four-micron-thick sections were cut from formalin-fixed, paraffin-embedded blocks and stained with hematoxylin and eosin for light microscopic examination. Immunohistochemical study was performed using automated immunostainers (BOND III, Leica Microsystems, Nussloch, Germany; or VENTANA Benchmark, Roche Diagnostics, Tucson, Arizona, USA) and the antibodies used are listed in Table 1.

Reverse-transcription polymerase chain reaction (RT-PCR) was performed to detect *NAB2::STAT6* fusion. Total RNA was extracted from paraffin sections and purified by

standard method. RT-PCR was performed using *NAB2* and *STAT6* gene-specific primers. PCR product bands were purified and subjected to DNA sequencing analysis. NCBI sequence NM_005967.3 (mRNA, *NAB2* gene) & NM_001178078.1 (mRNA, *STAT6* gene) were used as reference for analyses.

Results

Clinical Features

The clinical features are summarized in Table 2. The patients included three women and one man, aged 34 to 69 years (mean 52 years). They presented with obstructive mass lesions arising from the nasal septum ($n=2$), nasal cavity ($n=1$) or lacrimal sac ($n=1$), ranging from 1.5 to 4 cm in size. No recurrence was found after excision up to 7 years of follow up.

Pathologic Features

The tumors were firm, circumscribed, oval or bosselated with a smooth surface. The cut surfaces were whitish and homogeneous with scattered small cystic spaces.

Histologically, the tumor was well circumscribed and showed a fibroadenomatous architecture (Figs. 1, 2). The glandular component, constituting a prominent (cases 1, 2 and 4) to multifocal component (case 3), was represented by dilated to cystic ducts and hyperplastic seromucinous acini (Figs. 1A, B, 2B) which were found throughout or predominantly at the peripheral zone of the tumor. Lined by cuboidal to columnar cells with bland-looking nuclei (Fig. 2C), the ducts contained eosinophilic secretion and were surrounded by fibrous stroma. The seromucinous acini were arranged in discrete lobules or sometimes merged into the fibrocellular stroma. Focally, connection between the acini and ducts was discernible (Fig. 2A). In case 2, some glandular structures were lined by respiratory-type epithelium. There was no cytologic atypia or mitotic activity.

The mesenchymal component comprised spindle cells arranged in short, irregularly-oriented fascicles interspersed with collagenous to focally myxoid stroma. Keloid-like

Table 1 Antibodies used for immunohistochemical study

Antibody	Clone	Source	Dilution
STAT6	YE361 (RM)	Abcam	1:500
CD34	QBEnd10 (MM)	Dako	1:75
Pan-cytokeratin	MNF116 (MM)	Dako	1:500
Calponin	EP798Y (RM)	Thermo Scientific	1:300
P63	DAK-p63 (MM)	Dako	1:100
SMA	1A4 (MM)	Cell Marque	1:200
S100	Rabbit polyclonal antibody	Dako	1:4000
Ki67	SP6 (RM)	Thermo Scientific	1:200
Beta-catenin	14 (MM)	Cell Marque	1:1500

sma smooth muscle actin, *mm* mouse monoclonal antibody, *rm* rabbit monoclonal antibody

Table 2 Clinical features

Case	Sex/Age	Clinical features	Treatment	Outcome
1	F/67	2 cm mass in left nasal septum	Local excision	NED 7 years
2	F/34	4 cm polyp in left nasal cavity	Local excision	Lost to follow-up
3	M/39	1.5 cm mass in left nasolacrimal sac causing obstruction	Local excision	NED 5 years
4	F/69	1.5 cm polyp in right nasal septum	Local excision	NED 3 years

ned no evidence of disease

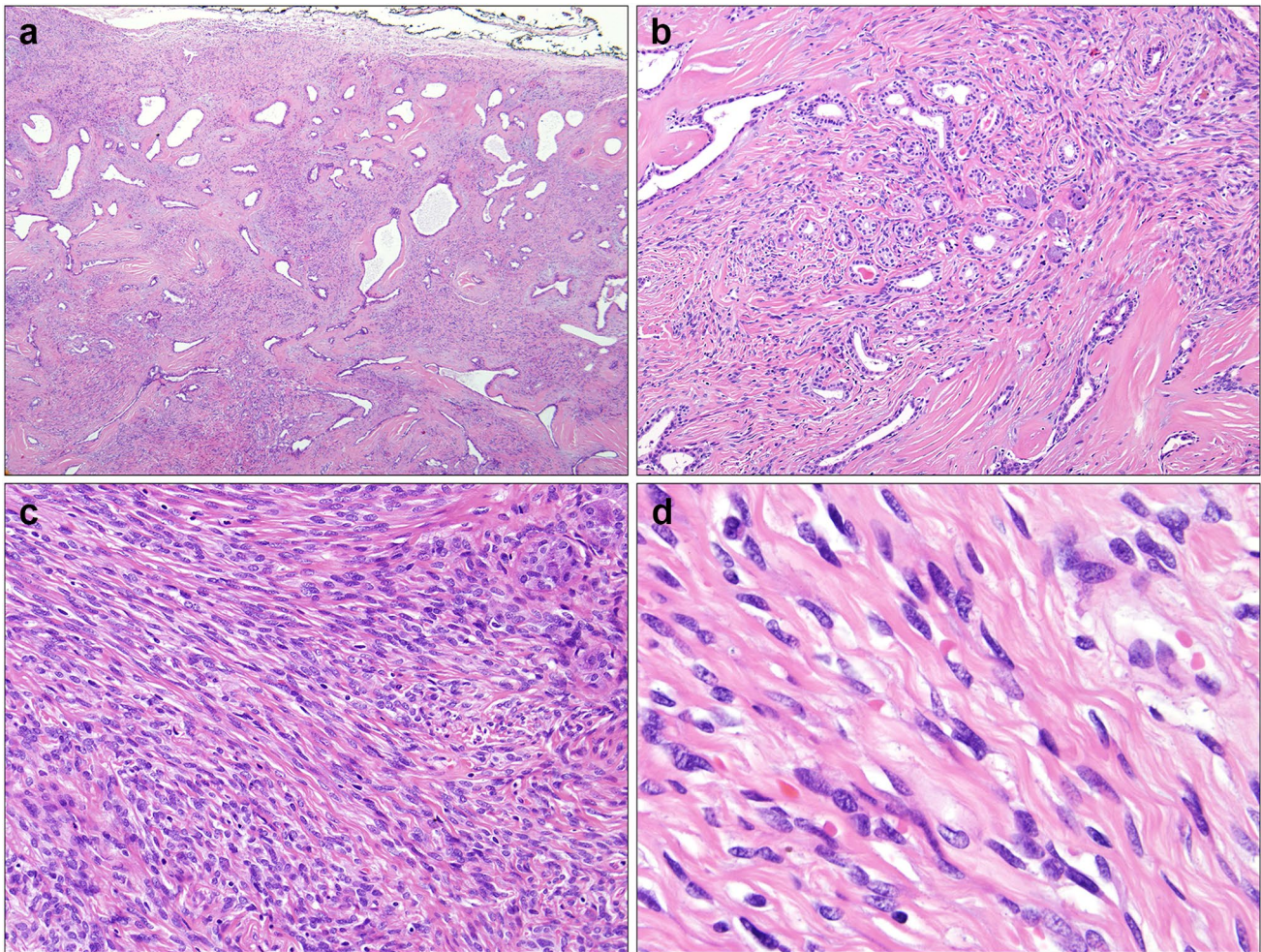


Fig. 1 Histological features of case 1 (Hematoxylin and eosin). **A** and **B** The biphasic tumor comprised variably dilated glands with preserved lobular architecture, intermingling with the spindle cell component. **C** and **D** The spindle cells were arranged in fascicles and

intimately associated with collagen fibers. They displayed elongated nuclei with even chromatin as well as indistinct cytoplasm. Features of the spindle cell component were those of an otherwise typical solitary fibrous tumor

collagen was readily seen. The spindle cells possessed elongated nuclei, fine chromatin, indistinct nucleoli, and imperceptible or ill-defined eosinophilic cytoplasm that appeared to merge with the collagenous stroma (Figs. 1C, D, 2D). The mitotic count was less than 1 per 10 high power fields, and there was no necrosis. No staghorn-shaped blood vessels were found.

Immunostaining showed that the epithelial cells were positive for cytokeratin (Fig. 3A) and negative for p63, SMA, S100, CD34 and STAT6. The myoepithelial/ basal cells around the acini and ducts were highlighted by p63 (Fig. 3B), SMA, and S100. In case 3, some ducts rimmed by p63-positive, SMA-negative basal cells were discernible, suggesting that larger excretory ducts were also entrapped within the tumor. The spindle cells showed diffuse and strong staining for CD34 (Fig. 3C) and STAT6 (Fig. 3D). They were negative for cytokeratin, S100, SMA and

calponin, and there was no nuclear staining for beta-catenin. The Ki67 proliferative index was less than 5%.

RT-PCR revealed *NAB2::STAT6* gene fusion in all cases. The breakpoint was identified between exon 4 of *NAB2* and exon 2 of *STAT6* for cases 1 and 2, and between exon 3 of *NAB2* and exon 18 of *STAT6* for case 3. For case 4, in addition to a major fusion transcript between exon 6 of *NAB2* and exon 17 of *STAT6*, there was a minor transcript joining exon 5 of *NAB2* and exon 19 of *STAT6*, with breakpoint located within exons.

Discussion

Sinonasal solitary fibrous tumor is uncommon, accounting for less than 0.1% of all sinonasal neoplasms. About 6% of the solitary fibrous tumors occur in the head and neck

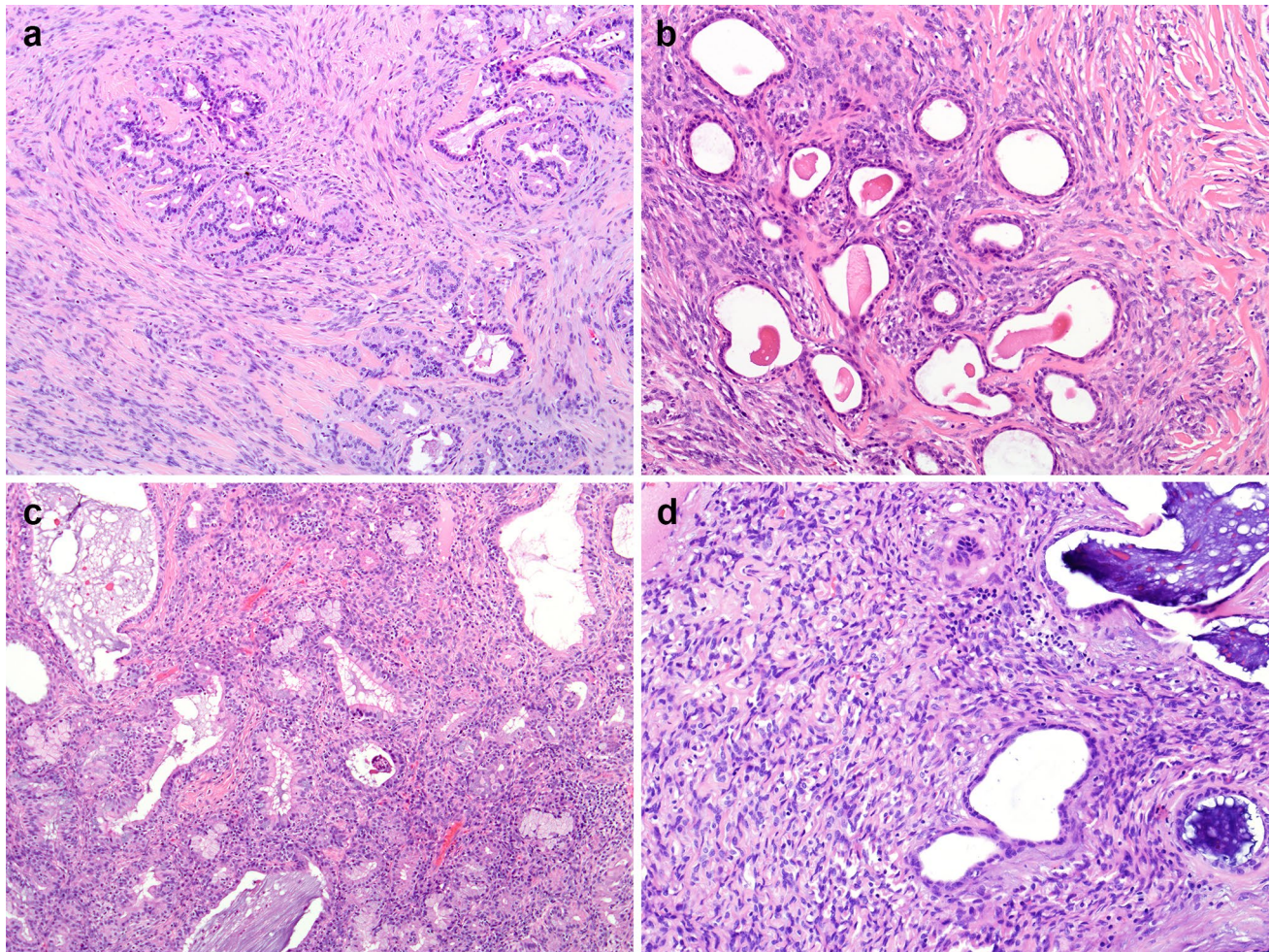


Fig. 2 Histological features of cases 2, 3, and 4 (Hematoxylin and eosin). **A** The glandular component displayed preserved lobular architecture and maintenance of the ductal-acinar organization (case 4). **B** Occasional glands were dilated (case 3). **C** The glands, which

included ducts and seromucinous acini, were lined by simple bland looking epithelium (case 2). **D** The spindle cells among the glands exhibited features of solitary fibrous tumor (case 2)

region, among which ~30% originate in the sinonasal tract [8]. The reported morphologic features of sinonasal solitary fibrous tumor are similar to those found in other parts of the body [9, 10]. In this series, we describe an unusual morphologic variant occurring in the sinonasal region characterized by the presence of a prominent intermingled glandular component, giving rise to a fibroadenomatoid pattern. The epithelial component features dilated ducts and hyperplastic acini which do not appear to be neoplastic because of preserved lobular architecture, maintenance of the ductal-acinar organization and luminal-abluminal cellular architecture, and lack of nuclear STAT6 staining. They most likely represent a hyperplastic process in response to the tumor, similar to that seen in granular cell tumor, which is commonly accompanied by striking mucosal epithelial hyperplasia [11, 12]. The morphologic features of the spindle cells are otherwise typical for solitary fibrous tumor, and the diagnosis is

confirmed by positive staining of CD34 and STAT6 and the presence of *NAB2::STAT6* gene fusion.

When solitary fibrous tumor occurs in glandular or epithelial tissues, the indigenous epithelial structures may be incorporated among the neoplastic spindle cells, as has been reported in the parotid gland in the form of acini and ducts in the peripheral portion of the tumor [13] and in the lung in the form of attenuated epithelial structures giving rise to a peculiar biphasic morphology described as “pseudopapillary variant” [14] or “pulmonary adenofibroma” [15]. For solitary fibrous tumor occurring in the sinonasal tract, cystic dilatation of entrapped glands and ducts has been briefly described by Smith et al. [8], and a similar case is recently reported by Baneckova et al. as an example of “solitary fibrous tumor with deceptive morphologic features” [16]. In the current series, the indigenous minor salivary acini, ducts and surface respiratory

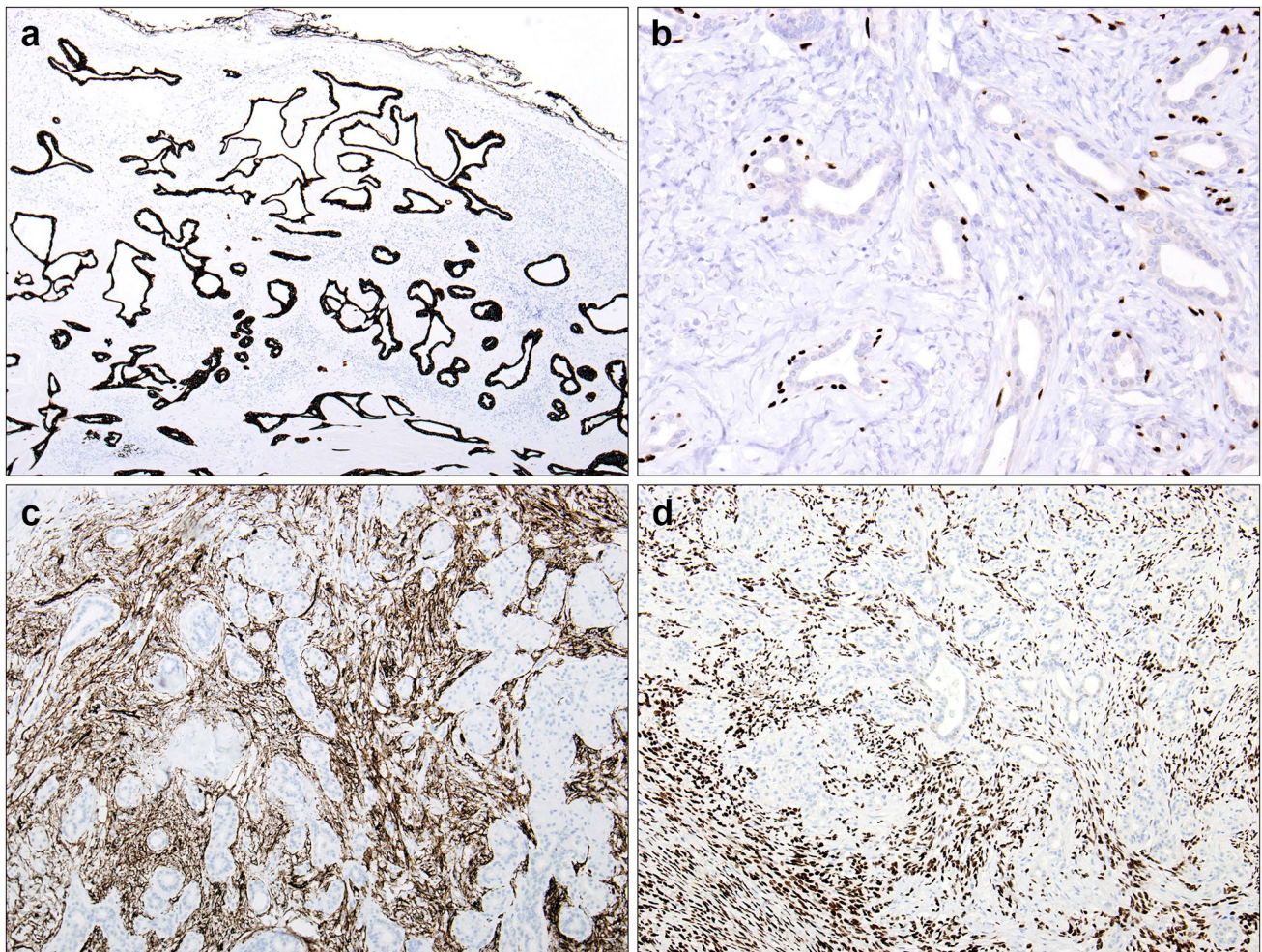


Fig. 3 Immunohistochemical profile of case 1. **A** The glands were lined by pan-cytokeratin-positive epithelial cells. **B** The epithelial cells were rimmed by p63-positive myoepithelial/ basal cells. The spindle cells were negative for both cytokeratin and p63. **C** and **D**

Staining for CD34 and STAT6 respectively, showing diffuse strong positivity in the spindle cells. The glandular component was negative for both markers

epithelium of the sinonasal tract undergo exuberant hyperplasia within the solitary fibrous tumor, resulting in a biphasic appearance that can evoke wide differential diagnoses. Respiratory epithelial adenomatoid hamartoma comprises hamartomatous proliferation of glands in a hypocellular fibrous stroma which should lack STAT6 immunostaining. In contrast to seromucinous hamartoma in which myoepithelial/ basal cells around small glands are absent or at most focal, the hyperplastic acini and ducts entrapped within the solitary fibrous tumors in our case series are all rimmed by myoepithelial/ basal cells; seromucinous hamartoma also lacks a STAT6-positive cellular spindle cell component, unless it occurs in combination with a solitary fibrous tumor. Pleomorphic adenoma features proliferation of glandular structures comprising epithelial and myoepithelial cells, and the latter may appear as fascicles of spindle cells; however, the classic

chondromyxoid stroma and immunopositivity of the spindle cells for myoepithelial markers are not seen in solitary fibrous tumor. While biphenotypic sinonasal sarcoma is commonly accompanied by proliferation and invagination of the covering epithelium [17], the collagen matrix accompanying the spindle cells is often less striking than that in solitary fibrous tumor; the spindle cells are characteristically positive for myogenic markers, S100 protein and PAX3 while being negative for STAT6. In biphasic synovial sarcoma, the epithelial component represents part of the neoplastic population which lacks ductal-acinar organization, and the tumor cells show immunoreactivity to SS18-SSX fusion-specific antibody while being negative for STAT6. The most important features suggesting the non-neoplastic nature of the glandular proliferation in adenofibromatous solitary fibrous tumor are the preserved lobular architecture and dual cell-layered composition.

The adenofibromatous variant can be distinguished from the rare solitary fibrous tumors with transdifferentiation by the lack of malignant cytologic features in the glandular component [16].

The potential correlation between specific *NAB2::STAT6* fusion variants and clinicopathological features has been explored by multiple previous studies. Most of the fusion variants belong to either *STAT6*-full or *STAT6-ΔDBD* type (i.e., fusion of any region of *NAB2* with 5' or 3' site of *STAT6* respectively), as proposed by Yuzawa et al. [18]. Many studies reported propensity for younger age, extra-thoracic location, smaller size, malignant histology and increased mitoses in *STAT6-ΔDBD* compared with *STAT6*-full tumors, yet data on prognostic implication have been conflicting [18–25]. In our series, the fusion variants in cases 1 and 2 were of *STAT6*-full type, while those in cases 3 and 4 belonged to *STAT6-ΔDBD* type. Thus the presence of adenofibromatoid features was common to tumors harboring both types of fusion variants.

In summary, we describe an unusual morphologic variant of solitary fibrous tumor in the sinonasal region characterized by intratumoral exuberant proliferation of indigenous glands. Awareness of this variant and use of appropriate immunostaining will aid in diagnosis. It is likely that solitary fibrous tumor occurring in other relatively enclosed anatomic sites with indigenous mucosal glands, such as the salivary glands, oral cavity, tracheobronchial mucosa or lacrimal gland, may potentially exhibit this variant morphology, as exemplified by a reported case in the lacrimal gland [26].

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Data Availability The data analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

Results of Studies Involving Humans and/or Animals Not applicable.

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