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Case Report

Pelvic cavity malignant solitary fibrous tumor with dedifferentiation and multifocal cytokeratin expression

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Abstract: Pelvic cavity small-sized malignant solitary fibrous tumors are rare. Surgeons easily misjudge these tumors as benign lesions, and they are usually resected by laparoscopic surgery. When accompanied by dedifferentiation, malignant solitary fibrous tumors are difficult to diagnose by pathologists. Here, we describe a challenging case. A 47-year-old man was accidentally found to have a pelvic mass after three months. Surgeons assumed a diagnosis of a benign tumor according to the Computed Tomography and Ultrasonography reports. The patient underwent laparoscopic surgery to resect the tumor. After the operation, the patient was diagnosed as having a malignant solitary fibrous tumor with dedifferentiation. The patient had a recurrence one year later. This pelvic cavity malignant solitary fibrous tumor was a rare case because of its dedifferentiation and cytokeratin expression. The expression of cytokeratin and the absence of vimentin and CD34 were pitfalls to diagnosis. In this case, there was still a high amount of malignancy despite the small size of the tumor. Clinical image and pathologic multidisciplinary analysis and core needle biopsies before surgery had a great effect on diagnosis and therapy of this disease. The case is a cautionary tale not only for pathologists but also for surgeons.

Keywords: Malignant solitary fibrous tumor, dedifferentiation, cytokeratin, CD34, vimentin, STAT-6, differential diagnosis

Background

Solitary fibrous tumors (SFTs) are uncommon mesenchymal spindle cell tumors. SFTs derive from fibroblasts and often occur in the visceral pleura [1]. SFTs can occur in any extrapleural area, such as head and neck, pelvic cavity, abdominal cavity, retroperitoneum, and surrounding soft tissues. The median age of SFT onset is between 40 and 60 [2]. Since 1931, when Klemperer and Rabin first reported five cases of solitary fibrous tumor that originated in the pleura, researchers and pathologists have gradually recognized solitary fibrous tumor as an independent tumor. Clinically, most patients present with slow-growing painless masses, and the majority are found by coincidence. Tumors located in the pelvic cavity and abdomen may result in abdominal distension or obstruction symptoms. Malignant solitary fibrous tumors (MSFTs) accompanied by dedifferentiation are a newly discovered, rare phenomenon. Our team diagnosed a case of MSFT accompanied by dedifferentiation in the pelvic cavity of a 46-year-old man. Here we discuss this unique case based on H&E morphology, pathological and morphological changes, immunohistochemical assays, diagnosis, and prognosis.

Case presentation

The 46-year-old male patient came to our hospital because of an “accidentally found pelvic mass for three months, with pain and distension lasting 7 days”. Physical examination showed swelling and hardness in the kidney and ureteral areas. The right side of the pelvic cavity had a palpable and substantial mass, with slight associated pain. Ultrasonography suggested a hypoechoic mass on the right side of the right lower abdominal bladder with an unclear boundary, irregular shape, and uneven internal echo. Color doppler flow imaging showed a spot color blood flow signal that could be seen inside the mass. Pelvic computed

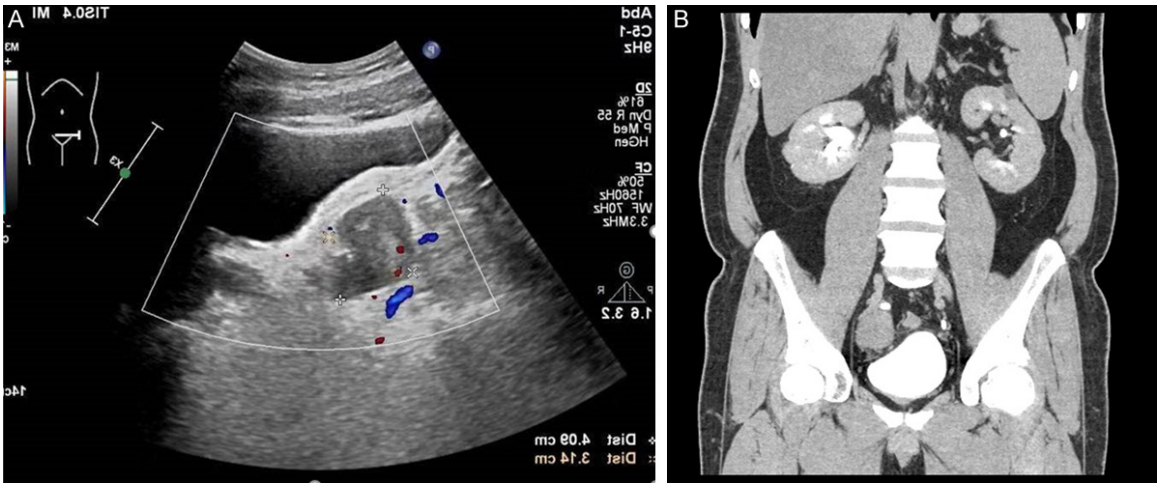

Figure 1. Ultrasonography and CT image of the pelvic cavity tumor. A. Ultrasonography suggested a hypoechoic mass on the right side of the lower abdominal bladder with an unclear boundary, irregular shape, uneven internal echo, and visible color blood flow signals. B. Computed tomography showed that the mass shadow on the right side of the pelvic cavity was impressed on the bladder and ureter.

tomography showed the mass shadow on the right side of the pelvic cavity, and the size was approximately 3.8 × 3.5 cm with uneven and obvious enhancement, and continuous enhancement. The adjacent ureter basin was compressed, the ureter and renal pelvis above the mass were dilated, and hydronephrosis was observed (**Figure 1A** and **1B**).

With an assumed diagnosis of a benign tumor, the patient underwent laparoscopic surgery to resect the pelvic tumor and replant the right ureter and bladder. An elliptical tumor was found on the right side of the bladder during the operation; the tumor was adhered to the bladder wall and the right ureter. The tumor had an abundant blood supply. Surgeons had difficulty separating the ureter and bladder wall from the mass because of an unclear boundary between the right ureter and the tumor. In addition, the bladder wall was adherent to the tumor; thus, a small part of the ureter and bladder wall was removed. Gross examination showed grayish-yellow and grayish-white fragments measuring 4 × 4 × 1 cm. Microscopically, mature adipocytes and fibroblasts and microcystic changes were observed in the center of the tumor, with a sparse cellularity (**Figure 2A** and **2B**). There were two types of surrounding tumor cells. Most of the tumor cells were pl ump, fusiform with obvious heteromorphism. The interstitium of the tumor cells showed erythematous collagen fibers with high mitotic activity, and about 15-20 mitotic cells per 10 high-power fields. Pathologic mitosis was observed easily; these tumor cells were dense and arranged in groups (**Figure 2C** and **2D**). The other tumor cells in some areas were oval, with circular nuclei and vacuolar cytoplasm. The tumor cells were well-defined and nested epithelioid with mitosis. Mitotic cells were observed easily (**Figure 2E** and **2F**).

Immunohistochemistry showed that the plump spindle cells had strongly positive, diffuse vimentin and CD34; BCL-2, MDM2, and CDK4 were moderately positive. Cytokeratin and CD10 were negative. Dedifferentiated regions contained weakly positive cytokeratin and CD-10; BCL-2, MDM2, CDK4 were weakly positive, whereas vimentin, CD34 and CD31 were negative. Both regions showed strongly positive, diffuse STAT6 and P16. CD99 was moderately positive. Ki-67 showed 20% expression. All tumor cells were negative for S-100, CD117, DOG-1, H-caldesmon, SMA, Factor-8, and α-Inhibin (**Figure 3**). Because there were mature adipocytes in the center of the tumor, and MDM2 and CDK4 were expressed, ultimately, the patient was diagnosed with a malignant solitary fibrous tumor with dedifferentiation. After surgery, the patient had a recurrence one year after the laparoscopic operation. The patient underwent an open operation to clear the recurrent lesion, and adjuvant radiotherapy confirmed no further recurrence.

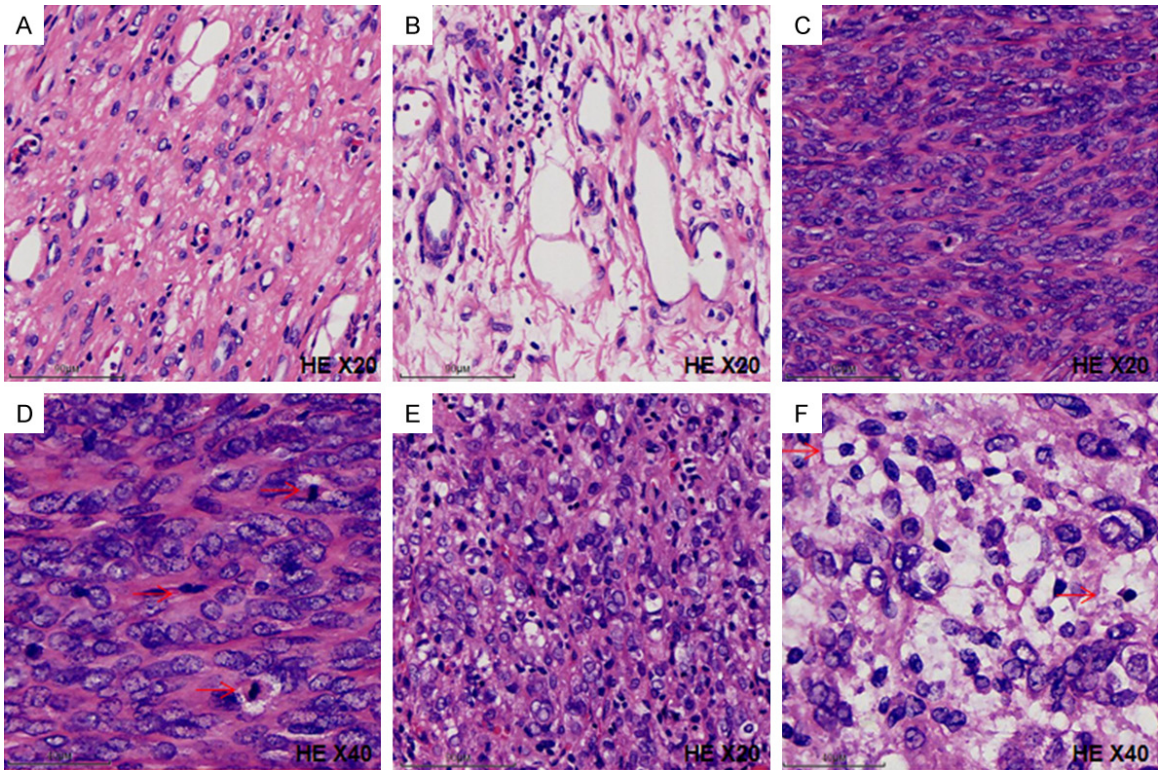

Figure 2. Hematoxylin-eosin staining (A) shows adipocyte metaplasia in the center of the tumor, (B) illustrates microcystic changes and adipocyte metaplasia; (C) and (D) show classical SFT tumor cells with plump spindle shape, unclear cell boundaries, interstitial red-stained vitreous degeneration, obvious cell atypia, and many mitotic figures (arrows indicate mitosis); (E) and (F) show epithelioid differentiation of tumor cells with oval shape, clear cell boundaries, transparent cytoplasm, and vacuolated, spider-like cells (arrows indicate these spider-like cells).

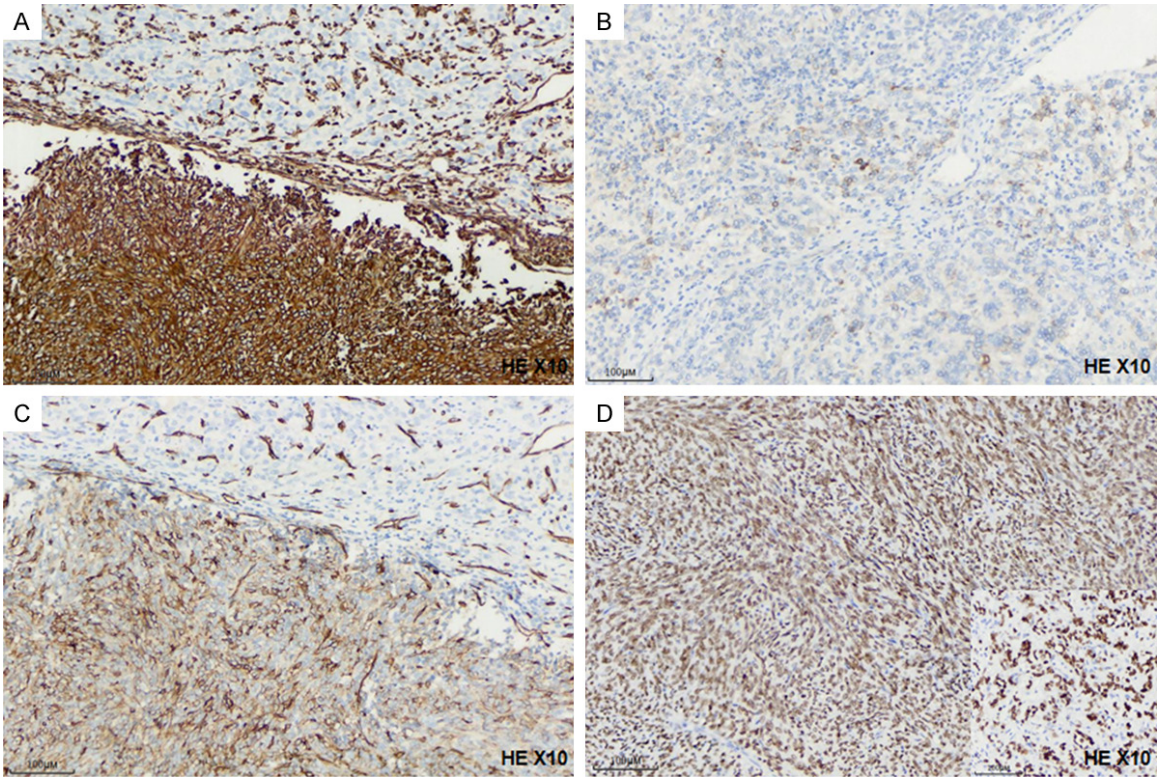

Figure 3. Immunohistochemical staining, (A) shows the expression of vimentin in spindle cell regions and dedifferentiated regions; (B) shows the expression of cytokeratin in dedifferentiated cell areas, (C) shows the expression of CD34 in spindle cell regions and dedifferentiated regions, (D) shows the expression of STAT6 in spindle cell regions and dedifferentiated regions (right corner).

Discussion

It is difficult to diagnose malignant solitary fibrous tumors (MSFTs) with accompanying dedifferentiation. This case describes a 46-year-old man with tumor adhesion to the ureter and bladder. Tumor cells had infiltrated the surrounding adipose tissue and showed behavior consistent with malignancy. The obvious heteromorphism and numerous mitoses were enough evidence to conclude that the tumor was malignant. Immunohistochemistry showed CD34, BCL-2, CD99, and STAT6 expression in most areas of the tumor; S-100, CD117, DOG-1, H-caldesmon, SMA, Factor-8, and α-Inhibin were negative in all tumor cells. Fibrosarcoma, myofibroblast sarcoma, pleomorphic undifferentiated sarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumor were not considered. However, epithelioid differentiation of tumor cells showed that vimentin and CD34 were not expressed and cytokeratin AE1/AE3, STAT6, BCL-2, CD99, and CD34 were positive. There are reports that solitary fibrous tumors (SFTs) accompanied by dedifferentiation express cytokeratin and desmin. Zhao et al. described a benign SFTs in the pelvic cavity that had multifocal expression of cytokeratin. However, immunohistochemistry can create challenges to diagnosis because SFTs must be distinguished from sarcomatoid carcinoma and synovial sarcoma [3]. We used fluorescence in situ hybridization to assess for SYT gene expression. Expression was negative; therefore, we excluded synovial sarcoma. However, MDM-2, CDK4, and P16 are positive in dedifferentiated liposarcoma. Thus, we also assayed for expression of MDM-2 and CDK4; we did not find any gene amplification. Combined with the immunohistochemistry and fluorescence in situ hybridization results, the patient was finally diagnosed as having a malignant solitary fibrous tumor with dedifferentiation.

SFTs are uncommon spindle cell tumors with no heterogeneity in benign cells. Microscopically, sparse spindle cells and dense spindle cells are arranged alternately. The tumor cells grow around blood vessels and produce a vascular epithelioma-like structure with abundant intercellular collagen fibers. Malignant solitary fibrous tumors in the extrapleural are rare clinically. According to the World Health Organization classification of bone and soft tissue, extrapleural MSFTs should satisfy the following criteria: active growth and dense distribution of cells, obvious cell anomalies, easily observed mitosis, >4 mitoses per 10 HPFs, visible tumor necrosis and/or infiltrative margins, and be morphologically similar to fibrosarcoma or undifferentiated sarcoma [4-6].

SFT is a type of mesenchymal spindle cell tumor, with complex and diversified histologic morphology. Morphologically, benign SFTs, highly malignant sarcoma, and dedifferentiated components can occur simultaneously in MSFTs. Dedifferentiated manifestations are various, such as poorly differentiated epithelioid cells or small round cells, accompanied by heterogeneous differentiation (usually manifested as the presence of osteosarcoma, rhabdomyosarcoma, and liposarcoma components), neuroendocrine differentiation and squamous differentiation [7-11]. Although most tumors exhibit classic spindle cell morphology, they may also be associated with myxoid/microcystic change, epithelioid morphology, lipomatous differentiation, and interstitial giant cells [12]. Due to the lack of specific morphologic manifestations, liposarcoma, fibrosarcoma, myofibroblastic sarcoma, pleomorphic undifferentiated sarcoma, leiomyosarcoma, and malignant peripheral schwannomas are the differential diagnosis of MSFTs. Therefore, diagnosis of SFTs relies heavily on immunohistochemistry. SFTs specifically express CD34, BCL-2, and CD99 to different degrees. In MSFTs, various dedifferentiated morphologies are seen besides classical spindle cell morphology, and CD34 expression can be absent [13]. Monoclonal STAT6 immunohistochemical staining has high sensitivity and specificity for SFTs, and it is particularly useful in the diagnosis of difficult SFTs cases [14]. STAT6 nuclear positive expression is a reliable diagnostic indicator for SFTs that are negative for CD34 expression [15]. But STAT6 was not expressed frequently in some

MSFTs in dedifferentiated regions [16]. The high expression of Ki-67 index and the strong staining for BCL-2 also have implications for identification of benign and malignant tumors [17]. Overexpression of IGF2 has significance for the diagnosis of malignant isolated fibrous tumors [18]. Ouladan et al. confirmed that STAT6 and ALDH1 (cytoplasmic expression) were the most sensitive and specific markers in the differential diagnosis of SFTs [19].

Besides immunohistochemical detection, recent genetic studies have shown significance in the diagnosis of soft tissue tumors. Vivero et al. showed that the GRIA2 gene was highly expressed in SFTs, and GRIA2 could be a marker for SFT diagnosis [20]. Moreover, a NAB-STAT6 gene fusion has been found in SFTs. CD34 negative-MSFTs can be diagnosed clearly with the combined expression of STAT6 and NAB2-STAT6 gene fusion [21]. However, some STAT6-positive patients lacked a NAB2-STAT6 gene fusion. Some patients had a NAB2ex4-STAT6ex2 fusion but were negative by STAT6 immunohistochemistry [22]. Therefore, the diagnosis of MSFTs should be based on immunohistochemistry of CD34, STAT6, ALDH1, BCL-2, CD99, and detection of a NAB2-STAT6 gene fusion.

Malignant solitary fibrous tumors with dedifferentiated expression tend to predict poor differentiation and worse prognosis. In a study of 10 MSFT patients with high-grade sarcomatoid growth patterns, seven patients died of the disease [12]. In another study of eight patients with MSFTs that had dedifferentiated features, four patients had distant metastasis, and three patients had metastasis and died within three years. Thus, MSFT with features of dedifferentiation is more aggressive, whereas a positive surgical margin and tumor size greater than 10 cm suggests lower survival and a higher rate of metastasis and recurrence. Hypercellularity, atypia of tumor cells, size of the tumor, mitotic rate, epithelioid morphology, hemorrhage, and necrosis are adverse prognostic factors of SFTs, and tumors with fewer mitoses were not prone to metastasis [23]. The patient described in this case still had a high degree of malignancy despite the small size of the tumor. The recurrence of the tumor after surgery suggested that MSFTs with dedifferentiation have a higher degree of malignancy.

Most surgeons rely on imaging; however, MSFT diagnosis is unreliable by imaging alone [24]. Surgery is the main treatment for MSFTs. Patients with malignant tumors or tumors that invade adjacent structures should undergo an entire resection with wide margins of adjacent tissue [25]. MSFT patients can also achieve a better therapeutic outcome by appropriate adjuvant radiotherapy and chemotherapy according to the size, degree of malignancy, and metastatic status of the tumor. However, in the treatment of MSFTs with dedifferentiation, application of the angiogenesis inhibitor pazotinib was more effective than the traditional treatment [26].

Conclusion

Patients will have a better prognosis if the benign or malignant lesion is accurately evaluated by core needle biopsies before surgery. Then, surgeons can select an appropriate method instead of blindly opting for laparoscopic surgery. Therefore, surgeons should pay attention to preoperative pathologic assessments. Clinical image-histopathologic multidisciplinary analysis has a great effect on diagnosis and therapy of the disease.

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The study was approved by the ethics committee of Longgang centry hospital of Shenzhen and the patient provided written informed consent.

Disclosure of conflict of interest

None.

Abbreviations

SFTs, Solitary fibrous tumors; MSFTs, Malignant solitary fibrous tumors; HPFs, high-power fields; SMA, smooth muscle actin.

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