



· 论 著 ·

1例甲状腺孤立性纤维性肿瘤的临床病理学特征分析并文献复习

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[摘要] **背景与目的:** 原发于甲状腺的孤立性纤维性肿瘤(solitary fibrosis tumor, SFT)非常罕见, 探讨甲状腺SFT的临床病理学特征及鉴别诊断。**方法:** 分析徐州医科大学附属医院收治的1例原发于甲状腺的SFT患者的临床资料、组织学及免疫组织化学特征, 并复习相关英文文献。**结果:** 患者男性, 37岁, 甲状腺右叶一边界清晰的肿物, 直径3.2 cm。光镜下肿瘤由排列较密集的梭形细胞构成, 无固定生长模式, 少量胶原沉积, 较多分支状血管形成。免疫表型信号转导及转录激活因子6(signal transducer and activator of transcription 6, STAT6)核弥漫强阳性, 波形蛋白(vimentin)、CD34、CD99阳性, Bcl-2弱阳性。本例患者随访15个月, 一般情况良好。英文文献报道中共25例患者有随访信息, 随访时间5~160个月, 仅1例恶性病例5个月后复发且有远处转移。**结论:** 发生在甲状腺的SFT很罕见, 通过特征性的组织学及免疫组织化学染色可以明确诊断, 肿瘤多以良性为主, 预后良好, 恶性少见, 易复发转移。确切的生物学行为需要长期随访, 治疗首选手术切除。

[关键词] 孤立性纤维性肿瘤; 甲状腺; 免疫组织化学; 信号转导及转录激活因子6

DOI: 10.19401/j.cnki.1007-3639.2020.06.009

中图分类号: R736.1 文献标志码: A 文章编号: 1007-3639 (2020)06-0462-06

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[Abstract] **Background and purpose:** Primary solitary fibrous tumor (SFT) of thyroid is very rare. This study aimed to explore the clinicopathological features and identification of thyroid SFT. **Methods:** We analyzed one case of primary thyroid SFT treated in Affiliated Hospital of Xuzhou Medical University, including the clinical manifestations, histological features and immunohistochemical phenotypes, and reviewed the relevant English literature. **Results:** The patient was a 37-year-old male with a well-circumscribed mass in the right lobe of the thyroid gland, and the mass was 3.2 cm in diameter. Microscopically, the tumor displayed proliferation of spindle cells growing in nonspecific "patternless" manner with few amounts of intercellular collagen bundles. The tumor vessels showed branching staghorn-like appearance. Immunohistochemistry showed the spindle cells were positive for signal transducers and activators of transcription 6 (STAT6) (strong, nuclear), vimentin, CD34, CD99 and Bcl-2 (weak). The patient was followed up for 15 months and in good condition. A total of 25 cases reported in the English literature were followed up for 5-160 months. Only one malignant case had recurrence and metastasis after 5 months. **Conclusion:** Thyroid SFT is an uncommon neoplasm, and histopathology and immunohistochemistry can confirm the diagnosis. Most of the tumors are benign with good prognosis. Malignant cases are rare with the risk of recurrence and metastasis. Long-term follow-up is essential to evaluate the prognosis, and surgical resection is the preferred treatment for SFT.

[Key words] Solitary fibrous tumor; Thyroid; Immunohistochemistry; Signal transducers and activators of transcription 6

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孤立性纤维性肿瘤 (solitary fibrosis tumor, SFT) 是一种少见的间叶组织来源的纤维母细胞性肿瘤, 最常见于胸膜, 其他部位如肺、乳腺、肝、肾等也可见, 约6%起自头颈部^[1], 原发于甲状腺的SFT非常罕见, 自1933年Taccagni等^[2]首次报道后, 至投稿时仅检索到共38例关于甲状腺SFT的英文文献报道。现以徐州医科大学附属医院收治的1例甲状腺SFT患者为例, 探讨其临床病理学特征、诊断和鉴别诊断、免疫组织化学特征及分子生物学研究进展, 并复习相关文献。

1 资料和方法

1.1 临床资料

患者男性, 37岁, 无意中发现甲状腺肿块4 d, 无疼痛, 无声音嘶哑, 无呼吸及吞咽困难, 既往体健。查体: 颈软, 气管居中, 甲状腺右叶可触及约3 cm×2 cm肿块, 光滑、界清, 随吞咽上下活动, 左叶未见异常, 颈部未扪及肿大淋巴结。彩色多普勒超声检查结果显示, 甲状腺右叶囊实性结节, TI-RADS 3类, 考虑结节性甲状腺肿可能。遂行右甲状腺全切手术, 术中切开颈白线, 显露甲状腺, 见甲状腺右叶肿块, 质地韧, 表面光滑, 界限清, 左叶未及肿物, 超声刀下保护右喉返神经、上下甲状旁腺, 切除右腺叶。术中快速冰冻切片病理学检查结果显示: 梭形细胞肿瘤, 待常规病理学检查。

1.2 方法

术后标本经4%的甲醛溶液固定, 常规脱水, 石蜡包埋, H-E染色。免疫组织化学检测采用EnVision法。一抗包括抗信号转导及转录激活因子6 (signal transducer and activator of transcription, STAT6)、CD34、CD99、波形蛋白 (vimentin)、Bcl-2、CKp、CK19、CD56、甲状腺转录因子1 (thyroid transcription factor-1, TTF-1)、甲状腺球蛋白 (thyroglobulin, TG)、嗜铬素A (chromogranin A, CgA)、突触素 (synaptophysin, Syn)、间皮细胞 (mesothelial cell, MC)、降钙素 (calcitonin)、Pax8、S100、结蛋白 (desmin) 和Ki-67, 二氨基联苯胺 (3,3'-diaminobenzidine, DAB) 显色, 所有抗体

及显色剂均购自福州迈新生物技术开发有限公司。

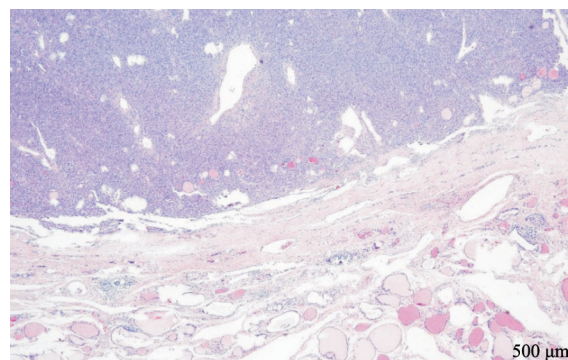
2 结果

2.1 大体检查

甲状腺组织1块, 大小为5.8 cm×4.3 cm×1.8 cm, 切面见一灰白色类圆形肿物, 直径3.2 cm, 有包膜, 局部囊性变, 灰红, 质地稍韧。

2.2 光镜检查

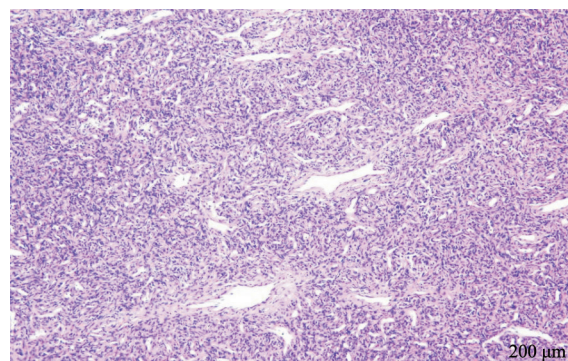
肿瘤边界清楚, 有包膜, 由大量增生的梭形细胞构成, 其内混有甲状腺滤泡 (图1), 细胞排列紊乱、较密集, 可呈束状、漩涡状, 局部见少量粉染胶原成分, 含较多薄壁不规则、分支状的血管 (图2)。细胞质浅染, 界限不清, 细胞核圆形-卵圆形, 核仁不明显, 未见明确核分裂相及坏死 (图3)。



(H-E, ×40)

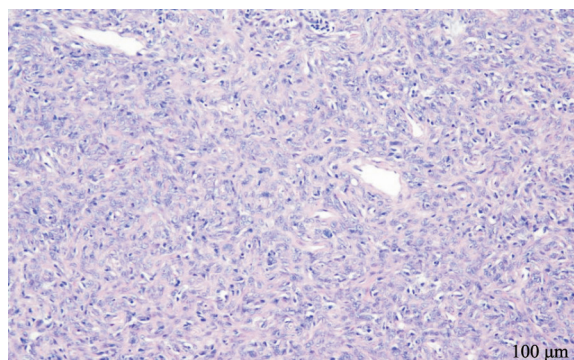
图1 肿瘤边界清晰, 由较密集的梭形细胞构成, 甲状腺滤泡包裹其内

Fig. 1 The tumor was well defined and composed of dense spindle cells, thyroid gland follicles were noted admixed with the spindle cells



(H-E, ×100)

图2 肿瘤细胞排列紊乱, 局部略呈漩涡状, 可见分支状血管
Fig. 2 The tumor exhibited a patternless growth, focal areas showed swirling structures, the staghorn tumor vessels were shown



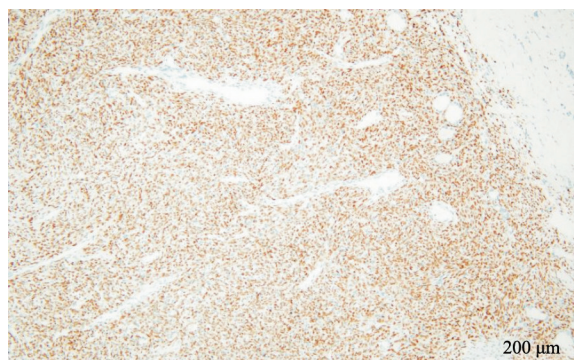
(H-E, ×200)

图3 细胞质轻染, 界限不清, 细胞核圆形-卵圆形, 未见明确核分裂及坏死

Fig. 3 The tumor cell cytoplasm were lightly stained and had indistinct border, the nuclei were round to oval, definite mitosis and necrosis were not observed

2.3 免疫组织化学

梭形细胞: STAT6核弥漫强阳性(图4), CD99(图5)、vimentin、Bcl-2(图6)、CD34均阳性; CKp、CK19、CD56、TTF1、TG、CgA、Syn、MC、calcitonin、Pax8、S100及desmin均阴性, Ki-67阳性率约8%。



(DAB, ×100)

图4 免疫组织化学(EnVision法)检测STAT6示肿瘤细胞的细胞核弥漫性强阳性

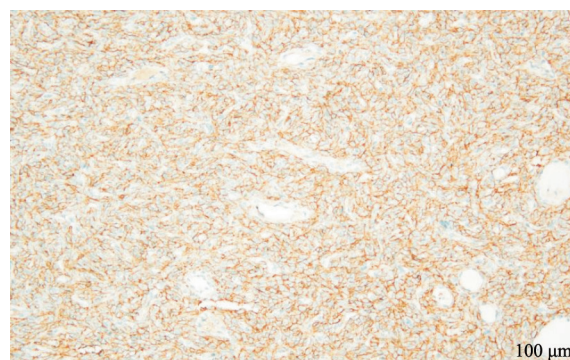
Fig. 4 Immunohistochemical (EnVision method) staining for STAT6 showed tumor cell nucleus strong and diffusive positive

2.4 病理学检查

甲状腺右叶: SFT。

2.5 术后及随访

患者住院期间情况稳定, 术后3 d拔引流管, 7 d后出院。口服左甲状腺素钠片6个月, 1片/d。随访15个月, 患者目前无声音嘶哑及饮水呛咳。彩色多普勒超声检查左甲状腺叶未见明显肿物, 胸部CT、腹部彩色多普勒超声未见异常。



(DAB, ×200)

图5 免疫组织化学(EnVision法)检测CD99示肿瘤细胞的细胞质阳性

Fig. 5 Immunohistochemical (EnVision method) staining for CD99 showed tumor cell cytoplasm positive



(DAB, ×100)

图6 免疫组织化学(EnVision法)检测Bcl-2示肿瘤细胞的细胞质弱阳性

Fig. 6 Immunohistochemical (EnVision method) staining for Bcl-2 showed tumor cell cytoplasm weakly positive

3 讨论

甲状腺SFT是一种病因不清、细胞起源不明的梭形细胞肿瘤, 可能来自甲状腺的滤泡旁细胞或间充质细胞^[3]。回顾报道的38篇英文文献, 甲状腺SFT患者年龄段分布较广, 以中年人为主, 平均年龄54岁, 性别分布无差异, 甲状腺左、右叶均可累及, 偶见于胸廓内甲状腺发生; 本文患者一般情况与文献报道相符(表1)。

临床表现无特殊, 最常见的是无痛性、生长缓慢的肿物, 可有周围组织的压迫症状, 如吞咽困难、呼吸困难、声音嘶哑。偶有肿瘤从甲状腺向下延伸, 表现为胸骨后甲状腺占位。患者甲状腺功能

正常。本文患者也是无意中发现无痛性甲状腺肿物,无其他临床症状,甲状腺功能亦正常。

超声检查结果显示实性占位性病变,偶有囊性变。CT同样显示实性肿物,伴不同程度周围组织受压,可有气管移位。放射性同位素检查结果显示为冷结节。本文患者彩超显示甲状腺右叶囊实性结节,无周围压迫征象。术中见肿瘤位于

甲状腺包膜内,与带状肌无明显粘连,喉返神经无侵犯。肿瘤大体表现为边界清晰的实性肿物,呈纤维状的灰白色或略深颜色,偶有囊性变,包膜有或无,出血、坏死、钙化不常见。恶性SFT肿物界限往往不清,坏死可见。肿瘤直径变化范围宽,平均5.9 cm(表1)。本例为类圆形肿物,直径3.2 cm,有包膜,局部囊性变。

表 1 本研究检索到的38例甲状腺SFT英文文献报道及本文病例特征概要

Tab. 1 38 cases of English literature summary and present case of thyroid SFT retrieved in this study

Case	Age/year	Gender	Site	Size D/cm	Atypia	Mitosis (>4/10 HPF)	Necrosis	Follow-up t/month
1 ^[2]	44	F	R	6.0	No	No	NA	60
2 ^[2]	61	M	L	6.0	No	No	NA	48
3 ^[2]	32	F	R	3.5	Yes	No	NA	60
22 ^[4]	61	M	L	3.5	No	No	No	60
23 ^[4]	42	F	R	4.7	No	No	No	84
18 ^[5]	64	M	R	5.0	No	No	No	60
19 ^[5]	41	M	R	3.0	No	No	No	60
6 ^[6]	28	F	NA	2.5	NA	No	No	NA
33 ^[7]	44	F	NA	7.0	NA	No	No	41
34 ^[7]	45	F	NA	8.2	NA	No	No	28
35 ^[7]	52	M	NA	7.0	NA	No	No	5
28 ^[8]	47	F	L	5.2	NA	NA	No	9
29 ^[8]	59	M	R	7.0	No	No	No	31
32 ^[9]	60	F	R	13.8	Yes	Yes	No	NA
25 ^[10]	76	F	R	4.0	Yes	Yes	Yes	5, recurrence
4 ^[11]	43	F	L	4.0	No	No	No	160
5 ^[12]	48	F	R	8.0	No	No	No	NA
7 ^[13]	43	F	L	3.5	No	No	No	NA
8 ^[13]	52	M	L	2.5	No	No	No	NA
9 ^[13]	44	M	L	2.0	Yes	No	No	NA
10 ^[13]	64	F	R	4.5	No	No	No	60
11 ^[13]	53	M	L	6.0	No	No	No	60
12 ^[13]	47	F	R	4.5	No	No	No	48
13 ^[13]	64	F	L	3.0	No	No	No	NA
14 ^[14]	56	M	R	8.0	No	No	No	12
15 ^[15]	68	M	L	9.7	No	No	No	NA
16 ^[16]	61	M	NA	5.0	No	No	No	NA
17 ^[17]	45	M	NA	5.0	No	No	No	NA
20 ^[18]	70	F	R	1.5	No	No	No	6
21 ^[19]	45	M	L	5.0	No	No	No	NA
24 ^[20]	51	M	L	7.0	NA	NA	NA	NA
26 ^[21]	58	M	Intrathoracic	8.0	No	No	No	NA
27 ^[22]	37	M	L	4.0	No	No	No	12
30 ^[23]	88	F	Intrathoracic	9.0	NA	No	Yes	36
31 ^[24]	78	M	R	3.0	No	No	No	12
36 ^[25]	41	F	L	11.0	Yes	No	NA	10
37 ^[26]	74	M	Intrathoracic	12.0	No	No	No	24
38 ^[27]	61	F	L	10.5	No	No	No	19
Present case	37	M	R	3.2	No	No	No	15

HPF: High power field; M: Male; F: Female; L: Left lobe; R: Right lobe; NA: Not available

组织学上与其他部位SFT表现相同^[4],本文作者检索到的38例文献中肿瘤均表现为由成纤维细胞样的梭形细长细胞构成,特征性病变是

富于细胞区和稀疏细胞区交替出现^[5],伴含量不等的胶原透明变性^[6],鹿角状的分支血管,似血管外皮瘤样改变。无特定生长模式,局部区

域呈模糊的束状、席纹状、波浪状、栅栏状。高倍镜下肿瘤细胞呈梭形、圆-卵圆形, 细胞核温和, 染色质细腻分散, 核仁不明显或无, 细胞质少, 界限不明显。肿瘤内常混有正常的甲状腺滤泡, 有文献认为这是两种组织的混合, 而非浸润^[7]。间质可有淋巴细胞或肥大细胞浸润^[8]。除2例恶性SFT外, 余36例符合良性SFT改变, 无明显异型性, 仅3例有轻-中度异型, 核分裂无或<4个/10高倍视野 (high power field, HPF), 坏死亦少见 (表1)。2例恶性甲状腺SFT^[9-10], 肿瘤细胞密度增加, 有明显的异型性, 核分裂相均>4个/10 HPF, 1例伴坏死。确切的良恶性鉴别并没有明确标准, 根据Vallat-Decou velaere等的报道^[28], 以下特征提示侵袭性行为: 细胞密度增加; 细胞有异型; 核分裂相增加 (>4个/10 HPF); 肿瘤坏死, 浸润边缘。有学者建议, 肿瘤≥10 cm, 应密切随访^[29]。2016年, Bahrami等^[30]回顾性研究SFT中端粒酶逆转录酶 (telomerase reverse transcriptase, TERT) 基因启动子突变患者的生存率明显低于野生型TERT基因携带者, 认为TERT可作为评估SFT侵袭性的潜在分子指标。本例甲状腺SFT边界清楚, 梭形细胞较密集, 疏密区不明显, 细胞排列呈束状、漩涡状, 胶原含量少, 未见典型的胶原带形成, 分支状血管较多, 间质淋巴细胞浸润, 未见核分裂相及坏死, 符合良性SFT形态特征。

近年来, 研究SFT中的基因改变时发现一种良/恶性SFT中均有表达的神经生长因子诱导基因 (nerve growth factor-induced gene, NGFI) A结合蛋白2 (NGFI-A-binding protein 2, NAB2) -STAT6融合基因, 进一步在遗传学水平上明确了SFT的基因特征^[31], 而STAT6的免疫组织化学检测与NAB2-STAT6基因融合产物具有高度的一致性、灵敏度和特异度, 故目前STAT6已被认为是一种可靠有效的免疫组织化学标志物, 可用于SFT的诊断。经典的SFT免疫表型还包括CD34、CD99、vimentin、Bcl-2阳性; CK、desmin、S100阴性; TG、TTF1阴性。本例患者肿瘤细胞STAT6核阳性, CD99、vimentin、Bcl-2、CD34均阳性, 甲状腺滤泡TG、TTF1阳性, 支持SFT的诊断。

甲状腺SFT是一种主要是来自甲状腺及周围组织的梭形细胞病变。(1) 具有梭形细胞形态的癌: ①未分化癌, 肿瘤细胞表现为不典型增生的梭形细胞, CKp、EMA、Pax8阳性, 且临床多为快速增长的颈部肿物, 与SFT生长缓慢不同; ②髓样癌, 肿瘤细胞可呈梭形, CK、CT、Syn、CgA、刚果红阳性; ③乳头状癌伴有结节性筋膜炎样间质亚型, 间质梭形细胞增生伴胶原化, 特别是上皮成分不明显时, 类似SFT形态, 可通过间质细胞vimentin、SMA和desmin阳性进行鉴别; ④滤泡癌/腺瘤, 偶尔也会呈现梭形细胞表现, TG、TTF1阳性可鉴别。(2) 间叶性肿瘤: ①平滑肌肿瘤, 细胞分布更均匀, 编织状排列, 细胞核端钝圆, 缺乏分支状血管, SMA、desmin阳性; ②外周神经鞘膜瘤, 可表现为类似SFT的细胞密度不均, 胶原化间质, 但S100阳性; ③单相性滑膜肉瘤以梭形细胞为主时, 需要鉴别, 但其一般无胶原化的间质及分支状血管, 可表达CK、EMA。以上肿瘤均很少见到SFT的STAT6核强阳性表达。另有一种罕见的胸腺样分化的梭形上皮肿瘤 (spindle epithelial tumor with thymus-like differentiation, SETTLE), 由梭形细胞与管状、乳头状或腺状结构混合组成的双相性外观, 而单相性以梭形细胞为主, 可表达CD99、Bcl-2, 这时易与SFT混淆, 可通过主要累及儿童和青少年, CK阳性, CD34、STAT6阴性进行鉴别。(3) 非肿瘤性病变: 如Riedel甲状腺炎等, 有广泛的纤维化及慢性炎, 伴静脉炎。

目前已知甲状腺的SFT预后较好^[10]。本例随访15个月, 患者一切情况良好。

本病有效的治疗手段仍是手术切除, 同时术后也能缓解各种压迫症状, 并获得标本以明确诊断, 而术前细针穿刺获得的组织量少, 多数仅见松散的梭形细胞, 确诊甲状腺SFT困难。因SFT是非滤泡起源的, 故促甲状腺激素 (thyroid-stimulating hormone, TSH) 抑制性治疗无效。

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