Relentless Placoid Chorioretinitis

A New Entity or an Unusual Variant of Serpiginous Chorioretinitis?

B. Eric Jones, MD; Lee M. Jampol, MD; Lawrence A. Yannuzzi, MD; Michael Tittl, MD; Mark W. Johnson, MD; Dennis P. Han, MD; Janet L. Davis, MD; David F. Williams, MD

Objective: To characterize an unusual clinical entity resembling acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and serpiginous choroiditis but with an atypical clinical course.

Patients: We describe 6 patients, aged 17 through 51 years, exhibiting this unusual entity who were seen at 6 different centers from 1984 to 1997.

Results: The acute retinal lesions in this series were similar to those of APMPPE or serpiginous choroiditis, both clinically and on fluorescein and indocyanine green angiography. However, the clinical course, number of lesions, and location of these lesions were atypical. These patients had evidence of numerous posterior and peripheral retinal lesions predating or occurring simultaneously with macular involvement. Older, healing pigmented lesions were often accompanied by the appearance of new active white placoid lesions. Additionally, these cases all demonstrated prolonged periods of activity resulting in the appearance of more than 50 and sometimes hundreds of lesions scattered throughout the fundus. Growth of subacute lesions and the appearance of new lesions continued for 5 to 24 months after initial examination, and relapses were common.

Conclusions: This entity has clinical features similar to APMPPE and serpiginous choroiditis but has a prolonged progressive clinical course and widespread distribution of lesions. It may represent a variant of serpiginous choroiditis or may be a new entity. We call it relentless placoid chorioretinitis.

Arch Ophthalmol. 2000;118:931-938

PATIENTS WITH acute posterior multifocal placoid pigment epitheliopathy (APMPPE) usually have bilateral posterior creamy white lesions at the level of the retinal pigment epithelium (RPE) and a self-limited monophasic clinical course, usually lasting 1 or 2 months at most.1,3 Permanent visual loss is usually mild. In contrast, a more long-term relapsing clinical course is typical of serpiginous choroiditis.6,8 The acute lesions of serpiginous choroiditis are usually present in the macula or peripapillary areas and are often active in only 1 eye at a time. Multiple recurrences are seen over a period of years in patients with serpiginous choroiditis as activity progresses across the posterior pole in a contiguous or a multifocal fashion. Healing of the lesions in this entity may occur slowly and show more extensive choroidal atrophy than seen with the lesions of APMPPE. When patients with serpiginous choroiditis have foveal involvement, there may be a more profound loss of vision than with APMPPE. A few patients have overlapping clinical features that make it difficult to characterize them as having APMPPE or serpiginous choroiditis.

We describe a group of 6 patients with a fundus disorder resembling both APMPPE and serpiginous choroiditis with an atypical clinical appearance and course. This may be a novel clinical entity or may represent an atypical clinical appearance and course for serpiginous choroiditis.

REPORT OF CASES

The patients described in this article were examined and followed up from 1984 to 1998 (Table). They were noted to have unusual clinical features that challenge conventional diagnoses. The period of clinical follow-up for these patients was 6 to 65 months (mean, 20 months). Our study consisted of a retrospective review of the medical and photographic records of this cohort.

CASE 1

A 46-year-old woman had throbbing discomfort in the left eye. Her history was remarkable for a flare-up of recurrent genital
herpesvirus type 2, 10 days prior to examination. Her visual acuity was 20/20 OU. Mild left conjunctival hyperemia was seen with a few cells present in the anterior chamber and anterior vitreous. Findings from fundus examination showed several small white placoid lesions at the level of the RPE in the far periphery of the left eye, some with early pigmentation. The right eye was completely normal. The patient was referred to us 2 days later with macular lesions apparent in the left eye (Figure 1, A).

Findings from a systemic medical workup revealed a history of exposure to herpes simplex (antiherpes simplex IgG titer, 1:16), cytomegalovirus (anticytomegalovirus IgG titer, 1:32; IgM titer, 1:16), varicella zoster virus (antivaricella zoster virus IgG titer, >1:32; IgM titer, <1:16), and toxoplasmosis (anti-toxoplasma IgG titer, >1:128; IgM titer, <1:16). Findings for Lyme disease, Bartonella species, and human immunodeficiency virus were negative. Other unremarkable study findings included those for rapid plasma reagin, fluorescent treponemal antibody-absorption, angiotensin-converting enzyme, chest x-ray film, and orbital magnetic resonance imaging.

The patient was seen 4 days later with additional lesions noted in the left macula (Figure 1, B). Fluorescein angiography showed early hypofluorescence with later staining. There was increased pigmentation of peripheral lesions. Topical corticosteroids and oral acyclovir, 800 mg, 5 times per day, were administered. Three days later, an increased number of active white lesions and growth of the subacute lesions were seen. This progression together with a recent history of genital herpesvirus type 2 prompted treatment with intravenous (IV) foscarnet sodium, 4900 mg every 12 hours, and ganciclovir sodium, 280 mg IV every 12 hours. Despite this therapy, the patient worsened with appearance of new retinal lesions and growth of older lesions. Twelve days after initial examination, her visual acuity decreased to 20/40 OS and an area of serous fluid was seen in the macula (Figure 1, C). Indocyanine green angiography was performed, which showed discrete areas of hypofluorescence (Figure 1, C) while fluorescein angiography showed enlargement of the areas of early hypofluorescence and later hyperfluorescence (not shown). Oral prednisone, 30 mg/d, was administered with an improvement in visual acuity to 20/25 OS noted within 12 hours. There was stabilization of vision and lesions. Intravenous ganciclovir and foscarnet were discontinued and oral famiciclovir was administered at 500 mg, 3 times per day. During the next 4 weeks, a gradual tapering of prednisone to 15 mg/d was performed. The patient then noted distorted images in the affected eye with visual acuity decreased to 20/60 OS. New active retinal lesions were present. Prednisone administration was increased to 80 mg/d and then gradually tapered. Visual acuity fluctuated during this time between 20/20 OS and 20/30 OS.

Nine weeks after initial examination, new active retinal lesions were again noted while the patient was receiving prednisone, 30 mg/d. These lesions were associated with increased vitreitis, sectorial optic nerve swelling, and small intraretinal hemorrhages (Figure 1, D). Prednisone administration was increased to 50 mg/d and continued at this dose for 1 month, with gradual control of activity noted. Famciclovir administration was discontinued. The patient began experiencing complications of long-term prednisone treatment with notable weight gain, sensitivity of the palms and soles, and corticosteroid facies. Cyclosporine, 100 mg/d, was administered to attempt to control activity and allow tapering of the corticosteroids. During the next year, prednisone administration was gradually tapered, but the patient still received cyclosporine without the appearance of new active lesions.

This patient again noted decreased visual acuity 15 months after initial examination with a diffuse corneal infiltrate noted in the left eye. Anterior stromal keratitis, possibly secondary to herpes simplex, was seen and responded well to topical corticosteroids. Cyclosporine administration was gradually tapered. The patient’s current visual acuity is 20/20 OU, 30 months after initial examination. There are more than 100 healed inactive lesions in the left eye (Figure 1, E). She is presently not receiving prednisone or cyclosporine. The right eye has remained free of lesions.
CASE 2

A 26-year-old man complained of decreased vision in the left eye with paracentral distortion and visual field loss beginning 1 month prior to initial examination. His visual acuity was 20/20 OD and 20/40 OS. He had a history of a nonspecific upper respiratory tract infection 6 weeks earlier, which was treated with ampicillin. On ex-

Figure 1. Case 1. A, B, C, Appearance of left fundus at initial examination. Healing pigmented and active lesions are present in the periphery, anterior to the equator. New active placoid lesions are seen in the macula at the level of the retinal pigment epithelium. Color photograph of the left eye (D) with fluorescein angiogram, mid-phase (E) at 40.8 seconds, and late-phase (F), at 12 minutes, obtained 6 days after initial examination with acute posterior multifocal placoid pigment epitheliopathy–like early hypofluorescence and late hyperfluorescence. G, H, Color photograph of the macula with enlarging creamy white active retinal lesions and focal subretinal fluid, 12 days after initial examination. Visual acuity was reduced to 20/40 OS. Indocyanine green angiography was performed with a digital image captured at 6 minutes, 20 seconds after injection of dye. I, J, Photographs showing recurrence of active lesions in the macula and nasal mid periphery at 9 weeks after initial examination. Nasal disc swelling is seen. K, L, Color fundus photographs showing numerous healed lesions scattered throughout the fundus at 5 months after initial examination. Visual acuity was 20/20 OS. No active lesions were present.
amination, there was 2+ anterior vitreitis in the left eye and creamy white lesions at the level of the RPE. These lesions involved the fovea with serous elevation of the neurosensory retina (Figure 2, A). Pigmented healing lesions were present in the periphery. There was trace vitreitis in the right eye. Areas of older, inactive pigmented scars were present in the superior right macula and mid periphery. These pigmentary changes had been noted almost 4 years previously. There was a small white area of possible activity along the inferotemporal arcade that did not involve the fovea. Fluorescein angiography showed early hypofluorescence with later hyperfluorescence of active lesions. No treatment was given. A systemic medical workup for this patient included human lymphocyte antigen typing, with B57, B60, Drw6, and Drw15 serotypes identified.

During the next 2 months, the active lesions of the left eye began to show pigmentation while new lesions appeared in the mid periphery. The subretinal fluid at the fovea resolved. The patient then noted decreased vision of the right eye with an active-appearing lesion noted along the inferotemporal arcade. Oral prednisone, 60 mg/d, was administered. Despite this treatment, the lesions in the right eye grew considerably. Four months after initial examination, a large active lesion involved the right fovea with visual acuity dropping to 20/400 OD. A separate active lesion appeared temporal to the fovea. A right periocular corticosteroid injection was administered. The prednisone was tapered as visual acuity improved to 20/60 OD and 20/20 OS. Six months after initial examination, active lesions were again noted in the periphery of the left eye. Thereafter, the patient was followed up on a yearly basis with the appearance of new pigmented areas of scarring indicating episodes of activity in the interim (Figure 2, B). Twenty-two months after initial examination, new active retinal lesions were again noted in the temporal and nasal periphery of the right eye. The final visual acuity remained stable at 20/60 OD and 20/20 OS.

CASE 3

A 51-year-old woman was seen for flashes and floaters in the right eye. Her history included breast cancer with use of tamoxifen citrate, 10 mg twice a day. Three weeks previous, this patient’s visual acuity was 20/15 OD and 20/20 OS with geographic retinal atrophy and scattered RPE clumping noted in the left eye by a referring ophthalmologist. Similar pigmentary changes had first been noted in the right eye 6 years previously. Her visual acuity was 20/20 OD and 20/60 OS. There was no afferent pupillary defect. Findings from examination showed areas of new white choriotreal lesions in the left macula. There were areas of confluent placoid retinal lesions to the fovea as well as large areas of atrophic pigmented scarring with white margins extending temporal and inferotemporal in the macula. Separate lesions were also present in the superior mid periphery. Fluorescein angiography of these lesions showed early hypofluorescence and late hyperfluorescence. A systemic medical workup revealed an anti-Epstein-Barr virus IgG titer of 1:80; IgM, negative findings; Epstein-Barr virus nuclear antigen, positive findings (early antigen). Findings for fluorescent treponemal antibody, Venereal Disease Research Laboratory test, and chest x-ray film were negative. No treatment was given.

Subsequent follow-up 6 months later revealed a visual acuity of 20/20 OD and 20/30 OS. Mild vitreous cells were seen in the left eye. Increased atrophy and pigmen-
tary changes were seen in the right fundus with definite progression and new white placoid lesions in the nasal retina of the left eye.

An electro-oculogram was performed, which showed an Arden ratio of 1.9 OD and 1.5 OS. Electoretinogram showed reduced scotopic and photopic response in the left eye, particularly the 30-Hz flicker with an amplitude of 53 (reference range, >75). Goldmann visual field testing showed paracentral scotomas and generalized constriction in the left eye without an increased blind spot. Findings from the electroretinogram and visual field examination of the right eye were normal. Further systemic workup revealed normal findings from antinuclear antibody and lupus anticoagulant antibody tests with T-cell and complete blood cell counts within the reference range. Test results were negative for antibody to human immunodeficiency virus or cytomegalovirus and positive for antihuman cytomegalovirus type 1 (IgG titer, >1:1000) and antihuman cytomegalovirus type 2 (IgG titer, >1:10 [1:100 by quantitative assay]). Findings from human lymphocyte antigen typing were unremarkable. No treatment was instituted.

The patient was examined 8 months following initial examination with a visual acuity of 20/20 OD and 20/30 OS. There were a few vitreous cells in the right eye and 1+ cells in the left. There were new white retinal lesions seen in both eyes with extensive atrophy present in the left. No treatment was given. At 11 months after initial examination, the patient had a visual acuity of 20/20 OD and 20/25 OS. Both eyes appeared quiet with no vitreous cells and no active chorioretinal lesions noted.

CASE 5

A 20-year-old man was seen for decreased vision in his left eye. He had a history of a brief, untreated nonspecific upper respiratory tract illness 1 month earlier. His visual acuity was 20/20 OD and 20/40 OS. Findings from slit-lamp examination showed iritis with keratic precipitates and 2+ vitreitis in both eyes. Results of fundus examination showed bilateral, peripapillary, flat, creamy white lesions at the level of the RPE in both eyes with involvement of the fovea in the left eye (Figure 4, A). The neurosensory retina was elevated in the left eye by shallow subretinal fluid. Retinal venous engorgement was noted. Inactive pigmented lesions were noted in the periphery. Fluorescein angiography showed early hypofluorescence of the placoid lesions with later hyperfluorescence. There was leakage at the disc.

![Figure 2. Case 2. Color photographs of the left eye of a 26-year-old man showing early appearance of active creamy white lesions in the posterior pole (A), with progression of lesions and pigmented scarring after 6 months (B).](image1)

![Figure 3. Case 3. A, Color photograph of the right macula of a 21-year-old man showing active lesions at initial examination. B, Six months later, new active lesions were seen scattered through the right fundus in addition to more than 50 healed lesions and an area with intraretinal hemorrhage.](image2)
A systemic medical workup revealed normal findings for complete blood cell count, rapid plasma reagin, erythrocyte sedimentation rate, and *Bartonella* antibody. No systemic corticosteroids were instituted initially; however, 3 weeks later, chorioretinal lesions had progressed to involve the fovea of each eye with a decrease in visual acuity to 20/100 OD and 20/400 OS. There were also new lesions present nasal to the optic nerve in the left eye. Bilateral disc swelling was present. The patient was then treated with oral prednisone, 80 mg/d, and doxycycline hyclate, 100 mg twice a day. Findings from magnetic resonance imaging of the brain and orbits with and without gadolinium were normal. Two months after initial examination, visual acuity was 20/50 OD and 20/30 OS with lesions showing pigmentation. Active borders were present along some of the older lesions. Vitreitis had decreased, and the bilateral optic disc edema was improved.

During the next 3 months, oral prednisone therapy was tapered as the patient slowly improved. Oral doxycycline was discontinued. Five months after onset, small, persistently active creamy white lesions as well as disc swelling edema were seen in the left eye (Figure 4, B). There were numerous areas of scarring present in each eye, possibly with subretinal fibrous metaplasia, forming contiguous paths through the macula. Visual acuity was 20/30 OD and 20/20 OS. Because of this persistent activity, oral famciclovir was administered 1 year after initial examination at 500 mg, 3 times per day. The areas of white activity at the tips of the lesions healed soon after famciclovir therapy was administered. The patient was seen finally at 13 months after initial examination with no active lesions and with a visual acuity of 20/20 OU.

**CASE 6**

A 17-year-old woman with a history of Ewing sarcoma, autoimmune thyroiditis, and recent aseptic meningitis (2 months earlier) complained of a pericentral scotoma in her right eye. This patient also experienced fatigue, joint and muscle aches, and morning stiffness. Examination by a referring ophthalmologist revealed yellow-white placoid lesions of the RPE in the posterior pole. Fluorescein angiography showed early hypofluorescence and late hyperfluorescence. The patient subsequently noted an inferior scotoma in the fellow left eye that gradually enlarged, prompting referral 1 month after onset of symptoms.

At our initial examination, visual acuity was 20/300 OD and 20/60 OS. The right eye showed mild disc...
edema with almost confluent placoid white lesions seen in the macula at the level of the RPE, with shallow subretinal fluid and cystoid macula edema (Figure 5, A). There were also approximately 20 peripheral pigmented retinal lesions present (right eye). Examination of the left eye also revealed mild disc edema. There were 2 creamy white placoid retinal lesions present in the left macula, 1 of which involved the fovea. The larger of these lesions was fading and had a pigmented border. No vitreous cells were seen. Fluorescein angiography showed early hypofluorescence and late hyperfluorescence.

Findings from a systemic medical workup were negative except for an increased erythrocyte sedimentation rate of 90 mm/h and thyroid autoantibody titer of 1:1600 (reference range, ≤1:400). Findings from fluorescent treponemal antibody, Venereal Disease Research Laboratory test, antinuclear antibody, rheumatoid factor, Lyme disease, and magnetic resonance imaging of the head were negative.

Oral prednisone, 50 mg/d, was administered. Despite this, the chorioretinal lesions progressed. Confluent involvement of the entire posterior pole in both eyes was seen at 1 month. The lesions progressed in the periphery as well. Foveal involvement reduced visual acuity to 2/200 OD and 20/300 OS. Prednisone administration was continued with slow healing of the lesions and gradual improvement in vision. Bilateral episcleritis was noted 3 months after initial examination with continued subacute active lesions noted in the periphery. Prednisone therapy was continued. Four months after initial examination, the patient's visual acuity was 20/200 OD and 20/60 OS with subepithelial corneal infiltrates temporarily noted in both eyes. Several new and subacute lesions in the peripheral fundus continued to be noted. Systemic corticosteroid dose was tapered gradually during the next 3 months with gradual improvement in vision and healing of the retinal lesions. Seven months after initial examination, the corticosteroid dose had been tapered to 5 mg/d and subsequently was discontinued with no new active lesions seen. Final visual acuity was 20/30 OD and 20/40 OS, 28 months following initial examination. More than 100 pigmented lesions were present in each eye (Figure 5, B).

### RESULTS

The demographic data for our 6 patients are summarized in the Table. These patients were aged 17 to 51 years and of various ethnic origins with 3 men and 3 women affected. The medical histories revealed no consistent medical disorder or preceding illness. Our first patient had a genital herpesvirus type 2 flare-up 10 days prior to onset of eye complaints. This patient later developed a unilateral diffuse subepithelial corneal infiltrate that responded well to topical steroids, thought to be herpetic in origin. One patient had a history of Hashimoto thyroiditis and aseptic meningitis. Two other patients had histories of nonspecific upper respiratory tract infections, 1 was treated previously with antibiotics.

Four of 6 patients had concurrently active bilateral chorioretinal involvement. Another patient (case 3) had inactive pigmentary scarring noted in the fellow eye 10 years previously. All patients exhibited whitish placoid lesions at the level of the RPE. While many of these lesions developed pigmented chorioretinal atrophy within weeks, all of the patients had long clinical courses of activity with persistent lesions, growth of previous lesions, and appearance of new lesions for 5 to 24 months after onset (mean duration of activity, 9 months). All of the involved eyes eventually demonstrated numerous (>50) lesions with involvement anterior and posterior to the equator. Areas of involved RPE and retina were sufficiently large and resulted in decreased electro-oculogram and electroretinogram results (scotopic, photopic, and 30-Hz flicker) in 1 patient (case 4). Fluorescein angiography was performed in all patients, demonstrating early hypofluorescence with later staining of the placoid lesions. Indocyanine green angiography showed hypofluorescence in the areas of the lesions in case 1.

One patient had iritis with keratic precipitates. One patient had episcleritis. Four of 6 patients were noted to have vitreitis, although this was frequently mild. Four patients had subretinal fluid present in the macula at some time during their clinical course. Three patients were noted to have diffuse or sectorial optic disc swelling.

Central vision was affected in all cases, dropping as much as 6 Snellen lines, reflecting the amount of foveal involvement. Most patients had a substantial return of their vision. One patient (case 4) received no treatment while another (case 2) received systemic corticosteroids only briefly. These 2 patients experienced relatively longer periods of activity in our series, with active lesions seen 8 and 24 months after onset of lesions. These 2 patients also each experienced a greater permanent decrease in visual acuity in 1 eye (20/70 OS and 20/60 OD, respectively). The remaining patients received systemic corticosteroids for longer periods and had final visual acuities of 20/20 to 20/40 OU with the exception of 1 eye with a history of dense amblyopia (case 3). One patient (case 1) was treated with IV and later oral antiviral agents initially without associated improvement. A short period later, oral corticosteroids were administered with prompt improvement in vision and lessened activity of the lesions. This patient had a final visual acuity of 20/20 OU and was the only patient to have unilateral involvement. A second patient received oral antiviral medication later in his clinical course (case 6) with clinical improvement temporarily associated with the medication. Cyclosporine was used successfully in 2 patients (case 1 and case 3) to facilitate withdrawal from systemic corticosteroids.

### COMMENT

This article characterizes an unusual clinical course in 6 patients that we call relentless placoid chorioretinitis (RPC). Our patients demonstrate retinal lesions, similar to those seen with APMPPE or serpiginous chorioretinitis, clinically and on fluorescein and indocyanine green angiography. However, these lesions occurred in a distinctive retinal distribution with a prolonged relapsing clinical course. These patients all had retinal lesions in the mid and far periphery, unlike typical APMPPE or serpiginous chorioiditis. In some of these cases, peripheral lesions predated active lesions in the posterior pole.
Many of the lesions showed some resolution with onset of chorioretinal atrophy within weeks, similar to the lesions of APMPPE. Despite this, all of the cases showed progression for periods longer than that characteristic of APMPPE, with growth of subacute lesions and later, somewhat capricious appearance of new lesions, resulting in more than 50 and often hundreds of lesions scattered throughout the retina. In addition, some of these patients also showed recurrences for months to years after initial onset, sometimes after long periods of quiescence. Similar patterns of recurrence with growth in areas of atrophy and appearance of new areas have been previously described in long-term follow-up studies of patients with APMPPE.9,10 The differential diagnosis in these patients realistically includes only APMPPE and serpiginous choroiditis. Although there was some resemblance to multifocal choroiditis, Harada disease, bird-shot chorioretinopathy, primary or metastatic neoplastic infiltration of the choroid, and granulomatous diseases such as syphilis, tuberculosis, and sarcoidosis,6-17 the systemic medical workup, clinical manifestation, and clinical course of these patients was not consistent with these origins.

The similarity in the appearance of the retinal lesions in the patients described here with those seen in typical APMPPE or serpiginous choroiditis suggest a common disease process, though the origin of these conditions is presently unknown. The patients in this series had some systemic clinical features previously reported in association with APMPPE, including nonspecific upper respiratory tract infections, thyroiditis, and aseptic meningitis,8,15-17; however, we observed no consistent pattern of systemic illness. While a possible association of recurring APMPPE with antibiotic treatment for prodromal illness has been previously considered,18 only 1 of 6 patients received such treatment. Previous reports of patients with APMPPE have also included many of the manifestations described in our patients, including uveitis, episcleritis,9 optic disc swelling,19 and subretinal fluid.20 A resemblance to some patients reported previously as severe or recurrent APMPPE9,10 or serpiginous choroiditis10 supports the conclusion that this entity has been sporadically observed in the past.

The best treatment for patients with RPC has yet to be determined. Apparent responses to treatments in our series were anecdotal and not consistent. The visual acuity was affected in all of our patients with RPC, dropping to as low as less than or equal to 20/300 OU with substantial return of visual acuity to 20/40 or better in 8 of 11 eyes. Systemic corticosteroids were used to treat 5 patients with subsequent healing and improved visual acuity; however, this disease can progress and recur despite corticosteroid therapy. The role of corticosteroids, antiviral medicines, and cyclosporine in the treatment of this disorder needs further study.

This case series describes 6 patients with an unusual clinical course resembling, but distinct from, APMPPE and serpiginous choroiditis. We suspect that many more patients with similar features have been observed by others, including prolonged periods of widespread and multifocal retinal activity resulting in the appearance of numerous (>50) lesions, lesions present anterior to the equator, healed lesions that involve the superficial choroid, and preservation of visual acuity despite involvement of the fovea. These features suggest that this disease may be a distinct clinical entity. Until a specific known origin or diagnostic testing becomes available for APMPPE or serpiginous choroiditis, we are unable to state with certainty that RPC is a new clinical entity.

Accepted for publication January 12, 2000.

This study was supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, NY (Dr Jampol). Dr Jones was a Heed/Knapp Fellow (1997-1998).

Corresponding author: Lee M. Jampol, MD, Department of Ophthalmology, Northwestern University Medical School, 645 N Michigan Ave, Suite 440, Chicago, IL 60611 (e-mail: l-jampol@nwu.edu).

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