AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Clinical and Histopathologic Ocular Findings in Disseminated *Mycobacterium chimaera* Infection after Cardiothoracic Surgery

Sandrine A. Zweifel, MD,[1] *Daniela Mihic-Probst, MD,*[2] *Christine A. Curcio, PhD,*[3] *Daniel Barthelmes, MD, PhD,*[1,4] *Andrea Thielken, MD,*[2] *Peter M. Keller, MD,*[5,6] *Barbara Hasse, MD,*[7,*] *Christian Böni, MD*[1,*]

Purpose: To investigate and characterize clinical and histopathologic ocular findings in patients with disseminated infection with *Mycobacterium chimaera*, a slow-growing nontuberculous mycobacterium (NTM), subsequent to cardiothoracic surgery.

Design: Observational case series.

Participants: Five white patients (10 eyes).

Methods: Analysis of clinical ocular findings, including visual acuity, slit-lamp biomicroscopy, spectral-domain optical coherence tomography (SD OCT), fundus autofluorescence (FAF), and fluorescein angiography/indocyanine green (ICG) angiography findings, of patients with a disseminated *M. chimaera* infection. Biomicroscopic and multimodal imaging findings were compared with the histopathology of 1 patient.

Main Outcome Measures: Clinical and histopathologic ocular findings of *M. chimaera*.

Results: The mean age of the 5 male patients, diagnosed with endocarditis or aortic graft infection, was 57.8 years. Clinical ocular findings included anterior and intermediate uveitis, optic disc swelling, and white-yellowish choroidal lesions. Multifocal choroidal lesions were observed bilaterally in all patients and were hyperfluorescent on fluorescein angiography, hypofluorescent on ICG angiography, and correlated with choroidal lesions on SD OCT. The extent of choroidal lesions varied from few in 2 patients to widespread miliary lesions in 3 patients leading to localized choroidal thickening with elevation of the overlying retinal layers. Spectral-domain optical coherence tomography through regressing lesions revealed altered outer retinal layers and choroidal hypertransmission. The ocular findings were correlated with the course of the systemic disease. Patients with few choroidal lesions had a favorable outcome, whereas all patients with widespread chorioretinitis died of systemic complications of *M. chimaera* infection despite long-term targeted antimicrobial therapy. Ocular tissue was obtained from 1 patient at autopsy. Necropsy of 2 eyes of 1 patient revealed prominent granulomatous lymphohistiocytic choroiditis with giant cells.

Conclusions: *M. chimaera* infection subsequent to cardiothoracic surgery is a novel entity that has been recently described. It involves multiple organ systems and can cause life-threatening disseminated disease. The ocular manifestations documented using multimodal imaging allow us to use the eye as a window to the systemic infection. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology*

Mycobacterium chimaera is a slow-growing nontuberculous mycobacterium (NTM) pertaining to the *Mycobacterial avium* complex.[1] *M. chimaera* was identified as a species within the *M. avium* complex in 2004. Nontuberculous mycobacteria have been recovered from drinking water in patients' households and other environmental sources, including soil, food, dust, aerosols, and animals.[2,3] *M. chimaera* infections usually cause respiratory infections and disseminated infections among immunocompromised patients. Outbreaks of *M. chimaera* infections recently were reported among patients who underwent cardiovascular surgery in Switzerland,[4,5] in other European countries,[6,7] and in the United States.[8] Many of these cases were linked to airborne contamination of heater-cooler units used during extracorporeal circulation.[9,10] *M. chimaera* has been implicated in prosthetic heart valve, prosthetic aortic graft, and disseminated infections among patients undergoing heart surgery.[4,5] Before this outbreak, mycobacterial cultures have not been part of the routine microbiological workup in the case of cardiovascular infections. On the basis of international experience (prevalence, 2 cases per million), we estimate that additional cases may continue to be identified over the coming years, given the long incubation period. Currently, there are no guidelines for the treatment of serious *M. chimaera* infections. Surgical excision of the infected cardiovascular device together with a combination of antimicrobial agents directed against *M. chimaera* is recommended, depending on susceptibility testing.[5]

http://dx.doi.org/10.1016/j.ophtha.2016.09.032
ISSN 0161-6420/16

These infections seem to have a preference for ocular involvement.[5] We present 5 cases of bilateral chorioretinitis associated with disseminated *M. chimaera* infections that were acquired during cardiopulmonary bypass surgery. We used multimodal chorioretinal imaging and histopathology for patient workup.

Methods

Case Detection

As of February 2015, a total of 6 patients with *M. chimaera* infection who had undergone cardiothoracic surgery at the Zurich Heart Center were identified. Methods of case identification have been described.[4,9] On the basis of a thorough histopathologic analysis of cardiac tissue in the first patient, *M. chimaera* could be identified by polymerase chain reaction (PCR).[4] In the subsequent patients, diagnosis was based on positive mycobacterial tissue cultures, 16SrRNA PCR, or mycobacterial blood cultures.[5]

We were able to obtain ophthalmologic findings in 5 of 6 patients treated at the University Hospital Zurich. One patient (case 1) of this series died before ophthalmological examination and is not described in this article. We collected ophthalmological information at baseline (diagnosis of systemic *M. chimaera* infection) and during prospective follow-up. In addition, data on the index surgery and data on the treatment course and outcome were collected. Institutional review board approval (Ethics Committee of the University of Zurich, BASEC-Nr. PB_2016-00264) was obtained, and all patients gave informed consent to publish their clinical data.

Ophthalmological Examinations

All patients underwent a complete ophthalmological examination, including biomicroscopy, color fundus photography including ultrawide-field photography using an Optomap scanning laser ophthalmoscope (Optos, Marlborough, MA), spectral-domain optical coherence tomography (SD OCT) including enhanced depth imaging (EDI), fundus autofluorescence (FAF) imaging, and fluorescein angiography/indocyanine green (ICG) angiography. The wide-field angiograms were obtained with the Optomap system or the ultrawide-field module for the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany).[11] The SD OCT and EDI optical coherence tomography (OCT) images were obtained with the Heidelberg Spectralis (version 1.9.10.0) as viewed with the contained Heidelberg software (Spectralis Viewing Module 6.0.9.0; Heidelberg Engineering). In this study, at least 31 B-scans were obtained within a $20^\circ \times 25^\circ$ rectangle centered on the macula, with the scan pattern adapted according to the location and size of the lesions. Choroidal imaging was obtained using the same instrument in EDI mode.[12] The FAF images were obtained in all patients using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph, HRA2; Heidelberg Engineering). In addition, automated static perimetry (60°, 169 stimuli; Octopus; Haag Streit, Köniz, Switzerland) was performed in all patients. The size of the lesions was measured on ICG angiograms.

The presence of any pathologic ocular findings, such as keratitis, uveitis, optic disc swelling, and retinal or choroidal abnormalities, was recorded. For classification of uveitis, criteria of the Standardization of Uveitis Nomenclature Working Group were applied.[13] In addition, the presence of any fluid on SD OCT was noted. After diagnosis of ocular involvement, eye examinations were performed at least every 3 to 4 months.

Histopathology

An autopsy was performed in 1 patient who died in the setting of a disseminated *M. chimaera* infection (case 5). A necropsy of his enucleated eyes was performed 41 hours after death. The relatively long death-to-preservation time occurred because the patient died in another hospital. After fixation in buffered 4% formalin, the right globe was sagittally, and the left globe was horizontally bisected and placed in a tissue processor. As soon as the tissue had been dehydrated and infiltrated with paraffin, the globes were cut into 2-mm slices before being embedded in paraffin. Slides 2-μm thick were cut and stained with hematoxylin-eosin, Brown–Brenn, periodic acid–Schiff, Grocott, Ziehl–Neelsen, and auramine-rhodamine. Immunohistochemistry was performed using an automated immunostainer (Ventana Medical Systems, Tucson, AZ), using antibodies against T-helper cells (anti-CD4, clone SP35, dilution 1:10; Ventana-Roche), cytotoxic T-cells (anti-CD8, clone C8/144/B, dilution 1:10; DAKO A/S, Glostrup, Denmark), macrophages (anti-CD68, clone PG-M1, dilution 1:50; DAKO A/S), and granulocytes (anti-MPO, dilution 1:200; NeoMarkers/Lab Vision Corp., Fremont, CA).

Microbiologic Investigation

We used the MGIT 960 microbiology system (Becton Dickinson and Co., Sparks, MD) and Middlebrook 7H11 agar plates incubated at 37°C for 7 weeks or until positive. Sequencing for the *16S* rRNA gene was performed as described by Peter-Getzlaff et al.[14] In addition, *Mycobacterium* genus–specific PCR was performed.[15]

Results

Patient Characteristics

Five white patients (10 eyes) aged between 51 and 65 years were examined. All patients were diagnosed with endocarditis or aortic graft infection with *M. chimaera* after cardiothoracic surgery with extracorporeal circulation performed in Zurich between June 2008 and May 2012. All patients had serology negative for human immunodeficiency virus. The median duration from cardiac surgery to diagnosis of *M. chimaera* infection was 20 months (range, 16–42 months). The median duration from cardiac surgery to diagnosis of ocular inflammatory abnormalities was 25 months (range, 20–63 months). The median follow-up duration after diagnosis of ocular abnormalities was 13 months (range, 1–21 months). All intraocular pressure measures were normal at all eye visits, with values between 9 and 19 mmHg. As of May 2016, 3 of these 5 patients had died of systemic complications related to uncontrolled *M. chimaera* infection despite prolonged antimicrobial therapy. Antimicrobial therapy consisted of clarithromycin, rifabutin, ethambutol, with or without amikacin, or moxifloxacin (Table 1).

Clinical Ocular Findings

Clinical ocular findings included mild anterior and intermediate uveitis, optic disc swelling, and white-yellowish choroidal lesions suggestive of chorioretinitis. The extent of the choroidal lesions varied from few choroidal lesions (2–5/eye) in 2 patients (cases 3 and 4) (Fig 1) to progressive and widespread lesions in 3 patients (cases 2, 5, and 6) (Figs 2–4). A detailed description of the ophthalmologic findings of each patient is given next, starting with the 2 patients with mild ocular abnormalities (cases 3 and 4) (Fig 1).