E-cadherin expression in plasmacytoid, signet ring cell and micropapillary variants of urothelial carcinoma: comparison with usual-type high-grade urothelial carcinoma

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Loss of E-cadherin expression has been linked to the invasive phenotypes of a variety of neoplasms, including lobular breast cancer. The expression of E-cadherin in variants of urothelial carcinoma relative to usual-type urothelial carcinoma, maximum depth of invasion and angiolymphatic invasion has not been well characterized. A total of eight cases of micropapillary urothelial carcinoma, four cases of plasmacytoid urothelial carcinoma, two cases of urothelial carcinoma with signet ring cell differentiation and two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation, all obtained from cystectomy/cystoprostatectomy cases, were identified. In all nine cases of usual-type invasive and noninvasive high-grade urothelial carcinoma were also included in the study. Immunohistochemical staining of E-cadherin was performed in all cases. Pathological parameters including depth of invasion and presence of angiolymphatic invasion were documented. **Maximum depth of invasion:** In micropapillary urothelial carcinoma, extravesical extension was seen in three of eight cases; muscularis propria invasion in four of eight cases; and lamina propria invasion in one of eight cases. In plasmacytoid urothelial carcinoma, extravesical extension was observed in two of four cases, and muscularis propria invasion and lamina propria invasion in one of four cases each. In urothelial carcinoma with signet ring cell differentiation, extravesical extension and muscularis propria invasion was seen in one of two cases each. In urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation, muscularis propria invasion and lamina propria invasion was observed in one of two cases each. In usual-type high-grade urothelial carcinoma, extravesical extension was seen in six of nine cases and noninvasive in three of nine cases. In angiolymphatic invasion, micropapillary urothelial carcinoma was observed in eight of eight cases; plasmacytoid urothelial carcinoma in two of four cases; urothelial carcinoma with signet ring cell differentiation in one of two cases; and urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation in one of two cases. Usual-type high-grade urothelial carcinoma was seen in six of nine cases. **E-cadherin expression:** All eight cases of micropapillary urothelial carcinoma were positive for E-cadherin in the micropapillary component and adjacent usual-type urothelial carcinoma. The four cases of plasmacytoid urothelial carcinoma, two cases of urothelial carcinoma with signet ring cell differentiation and two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation were all negative for E-cadherin. All nine additional cases of usual-type high-grade urothelial carcinoma were diffusely positive for E-cadherin. E-cadherin is diffusely positive in usual-type urothelial carcinoma and micropapillary urothelial carcinoma, irrespective of pathological stage and angiolymphatic invasion. Loss of E-cadherin expression may be a marker of plasmacytoid and signet ring cell differentiation in urothelial carcinoma.

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The cadherins are a family of transmembrane glycoproteins that are involved in homotypic calcium-dependent intercellular adhesions and include N-, P- and E-cadherin.¹ E-cadherin, the most extensively studied cadherin family member, is expressed in epithelial tissue and has an important

role in establishment and maintenance of tissue architecture.^{2,3} Reduced expression or loss of E-cadherin has been reported in various human carcinomas.^{4–15} Aberrant expression of E-cadherin in human urothelial carcinoma is thought to correlate with lack of differentiation, muscle invasion and distant metastasis; however, this concept remains somewhat controversial.^{12,15–18}

Greater than 90% of bladder carcinomas are usual-type urothelial carcinoma; however, a small subset of tumors are recognized as variants of urothelial carcinoma because of their distinctive histological appearance and/or poor prognosis.^{19,20} Two of these variant entities with poor prognosis are the plasmacytoid and micropapillary variants of urothelial carcinoma. The plasmacytoid variant is composed of discohesive oval-to-round cells with abundant eosinophilic cytoplasm and eccentrically located nuclei. Intracytoplasmic vacuoles may be present in these cells mimicking signet ring cells. This lesion may also be diffusely infiltrative or may be arranged in cords and in a single file pattern.^{21–23} The micropapillary variant may be comprised of two components, the superficial and invasive. The superficial component is comprised of slender filiform processes, often with a central fibrovascular core. The invasive component is comprised of small aggregates or nests of cells frequently seen in empty spaces 'retraction artifact' that mimic angiolymphatic invasion. Single tumor cells departing from the tight cell balls may be seen in the stroma.^{24,25}

The expression of E-cadherin in variants of urothelial carcinoma relative to usual-type urothelial carcinoma, maximum depth of invasion and angiolymphatic invasion has not been well characterized. The goal of our study is compare E-cadherin expression in micropapillary, plasmacytoid and signet ring cell variants of urothelial carcinoma and usual-type urothelial carcinoma.

Materials and methods

We identified eight cases of micropapillary urothelial carcinoma, four cases of plasmacytoid urothelial

carcinoma, two cases of urothelial carcinoma with signet ring cell urothelial carcinoma and two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation. A total of nine cases of usual-type invasive and noninvasive high-grade urothelial carcinoma were also included in the study. Immunohistochemical staining for E-cadherin (monoclonal antibody, clone: ECCD-2, 1:50, Zymed, South San Francisco, CA, USA) was performed in all cases. Immunohistochemical analysis was performed, after optimized epitope retrieval, with a polymer-based detection system. Sections were deparaffinized and rehydrated using deionized water. They were then heated in citrate buffer (pH 6.0), using an electric pressure cooker for 3 min at 12–15 p.s.i. (at ~120°C), and cooled for 10 min before staining. Fisher's exact test was performed to determine the statistical significance of E-cadherin expression in all cases. Each case was evaluated for depth of invasion and presence of angiolymphatic invasion. This study was completed following the guidelines of and with approval from the Emory University institutional review board.

Results

The immunohistochemical and pathological findings of eight cases of micropapillary urothelial carcinoma, four cases of plasmacytoid urothelial carcinoma, two cases of urothelial carcinoma with signet ring cell differentiation, two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation and nine cases of usual-type invasive and noninvasive high-grade urothelial carcinoma are listed in Table 1.

Immunohistochemical staining showed that all eight cases of micropapillary urothelial carcinoma were positive for E-cadherin in the micropapillary component and adjacent usual-type urothelial carcinoma (Figures 1a and b). The four cases of plasmacytoid urothelial carcinoma (Figures 2a and b), two cases with signet ring cell differentiation (Figures 3a and b) and two cases of urothelial

Table 1 Immunohistochemical and pathological findings in our cases of micropapillary urothelial carcinoma, signet ring cell urothelial carcinoma, plasmacytoid urothelial carcinoma, mixed plasmacytoid/signet ring cell urothelial carcinoma and nonvariant urothelial carcinoma

	Micropapillary urothelial carcinoma	Plasmacytoid urothelial carcinoma	Signet ring cell urothelial carcinoma	Mixed plasmacytoid/ signet ring cell urothelial carcinoma	Nonvariant urothelial carcinoma
<i>E-cadherin</i> ^a					
Positive ^a	8/8	0/4	0/2	0/2	9/9
Negative ^a	0/8	4/4	2/2	2/2	0/9
<i>Pathological findings</i>					
Angiolymphatic invasion	8/8	2/4	1/2	1/2	9/9
Lamina propria invasion	1/8	1/4	0/2	1/2	0/9
Muscularis propria invasion	4/8	1/4	1/2	1/2	3/9
Extravesical extension	3/8	2/4	1/2	0/2	6/9

^aFisher's exact test: *P*-value ≤0.0001.

Figure 1 (a) Micropapillary urothelial carcinoma. (b) Positive E-cadherin expression in micropapillary urothelial carcinoma.

Figure 2 (a) Plasmacytoid urothelial carcinoma. (b) Negative E-cadherin expression in plasmacytoid urothelial carcinoma.

carcinoma with mixed plasmacytoid and signet ring cell differentiation were negative for E-cadherin. All nine additional cases of usual-type high-grade urothelial carcinoma were diffusely positive for E-cadherin (Figures 4a and b). P -value ≤ 0.0001 for Fisher's exact test.

In the eight cases of micropapillary urothelial carcinoma, extravesical extension was present in three cases, muscularis propria invasion in four cases and lamina propria invasion in one case. In our four cases of plasmacytoid urothelial carcinoma, extravesical extension was present in two cases, muscularis propria invasion in one case and lamina propria invasion in one case. In our two cases of urothelial carcinoma with signet ring cell differentiation, extravesical extension was present in one case and muscularis propria invasion in the other. Of our two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation, muscularis propria invasion was present in one case and lamina propria invasion in the other. In our usual-type high-grade urothelial carcinoma, extravesical extension was present in six of nine cases. Of the nine cases, three were noninvasive.

Angiolymphatic invasion was identified in all eight cases of micropapillary urothelial carcinoma, in two of four cases of plasmacytoid urothelial carcinoma, one of two cases of urothelial carcinoma with signet ring cell differentiation, one of two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation and in six of nine cases of usual-type high-grade urothelial carcinoma.

Discussion

Epithelial cells mediate important barrier functions. They form tight homotypic interactions that contribute to the formation of these permeability barriers. Cadherins are a family of transmembrane glycoproteins that are involved in homotypic calcium-dependent intercellular adhesions as well as cell signaling. E-cadherin is a 120 kDa glycoprotein located on chromosome 16. This protein is expressed in all epithelial tissues and is associated with intracellular proteins called catenins that couple cadherins to actin microfilaments.²⁶ The E-cadherin/catenin complex is important for cellular

Figure 3 (a) Signet ring cell urothelial carcinoma, with overlying benign urothelium. (b) Negative E-cadherin expression in signet ring cell urothelial carcinoma (note positive expression in overlying benign urothelium).

polarity, maintenance of normal tissue morphology and cellular differentiation.²⁷ Loss of E-cadherin-mediated cell adhesion is involved in tumor progression and metastasis. There is also evidence that E-cadherin may have a role in invasion suppression.²⁸

Recent studies have demonstrated that loss of E-cadherin immunoreactivity may correlate with a lack of differentiation and aggressive behavior of breast, head and neck, lung, gastric, esophageal, colorectal, prostatic and urothelial carcinomas.^{5–7,15,29–35} Published studies on urothelial carcinoma show that loss of membranous E-cadherin immunoreactivity is strongly correlated with high grade and advanced stage.^{8,12,15,36–38} Whether or not loss of E-cadherin is correlated with disease progression or has any prognostic significance has been debated by several investigators.^{8,11,36,38–41} The nonvariant urothelial carcinoma in our study were diffusely positive for E-cadherin. Previous studies demonstrated a decreased or aberrant E-cadherin staining in tumors with deeper infiltration.^{8,12,15,36–38,41} The staining intensity was heterogeneous in our cases, and there

Figure 4 (a) Usual-type high-grade urothelial carcinoma. (b) Positive E-cadherin expression in usual-type high-grade urothelial carcinoma.

was no significant decrease or loss of staining in our high-grade carcinomas.

Recently, there has been an increased interest in the plasmacytoid variant of urothelial carcinoma. Three large series and numerous case reports have been published.^{21–23,42–60} This variant of urothelial carcinoma is considered to be a poorly differentiated neoplasm with aggressive behavior and poor prognosis. Microscopically, these tumors are diffusely infiltrative and the individual cells are often discohesive. Fritsche *et al*⁴³ put forth the hypothesis that E-cadherin loss may be associated with plasmacytoid differentiation in urothelial carcinoma.

A review of the literature shows 13 total cases of plasmacytoid urothelial carcinoma that were stained with E-cadherin. All of these cases lacked E-cadherin expression.^{43,46,49,51,57} In our study, all four cases of plasmacytoid urothelial carcinoma, and two cases of urothelial carcinoma with mixed plasmacytoid and signet ring cell differentiation and urothelial carcinoma with signet ring cell differentiation lacked E-cadherin expression (Fisher's exact test, P -value ≤ 0.0001). Angiolymphatic invasion was identified in half of these cases and the depth of invasion ranged from lamina propria invasion to extravesical extension. These results are consistent with previous case reports of plasmacytoid urothelial carcinoma lacking E-cadherin staining. It is conceivable that loss of E-cadherin-mediated cell adhesion likely contributes to the lack of cohesion and infiltrative appearance of plasmacytoid urothelial carcinoma.

Plasmacytoid urothelial carcinoma may have intracytoplasmic vacuoles, giving them a resemblance to signet ring cells.^{21–23} We included two cases of urothelial carcinoma with signet ring cell differentiation. Signet ring cell carcinoma of the bladder has been associated with aggressive behavior and poor clinical outcome.⁶¹ In a series examining the immunohistochemical features of primary signet ring cell carcinomas of the bladder, Thomas *et al*⁶² found that E-cadherin was lost in three of nine cases. Both of our cases of urothelial carcinoma with signet ring cell differentiation lacked E-cadherin staining. Aberrant expression or loss of E-cadherin expression may be associated with the distinctive morphology of urothelial carcinoma with signet ring cell differentiation, and may also contribute to its aggressive behavior.

Micropapillary variant of urothelial carcinoma is associated with high grade and high stage, as well as a tendency for vascular invasion. Patients with this variant of urothelial carcinoma typically have a poor prognosis. The invasive component is composed of cells forming small tight nests and balls that are frequently seen in empty spaces devoid of cellular lining.^{24,25} Owing to its unique morphology and propensity for vascular invasion, we were interested in this variant's E-cadherin expression. Maranchie *et al* reported three cases of micropapillary urothelial carcinoma showing normal levels of E-cadherin expression. Of the three, one micropapillary carcinoma had an abnormal cytoplasmic distribution, despite normal membrane-bound staining of the adjacent micropapillary urothelial carcinoma.⁶³ In another case report, E-cadherin staining was lost in the peripheral portions of cell clusters.⁶⁴ In all eight of our cases of micropapillary urothelial carcinoma, E-cadherin expression was homogeneously present in the membrane of the invasive component. Staining was not decreased or lost in the periphery of micropapillary cell clusters. All our cases had angiolymphatic invasion, and the depth of invasion ranged from lamina propria invasion to extravesical

extension. Our results indicate that E-cadherin does not correlate with this lesion's high grade and stage or its propensity for angiolymphatic invasion.

In addition to their distinct morphological features, loss of E-cadherin expression may be a marker of plasmacytoid and signet ring cell differentiation in urothelial carcinoma and may also have a role in the aggressive behavior of these variants of urothelial carcinoma.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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