Spectrum of presentation of intraocular metastases from cutaneous melanoma in the era of immunotherapy and targeted therapies

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AUTHOR CONTRIBUTIONS
SL—study conception and design, data collection, analysis and interpretation of results, manuscript preparation. AKA—data collection, analysis and interpretation of results. GRH—data collection, analysis and interpretation of results. MSS—study conception and design, analysis and interpretation of results, manuscript preparation.

COMPETING INTERESTS
The authors declare no competing interests.

SUMMARY

What was known before

- Intraocular metastases from cutaneous melanoma are rare but their incidence could be increasing because of improved patient survival. Some of these intraocular metastases can be responsive to systemic therapies used for the treatment of metastatic cutaneous melanoma.

What this study adds

- Previous episodes of uveitis might have disrupted the blood- ocular barrier which facilitates the entry of metastatic melanoma cells into the eye.
- Clinically, metastatic cutaneous melanoma to the eye can present as a 'masquerade syndrome', mimicking various other ophthalmic conditions.

BACKGROUND: Intraocular metastases from cutaneous melanoma are rare. Diagnosis can be challenging and there is currently no consensus on treatment However, with the increasing incidence of this cancer and improved survival of patients treated with targeted BRAF-MEK inhibitors and checkpoint inhibitors, it is likely that more cases will be referred to ocular oncology clinics. SUBJECTS: Single-centre retrospective study. We included all the patients diagnosed with intraocular metastases from cutaneous melanoma seen between 2017 and 2022.

RESULTS: The first patient had bilateral choroidal metastases and unilateral vitreous cells (treated with external beam radiotherapy and immunotherapy), the second had unilateral amelanotic vitreous metastasis (treated with vitrectomy and BRAF- MEK inhibitors) and the third had bilateral multifocal choroidal metastases (treated with BRAK-MEK inhibitors followed by immunotherapy). The fourth patient (previously reported) had unilateral anterior segment and vitreous metastases (treated with immunotherapy and enucleation), interestingly, two patients had a history of uveitis in the affected eye, unrelated to the ocular metastases. All four patients had synchronous systemic metastases.

CONCLUSIONS: The diagnosis of intraocular metastases from cutaneous melanoma is generally clinical but it is sometimes challenging because of possible masquerade syndromes. The presence of other extraocular metastatic sites is an indicator of the diagnosis. Cytopathologic proof combined with genetic analysis is sometimes necessary for diagnosis, especially with amelanotic vitreous debris or in rare cases where systemic screening is negative. New treatments with targeted BRAF-MEK inhibitors and checkpoint inhibition may avoid external beam radiotherapy and enucleation in some patients.

INTRODUCTION

Advances in the management of cutaneous melanoma have led to improved patient survival over the past 20 years, specifically in advanced stages [1]. Polychemotherapy used to be the mainstay of metastatic melanoma treatment but an impact on disease-free or overall survival was never shown in randomised trials, unlike novel therapeutic options such as immune checkpoint inhibitors and BRAF plus MEK inhibitors [2-4]. Extension of lifespan in treated patients could translate into an increased detection of metastases in organs such as the eye, previously considered rare sites for metastatic melanoma as patients previously did not have time to develop metastases in those sites.

To date, there is no consensus on the management of intraocular metastases from cutaneous melanoma but recent case reports and series show good responses after treatment with targeted BRAF-MEK inhibitors or immunotherapy, therefore avoiding historical treatment with external beam radiotherapy in some patients [5, 6]. These new treatment modalities could even achieve better outcomes in terms of eye preservation and visual outcomes in some patients although the literature is still scarce on the subject However, it is also known that vitreoretinal metastasis from cutaneous melanoma can develop despite systemic response to immunotherapy possibly due to a lack of ocular penetration [7] which means that treatment of intraocular metastases remains challenging despite the abovementioned therapeutic advances in cutaneous melanoma.

In the present series, we report four cases of intraocular metastases from cutaneous melanomas diagnosed between 2017 and 2022, demonstrating the spectrum of presentations. All four patients underwent treatment with BRAF-MEK inhibitors and/or immunotherapy. Treatment was started after the diagnosis of intraocular metastases in three cases; in the fourth case the intraocular metastases may have been present before treatment was started as there was iris heterochromia but the diagnosis was only made while the patient was being treated with immunotherapy.

Case 1

A 78-year-old female presented with blurred vision in the left eye for the last 2 weeks. She had recently noticed some moderately pigmented subcutaneous lumps on her scalp and neck. She had a history of BRAF wild-type cutaneous melanoma of the upper back which had been treated with surgery 11 months before the visual symptoms started. Histopathology had shown 3.6 mm Breslow thickness with ulceration and the stage was pT3b according to the 8th edition TNM classification. Sentinel lymph node analysis had been negative in the right axilla.

Visual acuity in the right eye was 6/9 and in the left 6/18. Fundus examination showed bilateral macular pigmented chor¬oidal masses (Fig. 1A, B). The right one measured 1.0 mm in thickness on B scan ultrasound (tumour base on fundus picture 1.5 DD—disc diameter) and the left 1.2 mm (tumour base on fundus picture 3 DD). In the left eye, there was visual loss as a consequence of subretinal fluid overlying the choroidal lesion on OCT scans and the presence of pigmented cells in the vitreous. The patient was subsequently found to have subcutaneous, liver, lung and splenic metastases from the primary cutaneous melanoma. She was started on pembrolizumab and underwent ocular external beam radiotherapy within a month after ocular clinical diagnosis at the dose of 20 grays in 5 sessions. A 4 mm solitary brain metastasis was found 6 months after the diagnosis of choroidal metastases and treated with Gamma knife radio¬surgery. At 17 months of follow-up, the patient was stable under pembrolizumab and reported no visual concern.

Case 2

A 49-year-old female presented with blurred vision and myodesopsia in the left eye which had started 3 months before, more precisely 10 days after a second craniotomy for metastases from BRAF-mutated cutaneous melanoma. She had a history of left gluteal primary cutaneous melanoma diagnosed 4 years previously with lymph node recurrence a year later treated with surgery. She developed a frontotemporal metastasis to the brain 2 years after the lymph node recurrence for which she was initially treated with immunotherapy (ipilimumab and nivolumab). Immunotherapy was stopped because of toxicity and the patient underwent resection of the frontotemporal lobe brain metastasis. She was then started on nivolumab as a single agent which also had to be stopped because of toxicity. Three months later

the patient underwent a second craniotomy for resection of a posterotemporal lobe metastasis. Of note, this patient also had a history of left recurrent idiopathic anterior uveitis over the last 14 years.

Visual acuity in the left eye was counting fingers and intraocular pressure was 37 mmHg. Examination revealed iris synechiae and an amelanotic dense vitreous opacity (Fig. 2A, B). The right eye was unremarkable (visual acuity 6/6 and intraocular pressure 14). The patient underwent a left diagnostic vitrectomy to rule out Terson's syndrome given that the left visual loss had started after a neurosurgical procedure (second craniotomy for brain metastases). During the vitreoretinal procedure, a total retinal detachment was noted with proliferative vitreoretinopathy and no visible retinal tears. Silicone oil was injected after retinotomy and drainage. Cytology showed metastatic cutaneous melanoma in the vitreous presenting as a scant population of large cells with abundant cytoplasm and prominent nuclei, strongly immunoreactive for melanA and HMB45. Two months after vitreoretinal surgery the patient developed iris neovascularisation, intraocular pressure was 50 mmHg and a posterior pole retinal detachment. The eye was comfortable and observation was advised.

Seven months after the second craniotomy two new brain metastases were found and treated with stereotactic radiosurgery (20 grays delivered in 5 fractions). There was no evidence of further active extracranial disease at that point. She was started on targeted therapy with dabrafenib and trametinib with no progression on FDG PET-CT and head MRI 7 months after the diagnosis of vitreous metastasis.

Case 3

A 56-year-old woman female presented with myodesopsia that had started a week before, followed 2 days later by right periocular pain. The patient reported episodes of vomiting over the last 6 months and loss of appetite over the last 4 months. She had also noticed black lumps on her fingernails on the right middle 3 fingers and the index finger of her left hand. A biopsy of lesions on the scalp and left nipple had shown BRAF-mutated melanoma of unknown primary location.

Visual acuity in the right eye was 6/12 and in the left 6/5. Intraocular pressure was normal in both eyes. Fundus examination showed multiple pigmented choroidal lesions in both eyes (Fig. 3A, B) and a right choroidal mass which had an irregular profile on the OCT scan. Brain MRI (magnetic resonance imaging) showed that the choroidal mass was T1 hyperintense and T2 hypointense, in keeping with the diagnosis of melanoma metastasis. There was also an enlargement of the anterior pituitary gland with no chiasmatic compression, as it just bulged into the suprasellar cistern not reaching the chiasm. This was thought to be a pituitary melanoma metastasis. CT (computed tomography) of the thorax, abdomen and pelvis with contrast only showed multiple simple hepatic cysts (a dominant left lobar cyst measuring 14.4 cm had a mass effect on the stomach) and scattered sclerotic foci within the dorsal spine with no evidence of cord compression. The patient was started on BRAF-MEK targeted therapy in medical oncology (dabrafenib and trametinib). The rationale for commencing targeted therapy in this stage IV melanoma rather than immunotherapy was the need for rapid response due to the sight-threatening multiple choroidal lesions. A month after the presentation there had been a reduction in the size of the right choroidal lesion on ocular ultrasound and another month later visual acuity was 6/6 in both eyes. At that point all the pigmented intraocular lesions were flat and there were no new ones (Fig. 3C, D). The mass lesion in the pituitary fossa had also reduced in size on the follow-up brain MRI. The left-hand lesion had become less pigmented under treatment but the patient continued to have streaky hyper-pigmented lesions on digits 2, 3 and 4 of the right hand. The patient was switched to immunotherapy after 6 months of BRAF-targeted therapy and the regressed intraocular lesions remained stable.

Case 4

This case has been published previously [8]. A 49-year-old woman female reported photopsia and dark floaters in her right eye before starting immunotherapy for metastatic cutaneous melanoma. She had also noticed progressive right eye darkening in comparison to the left eye. A primary cutaneous melanoma of the groin had been diagnosed 6 years before, followed 2 years later by another presumed primary cutaneous melanoma of the arm. Three years after the second melanoma she developed metastases to the brain, groin, parotid as well as metastatic

subcutaneous nodules. The patient was started on immunotherapy (ipilimumab and nivolumab) with a good response to the systemic metastases. Of note, this patient had a history of right Posner-Schlossman syndrome diagnosed 25 years before, for which she had recently undergone trabeculectomy as the intraocular pressure could not be controlled and there was visual loss in the right eye.

Examination in the ocular oncology clinic showed obvious iris heterochromia with the right iris brown and the left blue. Visual acuity was 6/24 in the right eye. There was an iris bombe with speckled pigmentation and thickening of the iris (on ultrasound biomicroscopy there was an elevation of 0.23 mm at the 6 o'clock position). Intraocular pressure in the right eye was 50. The angle was closed on gonioscopy with no iris neovascularization. The trabeculectomy bleb was flat and scarred with pigmentation within. There were clumps of pigmented cells in the vitreous, also visible on ocular ultrasound as intragel opacities. Examination of the left eye was unremarkable (visual acuity 6/5 and intraocular pressure 12). The patient underwent enucleation of the right eye after it became painful despite systemic treatment with immunotherapy. Histopathology showed metastatic cutaneous melanoma with epithelioid cells, mostly pigmented, likely a mixture of melanophages and melanoma cells. There were cells coating the posterior corneal surface extending onto the iris and trabecular meshwork and free-floating melanoma cells within the vitreous and coating the non-pigmented epithelium of the ciliary body with no retinal or choroidal invasion. The pigmented cells below the trabeculectomy bleb corresponded to melanophages on immunohistochemistry. The patient survived 21 months after she was first seen in ocular oncology.

DISCUSSION

Intraocular metastases from cutaneous melanoma are considered to be rare. In a series of 108 consecutive patients with metastatic cutaneous melanoma from 2014 only 1% were found to have choroidal metastases on screening [9]. However, the incidence may be increasing as a result of a higher incidence of cutaneous melanoma in the general population related to sunlight and UV exposure [10] and the availability of new treatment modalities such as targeted therapies and immunotherapy. These latter have resulted in prolonged survival of patients with

metastatic cutaneous melanoma [11] which may lead to increased detection of what are considered to be rare metastatic sites, such as the eye. Targeted BRAF-MEK inhibitors and immunotherapy have been associated with ophthalmic toxicities [12-14] when used for the treatment of metastatic cutaneous melanoma justifying systematic screening which could contribute to the early detection of asymptomatic intraocular metastases.

The metastatic pathway to the eye is presumed to be hematogenous as the eye has no lymphatics, which would account for the choroid being the most common ocular structure affected by metastases as it receives a brisk blood flow [15]. Thus, before the advent of targeted therapies and immunotherapy, 39% of patients with intraocular metastases from cutaneous melanoma had choroidal involvement. The second most frequent location was the vitreous (28%), followed by the retina (18%), iris (15%) and ciliary body (13%) [16]. It is unclear if the hematogenous dissemination to the eye is intravascular or extravascular with angiotropic melanoma cells migrating in a pericyte-like manner without intravasation [17]. Some authors showed permeation of tumour cells from retinal blood vessels on histopathology, which could explain how the melanoma cells enter the vitreous cavity [18]. Interestingly two patients in our series had pre-existing inflammatory conditions in the eye and later developed metastases from cutaneous melanoma, Posner-Schlossman syndrome in one case and recurrent anterior uveitis in the other. We hypothesise that there may have been a breach of the blood- ocular barrier following uveitic episodes in those cases which facilitated the entry of metastatic cells into the affected eye while sparing the other.

Early diagnosis of intraocular metastases from cutaneous melanoma is important as there are now several available treatment options which can preserve vision and therefore quality of life in the affected patients. Diagnosis is generally made on an association of clinical features and a history of cutaneous melanoma or occasionally after a biopsy of the intraocular lesion. Biopsy is necessary when the diagnosis solely based on clinical features is challenging, as sometimes ocular metastases from cutaneous melanoma can mimic other conditions such as primary uveal melanoma [19, 20] or bilateral diffuse uveal melanocytic proliferation (BDUMP). Intraocular metastases from cutaneous melanoma can involve any tissue in the

anterior or posterior segment of the eye. They can be unilateral or bilateral (19% of patients present with both eyes involved [16]). Both pigmented and amelanotic lesions have been reported. Amelanotic vitreous debris often requires diagnostic vitrectomy to rule out differential diagnoses, in particular drug-related inflammation in the context of checkpoint inhibition which is now the first-line treatment for many patients with metastatic cutaneous melanoma [18].

All four patients in our series presented with lesions which could have corresponded to non-metastatic ocular conditions had it not been for the history of cutaneous melanoma. The first case presented with bilateral unifocal pigmented choroidal lesions which made the diagnosis of choroidal melanoma unlikely as this would almost always be unilateral. The second case had a unilateral amelanotic vitreous opacity which could have corresponded to an old vitreous haemorrhage given the recent neurosurgical intervention. The third patient had multiple pigmented choroidal lesions similar to those discernible in BDUMP. The fourth case had a history of Posner-Schlossman syndrome which probably delayed the diagnosis of intraocular metastasis as heterochromia has been noted in some cases of Posner-Schlossman syndrome even though it is no longer considered a characteristic finding. In cases 1, 2 and 4 the history of cutaneous melanoma orientated towards the possibility of ocular metastases and case 3 had synchronous pigmented lesions elsewhere in the body very much in favour of metastatic cutaneous melanoma even if the primary was unknown. Systemic screening in patients with ocular metastases from cutaneous melanoma usually shows other synchronous extraocular metastases [16]. All four patients in this series had synchronous systemic metastases when the intraocular ones were diagnosed. A diagnostic biopsy of the intraocular lesion can be necessary if no other extraocular metastases are found. However, histopathological analysis cannot differentiate between primary and secondary melanoma in the eye [16] but the difference can be made using genetic testing as uveal and cutaneous melanoma have distinct genetic features [19, 20], Making the difference between these two entities has implications for the choice of treatment, as treatment of ocular metastases differs from that of primary uveal melanoma.

Treatment of intraocular metastases is still palliative despite progress in recent years which has led to improved survival in metastatic cutaneous melanoma. Options

currently include systemic treatment such as immunotherapy and targeted BRAF-MEK inhibitors if the melanoma is BRAF-mutated or ocular-specific treatments such as external beam radiotherapy and enucleation. Targeted therapies have been shown to achieve reduction of ocular metastases in BRAF-mutated melanoma [6] similar to the third patient in our series. Immunotherapy is now considered to be active in the central nervous system despite its immune privilege [21] but there is still some controversy as to whether immunotherapy is actually effective on intraocular metastases or not. Some authors think that this is not the case because of ocular immune privilege and the mode of action of immunotherapy which activates T cells rather than acting directly on the tumour [8] but others argue the contrary, saying that immunotherapy can shrink intraocular metastases from cutaneous melanoma [5]. It is known that immunotherapy causes a delayed treatment effect because of its indirect mechanism of action. This delayed treatment effect may give a false impression of ineffectiveness on some intraocular metastases. There could also be an 'unmasking' of certain intraocular metastases after the introduction of immunologic checkpoint blockage therapy as this phenomenon has been reported with intracranial metastases from cutaneous melanoma [22]. This corresponds to unmasking previous clinically silent metastatic disease, rather than representing new or progressive metastatic disease akin to pseudoprogression in radiology. Treatment with external beam radiotherapy (in BRAF wild-type melanoma) or BRAF-MEK inhibitors (in BRAF- mutated melanoma) should therefore be considered in case of immediate visual threat by intraocular metastases (cases 1 and 3 in the present series).

Enucleation is sometimes necessary, especially if there is a blind and painful eye. Patients at risk are those with metastatic deposits in the anterior segment (such as case 4) and those with vitreous metastases from cutaneous melanoma as they are at risk of developing neovascular glaucoma [23], in particular after vitrectomy [18] (as was observed in our second case). External beam radiotherapy has been reported to be often unsuccessful in achieving local tumour control when cutaneous melanoma is metastatic to the vitreous [23] but local treatment with a combination of intravitreous melphalan and bevacizumab resulted in the resolution of active disease in two patients [24] thus possibly avoiding enucleation.

CONCLUSION

Intraocular metastases from cutaneous melanoma are rare but their incidence may be increasing as a consequence of prolonged survival of patients with metastatic cutaneous melanoma. Any structure of the eye can be affected by metastatic deposits hence the possibility of masquerade syndromes. However, synchronous extraocular metastases are found in the majority of cases which can help with the diagnosis and therefore avoid a biopsy of the intraocular lesion. Treatment remains palliative but targeted therapies, immunotherapy and radiotherapy have been shown to stop the progression of intraocular metastases from cutaneous melanoma and therefore preserve vision in some patients. Interestingly, two patients in the present case series had a history of intraocular inflammation in the same eye that subsequently developed metastases from cutaneous melanoma. We hypothesise that disruption of the blood-ocular barrier may have facilitated the entry of metastatic melanoma cells.

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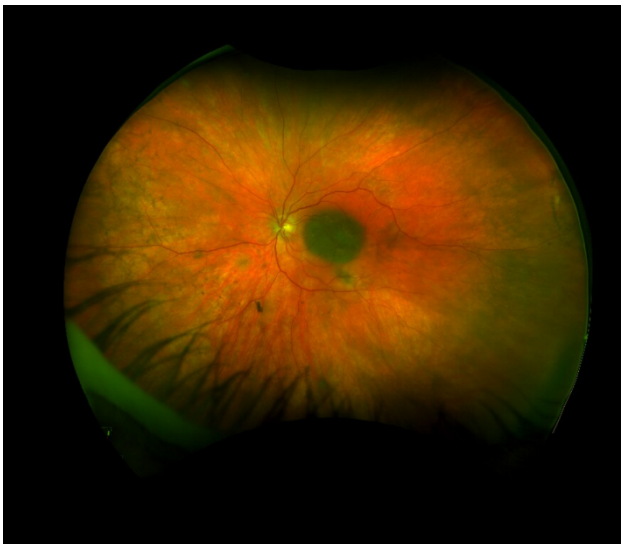
Fig. 1 Bilateral macular metastases. Case 1. A Colour picture of the right fundus showing a small pigmented macular choroidal mass. B The left fundus also shows a pigmented macular lesion, slightly larger in diameter.

A



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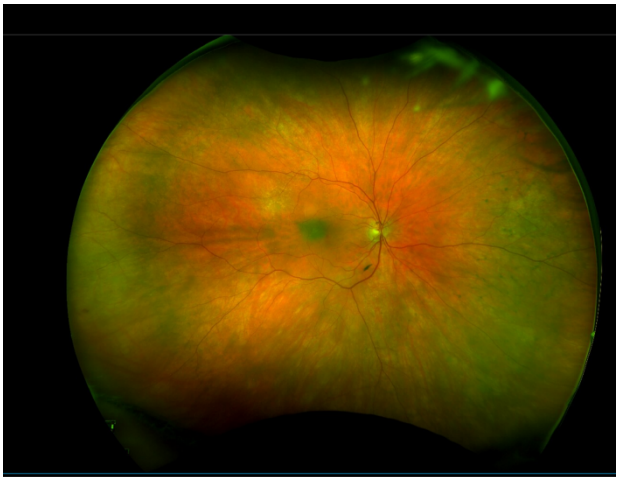
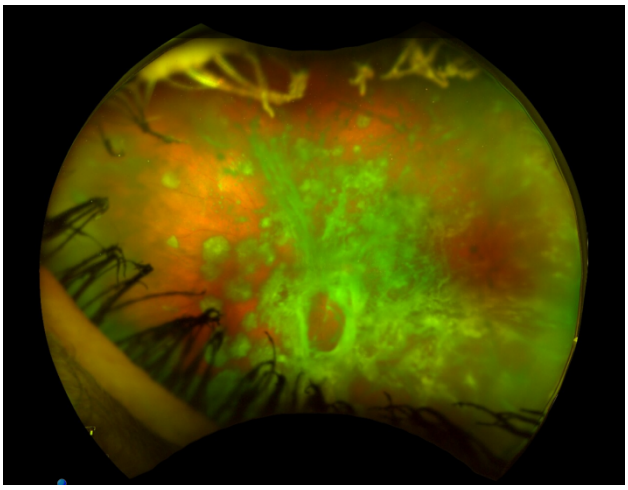


Fig. 2 Amelanotic vitreous metastasis. Case 2. A Colour picture of the left fundus showing an amelanotic dense vitreous opacity. B Ocular ultrasound corresponding to (A) showing the dense vitreous and the absence of any chorioretinal lesions.

A



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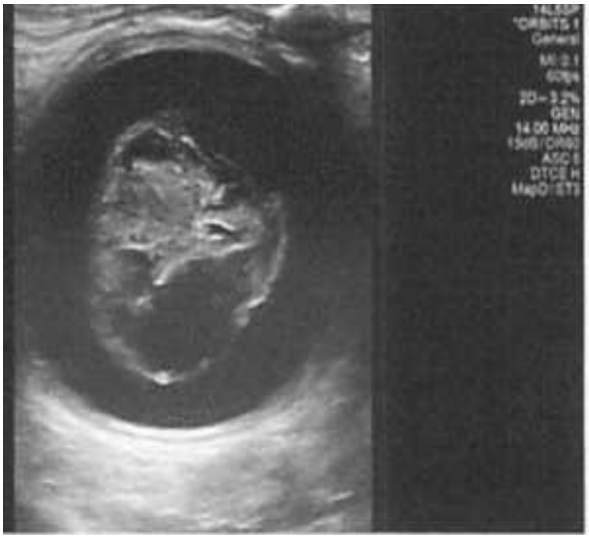
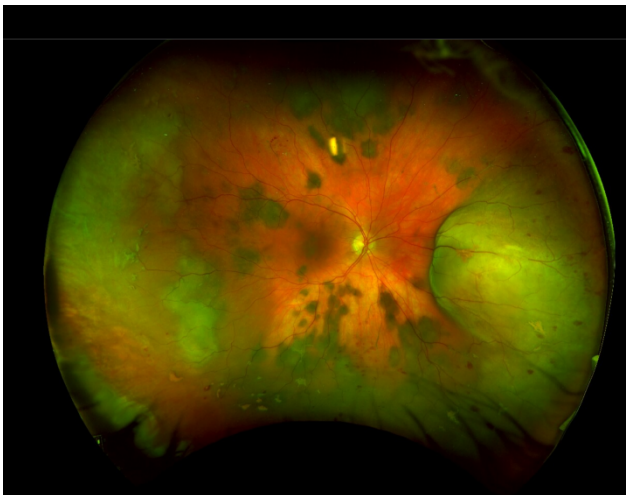


Fig. 3 Multiple diffuses bilateral choroidal metastases. Case 3. A Colour picture of the right fundus showing multiple pigmented choroidal lesions and a larger choroidal mass in the nasal quadrant. B Picture of the left fundus, also showing similar lesions. C Right fundus after 3 months of treatment with BRAF inhibitors, there has been a shrinkage of all the lesions. D Left fundus after the same treatment showing a similar response as in (C).

A



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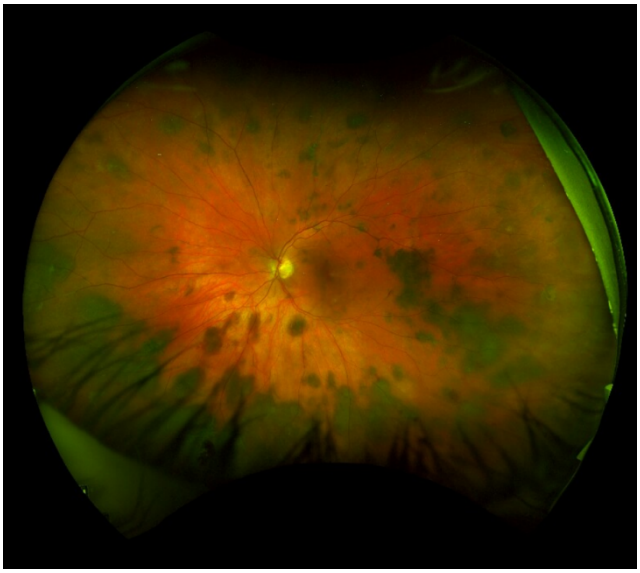

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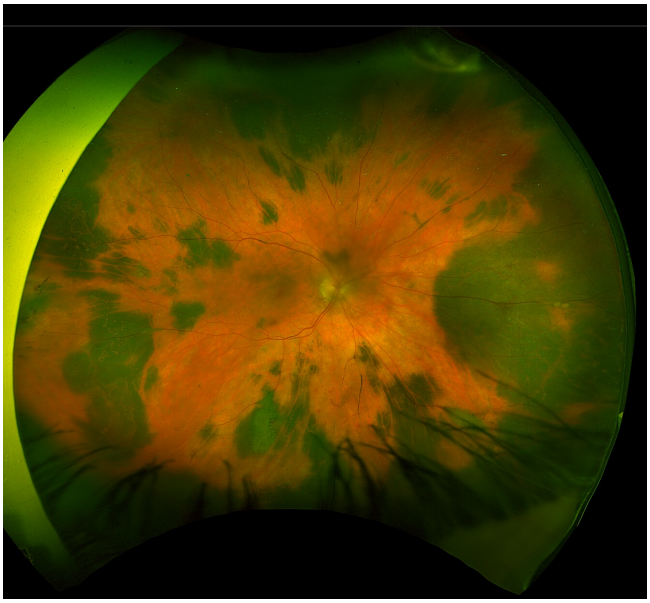

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