INVERTED PAPILLOMA OF THE BLADDER AND THEIR VARIANTS
VERSUS
INVERTED GROWTH PATTERNS OF CANCER

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Inverted papilloma of the bladder is thought to be benign, but some urothelial carcinomas show a prominent inverted growth pattern which may pose a diagnostic dilemma. A recent meta-analysis of 322 cases reported with respect to inverted papilloma of the lower urinary tract identified a recurrence rate of 3.85%. Moreover, 1.55%, 5.90% and 1.54% were associated with previous, simultaneous and subsequent urothelial cell carcinoma, respectively (1). These findings together with the known potential for misinterpretation of urothelial carcinoma with endophytic growth as inverted papilloma emphasizes the need of an appropriated approach to differential diagnosis of endophytic lesions of the bladder.

INVERTED PAPILLOMA (UROTHELIAL ADENOMA; BRUNNIAN ADENOMA)

Inverted papilloma comprises less than 1% of urothelial neoplasms and occurs at all ages with a few examples in children (2, 3). The mean age at diagnosis was 64 years (range, 37-87 years) and a peak frequency in the 6th and 7th decades (3, 4). It is more common in men than women (4:1 ratio) and usually presents with hematuria and irritative symptoms. The etiology is uncertain. Some consider this to be a neoplasm with malignant potential (5), whereas others consider it a reactive process similar to proliferative urothelial lesions such as cystitis glandularis and cystitis cystica. Ultrastructural, DNA-ploidy, and immunohistochemical studies indicate a similarity to normal urothelium and low-grade urothelial carcinoma (3, 6). Recent molecular data supports its benign nature based in the low amount of genetic anomalies found in most cases (7).

Most cases of inverted papilloma are located in the bladder trigone, but inverted papilloma can also be found in the ureter, renal pelvis, and urethra (3). Macroscopically, it is characteristically sessile or pedunculated, smooth surfaced, small 0.2-to-4.3 cm (mean, 0.9 cm in diameter), and single, but large multifocal lesions may occur (8, 9, 10). Microscopically, inverted papilloma consists of intramucosal and submucosal anastomosing islands and trabeculae of urothelium. The surface urothelium may be normal, attenuated, or elevated. There are two main patterns of inverted papilloma, including trabecular and glandular patterns (11). The trabecular pattern is composed of anastomosing cords and sheets of urothelium that are arranged at various angles to the mucosal surface. In some cases, cystic spaces lined by attenuated urothelium are present within the epithelial islands. These spaces may contain eosinophilic secretions which stain with PAS but not mucicarmine. The glandular pattern is composed of nests of urothelium with pseudoglandular or true glandular differentiation with goblet cells. Pseudoglandular spaces are lined by urothelium, whereas true glandular spaces contain mucous-secreting cells with mucicarminosphilic secretions, sometimes with intestinal metaplasia with goblet cells (11). In both patterns of inverted papilloma, the epithelial
elements are surrounded by an intact basement membrane and delicate fibrovascular stroma. Unusual growth patterns of inverted papilloma include basaloid, hyperplastic, spindle cell (also called as medullary), and neuroendocrine patterns, often with mixed forms. Neuroendocrine differentiation in inverted papilloma is characterized by numerous granular eosinophilic cells that are immunoreactive for chromogranin. Such cells are present in 40% of cases of typical inverted papilloma. Non-keratinizing squamous metaplasia is also common. Mild cytologic atypia is often encountered in inverted papilloma, and the precise demarcation with carcinoma is unresolved; fortunately, this is an uncommon problem, but there are cases that are difficult to resolve. In rare cases nuclear atypia may be prominent but these atypical nuclear features are most probably best considered degenerative in nature at present. Mitotic figures are rare or absent in inverted papilloma, unlike carcinoma. It is possible that inverted papilloma and papillary urothelial carcinoma are related, but this possibility is controversial and recent molecular data argues against (12, 13, 14, 15). The number of cases with coexistent urothelial carcinoma in situ or carcinoma has increased recently (16). In some cases, foci of papillary urothelial carcinoma appear to arise from an otherwise typical inverted papilloma (15, 16). Some cases diagnosed as inverted papilloma probably represent urothelial carcinoma with an inverted growth pattern (17, 18, 19, 20, 21, 22). A unique case associated with leiomyoma has been reported (5). Inverted papilloma are usually diploid (4, 5), although one of three cases with associated urothelial carcinoma was aneuploid (19). Recurrent lesions have been observed in less than 1% of the reported cases. An initial diagnosis of inverted papilloma should be challenged if progression is observed (3).

**UROTHELIAL CARCINOMA, INVERTED GROWTH**

In 1976, Cameron and Lupton (18) described 2 cases of urothelial carcinoma which mimicked inverted papilloma architecturally, but possessed high grade cytologic abnormalities. The potential for misinterpretation of such cases as inverted papilloma has been confirmed by other authors (17, 19, 20). In some cases the tumor has an identical architecture to inverted papilloma while others grow with more of a broad pushing front analogous to carcinoma (17). By definition, this variant of urothelial carcinoma has significant nuclear pleomorphism, mitotic figures, and architectural abnormalities consistent with low- or high-grade urothelial carcinoma (WHO, 2004) (23). In most cases, the overlying epithelium has similar abnormalities and often contains typical urothelial carcinoma. Inverted papilloma-type carcinoma with minimal cytologic and architectural abnormalities has high mitotic activity and high ki67 labeling index. An exophytic papillary or invasive component is often associated with the inverted element. However, in cases of inverted papilloma fragmented during transurethral resection, a pseudoexophytic pattern may result. The stromal “cores” in this instance are wider and more variable than the fibrovascular cores of true papillary neoplasms (17). In some instances, both inverted papilloma and inverted papilloma-type carcinoma are intimately admixed. Large papillary tumors with prominent endophytic growth “invade” the lamina propria with a pushing border (17). Unless this pattern is accompanied by true destructive stromal invasion the likelihood of
Metastasis is minimal, because the basement membrane is not truly breached (17, 18). The main problem associated with this type of growth is assessing the presence of invasion, especially when the tumor is seen intermingling with slender muscle bundles of lamina propria or in juxtaposition with well-defined fascicles of muscularis propria. The diagnosis of invasion should be made when there are irregularities of the contours of the neoplastic nests, if they have jagged edges, and if desmoplastic or inflammatory stroma is noted surrounding these nests (23).

Main differential diagnostic consideration is inverted papilloma with atypia (22). Available data confirms that these cases have rare mitotic figures and very low proliferation index as seen by ki67 labeling index. Some authors have proposed a cut off of <5% to favor a diagnosis of inverted papilloma (7). In addition, to date there has been no association with urothelial carcinoma in the follow up of individuals diagnosed with inverted papilloma with atypia. These atypical nuclear features are most probably best considered degenerative in nature.

There is insufficient data on the literature to indicate whether carcinoma with endophytic growth behave in a manner different to than what would be expected on a stage for stage basis. Main distinguishing features are summarized in Table 1.

REFERENCES

23. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics. Tumors of the urinary system and male genital organs. IARC Press, Lyon 2004
<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>UROTHELIAL CARCINOMA, INVERTED GROWTH</th>
<th>*INVERTED PAPILLOMA</th>
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<tbody>
<tr>
<td>Surface</td>
<td>Variable, usually exophytic papillary lesion present</td>
<td>Smooth, dome shaped, usually intact surface cytologically unremarkable</td>
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<tr>
<td>Growth pattern</td>
<td>Endophytic, lesional circumscription variable</td>
<td>Endophytic, expansive, sharply delineated, anastomosing cords and trabeculae</td>
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<td>Cytologic features</td>
<td>Maturation, spindling or palisading minimal to absent</td>
<td>Orderly polarized cells, some spindling and palisading at periphery, diffuse severe atypia absent. None-to-rare mitosis. No tumor necrosis</td>
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<tr>
<td>Biologic potential</td>
<td>Recurrences and progression may occur</td>
<td>Benign, no recurrences**</td>
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<tr>
<td>Immunohistochemistry</td>
<td>Variable, usually high p53 accumulation or Ki67-MIB1 counting (varies according to grade of differentiation)</td>
<td>Low p53 accumulation and Ki-67-MIB1 counting</td>
</tr>
<tr>
<td>Molecular analysis</td>
<td>Frequent FGFR3 mutation, chromosome 9 and 17 deletions</td>
<td>Rare deletions at chromosome 9 or 17, and rare FGFR·mutations</td>
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*May be associated with concomitant urothelial carcinoma

**Rare recurrences related to incomplete surgical excision