Choroidal involvement in Rosai-Dorfman disease successfully treated with cobimetinib

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Rosai-Dorfman disease (RDD) is a rare systemic pseudo-lymphomatous disorder with unknown etiology. No guidelines exist regarding its management and treatment when the disease is progressing. Choroidal involvement in RDD has rarely been reported and has often been misdiagnosed. We describe a case of a 64-year-old male diagnosed with RDD by means of choroidal biopsy, successfully treated with a MEK inhibitor, namely Cobimetinib, and its follow-up over 5 years, with good final anatomical and functional results. This is the first reported case of RDD diagnosed with an intraocular biopsy performed on a non-enucleated globe, thus preserving the integrity and function of the eye. This case emphasizes the need for a choroidal biopsy when the diagnosis is not straightforward and the starting of targeted therapy to retain a good visual function.

Key words: Choroidal biopsy, choroidal thickness, Cobimetinib, MEK inhibitor, Rosai-Dorfman disease

Rosai-Dorfman disease (RDD) is an uncommon histiocytic disorder characterized by a general painless enlargement of lymph nodes. However, around 40% of patients present extranodal involvement, including several different ophthalmic localizations, like orbital and epibulbar masses, scleritis, and serous retinal detachment.[1,2] Uveal involvement is exceptionally rare and often misdiagnosed.[3-5]

In most cases, RDD is self-limited, and observation is the first line of care. However, symptomatic or relapsing disease deserves treatment. Uniform guidelines about therapy are lacking, but recently, targeted therapy with MEK inhibitors like Cobimetinib, have been demonstrated to have promising results in RDD patients.

Herein, we present the first case of choroidal biopsy-proven RDD treated with Cobimetinib, and its follow-up over 5 years, with good anatomical and functional outcomes.

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Case Report

A 64-year-old Caucasian man was referred for a 7-month history of progressive vision loss in the right eye (RE). Family history was negative for eye diseases and the patient's medical and ophthalmic history were not contributory.

At presentation, the best-corrected visual acuity (BCVA) was 20/50 in the RE and 20/32 in the left eye (LE). Undilated slit-lamp biomicroscopy revealed bilateral quiet anterior segment with no sign of inflammation. The intraocular pressure was within normal limits in both eyes (OU).

Dilated fundus examination showed a yellowish lesion involving the posterior pole and extending nasally, in OU. In the RE, a choroidal nevus was noted infero-temporally to the macula [Fig. 1A]. Enhanced depth optical coherence tomography (EDI-OCT) of the RE showed a serous retinal detachment with disruption of photoreceptors layers temporally to the fovea [Fig. 1B] and confirmed the presence of the nevus [Fig. 1C]. In the LE, intraretinal fluid and a small serous retinal detachment were noted in the papillo-macular bundle [Fig. 2B and C]. Furthermore, a hyporeflective thickening of the choroid was noted bilaterally, corresponding to the fundus yellowish areas, causing a sloping appearance of the retino-choroidal interface [Figs. 1B, C and 2B-D].

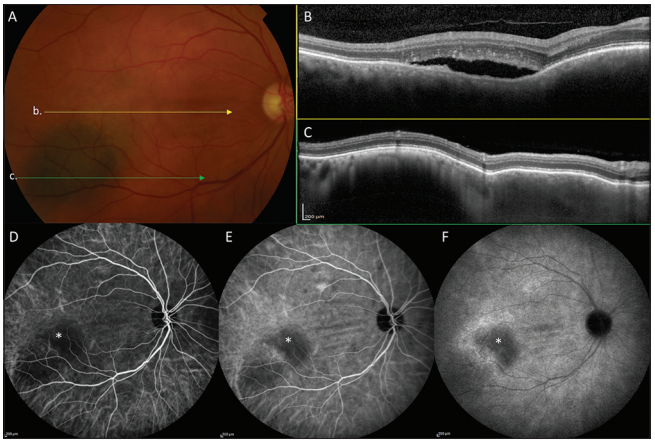

Figure 1: Multimodal imaging of Rosai-Dorfman choroidal involvement at baseline (right eye). (A) color fundus photography revealing a heterogeneous yellowish large area involving the posterior pole and a choroidal nevus. (B) OCT scan showing subretinal fluid temporally to the fovea, corresponding to the yellow line (b.) in figure A. (C) OCT scan showing the choroidal nevus, corresponding to the green line (c.) in figure A. (D-F) indocyanine green angiography showing a hypofluorescent large area involving the posterior pole that become iso/hyperfluorescent during the exam. The choroidal nevus remains hypofluorescent (asterisk)

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Fluorescein angiography was minimally contributory, showing the hyperfluorescence of the serous detachments (not showed), while indocyanine green angiography revealed early hypofluorescence fading in the late phases of the exam [1D-F and 2E, F]. The extensive systemic workup, including autoimmune and infectious panels, were all normal. However, after 4 months of observation, a worsening of BCVA and EDI-OCT findings were noted. In the neoplastic suspect, the patient underwent choroidal biopsy that revealed an infiltrate of large histiocytes showing emperipolesis and immunoreactivity with S-100 protein. These findings, as well as the expression of CD68 and CD163 with the absence of CD1a, suggested the diagnosis of Rosai-Dorfman disease. A total body imaging with PET-CT and brain MRI showed suggestive disease involvement of the cervical ganglia and the right tibia. The patient was initially treated with a pulse or intravenous steroids (Solumedrol 1,000 mg/day) for 3 days, followed by high doses of oral steroids (Prednisone 70 mg/day) tapered over 3 months. Despite the initial improvement of ocular manifestations, a worsening during the tapering of steroids occurred. Thus, therapy was switched to Cobimetinib 60 mg/day with optimal anatomical and functional responses. However, after a year, treatment was discontinued due to pruritus and high elevation of serum creatine phosphokinase, interpreted as Cobimetinib side effects. Despite the interruption of therapy, improvement continued, and at 5-year follow-up, BCVA was 20/63 in the RE and 20/25 in the LE with a further reduction in choroidal hyporeflectivity and choroidal thickness in OU [Fig. 3].

Discussion

This case emphasizes the need for a pathologic diagnosis in RDD patients with worsening intraocular disease and prompt targeted therapy to retain good visual acuity. In this case, the progressive deterioration of BCVA and the worsening of EDI-OCT findings led to choroidal biopsy with the diagnosis of RDD. A MEK inhibitor therapy with Cobimetinib was started, with improvement of the ocular manifestations and stable disease over an extended follow-up. This is the first reported case of RDD diagnosed with an intraocular biopsy performed on a non-enucleated globe, thus preserving the integrity and function of the eye.

Uveal involvement in RDD has rarely been reported[6,7] and often misdiagnosed, especially when being the first symptomatic localization of the disease. Our review of the literature found only five cases of uveal biopsy in RDD and were all done after enucleation [Table 1]. In three of the cases, enucleation was performed in the suspect of uveal melanoma.[3-5] Indeed, due to non-specific choroidal signs, differential diagnosis of choroidal RDD includes infiltrative diseases like malignant melanoma, benign lymphoid hyperplasia, choroidal lymphoma, metastasis and, paraneoplastic lesions.

The hypotheses regarding the pathogenesis of RDD refer either to a neoplastic disease or an immunologic/inflammatory disease. For this reason, several different treatments have been tried including corticosteroids, non-biologic and biologic disease modifying antirheumatic drugs, and antineoplastic agents.[1]

MEK-inhibitors are a group of drugs that inhibit the mitogen-activated protein kinase/extracellular signal regulated kinase (MAPK/ERK) pathway that has been classically found dysregulated in several tumors.[8] Recently, it has been found to be dysregulated also in histiocytosis like Langerhans cell histiocytosis, Erdheim-Chester disease, and RDD.[9] Cobimetinib is a MEK inhibitor that has been

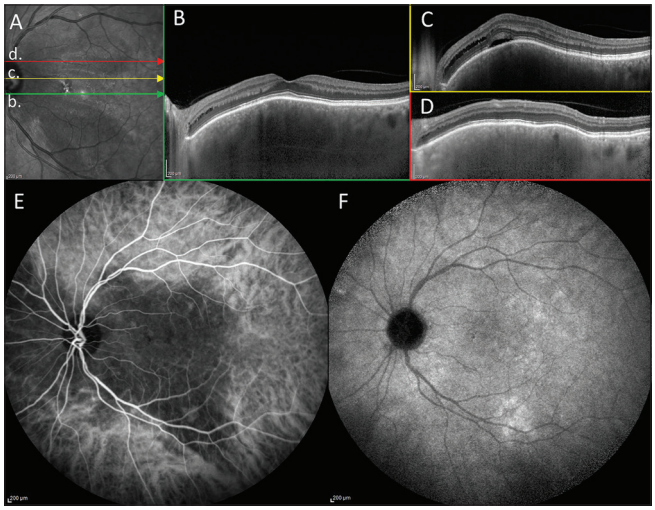

Figure 2: Multimodal imaging of Rosai-Dorfman choroidal involvement at baseline (left eye). (A) infrared imaging showing heterogeneous reflectivity at the posterior pole and RPE changes. (B) OCT through the fovea (corresponding to line b. in figure A) showing hyporeflectivity of the choroid. (C) OCT through the yellow line (c.) of figure A, showing a small serous retinal detachment and intraretinal fluid. (D) OCT through the red line (d.) of figure A, showing a sloping appearance of the retino-choroidal interface. (E and F) ICGA showing a hypofluorescent large area becoming iso/hyperfluorescent in the late phases

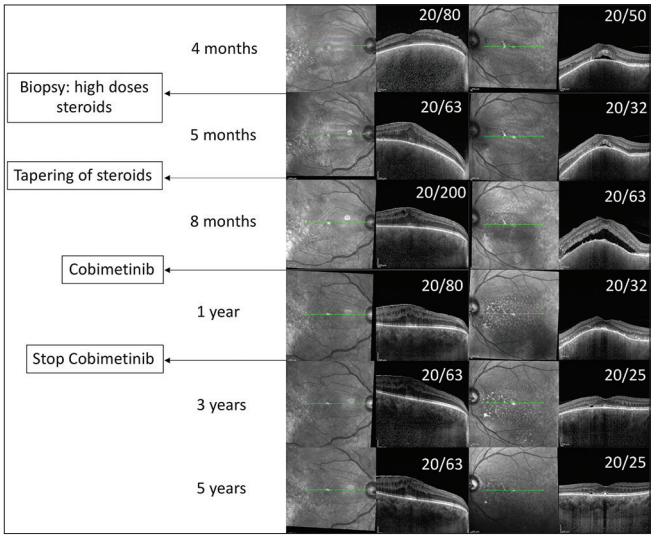

Figure 3: Infrared images, EDI-OCT, and BCVA (upper right) throughout five years of follow-up. Note the progressive thinning of the choroid in both of the eyes after starting Cobimetinib. In the right eye, an epiretinal membrane and some cystic spaces developed over time. In the left eye, a serous detachment involving the fovea that worsened with tapering of steroids and settled with the Cobimetinib can be seen. A disruption of the RPE-photoreceptor layer occurred, which resolved almost totally at the end of the follow-up

Table 1: Intraocular Rosai-Dorfman cases undergone ocular biopsy

Case #	Gender	Age (y)	Eye	Ophthalmic findings	Systemic involvement	Site of biopsy	Reference
1	M	22	unknown	Uveal tract infiltrates	Cervical, axillary, and inguinal lymph nodes, testis, skin	Enucleated globe	Foucar *et al.*, 1979
2	M	13	LE	Shallow anterior chamber, retinal detachment, phthisis bulbi	Bone, trachea, submandibular gland, eye, spinal cord, thymus, kidney, heart, liver, brain	Enucleated globe (postmortem)	Buchino *et al.*, 1982
3	M	40	LE	Choroidal mass and serous retinal detachment	None	Enucleated globe	Vermeulen *et al.*, 2013
4	F	18	RE	Ciliary body mass	None	Enucleated globe	Yousef *et al.*, 2018
5	F	72	RE	Choroidal mass and serous retinal detachment	None	Enucleated globe	Fogt *et al.*, 2019

successfully used in patients with extraocular localizations of RDD[10] but has never been reported to be used in RDD choroidal involvement.

Our patient positively responded to high doses of steroids, but a relapse of ocular manifestations during steroid tapering led to a switch to Cobimetinib with resolution of subretinal fluid, thinning of the choroid and improvement of visual acuity. The treatment was interrupted after one year due to side effects, but the improvement was noted up to five years from the start of therapy. To note, current studies suggest to discontinue Cobimetinib after 12 months and monitor for disease relapses. EDI-OCT was essential in monitoring the changes in retinal and choroidal architecture during the follow-up.

Conclusion

This is the first case of a biopsy-proven choroidal RDD treated with Cobimetinib that led to the preservation of the globe and good visual function over a long follow-up.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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