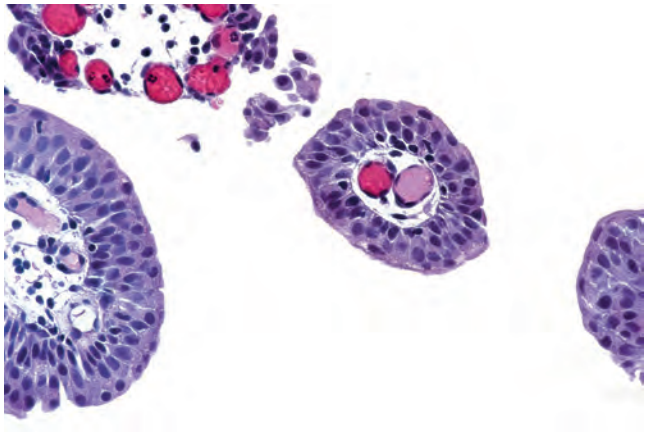

Figure 21-8 Papilloma consisting of small papillary fronds lined by normal-appearing urothelium.

attached to the mucosa by a stalk and are referred to as **exophytic papillomas**. The individual finger-like papillae have a central core of loose fibrovascular tissue covered by epithelium that is **histologically identical to normal urothelium** (Fig. 21-8). Recurrences and progression are rare but may occur. In contrast to exophytic papillomas, **inverted papillomas** are completely benign lesions consisting of inter-anastomosing cords of cytologically bland urothelium that extend down into the lamina propria.

- **Papillary urothelial neoplasms of low malignant potential** share many histologic features with papilloma, differing only in having thicker urothelium. At cystoscopy, these tumors tend to be larger than papillomas and may be indistinguishable from low- and high-grade papillary cancers. Recurrent tumors usually show the same morphology; progression to tumors of higher grade may occur but is rare.
- **Low-grade papillary urothelial carcinomas** have an orderly architectural and cytologic appearance. The cells are evenly spaced (i.e., maintain polarity) and cohesive. There is a mild degree of nuclear atypia consisting of scattered hyperchromatic nuclei, infrequent mitotic figures predominantly toward the base, and slight variation in nuclear size and shape (Fig. 21-9). These low-grade cancers may recur and, although infrequent, may also invade. Only rarely do these tumors pose a threat to the patient's life.

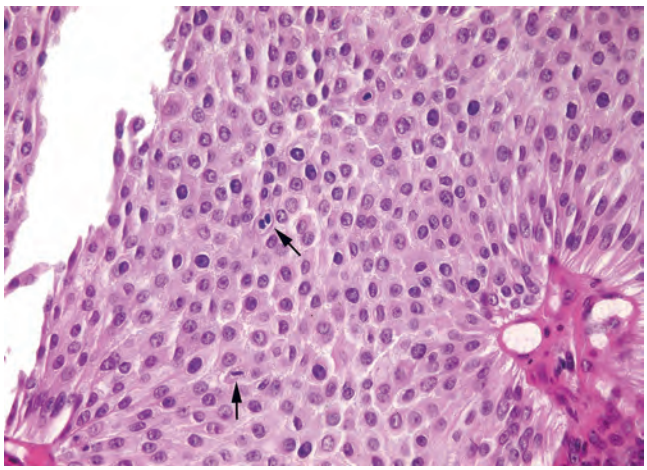

Figure 21-9 Low-grade papillary urothelial carcinoma with an overall orderly appearance, with a thicker lining than papilloma and scattered hyperchromatic nuclei and mitotic figures *(arrows)*.

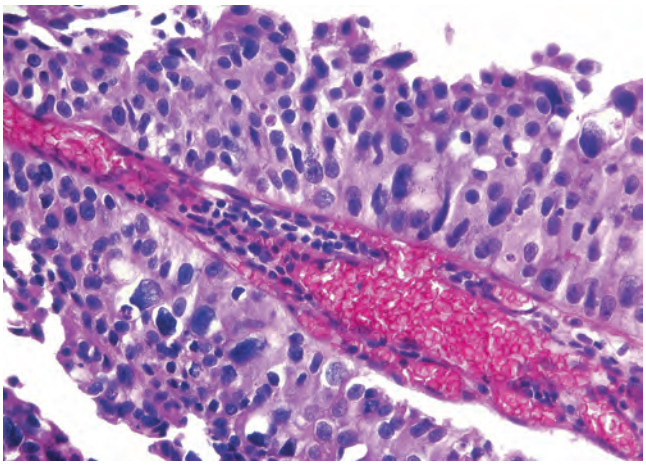

Figure 21-10 High-grade papillary urothelial carcinoma with marked cytologic atypia.

- **High-grade papillary urothelial cancers** contain dyscohesive cells with large hyperchromatic nuclei. Some of the tumor cells are highly anaplastic (Fig. 21-10). Mitotic figures, including atypical ones, are frequent. Architecturally, there is disarray and loss of polarity. As compared to low-grade lesions, these tumors have a much higher incidence of invasion into the muscular layer, a higher risk of progression, and, when associated with invasion, a significant metastatic potential.

In most series, less than 10% of low-grade cancers invade, but as many as 80% of high-grade urothelial carcinomas are invasive. Aggressive tumors may extend into the bladder wall, and, in more advanced stages, invade the adjacent prostate, seminal vesicles, ureters, and retroperitoneum. Some tumors produce fistulous communications to the vagina or rectum. About 40% of these deeply invasive tumors metastasize to regional lymph nodes. Hematogenous dissemination, principally to the liver, lungs, and bone marrow, may result.

Carcinoma in situ (CIS, or flat urothelial carcinoma) is defined by the presence of cytologically malignant cells within a flat urothelium. CIS may range from full-thickness cytologic atypia to scattered malignant cells in an otherwise normal urothelium, the latter termed **pagetoid spread** (Fig. 21-11). A common feature shared with high-grade papillary urothelial carcinoma is a lack of cohesiveness, which leads to the shedding of malignant cells into the urine. When shedding is extensive, only a few CIS cells may be left clinging to a largely denuded basement membrane. CIS usually appears as an area of mucosal reddening, granularity, or thickening without an evident intraluminal mass. It is commonly multifocal and may involve most of the bladder surface and extend into the ureters and urethra. If untreated, 50% to 75% of CIS cases progress to invasive cancer.

Invasive urothelial cancer (Fig. 21-12) may be associated with papillary urothelial cancer, usually high grade, or adjacent CIS. The extent of the invasion into the muscularis mucosae is of prognostic significance, and understaging on biopsy is a significant problem. The extent of spread **(staging)** at the time