Synovial Sarcoma—A Misnomer

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For an evaluation of the putative histogenetic relationship of synovia and synovial sarcomas, normal synovia, villonodular synovitis, and synovial sarcomas were compared for their patterns of expression of intermediate filaments of keratin and vimentin type and epithelial membrane antigen and for lectin binding sites. The lining cells in both normal synovia and villonodular synovitis reacted with anti-vimentin antibodies, but not with antibodies to different types of keratins or epithelial membrane antigen. The cleft-lining cells in synovial sarcoma, on the other hand, showed only keratin positivity, and epithelial membrane antigen could also be detected in these cells. Nonneoplastic synovial lining cells bound peanut agglutinin (PNA), *Ricinus communis* agglutinin (RCA), soybean agglutinin (SBA), concanavalin A (Con A), and wheat germ agglutinin (WGA) conjugates, but not *Ulex europaeus* I lectin (UEA I). In contrast, the epithelial-like cleft lining cells in synovial sarcomas showed an apical cytoplasmic binding of PNA, UEA I, RCA, and SBA, and binding of WGA to the whole cytoplasm but did not bind Con A. The distinct differences between synovial lining cells and synovial sarcoma cells speak against synovial cell features in synovial sarcoma. These results indicate that synovial sarcoma is a carcinosarcomalike tumor with true epithelial differentiation, and the term "synovial sarcoma" apparently is a misnomer that should be abandoned. (Am J Pathol 1984, 117:18–25)

SYNOVIAL SARCOMA is a distinct and generally recognized soft-tissue tumor.[1] The name of the tumor reflects its biphasic pattern, considered to be comparable with the structure of the normal synovial tissue presenting both lining cells and subsynovial stromal cells.[2] On the basis of such morphologic similarity, synovial sarcomas have been classified among synovial tumors.[3] The true synovial histogenesis/differentiation of synovial sarcoma, however, has remained open, because ultratructural studies have failed to show synovial features in synovial sarcomas.[4,5] It has been previously shown that, in contrast to most sarcomas but like carcinosarcomas, for instance, synovial sarcomas contain a keratin-positive epithelial component.[6–8]

In this study, we evaluated the intermediate filaments and lectin binding properties of synovial tissues and synovial sarcomas in an attempt to clarify their possible histogenetic relationship. The present results do not give any support to the putative histogenetic origin of synovial sarcoma from synovial lining cells, because these cells do not display epithelial markers and they show lectin binding that differs from that of synovial sarcomas.

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Materials and Methods

Tissue Lesions

Normal synovias from the knee joints (8 cases), cases of villonodular synovitis from the knee joints, also called synovial giant cell tumor or benign synovioma, (5 cases), and synovial sarcomas (15 cases) were investigated for the expression of intermediate filament proteins of keratin (epidermal prekeratin, cytokeratin) and vimentin type and epithelial membrane antigen. The binding of seven lectins in these lesions was also evaluated. The histologic identity of the lesions was evaluated by hematoxylin and eosin (H&E) staining and standard criteria.[1] Of the synovial sarcomas, 6 cases were from the thigh, 3 from the knee region, 2 from the foot, 2 from the antebrachium, 1 from retroperitoneum, and 1 from the supraclavicular space. In none of the cases could origin from normal synovial membranes or bursae be demonstrated. However, the 2 tumors from the foot were located in the neighborhood of the small joints.

Antibodies and Lectins

The preparation and characterization of the rabbit anti-epidermal prekeratin and anti-vimentin antibodies has been presented previously.[9,10] Keratin was obtained from plantar callus, and vimentin was obtained from cultured human fibroblasts. Anti-prekeratin antiserum reacted with different squamous and glandular epithelial cells, but not with fibroblasts. The anti-vimentin did not react with epithelial cells *in situ*, but reacted strongly with fibroblasts and related mesenchymal cells. Cytokeratin used for raising monoclonal antibodies in mice was obtained from LLC-PK cells (a pig renal tubular cell line). These antibodies (PKK1) reacted with different glandular epithelial cells and also with hepatocytes and renal tubular cells, but did not react at all with epidermal cells, thus showing reactivity different from that of antibodies to epidermal prekeratin.[11,12] Antibodies to epithelial membrane antigen[13] were purchased from Sera Lab Ltd., (Sussex, England). The fluorescein isothiocyanate (FITC)- or tetramethylrhodamine isothiocyanate (TRITC)-coupled lectins were purchased from Vector Laboratories (Burlingame, Calif), or from E-Y laboratories, (San Mateo, Calif), and their abbreviations and nominal sugar specificities are shown in Table 1.

Table 1—Nominal Sugar Specificities of the Seven Lectins Used in This Study

Lectin	Sugar specificity
PNA	D-galactose
UEA I	L-fucose
DBA	N-acetylgalactosamine
WGA	N-acetylglucosamine Sialic acid
RCA	Galactose
SBA	N-acetylgalactosamine Galactose
Con A	Glucose Mannose

Immunostaining

Formalin-fixed, routinely processed material was used throughout the study. According to our previous experience, such material gives better results in the immunohistochemistry with intermediate filament antibodies when first treated with a protease, eg, pepsin.[14,15] Recently, we have found that the protease-treated material is more suitable also for lectin-binding studies. Thus, all material was treated with 0.4% pepsin in 0.01 N HCl at 37 C for 30 minutes or 2 hours prior to the staining. After exposure to the primary antibodies, the sections were incubated with FITC-labeled goat anti-rabbit or anti-mouse immunoglobulins (dilution 1:40) for 30 minutes. After washing, the specimens were mounted in veronal-glycerol (buffer 1:1, pH 8.4). Antibodies to epithelial membrane antigen were used at a dilution of 1:300, and the immunostaining was performed by the use of the peroxidase-antiperoxidase (PAP) method.[16] The rabbit anti-goat antibodies and the PAP complex were purchased from Dakopatts (Copenhagen, Denmark). The fluorochrome-coupled lectins were applied on the sections at a concentration of 100 μg/ml, and the incubation time was 20 minutes. In control experiments, incubation with the corresponding sugars resulted in the loss of lectin binding. For fluorescence microscopy, a Zeiss Universal microscope equipped with an epiilluminator IIIRS and filters for FITC and TRITC fluorescence were used.

Results

Synovial Tissues

The normal cuboidal synovial lining cells displayed strong vimentin positivity in all cases, like the subsynovial connective tissue cells and the vascular endothelial cells (Figure 1a). The synovial lining cells and all stromal cells failed to react with antibodies to keratins (epidermal prekeratin, PKK1-cytokeratin antibodies). In villonodular synovitis, the synovial lining cells were hyperplastic, occasionally showing an epithelial-like appearance. These cells, like the subsynovial cells, however, showed strong vimentin positivity (Figure 1b)

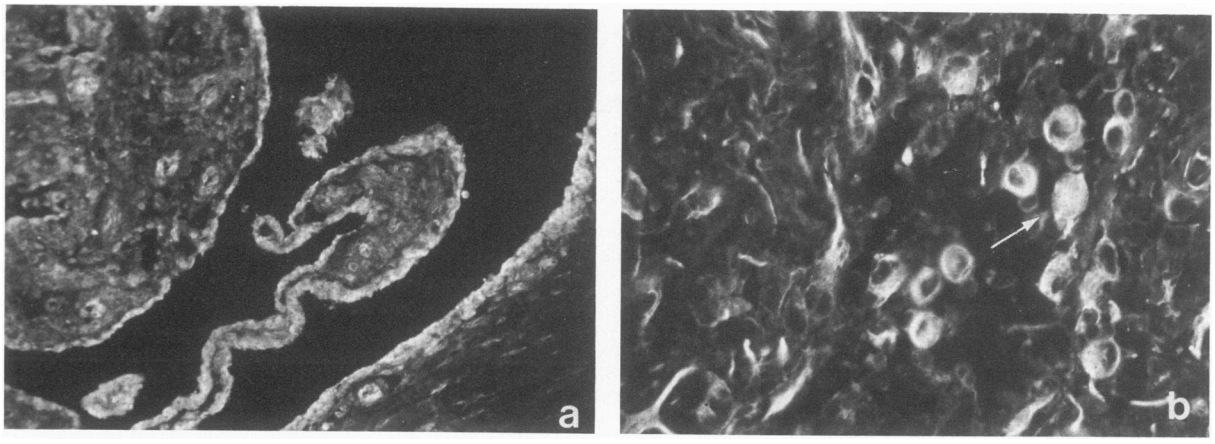

Figure 1—The synovial lining cells are vimentin-positive, like the vascular endothelial cells and the stromal cells (**a**). In villonodular synovitis, the hyperplastic lining cells (*arrow*) have morphologic resemblance to epithelial cells but still display only vimentin positivity, like the surrounding fibroblasts and histiocytes (**b**). (**a**, ×120; **b**, ×400)

and lacked keratin positivity. Epithelial membrane antigen-like immunoreactivity could not be detected in nonneoplastic synovial tissue.

In nonneoplastic synovial tissues, peanut agglutinin (PNA), *Ricinus communis* agglutinin (RCA), soybean agglutinin (SBA), wheat germ agglutinin (WGA), and concanavalin A (Con A) conjugates showed a general cytoplasmic staining in the synovial lining cells (Figure 2). PNA also bound to some isolated stromal cells, possibly histiocytes,[17] and to some endothelial cells; and RCA also bound to many stromal cells and to the stromal matrix, especially in the villonodular synovi-

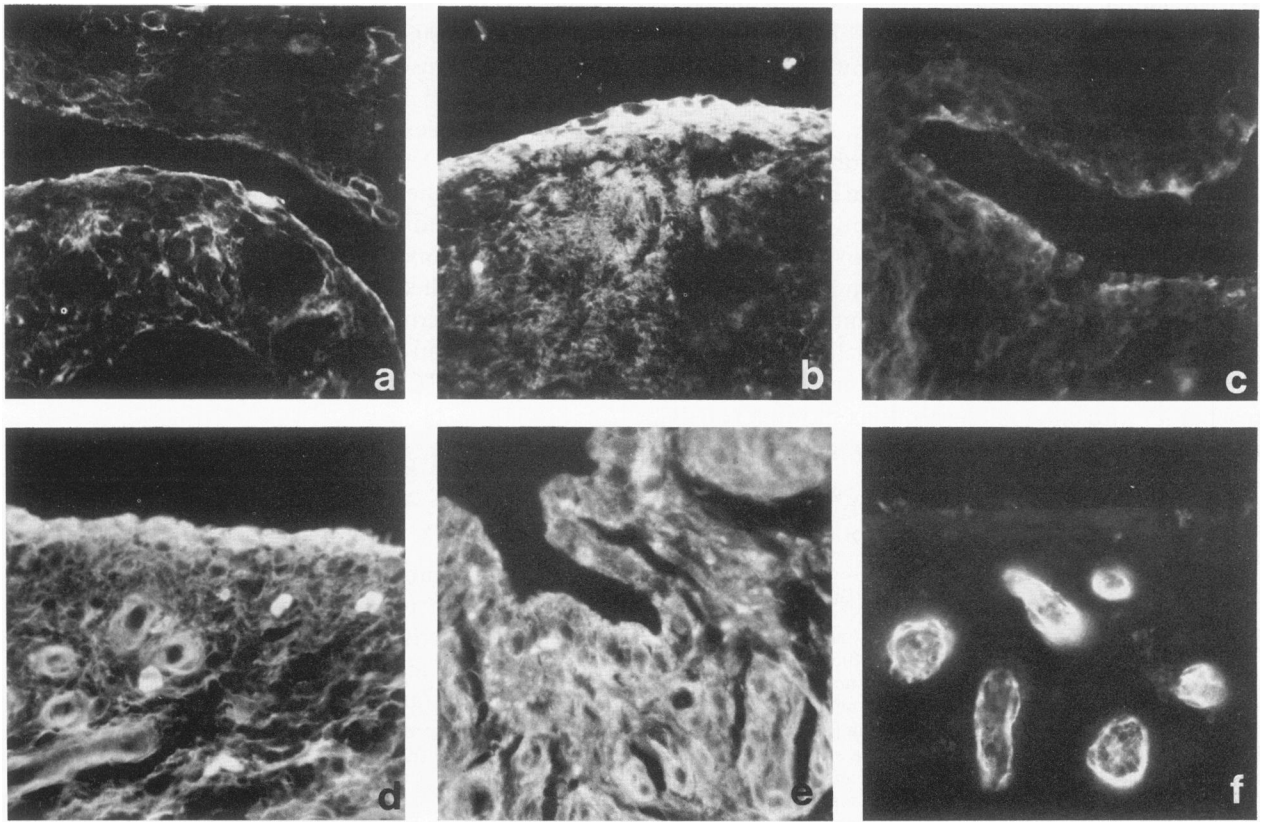

Figure 2—Lectin binding patterns of the synovial lining cells. The lining cells bind PNA (**a**), RCA (**b**), SBA (**c**), Con A (**d**), and WGA (**e**). Varying portions of the stromal cells and the matrix also bind these lectins. UEA I binds only to the vascular endothelial cells and not to the synovial lining cells (**f**). (×400)

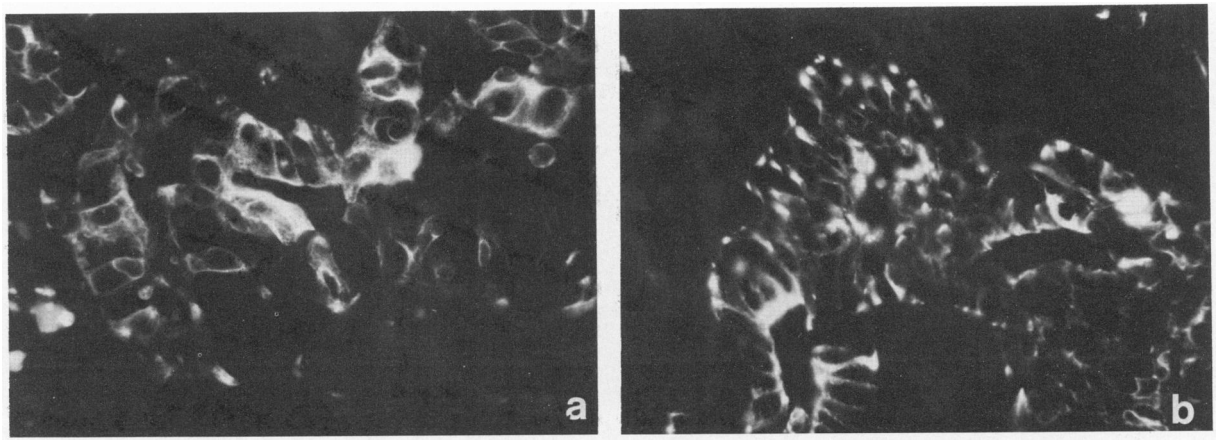

Figure 3—The epithelial-like cleft lining cells in synovial sarcomas are stained with antibodies to epidermal prekeratin (**a**) and with broadly cross-reacting cytokeratin antibodies (**b**). (×400)

tis. WGA and Con A bound both to the lining cells, to the subsynovial connective tissue cells, and to the pericellular matrix material (Figure 2). *Ulex europaeus* I lectin (UEA I) reacted only with vascular endothelial cells, and no reaction was obtained in synovial tissues with *Dolichos biflorus* (DBA).

Synovial Sarcomas

Most of the cuboidal or cylindrical epithelial-like cells lining the glandular slits reacted with both types of antikeratins: epidermal prekeratin antibodies (Figure 3a) and PKK1 cytokeratin antibodies (Figure 3b). The stromal spindlelike cells, unlike the epithelial-like cells, were vimentin-positive. In two of the tumors with the spindle cell "monophasic" pattern, single or groups of cytokeratin-positive cells were found. All synovial sarcomas showed positive staining with antibodies to epithelial membrane antigen, characteristically as a narrow rim in the apical cytoplasm of the epithelial-like cells (Figure 4a), or as a nonpolar cytoplasmic positivity in the "monophasic" tumors composed of spindle-like cells (Figure 4b).

The epithelial-like cells of the biphasic synovial sarcomas showed preferentially an apical cytoplasmic staining of the luminal surface of the glandular structures with PNA, UEA, RCA, and SBA (Figure 5). WGA bound to the epithelial cells and strongly to the stromal spindle cells and to the pericellular matrix material, but Con A showed mainly stromal binding (Figure 5).

Discussion

We compared normal synovia, villonodular synovitis, and synovial sarcomas for the expression of keratin and vimentin types of intermediate filament proteins and lectin binding sites in an attempt to determine the histogenetic relationship between synovia and synovial sarcoma. The results show that synovial sarcoma cells can be distinguished from synovial lining cells both

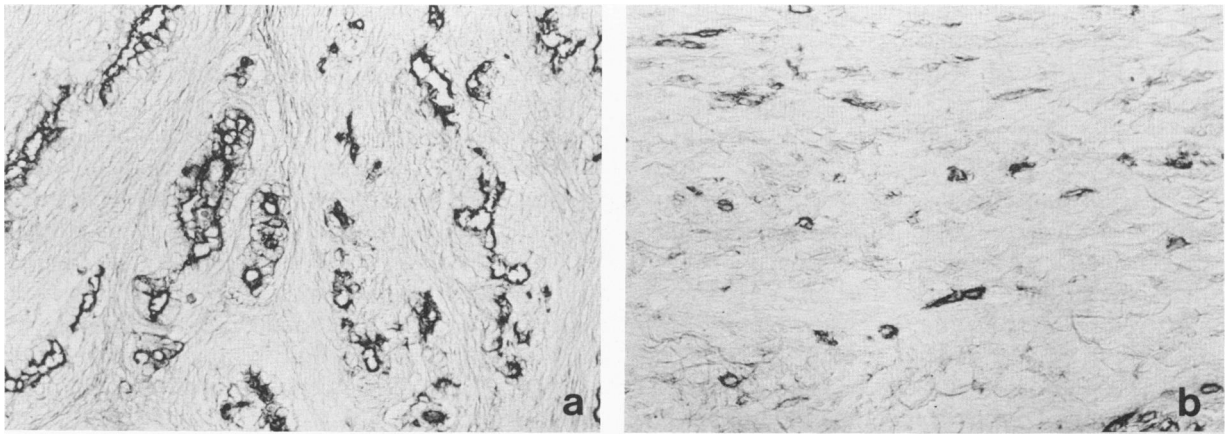

Figure 4—Antibodies to epithelial membrane antigen react with the luminal portion of the epithelial-like cells in synovial sarcoma (**a**), and these antibodies react with scattered single cells in synovial sarcoma of "monophasic" spindle cell type (**b**). (×400)

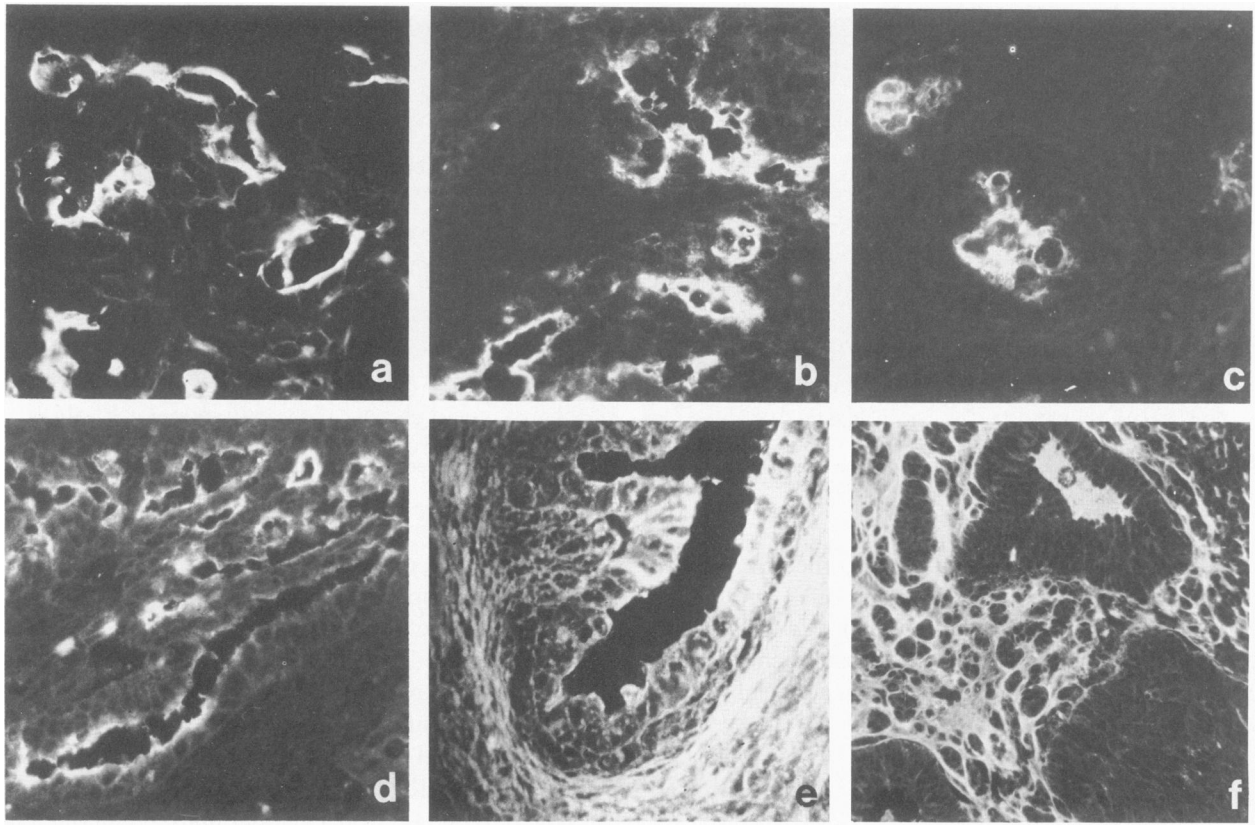

Figure 5—Lectin binding properties of the synovial sarcoma cells. The epithelial-like cleft lining cells bind PNA (**a**), RCA (**b**), SBA (**c**), and UEA I (**d**) preferentially to the apical portion of the cytoplasm, while both the epithelial-like cells and the stromal cells and matrix bind WGA (**e**). Con A binding is observed in the stromal cells and matrix and in the luminal content of a glandlike structure at the *center top* (**f**). (**a–d** and **f**, ×400; **e**, ×600)

in normal synovial tissue and in villonodular synovitis by their true epithelial features, not found in nonneoplastic synovial tissues. Also, the lectin binding patterns are distinctly different in synovia and synovial sarcomas.

Intermediate filament proteins are cytoplasmic constituents which are expressed in cells and corresponding tumors in a characteristic differentiation-dependent way; the intermediate filament expression of parental cell type is retained also in malignant tumors.[9,18] Thus, keratins, a family of related proteins, occur in epithelial cells and carcinomas, and have been shown to be good markers for epithelial differentiation.[19–32] Vimentin, on the other hand, occurs in mesenchymal nonmuscle cells and their sarcomas; and desmin occurs in muscle cells and tumors showing muscle differentiation.[19,33,34] With the exception of synovial sarcoma, sarcomas do not generally express keratin.[6–8,33] Very recently, however, Chase et al[35] demonstrated keratin-positive cells in 24 of 32 epithelioid sarcomas. Thus, many epithelioid sarcomas may also display true epithelial (although not glandular) differentiation.

The presence of keratin-type intermediate filament proteins in the epithelial-like cells of biphasic synovial sarcoma corroborates the true epithelial features of these cells.[6–8] In contrast, epithelial differentiation in terms of keratin expression cannot be revealed in synovial lining cells, which only express vimentin.[7,36,37] Thus, there is a fundamental difference between the cleft-lining epithelial cells of synovial sarcomas, on the one hand, and the synovial lining cells, on the other, speaking against their common differentiation pattern. Vimentin expression of synovial cells is in line with their apparent origin from primitive mesenchymal cells.[38,39]

Another epithelial feature present in the epithelial-like cells of synovial sarcoma and absent in synovial lining cells is the expression of epithelial membrane antigen. Epithelial membrane antigen occurs in most normal and neoplastic epithelial cells, and it has been shown to be a good marker for several types of epithelial tumors.[13,40,41] Sloane and Ormerod[41] found epithelial membrane antigen in synovial sarcomas and mesotheliomas "as exceptional positivity in mesenchymal tumors." Now it is known that both of these tumors are epithelial in terms of keratin positivity.[6–8,42] Interestingly, synovial sarcoma cells and synovial lin-

ing cells differ considerably also in their enzyme-histochemical properties. The former show enzyme activities involved in the specialized cellular transport functions often found in epithelia, but the latter do not.[43]

Synovial sarcoma has generally been considered to occur in the vicinity of joint bursae or tendon sheaths,[44] although it can also be found in extremities remote from joints,[2,45] in the neck,[46] or even in the abdominal wall,[45,47] where it is most remote from any joint. We found synovial sarcomas in the midthigh, retroperitoneum, and subclavicularly in the scalenic space. Connection with a joint cavity could not be demonstrated in any case. Interestingly, experimentally induced sarcomas in the synovial cavities generally show a fibrosarcomatous or anaplastic sarcomatous pattern, but occasionally clefts and "synovial differentiation" have been found.[48]

What does epithelial differentiation do inside muscles and other soft tissue components, which in normal states[18,19] or in neoplasias[33,34] do not contain any epithelial differentiation? Is synovial sarcoma a carcinoma of soft tissues? The highly organized relation between the epithelial and mesenchymal components in synovial sarcoma differs from the irregular appearance of the epithelial component and the heterogeneity of the reactive stromal cells as seen in many carcinomas. As a sign of lesser organization, many invasive carcinomas, such as mammary, prostatic, and pancreatic ones, lack basal laminas beneath the epithelial cells,[49,50] unlike synovial sarcoma epithelium, which is delineated by a laminin-positive continuous basal lamina.[5,51-53]

The histologic spectrum of tumors classified as synovial sarcomas include tumors with scanty epithelial differentiation among a sarcomatoid spindle cell population,[2,54,55] as well as typical biphasic tumors with spindle cell and epithelial-appearing elements and relatively purely epithelial-appearing tumors.[2,56] In this respect, synovial sarcomas resemble childhood nephroblastomas, which also exhibit epithelial differentiation and keratin positivity among mesenchymal-appearing cells.[57] Like in the synovial sarcoma epithelium, the highly organized nature of the epithelial tubules of nephroblastoma is also reflected by their basal lamina coverage.[58] In developing kidney, an analogous situation is seen. The epithelial tubules of the nephron develop from the nephrogenic mesenchyme to an epithelium.[59,60] Such transformation of the mesenchyme into an epithelium is a rare event in organogenesis.[59,60] Synovial sarcoma could thus also be considered a tumor with such an epitheliogenesis from the mesenchyme.

Lectins have a characteristic affinity for saccharide moieties of glycocompounds of cells and tissues.[61,62] The lectin binding pattern, reflecting the surface glycoprotein/glycolipid patterns of cells, can be used to characterize the cellular differentiation lineages and categorize the different cell populations in tissues.[63-66]

The lectin binding patterns in nonneoplastic synovial lining cells and the epithelial-like cells in synovial sarcomas were most markedly different in the expression of UEA I binding sites, found only in the synovial sarcoma epithelium (in addition to endothelial cells). The glycocompound patterns have a tendency to be simplified during malignant transformation,[11] and this leads to diminished binding of many lectins. Thus, for instance, the lectin binding properties in benign and malignant mammary gland epithelium differ by UEA I binding, which is found only in benign epithelium.[65] In benign and malignant pancreatic acinar cells, the lectin binding also differs as to UEA I, which is bound inconsistently to the malignant cells, but regularly to the normal acinar cells.[66] However, the opposite can happen: the colonic carcinoma cells can bind UEA I, while the normal mucosal cells do not, although the mucus binds UEA I.[67] Renal cell carcinomas lack binding or show weaker binding of many lectins as compared with proximal tubular cells, the most likely origin for these tumors.[11] Thus, the lectin binding differences with synovial cells and synovial sarcoma cells do not support and even speak against a common differentiation line.

In conclusion, "synovial sarcoma" appears to be a misnomer, and no proof can be obtained of this entity's histogenetic or differentiational relationship to synovial membrane cells. Thus the designation "synovial sarcoma" should be replaced with a more appropriate term, such as "primary carcinosarcoma of blastoma of soft tissues," which takes into account the dual epithelial and mesenchymal differentiation seen in this peculiar soft tissue tumor. This is important for the patient and also for the clinician, who often thinks of the tumor as a synovial neoplasm.

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