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Chlorambucil combination therapy in refractory serpiginous choroiditis: A cure?

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ABSTRACT

Purpose: To find a remedy for serpiginous choroiditis refractory to oral prednisone and chlorambucil treatment.
Observations: Eight eyes of four patients (all female) with advanced macular involvement secondary to serpiginous choroiditis were included in the study. The average age of the patients was 45.2 years. One eye of each patient was legally blind and the lesion was close to the fovea in the other eye. All four patients failed oral prednisone and chlorambucil therapy. However, case 1 responded to chlorambucil treatment after intravitreal dexamethasone implant implantation and discontinuation of oral prednisone. Case 2 responded to chlorambucil therapy when oral prednisone was stopped in combination with infliximab therapy. Due to long follow-up period of more than four years, these two cases are considered to be cured. Case 3 and case 4 were not able to achieve remission with chlorambucil and immunomodulatory therapy. They refused intravitreal steroid implant due to side effects profile.
Conclusions and importance: The stability of WBC counts within toxic levels close to normal or lower limits of normal (3000–4500 cells/μl) during treatment with chlorambucil is an essential factor for the success of this therapy. A combination of dexamethasone intravitreal implant with chlorambucil therapy can be an effective and promising regimen in inducing and maintaining remission in refractory serpiginous choroiditis patients who fail a combination of systemic corticosteroid and chlorambucil therapy.

1. Introduction

Serpiginous choroiditis (SC) is a rare, chronic, asymmetrically bilateral posterior uveitis with a recurrent course. The exact prevalence of SC is unknown; however, it is estimated between 1.6% and 5.3% of posterior uveitis cases in non-endemic areas for tuberculosis.[1] Major features of SC include choriocapillaris occlusive vasculitis, secondary endothelial cell injury, and subsequent atrophy of the retinal pigment epithelium, outer retina, and choroid.[2,3] Histopathology studies reveal lymphocytic infiltration in the choroid and, less commonly, around vessels.[4] The peripapillary area is classically involved in SC and accounts for 80% of the cases.[5] The prognosis of vision is poor when it involves the macula, especially in the macular variant of SC. Moreover, the macular variant has a higher risk of developing choroidal neovascularization in nearly half of the affected patients.[6,7] Fluorescein angiography (FA), indocyanine green angiography (ICG), optical coherence tomography (OCT), fundus autofluorescence (FAF), and microperimetry are the ancillary diagnostic tools and tests which help in the diagnosis, follow-up, and monitoring for secondary complications.[1]

Historically, the administration of high doses of oral or intravenous steroids was considered as the standard of care for patients with SC.[8] However, immunosuppressive agents such as azathioprine, cyclosporine, chlorambucil, and cyclophosphamide emerged as treatment options for steroid-free remission.[4,9–12] Of these, the alkylating agents cyclophosphamide and chlorambucil have been noted to have a high success rate in the treatment of SC.[4,10,12] Chlorambucil, being a potent alkylating agent, can interfere with DNA replication and cell division.[13] This medication can induce remission, maintain remission, and even cure this disease.[12]

Despite successful treatment of SC with alkylating agents, in some patients the disease can recur frequently and progress to affect the central vision. This becomes more important in patients with poor vision

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in the other eye secondary to SC or advanced SC encroaching the fovea in the affected eye. In this case series, we decided to evaluate possible remedies for refractory and recurrent SC in patients who have been treated with chlorambucil and oral or intravenous corticosteroids.

2. 4 Cases

Case 1. A sixty-year-old female was referred to us for the evaluation of macular SC OU. She had noticed blurry vision OS one month before her first visit with us. A geographic lesion with indistinct and irregular borders was observed in both eyes. The lesion was uni-centric OU, temporal to fovea OD and peripapillary with extension to fovea OS. FA and ICG showed the activity of the lesions in both eyes (Fig. 1A). Her best-corrected visual acuity (BCVA) was 20/20 OD and decreased OS to 20/100. Complete blood work-up for uveitis ruled out non-infectious and infectious posterior uveitis, including syphilis and tuberculosis. Based on these findings, she was diagnosed with autoimmune SC OU and was started on a combination of chlorambucil and daily oral prednisone. Chlorambucil was titrated based on her white blood cell (WBC) count. She had another flare-up while she was on 2 mg/day prednisone and had already stopped chlorambucil for three weeks due to WBC 3200 cells/μl. BCVA OS decreased to 20/125, and ICGA confirmed enlargement of the lesion. Chlorambucil was restarted to 2 mg every other day, and oral prednisone was increased to 5 mg/day. With this change in her regimen, the vision increased to the baseline before her last flare, to 20/40. Treatment with chlorambucil was stopped after one year. Her follow-up visit increased to every three months from monthly. Then, six months later, she was started on oral methotrexate 7.5 mg weekly by her rheumatologist because of her joint issues. She was followed every three months for seven months until she noticed a change in OS again. At that time, she was on oral methotrexate 15 mg weekly. BCVA OS decreased to 20/125, and ancillary tests showed activity at the border of the lesions on the foveal side (Fig. 1B). She received one dose of 1 g intravenous methylprednisolone, intravitreal injection of triamcinolone and bevacizumab, and was restarted on oral prednisone 80 mg/day. A week later, her methotrexate dose was boosted to methotrexate 25 mg weekly subcutaneous injections, and we tapered prednisone 10 mg weekly. In three months, oral prednisone was tapered and stopped. Three months later, her lesion became active and she developed choroidal neovascularization (CNV) for which she received a bevacizumab injection. She was restarted on chlorambucil and oral prednisone. The decision for local therapy with dexamethasone implant was made at this point, and she was put back on chlorambucil 2 mg every three days. She was on chlorambucil without oral prednisone, titrating the dose based on WBC for seventeen months, after which she was considered cured (Fig. 1C). In her last visit with us, her BCVA OD and OS were 20/20 and 20/50, respectively. The patient's average WBC count while on chlorambucil with prednisone, chlorambucil without prednisone, and chlorambucil after dexamethasone intravitreal implant were 5500 ± 2900, 4700 ± 1100 and 4100 ± 500 cells/μl, respectively. The total duration of treatment before dexamethasone intravitreal implant was 60 months and 17 months after dexamethasone intravitreal implant. The total length of follow-up is 132 months, and the total duration of remission off medication is 48 months (Table 1).

Case 2. A 42-year-old female was referred to us with blurry vision and field distortion OD for ten years and OS for eight years. Her vision was counting fingers at 1 m OD and 20/20 OS. At the time of presentation, the patient had already received multiple intravitreal anti-VEGF (bevacizumab) and triamcinolone injections OD. The geographic lesions were peripapillary OU, with foveal involvement OD. Initial FA revealed chorioretinal scarring with window defects OU and leakage on borders OD (Fig. 2A). On ICG, the area of hypolucency OS extended further into the macula, which was not seen on FA (Fig. 2B). Complete blood work-up for uveitis ruled out non-infectious and infectious posterior uveitis, including syphilis and tuberculosis. Based on these findings, she was diagnosed with autoimmune SC OU and we recommended therapy with chlorambucil. She sought a second opinion elsewhere, where she was started on mycophenolate mofetil (MMF) 1 g daily with infliximab 300 mg IV every four weeks and oral prednisone 80 mg/day with taper. MMF and infliximab were eventually discontinued due to elevated LFTs. On follow up at our clinic eighteen months after the initial consult, chlorambucil was finally started with dose adjustment based on weekly monitoring of WBC count to reach the endpoint of WBC count 3000–4500 cells/μl. While on chlorambucil 20mg and prednisone 40mg daily, the patient became symptomatic OS with new changes and leakage on FA OS, prompting boosting of oral prednisone to 80 mg; she also received one ranibizumab injection OS locally. Six weeks after starting treatment with chlorambucil (20mg at this time) and oral

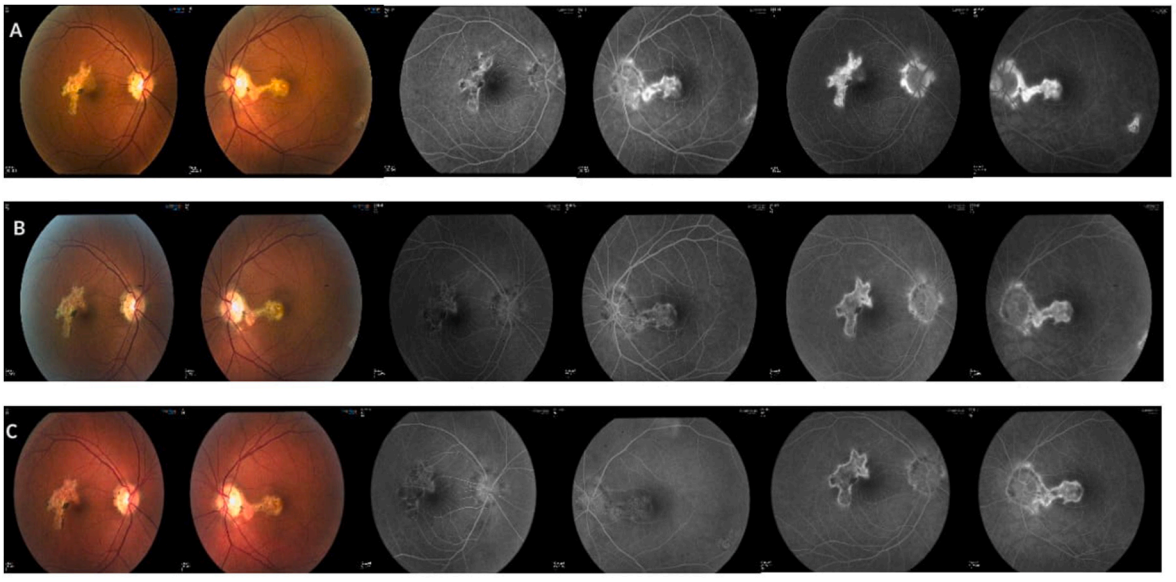

Fig. 1. A patient with bilateral serpiginous choroidopathy. (A) Serpiginous lesions in both eyes, encroaching the fovea in right eye and with foveal involvement in left eye. Fluoresecein angiography shows activity in both eyes. (B) The middle row shows progression towards the fovea with leakage pointing toward the fovea in the right eye. (C) Shows the stability of fundus photos and fluorescein angiography in both eyes at one year after intravitreal dexamethasone implant and chlorambucil treatment.

Table 1
Demographics and clinical characteristics of patients with resistant serpiginous choroiditis.

	Age years	Sex	Laterality	BCVA first visit	WBC (C + P) cells/μl (x 10^c)	WBC (C) cells/μl (x 10^c)	WBC (C + IMTor implan cells/μl (*10^c)	Duration of treatment before IMT	Duration of treatment after IMT	Duration of follow-up on chlorambucil	Duration of follow-up off chlorambucil	BCVA last visit
Patient 1 OD OS	60	F	Bilat	20/20 20/100	5.5 ± 2.9	4.7 ± 1.1	4.1 ± 0.5	60[a] months	17[b] months	60 months	83 months	20/20 20/50
Patient 2 OD OS	42	F	Bilat	1 mcf 20/20	5.7 ± 2.2	N/A	3.8 ± 0.5	40[c] months	19[d] months	49 months	60 months	1mcf 20/15
Patient 3 OD OS	32	F	Bilat	HM 20/20	8.8 ± 3.4	N/A	N/A	5 + 10 [e] months	N/A	5 months	N/A	HM 20/50
Patient 4 OD OS	47	F	Bilat	20/30 1mcf	6.2 ± 3.3	N/A	N/A	N/A	N/A	12 months	N/A	20/50 1mcf

BCVA:best corrected visual acuity; Bilat:bilateral; C:chlorambucil; CF:counting fingers; HM:hand motion; IMT:immunomodulatory therapy; P:prednisone; N/A:not applicable.
[a] Before intravitreal dexamethasone implant.
[b] After intravitreal dexamethasone implant.
[c] Before starting infliximab.
[d] After starting infliximab.
[e] 5 months chlorambucil and 10 months cyclophosphamide.

prednisone 80 mg daily, WBC count dropped down to 4900 cells/μl, so we started tapering prednisone. Two months after initiation of chlorambucil therapy, chlorambucil was stopped while tapering prednisone at 30 mg/day with a WBC count of 3300 cells/μl. At this point, FA, FAF, and OCT showed stability and quiescence. On a subsequent visit with her local ophthalmologist, infliximab 600 mg infusions every four weeks was started for activity OS, and eventually increased to 900 mg every four weeks in combination with chlorambucil. WBC count increased to 7900 cells/μl while on prednisone 10 mg with taper, and chlorambucil was restarted at 4 mg daily, eventually going up to 6 mg daily (Fig. 2B). Chlorambucil dose adjustment with weekly WBC count was continued. Meanwhile, she received a bevacizumab injection with her local ophthalmologist due to central vision distortion OD. On her eight-month of treatment, WBC count dipped to 2000 cells/μl, and chlorambucil was stopped. After one week, with WBC count creeping back up to 4800 cells/μl, chlorambucil was restarted at 2 mg/day. Disease activity was then noted at ten months from treatment initiation with no interventions at that time. On follow up at our clinic fourteen months after starting chlorambucil, the activity noted at ten months prompted treatment extension, and the patient was educated on the risks vs. benefits of this decision. Chlorambucil treatment was continued for a total duration of twenty-one months. FA and OCT macula findings were stable and the patient was asymptomatic (Fig. 2C,D). Subsequent consults established disease stability with no new symptoms or activity. Infliximab was eventually tapered by 100 mg every four weeks. On her last consult at our clinic, she was on infliximab 100 mg infusions every four weeks with a final VA of 20/400 OD and 20/15 OS and stable findings on FA and macula OCT. Her average WBC count was 5700 ± 2200 cells/μl while on chlorambucil with prednisone, and 3800 ± 500 cells/μl when she was on chlorambucil after starting infliximab infusions without prednisone. The total duration of treatment before and after beginning infliximab infusions was 40 and 19 months, respectively. The total length of follow-up is 108 months. The total period of remission off chlorambucil is 60 months (Table 1).

Case 3. A 32-year-old female presented with decreased vision, floaters, and photophobia OS. Vision OD was poor due to retinal detachment after a motor vehicle accident. Before presenting to her initial consultation at our clinic, complete blood work-up for uveitis had ruled out non-infectious and infectious posterior uveitis, including syphilis and tuberculosis and she had already been diagnosed with idiopathic SC. She had been on MMF 2 g daily, cyclosporin 25 mg and prednisone 30 mg daily for fourteen months. Her vision was hand-motion OD and 20/20 OS at presentation. A fundus examination revealed optic atrophy and a horizontal scar OD in addition to diffuse chorioretinal (CR) scarring in both eyes. Given the possibility of the activity of the lesion potentially affecting the fovea OS and her monocular status, chlorambucil and cyclophosphamide were discussed as treatment options.

The patient was started on chlorambucil 4 mg daily and continued on 25 mg of prednisone daily. A month later, her WBC count dropped from 14,800 to 12,100 cells/μl. However, she felt her vision had decreased once again after two weeks on chlorambucil. She was advised to increase chlorambucil to 6 mg/day from 4 mg/day, as well as increase prednisone to 40 mg daily. After one week at this dose, she reported stable vision OD. Chlorambucil dose adjustment with weekly WBC count and oral prednisone were continued until she reported stable vision and no other symptoms. At this time, she was advised to increase chlorambucil to 12 mg daily.

Approximately four months after her initial visit, the patient presented to our clinic with worsening scotoma and floaters OS. At this point, she was on prednisone 5 mg daily and chlorambucil 10 mg daily. She had stopped chlorambucil for a week due to fever, and the WBC count was at 11,200 cells/μl. FA and ICG showed active choroidal inflammation at the lesion border, especially OS. Later on, she developed a diffuse, itchy rash, and because of this side effect, she was started on bi-weekly cyclophosphamide pulse therapy. She had five doses of cyclophosphamide pulse therapy, and her WBC count was between 4500 and 6300 cells/μl. However, a few days later, she complained of decreased vision OS with more central involvement. Her local ophthalmologist increased her prednisone to 60 mg, and she received her next cyclophosphamide infusion four days later with WBC count at 4000 cells/μl. Cyclophosphamide therapy was finally stopped due to persistent skin rash.

In the interim, she followed up with her local ophthalmologist while on oral prednisone with different doses based on disease activity. Her next visit with us was seven years later, and vision OS had deteriorated

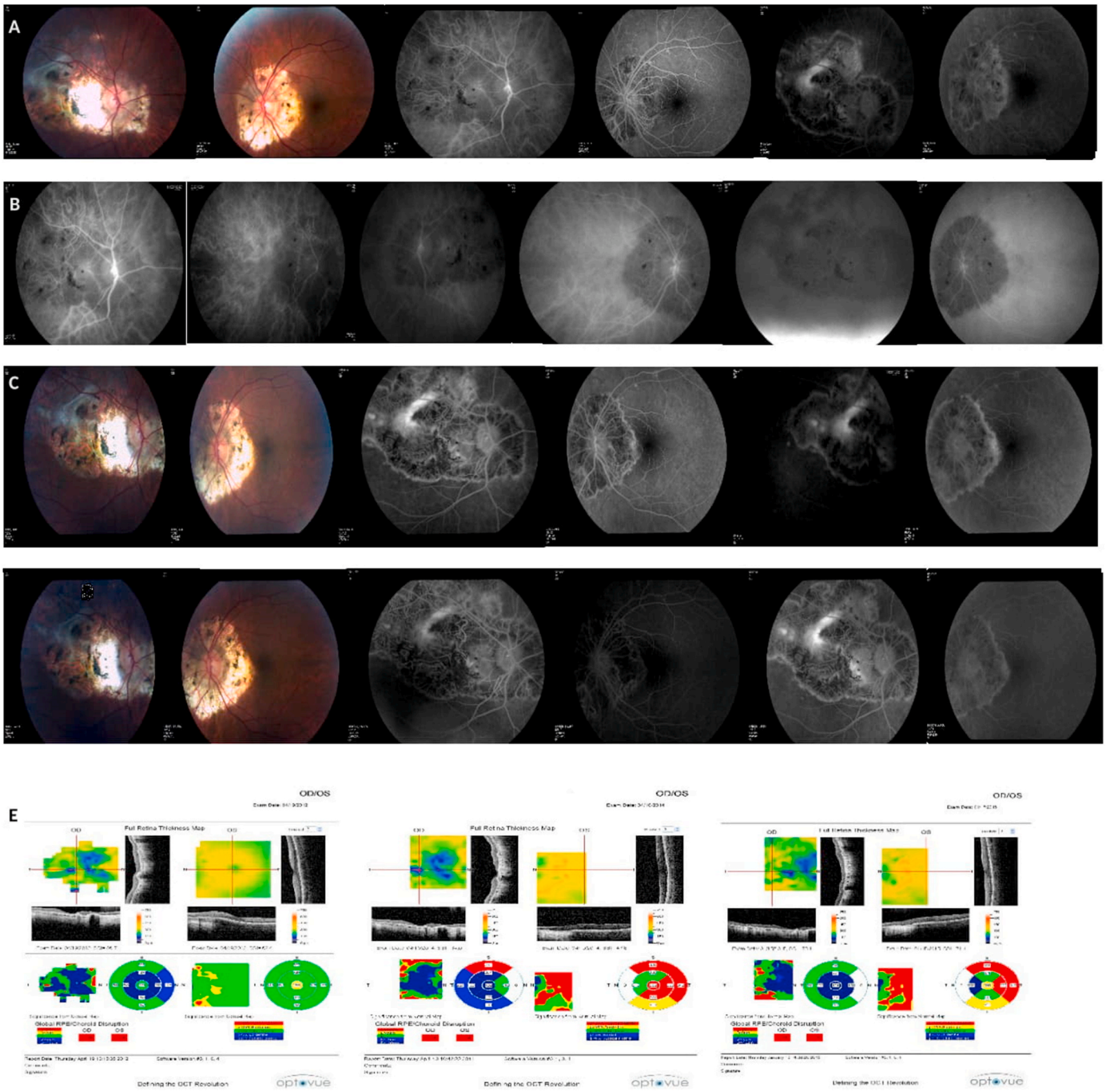

Fig. 2. (A) Fundus photo and fluorescein angiography of a patient with bilateral serpiginous choroiditis at the primary visit at our clinic. (B) The same patient during a recurrence in the left eye close to the fovea. (C,D) Stability of year after stopping chlorambucil while on infliximab tapering. (E) Macular optical coherence tomography at the first visit (left), during a recurrence (middle), and the last visit (right).

to 20/50. FA showed active inflammation OS in the form of enlarged CR lesions approaching the fovea with multifocal areas of leakage at the margins of the lesions (Fig. 3B). Up to that point, the patient had been off all immunomodulatory therapy (IMT) for seven years, yet only cyclophosphamide appeared to halt the progression of her disease. Monthly cyclophosphamide pulse therapy was resumed but was later stopped after eight months due to low WBC count. After this, she continued with oral prednisone 20 mg daily. At her last follow-up visit, chlorambucil was restarted due to the persistence of symptoms, worsening of vision OS, and the progression of lesion activity on imaging (Fig. 3C). Intravitreal steroid implants were also discussed. The patient was never able to taper off oral prednisone during treatment, and the average WBC count during her course of treatment was 8800 ± 3400 cells/μl. The total duration of treatment with chlorambucil was 5 months, cyclophosphamide was 10 months, and MMF plus cyclosporine was 14 months. The total duration of follow-up is 148 months. She has never been in remission for an extended period off medication (Table 1).

Case 4. A 47-year-old female was referred to our center with decreased vision OU for one month and had been started on prednisone 50 mg daily before her first visit with us. Her vision OD and OS were 20/30 and counting fingers at 1 m, respectively, at presentation. Dilated fundoscopy showed bilateral geographic lesions nasal to the fovea OD and involving the fovea OS (Fig. 4A). Complete blood work-up for uveitis ruled out non-infectious and infectious posterior uveitis,

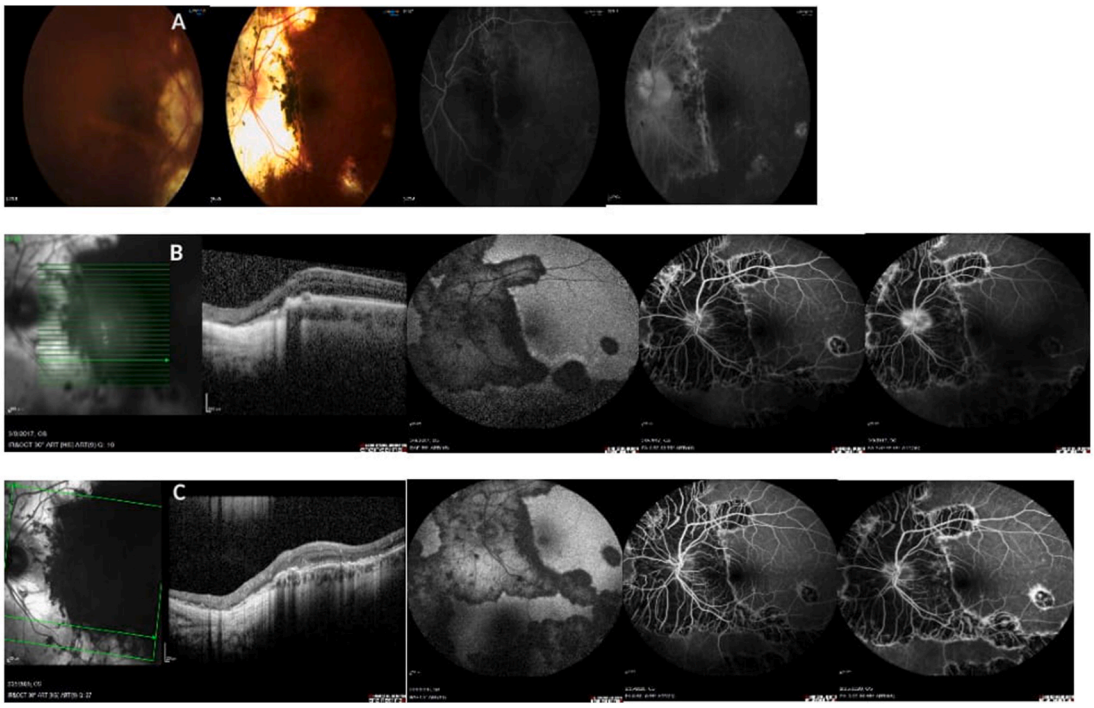

Fig. 3. (A) Fundus photo of both eyes of a patient with bilateral serpiginous choroiditis. History of traumatic retinal detachment surgery with legal blindness in the right eye and active serpiginous choroiditis in the left eye. Fluorescein angiography shows an active lesion in the left eye. (B) Optical coherence tomography, fundus autofluorescence, and fluorescein angiography during a recurrence where the patient was started on cyclophosphamide pulse therapy. (C) Progression of the lesion in the left eye with an active lesion in fluorescein angiography at her last visit. Intravitreal dexamethasone and triamcinolone implants were discussed at this visit.

including syphilis and tuberculosis. Based on these findings, and she was diagnosed with autoimmune SC OU. Oral prednisone was increased to 60 mg daily, and due to significant vision loss OS, she was started on chlorambucil 6 mg daily. Chlorambucil treatment with WBC count monitoring and tapering of oral prednisone was continued for a year. Once the oral prednisone taper was completed, she continued with chlorambucil monotherapy for five more months, at which time she had achieved remission. After four months; however, she had a flare-up OD, which was first treated with 1 g IV methylprednisolone infusion and intravenous methotrexate 200 mg/day. Subsequently, she was continued on subcutaneous methotrexate 15 mg weekly along with folic acid 1 mg/day for two years. She developed another flare-up when tapering methotrexate; hence methotrexate dose was boosted, and a combination of chlorambucil and oral prednisone was restarted. The patient was on chlorambucil and oral prednisone for one year, with an average WBC count of 6200 $\pm$ 3300 cells/μl. The patient was then on chlorambucil alone for another two months. She had been flare-free for twenty months when she had another episode. This time she was treated with intravenous and subcutaneous methotrexate. She had another flare during tapering of methotrexate and she is currently on a combination of chlorambucil, prednisone, and subcutaneous methotrexate therapy. The total duration of follow-up has been 116 months. She has never been in remission for an extended period (Table 1).

3. Discussion

The pathogenesis of serpiginous choroiditis (SC) is unknown. The course of the disease is indolent and can be asymptomatic until it involves the macula and the central vision. Many patients can have old scars even at the first visit when they are diagnosed with SC.[14] Laatikainen and Erkkila et al. reported that new lesions may appear at an interval of 3 months–4 years. They also demonstrated that active lesions resolve in a few weeks; however, signs of activity may last between 1 and 9 months.[14] Central vision is involved in 20%–50% of cases, with the likelihood increasing with longer duration of follow-up and disease activity.[8,14] Recurrences that affect the macula can cause severe visual loss of less than 20/200, which is typically irreversible and may induce CNV in the macula or around the optic disc.[15]

There are no controlled trials for the treatment of SC due to the rarity of the disease. Cytosine arabinoside, azathioprine, and oral prednisone were used with reported improved visual acuity in one month.[16] Employment of a combination of cyclosporine and oral prednisone as a treatment of active SC had conflicting results. Hopper and Kaplan reported a triple-agent regimen of azathioprine, cyclosporine, and oral prednisone that resulted in rapid control of the active SC and vision recovery; however, disease recurrence was the study's main problem.[9] Akpek et al. employed the same regimen in a more extended study and found that this regimen helped keep the inflammation quiet during treatment; however, it did not maintain remission off medication.[17]

Alkylating agents can bind to DNA, interfere with DNA replication, and subsequently interfere with cell division. Cyclophosphamide is commonly used because of its predictable, dose-dependent, and reversible adverse effects on WBC count[18]; nonetheless, it can result in serious side effects, some of which are life-threatening. These side effects include reversible hematuria, hemorrhagic cystitis, reversible alopecia, sterility, bladder cancer, lymphoma, and leukemia. Chlorambucil is another alkylating agent primarily used for the treatment of several lymphoproliferative diseases. It is a stable derivative of the nitrogen mustard.[19] Based on its ability to reduce circulating lymphocytes, chlorambucil is effective in the treatment of rheumatologic diseases, including juvenile rheumatoid arthritis, systemic lupus erythematosus, and nephrotic syndrome.[20–23] Given the availability of other conventional immunomodulatory agents and biologic response modifiers that yield better results with fewer unpredictable side effects, ophthalmologists are reluctant to use chlorambucil. Our knowledge about biologic response modifier agents is limited to a few case reports and some of our patients had already failed infliximab, mycophenolate mofetil, methotreaxte before their first presentation to us or during follow-up with us. Palmer et al. studied the side effects of chlorambucil and found that these side effects are related to the total dose and duration of

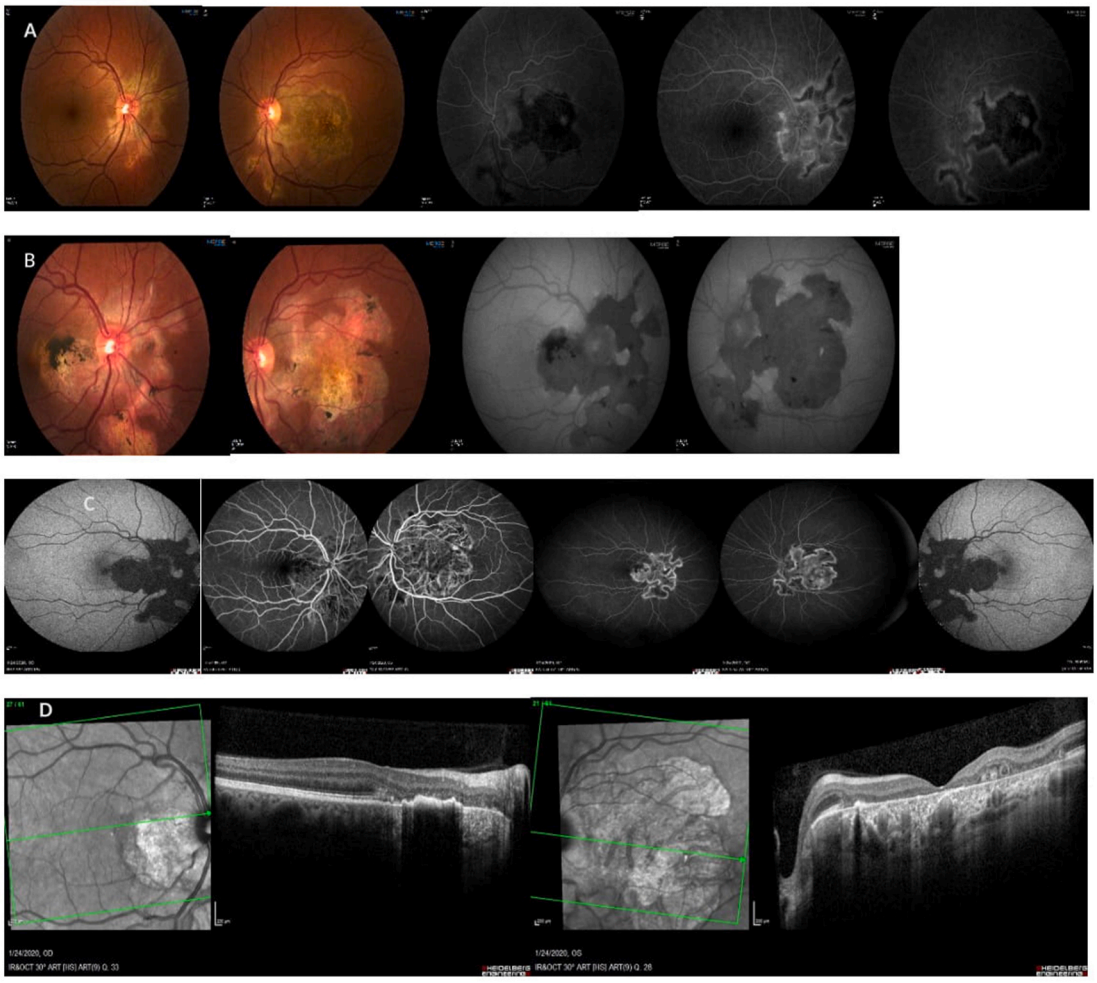

Fig. 4. A serpiginous choroiditis patient with multiple recurrences despite treatment with a combination of oral prednisone and chlorambucil therapy. (A) Color fundus photos and fluorescein angiography of both eyes at the first visit, which showed activity around the lesion in both eyes. (B) The second row shows the progression of lesions in both eyes during a recurrence on fundus photos and fundus autofluorescence. (C) Fundus autofluorescence and fluorescein angiography showed reactivation of the supratemporal area of the lesion in the right eye. (D) Optical coherence tomography shows the lesion, edema, and destruction of the supratemporal part of the lesion, compatible with fundus autofluorescence and fluorescein angiography. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

treatment.[24] However, Tessler et al. found chlorambucil to be a successful treatment for different types of uveitis with no severe complications during 12 years of follow-up. They also reported complete remission in all patients. Although chlorambucil dose in their study was administered regardless of body weight, it did not exceed 2.2 g per patient during the entire treatment.[25] Based on these findings, recent studies still rely on alkylating agents including cyclophosphamide and chlorambucil for classical and macular SC.[5,12,32]

It may take more time for chlorambucil to show its therapeutic and toxic effects. Patients on this medication should be monitored with weekly blood counts, specifically WBC and platelet counts, since its side effects are not always dose-related.[25] Chlorambucil is administered orally because it has excellent gastrointestinal absorption, and its superiority over cyclophosphamide is related to the absence of associated side effects such as hair loss, hemorrhagic cystitis, and bladder cancer.[26]

The recommendation for the daily and total dose of chlorambucil is equal to or less than 0.2 mg/kg and 2.2 g, respectively. These recommendations help avoid late complications such as lymphoma and leukemia.[27] Various doses of chlorambucil have been employed in the past in the field of ophthalmology. The use of lower doses of chlorambucil over an extended period, such as more than one year, without provoking bone marrow toxicity is one approach.[28–31] However, it has been demonstrated that sustained remission of the disease is achievable when the WBC count remained depressed for at least six weeks. This finding suggests that effective treatment with chlorambucil requires the induction of a toxic hematologic response.[25]

The recent literature shows that alkylating agents are still the most potent and effective treatment in patients with SC.[4,12,32] Venkatesh and colleagues showed that intravenous cyclophosphamide pulse therapy provided a rapid resolution of active lesions and helped maintain good functional visual acuity.[4] However, they admitted that this treatment might not prevent recurrences in patients with SC.[4] Venkatesh et al. also studied intravenous methylprednisolone and cyclophosphamide in macular SC; they, again demonstrated it could be effective in acute macular SC, yet admitted that this treatment had no effects on disease relapses in the long-term.[32] Ebrahimiadib et al. retrospectively studied 17 patients on chlorambucil with dose escalation based on weekly WBC count, with the target of 3000–4500 white blood cells/μl. They concluded that chlorambucil was well tolerated by the patients and was effective in preventing recurrences.[12] Although all these recent studies provided important facts regarding SC treatment, they did not discuss the next step for the patients who failed these treatments. In the current study, we decided to evaluate the possible causes of chlorambucil treatment failure in patients with resistant SC and to examine possible successful regimens in these patients. To the best of our knowledge, this study is the first one which evaluates the possible remedy for resistance

to chlorambucil as one of the most commonly employed medications in SC patients.

Histopathological studies in SC have demonstrated that lymphocytes infiltrate the choroid, and less commonly, vessels, leading to subsequent choriocapillaris occlusive vasculitis. This finding may indicate the important roles of lymphocytes in the pathogenesis of the disease.[5] The histopathology in SC is very similar to birdshot chorioretinopathy.[33,34] On the other hand, multiple studies have discussed the effects of long-term systemic corticosteroids on lymphocyte proliferation and T-cell population.[35,36] Ferrari et al. reported increased lymphocytes, including increased absolute numbers of T cells, $CD4^+$ and $CD8^+$ cells, after four weeks of corticosteroid therapy in idiopathic thrombocytopenic purpura (ITP).[35] Moreover, lymphocyte redistribution has been discussed in long-term steroid therapy.[36] These changes associated with long-term corticosteroid use may interfere with the aim of chlorambucil treatment, since cells with higher proliferation rates are the target of this therapy. The negative effect of long-term systemic corticosteroids on birdshot chorioretinopathy has been studied in the past.[37,38] Due to similarities between birdshot chorioretinopathy and SC in terms of histopathology, these facts can be applied to SC patients as well.

The target WBC count for chlorambucil therapy for SC is between 3000 and 4500 cells/μl. Chlorambucil dose adjustment is based on a weekly WBC count. In our experience, patients might be considered cured if there is no recurrence during the treatment period, which is around one year. Our observation in this case series showed that patients on high doses of systemic corticosteroids have unstable WBC count during chlorambucil therapy. Keeping this count in the satisfactory range for a reasonable period of at least six weeks can be challenging since it has been shown that induced toxic hematologic response is required for effective treatment with chlorambucil.[25] The first two patients in this case series achieved durable remission and were likely cured after employing local corticosteroids or systemic immunomodulatory therapy, which allowed us to stop systemic corticosteroid use during chlorambucil therapy. However, the third and fourth patients are still experiencing recurrences since all systemic immunomodulatory therapies were unable to induce steroid-free remission. Local corticosteroid therapy was also recommended for both of the patients, but its potential side effects and the patients' monocular statuses made this option unappealing.

We might be criticized for not employing local corticosteroid monotherapy without any systemic therapy. We believe that, although corticosteroids are the best option for controlling of acute ocular inflammation of any type, they are not potent enough to prime or reprogram the immune system[12] and not to respond to self-antigens as we expect with immunomodulatory therapy. This is similar to what occurs to pathologic cancer cells especially in blood cancers (lymphoma and leukemia) in patients who achieve remission with chemotherapy which is an advanced and more aggressive form of immunomodulatory therapy. Based on the above mentioned theory, corticosteroids as monotherapy cannot halt the inflammation thoroughly, so the ongoing inflammation can cause more cells destruction and epitopes exposures which might result in more resistant ocular inflammation which is believed to happen in patients with resistant autoimmune SC. we assume that the employment of systemic corticosteroid therapy, along with chlorambucil, is the main obstacle in achieving remission in patients with SC. This combination therapy is mostly seen in monocular patients or in vision-threatening SC where there is a lower threshold for aggressive systemic corticosteroid therapy in these patients.

We might also be criticized for using different therapies in one patient; however, we follow the strategy of "one change at a time" and this means that any time a conventional IMT is tried, we wait for three months with no changes to assess its effectiveness. For biologic response modifier agents, we wait for two months. This strategy makes interaction between medications unlikely. Moreover, since our mission is systemic steroid free remission, we only consider a medication to be effective if the inflammation stays in remission even after the effects of steroids are gone. Furthermore, none of these therapies induced long term remission in our patients.

Dexamethasone intravitreal implants have been employed in the treatment of active SC and serpiginous-like choroiditis.[39,40] In these studies, the authors showed the success of this implant in controlling active SC. Based on these studies, dexamethasone can be an alternative to high dose oral or intravenous corticosteroid without systemic side effects including its effects on bone marrow, secondary lymphoid tissues, and peripheral blood regarding WBC counts, especially lymphocytes.

One common fact between all patients in this case series is the instability of WBC count during chlorambucil therapy plus systemic corticosteroids. This issue was addressed in one patient with dexamethasone intravitreal implant and in another patient with infliximab therapy. Both patients allowed us to taper and stop oral prednisone during chlorambucil therapy. The latter patient has been in remission for four years, which is the time frame during which one would expect a new lesion based on the Laatikainen and Erkkila et al. study.[14] Despite this, this patient continues to take infliximab at a dose of 300 mg every four weeks since there is a fear of SC recurrence once infliximab therapy is terminated. However, this concept and hypothesis need further, more sophisticated examination.

This study had inherent limitations given its retrospective study design with a small sample size due to the rarity of cases of SC. It was even more challenging to find refractory cases with a reasonable follow-up period to expect a recurrence as all of these patients have at least 8 years of follow-up at our center without any serious side effects. Furthermore, all confounding factors cannot be controlled in a retrospective study. Regardless, we believe that confounding factors related to WBC might not interfere in this study since chlorambucil dose is adjusted based on WBC count and in clinical practice, changes in WBC count are typically more related to changes in corticosteroid dosage. Based on all these limitations, the results of this case series should be interpreted with caution and justifies the need for more potent studies.

4. Conclusion

The stability of WBC counts within toxic levels close to normal or lower limits of normal (3000–4500 cells/μl) during treatment with chlorambucil is an essential factor for the success of this therapy. A combination of dexamethasone intravitreal implant with chlorambucil therapy can be an effective and promising regimen in inducing and maintaining remission in refractory SC patients who fail a combination of systemic corticosteroid and chlorambucil therapy as the first line therapy. However, this primitive hypothesis should be investigated with more potent studies and larger sample sizes.

Patient consent

Consent to publish the personal information and cases details was obtained from all the patients.

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The other authors have nothing to declare.

Compliance with ethics guidelines

This study was approved by the New England Institutional Review Board, which has issued a waiver of informed consent for the retrospective chart review analysis. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All participants provided consent for publication if any identifying information is included in the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declaration of competing interest

No conflicting relationship exists for any author.

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