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Solitary Fibrous Tumor with Neuroendocrine and Squamous Dedifferentiation: A Potential Diagnostic Pitfall

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Abstract

Solitary fibrous tumor (SFT) is a ubiquitous mesenchymal neoplasm of deep soft tissue with variable and often unpredictable biological behavior. The lineage is presumed to be fibroblastic and histological features range from benign to overtly malignant with rare tumors showing “dedifferentiation” or transformation to undifferentiated pleomorphic sarcoma. Dedifferentiation in mesenchymal neoplasms is a phenomenon of histologic progression of a well-differentiated neoplasm to a high-grade sarcoma which can differentiate along divergent lines. It is extremely uncommon to encounter “transdifferentiation” to non-mesenchymal lineage and still maintaining the driver genetic event of the primary tumor. Herein we report two diagnostically challenging SFTs with transformation to neuroendocrine and squamous phenotypes. The index case is a pelvic malignant SFT which metastasized to the liver as a high grade neuroendocrine carcinoma. The second case is a recurrent brain tumor initially presenting as a typical SFT and evolving into a dedifferentiated SFT with foci of squamous differentiation. Positive immunohistochemical stains for CD34 and STAT6 and the detection of NAB2-STAT6 fusion supported the diagnosis of dedifferentiated SFT in both cases. In the first case, molecular study demonstrated that both the pelvic primary and liver metastasis harbored the same NAB2-STAT6 fusion. Dedifferentiation to a non-mesenchymal lineage/lineage infidelity can be a potential diagnostic pitfall in these tumors.

Keywords

solitary fibrous tumor; dedifferentiation; malignant transformation; transdifferentiation; neuroendocrine carcinoma; squamous differentiation

1. Introduction

Solitary fibrous tumor (SFT) is an uncommon mesenchymal neoplasm of deep soft tissue which is classically described as a tumor composed of round to fusiform cells surrounding

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followed by cDNA synthesis. cDNA undergoes end repair, dA tailing and ligation with Illumina molecular barcode adapters. SPRI-cleaned ligated fragments are subject to two rounds of PCR amplifications using two sets of gene specific primers (GSP1 used in PCR1 and a nested GSP2 pool that is 3' downstream of GSP1 and used in PCR2) and a primer complementary to the Illumina adapter. At the end of two PCR steps the final targeted amplicons are fully functional and ready for sequencing on an Illumina Miseq instrument (2×150bp). The Archer™ analysis software V5.0 is used for data analysis.

3. Case Summary

3.1. Case 1

The patient is a 41-year-old man who presented with abdominal discomfort. CT scan showed a large mass (14 cm) in the pelvic mesentery. The tumor and the attached rectosigmoid colon were resected. Histology showed a spindle cell neoplasm with hemangiopericytic growth pattern (Fig. 1A). In some areas, tumor cells were separated by heavily hyalinized thick bands of collagen with interspersed gaping blood vessels and perivascular hyalinization (Fig. 1B). In other areas, the tumor cells formed short fascicles with focal epithelioid morphology and concentrated around thin capillary type blood vessels (Fig. 1C). In these hypercellular areas, mitoses up to 13/10 high power fields and necrosis were present (Fig. 1D). Immunohistochemical studies showed that the tumor was diffusely positive for CD34 in the collagenized foci (Fig. 1E) and showed focal positivity for STAT6 (Fig. 1F), SMA and desmin in the hypercellular areas. The tumor was negative for CD117, DOG-1, and S-100. Targeted RNA sequencing, using the MSK – Solid Fusion assay, detected an in-frame fusion between NAB2 Exon 6 (NM_005967) and STAT6 Exon 16 (NM_001178078) (Fig. 1G). A diagnosis of malignant solitary fibrous tumor was made. After surgery, the patient was followed by periodic CT scans with no chemotherapy or radiation. At 5 months after surgery, CT scan showed multiple abdominal and pelvic masses and a lesion in the left hepatic lobe. Needle core biopsy of the liver mass showed a high grade undifferentiated neoplasm morphologically different from the patient's primary pelvic SFT. The tumor was composed of round to epithelioid cells with brisk mitosis, fine chromatin, and inconspicuous nucleoli, forming occasional pseudorosettes (Fig. 2A, B). Immunohistochemical stains showed the tumor cells to be positive for cytokeratins (both pancytokeratin and Cam5.2) (Fig. 2C), synaptophysin (Fig. 2D), CD56 and CD117 (focal), and negative for DOG-1, desmin, myogenin and TTF-1. Ki-67 proliferation rate was > 95% (Fig. 2E). The morphology and immunohistochemistry favored a poorly differentiated neuroendocrine carcinoma. Given the patient's history of pelvic malignant SFT, immunohistochemical stain for STAT6 was performed and showed strong and diffuse positivity in tumor cells (Fig 2F). The MSK-Solid Fusion assay showed NAB2-STAT6 fusion product identical to the fusion seen in the pelvic SFT, confirming that the liver tumor was indeed a metastasis from the pelvic SFT and showing lineage infidelity/transdifferentiation to a neuroendocrine phenotype (Fig. 2G). The patient received Sunitinib treatment after liver biopsy and was alive with residual disease at last follow-up at two and a half months after biopsy.

3.2. Case 2

The patient is a 32-year-old woman who first presented with a left occipital tumor when she was 18 years old. The tumor was resected and diagnosed as meningeal hemangiopericytoma. She remained free of disease for 10 years and then suffered multiple local recurrences. The recurrences were treated surgically with chemotherapy and radiation. Review of the archived pathology material confirmed the primary tumor as a hemangiopericytoma (Fig. 3A, B) aka. classical SFT according to the WHO classification 2016. Anaplastic transformation/dedifferentiation to high grade sarcoma was seen in later recurrences (Fig. 3C). In the last recurrence, however, tumor exhibited, in addition to dedifferentiated anaplastic areas, a high-grade round cell component as well as foci of well differentiated squamous component (Fig. 3D, E). Immunohistochemical studies showed the dedifferentiated tumor was positive for CD34 and focally positive for STAT6. The foci of squamous differentiation were positive for 34BE12 (Fig. 3F), CAM5.2, p63, and STAT6. Molecular testing by the MSK-Solid Fusion assay detected NAB2-STAT6 fusion in the tumor, confirming the diagnosis. The fusion was an in-frame fusion between NAB2 Exon 6 (NM_005967) and STAT6 Exon 15 (NM_001178081) (Fig. 3G). The patient was followed for 3 more months after the last recurrence with no evidence of disease at last follow-up.

4. Discussion

Solitary fibrous tumor is classified by WHO as a tumor with intermediate malignant potential and rarely metastasizing [3]. The biologic behavior of this tumor has remained unpredictable and SFTs with increased mitoses (>4/10HPFs), hypercellularity, pleomorphism, tumor necrosis, and/or infiltrative margins have been reported to behave in a more aggressive manner [2, 3]. Other risk factors for metastasis may also include tumor site, size, and patient age [2]. Recently, Demicco et al. proposed a risk stratification model for development of metastasis in solitary fibrous tumors, which included 4 variables: age, tumor size, mitotic count, and necrosis [2]. The authors found this 4-variable stratification provided significant discrimination between risk groups [2]. The term dedifferentiated SFT was introduced in 2009 for tumors which show two histologically distinct components, one composed of pathological features of typical SFT and a well demarcated second component composed of an undifferentiated pleomorphic sarcoma, undifferentiated small round cell tumor (Ewing-like), rhabdomyosarcoma, osteosarcoma or chondrosarcoma[5]. While in the past CD34 was the widely used diagnostic marker for this tumor, in a recent study by Doyle et al. diffuse and intense STAT6 expression was seen in 59 out of 60 SFTs [1] with only a small percentage of other tumors such as dedifferentiated liposarcomas, deep fibrous histiocytomas, desmoid tumors, and neurofibromas showing weak and patchy positivity for STAT6[1, 6, 7], suggesting strong and diffuse STAT6 immunostain is sensitive and specific for SFT.

Currently, detection of NAB2-STAT6 rearrangement is considered as the most specific diagnostic marker for SFT. NAB2-STAT6 gene rearrangement was first identified in SFTs in 2013 [8, 9]. In one study, NAB2-STAT6 fusion was detected in all of the 51 SFTs examined [9]. Recent discovery of the same fusion and consistent positivity for STAT6 in meningeal hemangiopericytomas allowed unification of these tumors to a single phenotype [10]. It is

noteworthy to mention that the immunostain of STAT6 and CD34 may be absent or only focally present in dedifferentiated SFT. In a study by Dagrada et al, STAT6 protein expression was focal or absent in 9 out of 11 dedifferentiated SFTs whereas NAB2-STAT6 fusion was detected in all of the eleven tumors [11]. Thus, it appears that NAB2-STAT6 fusion is more sensitive and specific for dedifferentiated SFTs.

The incidence of dedifferentiation in SFT is rare. In the study by Mosquera et al. dedifferentiation was found in less than 1% of SFT cases (8 out of 948 cases) [4]. Collini et al. identified 10 dedifferentiated SFTs in their review of 233 cases [5]. In these reports, the dedifferentiated components were composed of pleomorphic sarcoma, fibrosarcoma, and rarely chondrosarcoma and osteosarcoma. Thus far an epithelial or neuroendocrine differentiation in a dedifferentiated SFT has not been reported to the best of our knowledge. In our first case, the dedifferentiated component was positive for synaptophysin and focally positive for cytokeratin, raising the possibility of a poorly differentiated neuroendocrine carcinoma. Importantly in this case, the liver metastasis was the diagnostic biopsy for the dedifferentiated SFT and could readily be construed as a neuroendocrine carcinoma based on location and immunophenotype. The focal squamous differentiation of our second case is perhaps not that unusual as rarely this phenomenon has been seen in other sarcomas, such as Ewing sarcoma [12]. In previous studies, it has been reported that dedifferentiated component of SFT can be Ewing sarcoma-like based on morphological features of a round cell tumor [5]. It is possible that these Ewing-sarcoma-like components might have similar epithelial and neuroendocrine differentiation as seen in our first case.

Multiple variants of NAB2-STAT6 fusion have been reported in SFT, however, their prognostic significance is not well established. Barthelmess et al. identified 12 different variants in 48 SFTs [13]. The most common variant, NAB2ex4-STAT6ex2/3, is associated with classic more benign pleuropulmonary SFTs. The second most common fusion variant, NAB2ex6-STAT6ex16/17, is associated with deep soft tissue, pelvic, and retroperitoneal SFT and more aggressive behavior [13]. In a similar study by Tai et al, there were 12 types of junctional breakpoints in 73 fusion-positive cases, with 65 (89%) falling into 3 major types: NAB2ex4-STAT6ex2, NAB2ex6-STAT6ex16, and NAB2ex6-STAT6ex17 [14]. Tai et al also showed that most of the SFTs with NAB2ex4-STAT6ex2 fusion variant are intrathoracic and this fusion did not correlate with disease free survival [14]. In a series of 40 cases, Akaike et al. showed that SFTs with NAB2ex6-STAT6 16/18 harbored aggressive histological features including dedifferentiation [15]. Our case of pelvic SFT and liver metastases harbored the NAB2ex6-STAT6ex16 fusion, consistent with the findings by Akaike et al. [15]. The second case had NAB2ex6-STAT6ex15 fusion, which has not been previously described.

In summary, here we present two cases of SFT with dedifferentiation/malignant transformation showing morphological and immunophenotypic features of epithelial and neuroendocrine differentiation and still maintaining STAT6 positivity and NAB2-STAT6 fusion. Awareness of this phenomenon can alleviate potential diagnostic challenges particularly in biopsy material.

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- Dedifferentiation is a rare phenomenon in solitary fibrous tumors.
- We report two diagnostically challenging cases of solitary fibrous tumor which dedifferentiated to neuroendocrine and squamous phenotypes.
- The diagnosis of both cases was confirmed by immunohistochemical stains for CD34 and STAT6 and molecular study of NAB2-STAT6 fusion.

Figure 1.

Photomicrographs of the pelvic mass of Case 1. (A) The tumor is composed of spindle and ovoid cells arranged in haphazard short fascicles (100X) and (B) shows prominent collagenous stroma (200X), (C) hemangiopericytoma-like vasculature (400X), and (D) round to ovoid cells with brisk mitosis (400X). Immunohistochemical studies show the tumor is positive for (E) CD34 (200X) and (F) STAT6 (nuclear staining, 200X). (G) the MSK –Solid Fusion assay diagram showing fusion between NAB2 Exon 6 and STAT6 Exon 16.

Figure 2.

Photomicrographs of the liver metastasis of Case 1. (A) Low power shows sheets of round and epithelioid cells (100X) with (B) pseudorosette like structures (400X). (C) Immunohistochemical studies show tumor cells are positive for pancytokeratin (200X) and (D) synaptophysin (400X). (E) Tumor has high Ki-67 labeling (200X) and (F) strong nuclear STAT6 immunostaining (400X). (G) the MSK-Solid Fusion assay diagram showing the same fusion between NAB2 Exon 6 and STAT6 Exon 16.

Figure 3.

Photomicrographs of the primary and recurrent tumors of Case 2. (A, B) The primary tumor shows features of typical SFT including stag-horn vasculature, densely populated oval to spindle cells around the blood vessels (200X, 400X). (C) The recurrent tumor shows an undifferentiated neoplasm with round cell morphology (400X). (D, E) Dedifferentiated round cell tumor with foci of squamous differentiation (100X, 200X). (F) The squamous cells are positive for 34βE12 (400X). (G) the MSK –Solid Fusion assay diagram showing fusion between NAB2 Exon 6 and STAT6 Exon 15.

Table 1

Clinical features of the 2 cases (dSFT: dedifferentiated solitary fibrous tumor).

Case #	Age at diagnosis	Sex	Location (primary)	Diagnosis (primary)	Treatment	Metastasis	Local recurrence	Follow up (duration after diagnosis of dSFT)	Outcome
1	41	M	Pelvic	Malignant SFT	Surgical removal	Liver, 5 months after resection of primary tumor	5 months after resection of primary tumor	8 months (2.5 months)	Alive
2	18	F	Left occipital	Typical SFT	Surgical removal	No	Multiple, first recurrence at 10 years after resection of the primary tumor	14 years (3 months)	Alive