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Multifocal Cytokeratin Expression in a Dedifferentiated Solitary Fibrous Tumor With Heterologous Rhabdomyosarcomatous Differentiation: A Challenging Diagnosis!

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Abstract

We report the case of a dedifferentiated solitary fibrous tumor with heterologous rhabdomyosarcomatous differentiation in a 74-year-old male presenting with a rapidly growing, large soft tissue tumoral mass in the gluteal muscles of the right hip. Dedifferentiation in solitary fibrous tumor had not been recognized until very recently and is an extremely rare phenomenon in this tumor type. In the present case, the diagnosis of dedifferentiated solitary fibrous tumor was difficult because of the absence of areas of conventional solitary fibrous tumor with a predominantly poorly differentiated, anaplastic tumor component in the incision biopsy composed of heterogeneous areas with small blue round cell (Ewing sarcoma-like), rhabdoid, epithelioid, and pleomorphic morphology. Moreover, the "unforeseen" strong patchy to multifocal positivity for cytokeratin AE1/AE3 and desmin made the diagnosis of a dedifferentiated solitary fibrous tumor even more challenging in this case. The morphology (presence of branching thin-walled, hemangiopericytoma-like blood vessels) and the immunohistochemical profile (including STAT6 and GRIA2 positivity) were very useful to differentiate this very challenging case of a cytokeratin-positive dedifferentiated solitary fibrous tumor with heterologous rhabdomyosarcomatous differentiation from a broad list of differential diagnoses.

Keywords

solitary fibrous tumor, dedifferentiation, dedifferentiated solitary fibrous tumor, STAT6, GRIA2, cytokeratin, rhabdomyosarcomatous

A 74-year-old male patient, without important clinical history, presented with a rapidly (according to the patient in 1 month time) growing, large soft tissue tumoral mass in the gluteal muscles of the right hip. Histopathologic evaluation of the incision biopsy showed an infiltrative, poorly differentiated, high-grade malignant sarcomatous proliferation composed of highly cellular sheet-like areas with a variable pleomorphic, epithelioid, rhabdoid, and round cell morphology (Figure 1A-D). Geographic tumor necrosis and a high mitotic activity (up to 22 mitoses per 10 high-power fields), including atypical mitotic figures, were seen. Branching thin-walled, irregularly shaped (staghorn, hemangiopericytoma-like) blood vessels were easily observed at low power (Figure 1A). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections. The tumor cells were diffusely positive for CD34, CD99, BCL2, and GRIA2 (Figure 2A-C). Diffuse, strong nuclear expression of STAT6 was observed in the tumor (Figure 2D). A strong multifocal expression was seen for desmin and pan-cytokeratin AE1/AE3 (Figure 3A-C). The desmin-positive areas showed very focal nuclear positivity for myogenin (MYF4; Figure 3D). There was no reactivity of the tumor cells for NKX2.2, EMA, ERG, S100, SOX10, HMB45, melan A, TFE3, SMA, caldesmon, calponin, TLE1, and MDM2. The tumor cells showed preserved nuclear SMARCB1 (INI1) and SMARCA4 expression. Additional fluorescence in situ

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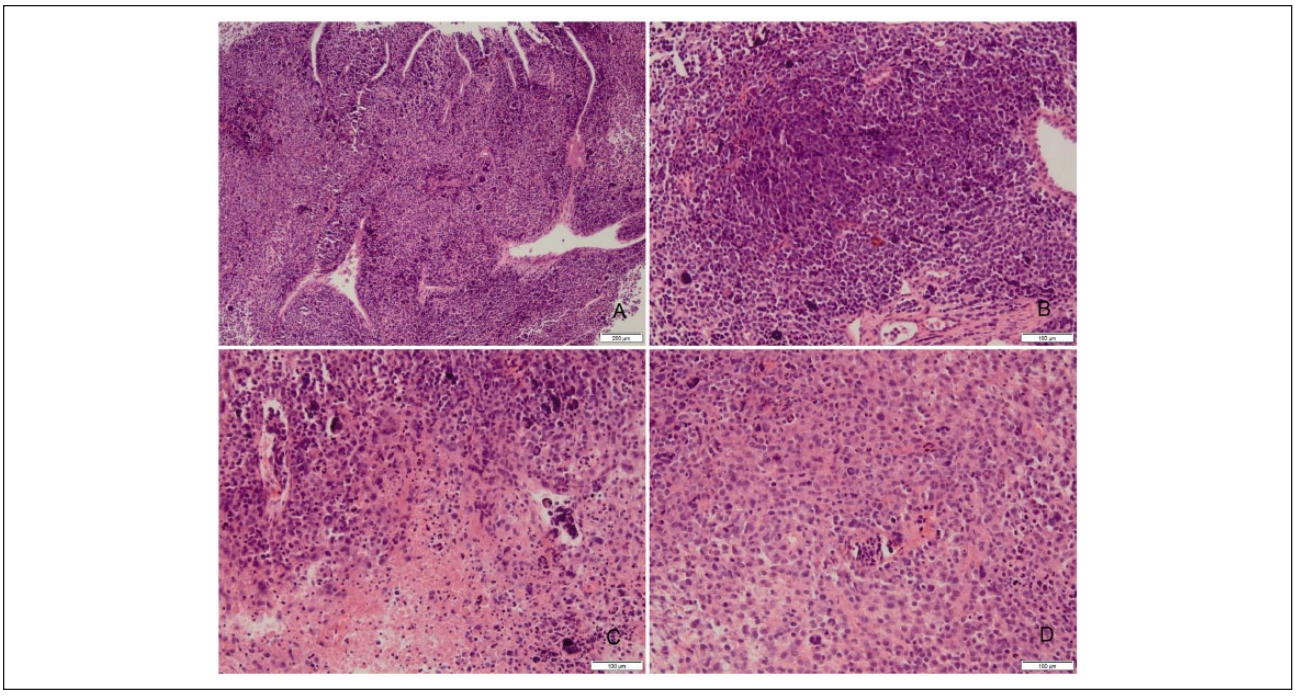

Figure 1. (A) Branching thin-walled, irregularly shaped (staghorn, hemangiopericytoma-like) blood vessels were easily observed at low power (hematoxylin and eosin, original magnification 40×). (B) Tumor area with a small blue round cell morphology (hematoxylin and eosin, original magnification 100×). (C) Tumor area with a more pleomorphic cell morphology. Note the high-grade cytonuclear atypia, pleomorphism, mitotic activity, and geographic tumor necrosis (hematoxylin and eosin, original magnification 100×). (D) Tumor area with an epithelioid and rhabdoid cell morphology (hematoxylin and eosin, original magnification 200×).

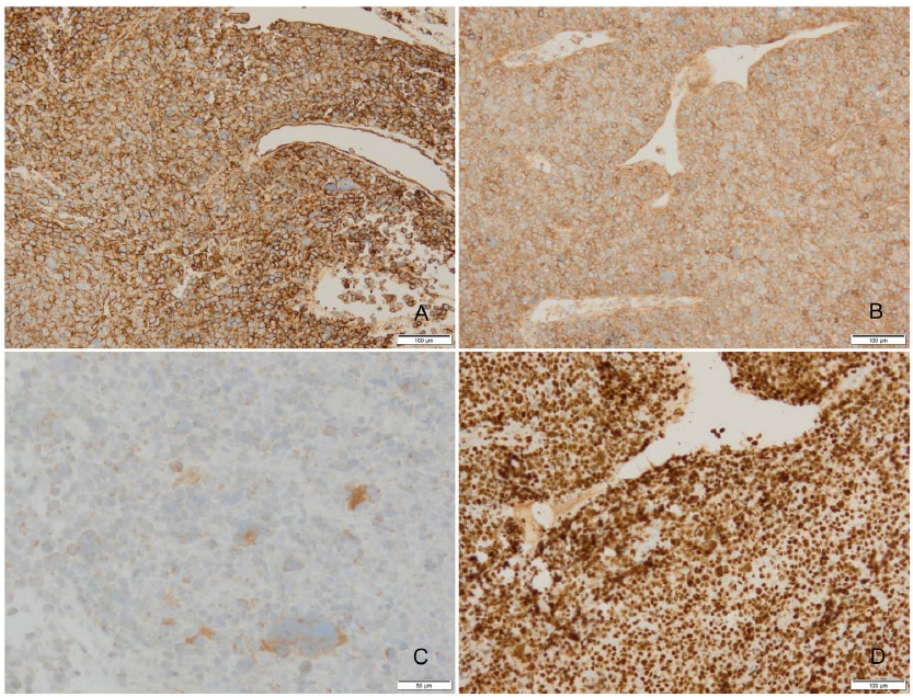

Figure 2. Diffuse cytoplasmic staining of the tumor cells for CD34 (A, original magnification 100×), CD99 (B, original magnification 100×), and GRIA2 (C, original magnification 200×). Strong and diffuse nuclear expression of the tumor cells for STAT6 (D, original magnification 100×).

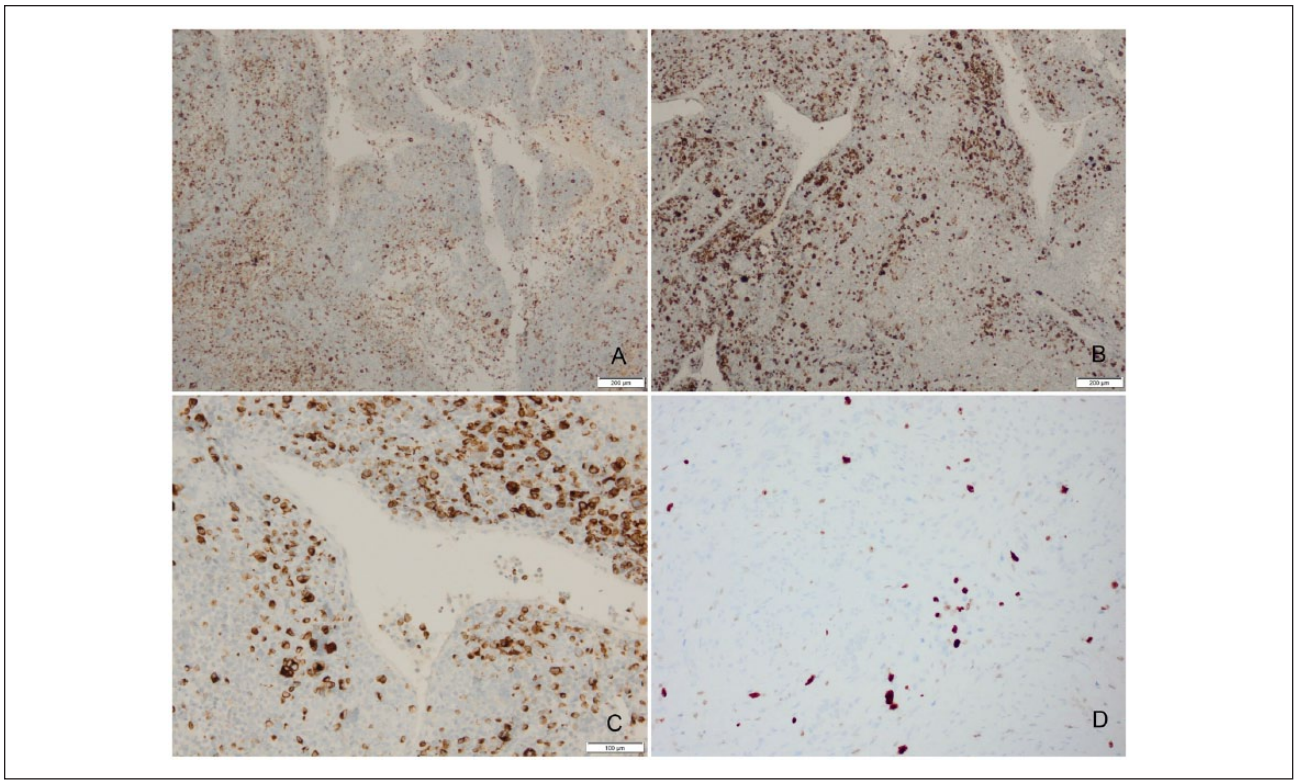

Figure 3. Strong and multifocal expression of the tumor cells for pan-cytokeratin AE1/AE3 (A, original magnification 40×) and desmin (B and C, original magnification 40× and 100×). Very focal nuclear positivity for myogenin (MYF4) in the desmin-positive tumor areas (D, original magnification 100×).

hybridization did not show amplification of the *MDM2* gene, nor rearrangements of the *EWSR1, SS18* (*SYT*), and *FOXO1* (*FKHR*) genes. These histological (staghorn, hemangiopericytoma-like vasculature), immunohistochemical (CD34, CD99, BCL2, GRIA2, and STAT6 positivity), and molecular findings were consistent with the diagnosis of a cytokeratin-positive dedifferentiated solitary fibrous tumor (SFT) with heterologous rhabdomyosarcomatous differentiation. Following this histopathologic diagnosis, clinical staging with thoracic and abdominal computed tomography was performed, and demonstrated multiple nodules in lungs and liver, compatible with diffuse metastatic disease. Therefore, no primary resection of the tumor was performed and palliative chemotherapy (doxorubicin and ifosfamide) was started. The patient died 3 months after diagnosis.

SFT is a relatively uncommon fibroblastic mesenchymal neoplasm, originally described as a tumor of the thoracic pleural surfaces. It has subsequently been reported to arise at almost any site, including the soft tissue, retroperitoneum, abdominal cavity, mediastinum, thyroid, liver, adrenal gland, and kidney.[1,2] The histologic hallmark of SFT is a branching, staghorn (hemangiopericytomatous) vascular pattern with a "patternless" proliferation of a round to spindle bland tumor cells and a hyalinized stroma. The vast majority of SFTs are morphologically and clinically benign. However, 5% to 10% of SFTs will recur and/or metastasize. The proposed histopathological criteria for malignancy in SFTs include mitotic activity of >4/10 high-power fields, hypercellularity, nuclear atypia, pleomorphism, and necrosis.[1,2] However, although the presence of these morphological features is usually associated with a worse clinical behavior, there is no strict correlation between morphology and clinical course and also morphologically benign-appearing SFTs can metastasize. Recently, Demicco et al reported on a novel risk stratification scheme for SFT, incorporating patient age, tumor size, mitotic activity, and necrosis, to predict risk of metastasis, clearly delineating patients at high risk for poor outcomes.[3,4] In addition to their largely unpredictable biological behavior, the diagnosis of histopathologically malignant SFTs may be further complicated by the overgrowth of a high-grade anaplastic component mimicking a high-grade pleomorphic, spindle, epithelioid, or small cell sarcoma, known as "dedifferentiation" in SFT ("dedifferentiated SFT").[5,6] Dedifferentiation is a well-known phenomenon in soft tissue and bone tumors such as atypical lipomatous tumor/well-differentiated liposarcoma, chondrosarcoma, osteosarcoma, and chordoma. However, dedifferentiation in SFT is exceptionally rare and had not been recognized in SFT

until Mosquera et al[5] described 8 "dedifferentiated tumor" cases showing abrupt transition from a low-grade SFT component to a high-grade sarcomatous component. Dedifferentiation is an alternative type of malignant progression in SFT, which is distinct from the more usual type of malignant histology in SFT as discussed above. In the present case, the diagnosis of dedifferentiated SFT was difficult because of the absence of areas of conventional ("low-grade") SFT with a predominantly anaplastic tumor component in the incision biopsy composed of heterogeneous areas with small blue round cell (Ewing sarcoma-like), rhabdoid, epithelioid, and pleomorphic morphology in the same tumor. Moreover, the "unforeseen" strong patchy to multifocal positivity for cytokeratin AE1/AE3 and desmin made the diagnosis of a dedifferentiated SFT even more challenging in this case. A few anecdotal single case reports of cytokeratin positivity in SFTs have been reported in the literature, including a small case series of malignant SFTs (however without dedifferentiation), and this can be a major diagnostic pitfall in that it can mislead one to interpret such a finding as proof of epithelial differentiation.[7] The patchy multifocal desmin and very focal nuclear myogenin (MYF4) expressions were compatible with divergent rhabdomyosarcomatous differentiation. Heterologous rhabdomyosarcomatous elements in dedifferentiated SFT are extremely rare.[6,8] Until recently, there were no known specific molecular markers of SFT, and the SFT immunophenotype (CD34, BCL2, and/or CD99) by itself was not specific and could be lost during disease progression/dedifferentiation. However, nuclear STAT6 staining was reported in 2014 by Doyle et al as an excellent immune marker for *NAB2-STAT6* gene fusion, which is the defining driver mutation of SFT, providing a sensitive and specific diagnostic marker for SFT.[9] However, it is important to mention that the sensitivity of STAT6 immunohistochemistry is lower in the setting of dedifferentiated SFTs, and STAT6 loss can be observed in dedifferentiated SFTs.[10,11] Moreover, STAT6 overexpression can also be seen in a subset of dedifferentiated liposarcomas, however. Based on the performed immunohistochemistry and fluorescence in situ hybridization (no MDM2 overexpression and no *MDM2* gene amplification), a diagnosis of a dedifferentiated liposarcoma with a SFT-like morphology was excluded in our case.[9,12,13] Gene expression studies of SFT revealed upregulation of GRIA2, and Vivero et al[14] described the utility of GRIA2 immunohistochemistry as an additional sensitive (however less specific) diagnostic tool to distinguish SFT from its mimics. Therefore, STAT6 in conjunction with GRIA2 expression was very useful to differentiate this very challenging case of a cytokeratin positive dedifferentiated SFT with heterologous rhabdomyosarcomatous differentiation from a broad list of differential diagnoses, including sarcomatoid carcinoma, Ewing sarcoma, pleomorphic rhabdomyosarcoma, pleomorphic leiomyosarcoma, malignant perivascular epithelioid cell tumor, dedifferentiated liposarcoma, or pleomorphic sarcoma not otherwise specified.

This case is, to our knowledge, the first report of multifocal cytokeratin expression in an extremely rare case of a dedifferentiated SFT with heterologous rhabdomyosarcomatous differentiation, further expanding the morphological and immunohistochemical spectrum of this rare, clinically highly aggressive subtype of SFT.

Declaration of Conflicting Interests

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Ethical Approval

This case study was performed in accordance with the code of conduct of the Medical Ethical Committee of the Ghent University Hospital.

Informed Consent

Not applicable.

Trial Registration

Not applicable.

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