—Original—

Expression and Localization of Basic Fibroblast Growth Factor and its mRNA in Solitary Fibrous Tumor

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Abstract

Solitary fibrous tumors (SFTs) represent a distinct neoplasm that should be included in the differential diagnosis of spindle-cell neoplasms of the soft tissue. Basic fibroblast growth factor (bFGF or FGF-2) is a mitogenic and angiogenic polypeptide produced by diverse cell types, including the cells derived from normal tissue and neoplastic lesions. In this study, the expression of bFGF, vimentin, CD 34, c-kit (or CD 117), desmin, S-100 protein, and α-smooth muscle actin (α-SMA) in SFTs, hemangiopericytomas (HPC), gastrointestinal stromal tumors (GIST), and dermatofibrosarcoma protuberans (DFSP) were evaluated to assess their usefulness in the differential diagnosis of these lesions. The expression of bFGF mRNA was also examined in SFTs by in situ hybridization (ISH) using a digoxigenin-labeled bFGF oligonucleotide probe. All the SFTs, GISTs and DFSPs exhibited strong and diffuse immunoreactivity for CD 34 and vimentin, and were completely negative for desmin, S-100 protein and α-SMA. The HPCs were positive for vimentin, but negative for CD 34. In all the SFTs, strong and diffuse nuclear immunostaining was observed with bFGF antibody, contrasting with the negative staining observed in the majority of the HPCs, GISTs, and DFSPs. The bFGF mRNA was also expressed in the SFT cells. The constitutive expression of the bFGF in the SFT widens the spectrum of available markers for these tumors, providing a useful addition to their differential diagnosis in difficult cases, and contributing to the understanding of their histogenesis and molecular pathogenesis.
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Key words: solitary fibrous tumor, basic fibroblast growth factor, immunohistochemistry, in situ hybridization

Introduction

Solitary fibrous tumors (SFTs) are uncommon neoplasms that most often involve the pleura, but can also arise at other serosal surfaces such as the pericardium and peritoneum or at non-serosal sites including the lung parenchyma, upper respiratory tract, orbit, thyroid, parotid gland, thymus, retroperitoneum, uterine cervix, liver, skin, prostate, and in the superficial soft tissues[1-9]. Most SFTs are characterized by a non-aggressive clinical course, although some can recur lo-

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cally or display malignant behaviors[1]. SFTs show a wide range of histological patterns including palisading, diffuse sclerosing areas and storiform or hemangiopericytomatous patterns. Various types of benign and malignant spindle-cell neoplasm must be considered in the differential diagnosis of SFTs.

SFTs arising from the lung or pleura are considered to be divided into localized fibrous tumors (LFTs) in the new Histological Classification of World Health Organization (WHO)[10]. Despite controversy regarding their histogenesis, SFTs are well-defined clinicopathologic entities exhibiting symptomatic features when they grow large or involve vital structures. Indeed, the histogenesis of SFT is more likely to be related to a CD-34 positive subset of spindle-shaped cells[11,12]. In most cases of SFT, neoplastic cells express high levels of CD 34, a 100 kD transmembrane protein expressed by hematopoietic precursors, normal and neoplastic endothelium, as well as interstitial fibroblastic cells present at various sites[11]. Accordingly, among the various immunohistochemical markers potentially useful in the diagnosis of SFT, CD 34 is currently considered to be the most reliable[13,14]. Nevertheless, a more precise immunophenotypic characterization of SFTs is still needed, because CD 34 is not a specific marker and some CD 34-negative SFTs have been reported[4,15].

We studied various immunophenotypical markers of SFT and found that all cases of SFT exhibited immunoreactivity to basic fibroblast growth factor (bFGF). bFGF is located on chromosome 4 and possesses three exons and two introns. Due to the different translation initiation sites, bFGF has four isoforms ranging from 18 to 26 kD. bFGF is believed to be important for the growth and neovascularization of solid tumors. Furthermore, bFGF can be observed in neoplastic cells and cells in tumor stroma including endothelial cells[16,17]. A secreted bFGF-binding protein has been proposed to serve as the angiogenic switch in cancer[18]. We analyzed a large series of the SFTs, HPCs, GISTs and DFSPs for bFGF by immunohistochemistry and in situ hybridization to evaluate its biological significance, and finally, to ascertain the possible diagnostic usefulness of bFGF as an adjunct marker of SFT.

Materials and Methods

Tissue samples

Thirty-five tissue specimens were retrieved from the authors' consultation files: 21 SFTs, 5 hemangiopericytomas (HPC), 5 gastrointestinal stromal tumors (GIST), and 4 dermatofibrosarcoma protuberans (DFSP). The tissue specimens had been fixed in formalin, and embedded in paraffin.

Immunohistochemistry

The monoclonal antibodies to vimentin (Clone V 9, Dako, Glostrup, Denmark; 1: 20), CD 34 (Clone Qbend 10, Immunotech, Marseille Cedex, France; 1: 100), c-kit (or CD 117, Dako, Kyoto, Japan; 1: 50), desmin (Dako, Glostrup, Denmark; 1: 25), S-100 protein (Dako, Glostrup, Denmark; 1: 1,000), and α-smooth muscle actin (α-SMA, Clone 1A4, Dako, Glostrup, Denmark; 1: 25) were used in this study. The polyclonal antibody to bFGF was purchased from Oncogene Science (Cambridge MA, USA, 1: 20). The labeling streptavidin biotin (LSAB) method using an LSAB kit (Dako, Carpinteria, CA) was performed according to the protocol of the manufacturers. The tissue sections with vimentin, bFGF, and c-kit antibody were preheated in a microwave oven in 10 mM citrate buffer, pH 6.0 for 15 minutes.

In Situ Hybridization (ISH)

The oligonucleotide probe for the bFGF (5'-CGG-GAA-GGC-GCC-GCT-GCC-GCC-3') and the sense probe (5'-GGC-GGC-AGC-GGC-GCC-TTC-CCG-3') were purchased from Greiner Japan (Tokyo, Japan). The oligonucleotides were then labeled with digoxigenin (DIG)-dUTP by the 3' tailing method using a DIG oligonucleotide tailing kit (Roche, Mannheim, Germany). ISH for the bFGF was performed on 12 cases of SFT as previously described[19]. Briefly, paraffin sections were deparaffinized in xylene, and dehydrated in descending grades (100 to 70%) of ethanol. They were then pretreated with proteinase K (100 ug/m*l*) and hybridized overnight with 100 ng/m*l* of DIG-labeled oligonucleotide probe. After the sections were washed, the hybridization signals were detected by alkaline phosphatase conjugated anti-digoxigenin antibodies using nitroblue tetrazolium and x-phosphate.

Results

Clinical findings

The clinical findings of the 35 cases are summarized in Table 1. The SFT group was composed of 12 women and 9 men (F: M ratio 1.3: 1) ranging in age from 29 to 89 years (mean 54). The patients with HPCs included 1 woman and 4 men ranging in age from 35 to 77 years (mean 52.6). The patients with GISTs included 2 women and 3 men ranging in age from 43 to 75 years (mean 59.5). The DFSP group was composed of 3 women and 1 man ranging in age from 48 to 71 years (mean 57).

Histological findings

The SFTs were composed of spindle cells arranged in a typically random 'patternless' pattern, with occasional neural-like or hemangiopericytoma-like areas characterized by the presence of dilated, branching, thin-walled blood vessels and with various amounts of wire-like collagen fibers (**Fig. 1A**). In contrast to the SFTs, the HPCs were typically cellular tumors composed of small, oval to slightly spindled cells. To a varying degree, all the tumors exhibited numerous

Table 1 Clinical Findings

Case	Sex	Age	Site	Size (cm)	Diagnoses
1	M	57	Right supradiaphragm	18×17.5×7	SFT
2	M	42	Prostate	5	SFT
3	F	50	Retroperitoneum	4.2×6.5	SFT
4	F	37	Right pleura	2.0×1.7×0.8	SFT
5	F	78	Left pleura	33×15×10	SFT
6	M	68	Iintrapelvic mass	14.2×9.5	SFT
7	M	NA	Inguinal soft tissue	NA	SFT
8	F	29	Brain, posterior fossa	3.5	SFT
9	F	80	Left pleura	3×3×1.8	SFT
10	F	44	Left pleura	7×6×2.5	SFT
11	F	89	Right pleura	3.5×2.3×3	SFT
12	M	52	Right pleura	12.5×12.5×7.5	SFT
13	F	67	Right pleura	3.7×2.5×1.7	SFT
14	M	44	Right pleura	3×2.5×1.8	SFT
15	F	47	Pleura	NA	SFT
16	F	48	Femur	5.5	SFT
17	M	41	Left pleura	6×6.5×3	SFT
18	F	61	Right pleura	NA	SFT
19	F	47	Left pleura	NA	SFT
20	M	51	Left shoulder	NA	SFT
21	M	49	Right popliteus	NA	SFT
22	M	77	Tongue	1.5×1.0×0.6	HPC
23	M	70	Left femur	NA	HPC
24	M	42	Right thigh	NA	HPC
25	M	35	Right temporal region	NA	HPC
26	F	39	Right breast	4.0×3.5×3.0	HPC
27	F	63	Stomach	6.0×4.5	GIST
28	M	43	Rectum	11×9×9	GIST
29	M	75	Liver	5.0×4.8×4.8	GIST
30	M	57	Liver	3×2×2	GIST
31	F	NA	Abdominal cavity	NA	GIST
32	F	48	Back	3.2×1.8×0.8	DFSP
33	F	52	Back	NA	DFSP
34	F	71	Abdomen	1.5	DFSP
35	M	NA	Back	NA	DFSP

NA : not available SFT : solitary fibrous tumor HPC : hemangiopericytoma
GIST : gastrointestinal stromal tumor DFSP : dermatofibrosarcoma protuberans

branching and thin-walled vessels (**Fig. 1B**). The GIST showed a spindle cell pattern with accumulations of extracellular collagen fibers (**Fig. 1C**). The DFSPs were characterized by cytologically bland spindled cells arranged in a monotonous storiform pattern and displaying a permeative growth into the subcutis (**Fig. 1D**).

Immunohistochemistry and in situ hybridization (ISH)

The immunohistochemical results are summarized in Table 2. The SFTs were characteristically vimentin, CD 34, and bFGF positive. All the SFTs, HPCs, GISTs, and DFSPs exhibited strong and diffuse immunoreactivity to vimentin, but not to desmin, S-100 protein or α-SMA. Strong and diffuse CD 34 expression was observed in all the SFTs, GISTs, and DFSPs and contrasted with the negative expression in the HPCs (**Fig. 2**). The GISTs also displayed strong c-kit positivity. Such staining was not seen in the SFTs, HPCs or DFSPs. All the SFTs and two cases of HPC exhibited intense and diffuse bFGF immunoreactivity, but it was not observed in all the GISTs and DFSPs (**Fig. 3**). bFGF immunoreactivity was observed in the nuclei of the SFTs, but it was detected in the cytoplasm of the HPCs. In all 12 cases of the SFT examined, bFGF mRNA was expressed in the cytoplasm of the tumor cells by ISH. No positive signal for bFGF mRNA was observed in the SFTs with the sense probe (**Fig. 4**).

Table 2 Immunohistochemical Findings

Stain	SFT (N=21)	HPC (N=5)	GIST (N=5)	DFSP (N=4)
Vimentin	21/21	5/5	5/5	4/4
CD34	21/21	0/5	5/5	4/4
c-kit	0/21	0/5	5/5	0/4
desmin	0/21	0/5	0/5	0/4
S-100 protein	0/21	0/5	0/5	0/4
α-SMA	0/21	0/5	0/5	0/4
bFGF	21/21	2/5	0/5	0/4

SFT : solitary fibrous tumor HPC : hemangiopericytoma GIST : gastrointestinal stromal tumor DFSP : dermatofibrosarcoma protuberans α-SMA : α-smooth muscle actin bFGF : basic fibroblast growth factor

Discussion

SFTs are a distinctive neoplasm first described in 1931 by Klemperer and Rabin[20]. Typically, SFTs are slow-growing, often pedunculated pleural tumors that most often occur in the fourth to fifth decades of life. However, they have also been found in numerous extrapleural sites[1-9]. In general, SFTs are diagnosed on the basis of its histologic features, with immunohistochemistry serving to support the diagnosis. Histologically, it is characterized by a typical morphologic appearance of alternating hypo- and hyper-cellular areas of spindle shaped cells, dense bands of collagen, and a hemangiopericytomatous vascular pattern. Because its morphologic pattern is not specific and there are no distinctive immunohistochemical features, it may be difficult to separate this tumor from other spindle cell neoplasms such as HPC, GIST, and DFSP. HPCs are the most difficult to distinguish from the extrapleural SFT. The variable clinical course associated with the HPC may reflect a misdiagnosis of the SFT as hemangiopericytoma. In fact, it has been found that some cases of SFT have been originally diagnosed as hemangiopericytoma because of the uniform hemangiopericytic pattern, but recurrent lesions showed the classic "patternless" pattern with hypo- and hypercellular areas of SFT[21]. Similar to SFTs, GISTs are also known for their variability in clinical behavior[22]. The DFSP is a dermal neoplasm of borderline malignancy, and shares with the SFT both morphological similarities and consistent CD 34 immunoreactivity, which may be potentially misleading[23].

Immunohistochemical examinations used to characterize SFTs have included reactivity to vimentin, CD 34, bFGF, S-100 protein, α-SMA, and desmin. In our series, the reactivity to vimentin and CD 34 was consistently positive to all SFTs, DFSPs, and GISTs, but the HPC was positive for vimentin, but negative to CD 34. However, CD 34 reactivity in the HPC has been previously reported[4,24]. CD 34, originally described as a hematopoietic progenitor cell antigen, has been identified subsequently in normal and neoplastic endothelial cells and in some other soft tissue tumors, particularly SFTs, GISTs and DFSPs[4,14,25]. The presence of this marker has been used to distinguish SFTs

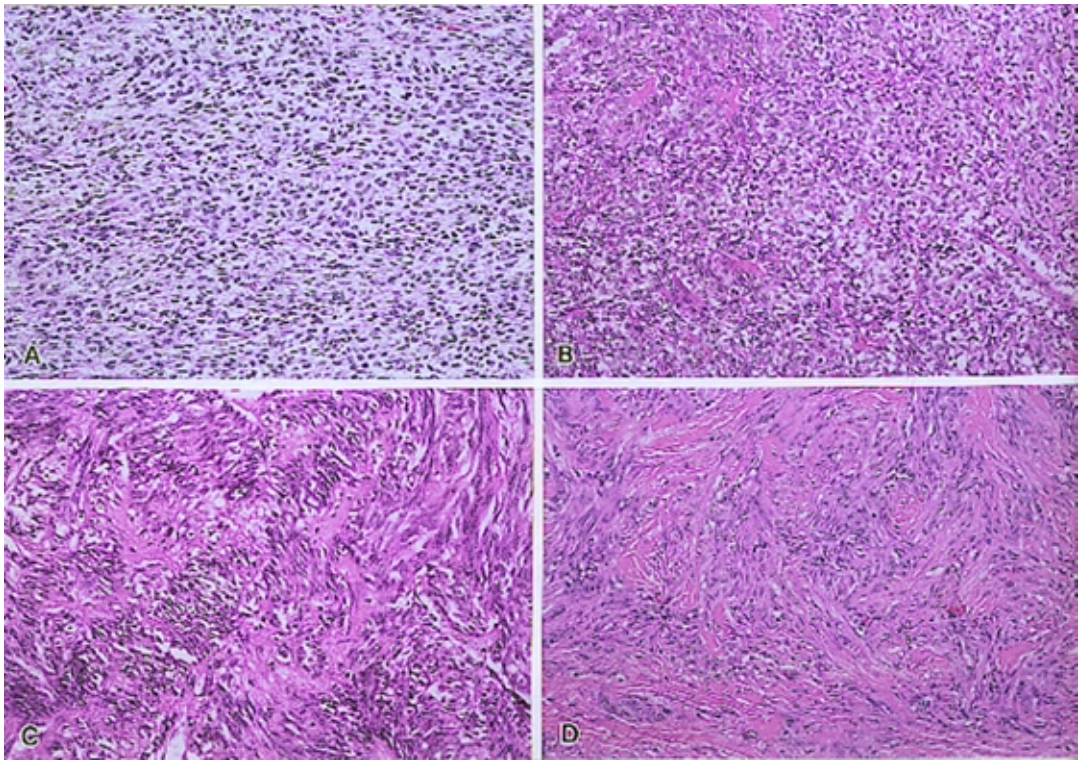

Fig. 1 H & E stain. A: Solitary fibrous tumor showing bland spindle shaped cells and disposition of collagen. B: Hemangiopericytoma. Ramifying vascular channels lined by endothelial cells show marked proliferation of spindle cells. C: Gastrointestinal stromal tumor. Spindle cells arranged in swirling fascicles. D: Dermatofibrosarcoma protuberans shows the appearance of radial whorls of spindle cells producing the storiform or cartwheel pattern. (×200)

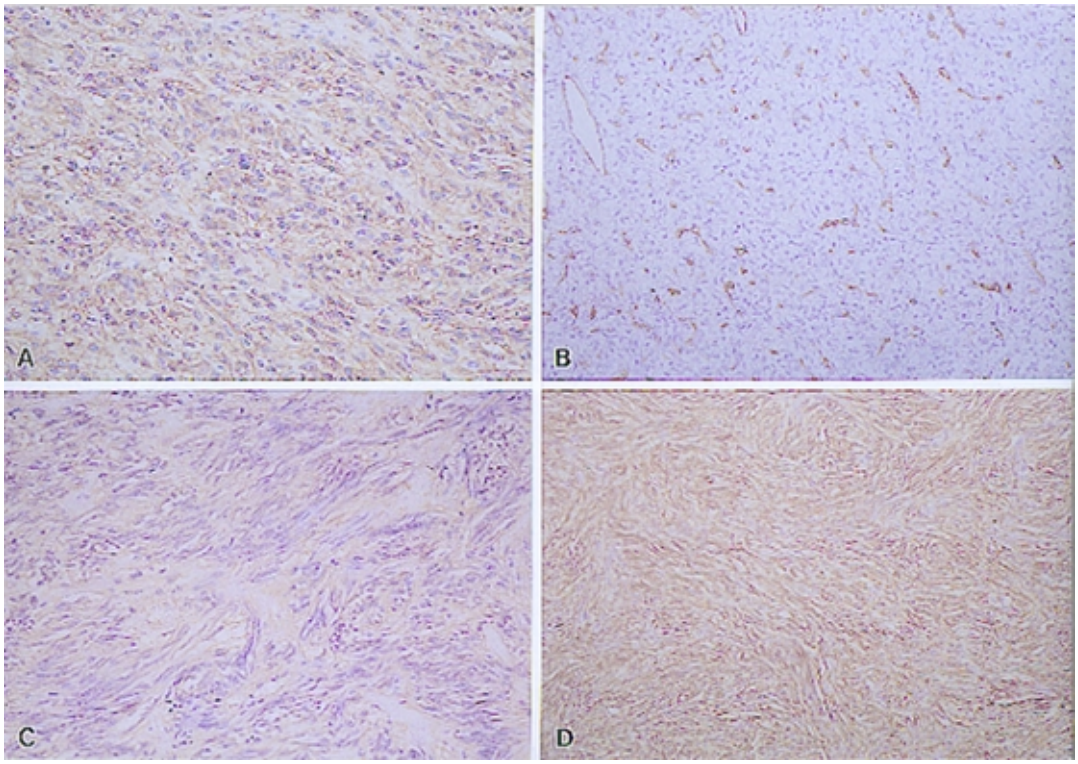

Fig. 2 Immunohistochemical staining of CD 34. CD 34 immunoreactivity was localized in solitary fibrous tumor (A), gastrointestinal stromal tumor (C), and dermatofibrosarcoma protuberans (D). In hemangiopericytoma, CD 34 immunostaining shows positive for vascular endothelium, but negative for the tumor cells (B). (×200)

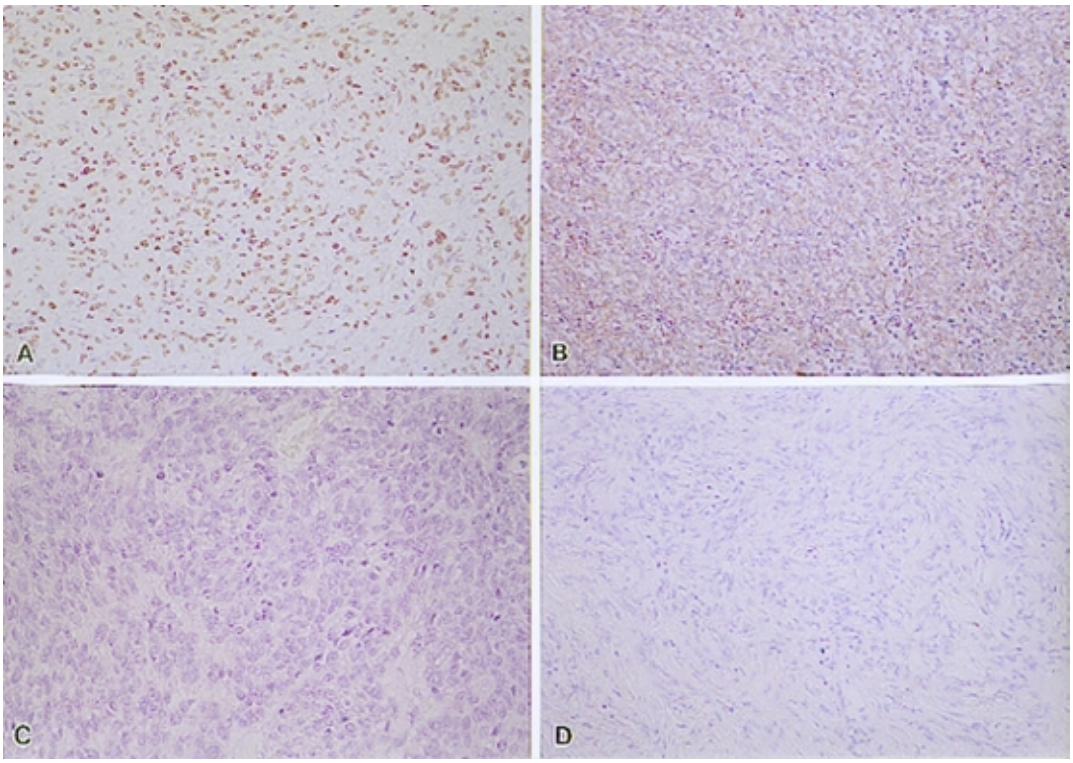

Fig. 3 Immunohistochemical staining of basic fibroblast growth factor (bFGF). bFGF immunoreactivity was localized in the nuclei of SFT (A) and in the cytoplasm of HPC (B), but not in GIST (C), and DFSP (D). (×200)

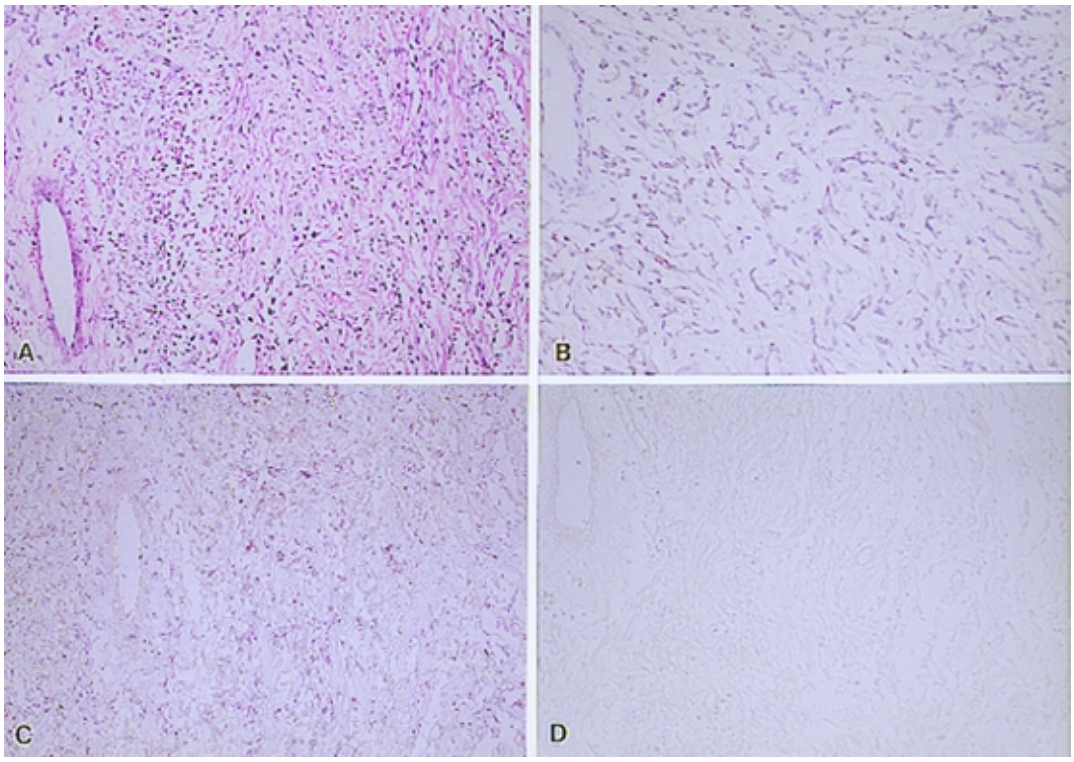

Fig. 4 The expression of basic fibroblast growth factor (bFGF) in the solitary fibrous tumor (SFT). A: H&E stain. B: bFGF immunoreactivity was localized in the nuclei of SFT. C: In situ hybridization (ISH) analysis showed bFGF mRNA was expressed in the tumor cells of SFT. D: ISH using a sense probe of bFGF revealed no positive staining in SFT. (×200)

from other tumors. Despite this, CD 34 cannot be used to distinguish SFTs from HPCs, GISTs, and DFSPs. Moreover, the absence of immunoreactivity to CD 34 does not exclude the diagnosis of SFT, because a few cases of SFT do not react for CD 34[4,15]. The use of a wider spectrum of immunocytochemical markers, including the bFGF, may result in a more precise characterization of the SFT.

bFGF is a mitogenic polypeptide produced by diverse tissues and is capable of promoting angiogenesis and mitogenesis through autocrine and possibly paracrine mechanisms in a wide variety of normal or transformed cells[26]. The presence of multiple forms of bFGF protein ranging from 18 kD to 26 kD in the endothelial and smooth muscle cells has been observed[27,28]. The localization of bFGF protein in the cells may be dependent on its molecular size. The 18 kD protein is considered to be predominantly localized within the cytoplasm, in contrast to the 21.5～26 kD forms, which are found mainly in the nuclei, supporting the notion of different biological functions for these proteins[27-29]. The localization of bFGF was very intense in the nuclei of tumor cells in all SFTs, whereas GISTs and DFSPs were completely negative. These findings further expand our knowledge regarding the phenotypical features of this peculiar tumor and can provide useful diagnostic information in difficult cases, especially when bFGF is used in combination with other markers, such as CD 34. The frequent presence of a prominent hemangiopericytomatous pattern can lead to the misdiagnosis of HPC. HPCs do not express any of the markers that would allow distinction from SFTs and show positivity for CD 34 and bFGF in some cases, which raises the question of a possible relationship between these two tumors. At present, it is often impossible to distinguish some SFTs from HPCs. However, bFGF immunoreactivity was observed in the nuclei of SFTs, but in the cytoplasm of HPCs. Therefore, the cytoplasmic localization of bFGF protein in HPCs may help to differentiate in the diagnosis of SFTs.

The lack of specificity of the histologic and immunohistochemical findings and data on the molecular mechanisms of SFTs probably reflect the histogenesis of this neoplasm, which has been debated since its initial description in 1931. bFGF, originally identified based on its mitogenicity to fibroblasts, has been shown to have a profound effect on various cell types influencing either proliferation or differentiation. The targeting of high molecular mass forms of bFGF to the nuclei is determined by the RG amino acid repeats located at multiple sites within the amino-terminal extension[28]. The specific function of these nuclear isoforms of bFGF is at present unclear. However, studies by Bouche et al. have suggested a direct effect of bFGF on the ribosomal gene expression[30]. Further, Tsuboi et al. have reported that clones of bovine capillary endothelial cells that expressed high levels of bFGF had a spindle morphology[31]. These observations may indicate that a possible explanation for the expression of bFGF in SFTs is the induction and localization of the high molecular weight bFGF isoform to the nuclei. The direct biological effects of the nuclear bFGF on cell proliferation are not yet precisely characterized. It is conceivable that nuclear bFGF may act as a mitogenic factor by initiating the activation of the genes or enzymes responsible for cell cycling in the nuclei. The overexpression of bFGF has been found in several human cancers[32,33]. Evidence is mounting that bFGF plays an important role in the interaction between malignant cells and their stromal environment. The above results support the possibilities that tumor cells are a cellular source of bFGF and that the bFGF expression of those cells is also one of the influencing factors in the development of SFT.

In summary, SFT is a rare lesion that can arise in virtually any location, and can be confused with several benign and malignant neoplasms. In this study, there was substantial immunohistochemical overlap among SFTs, HPCs, GISTs, and DFSPs. The observation that four tumors share vimentin and CD 34 positive immunotype suggests a histogenetic relationship, especially since SFT and HPC are closely related and probably in the same entity. The results of this investigation indicate that the bFGF expression may be useful in the differential diagnosis between SFT and the other CD 34-positive spindle cell tumors. We also recommend using bFGF in combination with other markers such as CD 34, vimentin, desmin, and S-100 protein. In this context, the bFGF expression may help in avoiding diagnostic confusion.

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