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ORIGINAL PAPER

Thyroid Gland Solitary Fibrous Tumor: Report of 3 Cases and a Comprehensive Review of the Literature

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Abstract

Solitary fibrous tumors of the thyroid gland are exceptionally rare. In order to further characterize the clinical and pathologic features of solitary fibrous tumor arising at this anatomic site, three cases of thyroid gland solitary fibrous tumor were analyzed in conjunction with 35 cases compiled from the English literature. Thyroid gland solitary fibrous tumors showed an equal sex distribution with a mean age at presentation of 54.4 years (range, 28–88 years). The patients typically presented with an asymptomatic, slow growing neck mass. Microscopically, the tumors were characterized by cytologically bland spindle cells with patternless growth, hypocellular and hypercellular areas, variable amounts of collagen, and ectatic, branching blood vessels. Two previous reported tumors were considered to be histologically malignant on the basis of increased mitotic activity, profound pleomorphism and tumor necrosis. Immunohistochemically, the tumor cells are variably positive with CD34, bcl-2, and CD99. STAT6 immunohistochemistry, performed on the current cases, demonstrated a strong, diffuse nuclear expression in all tumors. Among 26 patients with available follow up data (mean 47.3 months), one developed local recurrence and distant metastasis. Solitary fibrous tumors occurring in the thyroid gland are uncommon, but can be reliably diagnosed based on the presence of characteristic morphologic features as well as immunohistochemical expression of STAT6 and CD34. The majority of thyroid gland solitary fibrous tumors have exhibited an indolent clinical course, however experience is limited. The rare potential for aggressive clinical behavior requires clinical surveillance.

Keywords Solitary fibrous tumors · Thyroid gland · Immunohistochemistry · STAT6 · Neoplasms, vascular tissue · Follow-up studies

Introduction

Solitary fibrous tumor is an uncommon fibroblastic neoplasm that develops in a wide variety of anatomic sites. The tumor has a characteristic morphologic appearance of cytologically bland spindle cells haphazardly distributed within a collagenous stroma, variable cellularity, and prominent branching vessels. Solitary fibrous tumors have recently been further defined at the genetic level by the *NAB2-STAT6* gene fusion, corresponding to nuclear expression of the STAT6 protein [1–3]. Immunohistochemical detection of STAT6 has been shown to be highly sensitive and specific for the presence of the *NAB2-STAT6* gene fusion product, and STAT6 has become an effective immunohistochemical marker for confirming the diagnosis of solitary fibrous tumor [4–8].

Solitary fibrous tumors are well described in the head and neck region with most preferentially involving the sinonasal tract, orbit, and oral cavity [9–15]. By contrast, thyroid gland tumors are exceptional [9, 16–39]. Among prior published series of head and neck solitary fibrous tumors, only two examples of solitary fibrous tumor arising in the thyroid gland have been reported [9, 15], representing less than 1% of all solitary fibrous tumors affecting this anatomic region [10–14]. Thyroid gland solitary fibrous tumors may present a diagnostic challenge and there is limited data regarding the biologic potential of these tumors. In order to augment the present understanding of this rare tumor of the thyroid gland,

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the clinical and pathologic features of three new cases of thyroid gland solitary fibrous tumor confirmed with STAT6 immunohistochemistry were assessed along with an analysis of cases previously reported.

Materials and Methods

Three cases of solitary fibrous tumor involving the thyroid gland were identified from the files of the departments of pathology within Southern California Permanente Medical Group and Johns Hopkins Hospital between June 2007 and 2017. Hematoxylin and eosin stained slides from all cases along with previously performed immunohistochemical stains were reviewed. Additional immunohistochemical studies were performed on the cases using a monoclonal antibody directed against STAT6 (clone EP325; Cell Marque; Rocklin, California) utilizing standard techniques. Clinical data, treatment, and follow up information were obtained from electronic medical records augmented by the surgical pathology reports. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of an internal review board authorization (#5968) performed under the direction of Southern California Permanente Medical Group. A review of the English literature based on a PubMed search from 1966 to 2018 was performed and all cases of thyroid gland solitary fibrous tumor were reviewed.

Results

Clinical Features

The clinical features of the three cases of solitary fibrous tumor arising in the thyroid gland are summarized in Table 1. The patients included two females and one male with ages ranging from 44 to 52 years, with a mean age at presentation of 47 years. Two patients presented with a painless anterior neck mass or swelling. In one patient a palpable thyroid nodule was detected incidentally during routine physical examination. Various serum thyroid function tests (thyroid-stimulating hormone [TSH], triiodothyronine [T3], free thyroxine [T4], and thyroperoxidase [TPO] antibodies) were evaluated in two patients, with levels found to be within normal limits. Preoperative fine needle aspiration was performed in two patients. One specimen showed cytologically bland spindle cells, while the other was reported as non-diagnostic due to insufficient cellularity.

Pathologic Features

On gross examination, the tumors were well circumscribed and limited to the thyroid gland, with firm, yellow–white cut surfaces. All tumors were localized to one lobe of the thyroid gland and ranged from 7.0 to 8.2 cm in greatest dimension (mean, 7.4 cm; median, 7.0).

The three tumors exhibited similar histologic features. The tumors were well encapsulated and composed of a highly cellular, patternless proliferation of spindled cells with alternating hypo- and hypercellular areas (Figs. 1, 2). The lesional cells had a syncytial appearance with indistinct cell borders and cytologically bland, ovoid nuclei with scant cytoplasm (Fig. 3). Prominent, ectatic, branching, thin walled vessels were observed throughout. Hypocellular areas were composed predominantly of sclerotic fibrous tissue and thick bands of hyalinized collagen with rare spindle cells (Fig. 3). Present within areas of the tumors were entrapped colloid filled follicles of different sizes. There was no evidence of cellular pleomorphism or necrosis. Rare mitotic

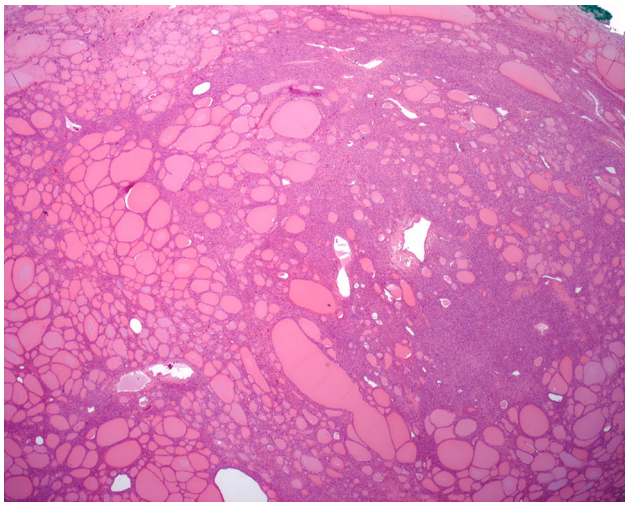

Fig. 1 Low power of a thyroid gland solitary fibrous tumor composed of spindled cells dissecting between thyroid gland follicles

Table 1 Clinicopathologic features of three cases of thyroid gland solitary fibrous tumor

Case no.	Age (in years)	Sex	Clinical presentation	Size (cm)	Treatment	Follow-up (months)
1	44	Female	Slow growing neck mass	7.0	Lobectomy	Alive, no evidence of disease, 41 months
2	45	Female	Neck swelling	8.2	Lobectomy	Alive, no evidence of disease, 28 months
3	52	Male	Incidental finding	7.0	Lobectomy	Alive, no evidence of disease, 5 months

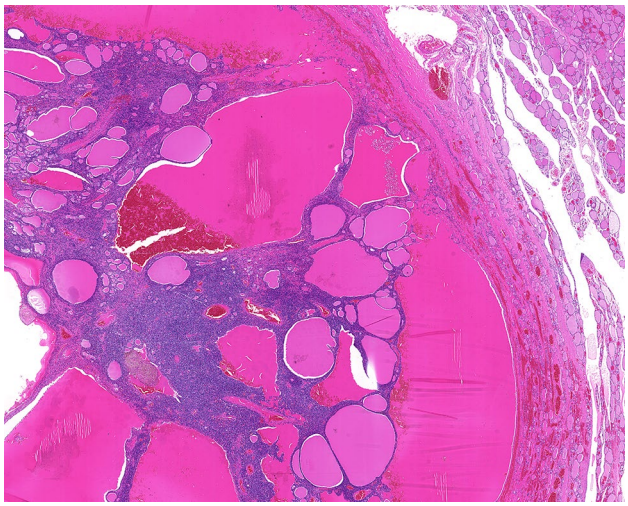

Fig. 2 This solitary fibrous tumor is quite cystic, with easily identified colloid between the spindled cells

figures were present (up to two mitoses per 5 mm^2) in one tumor, while the remaining tumors showed inconspicuous mitoses.

Immunohistochemical markers previously performed at the time of initial diagnoses were reviewed. The tumors were positive for CD34 (2/3; Fig. 4), bcl-2 (3/3; Fig. 4), and CD99 (1/2). Immunohistochemical analysis revealed strong and diffuse nuclear expression of STAT6 in all three cases (Fig. 4). The lesional spindle cells were negative for keratin (0/2), smooth muscle actin (0/1), desmin (0/1), thyroglobulin (0/2), TTF-1 (0/2), and calcitonin (0/2).

Treatment and Follow-Up

All of the tumors were removed by thyroid gland lobectomy without additional treatment. Clinical follow up was available for all patients with a mean duration of 24.7 months (range 5–41 months). None of the patients developed local recurrence or metastasis and all were alive with no evidence of disease at last follow-up.

Discussion

Solitary fibrous tumors have been described in a wide variety of anatomic sites, although only rarely reported to develop in the thyroid gland. Combining the cases in the present study with those previously described in the literature yields 38 examples of thyroid gland solitary fibrous tumor, the clinicopathologic features of which are summarized in Table 2 [9, 16–39]. Solitary fibrous tumor of the thyroid gland affects the sexes at an equal frequency, similar to the equal sex distribution of solitary fibrous tumor observed in other anatomic sites. Most patients are middle aged adults (mean 54.4 years; range 28–88 years). Thyroid gland solitary fibrous tumor typically presents clinically as a painless neck mass or swelling, commonly associated with a history of slow growth and present for an extended period of time. Rarely, the tumor may extend inferiorly from the thyroid gland and present as a mediastinal goiter/mass [30, 37]. While most patients are asymptomatic, uncommonly the tumor can compress the adjacent esophagus or trachea resulting in dyspnea, dysphagia, or hoarseness [27, 30, 33, 35–38]. Patients are euthyroid, with thyroid function tests within normal limits [20, 21, 24, 25, 29, 31–38]. Preoperative diagnosis of solitary fibrous tumor affecting the thyroid gland by fine needle aspiration is exceedingly difficult, as aspirates are generally non diagnostic due to low cellularity [17, 25, 27, 28, 31, 32, 38]. On occasion, bland spindle cells devoid of cytoplasm and fragments of collagenized stroma may be obtained, which may suggest the diagnosis [18, 26, 34, 36].

On gross examination, thyroid gland solitary fibrous tumor appears as a firm, well circumscribed mass with a fibrous white to tan cut surface, sometimes with cystic spaces. Tumor size is variable, ranging from 1.7 to 13.8 cm (mean 5.7 cm). The histologic features of solitary fibrous tumors of the thyroid gland are comparable to their counterparts in other anatomic locations. Tumors are variably cellular, comprised of cytologically bland, uniform spindle cells with scant cytoplasm with a haphazard or patternless distribution in a collagenous stroma with numerous branching ectatic vessels. Entrapped non-neoplastic thyroid gland follicles are frequently observed within the tumor. The intimate association is not a destructive invasion, but rather a merging or blending of the components. Histologic variants of solitary fibrous tumor include the fat-forming (lipomatous), myxoid and giant cell rich types. The former contains areas of mature adipose tissue, and has been described in two instances in the thyroid gland [19, 29]. The myxoid and giant cell rich variants of solitary fibrous tumor have not yet been reported at this site.

By immunohistochemistry, solitary fibrous tumors are consistently positive for STAT6 protein in a nuclear distribution, reflecting the presence of the *NAB2-STAT6* gene fusion characteristic of these neoplasms. STAT6 is currently the most sensitive and specific marker for establishing a diagnosis of solitary fibrous tumor [4–8]. Only strong and diffuse nuclear expression should be considered positive, as focal weak nuclear and cytoplasmic staining can be occasionally observed in neoplasms other than solitary fibrous tumor [4–6]. Solitary fibrous tumors also frequently coexpress CD34, bcl-2, and CD99, although these markers are not specific and are frequently expressed by other mesenchymal neoplasms. In general, solitary fibrous tumors are negative for keratins, actins, desmin, and S-100

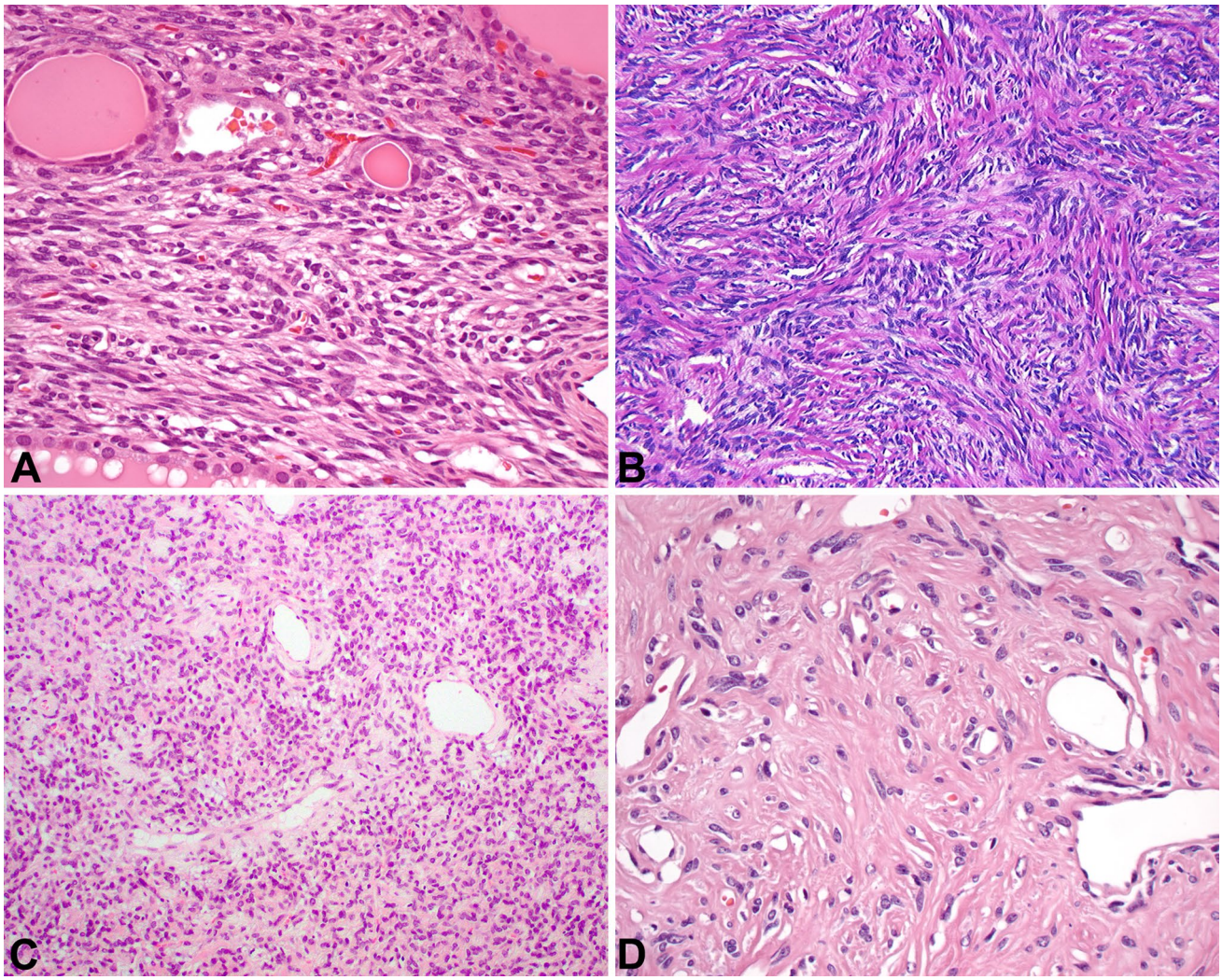

Fig. 3 The cellularity of thyroid gland solitary fibrous tumor is quite variable: **a** Thyroid gland follicles are noted admixed with the spindled cells. **b** A storiform pattern is present in this tumor. **c** The spindled cells are quite short in this tumor, with easily identified vessels. **d** This tumor is hypocellular, with more abundant collagen identified. Patulous vessels are present

protein. In the context of the thyroid gland, solitary fibrous tumors have been shown to lack expression of thyroglobulin, TTF-1, calcitonin, chromogranin, and synaptophysin [20, 22–29, 31, 32, 34, 36, 37, 39].

The histologic differential diagnosis of thyroid gland solitary fibrous tumor includes a variety of other spindle cell lesions which may affect this site. Several epithelial neoplasms of the thyroid gland may assume a spindled appearance and should be distinguished from solitary fibrous tumor. Follicular epithelium derived tumors including follicular adenoma, follicular carcinoma, and papillary carcinoma can occasionally exhibit a predominant component of cytologically bland spindle cells. These cells are thought to be metaplastic in nature and can be differentiated from solitary fibrous tumor by immunohistochemical positivity for keratin, thyroglobulin, and TTF-1, along with a lack of expression for CD34 and STAT6 [40–42].

Papillary carcinoma with desmoid-type fibromatosis, formerly papillary carcinoma with nodular fasciitis-like stroma, also features a prominent spindle cell component [43, 44]. The spindle cells are typically arranged in interlacing fascicles within a collagenous matrix, which can impart an appearance resembling solitary fibrous tumor, particularly in instances when the epithelial component of the tumor is inconspicuous. Entrapped follicles can be observed in thyroid gland solitary fibrous tumors, but the follicular cells lack the characteristic nuclear features of papillary carcinoma. The spindle cells of papillary carcinoma with desmoid-type fibromatosis, as the name of the tumor suggests, characteristically exhibit nuclear and cytoplasmic expression with

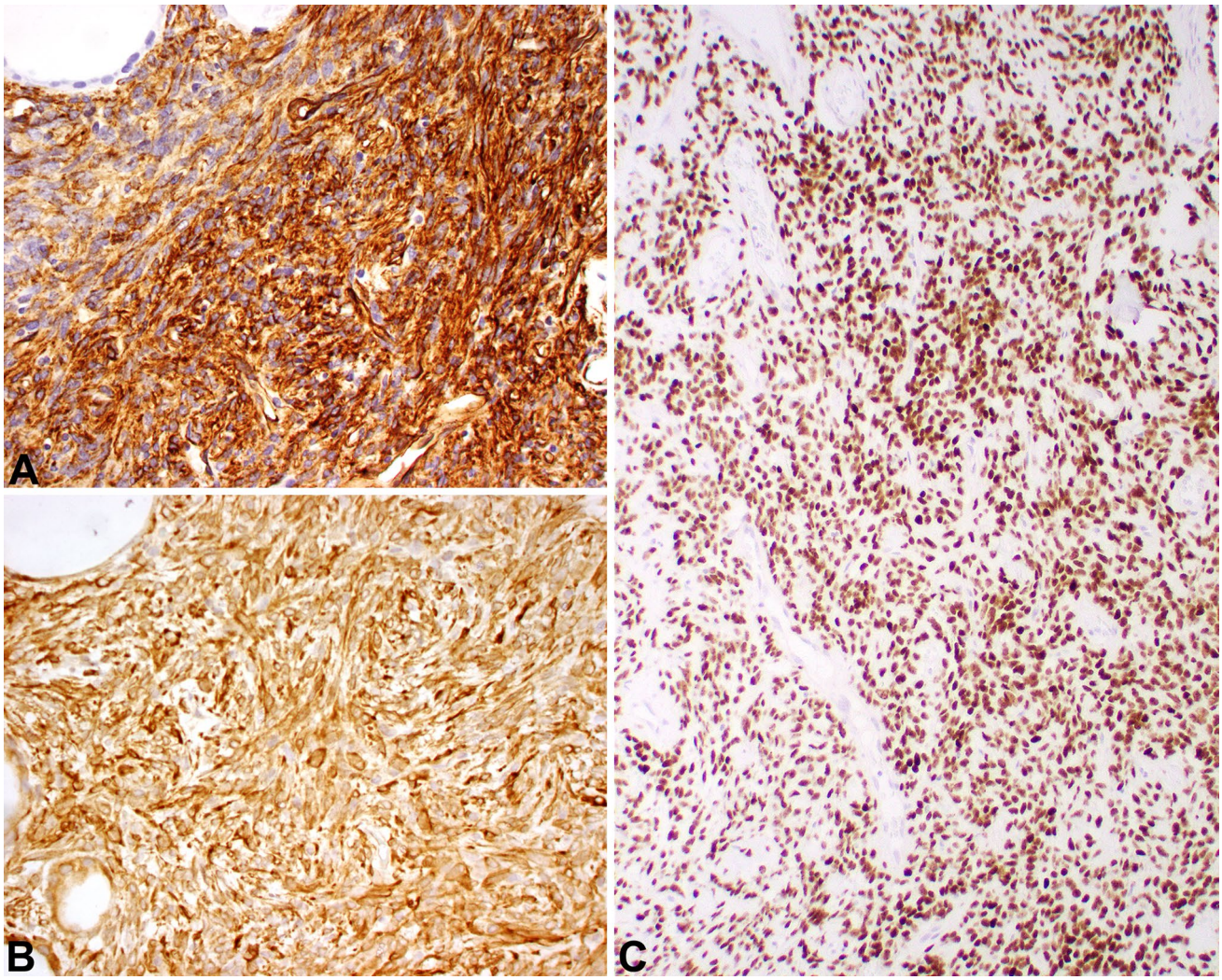

Fig. 4 The neoplastic cells show a strong and diffuse reaction with **a** CD34 (cytoplasmic), **b** bcl-2 (cytoplasmic), and **c** STAT6 (nuclear)

β-catenin similar to desmoid-type fibromatosis of soft tissue. It should be noted, however, that nuclear β-catenin expression has also been observed in some solitary fibrous tumors [45, 46], so the presence of β-catenin immunoreactivity has limited value in differentiating between these lesions. Unlike solitary fibrous tumor, the stromal component of papillary carcinoma with desmoid-type fibromatosis is positive for smooth muscle actin and negative with CD34.

The paucicellular variant of undifferentiated (anaplastic) thyroid carcinoma is characterized by mildly atypical spindle cells in a sclerotic stromal background that can morphologically resemble solitary fibrous tumor [47, 48]. Pancytokeratin, EMA and PAX8 positivity, if present, supports a diagnosis of undifferentiated carcinoma and can help to distinguish between these two entities. Clinically, a rapidly enlarging neck mass would also favor a diagnosis of undifferentiated carcinoma, as solitary fibrous tumors of the thyroid are typically slow growing lesions.

Constituent tumor cells of medullary thyroid carcinoma can be spindled, but unlike solitary fibrous tumor, are immunoreactive for keratin, calcitonin, and neuroendocrine markers such as chromogranin and synaptophysin. Spindle epithelial tumor with thymus-like differentiation (SETTLE) most commonly has a biphasic appearance comprised of spindle cells admixed with tubulopapillary or glandular structures; however the monophasic variant, composed predominantly of spindle cells, can be potentially mistaken for solitary fibrous tumor [49, 50]. SETTLE affects primarily children, adolescents, and young adults while thyroid gland solitary fibrous tumor typically occurs in middle age adults. The spindle cells of SETTLE may show CD99 and bcl-2 expression, but unlike solitary fibrous tumor, are strongly keratin positive and negative for CD34 and STAT6 [51].

Spindle cell mesenchymal neoplasms are perhaps the lesions most likely to be confused with solitary fibrous tumor. The main considerations in the differential diagnosis

Table 2 Literature summary and current cases of thyroid gland solitary fibrous tumor

Characteristics*	Number (n = 38)
Sex	
Female	19
Male	19
Age (in years)	
Range	28–88
Mean	54.4
Symptom duration (in months)	
Range	1–120
Mean	21.4
Clinical presentation	
Neck mass/swelling	36
Mediastinal mass	2
Dyspnea	4
Dysphagia	2
Hoarseness	2
Laterality	
Right	17
Left	17
Not reported	4
Tumor size (cm)	
Range	1.7–13.8
Mean	5.7
Patients with follow up (n = 26)	
Alive, no evidence of disease	25
Alive, with disease	1
Patients with recurrence or metastasis	1
Follow up (months)	
Range	5–252
Mean	47.3

*Not stated in all cases

would include smooth muscle tumors, peripheral nerve sheath tumors, and monophasic synovial sarcoma. All have been reported to occur in the thyroid gland, but similar to solitary fibrous tumor, are exceedingly rare [52–55]. Among documented primary smooth muscle tumors of the thyroid gland, most are leiomyosarcomas [52]. Morphologically, smooth muscle tumors have a more uniformly cellular appearance comprised of intersecting fascicles of spindle cells with blunt ended nuclei, and lack the branching vasculature of solitary fibrous tumor. Immunohistochemically, smooth muscle tumors can be distinguished from solitary fibrous tumor by positivity for smooth muscle actin and desmin and absence of expression of CD34 and STAT6.

Peripheral nerve sheath tumors may also be considered in the differential diagnosis of solitary fibrous tumor. Schwannomas, neurofibromas, and malignant peripheral sheath tumors may involve the thyroid gland [53, 54], though among the various nerve sheath tumors, schwannomas have been the most frequently reported at this site and are the most likely to be mistaken for solitary fibrous tumor due to their variable cellularity, frequently hyalinized stroma, and prominent blood vessels. Peripheral nerve sheath tumors can be distinguished from solitary fibrous tumor by expression of S-100 protein and SOX10, though malignant peripheral nerve sheath tumors are less consistently positive for these markers when compared to their benign counterparts. Benign and malignant peripheral nerve sheath tumors lack STAT6 expression.

Monophasic synovial sarcoma typically has a cellular, homogeneous appearance composed of uniform spindle cells arranged in sheets and fascicles, though not uncommonly may contain thick collagen bands, areas of dense hyalinizing fibrosis, and dilated, branching, thin walled vessels similar to solitary fibrous tumor. Unlike solitary fibrous tumor, synovial sarcoma usually shows some degree of keratin and EMA positivity, usually shows a strong nuclear TLE1 reaction while lacking CD34 and STAT6 expression.

Complete surgical excision is the treatment of choice for solitary fibrous tumors of the thyroid gland. Adjuvant therapies in addition to surgery have not been employed in the management of solitary fibrous tumors at this site. In general, solitary fibrous tumors are regarded as biologically indolent neoplasms with the capacity for local recurrence and rarely metastasis. Histologic features of malignancy, as defined by the World Health Organization, include the presence of hypercellularity, increased mitoses (> 4 mitoses per 2 mm^2), cytologic atypia, tumor necrosis, and/or infiltrative margins [56]. However, the clinical behavior of solitary fibrous tumors remains difficult to predict based solely on histologic parameters, as evidenced by a recent large single institution study demonstrating histologically benign tumors to have a similar potential for recurrence and disease specific death as those tumors classified as histologically malignant [57]. Several risk stratification models based on combining factors such as patient age, tumor size, mitotic count, cellularity, pleomorphism, tumor necrosis, and tumor site have been proposed as a means of predicting clinical outcome in patients with solitary fibrous tumor [58–60]. Due to their rarity, the various study cohorts used to generate these prognostic models likely did not include solitary fibrous tumors from the thyroid gland. Consequently, whether these models are applicable to thyroid gland solitary fibrous tumors remains unknown.

Thyroid gland solitary fibrous tumors appear to be associated with a favorable prognosis. Among 26 cases with follow up data, an adverse outcome was observed in only one patient who developed disease recurrence and distant metastasis [38]. This patient had a histologically malignant solitary fibrous tumor characterized by increased mitotic activity, high cellularity, and foci of necrosis, and suffered

from local recurrence at 5 months and pulmonary metastases at 6 months. One additional malignant example of thyroid gland solitary fibrous tumor has been reported, showing six mitoses per ten high power fields and tumor necrosis; however, no clinical follow up information was included [35]. Although most thyroid gland solitary fibrous tumors have behaved in a benign fashion, it should be recognized that follow up durations have been relatively short (mean 47.3 months). Evidence from other anatomic sites has shown solitary fibrous tumors to have a protracted natural history with late recurrences and metastases not infrequently occurring after 5 years [57, 58]. Finally, *TERT* promoter mutations may be associated with poor prognosis in other anatomic sites, thus as risk stratification schemes develop, *TERT* status may be considered useful [61, 62]. As such, long term surveillance of patients with solitary fibrous tumor of the thyroid gland seems prudent.

In summary, thyroid gland solitary fibrous tumor is rare. Solitary fibrous tumors at this site arise most commonly in middle aged adults and affect both sexes equally. Patients typically present with a slowly growing neck mass. The histologic appearance of solitary fibrous tumor can create a diagnostic challenge as spindle cell lesions are infrequently encountered in the thyroid gland. Immunohistochemical analysis can assist in separating solitary fibrous tumor from other thyroid gland spindle cell tumors in the differential diagnosis. Nuclear expression of STAT6, in particular, allows for reliable confirmation of a diagnosis of solitary fibrous tumor. Although experience is limited, thyroid gland solitary fibrous tumors appear to be associated with a good prognosis, with only one reported case exhibiting a biologically aggressive clinical course. As with solitary fibrous tumors at other anatomic sites, solitary fibrous tumors of the thyroid gland require long term clinical monitoring.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest as it relates to this research project.

Ethical Approval All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent.

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