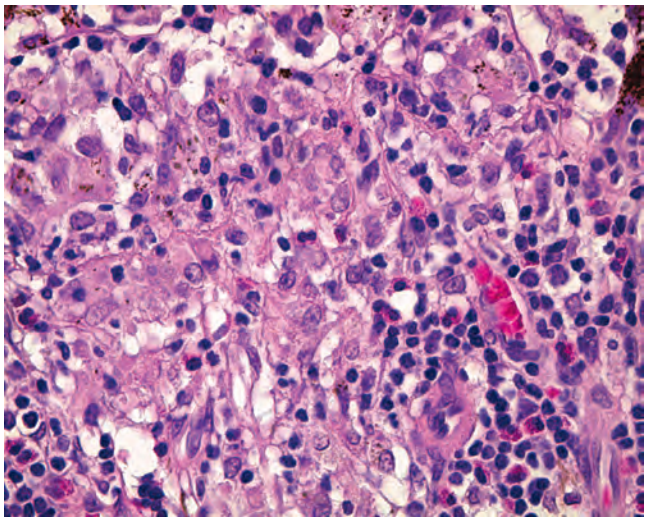

Figure 29-14 Sympathetic ophthalmia. The granulomatous inflammation depicted here was identified diffusely throughout the uvea. The uveal granulomas may contain melanin pigment and may be accompanied by eosinophils.

Sympathetic ophthalmia is treated by the administration of systemic immunosuppressive agents.

Neoplasms

The most common intraocular malignancy of adults is metastasis to the uvea, typically to the choroid. The occurrence of metastases to the eye is associated with an extremely short survival, and treatment of ocular metastases, usually by radiotherapy, is palliative.

Uveal Nevi and Melanomas

Uveal melanoma is the most common primary intraocular malignancy of adults. In the United States, these tumors account for approximately 5% of melanomas and have an age-adjusted incidence of 5.1 per million per year. Uveal nevi, especially choroidal nevi, are rather common, affecting an estimated 10% of the Caucasian population.

Epidemiology and Pathogenesis. Unlike cutaneous melanoma, the occurrence of uveal melanoma has remained stable over many years and there is no clear link between exposure to ultraviolet light and risk. In line with this observation, sequencing of tumor genomes has revealed that the molecular pathogenesis of uveal melanoma is distinct from that of cutaneous melanoma. The most important oncogenes in uveal melanoma are *GNAQ* and *GNA11*, both of which encode G-protein coupled receptors. Roughly 85% of uveal melanomas harbor a gain-of-function mutation in one of these genes that activate pathways that promote proliferation, such as the MAPK pathway (Chapter 7). Notably, uveal nevi are also associated with *GNAQ* and *GNA11* mutations yet rarely transform to melanoma, indicating that other genetic events also contribute to the development of uveal melanoma. One such event is loss of chromosome 3, which appears to be selected for because it leads to deletion of *BAP1*, a tumor suppressor gene on chromosome 3 that encodes a deubiquitinating enzyme. BAP1 is a component of protein complexes that place repressive marks on chromatin that lead to gene silencing; thus, uveal melanoma has joined the increasing list of cancers in which epigenetic alterations appear to have a central role in tumor pathogenesis (Chapter 7).

MORPHOLOGY

Histologically, uveal melanomas may contain two types of cells, spindle and epithelioid, in various proportions (Fig. 29-15). **Spindle cells** are fusiform in shape, whereas **epithelioid cells** are spherical and have greater cytologic atypicality. Like cutaneous melanomas, large numbers of tumor-infiltrating lymphocytes may be seen in some cases. An unusual feature that is commonly seen is the presence of looping slit-like spaces lined by laminin that surround packets of tumor cells. These spaces (which are not blood vessels) connect to blood vessels and serve as extravascular conduits for the transport of plasma and possibly blood. In vitro studies and examination of human tissues suggest that these unusual growth patterns are promoted by tumor cells through a process termed **vasculogenic mimicry.**

Uveal melanomas, with very rare exception, spread exclusively by a hematogenous route (the only exception being the rare case of melanoma that spreads through the sclera and invades the conjunctiva, thereby gaining access to conjunctival lymphatics). Most uveal melanomas spread first to the liver, an excellent example of a tumor-specific tropism for a particular metastatic site.

Clinical Features. Most uveal melanomas are incidental findings or present with visual symptoms, which may be related to retinal detachment or glaucoma. The prognosis of choroidal and ciliary body melanomas is related to (1) size (in contrast to cutaneous melanoma, the lateral extent of the tumor rather than tumor depth is the size dimension related to adverse outcome); (2) cell type (tumors containing epithelioid cells have a worse prognosis than do those containing exclusively spindle cells); (3) and proliferative index. Cytogenetic profiles, especially monosomy 3, and gene expression profiling may be helpful in stratifying patients into categories with differing risks of developing metastatic disease.

There seems to be no difference in survival between tumors treated by removal of the eye (enucleation) and those receiving eye-sparing radiotherapy, which is the treatment of choice. Melanomas situated exclusively in the iris tend to follow a relatively indolent course, whereas melanomas of the ciliary body and choroid are more aggressive.

Because these tumors are hidden from sight and are likely to have been present for some time before diagnosis, the prognosis is worse than for cutaneous melanoma. Although the 5-year survival rate is approximately 80%, the cumulative melanoma mortality rate is 40% at 10 years, increasing 1% per year thereafter. Metastases may appear "out of the blue" many years after treatment, making uveal melanoma a prime candidate for the investigation of the phenomenon of tumor dormancy. Targeted therapies such as MAPK inhibitors have shown some encouraging responses in clinical trials, but currently there is no proven effective treatment for metastatic uveal melanoma.