Chapter 41

Choroidal melanoma

Chiara M. Eandi[1,2] and Andrea Montesel[1]

[1]University of Lauanne, Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne, Switzerland; [2]University of Torino, Department of Surgical Sciences, Torino, Italy

Overview bullets

- 85%–90% of intraocular melanomas arise from the posterior uvea
- Most frequent primary malignant intraocular tumor in adults (six cases/million/year)
- Pigmented mass, well-circumscribed, located under the RPE
- Pigmentation varies from creamy-white to dark chocolate-brown
- Multiple shapes: dome or mushroom shaped, flat, multinodular, or small
- Size is based on the tumor thickness, including small (<3.0 mm), medium (3.1–8.0 mm), and large (8.1 mm or greater)
- Asymptomatic until it interferes with the visual structures (retina, optic nerve)
- Diagnosis: clinical fundus examination, fundus photography, and ultrasonography
- Treatment: conservative radiation therapy (brachytherapy or proton beam)
- Survival depends on the development of liver metastasis
- Around 20%–30% of UM patients die within 5 years and 45% die within 15 years
- Up to 50% of patients will suffer from metastases (mostly to liver)
- Cytogenetic mutations (monosomy 3) are risk factors for distant metastases

Pathogenesis

Choroidal melanoma (CM) is a rare malignancy that arises from the malignant transformation of melanocytes within the choroid. It represents 85%–90% of all uveal melanomas and is the most frequent primary intraocular malignancy in adults, occurring in approximately six individuals per million population annually.[1] The peak age for diagnosis is between 70 and 79 years, with an approximate median age of diagnosis at 63 years.[2]

It is considered to be a sporadic event, with a slight male preponderance, and is more common in the white population.[3] However, certain risk factors have been identified, including light-pigmented eyes, fair skin, inability to tan, ocular melanocytosis, dysplastic nevus syndrome, as well as BAP1 and MBD4 gene mutations.[4–6]

Clinical features and symptoms

Choroidal melanoma typically appears as a gray-brown choroidal lesion, with a range from creamy-white to dark chocolate-brown, even within one tumor, but it can present as partially pigmented (30% of the cases) and amelanotic (15% of the cases).[7] The funduscopic evaluation typically reveals a pigmented mass, well-circumscribed, located under the retinal pigment epithelium. The two most frequent types appearing on B-scan ultrasonography are dome-shaped (Fig. 41.1) if the axial tumor growth is contained by the Bruch's membrane and the sclera and are mushroom-shaped (Fig. 41.2) if the melanoma creates a Bruch's membrane rupture allowing the tumor cells to develop unrestrained under the neuro-retina.

Other possible growth patterns are diffuse melanoma, which has a mainly horizontal growth and is an infiltrative flat or slightly raised melanoma, and the multinodular melanoma (Fig. 41.3), which results from intratumoral metadifferentiation, leading to different cell clones with varying growth rates.[8] Choroidal melanoma is clinically grouped into three sizes based on the tumor thickness, including small (<3.0 mm), medium (3.1–8.0 mm), and large (8.1 mm or greater).[9] In a review of

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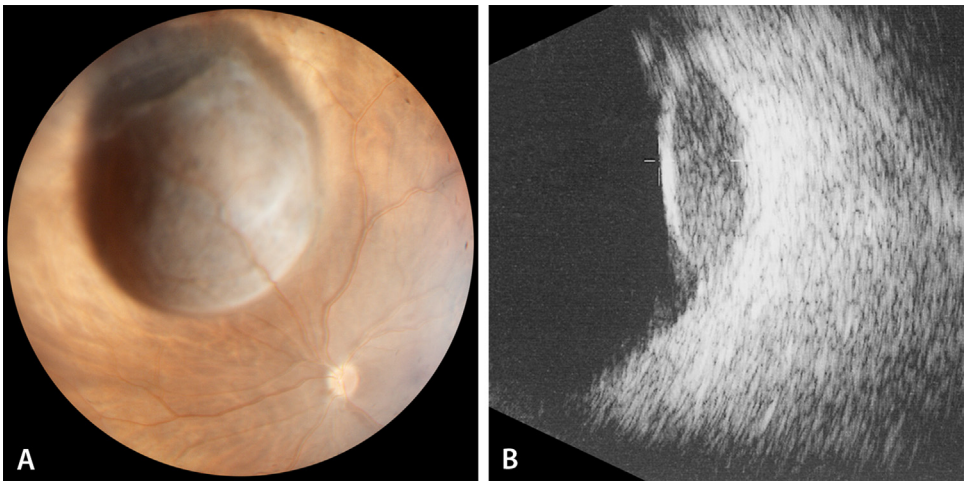

FIGURE 41.1 Dome-shaped choroidal melanoma. (A) Color fundus photography (Panoret-1000, CMT Medical Technologies Inc, Valley Stream, NY) of a pigmented mass within the nasal superior choroid in a 73-year-old female. A rupture of the RPE at the peripheral surface of the lesion can be noticed. VA = 1.0. (B) On 10-MHz B-scan ultrasonography, the tumor is dome-shaped and associated with subretinal fluid, explaining the flashes of light for which the patient initially consulted. $H = 4.9$ mm. H = height. *Courtesy of Dr A. Schalenbourg.*

7256 cases of choroidal melanoma, the mean basal diameter at presentation was 11.3 mm and the mean tumor thickness was 5.5 mm.[10]

Clinical manifestations of choroidal melanoma depend on the location and size of the tumor. Symptoms are nonspecific, often multiple, and tend to appear sequentially. It typically presents with painless loss of vision or metamorphopsia in most patients. However, larger tumors may also cause peripheral visual field loss and serous retinal detachment, leading to the perception of flashing or flickering lights (photopsia). Other manifestations include secondary glaucoma, cystoid macular edema, and moderate inflammatory reaction producing a Tyndall effect in the vitreous or anterior chamber.[11] Extraocular extension through the vortex veins and the posterior ciliary arteries, or optic nerve infiltration via the nerve portion close to the posterior eye wall are described as rare manifestations.[12,13] In a minority of cases with more peripheral tumors located outside the visual axis, CM may be entirely asymptomatic and the tumor is only detected during routine ophthalmic screening.[14]

Diagnosis

The diagnosis of choroidal melanoma is based on clinical examination of the patient with dilated fundus biomicroscopy and B-scan ultrasonography (10, 20, 35, and/or 50 MHz), usually without the need for invasive procedures or tissue sampling.

Multimodal imaging is helpful to confirm the diagnosis and enable clinicians to plan appropriate treatment decisions in specific conditions that present with similar clinical characteristics, such as small choroidal malignant melanoma and benign choroidal nevus.[15]

Different systems have been proposed to help clinicians in detecting CM. Shields et al. developed a well-known mnemonic "To Find Small Ocular Melanoma" acronym, encapsulating the following risk factors: thickness >2 mm, presence of subretinal fluid, symptoms of vision loss, orange pigment and tumor margin within 3 mm of the disc.[16] As recent years have seen advances in multimodal imaging techniques, this mnemonic has been revised to "To Find Small Ocular Melanoma Doing IMaging," with the "M" representing "Melanoma hollow" on ultrasound and "DIM" representing DIaMeter >5 mm' on fundus photography.[17] Using the TFSOM-DIM score system, the mean 5 year estimate of nevus growth into melanoma was reported as 1.1% for those with zero risk factors, 11% with one factor, 22% with two factors, 34% with three factors, 51% with four factors, and 55% with five risk factors.[18]

Damato et al. developed the MOLES acronym and scoring system, to help nonocular oncology experts to estimate the likelihood of malignancy in melanocytic choroidal tumors and to manage patients accordingly.[19] The acronym stands for Mushroom shape, Orange pigment, Large size, Enlargement, and Subretinal fluid, all of which are well-known to be indicators of malignancy. Each of these features is given a score of 0, 1, or 2 according to whether it is absent, borderline, or present. Roelofs et al. validated the MOLES system by reviewing the imaging of 451 treated choroidal melanomas and retrospectively gave these MOLES scores, found a sensitivity of 99.8% for indicating malignancy in melanocytic choroidal tumors (MOLES ≥3).[20]

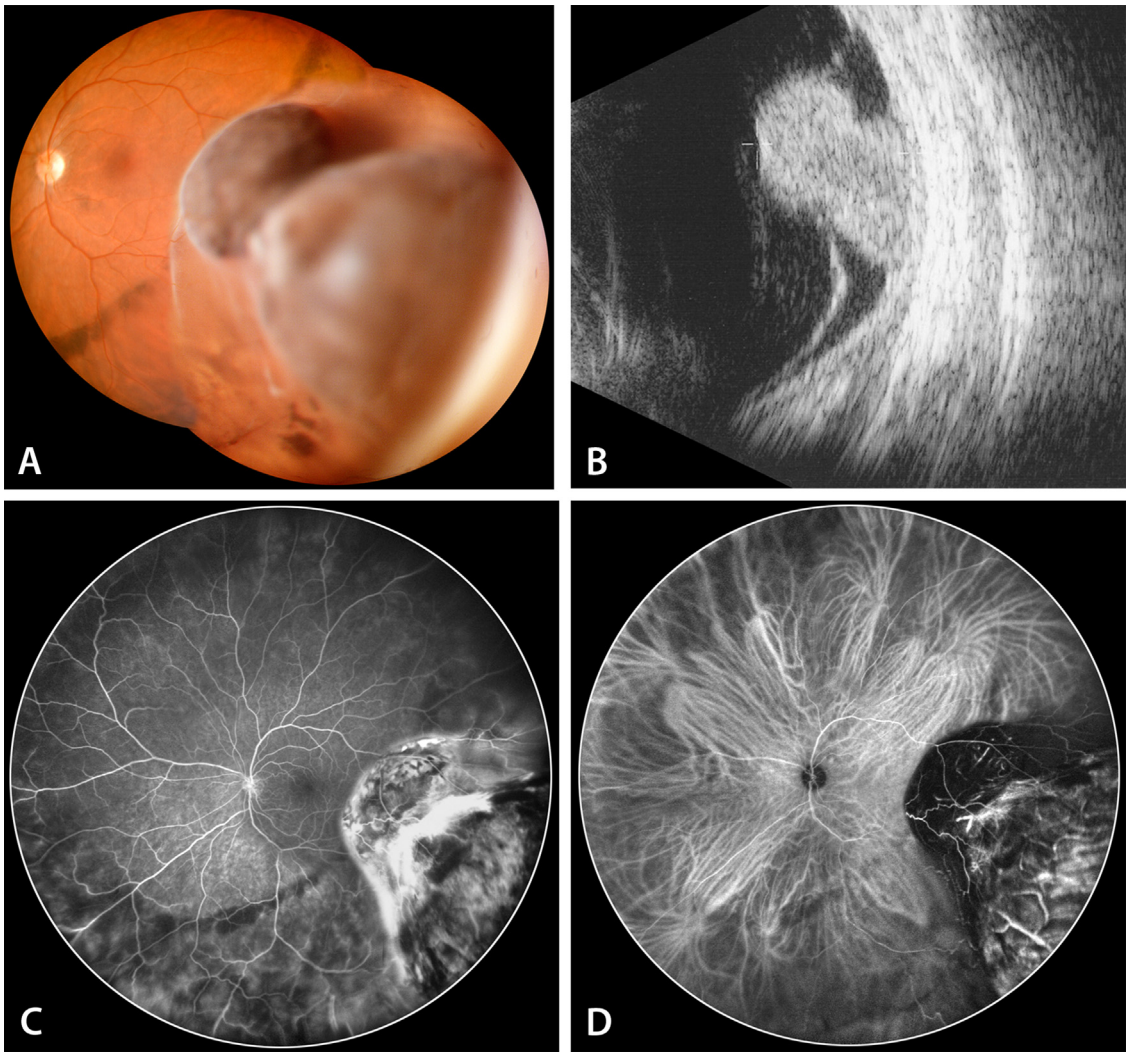

FIGURE 41.2 Large mushroom-shaped choroidal melanoma. (A) Composed color fundus photography (Panoret-1000, CMT Medical Technologies Inc., Valley Stream, NY) of a pigmented mass rising from the peripheral temporal inferior choroid in a 54-year-old male, complaining of a progressive nasal superior scotoma. VA = 1.0. An associated semicircular watershed line of subretinal pigment dispersion can be observed. (B) On 10 MHz B-scan ultrasonography, the tumor is mushroom shaped and complicated by an extensive retinal detachment. $H = 8.7$ mm. (C) On panoramic FA (Heidelberg Engineering spectralis widefield imaging using a staurenghi 150-degree contact lens), the mass presents an increasing hyperfluorescent diffusion from its surface. Signs of ischemia can be seen within the secondary inferior retinal detachment, even before radiation therapy. In consequence, intravitreal anti-VEGFs are also initiated, to avoid neovascular complications.[24] (D) On panoramic ICG-A (Heidelberg Engineering spectralis widefield imaging using a staurenghi 150-degree contact lens), the hypocyanescent mass presents a dilatation of its intratumoral vessels, and the associated inferior retinal detachment provokes a masking defect of the underlying choroidal vascularization, caused by an increased density of the subretinal fluid. *FA*, fluorescein angiography; *H*, height; *ICG-A*, indocyanine green angiography; *VA*, visual acuity; *VEGF*, vascular endothelial growth factor. *Courtesy of Dr A Schalenbourg.*

Differential diagnosis

According to the Collaborative Ocular Melanoma Study (COMS), the clinical misdiagnosis rate is 0.48%, supporting the fact that most intraocular tumors may be diagnosed clinically.[21] Shields and colleagues[22] reported that among 400 referrals for evaluation for posterior uveal melanoma, 8% were diagnosed with hemangiomas, 9.5% were diagnosed with retinal pigment-epithelium hypertrophy, 23.5% were diagnosed with disciform degeneration, and 26.5% were diagnosed with choroidal nevi.

Other differential diagnosis includes optic disk melanocytoma, a heavily pigmented dark tumor, typically located at the optic disk; congenital hypertrophy of the RPE (CHRPE), a benign pigmented fundus lesion with a similar diameter but flat, darker, and with a sharply delineated, often double contour; peripheral exudative hemorrhagic chorioretinopathy (PEHCR),

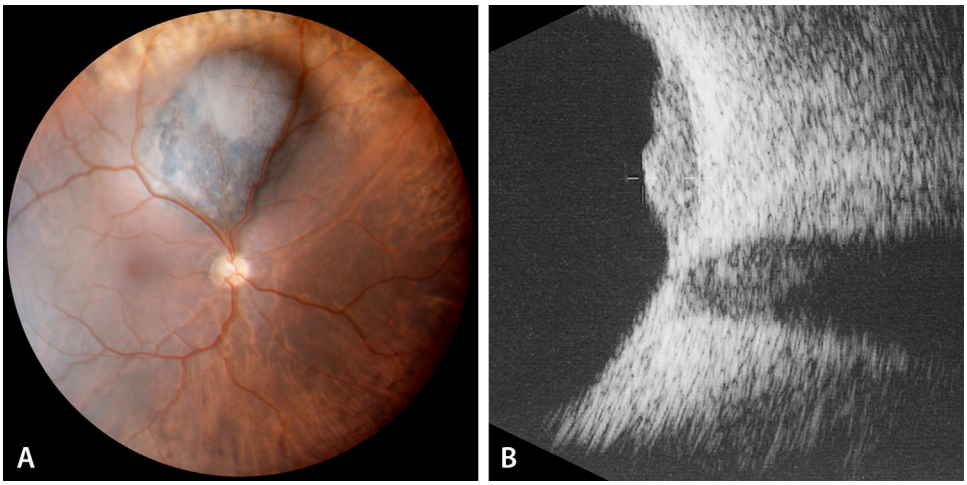

FIGURE 41.3 Multinodular choroidal melanoma. (A) Color fundus photography (Panoret-1000, CMT Medical Technologies Inc., Valley Stream, NY) of a binodular partially pigmented mass within the suprapapillary choroid in a 58-year-old female. Orange pigment is present on the surface of the inferior, more pigmented part. The superior lobe has a creamier color. VA = 0.7. Patient had been investigated over the past year and treated with oral steroids by neurologists because of "unexplained" photopsia. (B) On 10 MHz B-scan ultrasonography, the binodular shape can be observed, with a maximal *H* of 3.2 mm, as well as the infralesional subretinal fluid. *H* (height). *Courtesy of Dr A Schalenbourg.*

a peripheral retinal degeneration of the elderly manifesting with exudative and hemorrhagic changes, and subretinal or suprachoroidal hemorrhages.[9] Furthermore, amelanotic melanoma needs to be differentiated from solitary metastasis. However, probably the most challenging differential diagnosis is the small posterior melanomas (Fig. 41.4), which need to be differentiated from choroidal nevi. Small posterior melanomas usually present associated symptoms and risk factors such as subretinal fluid, contact of the tumor with the optic disc, absence of drusen, presence of hyperautofluorescent orange pigment, presence of pinpoints on fluorescein angiography and a thickness of more than 2 mm.[16,23,24] Documented tumor growth following periodic observation confirms the diagnosis.

Current research is focused on developing artificial intelligence (AI) models to identify risk factors for the malignant transformation of choroidal nevus based on ocular multimodal imaging features.[25,26] The concept of AI-based screening of ophthalmic imaging for both the presence of choroidal nevus and the factors that suggest potential transformation into melanoma has the potential to greatly enhance the detection and early treatment of melanoma within the eye.[27]

Imaging findings

Color fundus photography

Color fundus photography (FP) represents the gold standard imaging modality in the management of choroidal tumors. FP is very useful at baseline to define clinical characteristics of the tumor and during follow-up for monitoring local tumor control after treatment. In the last years, several new fundus cameras have been developed with different advantageous technical characteristics such as digital imaging. Moreover, the introduction of wide-field cameras allows to document not only posterior tumors but also peripheral lesions and their relationships with adjacent ocular structures.[28] However, it is fundamental to be aware of the limitations of these different cameras which might mislead the diagnosis and management of retinal diseases and ocular tumors in particular. The ultra-widefield (200 degrees) Optos camera (Optos PLC, Dunfermline, UK), a confocal scanning laser imaging technology, has the advantage of being a noncontact and nonmydriatic camera, but it is restricted in its ultra-wide angle, mainly to the horizontal axis, by the eyelashes sometimes obscuring fundus details. Moreover, color images are recomposed with only two reflected monochromatic laser images (red: 633 nm and green: 532 nm), resulting in color distortion due to the green shade over the image[29] (Fig. 41.4B). The last released Clarus 500 (Carl Zeiss Meditech Inc., Dublin, CA) has a potential 133 degrees the widest field of view with less color distortion, adding a grayish shade over the image. However, images present peripheral artifacts and aberrations due to the reconstruction process. The spectralis multicolor modality (Heidelberg Engineering Inc., Heidelberg, Germany) is also based on confocal scanning laser technology with a viewing angle limited to 30 degrees. The color images are the result of three simultaneously acquired color laser images reflected in the blue, green, and infrared spectrum, resulting in a false color. These "reconstitute" fundus color images, that do not reflect reality can seriously lead to misdiagnosis and eventually

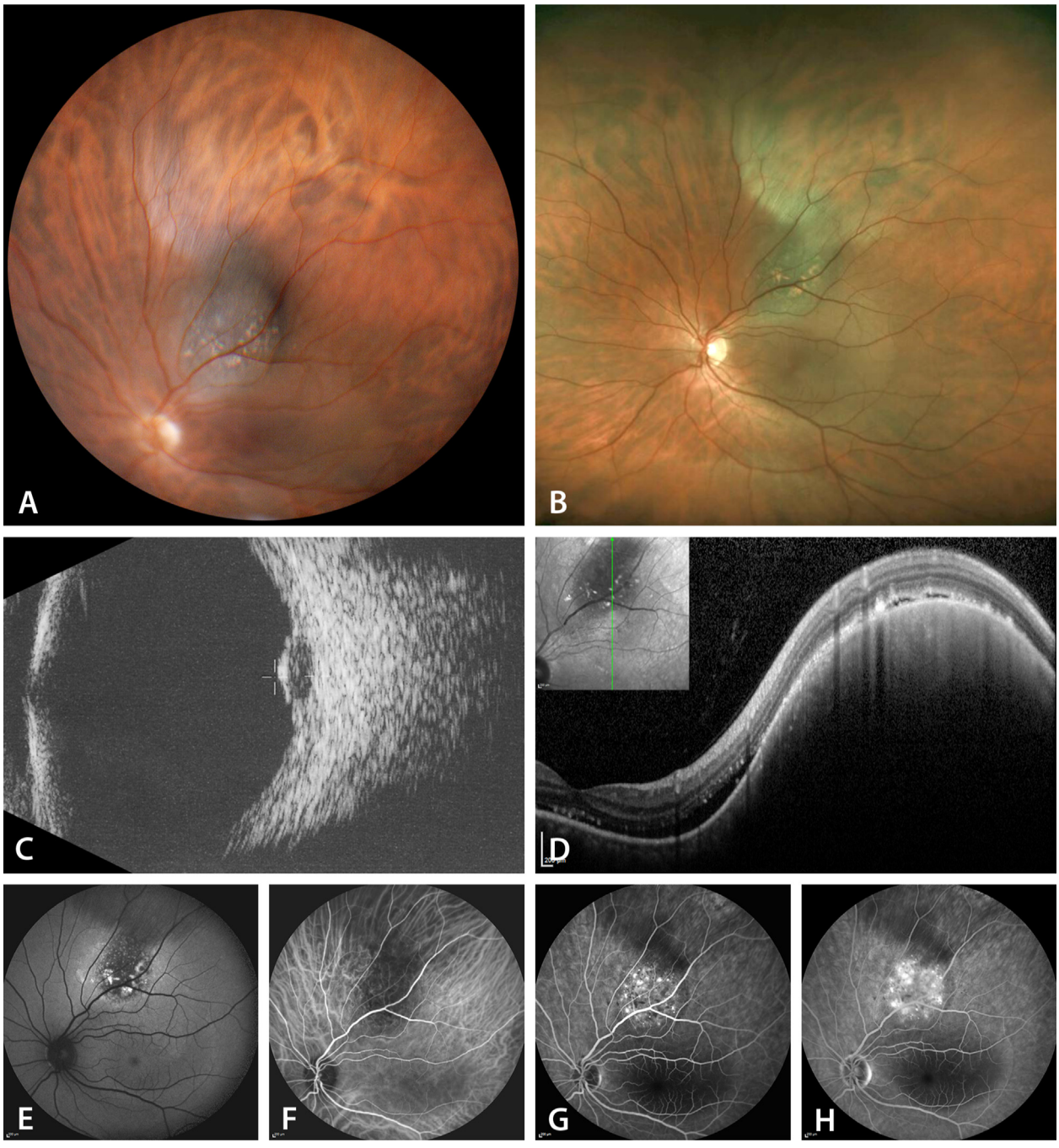

FIGURE 41.4 Small choroidal melanoma. (A) Color fundus photography (Panoret-1000, CMT Medical Technologies Inc., Valley Stream, NY) of a small pigmented mass within the supramacular choroid in a 62-year-old male. VA = 0.6. Patient had observed a relative grayish inferior scotoma over the past weeks. (B) Color fundus photography (Optos, PLC, Dunfermline, UK) of the same lesion, at the same day, but with a different camera. A green shade interferes with the actual tumor colors, and its margins are less in contrast with the surrounding choroid. There is also a lesser impression of a three-dimensional lesion (C) on 10 MHz B-scan ultrasonography, the tumor is dome-shaped. $H = 3.0$ mm (D) on B-scan OCT (Heidelberg Engineering spectralis), "shaggy" photoreceptors at the tumor's surface can be observed. Subretinal fluid surrounds the mass. (E) Orange pigment at the surface appears auto-fluorescent (Heidelberg Engineering spectralis). (F) On ICG-A (Heidelberg Engineering spectralis), the tumor provokes a masking defect. (G) On early FA, the orange pigment appears hypofluorescent. (H) On late FA (Heidelberg Engineering spectralis), the pinpoints, already visible at the early stage, present a progressive diffusion at the surface, causing a macular detachment. *FA*, fluorescein angiography; *H*, height; *ICG-A*, indocyanine green angiography; *OCT*, optical coherence tomography; *VA*, visual acuity; *VEGF*, vascular endothelial growth factor. *Courtesy of Dr A Schalenbourg.*

to the wrong treatment. In fact, color is one of the most important diagnostic features of choroidal tumors. Melanomas tend to be brown, gray black, or white. Hemangiomas are usually orange-red. Most metastases are white, with the exception of renal and carcinoid secondaries, which can be orange.[30]

The Panoret-1000 (CMT Medical Technologies Inc, Valley Stream, NY) is a contact lens-based imaging technology using transscleral illumination, as opposed to the transpupillary illumination of the other cameras, with a 100-degree field of view. The comprehensive color images are digitally recomposed from the three primary colors (red, green, and blue) reflected by the fundus. Fundus imaging is possible despite media opacities and a pupil diameter as small as 2.5 mm. Transscleral illumination allows a more accurate definition of the tumor extent because it provides better contrast between tumor margins and surrounding tissues (Fig. 41.4A).[29]

Optical coherence tomography

Optical coherence tomography (OCT) has a limited application in visualizing choroidal melanoma, but it can be helpful in detecting concomitant lesions in the retina such as subretinal fluid and/or exudative retinal detachment (Fig. 41.4D). A more modern technique, enhanced depth imaging (EDI) OCT, can visualize melanoma as choroidal shadowing, the degree of which depends on the pigmentation of the malignancy, due to deeper penetration of the light beam.[31] EDI-OCT can provide high-resolution images of the choroid and allow for accurate measurement of tumor thickness, which can be more accurate than ultrasonography in small-sized lesions.[32,33] This is secondary to difficulty on ultrasound in detecting the precise sclerochoroidal junction, poorer resolution of the overlying retina leading to an inadvertent inclusion with thickness measurement, and gross estimation with ultrasonographic calipers.[34] EDI-OCT features of choroidal melanomas include homogeneous optical reflectivity along the anterior surface, with shadowing throughout deeper layers of the tumors, loss of overlying photoreceptors, and compression and thinning of the choriocapillaris. A "shaggy" appearance of the photoreceptors overlying small choroidal melanoma has also been described, and it could represent edematous photoreceptors or macrophages with lipofuscin on the posterior surface of the detached retina.[33]

OCT angiography

OCT angiography (OCTA) has limitations in detecting the whole tumor vascular content details, probably due to the high pigment content of these lesions visible with the laser wavelength used and the common presence of image artifacts.[35] Nonetheless, recent advancements in OCTA technology, such as swept-source (SS) OCTA, have expanded its range of applications. SS-OCTA uses an increased laser wavelength and scan speeds allowing for increased penetration through the RPE and larger scan areas.[36] SS-OCTA has been proposed for the differential diagnosis of choroidal melanomas and choroidal nevi. Significant differences between these conditions were found for the pattern of reflectivity and presence/absence of avascular zones and vascular anomalies between choroidal melanomas, elevated choroidal nevi, and flat choroidal nevi.[37]

Recently, Pellegrini et al. assessed the role of OCTA in the investigation of the vascular network in different choroidal melanomas.[38] In their series of 22 eyes, using an SS-OCTA, they could image and obtain flow information in small to large melanomas regardless of their location, postulating that SS-OCTA could represent a useful tool for noninvasive assessment of CM intrinsic characteristics at baseline and allowing for an enhanced visualization of the changes occurring in response to treatment. Moreover, OCTA-derived quantitative metrics may offer promising tools in identifying structural and microvascular factors contributing to the visual outcome[39] and to the monitoring of intravitreal anti-VEGF treatment of eyes with radiation maculopathy after proton beam therapy.

Fundus fluorescein angiography and indocyanine green angiography

Fundus fluorescein angiography (FA) and indocyanine green angiography (ICGA) show no pathognomonic pattern and neither FA nor ICGA are considered essential in concluding the diagnostic process, but they may help distinguish choroidal melanoma from underlying pathologies. The most common findings on FA are an intrinsic tumor circulation ("dual" or "double" circulation) because of the superimposition of the intravascular fluorescence of the intact retinal vasculature over the fluorescence of large caliber vessels within choroidal tumor, mottled fluorescence during the arteriovenous phase, late progressive leakage, lesion staining, and multiple pinpoint leaks (hot spots) at the level of the retinal pigment epithelium (Fig. 41.4G,H).[40,41] Evidence of retinal vascular abnormalities such as microaneurysms, tortuous intraretinal capillaries, and zones of nonperfusion has also been reported on FFA.[24,42] CMs are usually hypofluorescent on ICGA (Fig. 41.4F), but some variations might depend on tumor thickness and pigmentation.[43,44] ICGA is mainly used to

study intratumoral microcirculation and changes in the surrounding choroidal vasculature, and it might potentially differentiate nonpigmented choroidal melanoma from choroidal hemangioma.[27]

FAF

Choroidal melanoma is associated with several degenerative changes in the overlying tissues, which has been named as "Tumor-Associated Retinal Pigment Epitheliopathy."[45] This secondary epitheliopathy is characterized by the shedding of photoreceptor outer segments and a localized detachment of the RPE, which together with an intense phagocytic activity is responsible for changes in fundus coloration and lipofuscin accumulation. Blue-light fundus autofluorescence (FAF) detects fluorophores and mostly lipofuscin, accumulating at the level of RPE cells and photoreceptor outer segments that appear as orange pigment at fundus examination.[46] Therefore, FAF could play a role in detecting early and small clumps of orange pigment, which is a well-known risk factor for small melanomas, and in differentiating between CM and naevus.[47] In choroidal nevi, FAF shows a normal pattern of background fundus fluorescence with no corresponding areas of hyper or hypofluorescence over the nevi, while CM usually appears as a confluent plaque-like hyperautofluorescent area with central hypoautofluorescence (Fig. 41.4E).[48] There is consensus that choroidal nevi rarely show brightly increased FAF due to orange pigment, whereas remarkably increased FAF (ranging from mildly to intensely) overlying choroidal melanomas derives from lipofuscin accumulation in RPE cells and in macrophages of malignant choroidal tumors usually seen as orange pigment over the lesion[49] with an excellent correlation between increased FAF and orange pigment.[50] However, increased FAF on the tumor surface does not necessarily indicate orange pigment but it may also result from pigmentation, fibrous metaplasia, or sub-RPE drusen.[51]

Ultrasonography

Ultrasonography (US) is the most valued diagnostic test. The combination of A-mode (8 MHz) and B-mode (10 MHz) ultrasonography is essential for measuring tumor dimensions, evaluating the extent, shape, and internal structure of the tumor, planning treatment, and monitoring the response to treatment.[7] CM typically demonstrates low to medium reflectivity due to their cellular homogeneous architecture. On A-scan ultrasonography, choroidal melanoma shows a high initial spike with medium to low internal echoes with smooth attenuation (angle kappa sign).[52,53] Vascular pulsations within the tumor can also be seen with this modality. On B-scan, classic features of choroidal melanoma are an acoustically silent zone within the melanoma, choroidal excavation (a depression free of echos lying beneath the tumor and behind the retinal surface overlying the tumor), and shadowing of orbital fat behind the lesion.[53,54] Lesions can appear as dome-shaped (Fig. 41.1B), mushroom-shaped (i.e., collar button) (Fig. 41.2B), or irregular in shape depending on the degree of Bruch's membrane rupture and axial tumor growth. The estimation of melanoma thickness by combined A-mode and B-mode ultrasonography provides reproducible and concordant values of tumor thickness, which is the most reliable and important measurement. Measurement of tumor diameter and tumor height can vary among trained operators, especially for small lesions. Nevertheless, various reports have suggested that up to 96% of choroidal melanomas can be correctly diagnosed with a combination of A and B-scan ultrasonography.[55] With US is also clearly visible the retinal detachment (Fig. 41.2B), a concomitant condition with uveal melanoma, seen as an accumulation of subretinal fluid that splits the layers (choroid and retina). Moreover, B-mode ultrasonography can also detect and highlight the presence of extrascleral extension of melanomas, and it is considered superior to MRI in the detection of extrascleral extension.[56] The protruding portion of the tumor has lower reflectivity than the orbital fat, making it identifiable.[57] Thus, the US is suitable for assessing tumor extrascleral extension and visualizing lesions even as small as 2 mm.[8] Color Doppler (CDI) is a noninvasive method that shows the blood flow in vessels with the flow direction.[55] CDI examination of CM will show evidence of perfusion in most instances, while choroidal nevi are minimally vascular.[58]

Clinical trials

The COMS is the largest study ever performed in ocular oncology, with 43 participating centers, more than 2000 recruited patients, and 28 publications.[59] CMOS aimed to determine the best management for uveal melanomas, depending on the size and comparing the treatment of radiation and enucleation.[60]

It was designed as a three-arm trial including two multicenter randomized clinical trials comparing the effectiveness of iodine 125 (I-125) brachytherapy to enucleation for the treatment of medium-size choroidal melanomas, and the effectiveness of enucleation with and without preoperative external-beam radiotherapy for large choroidal melanomas. The third arm was an observational study of the natural history of small choroidal melanomas.

The primary outcome measure was time to death from all-cause mortality. Secondary outcome measures included metastasis-free survival, cancer-free survival, and years of useful vision. The trial of enucleation alone versus preenucleation radiotherapy included 1003 patients with large choroidal melanoma (>10 mm in apical height and >16 mm in basal diameter) randomized to either enucleation or enucleation preceded by external-beam radiation. No difference was found between the two treatment arms (the 5 year all-cause mortality was 43% and 38%; 5 year tumor-related mortality was 28% and 26%; and 10 year tumor-related mortality was 40% and 45% in enucleation and enucleation with preoperative radiation, respectively), thus reporting no survival advantage attributable to preenucleation radiation and reassuring that primary enucleation does not accelerate death from metastatic melanoma.[61,62]

In 1317 patients with medium-sized choroidal melanoma (2.5−10 mm in apical height and ≤16 mm in basal diameter), 660 were randomized to enucleation and 657 to iodine-125 brachytherapy, reporting that mortality with histopathologically confirmed melanoma metastasis after brachytherapy with iodine-125 was no worse than following enucleation.[63] By 12 years, cumulative all-cause mortality was 43% in the brachytherapy arm and 41% in the enucleation arm. The 5-, 10-, and 12-year mortality with histopathologically confirmed melanoma metastasis was 10%, 18%, and 21%, respectively, in the brachytherapy arm, and 11%, 17%, and 17%, respectively, in the enucleation arm.[62,63] These results confirmed no survival differences between patients whose tumors were treated with I-125 brachytherapy and those treated with enucleation.

Overall, 204 patients were enrolled in the COMS natural history study of small melanomas (1.5−2.4 mm in apical height and 5−16 mm in basal diameter); 2- and 5-year Kaplan−Meier estimates of tumor growth was 21% and 31%, respectively. The 5 year all-cause mortality was 6% and tumor-related mortality was 1% in patients with small choroidal melanomas under observation.[64]

COMS results have had a positive impact on the standardization and accuracy of diagnosis and the clinical care of uveal melanoma. However, the original categorization of COMS patients was based solely on tumor size, although today uveal melanoma prognosis is known to be multifactorial and there is increased evidence that genetic profile governs prognosis and not just the modality of treatment. Given the currently available evidence, it would be indicated to continue to locally treat choroidal melanoma optimally to conserve the eye and vision when possible. Patients should be categorized based on their established clinical profile, histopathological characteristics, and gene expression profiles (GEP), and those at high risk for systemic metastasis should be considered for adjuvant therapy once its benefits have been well-established.[65]

Managements strategies

After a diagnosis of choroidal melanoma, treatment is focused on cancer control, followed by eye and vision preservation.[66] Before initiating ocular therapy for choroidal melanoma, it is essential to perform a systemic workup to ensure that there is no evidence of metastasis. Choroidal melanoma has a well-documented capacity to spread hematogenously, with the liver being the first and only site of metastasis in most patients (90%), followed by lungs (24%), bone (16%), skin, and central nervous system.[67,68] Once it is confirmed that the disease is confined to the eye, local ophthalmic therapy can be directed toward the primary tumor. It is uncommon for extraocular metastasis to occur at the time of initial ocular presentation, affecting less than 5% of patients.[69] However, if hematogenous spread is detected, then local therapy for the eye may be deferred in favor of systemic treatment, depending on the patient's symptomatology and overall clinical status. It is crucial to note that the management of uveal melanoma is highly individualized, and treatment decisions should be made based on a single patient's unique circumstances and overall health. Therefore, a comprehensive evaluation and discussion of treatment options with a multidisciplinary team are recommended to ensure the best possible outcome for the patient.[69]

Treatment of localized UM can currently be classified into eye salvage treatment or enucleation. As discussed in the previous paragraph, according to the COMS, there is no difference in survival whether choroidal melanoma is treated with enucleation or radiation therapy.[59] As a consequence, enucleation is only indicated when conservative treatment is either unsafe or unreasonable. The patient's preference to undergo or not undergo enucleation should also be taken into consideration.[8]

Radiation therapy

Local radiotherapy for choroidal melanoma is performed using two different sources, either a radioactive plaque or an external beam. The first technique, called brachytherapy, involves affixing a dish-shaped source on the sclera over the base of the intraocular tumor defined by transillumination.[70] Currently, the most frequently used plaques are ruthenium-106 (^{106}Ru/^{106}Rh) and iodine-125 (^{125}I), emitting beta and gamma irradiation, respectively.[8] Brachytherapy may be used for tumors less than 18 mm in basal diameter and up to 12 mm thickness in which there is a reasonable chance of salvaging

vision. Plaques are removed during a second intervention, once the required dose is delivered at the apex of the intraocular tumor (85−100 Gy for uveal melanoma). Brachytherapy indication is limited when the height and/or diameter of the tumor exceeds the capacity of the plaque or when the tumor location is unsuitable, for example, around the optic disk or on the iris.

External beam radiotherapy uses charged heavy particles such as protons, as a source of external beam irradiation. Protons produce low irradiation when penetrating a mass until they stop, at which point they deliver the maximum of their energy, called the "Bragg peak". By modulating the proton beam, the Bragg peaks can be accumulated, allowing delivery of a uniform radiation dose (60 Gy in four daily fractions for uveal melanoma) to a given target volume. Preceding the irradiation, tantalum clips are surgically sowed upon the sclera as points of reference with regard to the tumor base.[8,71] This treatment method enables the delivery of a concentrated dose of radiation to the tumor while minimizing exposure to the surrounding tissues. It is typically used for larger or posteriorly located tumors. Literature data suggest that brachytherapy and external beam radiotherapy are comparable for tumor control, visual outcome, and systemic prognosis, even if no modern randomized clinical trial exists comparing these modalities.[66,71,72] A study of all stages of UM revealed that, with a medium follow-up of 5 years, proton-beam-targeted therapy has a 96.4% control rate locally and preserves the eyes in 95% of cases.[73] The limitation of this technique is that it requires a cyclotron to accelerate the protons, adapted, with a stereotactic chair, for ocular treatment.[8]

Radiation therapy is associated with severe sight-limiting side effects. The severity, location, and incidence of radiation-induced complications are related to the type of radiation used, its method of delivery, the size of the tumor treated, and the amount of radiation delivered to normal ocular structures. Radiation effects are often delayed and therefore complications have been noted to increase over time. Complications include radiation-induced cataracts, retinopathy, maculopathy, optic neuropathy, toxic tumor syndrome, and secondary glaucoma.[74,75]

Enucleation

Choroidal melanomas are currently treated by eye-preserving radiotherapies. In the past, enucleation was the primary treatment for patients with CM before radiation therapy became available. However, in the present day, enucleation is indicated in the cases of large tumor diameter or a tumor target volume requiring more than half of the eye to be irradiated (defined using the COMS criteria) because of the high risk of secondary enucleation after conservative treatment in these cases, circumferential tumor invasion, when the limits of the tumor cannot be determined with confidence, in the presence of (sub)total retinal detachment, extrascleral spread, optic nerve invasion, patients suffering from complete vision loss, and pain due to secondary glaucoma.[76] Additional relative indications for enucleation in selected cases include the loss of visual function following radiation.

Prognosis and follow-up

Patients with UM are at lifetime risk of having metastasis even with treatment of primary malignancy. The survival of uveal melanoma patients depends on whether hematogenous spread has occurred before the treatment of the primary tumor. Nearly 50% of uveal melanoma patients will suffer from metastases, with the liver being the most common initially affected organ. Around 20%−30% of UM patients die within 5 years and 45% die within 15 years,[61,71] but the overall risk varies according to the clinical, histopathologic, and cytogenetic risk factors, and increases with advanced patient age and local tumor recurrence.[77]

Adverse cytogenetic mutations include, most importantly, a loss of the entire chromosome 3 (monosomy 3) and, secondly, an amplification of the long arm of chromosome 8 (8q gain).[78] The principal tumor suppressor gene lost in the former has been identified as the gene encoding BRCA1-associated protein 1 (BAP1) on chromosome 3p21.[79]

Although there are no consensus guidelines concerning optimal surveillance tests after initial management, MRI has demonstrated the highest sensitivity in identifying small liver lesions. Based on gene-expression profiling or cytogenetics, patients with low-risk disease should be considered for routine imaging, including chest CT, and abdomen and pelvis MRI every 6−12 months. In contrast, patients with a higher metastatic recurrence risk warrant a tighter follow-up, with imaging taken every 3−6 months.[80]

The risk of local tumor recurrence due to incomplete irradiation has been reported at 1.1%−4% at 5 years after proton therapy[81] at 4.2%−15% after iodine-125[82,83] and at up to 19% after ruthenium-106 plaque therapy.[84] The risk of neovascular glaucoma, complicating ischemic serous retinal detachment and a major cause of secondary enucleation after conservative radiotherapy, has considerably decreased with the prophylactic use of intravitreal antivascular endothelial growth factor, followed by laser treatment once the retina is reattached.[24] Visual prognosis depends on the anatomical

location of the tumor, its size, and the extent of the retinal detachment at diagnosis.[71] Other tumor and radiation-induced side effects responsible for vision loss include radiation-induced optic neuropathy and ischemic retinopathy and maculopathy.

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