



Bull's eye maculopathy associated with hereditary hemochromatosis

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ABSTRACT

Purpose: To report a case of bull's eye maculopathy, a novel finding in a patient with iron overload secondary to hereditary hemochromatosis with a homozygous mutation of the *HFE* gene.

Observations: A 39-year-old man with recently diagnosed hereditary hemochromatosis undergoing treatment by serial phlebotomy presented with bilateral progressive blurry vision and recent onset of photopsias and headaches. Fundus examination revealed a symmetric bull's eye maculopathy with photoreceptor loss and retinal pigment epithelium transmission defects in the area of speckled hyper- and hypo-pigmentation by multimodal imaging. Full field and multifocal electroretinograms demonstrated generalized rod and cone dysfunction with some central preservation of waveforms. Further systemic work-up revealed low ceruloplasmin, mildly decreased serum copper and zinc levels, and low urinary copper. The patient underwent testing for inherited retinal dystrophies, but was not found to have any known pathogenic gene mutations. His ferritin levels normalized with serial phlebotomy and his retinopathy did not appear to progress over 6 months with normalization of his iron levels.

Conclusions and Importance: We report a case of bull's eye maculopathy in a patient with hereditary hemochromatosis with no previous exposure to iron chelators and no known inherited retinal dystrophy. Ocular involvement in hereditary hemochromatosis is relatively rare. In this case, the patient's low serum ceruloplasmin is thought to have increased the amount of redox-active ferrous iron and potentiated retinal iron toxicity resulting in the observed retinopathy. To the authors' knowledge, this is a potentially novel ocular manifestation of hereditary hemochromatosis.

1. Introduction

Primary or hereditary hemochromatosis (HH) is characterized by iron overload in multiple organ systems. A genetic mutation, most commonly in the *HFE* gene, results in increased intestinal absorption of iron, later leading to iron overload throughout the body. The deposition of iron in ocular structures has long been described in several clinical studies^{1,2} with one histopathologic study demonstrating iron deposition in the sclera and ciliary epithelium.³

A clinical HH series by Hudson et al. demonstrated normal visual acuity without retinal pathology, including the peripapillary pigmentation described previously by Maddox in 1933.⁴ In addition, a study by Menghini et al. screened patients with HH treated by serial phlebotomy, including those with high and normal initial ferritin levels, to identify whether these individuals had any form of retinal degeneration based

on optical coherence tomography (OCT) and clinical exam. While a relatively small study size, the data showed no association of initial ferritin levels, a marker of iron overload, in association with retinal pathology.⁵ To our knowledge, this is the first case report of bull's eye maculopathy associated with HH in a patient without exposure to any iron chelator or identified inherited retinal dystrophies.

2. Case report

A 39-year-old man was referred to comprehensive ophthalmology clinic with gradual "blurring" of vision in both eyes over the past 1–3 years, and a three-week history of bilateral intermittent photopsias and headache. Best corrected visual acuity on presentation was 20/20-2 in the right eye and 20/25 in the left eye. Visual fields were full to confrontation and pupillary exam was normal. The anterior segment exam

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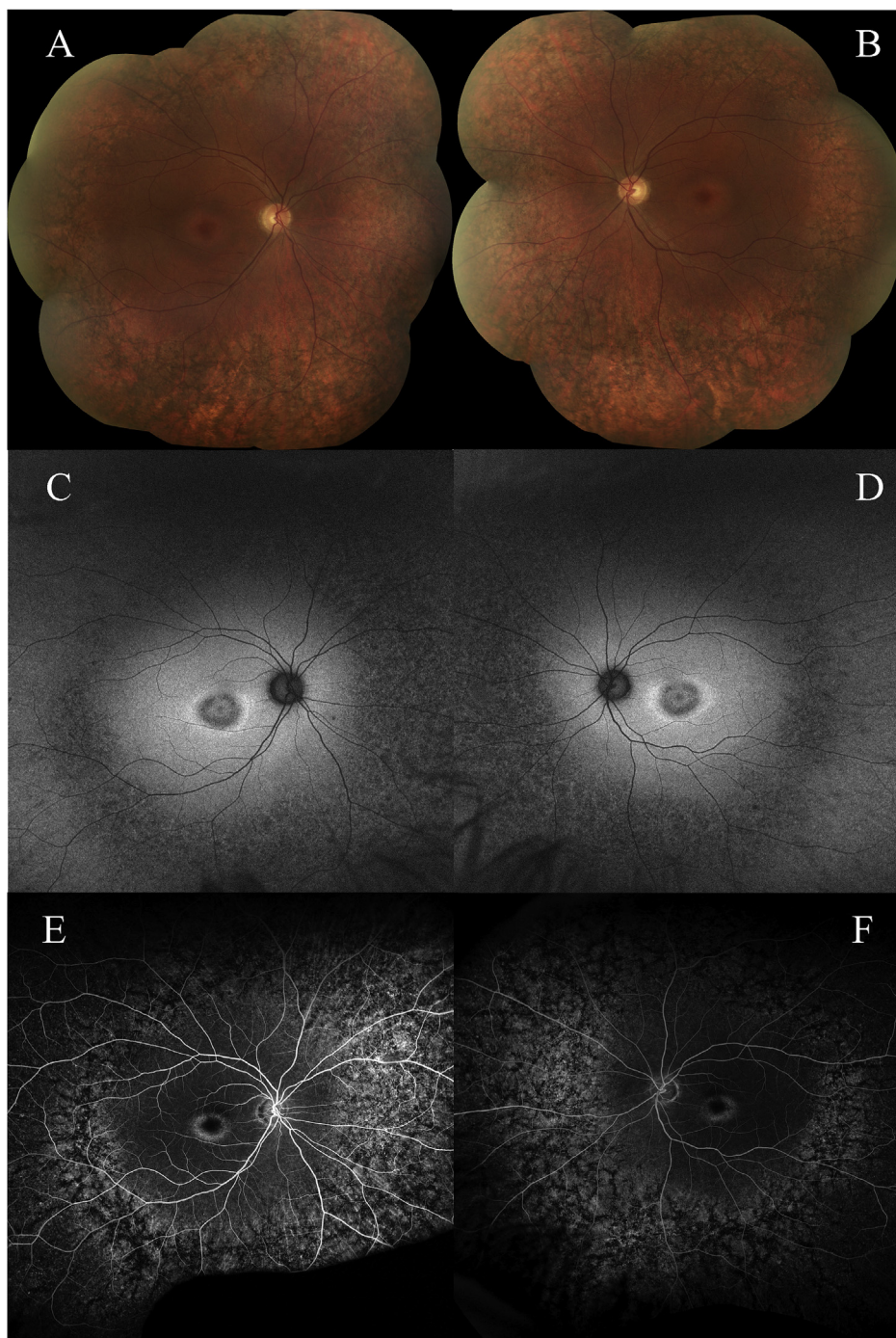


Fig. 1. Multimodal imaging, both eyes, at presentation.

Color fundus photograph montage (right eye, 1A; left eye, 1B) showed a central bull's eye maculopathy with mid-peripheral speckled hyperpigmentation. Fundus autofluorescence (right eye 1C; left eye 1D) revealed a ring of parafoveal hypoautofluorescence with an adjacent ring of hyperautofluorescence and patchy hyperautofluorescence in both eyes. Fluorescein angiography of right eye at early venous phase (1E) demonstrated mid-peripheral window defects corresponding to the areas of speckled hyperpigmentation seen on fundus photography. Fluorescein angiography of left eye at 1.5 minutes later (1F) showed a similar pattern of window defects without evidence of leakage. Late frames (not shown) did not reveal any areas of leakage in either eye.

was normal without cell or pigment abnormalities of the cornea or iris and no Kayser-Fleischer ring. On dilated fundus exam, the patient was found to have a bilateral bull's eye maculopathy with blunted foveal light reflex and extensive mid-peripheral speckled hyper- and hypopigmentation with sharp disc margins and no optic disc pallor. Fundus imaging documented these findings along with parafoveal and patchy mid-peripheral hypoautofluorescence with corresponding fluorescein angiographic transmission defects (Fig. 1). In addition, there was perifoveal hyperautofluorescence. Optical coherence tomography demonstrated a bull's eye pattern of photoreceptor loss with retinal pigment epithelium (RPE) transmission defects and apparent anterior migration of RPE cells (Fig. 2), and kinetic visual field demonstrated a corresponding paracentral scotoma (Fig. 3). The full field electroretinogram (ERG) demonstrated generalized rod and cone dysfunction

and the multifocal ERG (Fig. 4) showed profound loss of the paracentral ring corresponding to photoreceptor loss with some central preservation of waveforms.

The patient had recently been evaluated for unexplained malaise and found to have elevated ferritin of 1271 ng/mL (normal 22–322 mg/mL) with iron saturation of 90%. Genetic work-up revealed a homozygous p.C282Y mutations in *HFE*, the most common pathogenic mutation in HH.⁶ The patient began treatment with weekly therapeutic phlebotomy, to achieve a goal of ferritin < 50 ng/mL. The patient never received deferoxamine or other chelation therapy. Subsequently, he was found to have low serum ceruloplasmin of 12 mg/dL (normal 17–54 mg/dL), mild decrease in serum copper and zinc and low 24-h urinary copper. No additional systemic findings involving the liver or heart were identified in work-ups with cardiology and

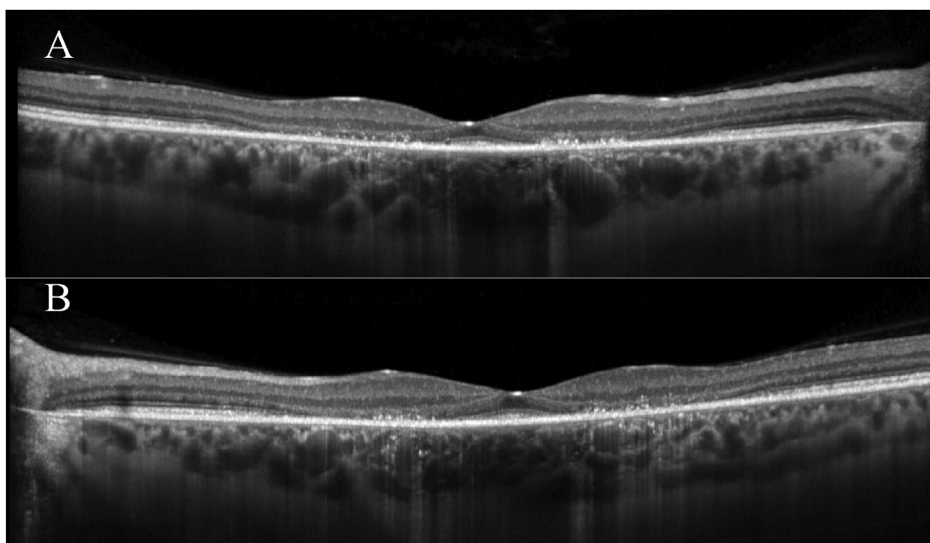


Fig. 2. Optical coherence tomography, both eyes, at presentation. Horizontal optical coherence tomography (OCT) sections (right eye, 2A; left eye, 2B), demonstrated a symmetric pattern of loss of the outer nuclear layer, external limiting membrane, and ellipsoid zone with irregularity and migrating punctate hyper-reflectivity of the underlying retinal pigment epithelium in a paracentral configuration corresponding to the bull's eye maculopathy. Intermittent hyper-transmission defects were noted in both eyes. No retinal fluid was identified in the volume scans of either eye. The vitreoretinal interface and the inner and middle retinal layers were unremarkable. Some preservation of the outer nuclear layer, external limiting membrane, and ellipsoid zone was noted centrally in each eye.

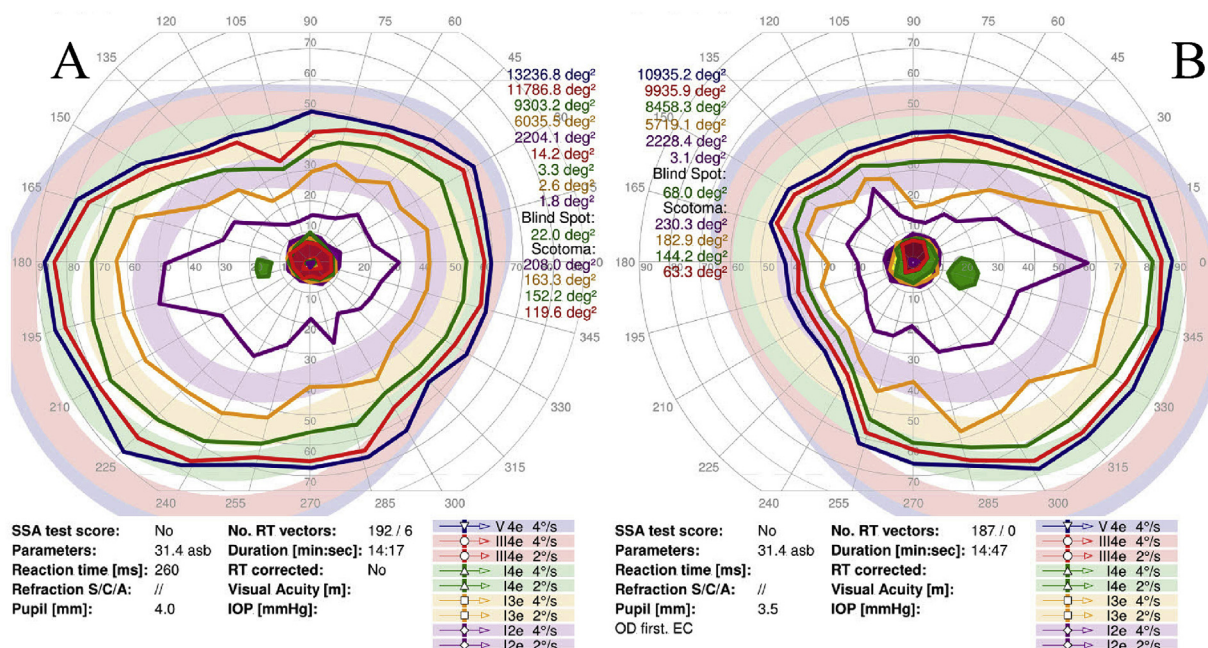


Fig. 3. Kinetic visual field, both eyes, at presentation. Octopus™ kinetic visual fields (left eye, 3A; right eye, 3B) revealed diffuse restriction of all isopters with a dense parafoveal ring scotoma in both eyes.

gastroenterology. Family history was significant for multiple relatives with cardiomyopathy and the patient's mother was found to be a compound heterozygote for two *HFE* mutations. No consanguinity was present in the patient's family history.

A genetic work-up for inherited retinal disorders was conducted using the Retinal Dystrophy Panel Plus (Blueprint Genetics, Helsinki, Finland). This was negative for a pathogenic variant consistent with this patient's phenotype among the 266 genes screened. Incidentally, the patient was found to be a carrier of a pathogenic variant in *CNGA1* (associated with autosomal recessive retinitis pigmentosa), as well as three variants of unknown significance (*PDE6B*, *COL2A1*, *PCARE*), which have not been reported as pathological and were not expected to be contributing to the clinical presentation. Whole exome sequencing (Whole Exome Family Plus, Blueprint Genetics, Helsinki, Finland) confirmed the inherited homozygous p.C282Y mutations in *HFE*, but demonstrated no other known pathological variants. Therefore, it was less likely that a heritable retinal dystrophy was responsible for the patient's clinical presentation.

At 9-month follow-up from initial presentation ferritin levels have been normalized through serial phlebotomy, and the visual acuity, clinical examination and retinal imaging all remained unchanged. The patient was referred to a low vision specialist and social worker for ongoing support.

3. Discussion

With the use of multimodal imaging and functional studies, the patient was found to have a clinical picture consistent with a subacute presentation of mixed cone-rod dysfunction in a bull's eye distribution. Genetic testing did not reveal any evidence for an inherited retinal dystrophy. Given the patient's recent diagnosis of symptomatic hereditary hemochromatosis with a homozygous p.C282Y mutation in *HFE* and significant iron overload, we postulate that the bilateral retinopathy is a consequence of his iron-overload state.

Two previous studies have demonstrated iron deposition in ocular tissues of patients with HH.^{2,3} However, there have been very few

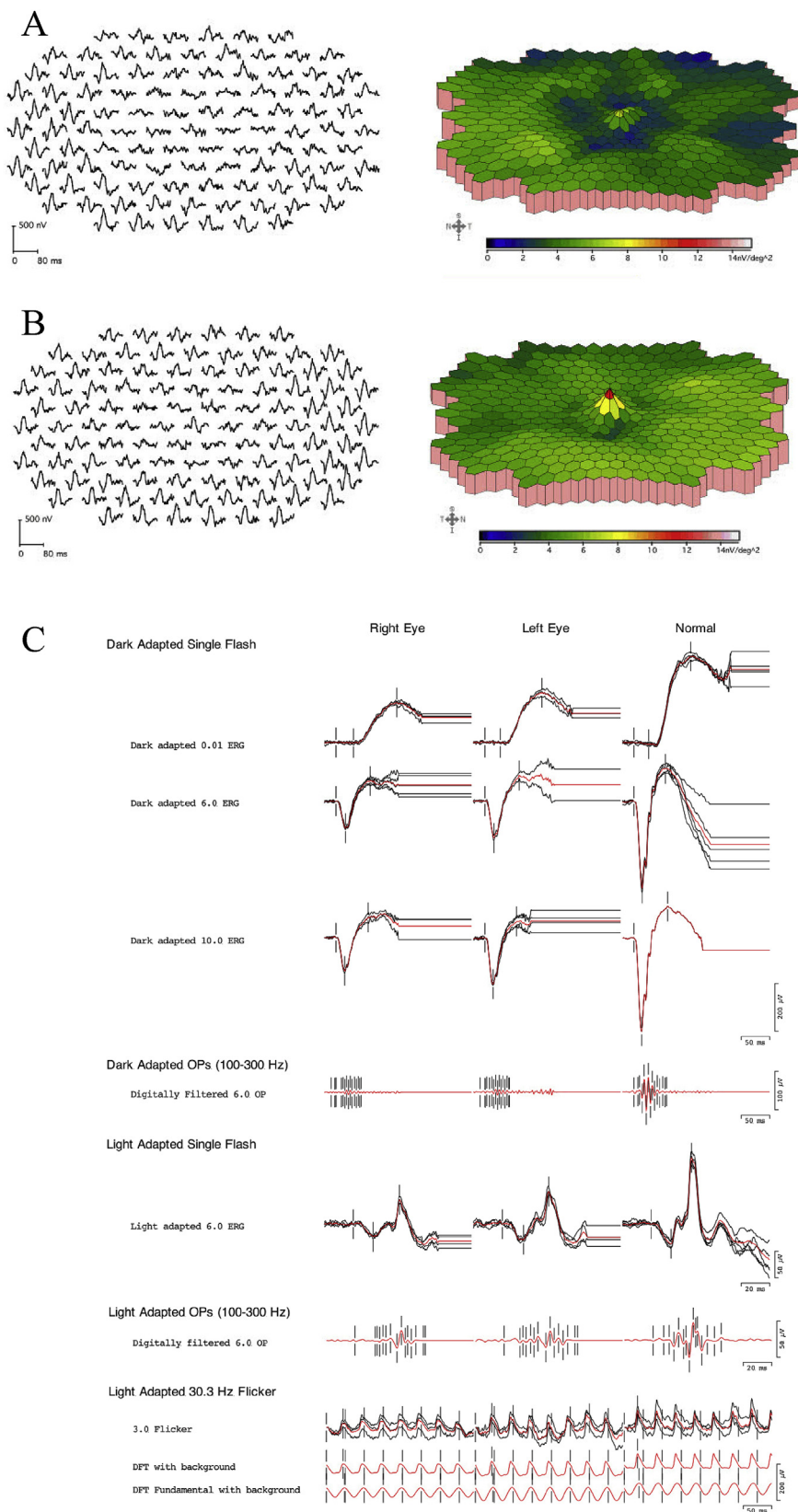


Fig. 4. Electroretinogram, both eyes, at presentation. Multifocal electroretinogram (ERG) (right eye, 4A; left eye, 4B) showed decreased amplitude densities with delayed latencies in both eyes. The full field ERG (4C) showed attenuation of the b-wave amplitude in dark and light adapted states with delayed implicit times in the dark-adapted state. The 30 Hz flicker also showed attenuated amplitude and delayed timing. Dark adapted oscillatory potentials showed severe attenuation suggestive of inner retinal dysfunction. Overall, the ERG demonstrated findings consistent with generalized dysfunction with a mixed rod-cone pattern that can be seen in genetic entities or acquired toxicities.

reports of HH in association with visual symptoms. One case report described a patient with a homozygous C282Y mutation of the *HFE* gene, who developed progressive vision loss despite maintenance of 20/20 vision in the right eye and 20/25 vision in the left eye. No additional genetic testing was performed in this patient, and serum ceruloplasmin

levels were not reported. He did not receive chelation therapy and was found to have an “unusual retinopathy” associated with hemochromatosis.⁷ One thalassemia patient with systemic iron overload due to multiple blood transfusions and treated with the iron chelator deferasirox developed a bull’s eye maculopathy, which might have been

caused by iron toxicity or by the chelator.⁸ In contrast, one case series reported 5 patients with HH who had screening eye exams following their diagnosis. All five patients had 20/20 or better vision. One patient subsequently was diagnosed with iris melanoma and underwent iridectomy, which showed no iron deposition in the uveal tissue on pathologic examination.⁴

It is unclear why the patient described in our case developed significant retinopathy, particularly given his lack of other classic pathologic findings of HH, including cardiomyopathy and diabetes. One hypothesis is that the patient's low serum ceruloplasmin levels may have facilitated a greater degree of ocular iron toxicity. We hypothesize that in the iron-overloaded state of HH with concurrent low ceruloplasmin levels, more serum iron may be in its ferrous form. This divalent form of iron is known to induce oxidative damage to cells, especially photoreceptors.⁹ Indeed, complete absence of ceruloplasmin in patients with the rare hereditary disease aceruloplasminemia causes RPE iron overload and retinal degeneration with RPE hypertrophy and atrophy, and corresponding window defects on fluorescein angiography in the macula,¹⁰ mid-periphery,¹¹ or both.^{12,13}

Mice have been used to model retinal iron accumulation and degeneration. One such model is hepcidin knockout mice, which represent a form of hereditary hemochromatosis in which the retina develops age-dependent accumulation of iron leading to RPE hypertrophy with degeneration of the overlying photoreceptors.¹⁴ A model of juvenile hemochromatosis is hemojuvelin knockout mice, which also shows age-dependent deposition of iron in the retina and RPE degeneration.¹⁵ A mouse model of aceruloplasminemia, the ceruloplasmin/hephaestin knockout mouse, also has age dependent iron accumulation in the neurosensory retina and RPE, with subsequent degeneration of both RPE and photoreceptors and subretinal neovascularization.^{16,17}

Given his low urinary copper and absence of Kayser-Fleischer rings, the patient did not have Wilson disease. Instead, it is possible that the low level of ceruloplasmin is related to HH itself. Cairo et al. demonstrated that some patients with HH have low serum ceruloplasmin compared to healthy controls and patients with acquired iron overload.¹⁸ Laine et al. also demonstrated decreased levels of serum ceruloplasmin in a cohort of men homozygous for the p.C282Y mutation in *HFE*, which subsequently normalized following serial phlebotomy with systemic iron normalization.¹⁹ In our patient, it is plausible that a combination of high serum iron due to the *HFE* mutations, and an abundance of ferrous iron due to the low ceruloplasmin, contributed to his bull's eye maculopathy. The reason for this specific pattern of iron-toxicity induced degeneration is unclear, but given the heterogeneous retinal degeneration patterns in aceruloplasminemia patients, as well as a case of early onset age-related macular degeneration following IV iron treatment in a 42 year old woman with high genetic risk for age-related macular degeneration,²⁰ it appears that the clinical manifestations of retinal iron toxicity are subject to modification by genetic and environmental factors. A remaining alternative hypothesis is the patient has a hereditary retinal degeneration undetected by the retinal dystrophy panel and whole exome sequencing. Although the whole exome sequencing study demonstrated no other known dominant pathogenic variants other than p.C282Y, the possibility remains that an unreported consequence of the carrier *CNGA1* mutation or an occult pathogenic genetic abnormality could account for these findings.

The patient's vision and retinal structure appeared stable during the follow-up period. He achieved near normalization of his ferritin levels, however his serum ceruloplasmin remains low and unchanged at 13 mg/dL following treatment with serial phlebotomy. Given disruption of the external limiting membrane and ellipsoid zone on OCT, there was a relatively limited expectation for visual recovery. Previous studies in a variety of retinal conditions, including hydroxychloroquine-associated toxicity and age-related macular degeneration, demonstrated that external limiting membrane integrity portended better visual prognosis with improved preservation of visual acuity.^{21,22} However, with normalization of the serum ferritin levels, it may be possible to halt further

progression of the retinopathy. The patient will require ongoing phlebotomy titrated to measures of iron stores, such as serum ferritin. The patient was started on copper and zinc supplementation and will require ongoing monitoring of these serum levels.

4. Conclusion

Hereditary hemochromatosis is a condition characterized by iron overload, which manifests with iron deposition in a variety of organs, including the eye. To the authors' knowledge, this is the first characterization of bull's eye maculopathy in a patient with a homozygous p.C282Y mutation causing hereditary hemochromatosis not undergoing chelation therapy which was possibly exacerbated by low serum ceruloplasmin resulting in increased redox-active ferrous iron.

Consent

Written consent to publish the case report was obtained from the patient. This report does not contain any personal information that could lead to the identification of the patient. Institutional review board approval was not sought in this case.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures.

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