Cystoid macular edema in a patient with Danon disease

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To report a patient with Danon retinopathy with cystoid macular edema treated with topical dorzolamide 2% eye drops and oral acetazolamide. A 37-year-old Caucasian man with Danon disease treated with topical and oral carbonic anhydrase inhibitors participated in the study. Examinations performed before and during treatment included visual acuity (VA), spectral-domain optical coherence tomography, and electroretinography. Following total 48 weeks of treatment, VA decreased from 20/30 OD, 20/200 OS, to 20/40 OD, CF OS. The mean central retinal thickness was unchanged from baseline 263 µm OD, 226 µm OS, after treatment 283 µm OD and 202 µm OS. In our case, carbonic anhydrase inhibitors were not effective. However, a general recommendation cannot be given based on a single case.

Key words: Carbonic anhydrase inhibitor, Danon disease, ERG, retinal disease, SD-OCT

Ophthalmic manifestations of DD include in males salt-and-pepper appearance of the midperipheral retina and loss of pigment in the retinal pigment epithelium (RPE) and in females a midperipheral pigmented retinopathy. Myopia, lens changes, abnormal visual fields, and abnormal electroretinogram have also been described. [4,5]

Case Report

A 37-year-old man of English descent presented with long-standing photophobia, reduced vision, and retinal pigmentary changes. He had infantile onset dilated cardiomyopathy requiring a cardiac transplant at age 20. He subsequently developed lymphoma in the left kidney, treated by nephrectomy and rituximab, and two bowel lymphomas treated with chemotherapy and rituximab. At age 29, he developed peripheral myopathy when DD was diagnosed on muscle biopsy. He took cyclosporin 100 mg bd, mycophenolate 500 mg bd, ramipril 10 mg daily, amlodipine 10 mg daily, pravastatin 20 mg daily, ezetimibe 10 mg daily, prednisolone 5 mg daily, and aspirin 100 mg daily.

On examination, he was highly myopic; best-corrected Snellen visual acuity (VA) was 20/30 in the right eye and 20/200 in the left eye. Slit-lamp biomicroscopy of the anterior segments was unremarkable. Fundoscopy revealed midperipheral pigmentary changes, with near-complete loss of RPE in the remaining retina. There was no posterior staphyloma in either eye. Cirrus spectral-domain optical coherence tomography (SD-OCT) (Zeiss, Germany) scanning demonstrated asymmetric macular cysts in the inner retinal layers and patchy photoreceptor loss in both maculae [Fig. 1, Table 1]. Humphrey visual field testing (Zeiss, Germany) showed bilateral central scotoma. Ishihara testing demonstrated congenital color deficiency. Full-field ERG testing was performed using a gold foil electrode according to the International Society for Clinical Electrophysiology of Vision standards (LKC Technologies, Inc.). This showed non-specific of males. Female mutation carriers show a milder phenotype. [4,5]

Danon disease (DD) (Online Mendelian Inheritance in Man 300257) is a rare, X-linked dominant disease characterized by cardiomyopathy, myopathy, and various degrees of mental retardation in males, first reported in 1981. [3]

The genetic locus for DD localizes to the lysosome-associated membrane protein-2 (LAMP2) gene. LAMP-2 protein is found in the lysosomal membrane where it is thought to protect the membrane from proteolytic enzymes and to act as a receptor for proteins imported into lysosomes. In its absence, autophagic vacuoles are seen in the heart and muscles. [2,3]

Cardiac disease in males is usually severe. In one study of 20 male patients, all patients except one died before 30 years. Implanted pacemakers and defibrillators and heart transplantation have improved life expectancy. Myopathy is typically mild and often asymptomatic. Symptomatic patients present with proximal limb muscle weakness that is slowly progressive. Mild mental retardation affects an estimated 70%

Figure 1: Fundus photographs right eye (a), left eye (b), infrared images right eye (c), left eye (d), and horizontal spectral-domain macular OCT scans at baseline right eye (e), left eye (f), and after treatment right eye (g), left eye (h) with oral acetazolamide of a patient with histologically confirmed Danon disease. These demonstrate the peppered pigmented mottling and cystic-appearing lesions within the macula with photoreceptor loss and minimal response to treatment.
abnormalities: scotopic responses were of reduced amplitude and normal implicit time; photopic responses were of normal amplitude but increased implicit time. He refused fluorescein angiography.

Treatment with the carbonic anhydrase inhibitor (CAI) dorzolamide 2% topically bd to both eyes was initiated. Following 30 weeks of treatment, the patient reported no change in central vision or glare symptoms. The fundus exams of each eye were similar to that of the baseline visit. There was no significant change in vision, central subfield thickness, or macular cube volume.

He was then treated with acetazolamide 500 mg daily while cyclosporine levels and renal function were monitored. Following 18 weeks of treatment, he reported no change in central vision or glare symptoms. Best-corrected VA was 20/40 in the right eye and CF in the left eye. Fundus exams of each eye were unchanged. Central subfield thickness, macular cube volume, and repeat ERG testing (Roland, Germany) showed no significant changes. He refused further treatments.

**Discussion**

Danon retinopathy is a rare X-linked disorder related to mutations in the LAMP2 gene. The patient showed characteristic signs of Danon retinopathy and his ERG results were typical of the disease. The patient was myopic, but the macular changes are not typical of pathologic myopic foveoschisis, typically a thickened retina at the posterior pole, with hyporeflective splitting between the outer and inner retina, or of progressive myopic maculopathy, both of which are usually detected in patients with a posterior staphyloma.[6,7]

Patients with retinal dystrophies have been reported to have both cystoid macular edema (CME) and non-CME macular cysts.[8] The patient refused fluorescein angiography, which is the diagnostic test to differentiate between CME and non-CME cysts, but the asymmetry of cystic changes seen on OCT is typical of CME associated with late hyperfluorescence on intravenous fluoresce in angiography and strongly suggests that the cysts are CME rather than non-CME cysts.[9] The CME is probably due to leakage of fluid through the RPE consequent to failure of the RPE pump. LAMP2 gene is expressed in RPE cells.[10] The reason for abnormal LAMP2 protein resulting in presumed RPE pump failure is not known. To our knowledge, this is the first reported case of CME in histologically confirmed DD.

In our case, topical dorzolamide 2% eye drops and oral acetazolamide were not effective in the treatment of CME associated with DD. The reasons for lack of effect may have included low dose of acetazolamide, limited by renal disease; pre-existing photoreceptor atrophy and long-standing visual loss, particularly in the left eye; and pre-existing RPE atrophy, given the mechanism of action of CAI via RPE acidification which helps to enhance chloride transport, and consequently water transport.[11] Also, any non-CME macular cysts may not respond to CAIs.

Lack of effect of CAI is in contrast to previous studies which have demonstrated a beneficial effect of CAIs in patients with retinal dystrophy and CME such as retinitis pigmentosa,[12] and patients with macular cysts, including X-linked retinoschisis and enhanced S-cone syndrome,[13] although some patients fail this treatment. Despite lack of response in our patient, we recommend consideration be given to carbonic anhydrase inhibition for patients with CME associated with Danon retinopathy, given the response seen in other retinal conditions with associated CME and macular cysts with this treatment. A further treatment option to consider for similar patients is intravitreal bevacizumab,[14] which this patient refused.

In conclusion, to our knowledge our patient is the first reported case of Danon retinopathy with CME. Treatment with topical or oral CAI was not effective in this patient. Danon retinopathy is a rare but important retinal dystrophy causing CME. It is suspected in males who have had a cardiac transplant and reduced vision.

**References**