



Multifocal Chorioretinal Scars Among People Infected With *Coccidioides immitis*

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Background

Coccidioidomycosis, the disease resulting from infection by the fungus *Coccidioides immitis*, generally produces a self-limited respiratory pneumonia. In around 10% of cases, there is a dissemination of fungi beyond the lungs that causes a myriad of systemic disorders. Disseminated infections of the eye are rare, but can cause a spectrum of ophthalmic problems including endophthalmitis and anterior uveitis.^{1-4,9,11} Uncontrolled infection can result in severe ocular disease and blindness.³

In a comprehensive literature review, Chopra and Sklar reported that ocular involvement in *C. immitis* infection occurs in .5% of cases.¹⁵ In contrast, Rodenbiker found that 5 individuals in a series of 54 coccidioidomycosis patients had inactive multifocal chorioretinal scarring, distinct from the better-appreciated coccidioidal choroiditis or endophthalmitis seen occasionally in severely ill patients with systemic disease.^{12,13} This uncontrolled study did not confirm that these lesions were specific to coccidioidomycosis.

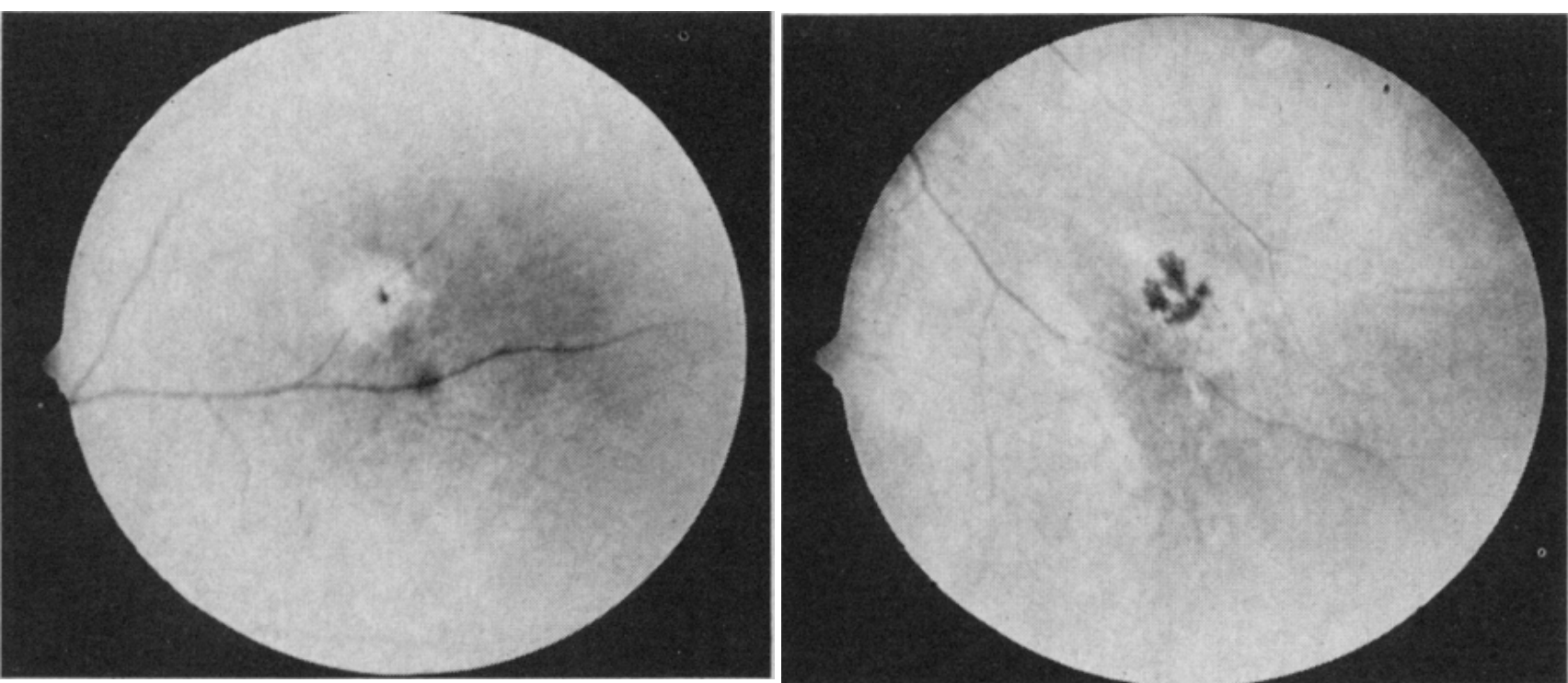


Fig. 1 Fundoscopic images from the Rodenbiker study showing findings of inactive chorioretinal scarring.¹³

It has been noted that these lesions are similar to those that are epidemiologically linked to infection by *Histoplasma capsulatum*, a fungus endemic to the Ohio River Valley.

Over the past 40 years since Rodenbiker's study, there have been a small number of isolated case reports describing incidental findings of the lesions described by Rodenbiker. One of us, AAC, continues to see chorioretinal lesions from patients in Bakersfield, where the prevalence of population seropositivity for *C. immitis* infection is estimated to be 50%. To date, these lesions have only been described in people who have had serious clinical disease. In some cases these lesions have been incidental findings, suggesting that, if they were sites of infection, they became inactive without local antifungal treatment. A better understanding of these inactive scars and their relationship to *C. immitis* infection would have implications for understanding whether asymptomatic individuals can have disseminated infection without clinically-apparent disease.

Research Plan

We have begun a multidisciplinary research program to study the effects of *C. immitis* infection on the eye. Our phases will occur as follows:

Phase 1: Comprehensive literature review and establishment of a case definition

Phase 2: Formulate a study design

Phase 3: Prospectively screen infected patients and test positive case definition

Phase 4: Create control group

Phase 5: Statistical analysis and evaluation of host and disease factors

To date, we have accomplished a comprehensive review of the literature to highlight the gap in understanding of ocular involvement in coccidioidomycosis. Reported cases of chorioretinal scarring are displayed (Table 1). We also succeeded in establishing a case definition (See "Case Definition").

Report	Location	Age	Sex	Race/Ethnicity	Employment	Ocular Sx	Non-Ocular Sx	Tx
Blumenkranz et al, 1977	San Joaquin Valley, CA	24	M	Native American	N/A	None initially, progressing to metamorphopsia	Erythematous rash, fever, cough, chest pain	Amphotericin B, miconazole
	Santa Clara, CA	48	M	White	N/A		Malaise, chest pain, SOB, dyspnea	Intravenous/intrathecal amphotericin B, oral ketoconazole
Rodenbiker et al, 1981	Tucson, AZ	36-44	M	White	Veteran	None	Non-disseminated respiratory	N
	Tucson, AZ	36-44	M	White	Veteran	None	Non-disseminated respiratory	N
	Tucson, AZ	36-44	M	White	Veteran	None	Non-disseminated respiratory	N
							Pulmonary and pleural involvement with cavitation and lobar collapse, synovial involvement of the wrist and ankle, kidney involvement.	Amphotericin B
	Tucson, AZ	36-44	M	White	Veteran	None		
	Tucson, AZ	36-44	M	Asian/Hispanic	Veteran	None	Non-disseminated respiratory	N
Nordstrom et al., 2019	Bakersfield, CA	27	M	Filipino	N/A	Decreased vision	Weakness, back pain, lymph node masses, paraspinal masses	Intravitreal amphotericin B deoxycholate, systemic amphotericin B
							Fever, night sweats, fatigue, and generalized weakness	
Quinlan & Gill, 2020	AZ	40	M	N/A	N/A	Decreased visual acuity		Fluconazole, voriconazole

Table 1 Comparison of demographic factors noted in case reports of presumed coccidioidal chorioretinal scarring.

With regard to Phase 2, we selected a case-control design (See Table 2). With our matching criteria and case definition, we hypothesize that there will be few or no patients with similar lesions in the control group. Case-control matching criteria will include: age, sex, race/ethnicity, occupation, time spent in *C. immitis* endemic area, and treatment for coccidioidomycosis. Subjects having lived in the Ohio River Valley will be excluded to avoid possibility of conflating lesions of interest with those related to Presumed Ocular Histoplasmosis Syndrome.

For our third phase, we propose to carry out a prospectively designed study in collaboration with the Valley Fever Institute at Kern Medical. We plan to screen 62 patients known to be *C. immitis* infected in order to confirm the prevalence of these lesions as described in previous studies and to test our case definition. We will use this data to recalculate our sample size to match the prevalence determined in our findings.

In Phase 4, we plan to examine a consecutive series of at least 124 people undergoing cataract surgery at the offices of Dr. David Hair. We propose testing them for evidence of infection with serologic tests and skin tests to create our group of controls. They will be tested for seropositivity as part of their pre-op prep. Each will have a detailed fundus examination if they are determined to be *C. immitis* infected. We will continue screening until we have assembled an appropriate control group based on the matching factors described in Figure 2.

Finally, for our fifth phase we will perform statistical analysis to determine if these lesions are associated with *C. immitis* infection. If we can prove a correlation, we will assess our patients for relationships between lesions and host and infection-related factors that are associated with chorioretinal lesions. If we find potentially important differences that haven't achieved statistical significance, we will do sample size calculations to confirm significance.

Prevalence of Retinal Scarring Controls	Prevalence of Retinal Scarring Cases	N- Cases (Unmatched Design)	N- Cases (Case-Control 1:1)
0.01%	5%	160	84
0.01%	10%	80	41
0.50%	5%	220	160
0.50%	10%	90	62
2.00%	5%	600	560
2.00%	10%	150	120

Table 2 Statistical estimation of number of subjects needed to determine association between lesions and *C. immitis* infection. We have selected the highlighted Case-Control scenario, and subject number to reflect 80% power at $p=.05$.

Case Definition

Peripheral, scattered, punched-out lesions generally less than a 1/3 disc diameter with sharp demarcation and varying degrees of pigmentation, often with gray-white material indicating fibrosis and gliosis at the base.

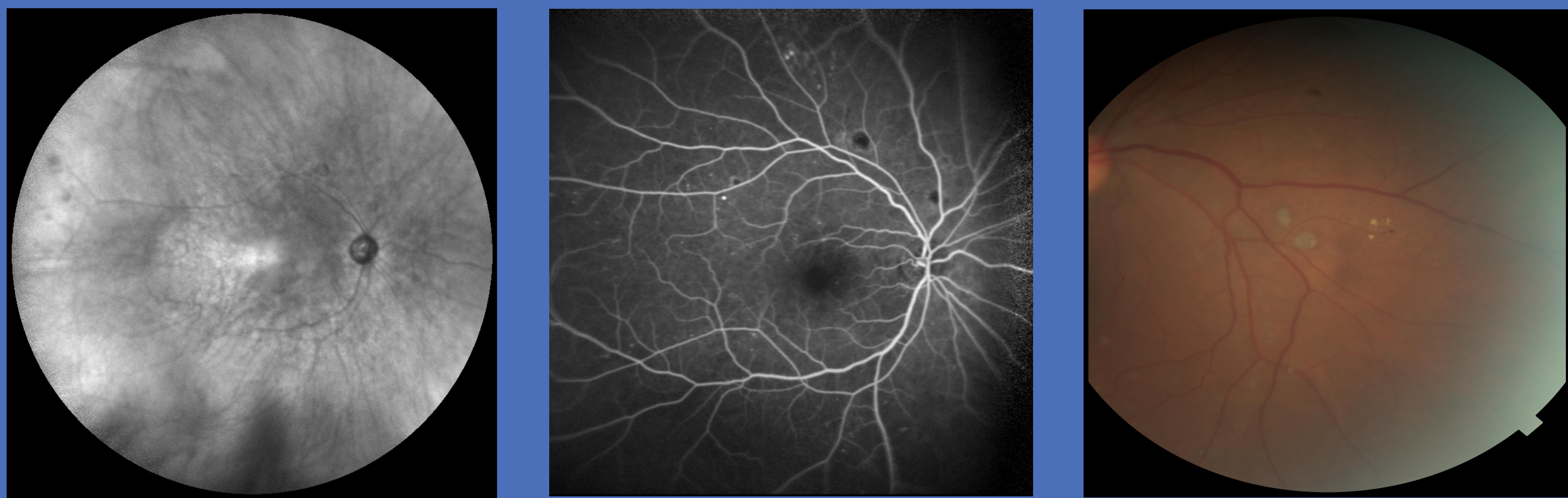


Fig. 2 Representative cases provided by Alessandro A. Castellarin, M.D.

Projected Timeline

We anticipate completion of this project over the next 2 years:

- 1) At the time of this presentation, Phases 1 and 2 have been completed.
- 2) Phase 3 is projected to be completed over the next 6 months (Feb 2022)
- 3) We hope to complete Phase 4 over the course of 12 months (Feb. 2023)
- 4) Phase 5 will be completed in 6 months (Aug. 2023)

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