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From Cell Biology to Tissue Engineering

A subset of solitary fibrous tumors express nuclear PAX8 and PAX2: a potential diagnostic pitfall

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Summary. Solitary fibrous tumor (SFT), a mesenchymal neoplasm with widespread anatomic distribution, can be diagnostically challenging in limited samples. We recently encountered an aspirate of a pancreatic mass, incorrectly interpreted as metastatic renal cell carcinoma based on strong PAX8 expression by immunohistochemistry (IHC). After resection, morphologic features with additional IHC (CD34 positivity) correctly identified this lesion as a SFT. PAX8 and PAX2 are commonly used as renal tumor markers; however, no series has investigated PAX8 or PAX2 expression in SFT. IHC for PAX8 and PAX2 was performed on 41 SFTs (biopsy and resections) from varying sites. Eight were histologically malignant and eight were recurrences of previous resections. PAX8 staining was observed at least focally in 26.8% (11 of 41) SFT cases; additionally, PAX2 was positive in 12.2% (5 of 41 cases) of SFTs. For PAX8 and PAX2 positive cases 45.6% and 40%, respectively, showed diffuse expression. No correlation was found between PAX8/PAX2 positivity and age, tumor size, site, malignancy, or recurrence. In conclusion, a substantial minority of SFTs express PAX8 and PAX2 via IHC. This presents a diagnostic pitfall when evaluating possible metastases from the kidney, particularly when primary tumors show sarcomatoid or spindle cell morphologies.

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Introduction

Solitary fibrous tumor (SFT) is an uncommon mesenchymal neoplasm initially described as "localized or fibrous mesothelioma" of the pleural surfaces (Hajdu et al., 2010; Fletcher et al., 2013). Over time, the understanding of the histogenesis of this neoplasm evolved to be of probable fibroblastic origin and the anatomic distribution of this tumor has been increasingly described in nearly all body sites. In the majority of cases the prognosis is good with complete surgical resection representing the foundation of treatment. However, approximately 10 to 20% of SFTs behave aggressively (the so-called "malignant SFT") with multiple recurrences and occasional metastases. Clinically aggressive behavior is correlated with histologic features such as the presence of necrosis, high mitotic rates (greater than 4 per 10 HPF), increased cellularity, cellular pleomorphism, and infiltrative growth; importantly, the presence of these features does not always predict a worse prognosis (Bertucci et al., 2013).

SFTs most reliably show strong, diffuse staining with CD34 as well as variable but reproducible staining for non-specific markers bcl-2, vimentin, and CD99. SFTs are typically, but not absolutely, negative for cytokeratins (although 20-30% express epithelial membrane antigen (Rao et al., 2013; Doyle et al., 2014)), and negative for smooth muscle markers, melanocytic

antigens, and c-Kit. Recent reports, including from our group, have described a novel, recurrent intra-chromosomal fusion between NAB2 and STAT6 on chromosome 12q13 in the vast majority of SFTs, providing a sensitive and specific molecular hallmark as well as a possible therapeutic target (Chmielecki et al., 2013; Mohajeri et al., 2013; Robinson et al., 2013; Schweizer et al., 2013).

PAX8 and PAX2 are commonly used as diagnostic immunohistochemical markers of primary and metastatic renal and Müllerian malignancies. PAX2 expression has been recorded in 71% of renal tumors; likewise 82% of renal neoplasms are positive for PAX8 (Ozcan et al., 2012). To date, neither PAX8 nor PAX2 expression has been described in SFT. Here, we show for the first time that a substantial minority of SFT express either PAX8 or PAX2 and discuss the potential implications of these findings in the context of using IHC as an ancillary test for pathologic diagnosis.

Materials and methods

Tissue samples

A total of 41 cases of SFTs were selected from the archives of the University of Michigan Department of Pathology case files following approval from the Institutional Review Board, with these selected cases diagnosed between 1991 and 2013. Written informed consent for usage of these samples had been obtained prior to tissue acquisition. Review of hematoxylin and eosin stained slides was performed (A.S.M., S.C.S., and L.P.K.). Available demographic and clinicopathologic data was obtained and tabulated for analysis.

Immunohistochemistry

Immunohistochemistry for PAX8 (Cellmarque, USA; prediluted rabbit polyclonal), PAX2 (Invitrogen, USA; rabbit polyclonal diluted 1:100), STAT6 (Santa Cruz Biotechnology, USA; rabbit polyclonal dilute 1:100) was performed using the Ventana DISCOVERY XT (Ventana Medical Systems, Inc., USA) automated slide staining system on formalin-fixed, paraffin-embedded (FFPE) tissue sections cut to a thickness of 4 μm. Following primary antibody incubation, secondary detection was performed with Ultramap anti-rabbit antibodies conjugated to horseradish peroxidase (Ventana Medical Systems, Inc., USA). Brown staining for PAX8, PAX2, and STAT6 protein expression was developed using ChromoMap DAB polymer (Ventana Medical Systems, Inc., USA), using Hematoxylin II as the counterstain. Appropriate positive and negative controls were included. Positive staining for PAX8, PAX2, and STAT6 was defined as brown nuclear immunoreactivity in neoplastic tissue. The intensity (0= no stain, 1+= unequivocal but weak, 2+ moderate, 3+ strong) and extent (<50% of neoplastic nuclei stained= focal, >50% of neoplastic nuclei stained= diffuse) were noted for each case with samples displaying either 2+ or 3+ intensity counted as positive.

Transcriptome sequencing (RNA-seq) for NAB2-STAT6 gene fusion

RNA was isolated from 10μm thick FFPE sections of the index case using Qiagen miRNAeasy kit according to the manufacturer's instructions (Qiagen, USA). RNA-Seq transcriptome libraries were prepared following Illumina's TruSeq RNA protocol, using 5ug of total RNA. cDNA synthesis, end repair, A-base addition and ligation of the Illumina-indexed adaptors were performed according to Illumina's protocol. Libraries were then size selected for cDNA fragments of 250-300 bp on a 3% Nusieve 3:1 (Lonza) agarose gel, recovered using QIAEX II gel extraction reagents (Qiagen) and PCR amplified using Phusion DNA polymerase (NEB) for 14 PCR cycles. Paired-end libraries were sequenced with the Illumina HiSeq 2000 (2×100-nt read length). Reads that passed the chastity filter of Illumina BaseCall software were used for subsequent analysis. Sequence alignments were subsequently processed to nominate the *NAB2-STAT6* gene fusion as previously described (Robinson et al., 2013). In brief, paired-end transcriptome reads passing filter were mapped to the human reference genome (hg19) and were processed to identify any that either contained or spanned a fusion junction. The reads underwent a series of filtering steps to remove false positives before being merged together to generate the final nominations of chimera. Reads supporting the presence of a fusion were realigned using BLAT (UCSC Genome Browser) to reconfirm the fusion breakpoint.

Results

Index case

A 57 year old male with a history of renal cell carcinoma, status post left radical nephrectomy 9 months prior (8.8 cm, Fuhrman grade 3 of 4 with no sarcomatoid features present, stage pT3a for renal sinus invasion), underwent routine surveillance CT scanning of his abdomen which noted a 1.4 cm hypervascular pancreatic head mass, suspicious for metastatic disease. Endoscopic ultrasound with fine needle aspiration was performed, and the cytologic interpretation was positive for neoplasm, and favored to represent metastatic renal cell carcinoma based on strong nuclear PAX8 staining of the cell block material (Fig. 1A,B). Shortly thereafter, he was scheduled for a Whipple resection of this pancreatic lesion.

Histologic examination of the pancreas demonstrated a well circumscribed mass composed of fibroblast-like spindle cells with fusiform nuclei and scanty cytoplasm arranged in vague fascicles with no

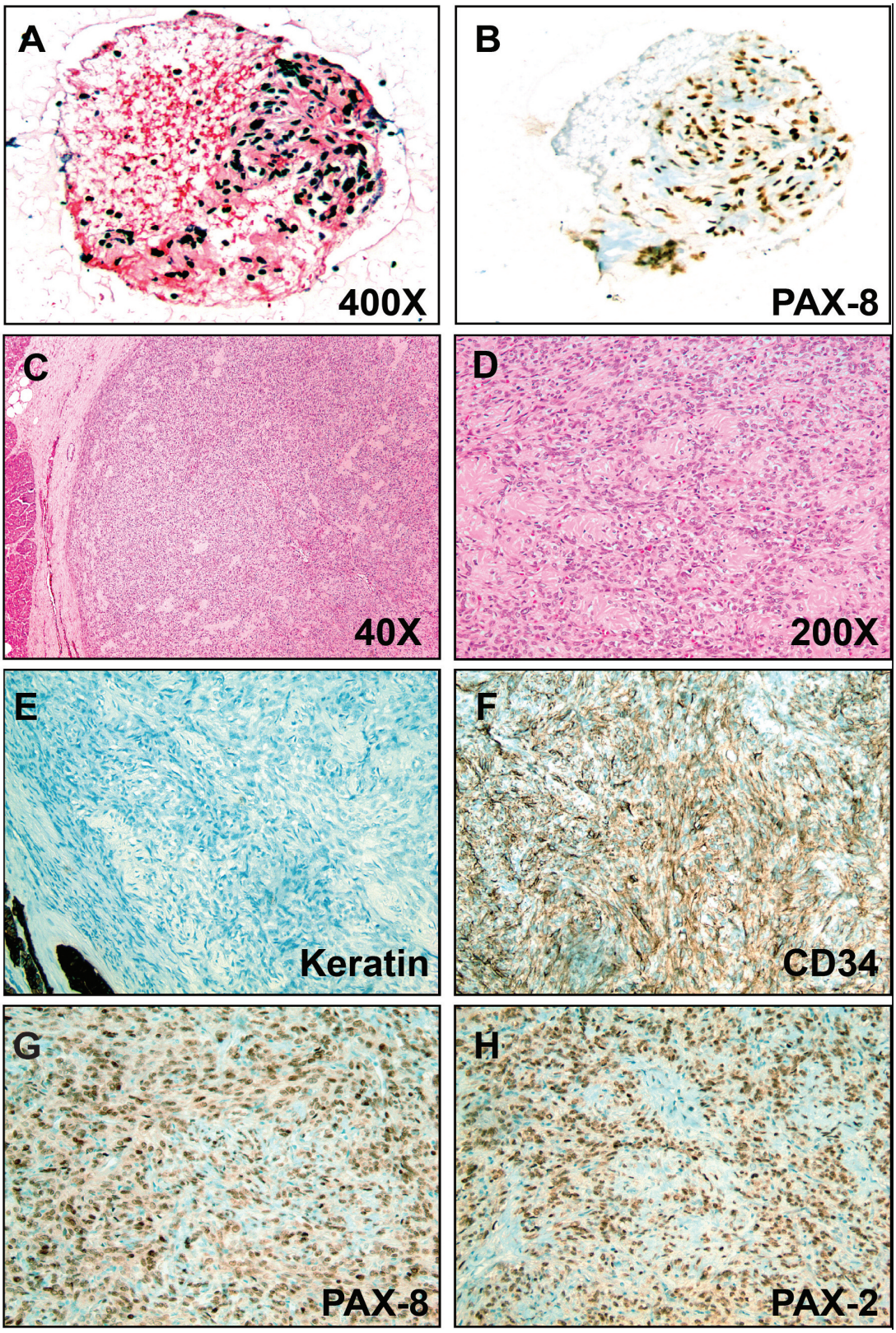

Fig. 1. A. High power hematoxylin and eosin (H&E) stained cell block section from original fine needle aspiration of 1.4 cm well circumscribed pancreatic head mass in a 57 year old male with a history of renal cell carcinoma, status post left radical nephrectomy (Fuhrman nuclear grade 3 of 4, stage pT3a). A small aggregate of hyperchromatic neoplastic cells is shown. **B.** Immunohistochemical (IHC) staining of the cell block specimen from part A for PAX8 shows strong nuclear positivity. Based on this, the aspirate was interpreted as positive for neoplasm, favor metastatic renal cell carcinoma. Shortly thereafter, the patient was scheduled for Whipple resection of the presumed metastases. **C.** Low power H&E view of the resected pancreatic lesion showing a well circumscribed cellular lesion distinct from the surrounding pancreatic parenchyma. **D.** Medium power H&E view showing spindle cell morphology arranged in vague fascicles with no discernable pattern, fusiform nuclei, and scanty cytoplasm with prominent collagenous stroma between the cells. **E.** The resected pancreatic mass completely lacked staining with cytokeratin cocktail (note strong staining of pancreatic parenchyma in the lower left corner). **F.** Tumor cells were strongly positive for CD34. The combined morphologic and immunohistochemical features led to the final diagnosis of a solitary fibrous tumor and not metastatic renal cell carcinoma. **G and H**. IHC performed on the resected pancreatic mass recapitulates the strong staining for PAX8 and PAX2 seen in the aspirate (part B), respectively. A, x 400; B, E-H, x 100; C, x 40; D, x 200

discernible pattern (Fig. 1C). A prominent collagenous stroma was present between the cells. No mitotic figures, necrosis, significant hyperchromasia of spindle cells, clear cell histology, branching fibrovascular septations, or other morphologic features of renal cell carcinoma were present (Fig. 1D). Immunohistochemical staining was performed, and the tumor cells again showed strong nuclear staining of PAX8, with additional strongly positive expression of PAX2 and CD34, and were negative for pancytokeratin (Fig. 1E-H), C-kit, DOG-1, synaptophysin, and chromogranin A (data not shown). Based on these findings, it was decided that the tumor actually represented a SFT and was not a metastatic lesion. Transcriptome sequencing of RNA isolated from FFPE sections of the tumor performed subsequently also identified the presence of a *NAB2-STAT6* gene fusion (Fig. 2), confirming the diagnosis of SFT.

Cohort summary

After encountering the above index case in the course of routine diagnostic practice, we decided to examine a cohort of SFTs for their expression of both PAX8 and PAX2 (Table 1). Review of 41 cases from 1991-2013 confirmed the diagnosis in all cases which came from a variety of anatomic sites, including the pleura and thorax (n=13), head and neck (n=20), abdomen and pelvis (n=5), extremities (n=2), and retroperitoneum (n=1). Previous CD34 staining was performed in 23 cases, with 19 of those showing positive

Table 1. PAX-8 and PAX-2 expression in solitary fibrous tumors.

Case	Location	Age	Sex	Size (cm)	Malignant	PAX8	PAX8 distribution	PAX2	PAX2 distribution
1	Groin	74	M	8.5	No	Negative	N/A	Negative	N/A
2	Pleura	63	F	5.3	No	Negative	N/A	Negative	N/A
3	Pleura	59	M	17.5	Yes	Negative	N/A	Negative	N/A
4	Nasal	44	M	4.3	No	Positive	Focal	Negative	N/A
5	Lung	54	M	17	Yes	Negative	N/A	Negative	N/A
6	Lung	48	M	7.5	No	Negative	N/A	Negative	N/A
7	Lung	77	F	11.6	No	Negative	N/A	Negative	N/A
8	Pleura	82	M	20	No	Negative	N/A	Negative	N/A
9	Pleura	58	M	16.4	Yes	Negative	N/A	Negative	N/A
10	Pleura	63	M	6.8	No	Positive	Diffuse	Negative	N/A
11	Leg	56	M	2.6	No	Positive	Diffuse	Positive	Focal
12	Pleura	76	F	15	No	Negative	N/A	Negative	N/A
13	Mediastinum	60	F	10.5	No	Negative	N/A	Negative	N/A
14*	Pleura	63	M	3	Yes	Negative	N/A	Negative	N/A
15	Groin	62	M	2.6	No	Positive	Focal	Positive	Focal
16*	Pelvis	76	M	6.2	Yes	Negative	N/A	Negative	N/A
17*	Sinus	50	F	2.7	No	Negative	N/A	Negative	N/A
18*	Orbit	67	F	2	No	Positive	Diffuse	Negative	N/A
19	Orbit	50	F	3	No	Positive	Diffuse	Positive	Diffuse
20	Pharynx	88	F	5.3	No	Positive	Diffuse	Positive	Diffuse
21	Pharynx	48	F	8	No	Negative	N/A	Negative	N/A
22	Temporal	16	F	5.1	No	Negative	N/A	Negative	N/A
23	Nose	29	F	1.5	No	Positive	Focal	Positive	Focal
24	Sinus	62	F	2.1	No	Negative	N/A	Negative	N/A
25*	Orbit	65	F	4.2	No	Negative	N/A	Negative	N/A
26	Orbit	59	M	4.3	No	Negative	N/A	Negative	N/A
27	Orbit	15	M	2.9	No	Negative	N/A	Negative	N/A
28	Orbit	28	M	1.2	No	Negative	N/A	Negative	N/A
29	Orbit	60	F	N/A	No	Positive	Focal	Negative	N/A
30	Orbit	30	M	1.8	No	Negative	N/A	Negative	N/A
31	Orbit	55	F	N/A	No	Positive	Focal	Negative	N/A
32*	Sinus	83	M	4	No	Negative	N/A	Negative	N/A
33	Orbit	44	M	N/A	No	Negative	N/A	Negative	N/A
34	Retroperitoneum	41	F	19	No	Negative	N/A	Negative	N/A
35*	Leg	49	F	3	Yes	Negative	N/A	Negative	N/A
36	Dura	74	M	3.5	No	Negative	N/A	Negative	N/A
37	Chest wall	82	F	7.5	No	Negative	N/A	Negative	N/A
38	Lung	55	M	1	Yes	Positive	Focal	Negative	N/A
39	Sacrum	46	F	5.7	No	Negative	N/A	Negative	N/A
40*	Abdomen	67	F	6.5	Yes	Negative	N/A	Negative	N/A
41	Sinus	48	F	N/A	No	Negative	N/A	Negative	N/A

*: indicates this sample was a recurrence of a previously resected solitary fibrous tumour, N/A: Not applicable.

staining (83%). Confirmation of the diagnosis of SFT was performed previously by whole transcriptome sequencing in 11 cases (Robinson et al., 2013) and by STAT6 immunohistochemistry in 12 additional cases (Demicco et al., 2015). Of the remaining 18 cases in our cohort, 14 had material suitable for STAT6 immunohistochemistry, which in all 14 cases demonstrated strong nuclear positivity. The mean patient age was 56.7 years (range 15-86 years). Tumors ranged

Table 2. PAX-8 status is not associated with tumor size, patient age, location, or malignant status.

	PAX-8 Positive	PAX-8 Negative	P-value
Thoracic	2	11	0.4507*
Extra-thoracic	9	19	
Malignant	1	7	0.4121*
Benign	10	23	
Average age	57.2	56.6	0.9231#
SD	14.63	18.41	
Average size	4.28	7.85	0.0634#
SD	3.757	5.74	

SD: Standard deviation. *: Fisher's two-tailed exact test. #: Student's two tailed unpaired T-test.

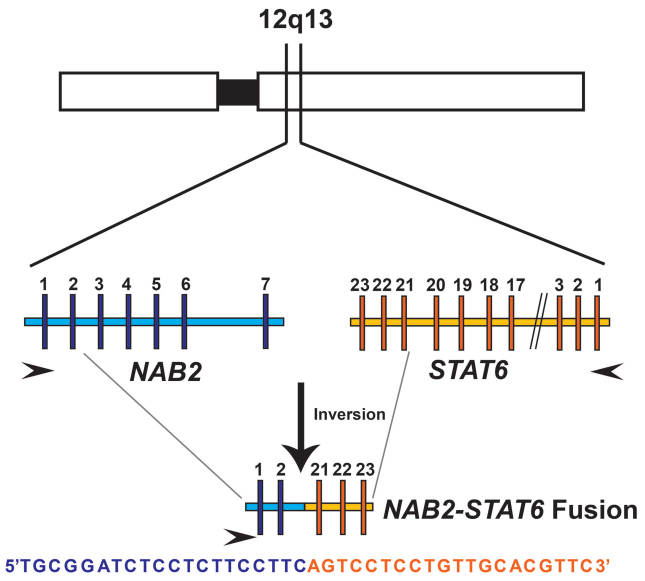

Fig. 2. Schematic representation of the NAB2-STAT6 gene fusion on chromosome 12q13 identified by RNA-seq of the pancreatic SFT described in the text.

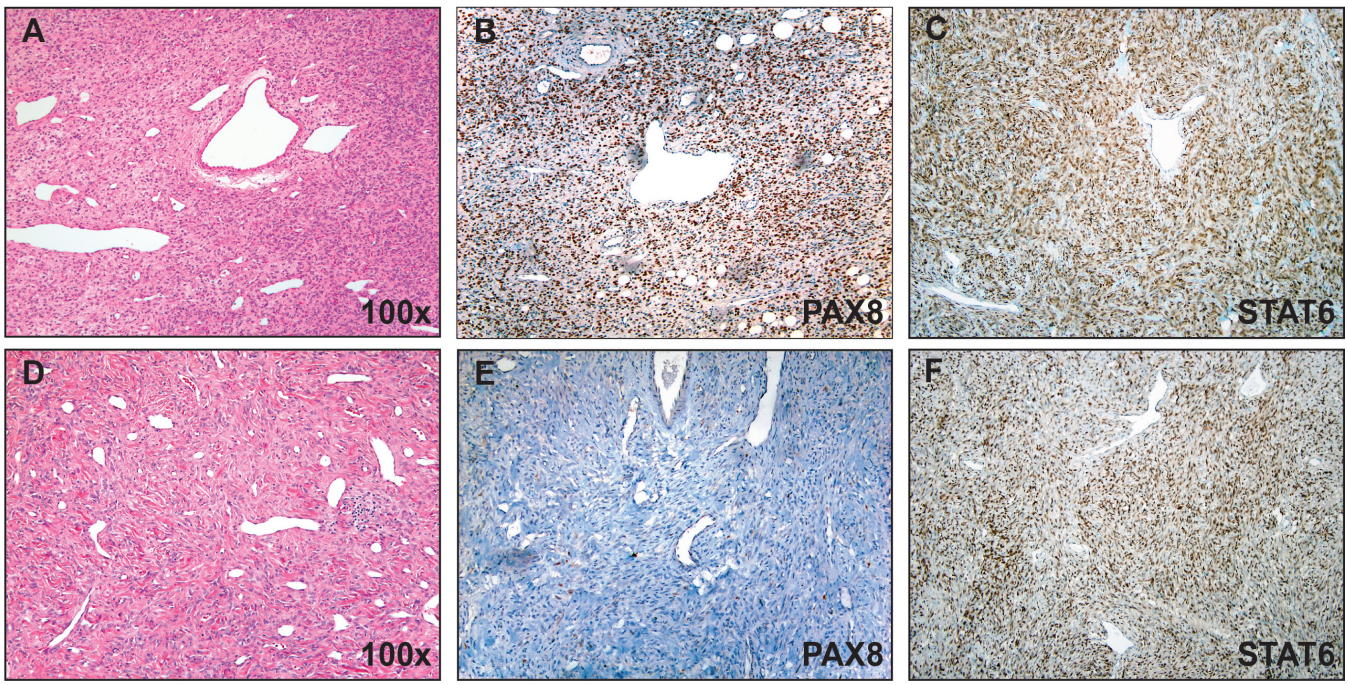

Fig. 3. A and D. Medium power hematoxylin and eosin (H&E) stained section from two representative solitary fibrous tumors tested for PAX8 and PAX2 expression (samples #22 and 35 from Table 1, respectively). **B and E**. PAX8 immunohistochemistry showing diffuse nuclear staining for PAX8 in panel **B** and negative staining in panel **D**. PAX2 staining (not shown) was identical to PAX8 in these two cases. **C and F.** STAT6 immunohistochemistry showing strong, diffuse nuclear expression in both cases. x 100

in size from 1.7 to 27 cm (mean 7.6 cm). Eight tumors were considered histologically malignant (based on nuclear atypia, mitotic rate, and presence of necrosis) and eight tumors were recurrences of previous incomplete resections.

PAX8 and PAX2 immunohistochemistry

Immunohistochemistry for PAX8 and PAX2 was performed as described in the methods and the results are shown in Table 1. PAX8 expression was detected in 11 of 41 SFT samples (26.8%), with five samples showing diffuse staining and six samples showing focal staining. PAX8 positivity was noted in one of eight malignant SFTs and in one of eight recurrent SFTs. Two of 14 thoracic SFTs were positive for PAX8, while 9 of 31 extra-thoracic SFTs expressed PAX8 (including 8 of 21 head and neck SFTs). The average size of PAX8 positive SFTs was 4.28 cm (range 1.0 to 6.8 cm) and the average size of PAX8 negative SFTs was 7.85 cm (range 1.2 to 20 cm). The average age of patients with PAX8 positive SFTs was 57.2 years (range 29 to 88 years) and the average age of patients with PAX8 negative SFTs was 56.6 years (range 15 to 83 years). No significant differences between PAX8 status and tumor size, site, malignant status, or patient age was noted (Table 2, Student's T-test and Fisher's exact test). Representative photomicrographs of PAX8 positive and negative SFTs are shown in Fig. 3. PAX2 expression was identified in 5 of 41 SFT samples (12.2%), with diffuse staining present in two cases and focal staining in the other three cases. All six PAX2 positive cases were also positive for PAX8. As with PAX8 staining, PAX2 expression was not significantly correlated with any clinicopathologic parameter (data not shown).

Discussion

The presence of a SFT within the pancreas is very rare, with only 11 cases reported to date (Luttges et al., 1999; Chatti et al., 2006; Gardini et al., 2007; Miyamoto et al., 2007; Kwon et al., 2008; Srinivasan et al., 2008; Chetty et al., 2009; Ishiwatari et al., 2009; Sugawara et al., 2010; Santos et al., 2012; Tasdemir et al., 2012; Chen et al., 2013). The large majority of these cases were in females (10 of 11), with the ages ranging from 41 to 78 years. Most were incidentally discovered during abdominal imaging, with a nearly even distribution between the head and body of the pancreas (5 cases and 6 cases, respectively). The tumors ranged in size from 2 to 13 cm, and none were described with malignant features. The index case in the current series of SFT was initially mistaken for metastatic renal cell carcinoma based on the patient's clinical history, imaging studies, and fine-needle aspiration results, including the fact that the tumor cells showed strong expression of PAX8.

PAX8 and PAX2 are members of the paired box family of transcription factors which regulate embryonic development of a number of tissues including the eye, central nervous system, thyroid, Müllerian duct derived, and the kidney (Ozcan et al., 2011, 2012). The PAX proteins are defined by the presence of the paired box domain, a 128 amino acid highly conserved region that regulates DNA binding and activation of transcriptional activity (Bopp et al., 1986; Treisman et al., 1991; Ordonez, 2012). Both PAX8 and PAX2 are expressed throughout embryonic renal and Müllerian development and maintain expression in epithelial cells in these locations in normal adult tissue as well. These facts have led to the development of antibodies of both factors for use as immunohistochemical markers with high sensitivity and specificity for epithelial tumors from these locations, although the use of polyclonal antibodies (as performed here) may lessen specificity due to possible cross-reactivity with other PAX family members (Morgan et al., 2013; Tacha et al., 2013; Toriyama et al., 2014).

Here, we describe for the first time PAX8 and PAX2 expression via IHC in a subset of solitary fibrous tumors. These PAX expressing SFTs show no preference for site, size, patient age, or malignant status. Although previous gene expression profiling studies of SFTs have shown that PAX8 is mildly upregulated compared to other soft tissue sarcomas, the biological significance of PAX8 or PAX2 expression within a SFT remains unclear (Bertucci et al., 2013). The frequency of PAX8 and PAX2 expression in SFT is sufficiently low to preclude either factor to be used as a diagnostic adjunct for diagnosis of these tumors; however, it is substantial enough to raise the potential for misdiagnosis of SFT as being from renal or Müllerian origin, as was the case for our index patient. PAX8 immunohistochemistry has been demonstrated to be useful in identifying sarcomatoid carcinomas, particularly from the thyroid and kidney (Bishop et al., 2011; Chang et al., 2013), and care must be taken to interpret PAX8 within the histologic, anatomic, and clinical context of an individual case. The possibility of the diagnostic pitfall described herein is enhanced in cases with a previous history of renal or gynecologic carcinomas, especially those with sarcomatoid or spindle cell differentiation.

These findings underscore the importance of not relying on a single immunohistochemical marker for finalizing a diagnosis and to consider the possibility of SFT in the differential diagnosis for any spindle cell lesion located in the pancreas.

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Conflict of interest. The authors declare they have no conflicts of interest.

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