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Resistant Serpiginous Choroiditis Successfully Treated with Oral Chlorambucil and Intravitreal Bevacizumab Injections

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Introduction

Serpiginous choroiditis is a recurrent, asymmetric, inflammatory condition affecting both eyes, characterized by choroidal inflammation with loss of the choriocapillaris, atrophy of or damage to the overlying retinal pigment epithelium, and photoreceptor degeneration.[1,2]

Patients with serpiginous choroiditis often present with reduced central vision, metamorphopsia, and scotoma. However, they may remain asymptomatic until the macula is affected. In most cases, the anterior chamber and vitreous remain quiet and clear. Diagnosis is generally straightforward when active choroiditis is seen alongside inactive scars that are typically found in the peripapillary area. Useful imaging techniques for confirming the diagnosis include fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT). Active lesions exhibit a hypoautofluorescent center bordered by a halo of hyperautofluorescence on FAF. Inactive lesions, however, appear uniformly dark, showing consistent hypoautofluorescence. FA of active lesions along the edge of an atrophic area reveal early hypofluorescence followed by late leakage. ICGA is marked by hypocyanescent areas that persist from the early to late phases. OCT can reveal signs of choroidal neovascularization (CNV).[2,3]

Treatment involves high-dose corticosteroids, which resolve the inflammation rapidly but often fail to prevent recurrence.[4] Immunosuppressive drugs, including methotrexate, azathioprine, cyclosporine, chlorambucil, and cyclophosphamide, can lead to longer periods of disease inactivity and minimize the side effects of high-dose systemic steroids. Alkylating agents must be used cautiously due to potentially severe complications, such as leukopenia and an increased risk of malignancy.[5] Tumor necrosis factor-alpha (TNF-α) inhibitors, including infliximab and adalimumab, are biological response modifiers that have been used to treat patients with serpiginous choroiditis, but their effectiveness has been limited.[6-8]

Herein, we present the case of a 70-year-old male with resistant serpiginous choroiditis treated with chlorambucil and intravitreal bevacizumab injections.

Case Report

A 70-year-old male presented with several days of blurry vision and metamorphopsia in the right eye. The left eye had poor vision due to presumed ocular histoplasmosis 20 years earlier, but there had been no problems with the right eye until recently. The patient was otherwise healthy, with no systemic diseases and no history of ocular or systemic surgery. He had not received any local or systemic ocular treatment and was not on any medication. On initial examination, best corrected visual acuity (BCVA) was 20/25 in the right eye and 20/250 in the left eye. Slit-lamp examination was unremarkable in both eyes, with no cells in the anterior chamber of either eye. Dilated ophthalmoscopy revealed peripapillary atrophic scarring extending from the optic disc nasally and superotemporally in the right eye, and extensive peripapillary atrophic scarring with pigment clumps extending from the disc both nasally and temporally in the left eye (Figures 1A, B). OCT of the macula in the right eye (Spectralis, Heidelberg Engineering, Inc., MA, USA) revealed an area of subretinal fluid (SRF) between the fovea and optic disc and the presence of CNV at the temporal border of the lesion (pitchfork sign). The left eye showed extensive atrophic scarring in the macula (Figures 1C-E). FAF revealed nasal peripapillary hypoautofluorescence and a band of hyperautofluorescence extending from the inferotemporal side of the lesion into the macula in the right eye. The left eye showed a large area of peripapillary hypoautofluorescence with a distinct border in the macula (Figures 1F, G). FA in the right eye showed leakage at the border of the lesion superotemporal to the optic disc and staining of the rest of the lesion. FA in the left eye revealed staining of the lesion (Figures 1H, I). At this point, the differential diagnoses included serpiginous choroiditis along with other etiologies for multifocal or placoid chorioretinitis like multifocal chorioretinitis, toxoplasmosis, syphilis, Lyme disease, sarcoidosis, and tuberculosis. Because of the presence of CNV, the patient was given an intravitreal bevacizumab injection. A complete uveitis workup was conducted.

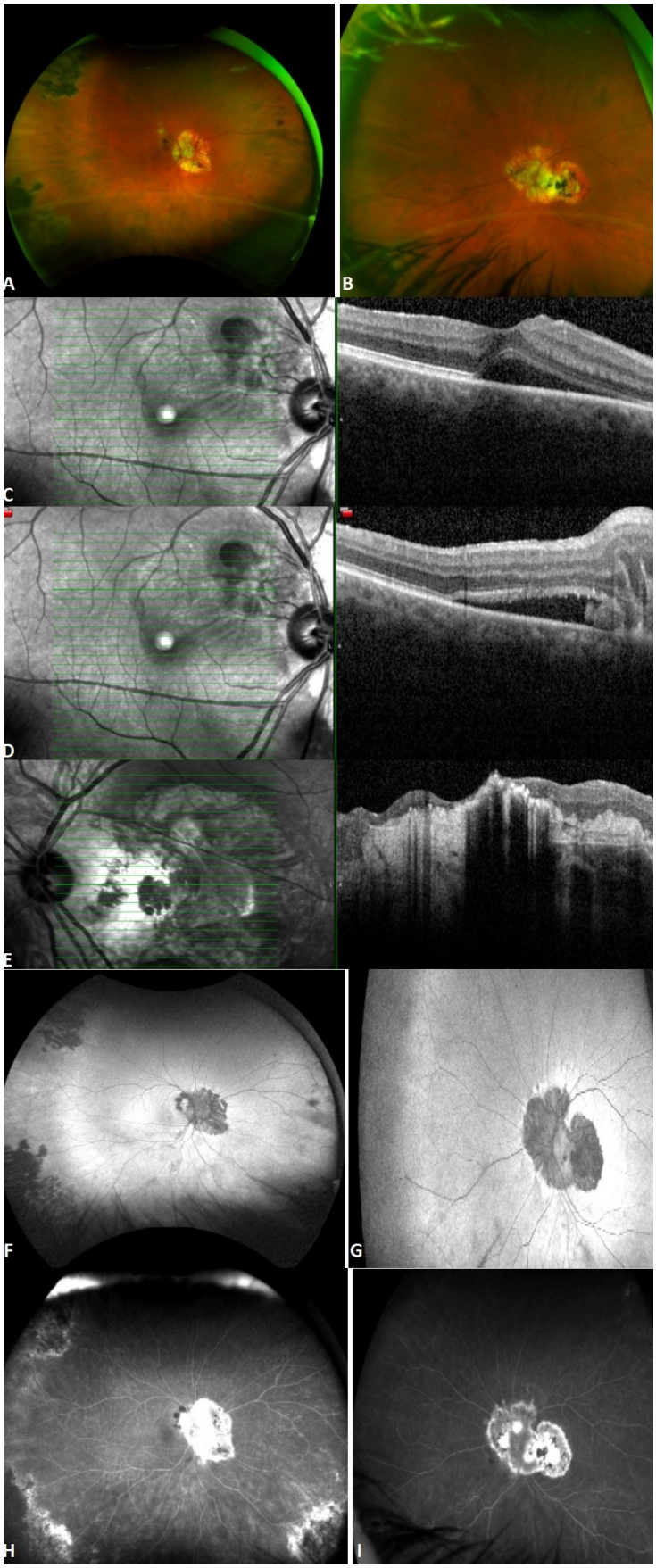

Figure 1. A. Dilated ophthalmoscopy of the right eye showed peripapillary atrophic scarring extending from the disc nasally and superotemporally and an elevated grayish lesion superotemporally in the macula with pigment. B. Dilated ophthalmoscopy of the left eye showed extensive peripapillary atrophic scarring with pigment clumps extending from the disc both nasally and temporally into the macula. C & D. Optical coherence tomography of the macula in the right eye revealed an area of subretinal fluid between the fovea and the disc and the presence of choroidal neovascularization in the inferotemporal border of the lesion (pitchfork sign). E. Diffuse atrophic scarring was present in the left eye with some fibrosis. F. Fundus autofluorescence in the right eye revealed nasal peripapillary hypoautofluorescence and a band of hyperautofluorescence extending from the inferotemporal side of the lesion into the macula. G. A large area of peripapillary hypoautofluorescence with a distinct border was present in the macula of the left eye. H. Fluorescein angiography (FA) in the right eye showed leakage at the border of the lesion superotemporal to the optic disc and staining of the rest. I. FA revealed staining of the lesion in the left eye.

The following lab tests were negative or within normal range: complete blood count, antinuclear antibody, C-reactive protein, erythrocyte sedimentation rate, rapid plasma reagin, and fluorescent treponemal antibody absorption tests for syphilis, toxoplasmosis IgG/IgM, Lyme disease Western blot, QuantiFERON-gold for tuberculosis, urinalysis, and lysozyme and angiotensin converting enzyme for sarcoidosis. A diagnosis of serpiginous choroiditis was made.

The patient was started on 1 mg/kg (70 mg) of prednisone daily, along with monthly intravitreal injections of bevacizumab. A close follow-up with dilated ophthalmoscopy, FAF, and OCT revealed inactive lesion and resolution of SRF after two monthly intravitreal bevacizumab injections (Figures 2A-C). Six months later, while on prednisone 5 mg

daily and intravitreal bevacizumab q6 weeks, SRF recurred (Figure 2D).

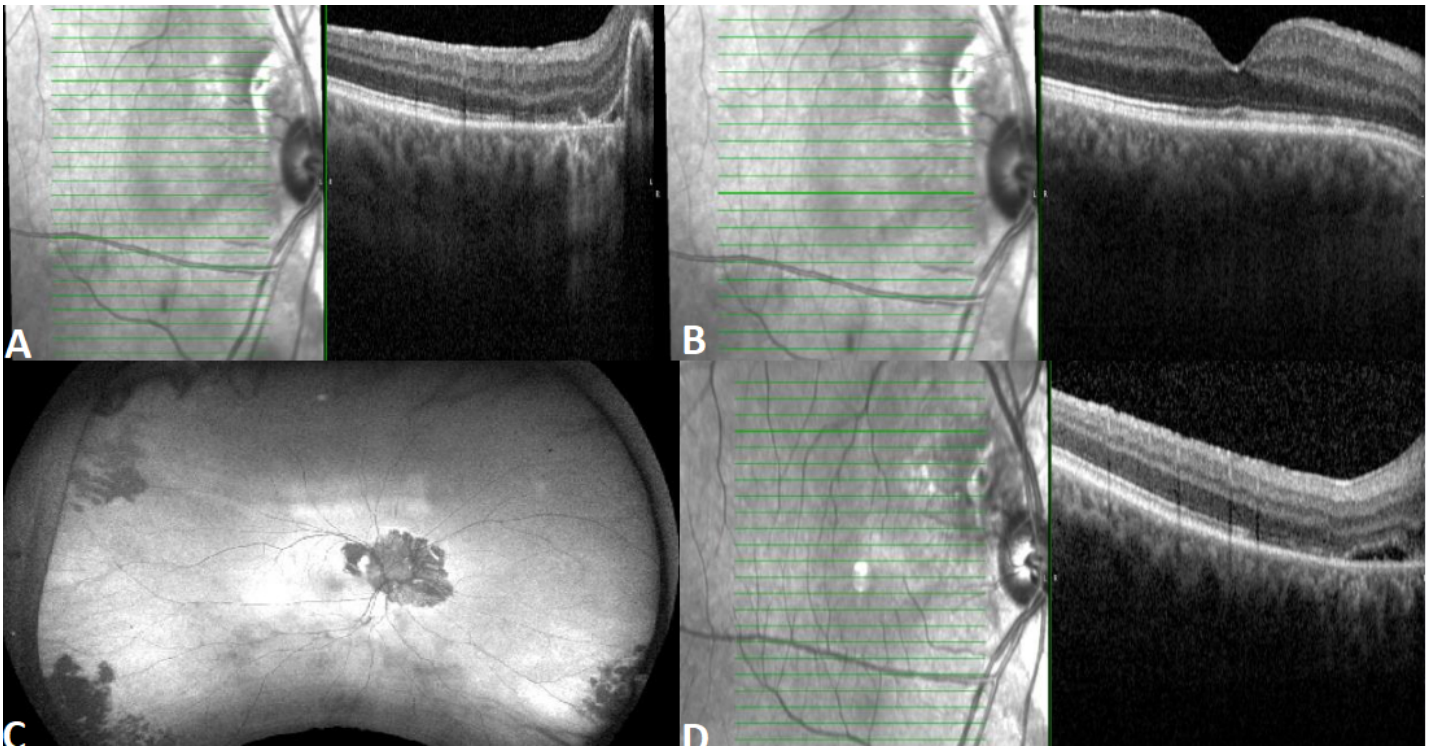

Figure 2. A & B. Optical coherence tomography (OCT) of the right eye revealed resolution of SRF after two monthly intravitreal bevacizumab injections. C. Fundus autofluorescence did not show hyperautofluorescence at the borders of the lesion. D. OCT of the right eye showed recurrent SRF while on prednisone 5 mg daily and intravitreal bevacizumab q6 weeks.

After discussing available therapeutic options including a repeat course of oral prednisone, an intravitreal dexamethasone implant, and immunomodulatory therapies such as chlorambucil, oral prednisone was discontinued. Another bevacizumab injection was given, and oral chlorambucil was initiated at 2 mg daily, with a weekly dose increase of 2 mg, along with weekly evaluation of WBC count to maintain levels at 3,500–4,000 cells/µl for 6–8 weeks.[9] This target was reached after 12 weeks, at a dose of 24 mg chlorambucil daily. Intravitreal bevacizumab injections were continued: monthly for three injections, followed by additional injections at 6, 8, and 12 weeks. The patient tolerated the treatment well, with no adverse effects noted during the course. After completion of this treatment regimen, OCT revealed no SRF. FAF revealed regression of the leading edge of the active lesion, with a clearly defined hypofluorescent border. Three years after completing the chlorambucil therapy, the patient remained in durable remission with BCVA 20/20 in the right eye, no visual

complaints, and no systemic adverse effects of treatment after being off medications and injections for more than two years (Figure 3).

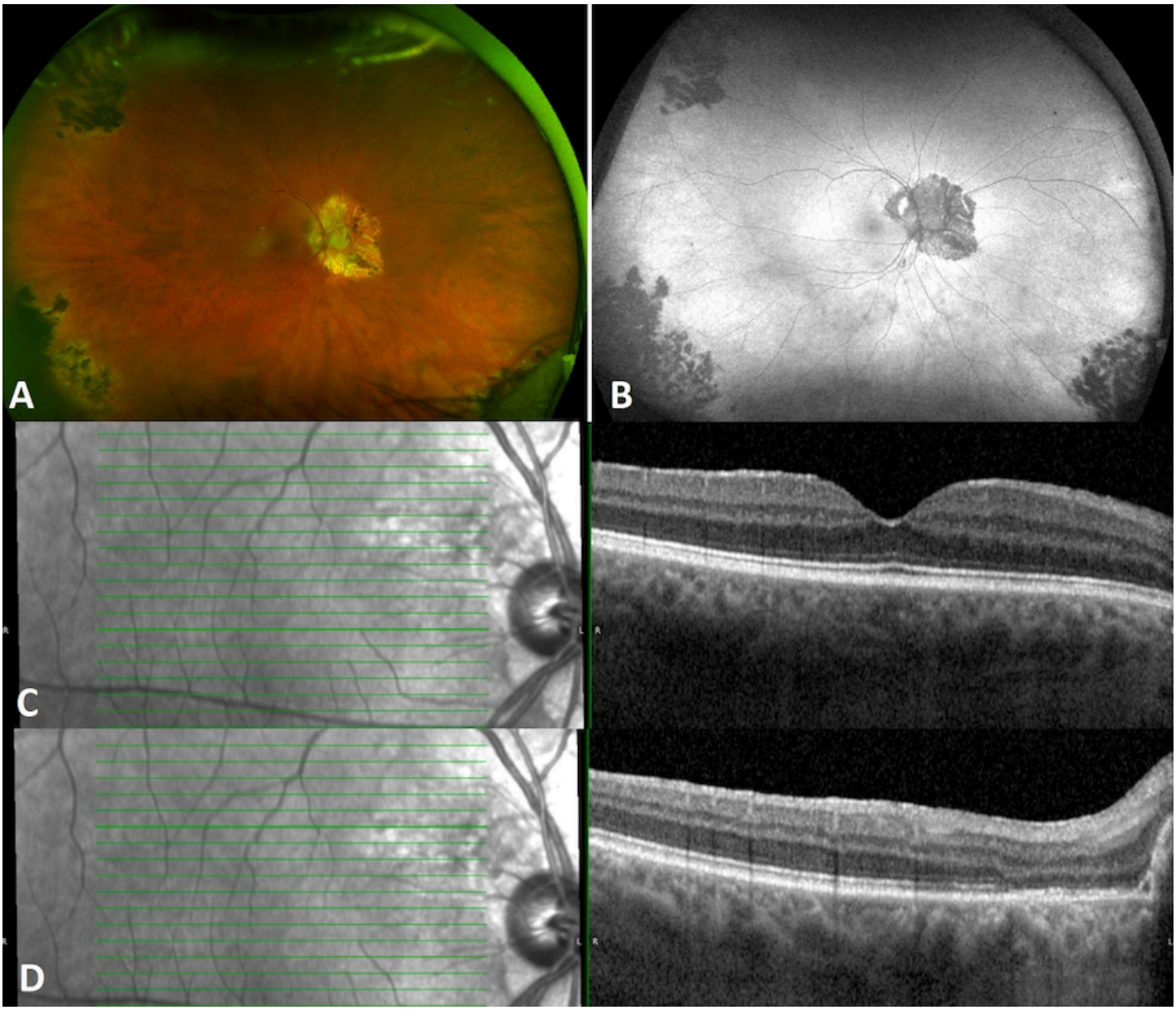

Figure 3. A. Dilated ophthalmoscopy of the right eye showed stable peripapillary atrophy extending from the disc nasally and superotemporally. B. Fundus autofluorescence of the right eye did not show any bands of hyperautofluorescence at the border of the lesion. C, D. Optical coherence tomography of the macula of the right eye revealed normal structure and contour of fovea with no subretinal or intraretinal fluid. Scar tissue was present at the border of the lesion superotemporal to the optic disc.

Discussion

The origin and pathophysiology of serpiginous choroiditis are unknown. It is classified as the occurrence of wavy or amoeboid-like lesions in the choroid, which can progress to a serpentine distribution of lesions

extending into the macula from the optic nerve, the turning point at which patients may become symptomatic. The progression of serpiginous choroiditis can lead to the development CNV, exacerbating these visual symptoms. Because the disease is rare worldwide, with an occurrence rate of less than 5% in uveitis patients,[10] it is challenging to standardize treatment approaches. The literature shows that corticosteroids, immunosuppressive agents, and intravitreal agents are effective for treating serpiginous choroiditis, and that the risk of recurrence during treatment taper or treatment discontinuation is important to assess when treating patients.[5]

Conventional immunomodulatory therapy and biologic response modifiers (TNF-α inhibitors) have been reported in case studies for the treatment of serpiginous choroiditis, but the evidence remains limited, and long-term follow-up data are lacking. In addition, recurrence rates have been high for both approaches.[3-8]

Ebrahimiadib et al. described 17 patients with serpiginous choroiditis, all with characteristic features of the disease similar to those of our patient, including serpiginous-like active and inactive lesions that were peripapillary, in the macula, or both. Sixteen patients were eventually treated with chlorambucil for between 3 and 24 months, with no recurrence in 13 patients (81.2%) at last follow-up (average: 43.9 ± 41.1; range: 5–120 months).[11] Some patients had a scar in at least one eye and vascular leakage in the macula. Patients had been treated with a combination of oral cyclosporine, intravitreal bevacizumab, oral prednisone, mycophenolate mofetil (MMF), and transeptal triamcinolone injection, but those treatments had failed. The majority of the patients initially received a combination therapy of cyclosporine and mycophenolate mofetil.

Chlorambucil treatment may have the most potential for reducing recurrence in individuals with serpiginous choroiditis. Goldstein et al. described a retrospective study of 53 patients treated with high-dose, short-term chlorambucil (2–9 months) for a wide range of uveitic conditions including serpiginous choroiditis, Behcet's disease, multifocal choroiditis, and sympathetic ophthalmia. Fifty-one of them were first started on corticosteroid and were tapering off at the start of chlorambucil treatment.[12] Chlorambucil doses ranged from 10 to 30 mg/day, with an average of 20 mg. The average duration of treatment was 16 weeks, but ranged from 7 to 40 weeks. Over an average follow-up period of 4 years, 77% of the patients had sustained remission. There were five cases of serpiginous choroiditis, and four of those achieved durable remission.[12] During the study, no one developed a malignancy, a known risk with this treatment.

Maleki et al. described a study of four patients with classic findings of serpiginous choroiditis treated with chlorambucil and oral or intravenous corticosteroids.[9] The authors concluded that systemic corticosteroid therapy could interfere with chlorambucil therapy due to the effect of systemic corticosteroids increasing WBC count and suggested intravitreal dexamethasone instead of systemic corticosteroid therapy along with chlorambucil. An intravitreal dexamethasone implant was denied by our patient's insurance company, so we decided to treat with chlorambucil as a single immunomodulatory agent. We propose that weekly monitoring and adjustment of WBC counts may allow achievement of the treatment goals more efficiently. One risk of chlorambucil as an immunosuppressive alkylating agent for serpiginous choroiditis is that it can lead to reduced DNA replication and life-threating complications such as leucopenia, thrombocytopenia, and malignancy.

weekly WBC monitoring may identify bone marrow suppression due to chlorambucil early. However, weekly laboratory monitoring is not feasible in all cases, and this approach relies on patient compliance. Our patient was treated with chlorambucil for a total of 20 weeks, but the therapeutic goal was achieved after 12 weeks of dose titration. The reason for maintaining a WBC range of 3,500–4,000 cells/μL was to produce sufficient immunosuppression to reset the immune system while minimizing the risk of severe infections associated with lower WBC counts.

Our patient experienced recurrent serpiginous choroiditis while receiving a low dose of prednisone and intravitreal bevacizumab injections. In light of the known effects of systemic corticosteroids on WBC counts, their potential interference with chlorambucil dose adjustments, and the risk of long-term systemic adverse effects, oral prednisone and intravitreal bevacizumab therapy were continued. This case illustrates that chlorambucil as a single immunomodulatory agent may be effective in inducing and maintaining remission of serpiginous choroiditis in some cases.

Conclusion

Oral chlorambucil as a single immunomodulatory agent alongside intravitreal injections of bevacizumab, with weekly WBC monitoring and dose adjustment to achieve treatment goals (a WBC count of 3,500–4,000 cells/μl for 6–8 weeks), showed promise as an approach to inducing durable remission of serpiginous choroiditis resistant to systemic corticosteroid therapy.

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Statement of Ethics

The patient gave oral and written consent to publish the data. The report does not include personal information that could identify the patient directly or indirectly. All medical interventions have been carried out according to the latest protocols of therapy. Reporting and writing are all in compliance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this topic.

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