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Ocular Fundus Tumours: A Simplified Clinical Classification

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Introduction

The diagnosis of the most common ocular fundus tumours can be achieved according to clinical features including their malignant potential, anatomical location within the eye, and relation to systemic disease, as well as imaging features. The majority of these tumours can be classified into four major categories according to their clinical presentation.

I- Melanotic Tumours

The source of melanin in the ocular fundus is either the choroidal melanocytes or the melanin in the retinal pigment epithelium (RPE). According to the melanin content within their cells, the melanotic tumours present with varying shades of brown colour.

1) Choroidal Melanotic Tumours:

a) Choroidal nevus: It is a small, flat, or slightly raised area of circumscribed choroidal

melanocytic proliferation. It grows very slowly over the years and eventually stabilizes, with an overall prevalence of about 2%. A chronic nevus demonstrates retinal degenerative changes on its surface due to chronic nutrition deprivation of the RPE by the nevus mass, which compresses and displaces choriocapillaries (**Figure 1A**). These degenerative changes manifest as RPE atrophy, RPE metaplasia into a grey collagenous membrane, RPE migration and proliferation around nearby blood vessels, drusen formation, and later intraretinal cysts or subretinal neovascular membrane (SRNVM) formation. A nevus in the macular area may lead to eventual central vision loss from gradual attrition of the RPE and subsequent degeneration of the overlying neuroretina.[1]

b) Uveal melanoma: This is the most common primary intraocular tumour in adults, with an annual incidence of 4–6/million in the population. Choroidal melanoma constitutes 85% of uveal melanoma, ciliary body melanoma is 10%, and iris melanoma is 5%. Choroidal melanoma typically presents as an elevated dome-shaped subretinal mass, which may be associated with subretinal fluid (SRF), lipofuscin deposits (orange pigment), or hemorrhage on its surface (**Figure 1B**).

The tumour may perforate through Bruch's membrane, in which case it assumes a collar button or mushroom configuration and may rarely invade the retina, causing pigment dispersion within the vitreous. Choroidal melanoma can be non-pigmented (amelanotic) or partially melanotic; it typically reveals low internal reflectivity and choroidal excavation in ultrasonography and dual circulation in fluorescein angiography (FA).[2,3]

c) Indeterminate melanocytic lesion (IML): This term describes a small choroidal lesion with mixed features between a nevus and a small melanoma, the biological nature of which cannot be ascertained by a single clinical exam (**Figure 1C**). The management is periodic observation every 3–4 months to detect progressive growth and, if noticed, the lesion is treated as a small melanoma. The clinical features suggestive of eventual growth in a small IML include tumour thickness >2 mm, subretinal fluid, visual symptoms, orange pigment, echogenic hollowness, and diameter >5 mm. The presence of 3 of these features predicts growth in 1/3 of the lesions.[4,5]

d) Choroidal melanocytoma: This is a form of nevus, which is characterized by larger cells that accommodate more melanin-filled melanosomes in their cytoplasm. Thus, it appears densely dark with feathery edges and surrounding pigment dispersion.

e) Pseudomelanoma: These are fundus lesions that are not of melanocytic origin but may simulate choroidal melanocytic lesions. These include subretinal hematoma of various causes, hemorrhagic pigment epithelium detachment, dilated ampulla of the vortex vein, uveal effusion that may simulate ring melanoma of the ciliary body, and scleral or orbital mass indenting the choroid.

2) Retinal Melanotic Tumours:

a) Congenital hypertrophy of the retinal pigment epithelium (CHRPE): It presents as single or multiple flat, grey-to-black lesions with well-demarcated edges. It may show lacunae devoid of RPE pigment (**Figure 1D**). Multiple CHRPE-like lesions of tadpoles-like morphology may be a manifestation of Gardner's syndrome. Torpedo maculopathy describes a paramacular albinotic patch of RPE that causes disruption of the overlying outer retina.[6]

b) Optic disc melanocytoma: Similar to uveal melanocytoma, it presents as a grey to black mass involving the optic disc, arising from melanocytes at the lamina cribrosa, and may be associated with a choroidal component (**Figure 1E**). It may display minimal growth in 10–15% of cases, but malignant transformation is exceedingly rare. It is typically asymptomatic but may show an afferent pupillary defect, enlargement of the blind spot, or arcuate field defect as compressive symptoms.[7]

c) Combined hamartoma of the retina and RPE: It manifests as a posterior pole area of retinal thickening with distorted vessels and traction of the surrounding retinal vessels. It has a grey hue from the RPE component. Fluorescein angiography highlights the abnormal vasculature, and optical coherence tomography (OCT) is diagnostic.[8] It is typically sporadic but could be a manifestation of neurofibromatosis type II.

d) RPE hamartoma: It is a localized small area of dark-coloured RPE thickening without impact on the overlying retina (**Figure 1F**).

e) RPE adenoma/ adenocarcinoma: This appears as a central or peripheral darkly pigmented, abruptly elevated mass (Derby-hat configuration) surrounded by SRF and hard exudates, with a feeder artery and a draining vein. Adenocarcinoma is locally aggressive but seldom metastasizes.[8,9]

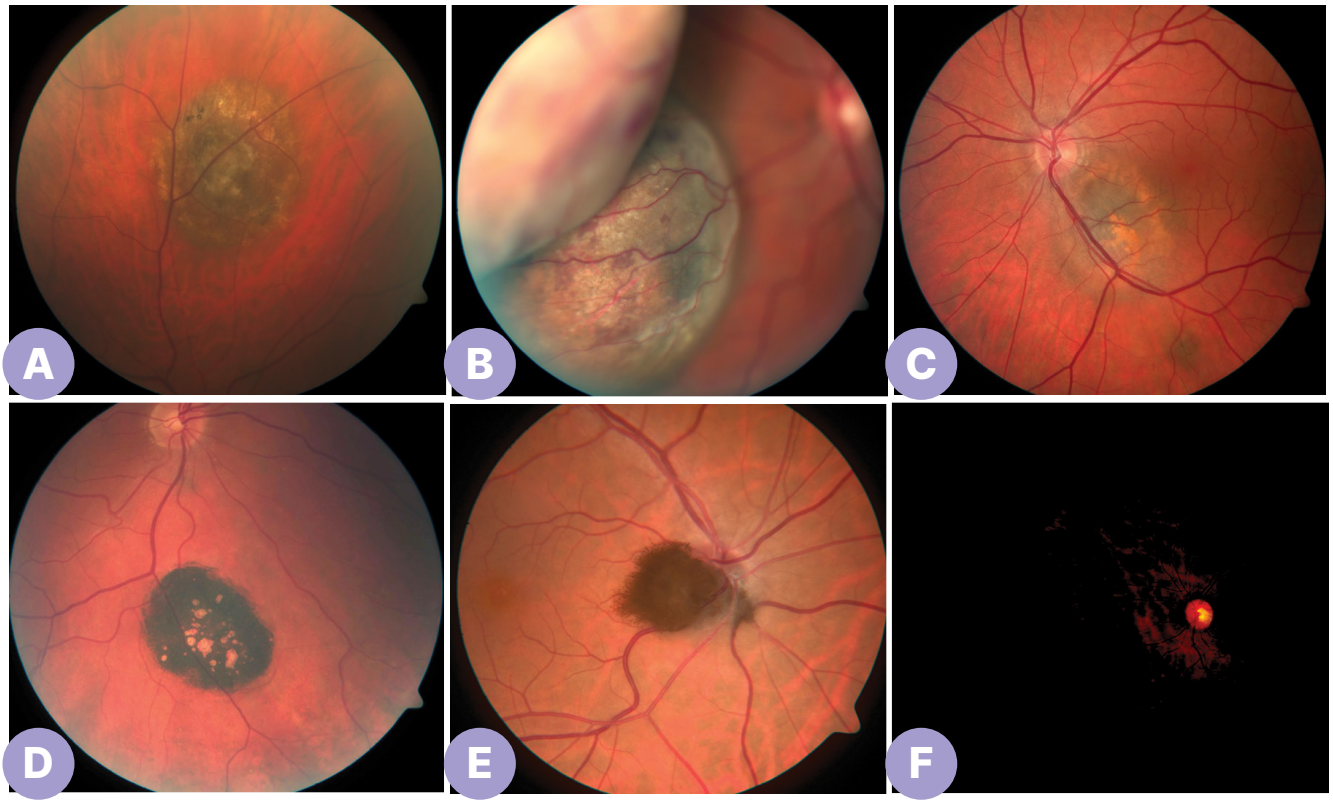

Figure 1. Melanotic fundus tumors; **A)** choroidal naevus appears flat with surface drusen; **B)** choroidal melanoma showing as choroidal pigmented mass with adjacent retinal detachment; **C)** Indeterminate melanocytic lesion (IML) appears slightly thicker with surface orange pigment; **D)** Congenital hypertrophy of the retina and RPE (CHRPE) appears as a well-demarcated flat dark lesion with amelanotic lacunae; **E)** Optic disc melanocytoma with feathery edge and pigment dispersion; **F)** RPE hamartoma appears as a dark small circumscribed lesion; *courtesy of Hatem Krema, MD, MSc, FRCS, FICO (Hon.)*.

f) Pigmented gliotic scar: This appears as a variegated retinal lesion resulting from RPE proliferation within a nonpigmented mass of gliosis.

g) Metastatic cutaneous melanoma mostly involves the retina and vitreous system, as well as diffuse perivascular pigmented clumps and dark vitreous debris.

II- Amelanotic Tumours

This is a group of non-pigmented tumours that are neither vascular nor calcified; they typically present as white to creamy yellow lesions.

1) Choroidal metastasis: Typically present in a patient with a history of systemic cancer, but 20% of patients are unaware of their systemic cancer. The most common primary site is the lung or breast. The most frequent presentation is a unilateral unifocal lesion, but metastases may be multifocal and bilateral. It differs from amelanotic choroidal melanoma in being rapidly growing, usually with significant SRF and "leopard skin" appearance from significant surface deposition of lipofuscin from the irritated RPE (**Figure 2A**). Unlike melanoma, metastasis displays a medium to high internal reflectivity in ultrasonography, a mountain-like "lumpy bumpy" profile in OCT, and an absence of dual circulation in FA. Diagnosis is usually clinically based, particularly with a history of systemic cancer, although a needle biopsy may be needed in a few cases.[10]

2) Amelanotic melanoma: This represents less than 20% of choroidal melanomas. It may show intrinsic vascularization or surface hemorrhage and may assume a configuration similar to pigmented melanoma (**Figure 2B**).

3) Intraocular lymphoma: It can be broadly classified into:

a) Vitreoretinal lymphoma of large B-cell lymphoma with +/- CNS involvement. This

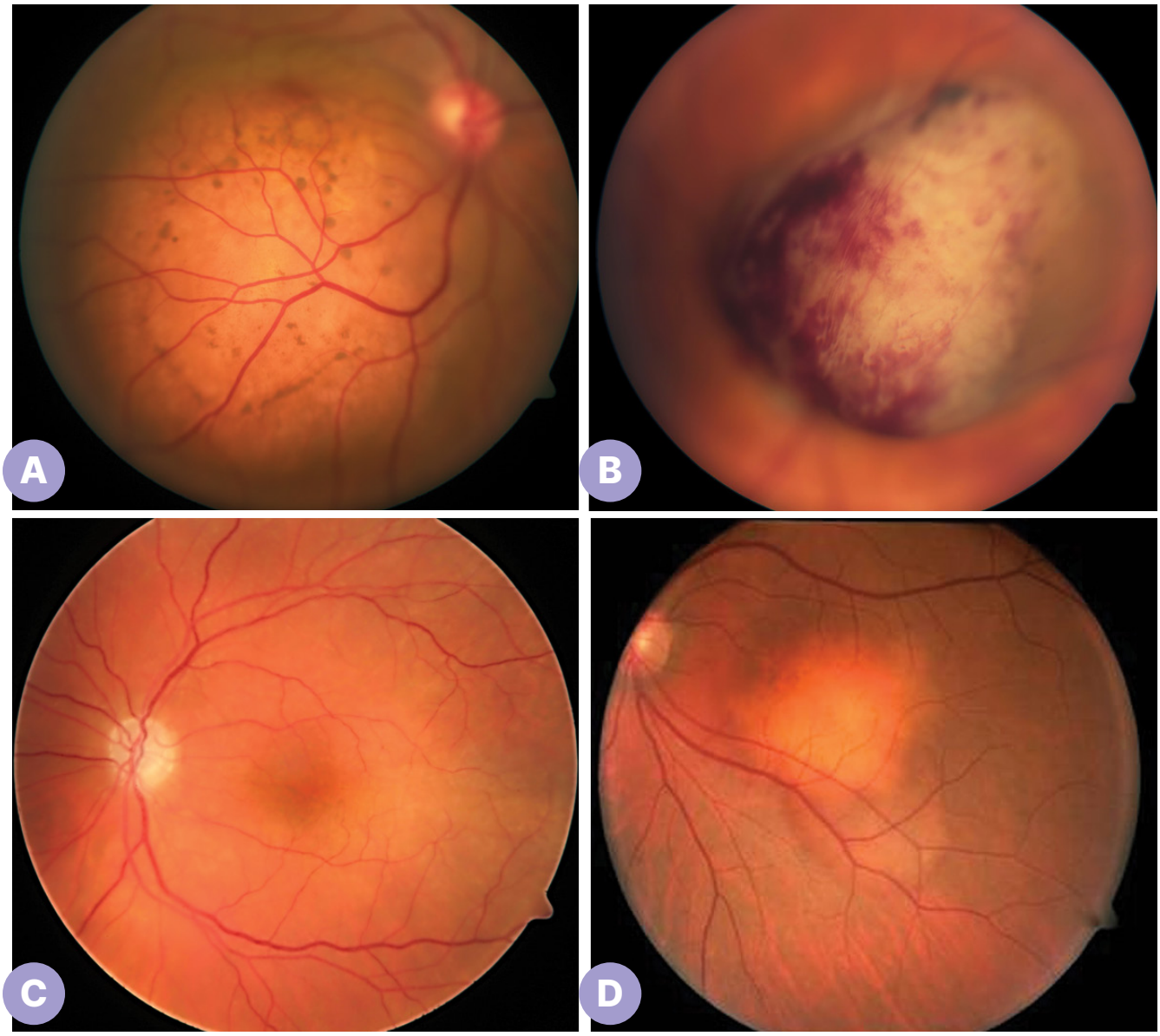

Figure 2. Amelanotic fundus tumours; **A)** Amelanotic melanoma with collar-button configuration and surface subretinal hemorrhage; **B)** Choroidal metastasis appears as an amelanotic choroidal mass with surface changes showing leopard-skin appearance; **C)** Choroidal lymphoma appears as ill-defined amelanotic choroidal infiltration; **D)** Choroidal granuloma of sarcoidosis appears as an amelanotic flat lesion with irregular margin with an adjacent pocket of subretinal fluid; *courtesy of Hatem Krema, MD, MSc, FRCS, FICO (Hon.)*.

manifests as steroid-resistant vitritis with patches of retinal infiltrates simulating retinitis. It runs an aggressive course with a high risk of recurrences and mortality.

b) Uveal and adnexal lymphoma: This manifests as single or multiple, unilateral or bilateral, choroidal infiltrates of non-Hodgkin's small B-cell lymphoma, forming diffuse thickening of the choroid or discrete masses (**Figure 2C**). These lesions may be associated with co-involvement of adnexal structures, such as a conjunctival salmon patch, or diffuse swelling in adjacent orbital structures. This lymphoma runs a less aggressive course.[11]

4) Choroidal granuloma: This manifests as single or multiple choroidal masses of irregular borders, adjacent satellite lesions, and local vitritis (**Figure 2D**). The nature of such lesions

may include sarcoidosis, tuberculosis, less likely toxoplasmosis, toxocariasis, cat-scratch disease, or other specific or non-specific inflammations. Uveitis work-up may lead to diagnosis, but a choroidal biopsy may be required in some cases.[12]

5) Retinal amelanotic tumours: These include rare tumours of the retinal supportive elements such as retinal schwannoma or medulloepithelioma of the nonpigmented epithelium of the ciliary body.

III- Vascular Tumours

These can be diagnosed in fundoscopy by their colour, which ranges from orange to bright red.

1) Circumscribed choroidal hemangioma: This presents as a solitary orange-pink circumscribed mass that may be associated with SRF (**Figure 3A**). It is sporadic but should be differentiated from vascular orange-colored solitary metastasis of renal, neuroendocrine and thyroid cancers and highly vascularized amelanotic melanoma. Hemangioma exhibits progressive fluorescence in the early phases of FA and "the ring sign" in the late phases of ICG.[13]

*2) Diffuse choroidal hemangioma: I*t is a manifestation of Sturge-Weber syndrome or Phacomatosis Pigmentovascularis.[14] It presents as an ill-defined orange-pink diffuse lesion that may involve most of the choroid, with thickened areas, termed "tomato ketchup fundus." It may be associated with significant transudative retinal detachment (**Figure 3B**).

3) Retinal hemangioblastoma: It is a manifestation of Von Hipple- Lindau disease. It presents as single or multiple, unilateral or bilateral, bright red lesions surrounded by SRF and hard exudates. Peripheral larger lesions may have a feeding artery and a draining vein, which are lacking in sizable lesions at the optic disc (**Figure 3C**). Acquired sporadic retinal capillary or cavernous hemangiomas are rare and not associated with systemic diseases.[15]

4) Vasoproliferative tumour of the ocular fundus (VPTOF): It presents as a peripheral retinal grey-pink growth, surrounded by SRF and hard exudates, but without the feeder vessels observed in hemangioblastoma (**Figure 3D**). The VPTOF may be multiple or bilateral but has no systemic association. Macular cysts and epiretinal membrane formation are frequently present due to VEGF secretion by the tumour. Secondary VPTOF may be associated with retinal disease and thought of as a reactive gliotic response.[16]

IV- Calcified Tumours

These tumours contain foci of calcification, detectable with ultrasonography as highly reflective areas within the tumour that cast an orbital shadow. In doubtful cases, a CT scan can confirm calcification.

1) Choroidal osteoma: It typically manifests in middle-aged females as a unilateral, slowly progressive juxtapapillary lesion, which is rather flat and vascularized with an irregular, rugged surface (**Figure 4A**). It may lead to significant vision loss from the attrition of the RPE in the macular area or the formation of SRNVM.[17]

2) Idiopathic sclerochoroidal calcification: It typically presents as ill-defined subretinal yellow lesions near the equator, mostly multifocal and bilateral. (**Figure 4B**). Some deeper lesions may not be observable by fundus exam and could be detected with ultrasonography of the equator. OCT shows subretinal lesions with an irregular profile, indenting the overlying normal retina. It may be associated with abnormalities in serum calcium, phosphorus, or potassium levels.[18]

3) Retinal Astrocytic Hamartoma: It is a benign growth of retinal glial cells that may present as a unilateral unifocal lesion or as multiple or bilateral lesions in association with tuberous sclerosis complex. Reactive astrocytic gliosis has been associated with NF1, retinitis pigmentosa, Stargardt's disease, and gyrate atrophy. Morphologically, the astrocytic hamartomas are classified into three types. **Type 1 (most common):** relatively flat, smooth, semitransparent lesions without calcification; **Type 2:** raised, multinodular ("mulberry-like"), opaque, totally calcified lesions; **Type 3:** lesions with mixed features of Types 1 and 2 (**Figure 4C**). Astrocytoma is a neoplastic growth. Giant astrocytoma with aggressive behaviour has been rarely reported.[19]

4) Retinoblastoma (RB): It is the most common pediatric intraocular cancer. It presents as leukocoria in half of the patients and strabismus in one-third. Sporadic Rb is unilateral and unifocal, but germline-mutation RB may be unifocal or multifocal and bilateral. Endophytic RB may simulate astrocytic hamartoma, while exophytic RB may simulate Coats' disease, which presents with abnormal peripheral retinal vessels and copious

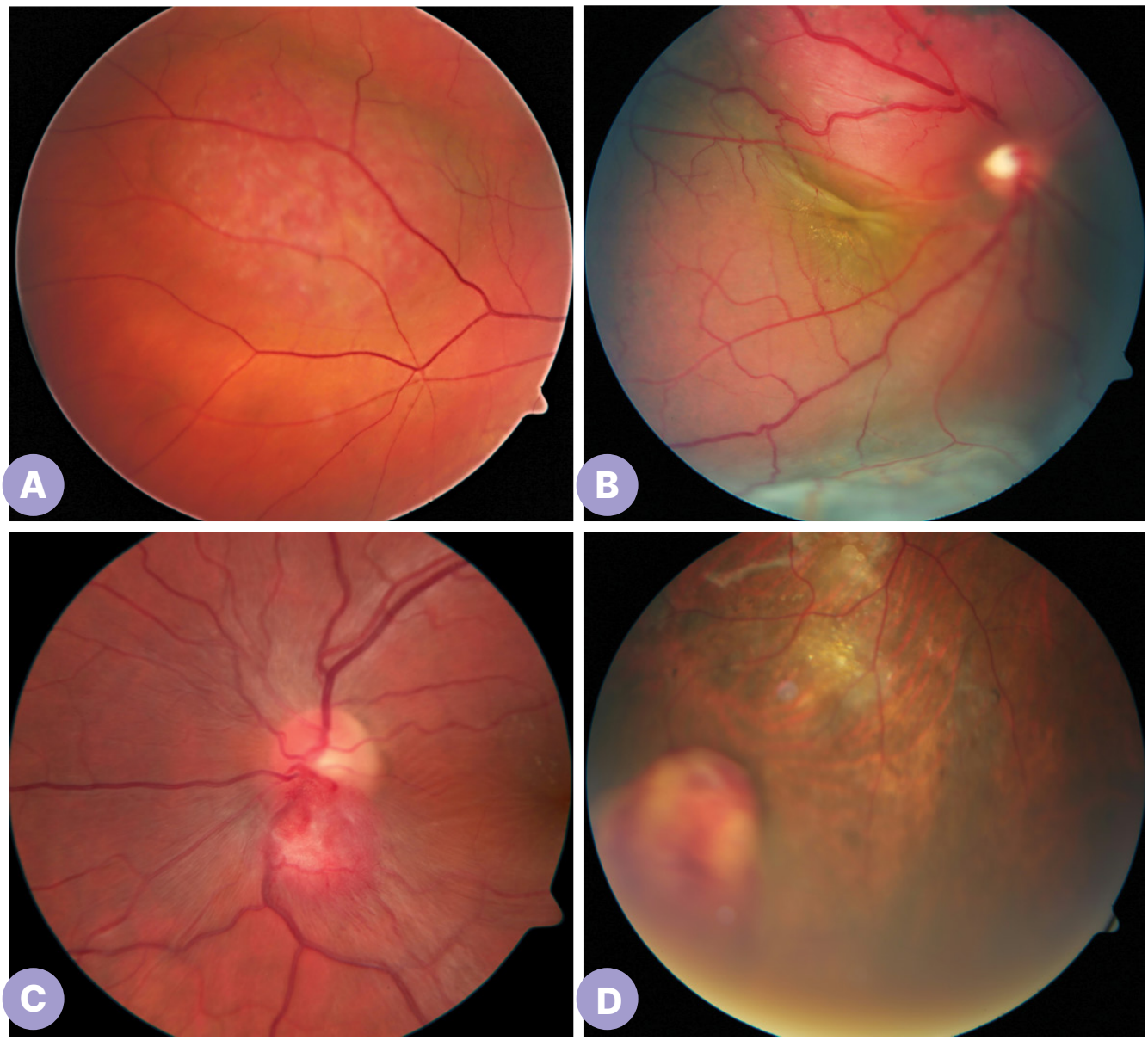

Figure 3. Vascular fundus tumours: **A)** Circumscribed capillary hemangioma; **B)** Diffuse capillary hemangioma with overlying retinal detachment; **C)** Retinal hemangioblastoma at the inferior edge of the optic disc; **D)** Vasoproliferative tumour with associated hard exudates; *courtesy of Hatem Krema, MD, MSc, FRCS, FICO (Hon.).*

creamy yellow exudation; nevertheless, clinical differentiation may not be possible in some cases (**Figure 4D**). Other causes of leukocoria include retinopathy of prematurity, retinal dysplasia, and coloboma, uveitis, and persistent hyperplastic primary vitreous. Adult aggressive RB is rare, yet a retinoma may be incidentally discovered in an adult as a dormant lesion.[20]

Conclusion

The diagnosis of the most frequent ocular fundus tumours depends mainly on clinical and imaging features without the need for a diagnostic biopsy. The presented simplified classification herein can help clinicians distinguish between the majority of the common fundus tumours encountered in their practice.

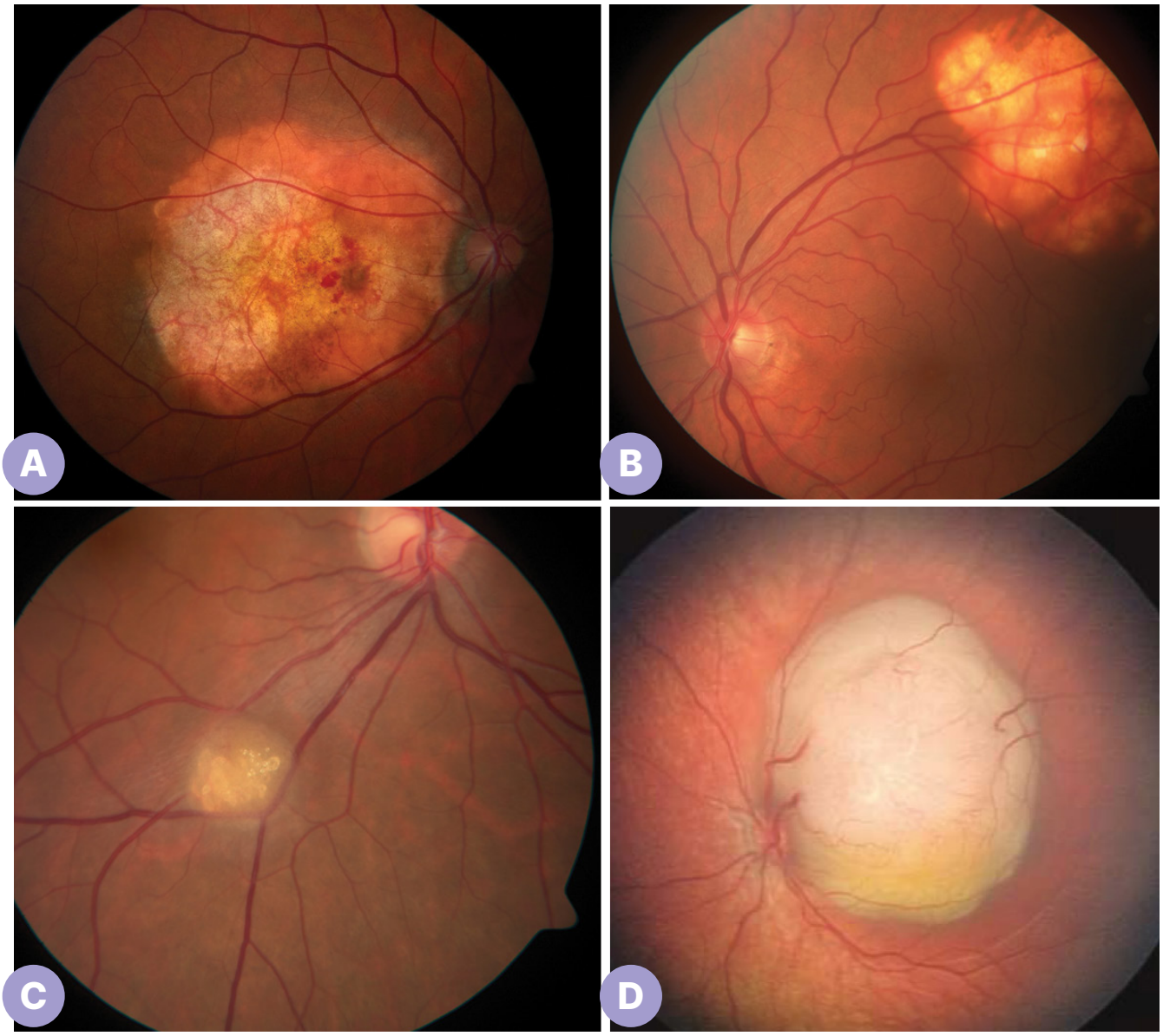

Figure 4. Calcified fundus tumors: **A)** Choroidal osteoma appears as a rugged surface posterior pole lesion with intrinsic vessels; **B)** Idiopathic sclerochoroidal calcification appears as a choroidal glistening irregular mass at the fundus mid periphery under the arcades; **C)** Retinal astrocytic hamartoma appears as retinal mass gelatinous mass with foci of calcifications; **D)** Retinoblastoma, endophytic type, presenting as a white mass with feeder retinal vessels and glistening intrinsic calcification; *courtesy of Hatem Krema, MD, MSc, FRCS, FICO (Hon.)*.

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Financial Disclosures

None declared.

References

1. Chien JL, Sioufi K, Surakiatchanukul T, et al. Choroidal nevus: a review of prevalence, features, genetics, risks, and outcomes. Curr Opin Ophthalmol. 2017 May;28(3):228-37.
2. Shields CL, Kels JG, Shields JA. Melanoma of the eye: revealing hidden secrets, one at a time. Clin Dermatol. 2015 Mar-Apr;33(2):183-96.
3. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond). 2017 Feb;31(2):241-57.
4. Kaur G, Anthony SA. Multimodal imaging of suspicious choroidal neoplasms in a primary eye-care clinic. Clin Exp Optom. 2017 Nov;100(6):549-62
5. Dalvin LA, Shields CL, Ancona-Lezama DA, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. Br J Ophthalmol. 2019 Oct;103(10):1441-7.
6. Bonnet LA, Conway RM, Lim LA. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) as a screening marker for familial adenomatous polyposis (FAP). Systematic literature review and screening recommendations. Clin Ophthalmol. 2022 Mar 15;16:765-74.
7. Shields JA, Demirci H, Mashayekhi A, et al. Melanocytoma of the optic disk: A review. Indian J Ophthalmol. 2019 Dec;67(12):1949-58.
8. Font RL, Moura RA, Shetlar DJ, et al. Combined hamartoma of sensory retina and retinal pigment epithelium. Retina. 1989;9(4):302-11.
9. Shields JA, Shields CL. Tumors and related lesions of the pigmented epithelium. Asia Pac J Ophthalmol (Phila). 2017 Mar-Apr;6(2):215-23.
10. Shields CL, Kalafatis NE, Gad M, et al. Metastatic tumours to the eye. Review of metastasis to the iris, ciliary body, choroid, retina, optic disc, vitreous, and/or lens capsule. Eye (Lond). 2023 Apr;37(5):809-14.
11. White VA. Understanding and classification of ocular lymphomas. Ocul Oncol Pathol. 2019 Oct;5(6):379-86.
12. Hage DG, Wahab CH, Kheir WJ. Choroidal sarcoid granuloma: a case report and review of the literature. J Ophthalmic Inflamm Infect. 2022 Sep 29;12(1):31.
13. Lupidi M, Centini C, Castellucci G, et al. New insights on circumscribed choroidal hemangioma: "bench to bedside". Graefes Arch Clin Exp Ophthalmol. 2024 Apr;262(4):1093-1110.
14. Ciancimino C, Di Pippo M, Rullo D, et al. An update on multimodal ophthalmological imaging of diffuse choroidal hemangioma in Sturge-Weber syndrome. Vision (Basel). 2023 Oct 6;7(4):64.
15. de Paula A, Abdolrahimzadeh S, Fragiotta S, et al. Current concepts on ocular vascular abnormalities in the phakomatoses. Semin Ophthalmol. 2021 Oct 3;36(7):549-60.
16. Ebrahimiadib N, Maleki A, Fadakar K, et al. Vascular abnormalities in uveitis. Surv Ophthalmol. 2021 Jul-Aug;66(4):653-67.
17. Alameddine RM, Mansour AM, Kahtani E. Review of choroidal osteomas. Middle East Afr J Ophthalmol. 2014 Jul-Sep;21(3):244-50.
18. Shields JA, Shields CL. CME review: sclerochoroidal calcification: the 2001 Harold Gifford Lecture. Retina. 2002 Jun;22(3):251-61.
19. Hodgson N, Kinori M, Goldbaum MH, et al. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017 Jan;45(1):81-6.
20. Zhou M, Tang J, Fan J, et al. Recent progress in retinoblastoma: Pathogenesis, presentation, diagnosis and management. Asia Pac J Ophthalmol (Phila). 2024 Mar-Apr;13(2):100058.