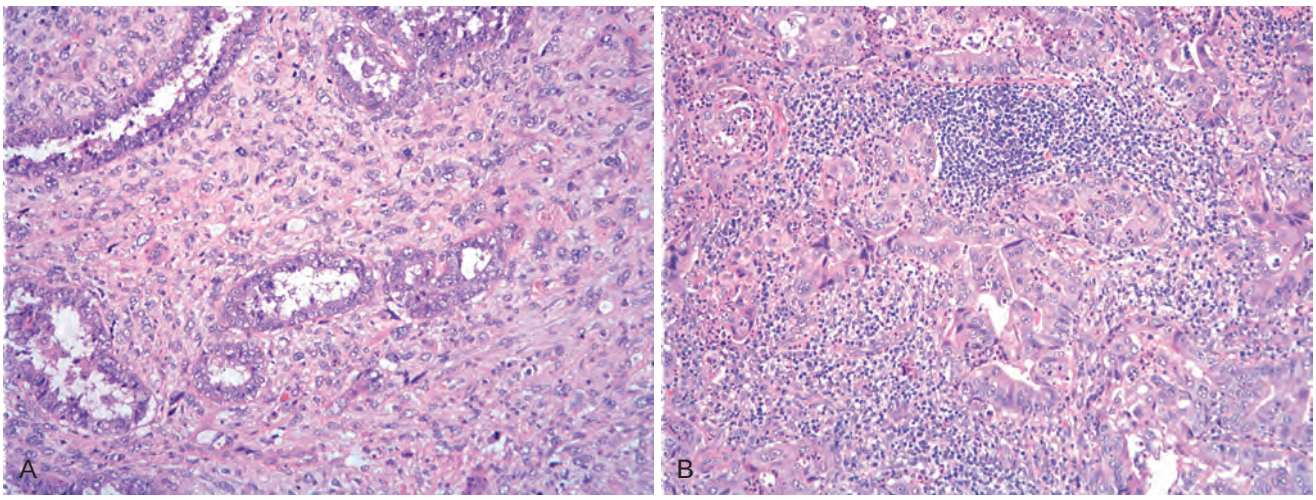

Figure 22-27 Malignant mixed müllerian tumor (MMMT). **A,** Micrograph showing both malignant epithelial and stromal components. **B,** Lymph node metastasis from a MMMT showing only the epithelial component, as is typically the case.

- Endometrioid (type I) carcinoma is often preceded by atypical hyperplasia and commonly has mutations in the *PTEN*, *PIK3CA*, *KRAS,* and *ARID1A* genes.
- Serous (type II) carcinoma is associated with serous endometrial intraepithelial carcinoma and the most common mutations are in *TP53*. *TP53* mutations are also found in precursor lesions.
- Stage remains the most important factor in outcome; serous tumors are much more likely to present at advanced stage and have a decidedly worse prognosis.
- Malignant mixed müllerian tumors (MMMTs) are carcinosarcomas that resemble endometrial carcinoma genetically and have poor outcomes with current therapies.

Tumors of Endometrial Stroma

These relatively uncommon tumors comprise less than 5% of endometrial cancers and include stromal neoplasms admixed with benign glands (adenosarcomas) and pure stromal neoplasms.

Adenosarcomas

Adenosarcomas present most commonly as large broad-based endometrial polypoid growths that may prolapse through the cervical os. The diagnosis is based on the presence of malignant-appearing stroma, which coexists with benign but abnormally shaped endometrial glands. These tumors predominate in women between the fourth and fifth decades and are generally considered to be a low-grade malignancy; recurrences develop in one fourth of cases and are nearly always confined to the pelvis. The principal diagnostic dilemma is distinguishing these tumors from large benign polyps. The distinction is important, because adenosarcoma is estrogen-sensitive and responds to oophorectomy.

Stromal Tumors

The endometrium occasionally gives rise to neoplasms that resemble normal stromal cells. Endometrial stromal neoplasms are divided into two categories: (1) benign stromal nodules and (2) endometrial stromal sarcomas. The stromal sarcomas may be further divided into low-grade and high-grade types depending on their differentiation.

Clues to the pathogenesis of stromal sarcomas have come from the identification of several recurrent chromosomal aberrations that are quite specific for these malignancies. As with many sarcomas, stromal sarcomas are associated with chromosomal translocations that create fusion genes. Low-grade endometrial stromal sarcomas usually have translocations in which portions of the *JAZF1* gene, which encode a transcriptional repressor, is fused to a second gene belonging to the polycomb gene family, such as *SUZ12*. Polycomb proteins participate in complexes that introduce repressive histone marks into chromatin, thereby silencing genes, and it is hypothesized that the JAZF1 fusion proteins act by disrupting the function of the polycomb complex, leading to misexpression of oncogenic genes. Recently, high-grade endometrial stromal sarcomas have been observed to contain different chromosomal translocations that also result in the formation of fusion genes, which are presumed to be pathogenically significant but are currently of unknown function.

About half of stromal sarcomas recur; relapse rates range from 36% to more than 80% for stage I and stage III/IV tumors, respectively. Unfortunately, relapse is not reliably predicted by either mitotic index or the degree of cytologic atypia. Distant metastases may announce their presence decades after the initial diagnosis, and death from metastatic tumor occurs in about 15% of cases. Five-year survival rates average 50% for low-grade tumors and are even lower for high-grade tumors.

Tumors of the Myometrium

Leiomyomas

Uterine leiomyoma (commonly called *fibroids*) is perhaps the most common tumor in women. They are benign smooth muscle neoplasms that may occur singly, but more often are multiple. Most leiomyomas have normal