Spindle Cell Epithelioma of the Vagina Shows Immunohistochemical Staining Supporting Its Origin From a Primitive/Progenitor Cell Population

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Spindle cell epitheliomas of the vagina (SCEVs) coexpress epithelial and mesenchymal markers and were first described as a “mixed tumors of the vagina.” However, unlike mixed tumors of other organs, which are believed to originate from myoepithelial cells, SCEVs neither immunohistochemically nor ultrastructurally show features of myoepithelial cells. The present expanded battery of immunohistochemical stains is presented on this rare tumor, including cytokeratin AE1/AE3, CK7, CK20, S100 protein, epithelial membrane antigen, α-smooth muscle actin, desmin, CD34, CD99, Bcl-2, vimentin, estrogen and progesterone receptors, and Ki-67. There was minimal expression of α-smooth muscle actin and negative staining with S100 protein, with coexpression of cytokeratins and vimentin and expression of estrogen and progesterone receptors, as previously reported in SCEVs. In addition, diffuse expression of CD34, CD99, and Bcl-2 immunohistochemical stains was found, which has not previously been reported. The coexpression of CD34, CD99, and Bcl-2 in SCEVs is consistent with its origin from a primitive/progenitor cell population.

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pindle cell epitheliomas of the vagina (SCEVs) or “mixed tumors of the vagina” have some important differences from mixed tumors that arise in other areas, such as skin, salivary glands, breast, mediastinum, and trachea. All the latter tumors appear to arise from myoepithelial cells. However, an origin of myoepithelial cells was questioned in the largest review of SCEVs by Branton and Tavassoli. They pointed out that SCEVs are well circumscribed but not encapsulated tumor (Figure 1). The margins were expansile and located within a few millimeters of the overlying epithelium (Figure 2). Small vessels were seen throughout the tumor, some of them branched. In some areas, the cells formed cords and had a more epithelioid appearance (Figure 2). In some areas, there was hyaline matrix material between tumor cells (Figure 2). Small vessels were seen throughout the tumor, some of them branched.

Histopathologic Findings

The biopsy specimen measured approximately 2 × 4 cm in greatest dimensions and appeared completely excised on the sections examined. Biopsy sections showed a well-circumscribed but not encapsulated tumor (Figure 1). The margins were expansile and located within a few millimeters of the overlying epithelium (Figure 2).

The tumor was composed of a spindle cell population, with some more epithelioid cells, but no component that showed definitive epithelial features or squamous differentiation. The spindle cells were small, with sparse, faintly granular cytoplasm and poorly defined cell borders (Figures 1 and 2). The nuclei were dark, slightly vesicular, and ovoid and had fine chromatin. In some areas the spindle cells showed no pattern, whereas in other areas the cells formed cords and had a more epithelioid appearance (Figure 2). In some areas, there was hyaline matrix material between tumor cells (Figure 2). Small vessels were seen throughout the tumor, some of them branched.

Immunohistochemical Stains

The tumor expressed vimentin (BioGenex, San Ramon, Calif), CD34 (QBEND 10, BioGenex), CD99 (Signet, Dedham, Mass), and Bcl-2 (Dako, Carpinteria, Calif) diffusely (Figures 3 through

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Figure 1. Biopsy specimen showing a well-circumscribed but not encapsulated tumor with numerous small vessels throughout, some branched. There are spindle cells and more epithelioid cells. The cells were small, with sparse, faintly granular cytoplasm and poorly defined cell borders. Nuclei are dark, slightly vesicular, and ovoid and have fine chromatin. In some areas there is no pattern, whereas in other areas the cells formed cords and are more epithelioid in appearance. In some areas, there is prominent hyaline matrix material between tumor cells (hematoxylin-eosin, original magnification ×100).

Figure 2. Higher-power view of the biopsy specimen shown in Figure 1 (hematoxylin-eosin, original magnification ×200).

Figure 3. Immunohistochemical staining for CD34 showing diffuse staining of tumor cells (original magnification ×100).

Figure 4. Immunohistochemical staining for CD99 showing diffuse staining of tumor cells (original magnification ×200).

Figure 5. Immunohistochemical staining for bcl-2 showing diffuse staining of tumor cells (original magnification ×200).

Figure 6. Immunohistochemical staining for CK7 showing positive staining in some of the tumor cells (original magnification ×200).
5). The tumor cells stained intensely but not diffusely in areas with AE1/AE3 (Dako) and CK7 (BioGenex) (Figure 6), CK20 (Dako) and α-smooth muscle actin (Dako) showed minimal staining, and epithelial membrane antigen (Dako) showed weak expression in scattered cells. Desmin (Dako) and S100 protein (BioGenex) were negative. Estrogen and progesterone receptors (Dako) showed moderately intense expression in most tumor cells. Ki-67 (MIB-1, Dako) showed scattered nuclear expression throughout the tumor that averaged approximately 4 to 5 positive cells per high-power ×40 field averaging 10 random fields.

**COMMENT**

Tumors that show both epithelial and mesenchymal features are uncommon but occur in various anatomic sites. The origin of mixed tumors from most sites has been ascribed to myoepithelial cells. These mixed tumors may show variable amounts of epithelial and mesenchymal components, which not uncommonly show chondroid and osseous differentiation. They not only coexpress vimentin and cytokeratin but, at least in areas, coexpress α-smooth muscle actin and/or S100 protein. In addition, they commonly coexpress other intermediate filament proteins such as glial filament acidic protein.

However, SCEVs are distinctive because they express little if any α-smooth muscle actin and S100 protein or intermediate filaments other than cytokeratin and vimentin. In addition, SCEVs appear to lack myoepithelial differentiation ultrastructurally, and they lack the spectrum of morphologic mesenchymal tissue (ie, chondroid and bone) seen in other mixed tumors.

Although most SCEVs do express hormonal receptors, the significance of this is not known, since estrogen and progesterone receptors are commonly expressed in the area even in vaginal fibroepithelial polyps. In the present case of SCEV, there was diffuse expression of immunohistochemical stains CD34, CD99, and Bcl-2 not previously reported. CD34 is a 115-kd, heavily glycosylated transmembrane protein first identified on hematopoietic stems and committed progenitor cells. Within the hair follicles, cells that coexpress CD34 and cytokeratin are found within the outer root sheath, where the follicular stem cells are believed to reside. Although CD34 expression is seen in a diverse group of benign and malignant mesenchymal cell populations, its expression appears characteristic of mesenchymal progenitor cell populations.

CD99 is the product of the MIC2 gene and is a glycoprotein that is involved in β3-integrin–independent cell adhesion, which depends on activation of protein kinase and reorganization of the cytoskeleton. Although the spectrum of malignant and benign tumors that express CD99 is ever expanding, it is characteristic of primitive neuroectodermal tumors within the Ewing family. These tumors show cytoketic defects that result in rearrangements of the EWS gene, with ETS transcription factor genes leading to markedly increased expression of CD99.

In addition, lymphoblastic leukemia or lymphoma of precursor lymphocytes of both B- and T-cell phenotype commonly express CD99. Most of these primitive, precursor, or progenitor cell populations also express Bcl-2. Again, Bcl-2 expression is not specific, but even in adult mammalian tissues Bcl-2 has a restricted distribution and is expressed mainly in progenitor cells and long-lived cells in various organs. Bcl-2 is an antiapoptotic molecule that moderates mitochondrial pore formation, and it has been shown that CD99 also has a role in modulating apoptosis. Resistance to apoptosis is a characteristic of progenitor cell populations. Thus, coexpression of CD34, CD99, and Bcl-2 without immunohistochemical or ultrastructural evidence of myofibroblastic differentiation is consistent with the origin of SCEVs from more primitive, less differentiated cells than other mixed tumors.

In recent years, an ever-widening spectrum of CD34+ tumors has been described; some have features similar to those in SCEVs, and these CD34+ tumors were considered in the differential diagnosis. Solitary fibrous tumors (SFTs) are uncommon soft tissue neoplasms that are believed to be of mesenchymal origin. Although they were first described in the pleura, they have since been described arising in other serosal surfaces and many other sites. Morphologically, SFTs are well-circumscribed but not encapsulated tumors composed of bland spindle-shaped cells with several architectural appearances, including a storiform pattern, fascicles of spindle cells with a wavy, neural appearance, a patternless pattern, abundant myxoid matrix in areas, densely cellular fascicles of spindle cells with a herringbone pattern, and SFTs with atypical multinucleated giant cells admixed with the spindle cell proliferation. Mitoses and areas of necrosis are not identified except in the densely cellular variants, where there may be some nuclear atypia and scattered mitotic figures. The SFTs are characterized by prominent vascularity, often with branching vessels as seen in hemangiopericytomas and SCEVs. Although scant collagen may be seen in SFTs, more advanced degrees of collagenization with spindle cells separated by strands of ropelike collagen may be seen. Although this collagenized pattern is distinctive, it may be mistaken for the cosinophilic matrix material seen in SCEVs. In addition, SFTs show strong CD34 reactivity and CD99 expression, and they are negative for S100 protein, HMB-45, and α-smooth muscle actin, but they show no morphologic, immunohistochemical, or ultrastructural evidence of epithelial derivation. Similarly, hemangiopericytomas and schwannomas may show diffuse staining for CD34 but lack morphologic, immunohistochemical, and ultrastructural evidence of an epithelial origin. In addition, schwannomas express S100 protein and are encapsulated.

Mixed epithelial-mesenchymal tumors of female genital tract are rare. By definition, all these tumors contain intimately admixed epithelial and mesenchymal elements by standard light microscopic examination. They may occur as both benign (adenofibroma and adenomyoma variants, an intermediate variant [atypical polypoid adenomyoma]) and malignant variants (adenosarcoma, carcinosarcoma [malignant mixed mesodermal tumor, malignant mixed Mullerian tumor], and carcinoma). Unlike SCEVs, mixed epithelial-mesenchymal tumors occur in the uterus as polypoid, circumscribed, usually solitary masses. Clinically, they present with vaginal bleeding. Adenofibromas show epithelium that is usually of proliferative endometrial type; however, a flattened single cell cuboidal cell can be seen admixed with a benign variably fibrous stroma. Adenomyomas are characterized by an intimate admixture of benign endometrial glands without architectural complexity and a stroma composed of smooth muscle and fibrous tissue. Adenosarcomas show an admixture of a benign epithelial component and a sarcomatous component, whereas carcinosarcomas are characterized by an admixture of malignant epithelial and mesenchymal elements, and carcinofibromas are composed of a malig-
nant epithelial component and benign fibrous component. The malignant components of these tumors show an aggressive infiltrative growth pattern and metastatic potential.

Rare malignant mixed tumors of the vagina do occur. They show a biphasic pattern of glands and spindle cells, which resemble synovial sarcoma. These tumors lack the circumcision seen in SCEV with more cytologic atypia and a higher mitotic rate. Malignant mixed tumors of the vagina have been proposed to arise from the Gartner ducts or related mesonephric rests.

The origin of SCEVs has been proposed to be from a possible embryonic remnant. Although the embryologic development of the vagina is controversial, the hymenal ring appears to be derived from the urogenital sinus. The greatest controversy exists on the relative contributions of the Mullerian ducts and urogenital sinus to the development of the vagina. Some people believe that the proximal two thirds to four fifths of the vagina is derived from the Mullerian ducts, whereas the urogenital sinus forms the remaining distal portion. Still others believe that the Mullerian ducts descend to the level of the hymenal ring, fuse, and then are invaded distally by urogenital sinus tissue that ultimately forms vaginal epithelium.

The second theory suggests that foci of primordial vaginal epithelium may migrate and develop aberrantly, resulting in abnormal growths later in adult life. The expression of both epithelial and mesenchymal markers is well known with Mullerian-derived tissue. Mullerian-derived tumors express cytokeratin AE1/AE3, vimentin, and CK7 with weak to minimal CK20 staining. Wolffian adnexal tumors, so-called female adnexal tumor of probable Wolffian origin, also show varying morphologic structures with solid (spindle cells), tubular (lined by cuboidal and attenuated cells) patterns. Wolffian adnexal tumors also coexpress vimentin and AE1/AE3 and have been shown to express CK7 with minimal expression of CK20. Since urothelial epithelium expresses both CK7 and CK20 and the tumor we examined showed only CK7 staining, this may favor a Mullerian or possible Wolffian origin. Ki-67 expression showed only a small percentage of the cells were cycling, and to date none of these tumors have metastasized. Complete surgical excision is considered curative.

Most mixed tumors demonstrate an orderly sequence of transformation or metaplasia from an epithelial to a mesenchymal phenotype and in many cases show the development of relatively mature epithelial and/or mesenchymal elements. The SCEVs on the other hand appear to arise from a primitive/progenitor cell that coexpresses CD34, CD99, Bcl-2, cytokeratin, and vimentin and shows little or no mature epithelial or mesenchymal components.

References