The risk of cancer development in VIN depends on duration and extent of disease, and the immune status of the patient. Invasive carcinomas associated with lichen sclerosus, squamous cell hyperplasia, and differentiated VIN may develop in an insidious fashion and may be misinterpreted as dermatitis or leukoplakia for long periods. Once invasive cancer develops, the risk of metastatic spread is linked to the size of tumor, depth of invasion, and involvement of lymphatic vessels. The initial spread is to inguinal, pelvic, iliac, and periaortic lymph nodes. Ultimately, lymphohematogenous dissemination to the lungs, liver, and other internal organs may occur. Patients with lesions less than 2 cm in diameter have a 90% 5-year survival after treatment with vulvectomy and lymphadenectomy; however, larger lesions with lymph node involvement have poor prognosis.

Glandular Neoplastic Lesions

Like the breast, the vulva contains modified apocrine sweat glands. Presumably because of these "breastlike" features, the vulva may be involved by two tumors with counterparts in the breast, namely papillary hidradenoma and extramammary Paget disease.

Papillary Hidradenoma

Papillary hidradenoma presents as a sharply circumscribed nodule, most commonly on the labia majora or interlabial folds, and may be confused clinically with carcinoma because of its tendency to ulcerate. *Its histologic appearance is identical to that of intraductal papilloma of the breast* and consists of papillary projections covered with two layers of cells: an upper layer of columnar secretory cells covering a deeper layer of flattened myoepithelial cells. These myoepithelial elements are characteristic of sweat glands and sweat gland tumors (Fig. 22-9).

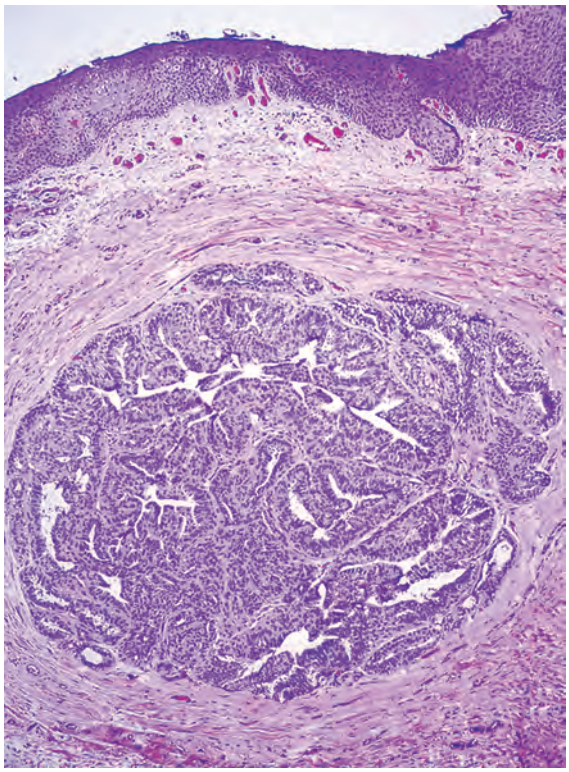

Figure 22-9 Papillary hidradenoma of the vulva, a well-circumscribed tumor composed of benign papillary projections covered with columnar secretory epithelium and underlying myoepithelial cells.

Extramammary Paget Disease

This curious and rare lesion of the vulva is *similar in its manifestations to Paget disease of the breast* (Chapter 23). In the vulva, it presents as a pruritic, red, crusted, maplike area, usually on the labia majora.

In contrast to Paget disease of the nipple, in which 100% of patients have an underlying ductal breast carcinoma, vulvar Paget is typically not associated with underlying cancer and is confined to the epidermis of vulvar skin. The treatment consists of wide local excision. Paget cells spread laterally within the epidermis and may be present beyond the confines of the grossly visible lesion. As a result, the tumor cells may not be completely excised and the disease can recur. Intraepidermal Paget disease may persist for many years or even decades without invasion or metastases. In the rare instances when invasion develops, the prognosis is poor.

MORPHOLOGY

Paget disease is a distinctive intraepithelial proliferation of malignant cells. Paget cells are larger than surrounding keratinocytes and are seen singly or in small clusters within the epidermis (Fig. 22-10*A*). The cells have pale cytoplasm containing mucopolysaccharide that stains with periodic acid–Schiff (PAS), Alcian blue, or mucicarmine stains. In addition, the cells express cytokeratin 7 (Fig. 22-10*B*). Ultrastructurally, Paget cells display apocrine, eccrine, and keratinocyte differentiation and presumably arise from multipotent cells found within the mammary-like gland ducts of the vulvar skin.

KEY CONCEPTS

- Approximately 30% of vulvar cancers are caused by infection with high risk HPVs, principally HPV-16. These cancers develop from an in situ lesion termed *classic vulvar intraepithelial neoplasia* (classic VIN).
- Most vulvar cancers (70%) are not related to HPV and develop in a background of lichen sclerosus or squamous cell hyperplasia from the premalignant lesion called *differentiated vulvar intraepithelial neoplasia* (differentiated VIN).