Synovial Sarcoma in Knee Joint, Mimicking Low-grade Sarcoma Confirmed by Molecular Detection of *SYT* Gene Split

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Abstract. *A 10-year-old boy underwent arthroscopic curettage for an intra-articular mass in knee joint. The tumor was diagnosed as low-grade fibrous sarcoma. Five years later, the patient presented with a recurrent tumor. The patient underwent a marginal excision with knee joint preservation and without adjuvant therapy. Two years after the last surgery, the patient is thriving with no evidence of recurrent or metastatic disease. The final diagnosis was synovial sarcoma confirmed via a SYT gene split performed with fluorescent in situ hybridization (FISH), although the tumor appeared as a low-grade fibrous type in a hematoxylin-eosin section. The first curetted specimen was also confirmed to bear a SYT gene split. Synovial sarcoma has been conventionally recognized as a high-grade sarcoma. Our patient had a tumor that exhibited the characteristics of both a histologically and clinically low-grade tumor. From the present case, we consider that low-grade variants of synovial sarcoma do exist although their existence remains controversial.*

Intra-articular tumors are rare, and most of them are benign types, such as lipomas, synovial hemangiomas, synovial osteochondromatosis, pigmented villonodular synovitis, giant cell tumors of tendon sheath, and ganglions (1). Even though synovial sarcomas rarely occur in joints, they occur primarily in extra-articular areas of the extremities near tendon sheaths and are the most frequent malignancies among intra-articular tumors. It has been reported that intra-articular synovial sarcomas account for <5% of all synovial sarcomas (1, 2).

Cytogenetic and molecular studies show that synovial sarcomas are associated with a specific chromosomal translocation between chromosome X and chromosome 18, t(X; 18). This translocation results from a split of the SYT gene on chromosome 18 at locus q11.2 and *SSX* gene on chromosome X, generating the *SYT-SSX* fusion gene (3-5). It has been reported that the specificity of the detection of the *SYT-SSX* fusion gene by using reverse transcription polymerase chain reaction (RT-PCR) or the *SYT* gene split by using fluorescent *in situ* hybridization (FISH) in the diagnosis of synovial sarcoma, is 100% (4, 5).

The present study presents a rare case of synovial sarcoma occurring in the knee joint of an adolescent male, histologically-mimicking a low-grade sarcoma. The diagnosis was confirmed *via* the presence of the *SYT* gene split by FISH.

The study was approved by our University ethical committee and has been performed in accordance with the ethical standard laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the patient and his parents for publishing this case report.

Case Report

A 10-year-old boy presented to its local Hospital in 2006, with pain and limited range of motion in the right knee joint. Magnetic resonance imaging (MRI) showed a tumor anterior to the posterior cruciate ligament (PCL) in the right knee joint; the tumor had a low signal in the T1-weighted image and heterogeneous high signals in the T2-weighted images (Figure 1). The tumor was clinically suspected to be a ganglion, and arthroscopic resection (intralesional curettage) had been performed at the previous treating hospital. Pathological findings revealed that the tumor appeared as a low-grade sarcoma. The patient had been followed-up every year with an MRI. However, 2 years after the first surgery, a recurrent gradually-developing tumor was identified. The patient was then referred to the authors' Institution in 2011 at the age of 15 years.

Physical examination revealed a limping gait due to 30˚ extension restriction of the right knee joint and atrophy of the entire right extremity. Laboratory data were normal. Plain

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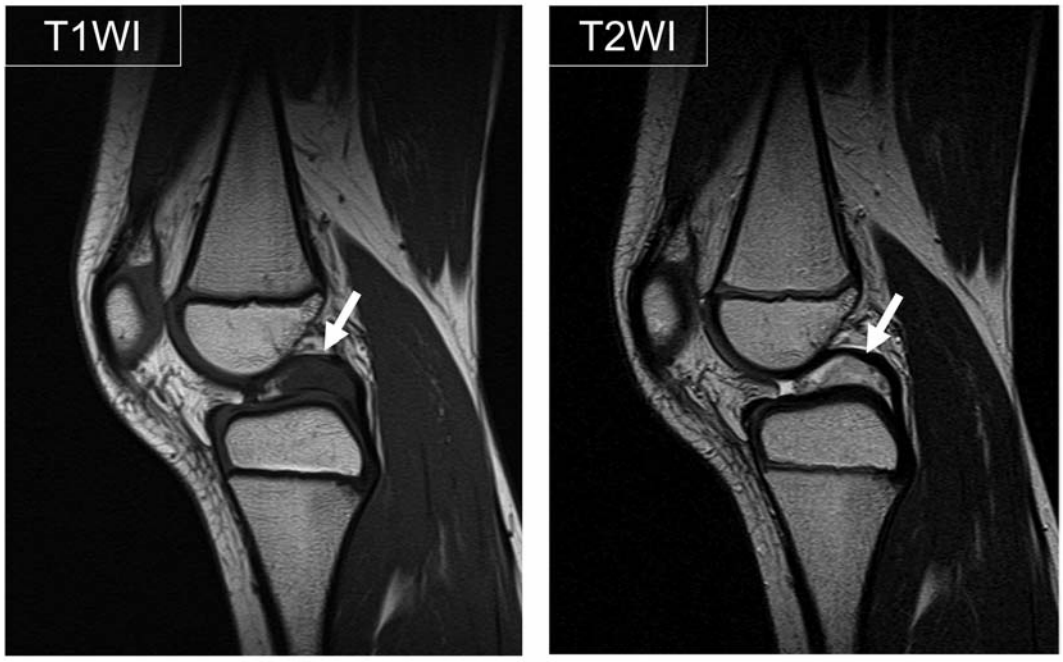

Figure 1. *An MR image taken at a first surgery. A mass is located in front of the PCL with low intensity in the T1-weighted image and heterogeneous high intensity in the T2-weighted images.*

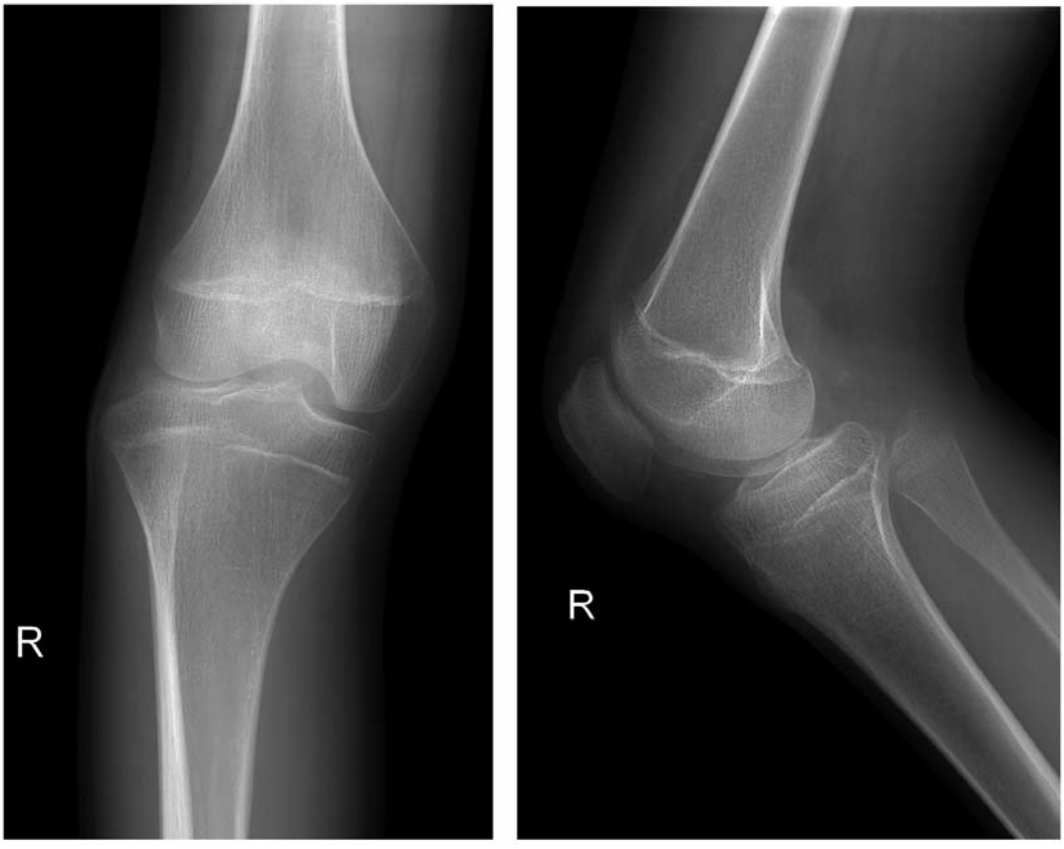

Figure 2. *A radiograph taken at the initial visit to our Hospital, showing a lateral tibial thrust at the right knee joint.*

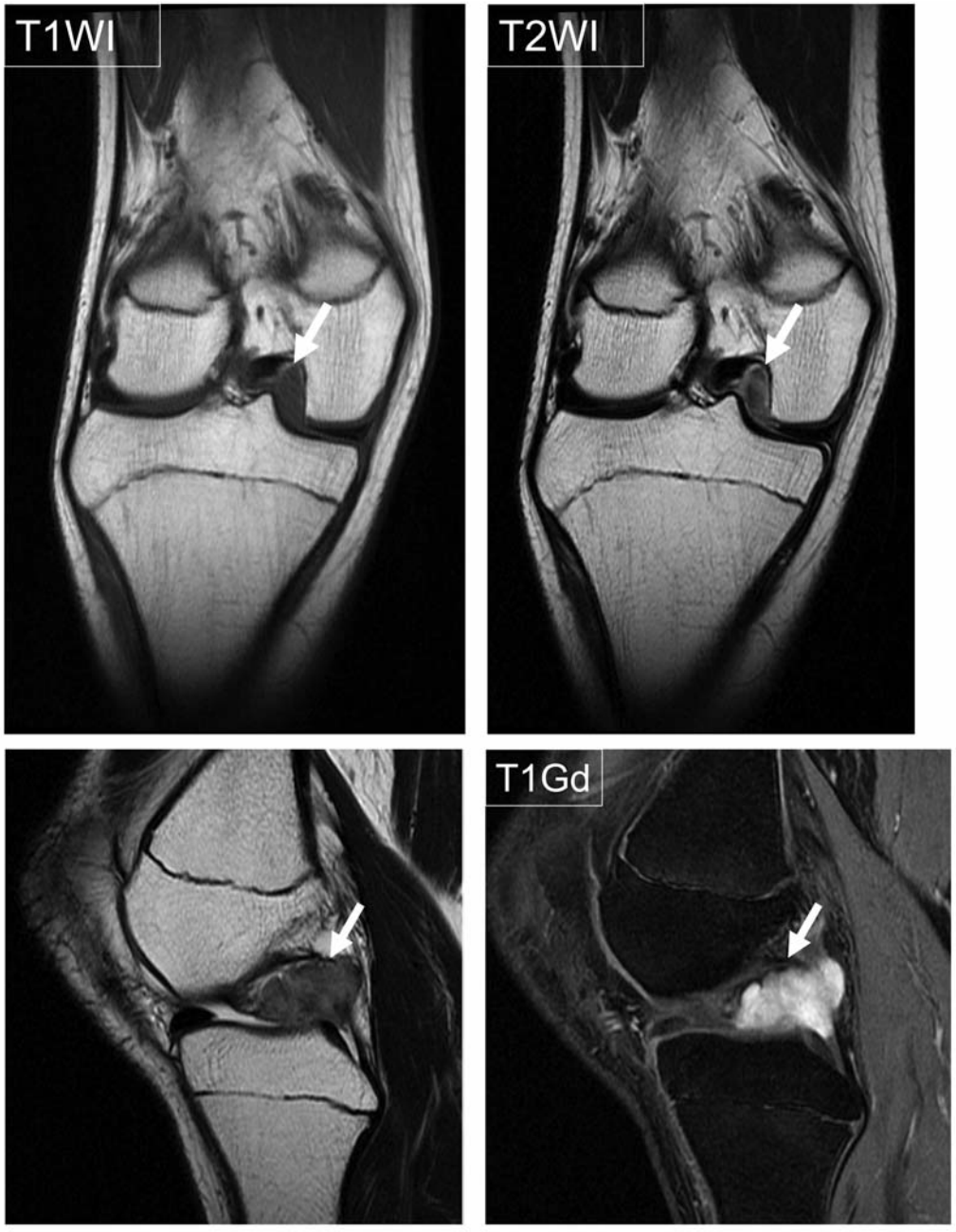

Figure 3. *An MR image taken at the initial visit to our Hospital. Recurrent tumor was found in the intercondylar fossa adjacent to medial condyle, with the same intensity of the primary tumor and strong enhancement with gadolinium on T1-weighted image.*

radiographs showed a lateral tibial thrust of the right knee joint (Figure 2). MRI scans revealed a recurrent tumor in the intercondylar fossa adjacent to medial condyle, with the same intensity as the primary tumor and strong enhancement in T1-weighted image after administration of gadolinium (Figure 3). No pulmonary metastasis was detected on chest computed tomography (CT).

After consultation with the patient and his family, marginal excision was performed to preserve the knee joint. A surgical incision was made on the popliteal fossa, and after opening a joint capsule, there was a well-circumscribed, white lobulated tumor that was attached to the medial condyle and PCL (Figure 4). The tumor was completely excised together with a fraction of the PCL. The patient did

not receive any adjuvant therapy, such as radiotherapy or chemotherapy. Two years after the last surgical intervention, the patient is thriving with no evidence of recurrent or metastatic disease.

Pathological findings. Grossly, the tumor measured 2.1×2.0×1.5 cm and had a smooth surface. It was lobulated and whitish gray in color (Figure 5). Histologically, the tumor displayed nodular proliferation of spindle cells with fibrous and myxomatous stroma. Collagen fibers, calcification, and a herringbone pattern were observed focally. Mitotic figures and cellular atypism were not remarkable (Figure 6). Immunohistochemically, the tumor cells were positive for vimentin, and focally positive for a-SMA. Stains for epithelial markers such as cytokeratin, AE1/AE3, and epithelial membrane antigen were negative in the tumor, and CD34, bcl-2, and MUC4 were also negative. The Ki-67 labeling index of the tumor was <1%. The specimen resected at the previous hospital had similar features. Although the tumor was first suspected to be of low-grade fibrous type, we sought to detect the presence of an *SYT* gene split by using FISH because synovial sarcoma was considered part of the differential diagnosis.

FISH was performed by using an LSI *SYT* Dual Color Break-Apart Rearrangement Probe (Vysis, Abbott Laboratories Inc., Maidenhead, Berkshire, UK). One end of the probe was labeled with spectrum orange™ (telomeric, 5' to SS18, 650 Kb) and the other with spectrum green™ (centromeric, 3' to SS18, 1040 Kb). Sections were de-paraffinized in xylene (3×5 min) and dehydrated in ethanol (3×3 min). Sections were pre-treated by using Paraffin Pretreatment Reagent Kit II (Vysis). This involved placing the slides in 50 mL of pre-treatment solution at 80˚C for 50 min, followed by 3 min in distilled water, 20 min in a protease solution at 37˚C, washing in distilled water for 3 min, and dehydration for 1 min in increasing concentrations of alcohol (70, 85, and 100%) after which they were air-dried. Ten microlitres of probe mixture (1 μL probe, 2 μL dH_2O and 7 μL hybridizing buffer) were applied to the slides and overlaid with a coverslip, which was sealed with rubber cement. The slides were denatured for 5 min at 73˚C and hybridized for at least 16 h at 37˚C. Following hybridization, the slides were washed twice with saline sodium citrate/0.3% NP40 at room temperature for 5 min, at 73˚C for 2 min, and again at room temperature for 1 min. After air-drying in the dark, the section was counter-stained with a DAPI-II antifade solution (Vysis). The slides were analyzed under a fluorescence microscope (Olympus, Tokyo, Japan) equipped with a mercury lamp, DAPI/FITC/Rhodamine triple filter, and individual DAPI, FITC, and rhodamine filters. A probe was considered to be split when the orange and green signals were separated by a distance greater than the size of one hybridization signal (spectrum orange 650 kb). We analyzed both resected tumors, the one obtained at our Institution and the one from the previous Institution, and confirmed an *SYT* gene split in both tumors (Figure 7).

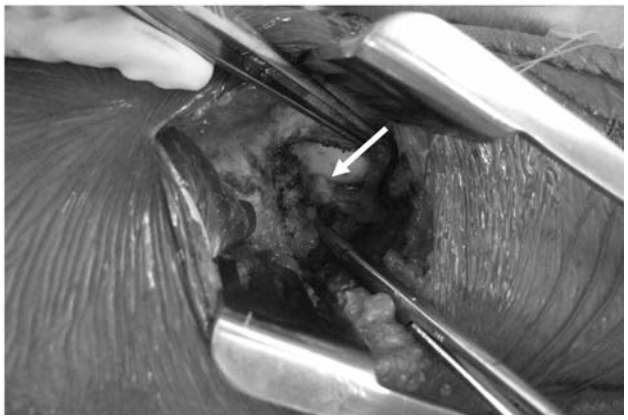

Figure 4. *Intraoperative findings. After opening the joint capsule, there was a well-circumscribed, white lobulated tumor that was attached to the medial condyle and PCL.*

Discussion

Intra-articular synovial sarcoma is extremely rare and there have been few reports of well-documented cases (6-8). In most cases, intra-articular synovial sarcoma was clinically mistaken for benign articular diseases, such as synovial osteochondromatosis, pigmented villonodular synovitis, and intra-articular loose bodies (8-10). In this case, the tumor was also suspected as being a benign tumor based on its clinical course, radiographic findings, and location. The patient then underwent curettage at the previous Institution. It is difficult to assess the precise characteristics and the prognosis of intra-articular synovial sarcoma as it is exceedingly rare. One patient reported by McLain *et al*. died 4 months after surgery, with multiple pulmonary metastases (9). Another patient, described by McKinney *et al*. showed no evidence of disease 9 years after local excision (10). Some factors for synovial sarcoma have been associated with poor prognosis, such as deep tissue location, large tumor size, monophasic subtype, high histologic grade, and metastasis at presentation (11-13). However, it is unclear whether the occurrence of this synovial sarcoma in a joint could affect the prognosis of the patients.

Despite tumor recurrence and long disease duration, this case was contained locally and no metastasis was observed after the last marginal excision. This might be because of the histologically-inconspicuous aspect of this particular tumor. According to the Federation Nationale des Centres de Lutte le

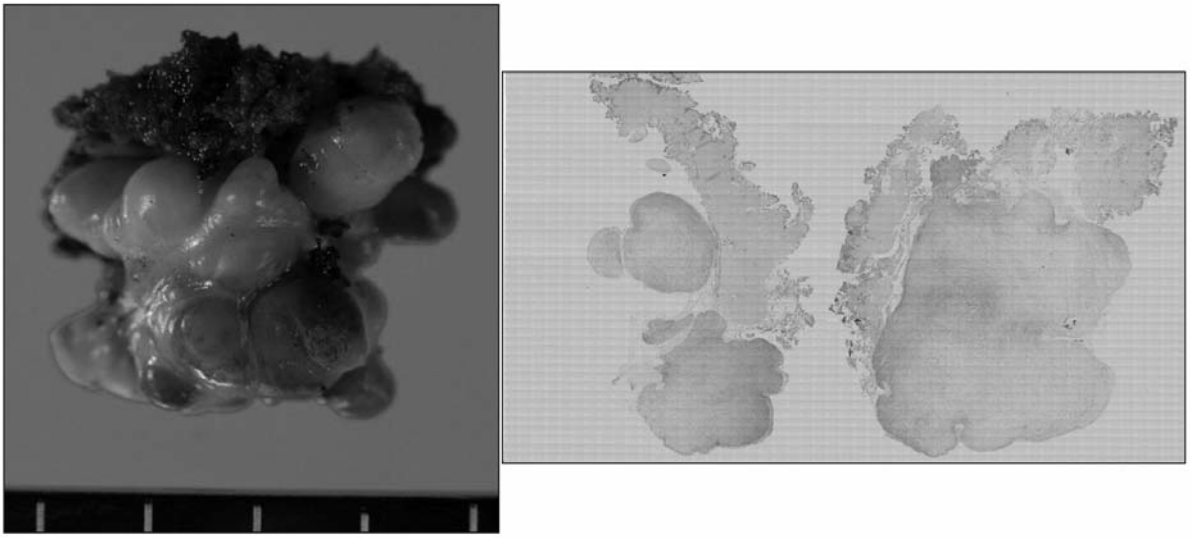

Figure 5. *Gross pathology. The tumor had a smooth lobulated surface.*

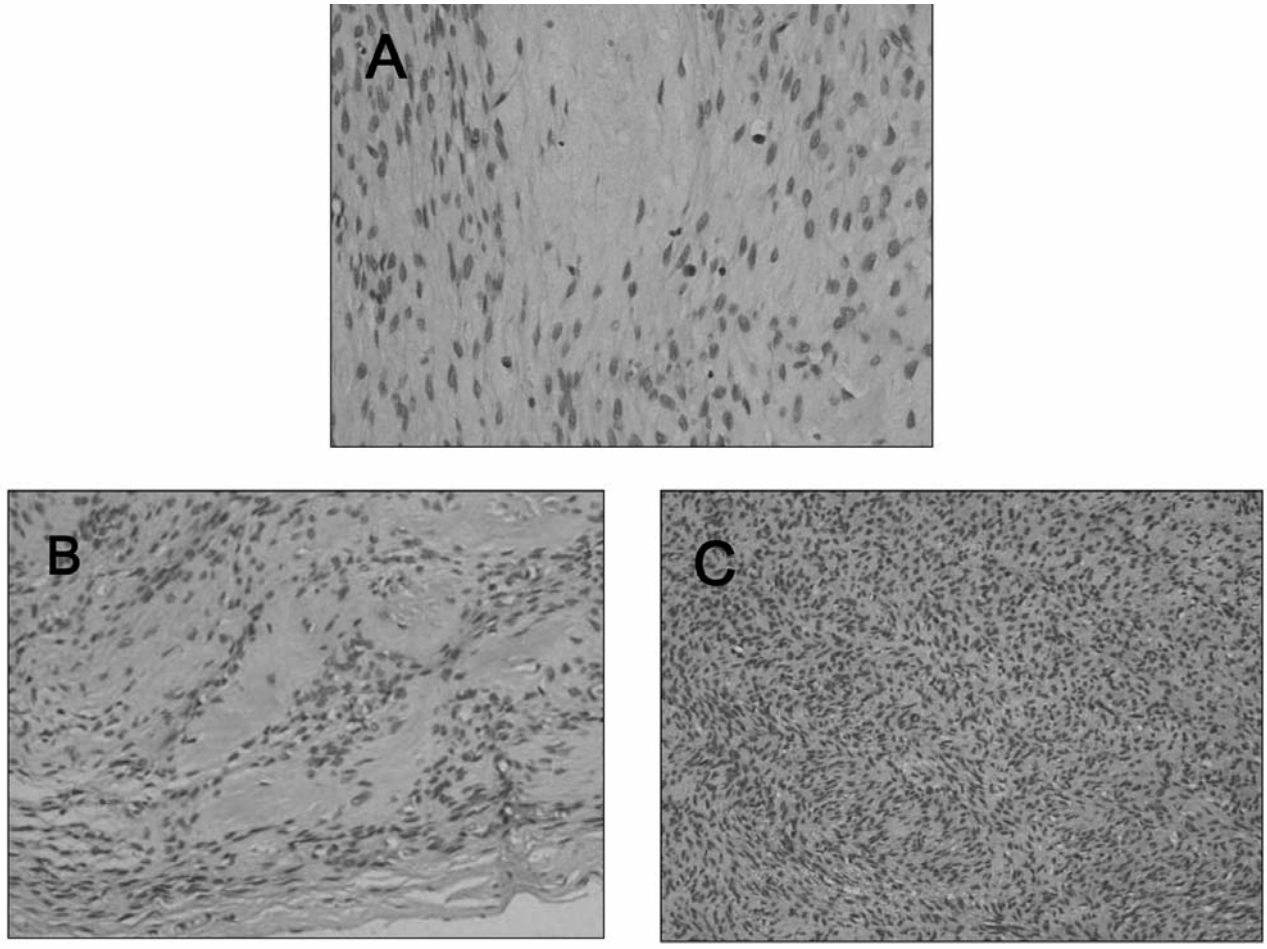

Figure 6. *Histological findings. Nodular proliferation of spindle cells with fibrous and myxomatous stroma was found (A). Collagen fiber, calcification (B) and herring-bone pattern (C) was focally observed.*

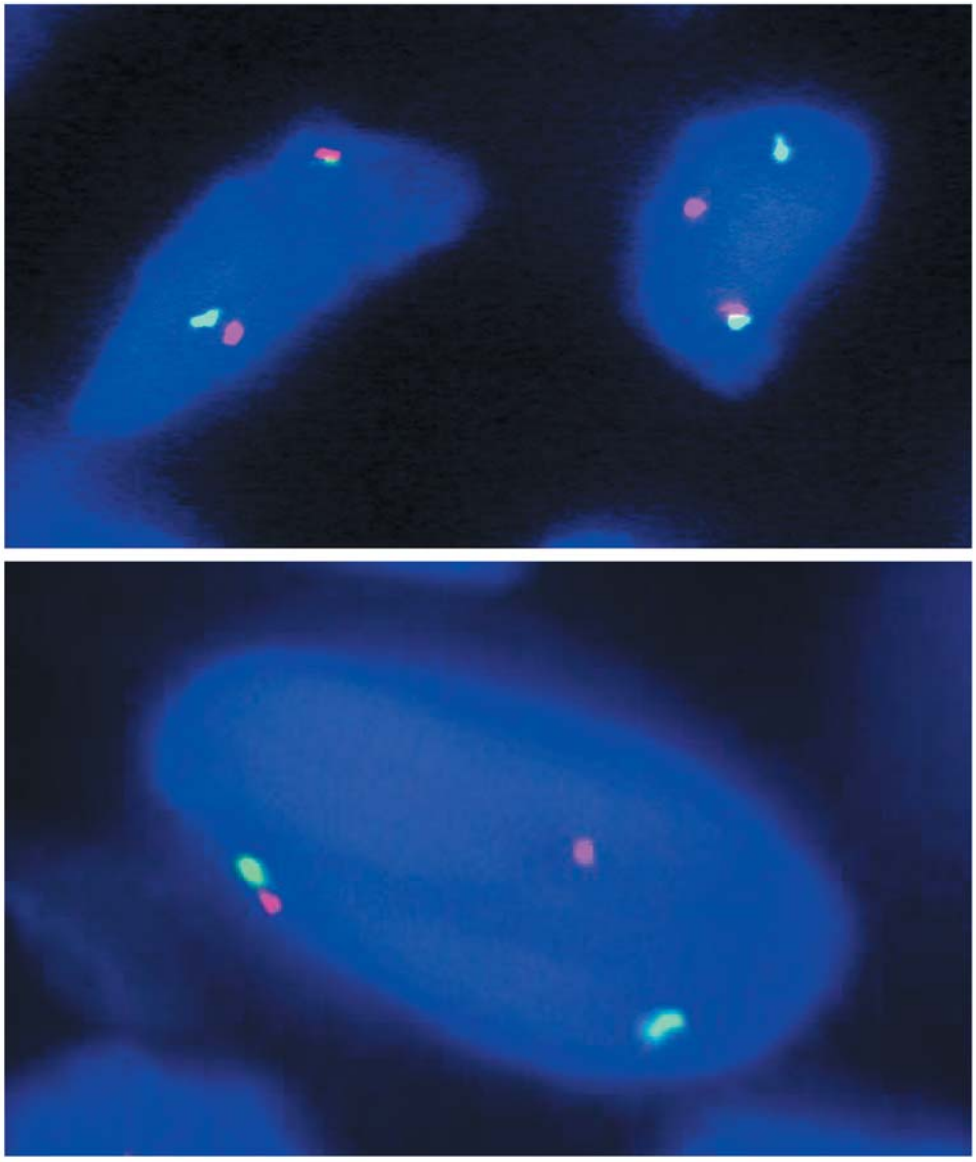

Figure 7. *FISH for the SYT gene split. Cells carrying the SYT gene break specific for synovial sarcoma demonstrate one red, one green, and one fusion orange signal pattern.*

Cancer (FNCLCC) system (14), synovial sarcoma is automatically assigned a differentiation score of 3, regardless of the actual morphological degree of differentiation. Thus, each tumor is scored as 1-3 for numbers of mitoses (0-9, 10-19, 20, or more) and 0-2 for percentage of necrosis (0, <50%, or >50%). Grade 2 tumors have a total score of 4 or 5, and Grade 3 tumors, a score of 6, 7, or 8. As a result, synovial sarcoma could be classified as either Grade 2 or 3. In the present case, the total FNCLCC system score was 4 and the tumor was classified as Grade 2. However, this tumor had the histological appearance of a low-grade tumor at first glance. Synovial sarcoma has been conventionally recognized as a high-grade sarcoma with poor prognosis. Nevertheless, it has become apparent that low-grade variants exist in a small percentage (15). Some authors believe that histological grade is not a prognostic factor for synovial sarcoma, which should be considered a uniformly high-grade tumor (16, 17). Other authors have reported that histological grade is of prognostic value in synovial sarcoma (11, 18). Thus, this is still a controversial issue. However, from the clinicalal course of this case, we believe that histologic grade and findings, such as mitosis and necrosis, might affect the prognosis of patients with synovial sarcoma. It might be also controversial how intra-articular synovial sarcomas with such low-grade aspect

should be treated (wide excision with extra-articular resection or marginal excision with joint preservation).

In conclusion, through this case report, we recommend that intra-articular synovial sarcoma should be considered as a diagnostic possibility for intra-articular tumors. Taken together, this patient's clinical outcome and the results of other case reports suggest that the histological grade of synovial sarcoma could be a relevant prognostic factor.

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