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Ophthalmic Pathology Update

Ocular melanoma

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Abstract

Ocular melanomas comprise uveal and conjunctival sub-types, which are very different from each other. A large majority of uveal melanomas involve the choroid, with less than 10% being confined to the ciliary body and iris. They tend to metastasize haematogenously, almost always involving the liver. Therapeutic methods include various forms of radiotherapy, surgical resection and phototherapy, which are often used in combination. Conjunctival melanomas show many similarities to their cutaneous counterparts, often metastasizing by lymphatic spread. Treatment consists of excision of invasive melanoma with adjunctive radiotherapy and/or cryotherapy and topical chemotherapy for intra-epithelial disease. The management of patients with ocular melanomas demands a good understanding of the pathology of these tumours. Pathological examination of the tumour indicates the prognosis and hence the need for further investigation and treatment. The scope of the pathologist is enhanced thanks to advances in molecular biology.

Keywords: Melanoma, Eye, Uvea, Conjunctiva, Pathology

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Introduction

Ocular melanomas are rare, especially in countries such as Saudi Arabia. Nevertheless, it behoves clinicians to have some knowledge of this disease so that when they encounter individuals with this condition they can offer the standard of care that these patients deserve. Even though such patients may be referred to an ocular oncology centre overseas, the success of their management depends greatly on the care that is provided at the home hospital, which would include diagnosis, counselling and long-term follow-up.

As with any disease, a good understanding of the underlying pathology is fundamental to patient care. There are many excellent sources of information on the pathology of ocular melanomas; however, some articles have become outdated because of rapid advances that have occurred in recent years, and other texts are not easily accessible.

The aims of this article are to provide a succinct yet practical overview of the pathology of ocular melanomas, with a guide to the more detailed literature on the subject. It is hoped that this review will be relevant not only to pathologists but also to ophthalmologists and oncologists.

Uveal melanoma

Introduction

Uveal melanomas account for approximately 98% of all ocular melanomas. More than 90% of intraocular melanomas

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arise in the choroid, with about 3–4% developing in the iris and the remainder in the ciliary body.[1]

In Caucasians, uveal melanomas have an incidence of approximately 7 per million per year.[2] Presentation peaks at the age of sixty years and is rare before adulthood. Males and females are affected in equal numbers, although iris melanomas tend to be slightly more common in women whereas choroidal melanomas are more common in men.[1]

Risk factors for uveal melanoma include: light skin, blue eyes, tendency to cutaneous naevi, congenital ocular melanocytosis, uveal melanocytoma and neurofibromatosis. The role of sunlight is uncertain but it is noteworthy that most iris melanomas occur inferiorly, where there is less protection from the upper eyelid.

Histology

According to the modified Callendar classification, uveal melanoma cytomorphology is categorized as: spindle; epithelioid; and mixed. Spindle cells are long and narrow, with large nuclei and nucleoli.[3] They were previously called 'spindle-B' cells to differentiate them from Spindle A cells with furrowed nuclei, which are now considered to be benign. Epithelioid cells are larger, with eosinophilic cytoplasm and can be poorly cohesive (Fig. 1a). Rarely, the tumour is entirely necrotic so that the cytomorphology is unclassifiable. Immunohistochemistry staining of proteins such as Heat Shock Protein 27 (HSP-27) may be used for prognostic purposes (Fig. 1b).[4] Conventionally, mitoses are counted per forty high-power fields using sections stained with haematoxylin and eosin. (Fig. 1c). Other methods can be deployed, using stains such as Ser-10 (also known as PHH3).[5]

Uveal melanomas often contain lymphocytes and macrophages, which are mentioned in reports because of their prognostic significance, greater numbers of such cells correlating with increased mortality.

There are a variety of extravascular matrix patterns, best shown using the periodic-acid schiff (PAS) reagent, without counter-staining. The most significant are the so-called 'closed loops' (Fig. 1d), which correlate with aggressive behaviour.[6]

Molecular biology

Uveal melanomas tend to show a variety of non-random chromosomal abnormalities. The most important of these are: chromosome 3 loss, which can be partial or total (the latter being referred to as 'monosomy 3'); chromosome 8q gains, occurring either as isodisomy 8q or trisomy; and gains in 6p, usually developing as a result of isochromosome formation. These abnormalities tend to occur as a result of chromosomal instability, with the abnormal separation of sister chromatids during cell division. Chromosome 3 loss and 8q gain are associated with a poor prognosis whereas chromosome 6p gain correlates with an improved survival probability.[7,8]

On the basis of gene expression profiling, uveal melanomas have been categorized as ''Class 1'' and ''Class 2'', the latter being associated with a high-risk of metastatic disease.[9]

Mutations of guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and GNA11 occur in a mutually-exclusive pattern in about 80% of uveal melanomas.[9] Mutations of the BRCA1-associated protein (BAP1) on chromosome 3p21.1 are also common and these are associated with metastatic disease.[9,10]

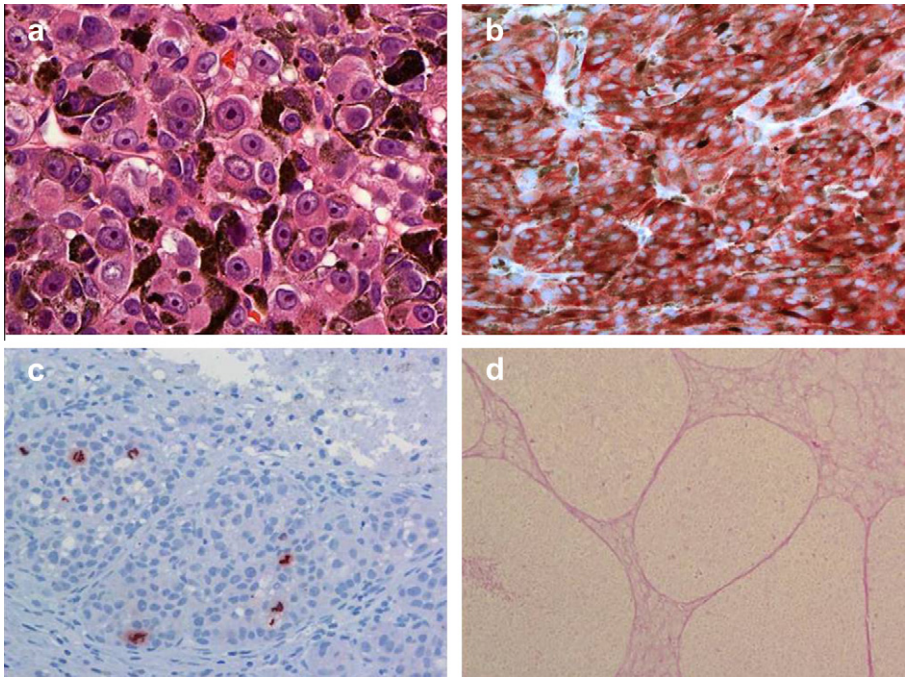

Figure 1. Histopathology of uveal melanoma (a) haematoxylin and eosin slide showing epithelioid cells*; (b) staining for HSP-27, which is associated with a good prognosis; (c) mitoses, stained with Ser-10 (PHH3)*; and (d) ''closed'' loops*. *From Damato BE et al., Progress in Retinal and Eye Research (2011).[15]