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MAJOR REVIEW

Serpiginous Choroiditis

Wee-Kiak Lim, FRCOphth, FRCS(Ed), MMED,[1,2] **Ronald R Buggage, MD,**[1] **and Robert B Nussenblatt, MD**[1]

[1]*National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA; and* [2]*Singapore National Eye Centre, Singapore*

Abstract. Serpiginous choroiditis is a rare, usually bilateral, chronic, progressive, recurrent inflammation of the choroid, retinal pigment epithelium, and choriocapillaris of unknown etiology. Based on clinical presentation, it can be classified into 1) peripapillary, 2) macular, and 3) ampiginous types. The clinical course, regardless of the presentation, is progressive with multiple recurrences leading to potentially significant visual loss. Visual outcome is directly related to the involvement of the para-fovea and fovea by the lesions or secondary choroidal neovascularization. The histological findings of the lesions are atrophy of the choriocapillaris, retinal pigment epithelium and photoreceptor cells, and moderate diffuse lymphocytic infiltrates throughout the choroid. Multiple etiologies including autoimmunity, infection, vasculopathy, and degeneration were proposed but none is well supported by clinical and laboratory evidence. Fluorescein and indocyanine green angiography have been useful in the assessment of the extent and the activity of lesions. Due to the insidious and progressive clinical course, an assessment of treatment outcomes needs long term follow-up. Currently, treatment with immunosuppressive and alkylating agents have shown possible efficacy in small case series. Larger clinical studies and interventional trials are required to further our understanding of the pathogenesis, etiology, and for the evaluation of treatment strategies. (**Surv Ophthalmol 50**:231–244, 2005. © 2005 Elsevier Inc. All rights reserved.)

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I. Introduction

Serpiginous choroiditis is a rare, usually bilateral, chronic, progressive, recurrent inflammation of the retinal pigment epithelium, choriocapillaris, and choroid of unknown etiology.[1,8,18] The earliest description of the condition, known as "peripapillary retinochoroiditis," was in 1932 by Junius. Thereafter, it was known by many different names: peripapillary choroidal sclerosis (Sorsby, 1939); helicoid peripapillary chorioretinal degeneration (Franceschetti, 1962);[23]

geographic helicoid peripapillary choroidopathy (Schatz, 1974); geographic choroiditis (Baarsma, 1976);[6] geographic choroidopathy (Hamilton, 1974);[32] and geographic helicoid choroidopathy and serpiginous choroidopathy (Gass, 1987).[27] The complete clinical features and fluorescein angiographic findings of serpiginous choroiditis as we currently recognize it was described in 1970s.[42] Following the initial description, variants of the disease including macular helicoid chorioretinal degeneration,[33] macular

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serpiginous choroiditis,[50] ampiginous choroiditis,[13] and relentless placoid chorioretinitis[39] have been reported. The numerous nomenclatures and variants of this condition reflect the wide spectrum of the disease presentation. Equally mystifying are the multiple etiologies proposed and the different treatments attempted for serpiginous choroiditis. Because of the rarity and the variable course of disease, which may have months to years of quiescence between recurrences, our understanding of this disease remains limited and the long-term management of patients with serpiginous choroiditis remains a challenge.

II. Epidemiology

Serpiginous choroiditis is a rare clinical entity constituting less than 5% of posterior uveitis in most uveitis epidemiological reports[15] with the exception of one from India,[10] which reported 19% of their posterior uveitis cases being serpiginous choroiditis. The disease tends to affect healthy young to middle-aged adults with most studies reporting a higher prevalence in men than women.[3–5,16,17,42,76] There is no racial predilection. It was initially reported in white patients[13,14] but was also found in Asians, African-Americans, and Hispanics in subsequent reports.[10,25,31] There is no familial predisposition. In a Finnish study, HLA B7 was found to be more prevalent in patients with serpiginous choroiditis (54.5%) than the general population (24.3%).[21] Most cases of serpiginous choroiditis are not associated with systemic disease, although there are isolated reports of patients with serpiginous choroiditis and systemic disease such as Crohn disease,[79] celiac disease,[53] extrapyramidal dystonia,[64] polyarteritis nodsa,[60] and sarcoidosis.[20] These probably represent coincidence rather than association.

III. Clinical Features

Although it is usually a bilateral disease, the typical presentation is an unilateral decrease in central vision, metamorphopsia, or scotoma. External examination of the eye is typically normal with no inflammatory cells or flare seen in the anterior segment or anterior vitreous. However, non-granulomatous anterior uveitis in patients with serpiginous choroiditis was observed in one study,[51] and fine pigmented cells in the vitreous humor has been described in up to 50% of eyes in some series.[16,27] The peripapillary serpentine lesions in the fundus are characteristic but variations have been reported. Although the lesions are typically not multifocal, some authors have categorized this condition as a white dot syndrome.[74] Based on the appearance of the fundus lesions, the following distinct clinical presentations have been discerned.

A. CLASSIC (PERIPAPILLARY GEOGRAPHIC) (FIG. 1)

About 80% of the cases of serpiginous choroiditis reported in the literature are classic or of the peripapillary geographical type. The active disease begins with ill-defined patches of grayish or creamy yellow sub-retinal infiltrates originating in the peripapillary region and progress in an irregular serpentine fashion centrifugally. Centripetal extensions of lesions occurred in 3 out of 17 eyes in one report.[42] The overlying retina is usually edematous and occasionally a serous retinal detachment may occur.[36] These active lesions will resolve over 6–8 weeks, with or without treatment, leaving an area of atrophy involving both the choriocapillaris and the overlying retinal pigment epithelium (RPE). Multiple lesions in different stages of resolution are typical of the disease and may be observed in the affected eye. Recurrences usually, but not always, occur at the edges of previous atrophic scars. The disease is characterized by multiple recurrences at variable intervals, ranging from months to years. With each new episode of activity, there is an extension of the choriocapillaris and RPE atrophy in a geographic or serpentine pattern. Skip islands of normal outer retina and choriocapillaris surrounded by atrophy may be seen as the disease progresses peripherally. In chronic cases, chorioretinal atrophy, subretinal fibrosis, and extensive RPE pigment clumping may be observed.

The disease runs an insidious course with many patients remaining asymptomatic until the macula is involved. About two-thirds of patients with serpiginous choroiditis have scars in one or both eyes at initial presentation.[44] In one study, more than half
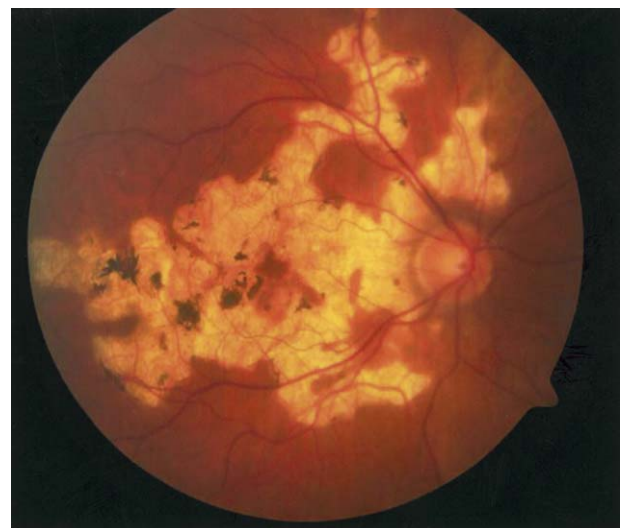

Fig. 1. Color fundus photograph of peripapillary serpiginous choroiditis (Inactive).

of the patients developed recurrences within an interval of 3 months to 4 years and in some the progression was only evident on serial fundus photography.[44] Visual loss is directly correlated to the proximity of the lesion to the fovea and incomplete recovery may occur with resolution of parafoveal lesions. As a result of the multiple recurrences and formation of new areas of choriocapillaris atrophy, up to 75% of the patients developed visual loss in one or both eyes with the final visual acuity of less than 20/200 in up to 25% of the eyes despite treatment.[17]

B. MACULAR SERPIGINOUS CHOROIDITIS (TABLE 1 AND FIG. 2)

Munteanu reported 5.9% of serpiginous choroiditis began in the macula.[54] This atypical presentation termed "macular serpiginous choroiditis" was first described by Hardy and Schartz in 1987.[33] They reported 8 out of 31 patients with serpiginous choroiditis who had the typical chorioretinal serpentine lesions in the macula but not continuous with the disk. Except for the location of the lesions and the worse visual prognosis due to early foveal involvement and higher risk of secondary choroidal neovascularisation (CNV), there was no difference between peripappillary and macular serpiginous choroiditis in the demographic characteristics of the patients and the angiographic features. Mansour et al reported 7 eyes in 4 patients with macular serpiginous choroiditis and all were associated with poor visual outcome, which he attributed to the foveal involvement and secondary CNV.[50] However, Sahu et al in a more recent report of 9 eyes in 6 patients with macular serpiginous did not observe any CNV.[65] Because the visual prognosis in serpiginous choroiditis correlates with the proximity of the lesion to the fovea, it is not unexpected that macular serpiginous choroiditis may have a higher risk for poor visual outcome than peripappillary serpiginous choroiditis.

In most ophthalmology textbooks, serpiginous choroiditis is described in the classic peripapillary presentation. Macular serpiginous choroiditis may be under-diagnosed as many of these cases may be misdiagnosed as other macular conditions such as age-related macular degeneration, toxoplasmosis, and macular dystrophy.

C. ATYPICAL VARIANTS—"AMPIGINOUS" CHOROIDITIS (FIG. 3)

Occasionally the lesions may also occur in the periphery in isolation or in a multifocal pattern described in a few reports as "multifocal serpiginous choroiditis,"[31] "ampiginous choroiditis,"[13,56] or most recently as "relentless placoid chorioretinitis."[39] Lyness and Bird in 1984 described a recurrent form of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) that resembles serpiginous choroiditis in its bilateral nature, fluorescein angiographic features, resultant pigmentary disturbances and the recurrent clinical course.[49] The only difference was the multifocal nature of the lesions which were not extensions of the old lesions.

Since then, there were reports suggesting the two diseases may represent different parts of the clinical spectrum of the same condition.[58] In his series of patients with serpiginous choroiditis, Weiss reported a patient with the characteristic course and fundus appearance of serpiginous choroiditis that developed new small, isolated round white plaque-like lesions similar to those seen in APMPPE.[76] These isolated lesions coalesced leaving behind a typical serpiginous atrophic lesion with loss of the RPE and choroid. Nussenblatt described patients with similar findings and suggested this condition was a variant of serpiginous choroiditis which he termed "ampiginous choroiditis."[56] Gupta et al reported 20 out of 86 patients with serpiginous choroiditis, who presented initially as APMPPE and had progressed over years to serpiginous choroiditis.[24] Compared to patients with typical peripapillary serpiginous choroiditis, those with ampiginous choroiditis tend to have less central foveal involvement. There was no difference in the presence of anterior segment inflammation, vitritis, or the

TABLE 1

Macular Serpiginous Choroiditis

|	No. of Patients	Follow-up	Treatment	CNV	Outcome
Sahu, 2002[53]	6 (9 eyes) M:F 4:2 Mean age=30.5 years	18 months (2–36)	Retrobulbar and oral steroids, AZA (2 patients)	No eye develops CNV	1/3 of eyes had final VA <20/200
Mansour, 1988[42]	4 (7 eyes) M:F 3:1 Mean age=52 years (42–58)	37 months (10–65)	–	3 eyes—treated with krypton red laser photocoagulation	All had significant visual loss
Hardy, 1987[27]	8 (11 eyes) M:F 6:2 Mean age=49 years (21–69)	39 months (3–100)	Retrobulbar and oral steroids	3 eyes—treated with Argon laser photocoagulation	Preserved vision in all 8 eyes
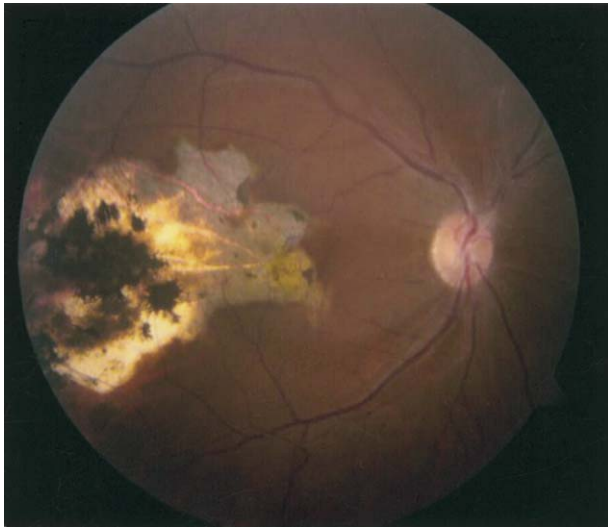
Fig. 2. Color fundus photograph of macular serpiginous choroiditis (Inactive).

number of recurrences between both groups of disease.[31] In another recent report, Jones and associates described six patients with a clinical entity, termed "relentless placoid chorioretinitis," having clinical and angiographic features similar to ampiginous choroiditis, resembling APMPPE and serpiginous choroiditis with a relapsing and progressive clinical course.[39] The lesions in relentless placoid chorioretinitis are described as progressive and involve the entire retina from posterior pole to periphery. The fluorescein and indocyanine green angiographic features of ampiginous choroiditis reported by Bouchenaki[13] and Gupta[31] were similar to the classic peripapillary serpiginous choroiditis.
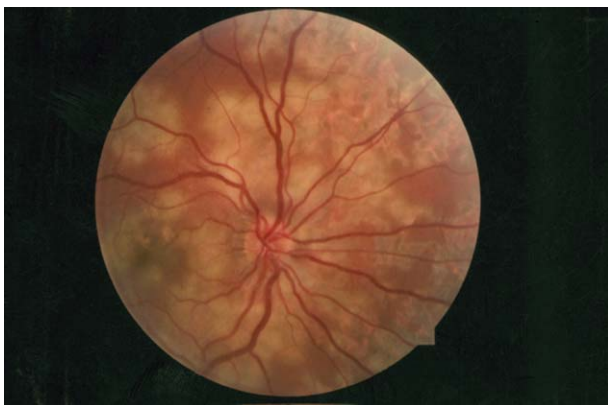

Fig. 3. Color fundus photograph of ampiginous choroiditis (a mixture of active and inactive lesions).

Given the similar demographics, angiographic features and clinical course, ampiginous choroiditis, including recurrent APMMPE and relentless placoid chorioretinitis, most likely represents a variant of serpiginous choroiditis.

IV. Investigations

A. FLUORESCEIN AND INDOCYANINE GREEN ANGIOGRAPHY (FIG. 4)

There are characteristic features on fundus fluorescein angiography (FFA) of patients with serpiginous choroiditis but these are not pathognomonic. In the atrophic areas, the main findings were early hypofluorescence secondary to atrophy of choriocapillaris and progressive hyperfluorescence at the margins of the lesion with eventual diffuse late staining of the underlying sclera and fibrosis. The active lesions, which occurred at the borders of the old lesion, blocks fluorescein early and show diffuse staining and leakage progressively in the late frames.[73] In one report, late diffusion of dye to part of the margin of the lesion was observed to be followed by an extension of the lesion over the same area two months later, suggesting that the late diffusion of dye observed was an active lesion.[73] It is still a debate whether the early hypofluorescence observed in the active lesions represent blockage of perfusion by space-occupying inflammatory lesions or choroidal non-perfusion as the primary pathological event. Given the lack of similar angiographic appearance with pathology associated with choroidal infiltration such as malignant metastases and the resemblance of serpiginous choroiditis to vascular occlusive conditions, the latter seems more plausible. Other conditions sharing similar angiographic features, such as APMPPE, multifocal choroiditis, choroidal tuberculosis, syphilis, and outer retinal toxoplasmosis should be included in the differential diagnosis of serpiginous choroiditis.

Because serpiginous choroiditis is a disease primarily involving the choriocapillaris and RPE, indocyanine green angiography (ICGA), well-recognized for enhanced imaging of the choroidal circulation, is well-suited to evaluate this condition.[13,26,28,29,66,70,72,73] In serpiginous choroiditis, the ICGA pattern is characterized by hypofluorescent areas beginning from the early to the late phase which is indicative of choriocapillaris non-perfusion and corresponding to a primary inflammatory choriocapillaropathy as proposed by Bouchenaki et al.[13] Van Liefferinge et al reported less extensive hypofluorescent areas in the late phase as compared to the early phase on ICGA and proposed that a delayed filling of the choriocapillaris rather than non-perfusion may occur in serpiginous choroiditis.[73] On ICGA, the hypofluorescent
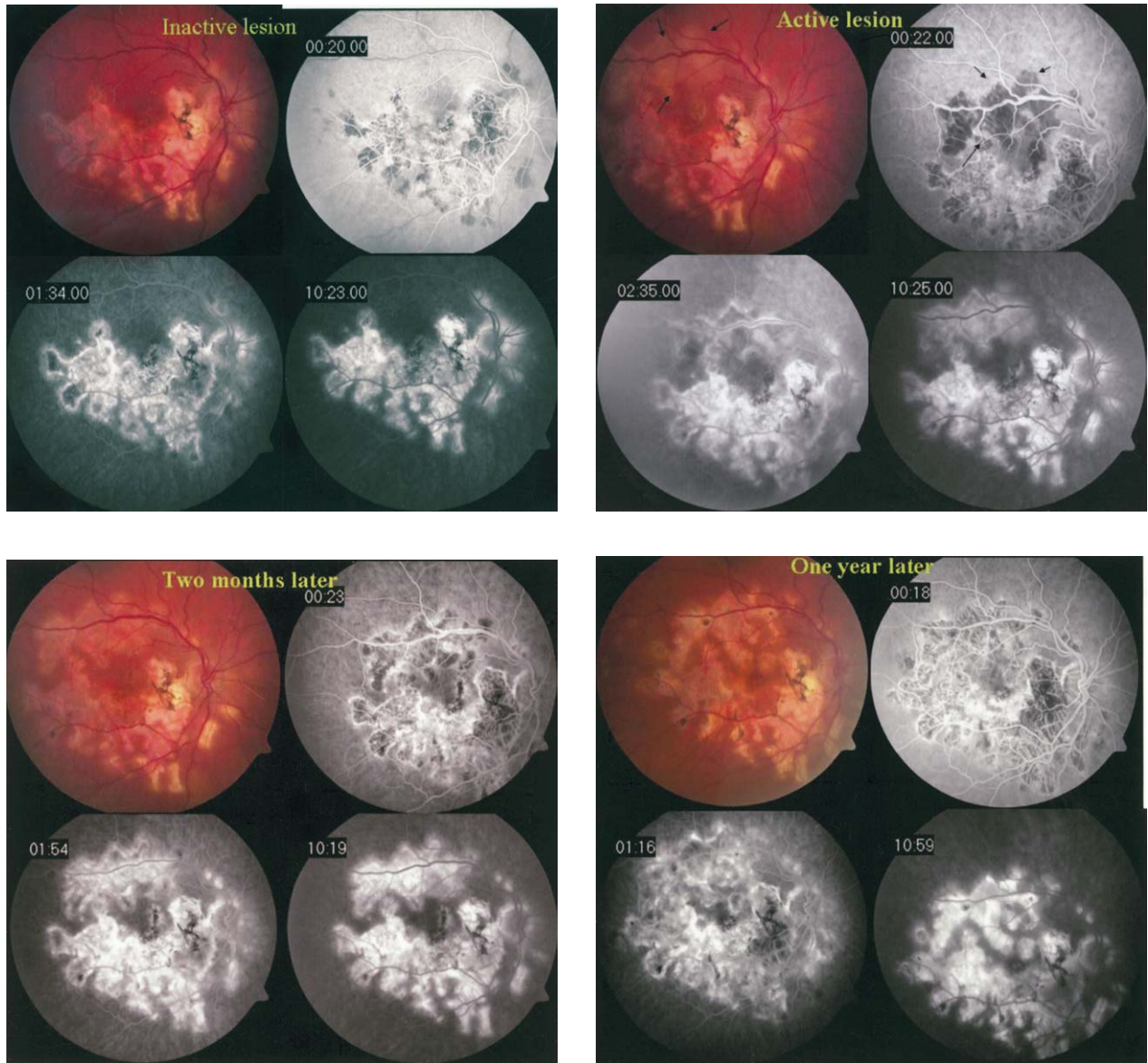
Fig. 4. Serial fundus photography and fundus fluorescein angiography of an active lesion resolving to an inactive lesion of serpiginous choroidtis. *Top left:* Inactive lesion showing early hypofluorescence secondary to atrophy of choriocapillaris and progressive hyperfluorescence at the margins of the lesion with eventual diffuse late staining of the underlying sclera. *Top right:* New active lesion over the superior arcade showing blocked fluorescein early with indistinct margins and more diffuse staining and leakage progressively in the late frames. *Bottom:* The transition of an active lesion to an inactive lesion over time (2 months and 1 year).

area observed may extend beyond the area of clinically observable lesions and that seen on the FFA.[28,29,66,70] In some reports,[66,70,73] there were lesions undetected with the FFA but apparent on ICGA. In subclinical cases, late hyperfluorescent zones adjacent to the hypofluorescent lesions might represent active foci of inflammation with overt leakage of ICG from choroidal vessels.[28,29] From the findings of these reports, it has been proposed that only through the use of ICGA can the true extent of the disease can be evaluated. Hence the ICGA has

been proposed to be helpful for the follow-up of patients with serpiginous choroiditis.

B. VISUAL FIELDS

The visual field demonstrates absolute and/or relative scotomata corresponding to the geographic lesion.[16,76] In active lesions, especially parafoveal or foveal, the scotoma is usually dense and with time, the scotoma may become less dense as the active lesions resolve over months.

C. ELECTRORETINOGRAM AND ELECTROOCULOGRAPHY

The ERG and EOG are unhelpful in the evaluation of disease progression, as the primary pathology is believed to be below the retina. They have been described as normal in most cases except in those with extensive and late disease.[16]

V. Differential Diagnosis

The main differential diagnoses are conditions that affect the choriocapillaris, such as APMPPE, tuberculosis, outer retinal toxoplasmosis, and choroidal ischemia.[48,68] Despite similar clinical and angiographic features, these conditions are distinct from serpiginous choroiditis and the management differs significantly. Rarely, other conditions may also present with a clinical picture resembling serpiginous choroiditis. There are reports of posterior scleritis mimicking as macular serpiginous choroiditis,[69] systemic non-Hodgkin's lymphoma presenting as serpiginous chorioditis,[63] and juvenile atrophy of pigment epithelium and choriocapillaris in two brothers with bilateral lesions showing features similar to serpiginous choroiditis.[37]

A. ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY (APMPPE)

Similar to serpiginous choroiditis, APMPPE is a bilateral condition affecting young adults, usually younger and more symmetrical than in serpiginous choroiditis. One-third of the patients have a viral illness preceding the onset of acute loss of vision with choroidal inflammation.[9,19] The lesions are multifocal and randomly scattered in the posterior pole. The acute lesions of APMMPE are similar; both are yellowish and involve the choroid, retina, and RPE. Angiographically, the acute lesions in APMMPE are indistinguishable from serpiginous choroiditis showing early blockage of fluorescence and late hyperfluorescence. The key difference is the clinical course. APMMPE lesions usually resolve spontaneously in two weeks, leaving a mottled RPE without significant choroidal atrophy. Visual prognosis in the majority of APMMPE cases is excellent as the visual recovery is usually complete, and unlike serpiginous choroiditis, secondary choroidal neovascularization in APMMPE, although reported,[22] is rare and recurrence is uncommon.

B. TOXOPLASMOSIS

It may be difficult to distinguish between a toxoplasmosis chorioretinal scar and an atrophied scar of serpiginous choroiditis. The recurrence of the disease, similar to serpiginous choroiditis, is usually at the margin of the old lesions and they share similar angiographic features on both FFA and ICG. However, the active lesion of toxoplasmosis is characterized by prominent vitreal inflammation and unlike serpiginous choroiditis, they can occur anywhere in the fundus. These patients have a positive toxoplasmosis serology.

C. TUBERCULOSIS

Tuberculosis infection, like serpiginous choroiditis, affects the choroid and may give rise to similar choroidal scars. In one study, there were 32 patients who were initially diagnosed as ocular tuberculosis but subsequently reclassified as serpiginous choroiditis.[80] Gupta et al reported 11 eyes in 7 patients with the diagnosis of choroidal tuberculosis presenting with serpiginous choroiditis like lesions.[30] All the patients had strongly positive tuberculin skin tests and positive chest radiographs, which supported the diagnosis. Four out of 11 eyes presented with choroiditis in an amoeboid pattern typical of serpiginous choroiditis, another 4 out of 11 eyes presented with multifocal lesions like ampiginous choroiditis and the remaining 3 eyes presented as a mixture of both. These reports highlighted the difficulty in distinguishing between these two conditions from one another. However, unlike serpiginous choroiditis, patients with ocular tuberculosis frequently present with vitritis, constitutional symptoms, such as loss of weight, appetite, and fever, other systemic involvement, and a positive tuberculin skin test. Treatment with anti-tuberculosis drugs in these cases lead to resolution of the lesions and visual improvement.[30]

D. MULTIFOCAL CHOROIDITIS

Unlike serpiginous choroiditis, patients with multifocal choroiditis usually have significant vitritis and anterior uveitis, hence, the condition is also known as multifocal choroiditis and panuveitis. The lesions in multifocal choroiditis are similar to those observed in ocular histoplasmosis. They are 20 to 200 μm in diameter and are distributed throughout the fundus, more in the posterior pole. Although the angiographic appearance of lesions of both conditions is similar, showing early hypofluorescence and late staining, multifocal choroiditis is clinically distinct from serpiginous choroiditis by the smaller lesions and the prominent vitritis.

E. CHOROIDAL ISCHEMIA

The angiographic features of choroidal ischemia and serpiginous choroiditis are similar. Hayreh et al demonstrated lesions similar to serpiginous choroiditis after cilioretinal artery occlusion.[34] Hence, vascular occlusion was proposed as one of the contributing

factors to the pathogenesis of the disease. Conditions that may result in occlusion of posterior ciliary vessels, such as hypertension, disseminated intravascular coagulation, thrombocytopenic purpura, and systemic vasculitis (including system lupus erythematosus and polyarteritis nodosa), should be excluded.

F. OTHER

Other inflammatory diseases and infections, such as sarcoidosis,[20] syphilis, histoplasmosis, and so forth, that may involve the choriocapillaris and RPE, could occasionally give the same clinical presentation as serpiginous choroiditis.

VI. Pathology

There are few clinicopathological reports on serpiginous choroiditis.[27,78] Wu et al reported the clinicopathologic features of the left eye of a patient with a 29-year history of progressive serpiginous choroiditis complicated by secondary choroidal neovascularization that was treated with laser photocoagulation.[78] The main histological findings of the lesions were atrophy of the choriocapillaris, RPE, and photoreceptor cells. The most affected layer was the choriocapillaris, which appeared acellular, whereas the larger choroidal vessels remained unremarkable. Moderate diffuse lymphocytic infiltrates were seen throughout the choroid but were more prominent at the margin of the lesion. Although there was predominantly atrophy of the RPE, there were a few areas of RPE hypertrophy correlating to the clinical finding of pigment clumping at the margin. Defects in the Bruch's membrane with extension of fibroglial scars into the subretinal space and lymphocytic infiltrations of the walls of the retinal veins were also described. The former were seen specifically in some infectious diseases like syphilis and ocular histoplasmosis raising the possibility of an infectious etiology in this condition.

VII. Pathogenesis

The pathogenesis of serpiginous choroiditis remains unknown despite various studies attempting to identify infectious agents, immunological disorders, and vascular disorders associated with the condition.

A. AUTOIMMUNE

The inflammatory nature of the disease has long been proposed[6] and is supported by clinical observations of vitritis,[16] anterior uveitis,[51] and pheblitis[24] in some patients. It is also supported by the finding of an inflammatory lymphocytic infiltrate in the choroid and vessel wall in one histopathological report.[78] The association with the MHC molecule HLA B7 in

a Finnish population and the finding of decreased complement factor C3 in three patients with serpiginous choroiditis have been given as further evidence of an autoimmune etiology.[21] The immune responsiveness to bovine retinal S-antigens by in vitro lymphocyte proliferation assay, leukocyte migration inhibition, and ELISA have been studied[12] and sensitization to S-antigen was noted in patients with serpiginous choroiditis. The accelerated resolution of active lesions in serpiginous choroiditis when treated with steroids and various anti-inflammatory agents also indicates that inflammation may play an important role in the pathogenesis of serpiginous choroiditis.[57]

B. INFECTIVE

Various infectious agents have been implicated in the pathogenesis of serpiginous choroiditis. In an earlier case series, skin hypersensitivity to tuberculin was reported in some patients with serpiginous choriditis and an association with tuberculosis was proposed.[42] However, results of treatment of the condition with anti-tuberculosis antibiotics were conflicting. Laatifkainen and Erkkila reported 9 patients with serpiginous choroiditis and all had positive tuberculin skin tests.[42] Among the patients, 2 had a history of pulmonary tuberculosis and 2 had family members with tuberculosis. All patients who were treated with anti-tuberculosis drugs had disease progression. More recently, Gupta et al reported 7 cases of ocular tuberculosis, the diagnosis based on positive tuberculin skin tests and chest radiographs, who presented clinically as serpiginous choroiditis.[30] Treatment with anti-tuberculosis therapy was associated with a good clinical response and visual improvement. A subset of patients with serpiginous choroiditis may have active tuberculous choroiditis or an autoimmune response triggered by tuberculosis manifesting clinically as serpiginous choroiditis.

Gass et al reported a case of serpiginous choroiditis following herpes zoster ophthalmicus and suggested a possible viral etiology in some patients with serpiginous choroiditis.[27] Although serological studies in most case series do not support a viral etiology, Priya et al reported two-thirds of aqueous humor samples from 9 patients were positive for varicella zoster virus (VZV) or herpes simplex virus (HSV) using the polymerase chain reaction.[61] Five were positive for VZV and one was positive for HSV. They suggested that herpes viruses might have a role in the pathogenesis of the disease in a subset of patients with serpiginous choroiditis. Attempts to treat the disease with anti-viral agents did not show any positive clinical results. Christmas reported disease recurrences on 2 patients while on acyclovir therapy.[17] However, there

were some unpublished clinical data that might suggest efficacy in prevention of disease recurrences in some patients (personal communication with David Callanan, MD). The exact role of infection in the pathogenesis of this condition remains unclear as the current support for an infectious etiology is largely derived from observations in small case series.

C. VASCULAR DISEASE

Serpiginous choroiditis or a subset of the disease has also been proposed to be a vasculopathy either primary or secondary to systemic disease.[7,25,73] Mulder et al described a patient with celiac disease, autoimmune thrombocytopenic purpura, and HLA-antigen of B8 and Dw3 with serpiginous choroiditis.[53] Pinto et al reported serpiginous choroiditis like lesions in one eye of a patient with bilateral choroidal vasculitis associated with polyarteritis nodosa.[60] Elevated factor VIII (von Willebrand factor), seen in patients with Raynaud's phenomenon, scleroderma, and polymylgia rheumatica, was reported in 6 out of 8 patients with serpiginous choroiditis in one study.[40] The clinical presentation of pheblitis,[24] branch retinal vein occlusions,[24] histopathological findings of a lymphocytic infiltrate around the vessel walls,[78] and characteristic angiographic findings of choriocapillaris non-perfusion,[13] all suggested vascular involvement and that closure may be important in the pathogenesis.[25] Early reports by Hayreh at al showed closure of cilioretinal vessels produced clinical lesions resembling serpiginous choroiditis.[34] Babel proposed that a subset of serpiginous choroiditis could originate from occlusion of one or several of the short ciliary vessels and the corresponding choriocapillary network.[7] Although plausible, there is little support for a vasculopathy etiology as most patients with serpiginous choroiditis do not manifest any signs associated with a systemic vasculopathy.

D. DEGENERATIVE

Due to the chronic and progressive nature of the disease in some patients and the occurrence of the disease in the fourth to fifth decade of life, degeneration as a primary etiology has been proposed.[52] One case of serpiginous choroiditis associated with a non-genetic hemidystonia, a unilateral extrapyramidal dystonia, was reported.[64] But the episodic nature and asymmetric presentation of the disease, the lack of a familial association, and the frequent recovery of vision after a recurrence are all atypical of a degenerative condition. The association with any degenerative disease could be coincidental.

With the multiple and diverse possibilities of etiology and pathogenesis postulated for serpiginous choroiditis, there could be many different mechanisms involved in the initiation of pathogenesis that converge into one common pathway to present as a single clinical entity.

VIII. Complications

The most common and visually significant ocular complication associated with serpiginous choroiditis is choroidal neovascularization (CNV) (Fig. 5).[62] It occurs in 13–35% of the patients with serpiginous choroiditis.[11,17] Occasionally, CNV may be the first presentation of serpiginous chorioditis.[46] Jampol et al reported CNV in 3 patients with serpiginous choroiditis and successfully treated 2 of them with argon laser photocoagulation.[38] Blumenkranz et al reported that 7 out of 53 patients with serpiginous choroiditis developed neovascularization and none could be successfully treated by photocoagulation.[11] Laatikainen and Erkikila reported CNV in 3 out of 15 patients with serpiginous choroiditis who were followed for 1–10 years (mean 4.9 years). Treatment with argon laser was also not successful in one eye, whereas in another eye, CNV was observed to resolve spontaneously with the onset of atrophy of the surrounding choriocapillaris and RPE.[43] The remaining eye had subfoveal CNV and was managed conservatively.

Navajas et al reported a patient with peripapillary CNV secondary to serpiginous choroiditis treated successfully with a single indocyanine green–mediated photothrombosis combined with intravitreal triamcinolone acetonide injection.[55] Although other treatment modalities for CNV such as photodynamic therapy and feeder vessels laser ablation have not been reported in patients with serpiginous choroiditis, they will probably be effective as long as the intraocular inflammation is controlled.

Others have reported ocular conditions that may be considered as complications associated with serpiginous choroiditis and these include branch retinal vein occlusion,[11,24] periphlebitis,[24] pigment epithelium detachment,[36,77] serous retinal detachment,[36] cystoid macular edema,[71] optic disk neovascularization,[43,77] subretinal fibrosis,[31] and anterior uveitis.[51] Hoyng et al reported atypical macular lesions characterized by RPE and serous detachments in two patients with serpiginous choroiditis.[36] Both were treated with oral prednisolone and resolved without scarring. Kohl et al reported a case of serpiginious choroiditis complicated by a reactive proliferative and fibrous metaplasia of the RPE.[41] Gupta at el reported a significantly higher prevalence of subretinal fibrosis in those with classic peripapillary serpinous choroiditis than those with an amipiginous choroiditis presentation.[31] Steinmetz reported a patient with serpiginous choroiditis complicated by cystoid macular edema, which was successfully treated
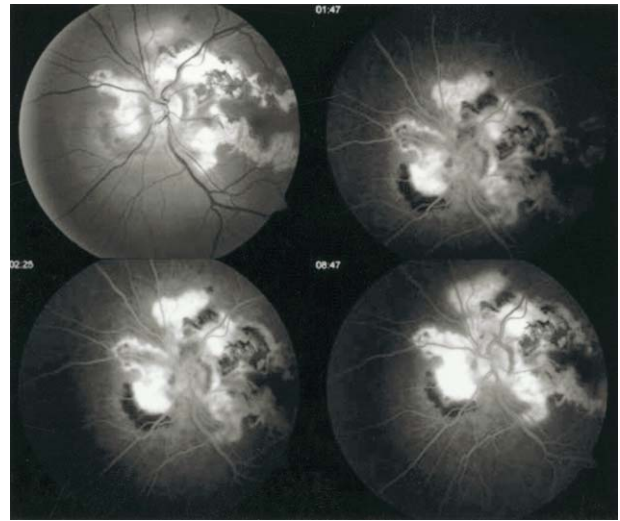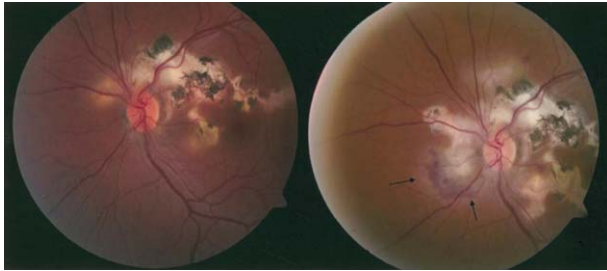
Fig. 5.   *Top:* Fundus photography showing development of choroidal neovascular lesion (arrow). *Bottom:* Fundus fluorescein angiography of choroidal neovascularization secondary to serpiginous choroiditis.

with acetazolamide.[71] Because of the rarity of the condition, the prevalence and incidence of ocular complications associated with serpiginous cannot be ascertained. The above reports represent isolated cases with rare occurrences of ocular conditions that may be associated with serpiginous choroiditis.

IX. Therapeutic Approach

The long-term natural history of serpiginous choroiditis is one of multiple recurrences and progressive scarring which may eventually involve the fovea and results in poor visual outcome. Without treatment, the active lesions typically resolve over a few months with a gradual extension of the primary lesion, however lesions may remain active for as long as nine months. The extrafoveal lesions are usually insidious and patients are often asymptomatic (up to 30%), hence many may remain undiagnosed. Parafoveal and foveal involvement, which usually results in early visual loss, is frequently the reason a patient seeks medical attention. Unfortunately, at this stage, there is usually extensive scarring and the risk of permanent visual loss is high. The frequent recurrences also increase the risk of secondary choroidal neovascularization, another important cause of visual loss in patients with serpiginous choroiditis. Hence, the goal of any successful therapy would be the rapid control of the active lesions during recurrences, and the prevention of further recurrences and progression of the disease. The natural history seems very variable. Therefore, to demonstrate the success of any therapeutic appproach for serpiginous choroiditis, a long follow-up with serial fundus photographics and angiographics to show non-progression

is required. Final visual acuity, although obviously important, does not provide an objective measure of non-progression in cases where extra-foveal recurrences continue to affect the eye and cause more scarring. Even if central visual acuity is preserved, the ensuing scotoma caused by the atrophic parafoveal lesions can be debilitating[59] and be a nidus for future CNV.

In keeping with the diverse etiologies proposed, there were many different treatments attempted for serpiginous choroiditis, including antibiotics,[42,44] anti-virals,[17] antimetabolites,[42] and immunosuppressive therapy. But there are limited data on long-term follow-up to evaluate efficacy of the different treatment regimes. To date, there have been 219 patients in 11 reports with reported treatments and outcomes (Table 2).

A. CORTICOSTEROIDS

Earlier reports have shown that systemic corticosteroids and retrobulbar steroidal injections were effective in controlling the active lesions and shortening the duration of active disease.[76] However, corticosteroids have been reported to have no effect on the prevention of recurrences. Patients often relapse during tapering or after discontinuation of steroid therapy.[16,17] Hence, short-term treatment with corticosteroids does not alter the natural course of the disease and the final visual outcome remains unsatisfactory in the long run. There is no report on the use of intravitreal steroid in the management of serpiginous choroiditis. Intravitreal steroid, like systemic and periocular, will likely be efficacious in the treatment of the acute lesions, but will probably not prevent the recurrences unless it is administered on a

TABLE 2

Serpiginous Choroiditis—Treatment and Outcome

	No. of Patients	Follow-up	Treatment	CNV	Outcome
Gupta, 2002[26]	86 M:F 61:25 Mean age = 30 years (11–57)	2–8 years	Systemic corticosteroids +/− immunosuppressives (AZA {2}, cyclophosphamide {1})	Only 1 eye developed CNV	65% achieved final VA of 20/40 or better.
Akpek, 2002[3]	9 M:F 5:4 Mean age = 55 years (40–75)	15–96 months after treatment	Chlorambucil or cyclophosphamide	1 patient	No recurrences while on treatment. No further vision lost. 7/9 patients achieved drug remission.
Christmas, 2002[14]	17 M:F 13:4 Mean age = 40 years (17–63)	5 months–26 years	Systemic corticosteroids +/− immunosuppressives (CSA, AZA, MC), acyclovir (3 patents)	12 out of 34 eyes had CNV	9/34 eyes had final VA ≤ 20/200
Munteanu, 2001[45]	34 M:F 19:15 Mean age = 36 years (29–68)	Not reported	Triple agents - prednisolone, CSA and AZA	Nil	"Satisfying" results but no detail of visual outcome reported
Akpek, 2001[4]	6 M:F 3:2 Mean age = 52 years (31–66)	17–105 months	CSA + AZA (3 patients), CSA only (1 patient), Cyclophosphamide (2 patients)	Nil	2 patients recurred on treatment (CSA alone, CSA+AZA). 10 eyes had improved VA.
Araujo, 2000[5]	7 (14 eyes) M:F 5:2 Mean age = 34 years (24–44)	1.3–13 years	Systemic corticosteroids + CSA +/− AZA {2}, FK506/MC {1})	Nil	3/14 eyes had improved VA. 10/14 eyes had unchanged VA and 1 eye lost distance VA due to cataract.
Secchi, 1990[55]	7 Age and gender not reported	6–21 months	CSA	Nil	9 out of 14 eyes improved.
Laatikainen, 1981[37]	15 M:F 7:8 Mean age = 35 years (20–65)	1–10 years	Anti-tuberculous medications or systemic corticosteroids	2 eyes with CNV	Progression and recurrences not halted by treatment.
Weiss, 1979[64a]	9 (17 eyes) M:F 7:2 Mean age = 46 years (22–58)	2–10 years	7 out of 9 patients received steroids by various route	Nil	3/17 had VA < 20/200.
Chisholm, 1976[13]	20 M:F 11:9 Mean age = 47.5 years (29–70)	Up to 9 years	Systemic corticosteroids	Nil	Only 3 eyes had significant decreased in VA due to macular involvement.
Laatikainen, 1974[35]	9 M:F 6:3 Mean age = 30 years (19–50)	2–13 months	Anti-tuberculosis medications (7) Antimetobolites- cytosine arabinoside and AZA(2)	Nil	All patients on anti-tuberculosis medications had disease progression. 2 on antimetabolites showed some improvement.

CSA = cyclosporine A; AZA = Azathoprine; MC = mycophenolate mofetil.

continuous basis and for a prolonged duration such as a long-acting steroid implant.

B. CYCLOSPORINE A, AZATHIOPRINE, AND MYCOPHENOLATE MOFETIL

The results with cyclosporine A mono-therapy for serpiginous choroiditis have been mixed. There were initial reports on treatment failure with cyclosporine A,[47] and there were subsequent reports with treatment success.[5,67] Araujo et al reported favorable results with 7 patients (14 eyes) treated with oral cyclosporine A (3–5 mg/kg/day) for a duration ranging from 1.3–5 years (median 3 years).[5] Five out of seven patients achieved remission and had no recurrences while on therapy. One patient, refractory to treatment, was switched to FK506 and mycophenolate mofetil and one patient relapsed on low-dose cyclosporine A. Secchi et al also reported favorable results with 7 patients treated with oral cyclosporine A (4–7 mg/kg/day). Nine out of 14 eyes had improvement in visual acuity whereas the remaining 5 were unchanged.[67] Christmas et al reported 4 out of 6 patients with serpiginous choroiditis treated with 2–40 months of immunosuppressive drugs, such as cyclosporine A, azathioprine, or mycophenolate mofetil, successfully discontinued their therapy without recurrences.[17] Akpek et al reported that 2 out of 4 patients with serpiginous choroiditis who were treated with cyclosporine alone or combined with azathioprine experienced a recurrence while on therapy.[4]

C. TRIPLE-AGENT THERAPY

Combination therapy consisting of cyclosporine A, azathioprine, and prednisolone was first described by Hooper and Kaplan to control inflammation rapidly and promoted visual recovery in 5 patients with bilateral serpiginous choroiditis.[35] The therapy was administered for 8 weeks and tapered. Two patients relapsed during tapering and the remaining patients were in remission while they were maintained on low-dose triple immunosuppressive therapy or azathioprine and prednisolone. Another study of four patients maintained on low dose triple agent therapy for 12–69 months (median 39 months) reported a similarly favorable outcome. Three out of four patients achieved drug-free remission.[4] Munteau et al also reported satisfying results with triple-agent therapy on 34 patients with serpiginous choroiditis.[54] Further studies using the triple-agent therapy also demonstrated good control of inflammation with minimal side effects.[75]

D. ALKYLATING AGENTS AND ANITMETABOLITES

The efficacy of antimetabolites in serpiginous choroiditis was suggested in early literature but its application remained limited due to the potential serious adverse effects. Laatikainen reported visual improvement in 2 patients with sight-threatening disease treated with cytosine arabinoside combined with azathioprine.[42] In later reports, alkylating agents, such as cyclophosphamide and chlorambucil, appeared to be effective in rapidly controlling the inflammation and producing a long-term drug-free remission in patients with serpiginous choroiditis. Alpek at al reported the use of alkylating agents (cyclophosamide or chlorambucil) in 9 patients with active vision-threatening serpiginous choroiditis which progressed despite initial conventional steroid and triple-agent therapy (2 patients).[3] All patients had no recurrences while on the therapy and had preservation of vision. Two-thirds of patients had a visual improvement and 7 out of 9 patients achieved drug-free remission. However, one patient developed bladder epithelial carcinoma, which may have been related to the use of cyclophosphamide. Alkylating agents should be used with caution in view of the potential life-threatening complications reported. Because of the potentially serious side effects, alkylating agents should be reserved for patients with sight-threatening lesions who have failed other conventional immunosuppressive therapy. The patient needs to participate in this decision after being informed of the possible long-term effects of this therapeutic approach.

Caution must be taken in the interpretation of these reports as the patients may be different in stage and activity of the disease and there was no standardized method of measurement of disease activity and clinical criteria for recurrences. It is possible that immunosuppressive therapy as monotherapy may be efficacious in a subset of patients who present early in the course of this disease. Without larger (multicenter) trials, it will be difficult to determine what is the best treatment strategy.

X. Conclusions

No randomized clinical trial on the treatment of serpiginous choroiditis has been performed and treatment remains limited to conventional steroidal, anti-microbial, and immunosuppressive therapy.[2] As it is a rare condition with an insidious clinical progression, the conduct of such a clinical trial would be difficult. Based on the studies reported so far, the rapid control of any active lesions with aggressive immunosuppression and thereafter the maintence on appropriate immunosuppressive for at least 6 months to prevent any immediate recurrence can be considered in the initial management of patients with serpiginous choroiditis. Subsequent treatment will depend on the severity of the disease, for example, foveal threatening lesions in an only seeing eye, physical status (e.g., age and any associated systemic disease), concerns such as fertility, and the response to

initial immunosuppressive therapy. The treatment benefits must be titrated against the potential risk of adverse effects from treatment. Given the insidious progression, serial color fundus photography and angiography, as well as self-monitoring with an Amsler chart[45] in patients with serpiginous choroiditis may be useful in the early detection of recurrence and progression. The only way to better understand this rare entity is through multicenter studies so that a sufficient number of patients can be evaluated for the etiology, pathogenesis, and efficacy of different treatment strategies. Until then, our proposed treatment algorithm is that of a stepladder approach, using systemic corticosteroids and periocular steroidal injections as a first line to control active lesions and concurrently using immunosuppressive therapy such as cyclosporine A, azathioprine, or mycophenolate mofetil as monotherapy for maintenance. Failing which, combination therapy similar to triple therapy or alkylating agents, after proper risk apprisal with the patients, could be considered.

Method of Literature Search

This review included all published reports of serpiginous choroiditis, English and non-English language papers, in the literature from 1962 through January 2004. The following databases were searched: PubMed and MEDLINE. The keywords included *serpiginous choroiditis, serpiginous choroidopathy, geographic choroidopathy, geographic choroidopathy,and geographic helicoids choroidopathy*. Textbooks that included information on the serpiginous choroiditis were examined for relevant reports, and published reports identified through reference lists of other articles were also included.

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Outline

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