

Re: 53185

Le Zhang

Editor

World Journal of Clinical Cases

Dear Le Zhang,

We thank the editorial board for the comments about our manuscript (53185) entitled “Extrapleural solitary fibrous tumor of the thyroid gland: A case report and literature review”.

The manuscript has been thoroughly revised according to the reviewer’s comments.

We look forward to hearing your positive response to this revised manuscript.

Below are the answers to the reviewer’s comments.

Reviewer’s comments:

*The authors report a case of thyroid SFT with a comprehensive literature review. The paper is generally well-written with a good command of English. It is true that thyroid SFTs are relatively rare; but since there have been a number of reports of such neoplasms, there have to be some ‘charming points’ for this paper to be made open to the public. I have a few points of concern about this paper. If the authors can address the following points, I believe, this paper will surely enhance its scientific value.*

**1. It is strange that this paper does not mention a word about ‘STAT6’ or ‘NAB2-STAT6**

*fusion'. NAB2-STAT6 fusion is now considered the pathognomonic genetic alteration of SFTs, and to detect it is crucial for the definite diagnosis of SFTs.*

**Answer:**

The paragraph about STAT6 or NAB2-STAT6 fusion has been added to Discussion.

A gene fusion between NAB2 and STAT6 on chromosome 12q13 has been recently identified to be the pathognomonic molecular aberration in SFT[23]. NAB2 is a repressor of EGR1 target genes. EGR1 is a transcription factor that couples growth factor signaling with the induction of nuclear programs of cellular proliferation and differentiation. The NAB2 fusion gains an activation domain from STAT6, which converts NAB2 into a potent transcriptional activator of EGR1. This leads to constitutive activation of EGR-mediated transcription that drives neoplastic progression. The protein STAT6 detectable by immunohistochemistry, is shown to be a reliable marker for the NAB2-STAT6 gene fusion[24,25]. STAT6 immunohistochemistry is a highly sensitive and specific diagnostic marker for SFT[26,27]. Even in our case, STAT6 immunohistochemistry showed the diffuse strong nuclear positivity. This testing can be considered as an invaluable adjunct in the diagnosis of SFT.

23. **Robinson DR**, Wu YM, Kalyana-Sundaram S, Cao X, Lonigro RJ, Sung YS, Chen CL, Zhang L, Wang R, Su F, Iyer MK, Roychowdhury S, Siddiqui J, Pienta KJ, Kunju LP, Talpaz M, Mosquera JM, Singer S, Schuetze SM, Antonescu CR, Chinnaiyan AM. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. *Nat Genet.* 2013;**45**:180–185.
24. **Doyle LA**, Vivero M, Fletcher CD, Mertens F, Hornick JL. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. *Mod Pathol.* 2014;**27**:390–395.
25. **Barthelmeß S**, Geddert H, Boltze C, Moskalev EA, Bieg M, Sirbu H, Brors B,

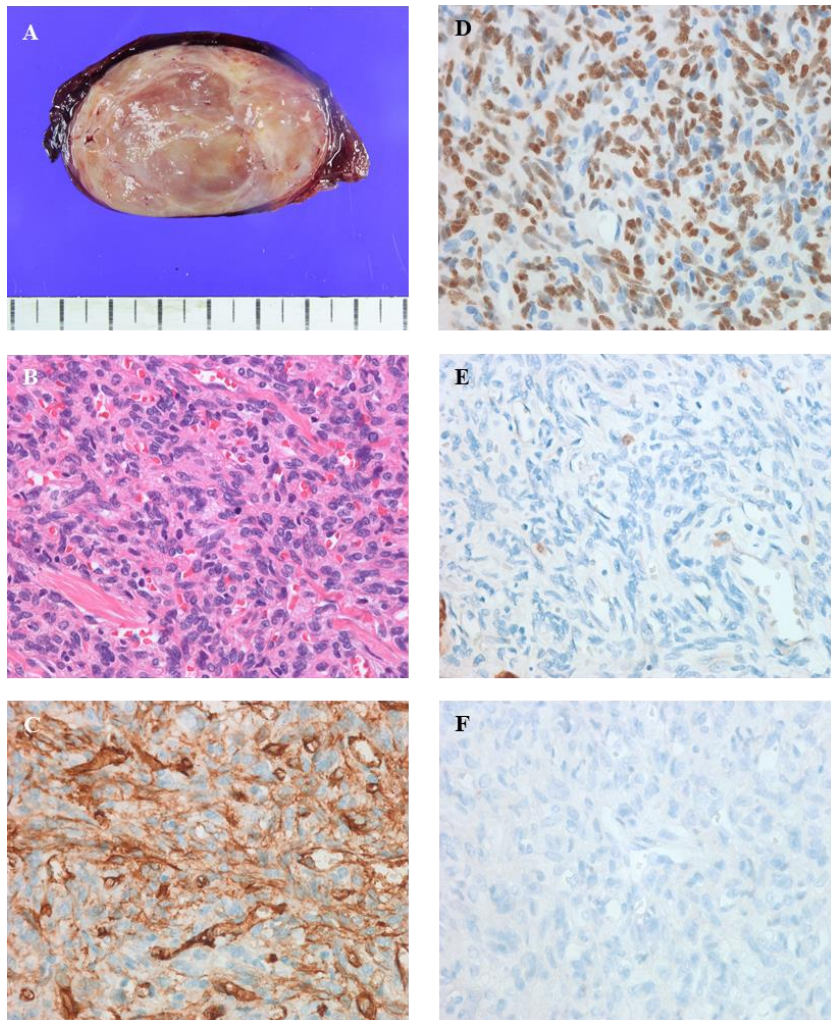
- Wiemann S, Hartmann A, Agaimy A, Haller F. Solitary fibrous tumors/hemangiopericytomas with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. *Am J Pathol*. 2014;**184**:1209-1218.
26. **Yoshida A**, Tsuta K, Ohno 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**:552–529.
27. **Cheah AL**, Billings SD, Goldblum JR, Carver P, Tanas MZ, Rubin BP. STAT6 rabbit monoclonal antibody is a robust diagnostic tool for the distinction of solitary fibrous tumour from its mimics. *Pathology*. 2014;**46**:389–395.

*2. STAT6-immunohistochemistry is an easy-to-perform, and yet a reliable method that reflects NAB2-STAT6 fusion; the nuclear expression of STAT6 is a reflection of this genetic alteration. So it is mandatory to show either STAT6-immunohistochemistry or genetic analyses of NAB2-STAT6 for this case as well, particularly because we are given a number of thyroid SFTs. The authors report CD34-positivity in this case, but that CD34 is positive is not specific to SFTs at all. But nuclear expression of STAT6 is completely specific to SFTs. Please show the results of these analyses with an appropriate presentation of them (photos, figures, etc.).*

**Answer:**

The histologic photograph immunohistochemically stained by STAT6 has been added in **Figure 3**.

**Figure 3** Histology of a surgical specimen examined under light microscope (LM). A: Gross image; B: Hematoxylin and eosin staining (LM,  $\times 40$ ); C: *CD34* (LM,  $\times 400$ ); D: **STAT6** (LM,  $\times 400$ ); E: *CK* (LM,  $\times 400$ ); F: *TTF-1* (LM,  $\times 400$ ).



*3. Please incorporate the following points into the table 1. -Treatment (please show how each case was treated) -Please show whether or not each case was analyzed with STAT6-immunohistochemistry or genetic analyses of NAB2-STAT6 fusion.*

**Answer:**

Into **Table 1**, we incorporate treatment along with analysis of STAT6-immunohistochemistry or genetic analyses of NAB2-STAT6 fusion.

**Table 1** A summary of the clinicopathological features in the reported cases of SFT-T.

Case	Years	Studies	Age	Sex	Site	Size (cm)	Atypia	Mitosis*	Necrosis	STAT6	Treatment	F/U (month)
1	1993	Taccagni[3]	44	F	R	6	No	Rare	NA	NA	Lobectomy	NED (60)
2	1993	Taccagni[3]	61	M	L	6	No	No	NA	NA	Subtotal	NED (48)
3	1993	Taccagni[3]	32	F	R	3.5	Yes	Rare	NA	NA	Lobectomy	NED (60)
4	1994	Camesselle-Teijeir[8]	43	F	L	4	No	No	No	NA	Subtotal	NED (160)
5	1997	Kie[7]	48	F	R	8	No	No	No	NA	Lobectomy	NA
6	1999	Brunnerman[31]	28	F	NA	2.5	NA	4	NA	NA	NA	NA
7	2001	Rodriguez[32]	43	F	L	3.5	No	2	No	NA	NA	NA
8	2001	Rodriguez[32]	52	M	L	2.5	No	No	No	NA	NA	NA
9	2001	Rodriguez[32]	44	M	L	2	Yes	1	No	NA	NA	NA
10	2001	Rodriguez[32]	64	F	R	4.	No	2	No	NA	NA	NED (60)
11	2001	Rodriguez[32]	53	M	L	6	No	1	No	NA	NA	NED (60)
12	2001	Rodriguez[32]	47	F	R	4.5	No	No	No	NA	NA	NED (48)
13	2001	Rodriguez[32]	64	F	L	3	No	No	No	NA	NA	NA
14	2001	Deshmukh[5]	56	M	R	8	No	No	No	NA	Lobectomy	NED (12)
15	2003	Bohorquez[6]	68	M	L	9.7	No	No	No	NA	Lobectomy	NA
16	2003	Parwani[18]	61	M	L	5	No	No	No	NA	Subtotal	NA
17	2004	Babouk[33]	45	M	L	5	No	No	No	NA	Lobectomy	NA
18	2006	Tanahashi[16]	64	M	R	5	No	No	No	NA	Subtotal	NED (57)
19	2006	Tanahashi[16]	41	M	R	3	No	No	No	NA	Lobectomy	NED (45)
20	2006	Papi[34]	70	F	R	1.5	No	No	No	NA	Total	NED (6)
21	2008	Santeusanio[22]	61	M	R	3.5	No	No	No	NA	Subtotal	NED (60)
22	2008	Santeusanio[22]	42	F	R	4.7	No	No	No	NA	Lobectomy	NED (84)
23	2009	Farrag[10]	51	M	L	7	NA	NA	NA	NA	Lobectomy	NA
24	2010	Ning[12]	76	F	R	4	Yes	High	Yes	NA	Lobectomy	RC/ MT (5)
25	2010	Larsen[11]	58	M	IT	8	No	Low	No	NA	Lobectomy	NA
26	2010	Cox[35]	69	F	NA	2.2	NA	NA	NA	NA	NA	NA
27	2011	Song[9]	37	M	L	4	No	<1	No	NA	Subtotal	NED (12)
28	2011	Verdi[17]	47	F	L	5.2	NA	NA	No	NA	Lobectomy	NED (9)
29	2011	Verdi[17]	59	M	R	7	No	No	No	NA	Lobectomy	NED (31)
30	2013	Lin[36]	88	F	IT	9	NA	<1	Yes	NA	Subtotal	NED (36)
31	2013	Mizuuchi[30]	78	M	R	3	No	No	No	NA	Subtotal	NED (12)
32	2013	Alves Filho[13]	60	F	R	13.8	Yes	6	No	NA	Subtotal	NA
33	2014	Boonlorm[14]	61	F	L	10.5	No	No	No	NA	Subtotal	NED (19)
34	2019	Ghasemi-rad[15]	41	F	L	11	Yes	High	No	Positive	Total	NED (10)
35	2019	Thompson[4]	44	F	NA	7	NA	NA	NA	Positive	Lobectomy	NED (41)
36	2019	Thompson[4]	45	F	NA	8.2	NA	NA	NA	Positive	Lobectomy	NED (28)
37	2019	Thompson[4]	52	M	NA	7	NA	NA	NA	Positive	Lobectomy	NED (5)
38	2019	Present case	59	M	L	5.5	Yes	5	No	Positive	Lobectomy	NED (17)

\* The mitosis is counted per 10 high power fields.

M: male; F: female; R: right lobe; L: left lobe; IT: intrathoracic; NA: not available; NED: no evidence of disease; RC: recurrence; MT: metastasis.

Thank you for your kind consideration. We believe that the diligent efforts of your reviewer have improved our paper.

Yours sincerely,

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