Case Report

Effects of Disseminated Mycobacterial Infection on Age-Related Macular Degeneration

Geoffrey Collett\textsuperscript{a} Natalia Lopez\textsuperscript{b} Pedro F. Lopez\textsuperscript{b}

\textsuperscript{a}FIU Herbert Wertheim College of Medicine, Miami, FL, USA; \textsuperscript{b}Center for Excellence in Eye Care, Miami, FL, USA

Keywords
Exudative age-related macular degeneration · Mycobacterium chelonae · Disseminated infection · Autoimmune disease

Abstract
Our patient, in the 7th decade of life, presented with worsening blurry vision over 3 weeks. The pertinent history included nonexudative age-related macular degeneration, recent pulmonary mycobacterial infection, and autoimmune pancreatitis. The patient had decreased visual acuity in both eyes; the remaining findings of our examination were relatively benign. The diagnosis of bilateral exudative age-related macular degeneration was aided by ocular imaging. Not only were exudative changes confirmed, but one modality suggested an underlying occult choroiditis, which presumably fueled a local inflammatory drive leading to evolution of the disease. Given the choroiditis developed in the setting of a recent Mycobacterium chelonae infection, dissemination of the organism must be considered a potential culprit. Additionally, a chronic inflammatory state perhaps played a simultaneous immunologic role. We feel the proposed pathogenic mechanism outlined sufficiently accounts for the rare event, that is, development of subacute bilateral exudative maculopathy. The patient responded well to bilateral intravitreal aflibercept injections. After 1 month, visual acuity was found to be near baseline and ocular imaging showed significant resolution of the exudative changes. An additional follow-up 3 months after confirmed similar stability. This case required thorough investigation of seemingly unrelated components within the patient’s history. We stress the importance of obtaining appropriate documentation from fellow health care
teams when suspicious clinical presentations arise. During our investigation, we identified
cryptic retinal lesions by way of angiography – leading us to recommend usage of such
methods in complex cases. We also summarize the implemented aflibercept course and the
favorable response to such treatment.

Introduction

*Mycobacterium chelonae* is a nontuberculous mycobacterium that belongs to the sub-
class of rapidly growing mycobacteria. It has been reported to cause surgical wound infec-
tions such as keratitis following laser-assisted in situ keratomileusis – usually presenting 10
or more days after the procedure [1]. *M. chelonae* is most often associated with both pulm-
onary and disseminated disease [2]. Effects on most preexisting ophthalmic conditions such
as age-related macular degeneration have not been well described [3]. The most frequent
pulmonary symptom is cough, but hemoptysis, weight loss, and fever may also occur. Along
with clinical findings, diagnosis of *M. chelonae* infection is aided by radiologic and microbio-
logic methods. Hematogenous dissemination is rare but may occur in immunocompromised
patients with underlying conditions such as malignancy, organ transplantation, or autoim-
mune disorder [4].

Case Report

Our patient presented in the 7th decade of life with blurry vision over a 3 week time
span. The pertinent ophthalmic history included nonexudative age-related macular degen-
eration and open-angle glaucoma. The additional history revealed pancreatic insufficiency,
hypertension, and hypercholesterolemia. The medication list included latanoprost, pancrelip-
pase, losartan, and atorvastatin. The patient was unable to identify whether the symptoms
were related to one eye or both. This process had worsened gradually and primarily affected
the "middle" portion of the visual field. The patient denied associated eye pain, photophobia,
headaches, entopsias, or photopsias. The patient had not experienced any episodes of amauro-
sis fugax or syncope, nor focal neurologic deficits such as asthenia or paresthesias.

An examination 2 months previously, during a follow-up visit for glaucoma, had re-
vealed no changes in visual acuity. Furthermore, ocular imaging 10 months previously had
displayed moderate, yet stable, bilateral nonexudative age-related maculopathy with no
signs of choroidal neovascularization. Review of the systems yielded a “recent lung infection"
that had required hospitalization 3 months previously. The symptoms had been cough and
sputum production. No fevers, chills, or hypotension had been present. The patient recalled
that the causative agent had been “a cousin of tuberculosis.” A hospital evaluation at that
time had revealed mild leukocytosis and an elevated erythrocyte sedimentation rate. Chest
CT had revealed that an asymptomatic right-sided pulmonary nodule, first detected in 2008,
had increased in size. Sputum cultures and serum PCR had revealed the presence of *M. che-
lonae*. Pulmonary and infectious disease consultants had not recommended antimicrobial
treatment due to concerns about drug intolerance and toxicity. It is unclear what their pro-
posed antimicrobial regimen had been. Spontaneous resolution of the lung disease and its
symptoms had been occurring over approximately 2 months and was followed up with serial
chest CT scans.
We were also compelled to further investigate the history of pancreatic insufficiency, and the patient reported “an autoimmune problem” as the cause. We discovered that the patient had undergone excision of a pancreatic mass in 2004 and that the postoperative diagnosis had turned out to be autoimmune pancreatitis. No adjuvant immunosuppressive therapy had been implemented. The patient has been deemed stable since the procedure, with only pancreatic enzyme replacement. The literature showed that this is not an uncommon presentation – a study of 26 autoimmune pancreatitis patients found 85% to have a mass or prominence upon abdominal imaging [5]. It is important to reiterate once more that autoimmune disease has been identified as a risk factor for mycobacterial hematogenous dissemination [4].

An ophthalmic examination revealed a visual acuity of 20/200 in the right eye and of 20/80 in the left eye. Two months prior these had been 20/50 and 20/30, respectively. The Amsler grid revealed bilateral metamorphopsia and relative scotomas. The confrontational peripheral visual fields were normal. Intraocular tension was 11 mm Hg in the right eye and 10 mm Hg in the left. Slit lamp examination disclosed no signs of keratopathy or uveitis. Funduscopy revealed a clear vitreous without retinal hemorrhage, cotton wool spots, or visible choroiditis. Moderate maculopathy with drusen deposits and focal hyperpigmentation were evident bilaterally. There were also subtle bilateral retinal epithelial elevations noted. The optic nerves displayed a cup-to-disc ratio of 0.7 in both eyes.

Optical coherence tomography (OCT) 10 months prior to the visit had shown only moderate bilateral nonexudative age-related maculopathy (Fig. 1a, Fig. 2a). OCT of the right eye during the visit showed the presence of fibrovascular retinal pigment epithelial detachment consistent with a choroidal neovascular membrane and overlying subretinal fluid (Fig. 1b). Similar but more subtle findings were also evident in the left eye (Fig. 2b). Given these findings that were consistent with development of subacute bilateral exudative age-related macular degeneration, the patient was started on an intravitreal aflibercept regimen [6]. This included immediate intervention in the right eye with the same dose on the left eye 1 week later. Injections were continued bilaterally for a 3-month induction period without clinical relapse of the exudative maculopathy. One month after treatment had been initiated, the patient’s visual acuity was near baseline, and OCT imaging showed complete resolution of the subretinal fluid and a marked reduction of the fibrovascular pigment epithelial detachment (Fig. 1c, Fig. 2c). A prior study had shown improvement in visual acuity and a reduction in choroidal neovascular membrane thickness in individuals with underlying infectious/inflammatory diseases that were treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) [7]. The similarity in outcomes should garner interest in standardizing treatment for such patients through further studies.

Even with the positive outcome for our patient, we must bring forth the most interesting findings during the initial visit, which were provided by fluorescein plus indocyanine green (ICG) angiography. The fluorescein finding of stippled hyperfluorescence was consistent with choroidal neovascular membranes bilaterally (Fig. 3a, Fig. 4a, red arrow). ICG revealed larger choroidal neovascular membranes, particularly in the xanthophyll-rich foveae. More interestingly, multifocal areas of hypocyanescence within the choroidal neovascular membrane plaques were evident (Fig. 3a, Fig. 4a, green arrows). Many of these did not correspond to focal hyperpigmentation or retinal atrophy and suggested the possibility of an occult choroiditic process. Additionally, larger bilateral hypocyanescent lesions were identified in the periphery via ICG only (Fig. 3b, Fig. 4b, yellow arrows) and further added to our suspicion of cryptic choroiditis. We recommend this modality be used to assess clinically uniden-
tifiable choroiditic diseases, especially in patients with inexplicable progression of macular degeneration such as the present one.

**Discussion**

We consider the development of subacute bilateral exudative age-related maculopathy a rare occurrence. The incidence of subacute bilateral transformation from nonexudative to exudative maculopathy was not clearly defined by the literature, but the event is quite rare in our experience. The possibility that this event was secondary to *M. chelonae* dissemination is intriguing as well as likely given the prior systemic evidence of elevated white blood cell count as well as PCR findings. A prior history of autoimmune disease (pancreatitis) is also a risk factor for dissemination, despite its stable course status post surgery. We cannot discard – and, in fact, we embrace – the possibility that mycobacterial dissemination and subsequent bilateral cryptic choroiditis may have occurred, an event that tipped the scales from the patient's preexisting nonexudative macular degeneration towards the exudative variety we encountered at the time of our evaluation and intervention. In such a scenario, the resulting intense concentration of choroiditic proangiogenic factors in the subfoveal area with pre-existing drusen could have culminated in the development of concurrent subacute bilateral exudative maculopathy. The multifocal hypocyanescent choroidal lesions identified bilaterally on ICG angiography (but neither on clinical funduscopy nor using fluorescein) were in fact suggestive of a choroiditic process. Preexisting nonexudative age-related macular pathology (such as retinal pigment epithelial hyperplasia and retinal atrophy) was diagnostically confounding – since these may be similar in size and in ICG angiographic appearance [8]. However, we must reemphasize that the isolated ICG findings of multifocal hypocyanescent areas in the foveae and retinal periphery allowed for discernment of a potentially co-existing choroidal disease. Therefore, we propose that ICG angiography be considered to allow the identification of coexisting choroidal pathologies in similarly complex cases.

Hematogenous mycobacterial dissemination affecting both maculae is quite probable given that macular choroidal blood flow is among the strongest in the human body – this is necessary for heat dissipation from the focused ambient light onto the fovea. This mechanism would account for the ICG findings suggestive of cryptic choroiditis, which could significantly contribute to a local proangiogenic response. We believe a chronic inflammatory component also played a role in the pathophysiology, and the elevated erythrocyte sedimentation rate obtained in our patient could be a representation of this. This inflammatory state perhaps shared its immunologic origin with the autoimmune pancreatitis given that this entity has been associated with chronic inflammatory conditions such as multifocal fibrosclerosis [9]. VEGF secretion by transdifferentiated retinal pigment epithelial cells and macrophages appears to be the final common pathway in the transition from nonneovascular to neovascular age-related macular degeneration [10]. In the setting of Mycobacterium-induced choroiditis, we hypothesize that partially transdifferentiated retinal pigment epithelial cells over the nonexudative drusen deposits in our patient may have been triggered to complete their VEGF-secreting transformation by proangiogenic cytokines such as tumor necrosis factor-α, interferon-γ, and interleukin-6 [11, 12]. In a potentially important manner, proangiogenic M2 macrophages – which are more prominent in chronic inflammatory states (and thus in chronic choroiditis) – may have further contributed to the choroidal neovascular diathesis [13]. However, no laboratory tests were obtained to confirm elevated levels of M2 macrophages. This perfect immunologic storm may have ultimately culminated in the bur-
geoning of simultaneous bilateral exudative age-related macular degeneration from a pre-existing nonexudative disease.

We believe this case is unique in that it defines a discrete trigger of what would otherwise be a transformation of nonexudative to exudative age-related maculopathy. The “discrete trigger” hypothesis is supported by the temporal relationship between development of simultaneous subacute bilateral choroidal neovascular membranes, pulmonary mycobacterial infection with systemic laboratory findings, and imaging results suggestive of choroiditis. The favorable outcome for this patient following anti-VEGF therapy in the setting of inflammatory choroidal neovascularization is not fully understood. We humbly hope our hypothesis provides insight into the grand mechanism at work. We also hope this novel case brings further attention to the development of optimal treatment regimens for patients suffering from choroiditis-induced – or, more generally, inflammation-mediated – exudative age-related macular degeneration.

**Statement of Ethics**

Personal identifiers were removed because consent to publishing such information was not obtained.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

**References**

1. Chang MA, Jain S, Azar DT: Infections following laser in situ keratomileusis: an integration of the published literature. Surv Ophthalmol 2004;49:269–280.
2. Wallace RJ Jr, Brown BA, Onyi GO: Skin, soft tissue, and bone infections due to *Mycobacterium chelonae chelonae*: importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. J Infect Dis 1992;166:405–412.
3. Moorthy RS, Valluri S, Rao NA: Nontuberculous mycobacterial ocular and adnexal infections. Surv Ophthalmol 2012;57:202–235.
4. Ingram CW, Tanner DC, Durack DT, Kernodle GW Jr, Corey GR: Disseminated infection with rapidly growing mycobacteria. Clin Infect Dis 1993;16:463–471.
5. Raina A, Yadav D, Krasinskas AM, et al: Evaluation and management of autoimmune pancreatitis: experience at a large US center. Am J Gastroenterol 2009;104:2295–2306.
6. Ng EW, Adams AP: Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Can J Ophthalmol 2005;40:352–368.
7. Rouvas A, Petrou P, Douvali M, et al: Intravitreal ranibizumab for the treatment of inflammatory choroidal neovascularization. Retina 2011;31:871–879.
8. Lopez PF, Grosfeldt HE, Lambert HM, et al: Pathologic features of surgically excised subretinal neovascular membranes in age-related macular degeneration. Am J Ophthalmol 1991;112:647–646.
9. Kamisawa T, Funata N, Hayashi Y, et al: Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut 2003;52:683–687.
10. Lopez PF, Sippy BD, Lambert HM, Thach AB, Hinton DR: Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. Invest Ophthalmol Vis Sci 1996;37:855–868.
11. Brogi E, Wu T, Namiki A, Isner JM: Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. Circulation 1994;90:649–652.
Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ: Interleukin 6 induces the expression of vascular endothelial growth factor. J Biol Chem 1996;271:736–741.

Cao X, Shen D, Patel MM, et al: Macrophage polarization in the maculae of age-related macular degeneration: a pilot study. Pathol Int 2011;61:528–535.

**Fig. 1.** Optical coherence tomography images of the right eye 10 months prior to the visit (a), at the sentinel visit (b), and 1 month after the visit (c). There was evidence of a fibrovascular neovascular membrane and overlying subretinal fluid (b, yellow arrow). Note that 10 months previously there had been no such evidence (a), and complete resolution of this process had taken place 1 month after having started aflibercept treatment (c).
Fig. 2. Optical coherence tomography images of the left eye 10 months prior to the visit (a), at the sentinel visit (b), and 1 month after the visit (c). There was evidence of a fibrovascular neovascular membrane and overlying subretinal fluid, more subtle than in the right eye (b, yellow arrow). Note that 10 months previously there had been no such evidence (a), and complete resolution of this process had taken place 1 month after having started aflibercept treatment (c).
Fig. 3. Fluorescein plus indocyanine green (ICG) angiograms of the right eye.  

**a** Central area.  
There was stippled hyperfluorescence on the fluorescein angiogram consistent with a choroidal neovascular membrane (a, red arrow).  
The ICG angiogram showed multiple hypocyanescent plaques within the choroidal neovascular membrane (a, green arrows) suspicious for an occult choroiditic process.  
The peripheral ICG angiogram revealed larger areas of hypocyanescence (b, yellow arrows), increasing our suspicion.
**Fig. 4.** Fluorescein plus indocyanine green (ICG) angiograms of the left eye. **a** Central area. **b** Peripheral area. There was stippled hyperfluorescence on the fluorescein angiogram consistent with a choroidal neovascular membrane (**a**, red arrow). Centrally located hypocyanescent plaques were identified on the ICG angiogram (**a**, green arrows). The ICG angiogram showed peripheral hypocyanescent lesions as well (**b**, yellow arrows). Both ICG findings are suggestive of an occult choroiditic process.