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Bilateral, geographic, peripapillary, chorioretinal atrophy in a patient with porphyria cutanea tarda and high iron stores

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KEYWORDS
Porphyria cutanea tarda;
Hepatitis C virus;
Peginterferon alpha-2A with ribavirin;
Acute zonal occult outer retinopathy;
Acute idiopathic blind spot enlargement;
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Bilateral peripapillary retinal atrophy;
Lipofuscin

Abstract

PURPOSE: Porphyria cutanea tarda (PCT) is a systemic disease caused by a deficiency of the enzyme uroporphyrinogen decarboxylase, which is the fifth enzyme in the heme biosynthetic pathway. This deficiency prevents porphyrin and its byproducts from producing heme.

CASE REPORT: This case report presents a patient with PCT that is further complicated by high iron stores, chronic hepatitis C virus (HCV), and a history of alcoholism. Bilateral, geographic, peripapillary chorioretinal atrophy is evident and shows progression over a significant period despite improving the PCT.

CONCLUSION: A bilateral and progressive appearance of a retinal pathology in a middle-age male patient, with no family ocular history, suggests systemic causation. One theory includes a back flow of porphyrin byproducts from PCT. This is exacerbated by a less-than-productive liver caused by high iron stores, chronic HCV, and a history of alcoholism, which prevents the normal filtering process to occur. We believe this is the first report of a case of presumed bilateral, geographic, peripapillary chorioretinal atrophy in a patient with PCT, complicated by high iron stores, HCV, and alcoholism.
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Porphyria cutanea tarda (PCT) is a systemic disease caused by a deficiency of the enzyme uroporphyrinogen decarboxylase (UROD), which is the fifth enzyme in the "heme biosynthetic pathway."[1] This deficiency prevents porphyrin and its byproducts from producing heme. Medical literature has documented the following as the most common anterior segment clinical signs in people with porphyrias: corneal and conjunctival scarring, ectropion, scleral necrosis, hypertrichosis, and madarosis.[2] There have been no detailed retinal findings with porphyrias, or specifically PCT. Excessive serum iron can also exacerbate PCT. Iron is essential for many of the body's intracellular functions, notably in hemoglobin (HGB) production. An iron deficiency can cause anemia, whereas an excess can be toxic because of the oxidative stress. Although iron is a critical element in human metabolism, it is also a potent source of highly reactive free radicals. For example, iron in the Fe^{2+} form reacts with hydrogen peroxide (H_2O_2) in the Fenton reaction to produce highly reactive hydroxyl radicals:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH + OH^-$$

Scientific evidence has shown that abundant quantities of iron have been detected in many areas of the body as a result of unbalanced HGB synthesis. This can allow an

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undesirable accumulation of byproducts within tissues. Various conditions of increased concentrations have been found in the skin, liver, pancreas, heart, and joints.[3] These iron concentrations have been evident in hepatic cell siderosis in hemochromatosis as well as in many ocular structures, including the eyelids, cornea, and retina.[4] Because there is no major physiologic pathway for iron excretion,[5] iron overload can cause extensive tissue damage even in mild excess.[6] A few diseases that involve iron-mediated oxidative damage include Alzheimer's disease, alcohol-induced liver disease, and chronic hepatitis C virus (HCV).[6] We believe this is the first report of a case of presumed bilateral, geographic, peripapillary, chorioretinal atrophy in a patient with PCT, complicated by high iron stores, HCV, and alcoholism.

Case report

A 58-year-old black man with PCT, chronic HCV (genotype 1), and a history of alcoholism entered the eye clinic with a primary complaint of decreased near vision. The patient's records indicated his most previous dilated fundus examination (DFE), conducted 2 years previously by a civilian ophthalmologist, found unremarkable findings in both eyes. The patient denied previous ocular injuries or known surgeries. He admitted to intravenous drug use in his 30s. He additionally reported posttraumatic stress disorder, erectile dysfunction, hypertension, gastroesophageal reflux disorder, passive-aggressive personality disorder, and vertigo. Systemic medications included citalopram hydrobromide, felodipine, meclizine, ziprasidone, omeprazole, hydroxyzine amoate, and indomethacin. He denied any family history of ocular or systemic disorders, including cancer. He had no known allergies. It was found that the patient's HCV had previously been treated with a combination of peginterferon alpha-2A ([PEG-IFN] Pegasys®, Hoffman-LaRoche, Basel, Switzerland) and ribavirin (RBV). The patient was treated for a total of 4 months; however, treatment had been discontinued for 6 months before his initial DFE in our clinic.

The patient's best-corrected visual acuities (VAs) were 20/20 in the right eye (OD) and in the left eye (OS). Pupillary function, extraocular motility, confrontation visual fields (VF), and color vision were all normal. The anterior segment evaluation was unremarkable, and ocular tensions were within normal limits. DFE found optic nerve heads (ONH) with moderate cupping, healthy neuroretinal rim tissue, and no evidence of neural rim notching. Geographic retinal atrophy bilaterally radiated over time from the ONHs toward the maculae and midperiphery in a "fluid-spilled" fashion. (*See* Figures 1A and B. Note that the actual photographs, taken 20 months after the initial visit, show the progression when compared with Figures 3A and B.) Within the outline of each lesion was an orange-speckled substance. After a follow-up examination at 13 months, progression of this atrophy was documented in most directions, including the movement of the orange substance further from the ONH on the new outline. There were no inflammatory signs during any of the examinations.

Additional ocular tests were essential to assist in differentiating all possible diagnoses, as the disorder was bilateral and progressive. Subjective Amsler grid testing found a gross superotemporal defect in the OD and in the OS, an inferotemporal defect, which correlated directly with the retinal lesions. To better appreciate these defects, an automated threshold VF (*see* Figures 2A and B) showed relative scotomata surrounding the blind spot bilaterally. The right defect was fairly symmetrical inferiorly and superiorly around the blind spot. The left defect emanated from the inferior portion of the blind spot. Fluorescein angiography (FA) (*see* Figures 3A and B) found a general hyperfluorescence within each lesion through early to late stages and a speckled hypofluorescence at the edge of the lesion. Indocyanine green angiography (ICGA) (*see* Figures 4A and B) found the lesions to be hyperfluorescent and isofluorescent in various areas during the arteriovenous phase. Late stages showed no late staining. The leading edge of orange substance proved to be hypofluorescent during all stages. The fundus autofluorescent (FAF) (*see* Figures 5A and B) images showed this substance to be autofluorescent, with other autofluorescent spots within each lesion. Time-domain Stratus (software v. 4.0; Carl Zeiss Meditec, Dublin, California) ocular coherence tomography showed there was no thickening of the geographic zone within the lesion, including the edge. Findings on an electroretinogram (ERG) (*see* Figures 6A and B) proved to be abnormal. The 30-Hz flicker rate was within normal amplitude, and implicit time ranges were also within normal limits in both eyes. However, all of the other amplitudes were below normal and approximately equal for both eyes. These results were indicative of mildly attenuated cone system function and moderately attenuated rod system function in both eyes. After obtaining all information and test results, the clinic retinologist reviewed the case and agreed with the theory involving excessive serum iron levels. He was also concerned that this may have been a side effect from the combination of PEG-IFN and RBV. He did not suggest any further testing beyond what was performed.

A thorough systemic record review was performed. A recent liver biopsy found mild to moderate chronic active hepatitis. Dermatology confirmed the diagnosis of PCT by the appearance of atypical hypertrichosis and blistering in sun-exposed areas of the skin. A chest X-ray showed no lung infiltrates and no evidence of active cardiopulmonary disease.

Blood serum laboratory testing (*see* Table 1) found continuously high iron and ferritin over 5 months with normal total iron binding capacity. Results of additional laboratory testing were negative for the possible hemochromatosis genes of C282Y (accounts for $>$ 90% of clinically diagnosed hemochromatosis) and H63D. Plasma porphyrin screen had elevated levels of uroporphyrin and heptacarboxyporphyrin, and levels of the amino acid ornithine were decreased. Complete blood count was requested