Complement Proteins in the Retina in Cancer-Associated Retinopathy

Cancer-associated retinopathy (CAR) is a paraneoplastic syndrome typically associated with autoantibodies against cancer antigens that cross-react with antigens in the retina. Of the retinal autoantibodies in patients with CAR, antirecoverin is the most convincingly implicated. The autoantibodies possibly destroy photoreceptor cells through the classical complement pathway. However, to our knowledge, an evaluation of the complement pathway in patients with CAR has not been published to date. We searched for complement proteins in the retina of an affected eye.

Methods | This case series study was approved by the institutional review boards of the University of Pennsylvania and the Novartis Institutes of Biomedical Research. The boards waived the informed consent requirement from the patient’s next of kin after failure to locate them despite numerous careful and dutiful attempts.

We retrieved archived paraffin blocks of an eye of a deceased patient with CAR. We used sections of normal (without CAR) human eyes (obtained from Lions Eye Bank) as negative controls and normal human liver cells (obtained from Avaden) as positive controls. Antibodies were used to identify complement factors C3 (LS-B13028), C9 (LS-B4849), and B (LS-B13829). These antibodies were confirmed to be specific for their respective complement proteins using indirect enzyme-linked immunosorbent assay (ELISA) and a panel of 16 complement proteins (C1q,Clr,C1s,C1-INH,C2,C3,C3-H2O,C5,C6,C7,C8, and C9, as well as factors B, D, I, and P), 6 complement protein fragments (C3b, iC3b, C3c, C3d, C4a, and C4b), and 2 complement complexes (C1 and the membrane attack complex). Complement proteins in paraffin sections were detected with immunohistochemical methods similar to the standard immunohistochemistry protocol (Ventana Discovery XT; Atlas Antibodies).

Results | The patient died of metastatic mixed müllerian tumor of the uterus. About 6 months before death, a decrease in central vision and severe constriction of visual fields were observed. The serum had antirecoverin antibodies (titer of 1:3200). Histopathologic examination results of the patient’s eye obtained at autopsy showed that most of the retina had no photoreceptor cells (Figure 1; see also Figure 4 in Goldstein et al). A few areas had patches of remaining photoreceptors. With immunocytochemistry, C3 and C9 (Figure 1 and Figure 2) were clearly detectable in the layer of inner and outer segments of the surviving photoreceptors. In addition, C3 and C9 were de-
tected around the cell bodies of most retinal pigment epithelium (RPE) cells, in the regions of surviving photoreceptors and where the photoreceptors had degenerated. Factor B staining was inconclusive (Figure 2) owing to faint, patchy staining of some outer segments and around some RPE cells. C3 and C9 were detected in the endothelium of choroidal blood vessels (Figures 1 and 2). In sections of a normal human eye, no complement factor was detected in the retina or RPE, whereas the anti-C9 antibody highlighted Bruch membrane (Figure 2). Normal human liver cells had detectable C3, C9, and factor B.

Discussion | Our results indicate that complement factors were present in or around the degenerating photoreceptor inner and outer segments and the RPE in an eye with CAR. In particular, C3 and C9 were in the photoreceptors and the RPE. C3 and C9 are fundamental components of the classical complement pathway activated by antibody-antigen complexes on cell surfaces. These findings provide evidence for one of the proposed mechanisms of photoreceptor loss in CAR. Autoantibodies attach to photoreceptor cells and subsequently activate the classical complement pathway, resulting in cell lysis mediated by the membrane attack complex, of which C9 is a major component.

The reason that the photoreceptors degenerate but the RPE does not is still unknown, even though complement proteins are found around both cell types. It is possible that complement inhibitory proteins expressed by the RPE protect the RPE.5,6 Results from additional cases that support the findings of the present study may serve as a rationale for testing anticomplement drugs for this blinding disease.

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OBSERVATION

Ophthalmic and Central Retinal Artery Occlusion Following Triamcinolone Injection of the Lacrimal Gland

Central retinal artery occlusion (CRAO) can be an ophthalmic emergency; it usually is secondary to an embolus and often results in debilitating visual outcomes. Etiologies of nonarteritic CRAO include trauma, hypercoagulable states, sickle cell disease, and vasospastic migraine. Rarely, iatrogenic embolus can lead to CRAO1-4; for example, cosmetic facial filler injections, such as autologous fat, hyaluronic acid, or collagen, have been implicated.5 Herein, we discuss a unique scenario of ophthalmic artery occlusion and CRAO following periocular triamcinolone acetonide injection.

Report of a Case | A 72-year-old woman with a history of controlled hypertension, thyroid eye disease, and bilateral orbital decompression surgery underwent repeated left orbital decompression with lacrimal gland triamcinolone injection and noted vision loss on patch removal the day after surgery. Examination on postoperative day 1 noted visual acuity of counting fingers OS, positive left afferent pupillary defect, and corneal edema. At postoperative day 6, visual acuity worsened to light perception OS despite improved corneal edema. Posterior segment examination did not reveal optic disc pallor or edema but did exhibit retinal whitening, a cherry-red spot, and multiple intra-arterial yellowish plaques (Figure 1). Optical coherence tomography demonstrated hyperreflectivity and thickening of the inner and middle retinal layers corresponding to the areas of retinal whitening on examination. Fluorescein angiography showed abrupt cessation of arterial blood flow at the embolic plaques seen on examination, marked macular hypofluorescence, and nasal hyperfluorescence and hyperfluorescence (Figure 2). While the etiology was presumed to be iatrogenic triamcinolone embolus, the patient underwent urgent stroke workup. At postoperative month 1, visual acuity remained light perception OS.

Discussion | To our knowledge, only a handful of case reports exist wherein periocular steroid injection precipitated CRAO,1-4

![Figure 1. Posterior Segment Examination of Left Eye Posterior Pole](https://example.com/figure1)

Fundus imaging in the left eye demonstrated intra-arterial plaques (arrowheads) and relative macular whitening surrounding a cherry-red spot. The image was captured using the P200C Scanning Laser Ophthalmoscope (Optos).

![Figure 2. Wide-angle Fluorescein Angiography](https://example.com/figure2)

Imaging of the left eye demonstrates areas of nonperfusion distal to intra-arterial plaques (white arrowheads) noted on clinical examination. Superonasal hypofluorescence and hyperfluorescence (blue arrowhead) is shown, which was preceded by hypofluorescence in early-stage images. Macular ischemia is prominent as well as spotty choroidal perfusion nasally and superiorly. Note the delayed filling in the more temporal portion of a retinal vein (dotted circle), which is draining a nonperfused area. The image was taken at 59 seconds and was captured using the P200C Scanning Laser Ophthalmoscope (Optos).