CASE REPORT Libri Oncol., Vol. 33 (2005), N^{o} 1-3, 41 – 46

POORLY DIFFERENTIATED SYNOVIAL SARCOMA – A CASE REPORT

IRENA RANOGAJEC[1], VESNA RAMLJAK[1], IRENA NOVOSEL[2], IVA BOBUŠ-KELČEC[1] and DANKO VELIMIR VRDOLJAK[3]

[1]Department of Clinical Cytology, [3]Department of Surgical Oncology, University Hospital for Tumors, Zagreb, Croatia
[2]Department of Pathology, General Hospital «Dr Ivo Pedišić», Sisak, Croatia

Summary

We report a rare case of primary poorly differentiated synovial sarcoma (SS) in axillary region confirmed by histology.

SS accounts for 5-10% of soft tissue sarcomas. Approximately 20% of the cases have poorly differentiated appearance, most often characterized by undifferentiated round cell morphology resembling Ewing's sarcoma.

The differential diagnosis includes ES/PNET family of tumors, rhabdomyosarcoma, desmoid fibromatosis, and malignant melanoma.

A 46-year-old female presented to our hospital complaining of a 10 cm slightly painful mass in the right axillary region of a 2-month duration. Clinical examination (CT, ultrasound) showed an expansive tumor mass. Cytological analysis showed the diagnosis of suspected sarcoma. Surgical treatment was performed.

Histopathological and immunohistochemical analysis confirmed the diagnosis of poorly differentiated SS.

In spite of additional methods as immunocytochemistry, the poorly differentiated variant of SS can be easily mistaken for numerous other tumors in cytological smears due to its complex, overlapping morphology and still limited experience of cytopathologists in the field of rare soft tissue tumors. Nevertheless, recognition of this variant of SS is of a major concern for its worse prognosis.

KEY WORDS: *synovial sarcoma, FNA cytology, immunocytochemistry*

SLABO DIFERENCIRANI SINOVIJALNI SARKOM – PRIKAZ SLUČAJA

Sažetak

U radu prikazujemo rijedak slučaj primarnog slabo diferenciranog sinovijalnog sarkoma (SS) aksilarne regije čija je dijagnoza potvrđena patohistološkom analizom.

Sinovijalni sarkom čini 5-10% mekotkivnih sarkoma. Oko 20% slučajeva ima sliku slabo diferencirane varijante, malih okruglih stanica podsjećajući na Ewingov sarkom. Diferencijana dijagnoza uključuje ES/PNET skupinu tumora, rabdomiosarkom, desmoidnu fibromatozu i maligni melanom.

Četrdesetšestogodišnja pacijentica primljena je u našu ustanovu žaleći se na lagano bolnu 10 cm veliku tumorsku masu u desnoj aksilarnoj regiji u trajanju od dva mjeseca. Klinički pregled (CT; UZV) potvrdili su ekspanzivnu tumorsku masu, a citološka analiza upućivala je na dijagnozu sarkoma te je učinjen operativni zahvat.

Histološka i imunohistokemijska analiza potvrdila je dijagnozu slabo diferenciranog SS.

Unatoč primjeni dodatnih metoda citološke analize, poput imunocitokemije, slabo diferencirana varijanta sinovijalnog sarkoma može se lako, zbog kompleksne, preklapajuće morfologije kao i ograničenog iskustva citologa na polju rijetkih tumora mekih tkiva, zamijeniti s drugim tumorima. Ipak prepoznavanje ove varijante SS od važnosti je zbog njegove lošije prognoze.

KLJUČNE RIJEČI: *sinovijalni sarkom, aspiracijska citodijagnostika, imunocitokemija*

INTRODUCTION

Synovial sarcoma (SS) is the fourth most common soft tissue sarcoma in adults and the second most common soft tissue sarcoma in children. Classically, SS presents most often as a para-articular soft tissue mass with a biphasic histologic appearence (1).

SS accounts for 5-10% of soft tissue sarcomas. It can occur at any age including childhood, but most commonly in young and middle-aged adults. The majority arises in the extremities and the trunk, and about 90% are deep-seated (2).

The histogenesis has been debated, and at present SS is considered to derive not from synovial tissue but from multipotent stem cells capable of differentiating into tumor cells with mesenchymal as well as epithelial features (3).

Histologically, according to the WHO classification, SS is biphasic or monophasic. Biphasic SS has epithelial and spindle cell components in varying proportions. The spindle cell component often occurs alone as monophasic SS. Purely glandular monophasic SS theoretically exists, but is indistinguishable from adenocarcinoma without cytogenetics. SS composed of plump epithelioid cells has sometimes been termed monophasic epithelial SS, but examples with rhabdoid cells are included with poorly differentiated SS. About one third of SS show focal tumor calcification and is termed calcifying SS. Areas with high cellularity, numerous mitoses and often necrosis in some tumors predominate and form *poorly differentiated SS* (4). Immunohistochemically, most SS stain positively for cytokeratins (CK 7 and CK 19) and epithelial membrane antigen (EMA). More than a half are positive for CD99 and Bcl-2, and up to a third stain for S-100 protein (2,5). The majority of SS including poorly differentiated forms share a chromosomal aberration t(X; 18)(p11;q11.2), creating the chimeric product SYT/SSX1 or SYT/SSX2 in more than 90% of cases (1,2).

The best outcomes are in childhood patients, in tumors which are <5cm in diameter, have<10mitoses/10hpf and no necrosis. Prognosis does not differ between monophasic and biphasic tumors or in relation to immunophenotype. Five-year and 10-years survival account for 36-76% and 20-63%, respectively (4).

PATIENTS AND METHODS

A 46-year-old female patient presented to our hospital complaining of a 10 cm slightly painful mass in the right axillary region of a 2-month duration.

Ultrasound and computed tomography detected an expansive tumor mass. The specimens obtained by fine-needle aspiration (FNA) were stained with May-Grünwald-Giemsa (MGG) and additionally immunocytochemicaly analyzed for epithelial antigen (BerEp4), cytokeratin 7 (CK7), cytokeratin 20 (CK20), vimentin (VIM) and desmin. The cytological diagnosis of sarcoma was confirmed. Surgical treatment was indicated, and paraffin-embedded tumor samples were sliced into 5 μm sections and standard stained with Hemalaun-Eosin (H&E). The sections were subsequently analyzed by S-100, VIM, EMA, melanosome (HMB45), melanA, CD31, neuron specific enolase (NSE), CK7, CK20, thyroid transcription factor (TTF-1) and smooth muscle actin (SMA).

RESULTS

Cytological findings

The cellular yield was generally rich. The aspirates displayed a mixture of dispersed cells and irregular tumor tissue fragments with very rarely a myxoid background substance (Figure 1). The tumor cells were small to medium-sized with rounded or ovoid nuclei (Figure 2). The nu-

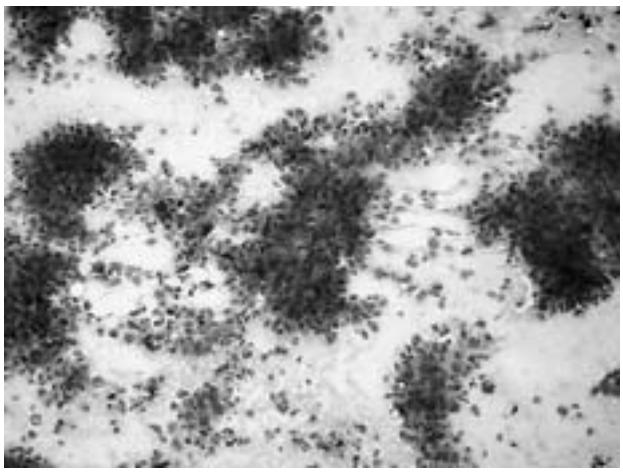

Figure 1. Synovial sarcoma (MGGx10)

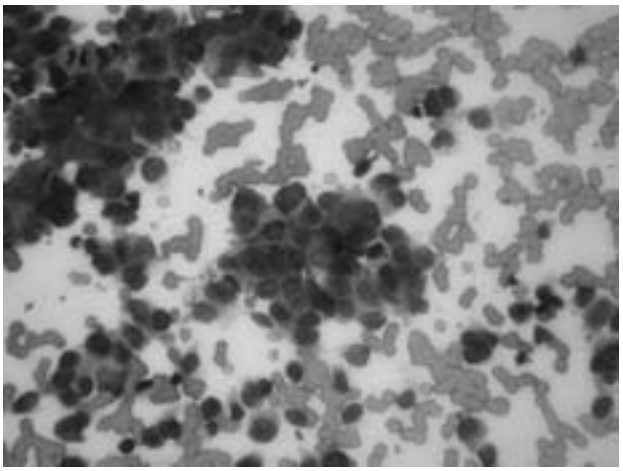

Figure 2. Synovial sarcoma (MGGx40)

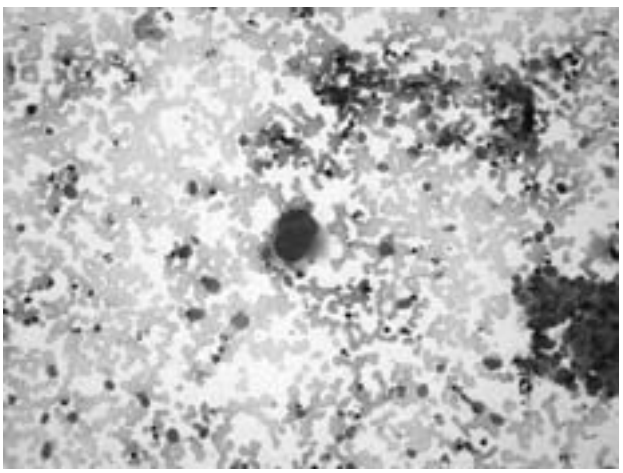

Figure 3. Synovial sarcoma (MGGx20)

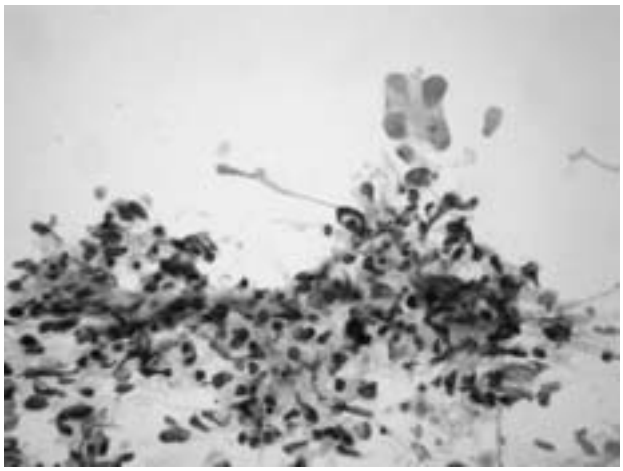

Figure 4. Synovial sarcoma (BerEP4x40)

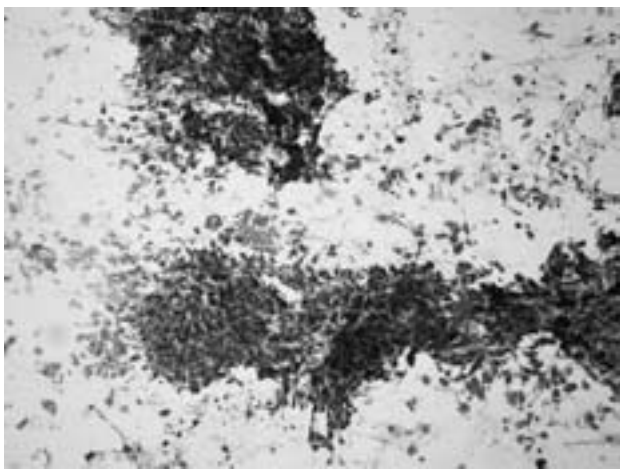

Figure 5. Synovial sarcoma (VIMx10)

clear chromatin was usually bland, and the cytoplasm was scanty or medium sized. There were also some binuclear or multinuclear large cells with rounded nuclei, prominent nucleoli and abundant cytoplasm (Figure 3). Large naked nuclei and mitoses were found in most aspirates. Immunostains BerEP4, CK7, CK20, VIM and desmin were performed. The cells were weakly positive for BerEP4 (Figure 4) and CK20, negative for CK7, and desmin and strongly positive for vimentin (Figure 5).

Histopathological findings

The resected tumor measured 4x3x3.5 cm. Serial slicing revealed extensive necrosis. Histologically, tumor of high cellularity was composed of large cells with pronounced nuclear pleomorphism, prominent one to three nucleoli, and numerous mitoses, resulting in an epithelioid appearance in some areas (Figure 6), and spindle appearance in others (Figure 7). There were also smaller atypical cells with rounded hyperchromatic nuclei and less cytoplasm. Neither of tumor microscopic fields showed glandular formations. The tumor cells surrounded dilated vascular spaces of hemangiopericytomatous appearance. Immunohistochemical analysis confirmed the diagnosis of poorly differentiated biphasic synovial sarcoma. Namely, all tumor cells showed strong positivity for vimentin and S-100 (Figure 8), and focal positivity for EMA (Figure 9). The cells were negative for HMB45, Melan-A, CD31, NSE, SMA, CK7, CK20 and TTF1.

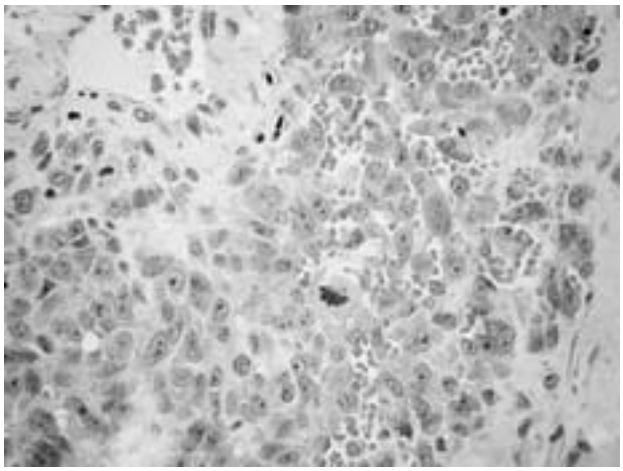

Figure 6. Synovial sarcoma (H&Ex40)

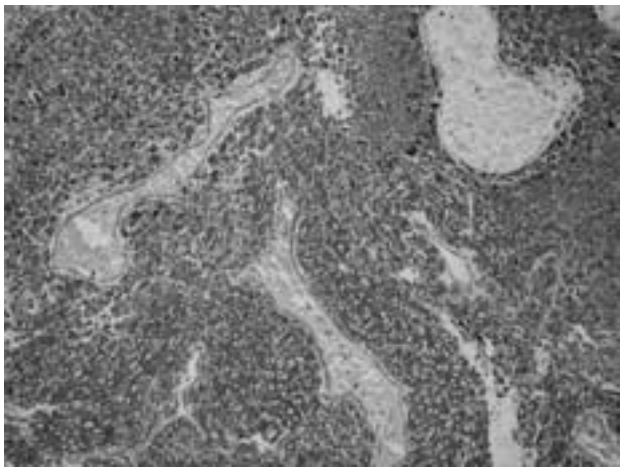

Figure 8. Synovial sarcoma (S-100x10)

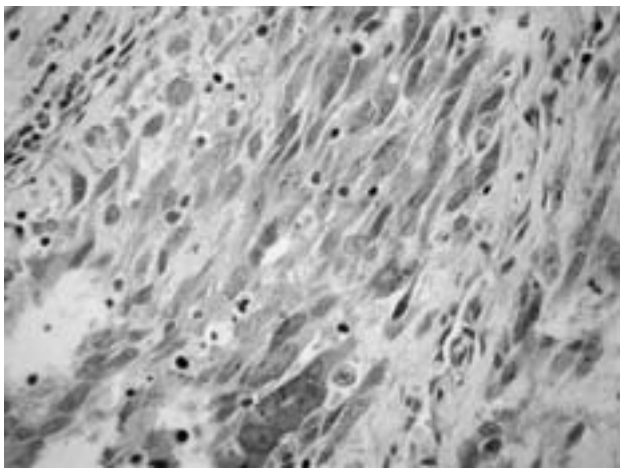

Figure 7. Synovial sarcoma (H&Ex40)

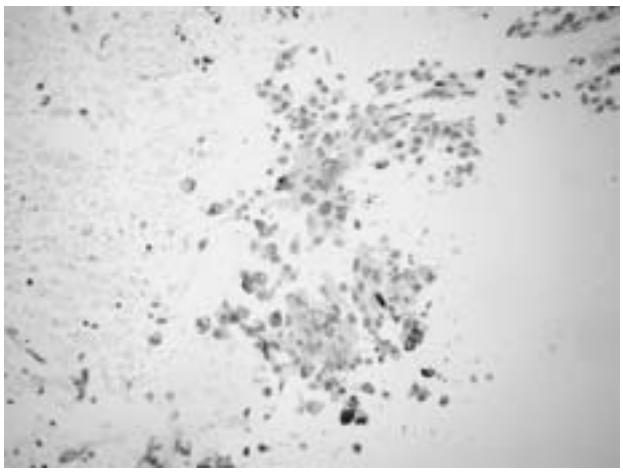

Figure 9. Synovial sarcoma (EMAx20)

DISCUSSION

Approximately 20% of cases have poorly differentiated appearance, most often characterized by undifferentiated round cell morphology resembling small round cell tumors, especially PNET. The cells are sometimes larger with more cytoplasm and can appear rhabdoid. Rarely, the spindle cells of MSS can be pleomorphic. PDSS have the same immunophenotype and genetic abnormalities as regular SS. Recognition of this subtype of SS is of practical importance because it behaves more aggressively and metastasizes in a larger percentage of cases (4).

The cytological features of SS have been evaluated in some series of tumors and in numerous case reports (1,6). Such lesions present a diagnostic challenge on FNA due to several factors, particularly when the aspirate material displays monophasic, small cell or poorly differentiated morphology (7). Because of phenotypic heterogeneity and the limited experience of cytopathologists, the cytologic representative series of these tumors are limited (8).

Cytological features of SS with poorly differentiated morphology include a similar pattern of dispersed cells and tumor tissue fragments as in monophasic and biphasic SS. The tumor is composed of small rounded cells with scanty cytoplasm and rounded bland nuclei, spindle-shaped cells with fusiform atypical, hyperchromatic nuclei and large cells with rounded nuclei, prominent nucleoli and abundant cytoplasm (2). The following features have also been described to be

characteristic of SS: smears are cell-rich, stroma-poor, of striking uniformity, lacking nuclear pleomorphism, and composed mostly of ovoid to rounded tumor cells with scant tapering cytoplasm. The presence of a classical pattern is highly suggestive of SS and the presence of epithelial cells is mandatory (8).

In our case, the aspirates were usually rich with clusters and single tumor cells with medium sized cytoplasm and hyperchromatic nuclei. Sometimes, there were also larger tumor cells with binuclear or multinuclear pattern, pseudopapillary tissue fragments and rarely a myxoid background substance.

The diagnosis of SS may be established on morphology alone when the aspirate is of excellent quality and classic biphasic elements are seen; but most cases will require confirmation by another method. The differential diagnosis include ES/PNET family of tumors, rhabdomyosarcoma, desmoid fibromatosis, and malignant melanoma (3,8). Ewing's/PNET are usually composed of isolated or sparsely clustered round to oval cells with central nuclei. Pseudopapillary structures usually seen in SS are rare in Ewing's/PNET. Periodic-acid-Schiff stain is strongly positive and specific cytogenetic aberrations t(11,22) are common findings in these tumors. The presence of epithelioid cells, spindle-shaped cells, macrophage with «dirty» cytoplasm, intranuclear inclusions, and binucleated cells by FNA favor the diagnosis of malignant melanoma (8). If a smear is paucicellular, showing only few clusters of spindle cells, it is difficult to distinguish the tumor from other spindle cell neoplasms such as desmoid fibromatosis (2). But the patterns in cellular aspirates are different because desmoid shows fragments of a fibrilar intercellular substance mixed with mesenchymal spindle cells (3). Rhabdomyoblastic differentiation in variable proportion of tumor cells; eccentric nuclei, eosinophilic or gray-blue cytoplasm favor the diagnosis of the alveolar rhabdomyosarcoma but additional techniques are also needed to establish the diagnosis (2).

Immunohistochemical expression of cytokeratin and vimentin and lack of expression of CD99 can help confirm the diagnosis of SS, but the monophasic variant can be negative for cytokeratin as the poorly differentiated SS can express CD99 (1). Distinctive immunocytochemical analysis may be inconclusive, since the poorly diferentiated SS may be keratin or EMA negative, whereas several malignant peripheral nerve sheath tumors exhibit keratin positivity (8).

In our case, immunocytochemical analysis excluded the diagnosis of malignant melanoma, poorly differentiated carcinoma and alveolar rhabdomyosarcoma but in differential diagnosis the diagnosis of ES/PNET tumors was still considered.

Histological and immunohystochemical analysis confirmed the definitive diagnosis of biphasic synovial sarcoma (poorly differentiated).

It is now well-established that cytogenetic analysis is a novel and objective tool for the diagnosis of soft-tissue tumors and is more sensitive than conventional morphological methods. It has been proposed that FNA exhibiting a morphology suggestive of SS is sufficient for a definitive diagnosis of SS only when combined with a cytology-based cytogenetic analysis (8,9).

The cytogenetic analysis of the obtained material was not performed in our case. The authors are aware that proof of specific chromosomal aberration is lacking to complete a definitive diagnosis of SS, but such a cytogenetic analysis has not yet become a routine method.

CONCLUSION

This is a rare case of poorly differentiated primary synovial sarcoma in the axillary region. In the absence of the classical pattern, or epithelial cells, the diagnosis of SS by FNA may be difficult and may require ancillary techniques such as immunocytochemistry, genetic studies or electron microscopy. The poorly differentiated variant analyzed cytomorphologicaly, even using additional methods as immunocytochemistry can be mistaken for numerous other tumors due to its complex morphology and still limited experience of cytopathologists in this field. Nevertheless, recognition of this subtype is of major concern for its association with a worse prognosis. Six months after radical surgery and chemotherapy, the patient presents without metastatic disease.

REFERENCES

1. Dabbs DJ. Diagnostic Immunohistochemistry. New York: Churchill Livingstone, 2002; 530-1.
2. Akerman M, Domanski HA. The cytology of Soft Tissue Tumours. Basel: Karger, 2003; 98-9.
3. Akerman M, Willen H, Carlen B et al. Fine needle aspiration (FNA) of synovial sarcoma - a comparative histological-cytological study of 15 cases, including immunohistochemical, electron microscopic and cytogenetic examination and DNA-ploidy analysis. Cytopathology 1996; 7: 187-200.
4. Fisher C, de Bruijn DRH, Geurts van Kessel A. Synovial sarcoma. In: Fletcher CDM, Unni KK, Mertens F, eds. WHO classification of soft tissue tumours. Lyon: IARC Press; 2002: 200-4.
5. Folpe SL, Schmidt RA, Chapman A et al. Poorly differentiated synovial sarcoma: Immunohistochemical distinction from primitive neuroectodermal tumors and high grade malignant MPNST. Am J Surg Pathol 1998; 22: 673-82.
6. Silverman JF, Landreneau RJ, Sturgis CD et al. Small cell variant of synovial sarcoma: Fine needle aspiration with ancillary features and potential diagnostic pitfalls. Diagn Cytopathol 2000; 23: 118-23.
7. Taylor CA, Barnhart A, Pettenati M et al. Primary pleuropulmonary synovial sarcoma diagnosed by fine needle aspiration with cytogenetic confirmation. Acta Cytologica 2005; 6: 673-6.
8. Klijanienko J, Caillaud J-M, Lagace R et al. Cytohistologic correlations in 56 synovial sarcomas in 36 patients: The Institute Curie Experience. Diagnostic Cytopathology 2002; 27: 96-102.
9. Akerman M. Fine needle aspiration cytology of soft tissue sarcoma: benefits and limitations. Sarcoma 1998; 2: 155-61.

Author's address: Irena Ranogajec, M.D., Department of Clinical Cytology. University Hospital for Tumors, Ilica 197, 10 000 Zagreb,Croatia; E-mail: irena.ranogajec@kzt.hr