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# Therapeutic Challenges in Birdshot Chorioretinopathy Over 16 Years

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## Abstract

We describe the therapeutic course of a patient with birdshot chorioretinopathy over 16 years. A woman first assessed in 2010 and followed regularly from 2015 to 2026 had human leukocyte antigen A29 (HLA-A29)-positive disease with bilateral cystoid macular edema. Prednisolone and ciclosporin initially controlled edema, but recurrence during tapering and treatment-associated morbidity complicated maintenance. Adalimumab produced initial anatomical improvement, followed by recurrent edema requiring right-eye intravitreal dexamethasone implants. Intravenous tocilizumab was introduced in December 2018 at 8 mg/kg every four weeks, with subsequent resolution of persistent left-eye edema and gradual withdrawal of ciclosporin. Tocilizumab was reduced to 4 mg/kg in January 2022 and discontinued in April 2023 after prolonged clinical stability. Bilateral edema and retinal vascular inflammation recurred by August 2023. Reintroduction at 4 mg/kg every four weeks was followed by documented edema resolution by December 2023. The interval was extended to six weeks in January 2026, with no macular edema in August 2026. Visual recovery remained limited in the presence of established macular atrophy. This course illustrates individualized treatment decisions across sequential conventional and biologic therapies. The withdrawal and reintroduction observations are hypothesis-generating; the retrospective single-patient design and concurrent treatments preclude conclusions about comparative efficacy or causality.

**Categories:** Therapeutics, Ophthalmology
**Keywords:** adalimumab, birdshot chorioretinopathy, ciclosporin, cystoid macular edema, immunosuppression, tocilizumab

## Introduction

Birdshot chorioretinopathy is a rare bilateral posterior uveitis characterized by cream-colored choroidal lesions, vitritis, and retinal vascular inflammation. It predominantly affects middle-aged individuals of European ancestry and is strongly associated with human leukocyte antigen A29 (HLA-A29) [1,2]. Population prevalence is poorly established; an estimate of approximately one case per 100,000 people in the United States has been proposed, rather than directly measured in a population survey [1]. Genetic associations involving HLA-A29 and endoplasmic reticulum aminopeptidase 2 (ERAP2) implicate altered antigen processing and presentation, although the initiating antigen and complete pathogenic pathway remain unresolved [2].

Diagnosis combines a characteristic phenotype with exclusion of alternative causes, rather than exclusion alone. The Standardization of Uveitis Nomenclature (SUN) classification criteria incorporate typical bilateral lesions and limited anterior inflammation or multifocal choroiditis with HLA-A29 positivity and characteristic fundus or indocyanine green angiographic findings [1]. Within the broader differential of white dot syndromes, acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is a distinct entity, typically presenting acutely with placoid lesions and early hypofluorescence followed by diffuse late hyperfluorescence on fluorescein angiography [3]. Syphilis, sarcoidosis, tuberculosis, and masquerade syndromes also require consideration according to the presentation.

Visual impairment may reflect recurrent macular edema, persistent retinal inflammation, or irreversible retinal damage; cataract can further impair acuity [4]. Consequently, assessment requires clinical examination and multimodal imaging, with functional testing where available. Long-term corticosteroid-sparing treatment is frequently necessary, sometimes combining agents [5,6]. In a cohort evaluating remission and relapse, approximately one-quarter of patients achieved sustained drug-free remission by four years, underscoring the uncertainty surrounding treatment withdrawal [7].

Biologic therapy may be considered when conventional agents provide insufficient control or cause unacceptable toxicity. Birdshot-specific observational data support adalimumab, a tumor necrosis factor inhibitor, although complete remission is not consistently achieved [8]. Tocilizumab blocks the interleukin-6 (IL-6) receptor and offers an alternative mechanism in refractory uveitis, particularly when macular edema persists. Evidence includes small retrospective series and the open-label STOP-Uveitis study, with more limited birdshot-specific follow-up [9-11]. These studies do not establish superiority over conventional immunosuppression or define an optimal maintenance or withdrawal regimen.

This report contributes a 16-year account of sequential conventional and biologic immunosuppression, local corticosteroid treatment, toxicity-related constraints, and individualized tapering. Its clinical value lies in integrating these decisions across the disease course, including relapse after tocilizumab withdrawal and subsequent edema control after reintroduction, while documenting persistent structural damage despite anatomical improvement.

## Case Presentation

### Initial presentation and conventional immunosuppression

A 51-year-old woman was assessed in October 2010 after 4-5 months of bilateral floaters and progressive visual decline. Visual acuity was approximately 0.70 logarithm of the minimum angle of resolution (logMAR) in each eye. Vitritis, venous sheathing, choroidal lesions, and optic disc edema were documented. Historical optical coherence tomography (OCT), subsequently reviewed in the clinical record, showed bilateral cystoid macular edema. The patient was lost to follow-up until August 2015.

At re-presentation, aged 56 years, visual acuity was 1.30 logMAR in the right eye and counting fingers at one meter in the left eye. Both anterior segments were quiet. Fundus examination documented mild vitritis, bilateral cream-colored choroidal lesions radiating from the optic discs, disc edema, macular edema, and retinal perivasculitis. A numerical vitreous inflammation grade was not recorded. The 2015 fluorescein angiograms showed retinal vascular leakage (Figure *1*).

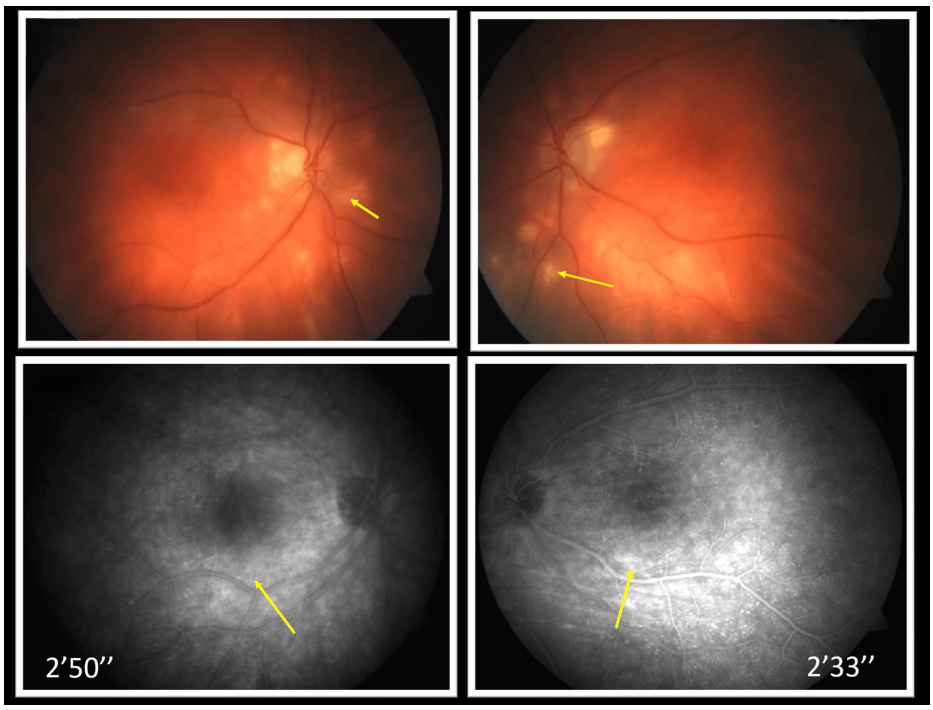



**FIGURE 1: Fundus photography and fluorescein angiography in 2015**

The right eye is shown in the left column and the left eye in the right column. Yellow arrows in the upper panels indicate representative cream-colored choroidal lesions. Retinal vascular leakage is also visible (yellow arrows in both lower panels). The displayed times refer to the angiographic phase after dye injection.

HLA-A29 testing was positive. The available workup included nonreactive syphilis and human immunodeficiency virus (HIV) serology, a negative interferon-gamma release assay (IGRA), and serum angiotensin-converting enzyme within the laboratory reference interval. Chest radiography and cranial computed tomography were reported as normal. The bilateral lesion pattern, quiet anterior segments, vitritis, retinal vasculitis, and HLA-A29 positivity supported birdshot chorioretinopathy, consistent with the phenotype described in the SUN classification framework [1]. Nonreactive treponemal testing and the absence of supporting chest radiographic findings reduced support for syphilis and sarcoidosis, respectively. The chronic course and lesion morphology favored birdshot over APMPPE. The later latent tuberculosis assessment is described separately below and was not interpreted as evidence that tuberculosis caused the ocular disease.

Selected diagnostic and safety-related laboratory results are summarized in Table *1*; the complete available panel is retained in the Appendices (Supplementary Laboratory Results). Hypercholesterolemia and elevated

immunoglobulin A were among the abnormalities. Minor biochemical, coagulation, and urinary deviations are identified in the supplement; the record does not establish their relationship to the ocular disease or treatment. The undated creatinine value of 0.7 mg/dL is separate from the later renal dysfunction documented clinically.

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| **HLA-A*29** | **Positive** | - | Not applicable (genotype) |
| HLA-B*5 | Negative | - | Not applicable (genotype) |
| HLA-B27 | Negative | - | NR |
| Antinuclear antibodies (immunofluorescence) | Negative | - | NR |
| Anti-DNA antibodies | Negative | - | NR |
| ENA screen | 0.10 | Index | Negative |
| Anti-PR3 antibodies | 0.10 | U/mL | 0.00-3.00 |
| Anti-MPO antibodies | 0.20 | U/mL | 0.00-5.00 |
| Angiotensin-converting enzyme | 46.7 | U/L | 8.0-52.0 |
| **Lysozyme** | **0.93** | mg/dL | 0.96-1.71 |
| Treponema pallidum total antibodies | <0.10 | Index | Nonreactive |
| HIV-1/2 antigen/antibodies | 0.30 | Index | Nonreactive |
| QuantiFERON-TB Gold | Negative | - | NR |
| Hepatitis B surface antigen | 0.14 | Index | Nonreactive |
| Hepatitis B surface antibodies | <3.1 | mIU/mL | Nonreactive |
| Hepatitis B core antibodies | <0.07 | Index | Negative: <0.5, positive: ≥0.5 |
| Hepatitis C total antibodies | 0.12 | Index | Nonreactive |
| Leukocytes | 9.40 | $\times 10^9$/L | 4.50-11.50 |
| Hemoglobin | 15 | g/dL | 12-15 |
| Platelets | 185 | $\times 10^9$/L | 150-450 |
| Erythrocyte sedimentation rate | 3 | mm at 1 hour | 0-20 |
| Creatinine | 0.7 | mg/dL | 0.5-1.2 |
| Alanine aminotransferase | 26 | U/L | 3-31 |
| Aspartate aminotransferase | 19 | U/L | 3-31 |
| Total cholesterol | **276** | mg/dL | <200 |
| LDL cholesterol | **182.4** | mg/dL | 100.0-129.0 |
| Immunoglobulin A | **552** | mg/dL | 40-350 |
| High-sensitivity C-reactive protein | 0.24 | mg/dL | <0.50 |

**TABLE 1: Selected laboratory investigations relevant to diagnosis and systemic assessment**

Bold numerical results fall outside the reporting laboratory's reference interval. HLA-A29 positivity supports the clinical diagnosis but is not diagnostic in isolation. The undated negative IGRA is separate from the positive tuberculin skin test recorded in May 2018. The undated creatinine of 0.7 mg/dL is not the 2017 value discussed in the text. Full results, including other deviations, are retained in the Appendices.

HLA: human leukocyte antigen, HIV: human immunodeficiency virus, ENA: extractable nuclear antigens, PR3: proteinase 3, MPO: myeloperoxidase, DNA: deoxyribonucleic acid, LDL: low-density lipoprotein, IGRA: interferon-gamma release assay, NR: not reported

A dash denotes a qualitative result without a unit. HLA-B*5 is retained as reported in the molecular typing result; the request page listed HLA-B51.

Oral prednisolone 60 mg/day was initiated in August 2015, and ciclosporin 5 mg/kg/day in two divided doses was added in September. Ciclosporin was maintained at approximately this weight-based dose for two years, with reduction beginning after adalimumab introduction in June 2017. OCT showed resolution of edema by November 2015, revealing marked macular atrophy (Figure *2A*-*2D*), with limited visual improvement.

Recurrent edema during prednisolone tapering in July 2016 prompted an increase from 15 to 20 mg/day; ciclosporin was documented at 200 mg twice daily during this period.

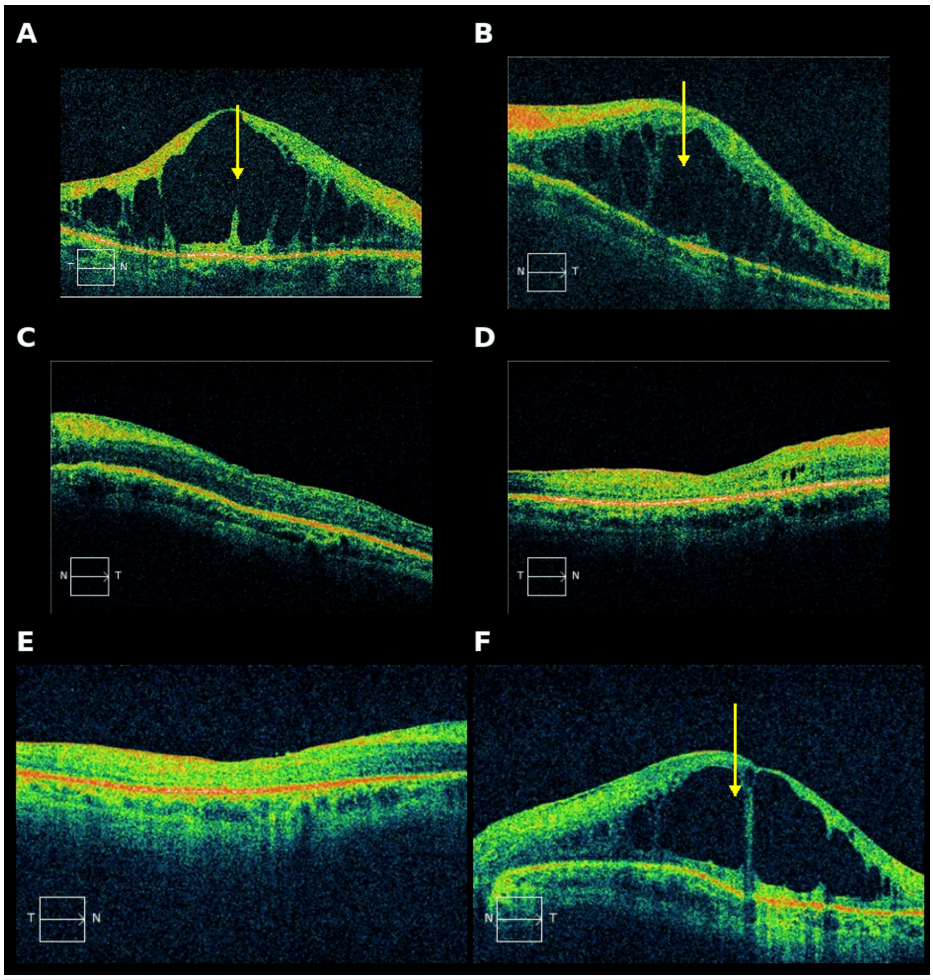



**FIGURE 2: Optical coherence tomography during conventional and local treatment**

(A) Right eye and (B) left eye cystoid macular edema in 2015. (C) Right eye and (D) left eye edema reduction with macular thinning after prednisolone and ciclosporin. (E) Dry right macula and (F) persistent left-eye edema during the 2018 local treatment phase. Yellow arrows identify intraretinal cystoid spaces. Panels were extracted from the earlier conference poster; exact acquisition dates for the response panels were not available. Original scan orientations and embedded nasal (N) and temporal (T) markers were preserved; panels are not presented as geometrically matched scans.

Maintenance treatment was complicated by substantial morbidity. Hypertension required antihypertensive treatment, and osteoporosis with multiple vertebral compression fractures was identified during prolonged corticosteroid exposure. Gingival hypertrophy and hirsutism were recorded during ciclosporin treatment. Renal dysfunction, with creatinine reaching approximately 1.4 mg/dL in 2017 compared with earlier values of 0.8-1.0 mg/dL, further constrained treatment. These findings prompted efforts to reduce conventional immunosuppression while maintaining ocular control.

## Adalimumab and local corticosteroid treatment

Tuberculosis clinic evaluation before adalimumab was negative, with a 0-mm tuberculin skin test in February 2017, negative IGRA reported in May 2017, and negative sputum investigations. Recurrent ocular activity and the burden of conventional treatment prompted the introduction of adalimumab 40 mg subcutaneously every two weeks in June 2017. Initial OCT improvement was documented, more prominently in the right eye. Ciclosporin reduction began with the introduction of adalimumab, and prednisolone was discontinued in January 2018.

Macular edema recurred in March 2018. A right-eye intravitreal dexamethasone implant was administered in April. During tuberculosis surveillance in May 2018, the tuberculin skin test measured 10 mm, while

repeat IGRA remained negative. Sputum smear examinations were negative; the available culture record reported a negative first specimen and a contaminated second specimen. The tuberculosis clinic prescribed a nine-month course of isoniazid for latent tuberculosis, beginning in July 2018.

A second right-eye dexamethasone implant was administered in November 2018. Local treatment improved right-eye edema, whereas substantial left-eye edema persisted (Figure *2E*-*2F*). Adalimumab was discontinued in 2018 because sustained control was inadequate, prompting a switch in systemic treatment mechanism. Isoniazid treatment was already ongoing at that time.

## Tocilizumab and gradual treatment reduction

Intravenous tocilizumab was initiated in December 2018 at 8 mg/kg every four weeks, with concomitant ciclosporin initially maintained at 150 mg/day. The December OCT showed a dry, thinned right macula and marked left-eye edema. This examination was obtained just after the first infusion and shortly after the second right-eye dexamethasone implant; it was not an untreated bilateral baseline.

Left-eye edema improved by February 2019. Isoniazid was completed in April 2019, with continued tuberculosis clinic surveillance. By May 2019, edema had resolved with persistent macular atrophy (Figure *3*). In 2020, an eight-day history of productive cough with persistent purulent sputum, without fever, prompted treatment with cefuroxime 500 mg twice daily. Bilateral rhonchi were recorded with preserved breath sounds. The tocilizumab infusion was postponed for one week pending reassessment.

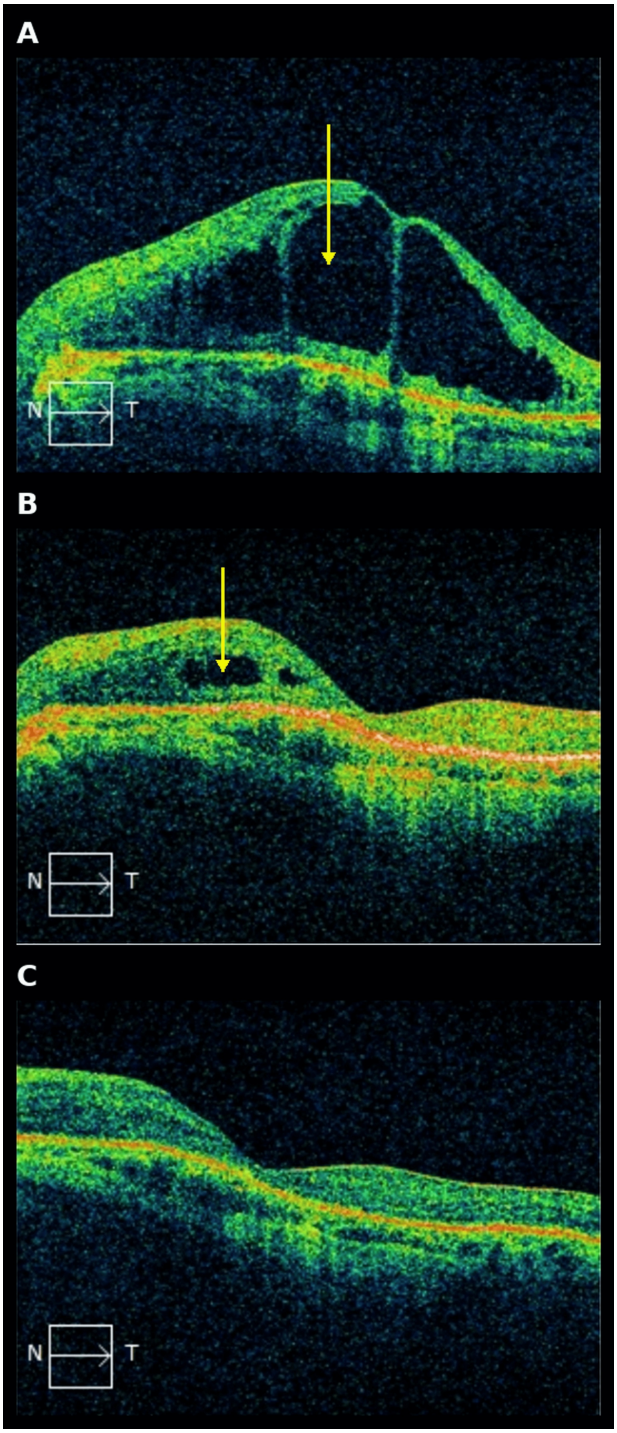



**FIGURE 3: Left-eye optical coherence tomography during early tocilizumab treatment**

All panels show the left eye. (A) December 2018: marked cystoid macular edema. (B) February 2019: improvement with residual parafoveal cysts. (C) May 2019: resolution of edema with macular thinning. Yellow arrows identify cystoid spaces in A and B. Embedded N and T markers denote nasal and temporal orientation.

Sustained clinical stability permitted further ciclosporin tapering and discontinuation in July 2021. Tocilizumab was reduced to 4 mg/kg every four weeks in January 2022. OCT continued to show macular atrophy without edema, and indocyanine green angiography (ICGA) in July 2022 was reported as showing no hypocyanescent spots. Tocilizumab was discontinued in April 2023 because of prolonged clinical stability.

## Recurrence after withdrawal and subsequent course

In August 2023, visual deterioration was accompanied by recurrent bilateral intraretinal cysts on OCT and

retinal vascular inflammation on angiographic assessment, more pronounced in the left eye. Tocilizumab was reintroduced at 4 mg/kg intravenously every four weeks. The December 2023 clinical record documented absence of macular edema on OCT.

Cataract surgery was performed in the left eye in 2024 and the right eye in 2025. In May 2025, uncorrected visual acuity was 0.70 logMAR in the right eye and counting fingers at two meters in the left eye. Macular edema remained absent, with persistent macular atrophy.

In January 2026, the tocilizumab interval was extended to six weeks while maintaining 4 mg/kg per infusion. OCT in August 2026 showed macular thinning without intraretinal fluid in either eye (Figure *4*). Uncorrected visual acuity was 1.05 logMAR in the right eye, with posterior capsule opacification treated with neodymium-doped yttrium aluminum garnet (Nd:YAG) capsulotomy, and counting fingers at two meters in the left eye. Post-capsulotomy visual acuity was not available. Table *2* summarizes treatment decisions and the available visual and imaging outcomes.

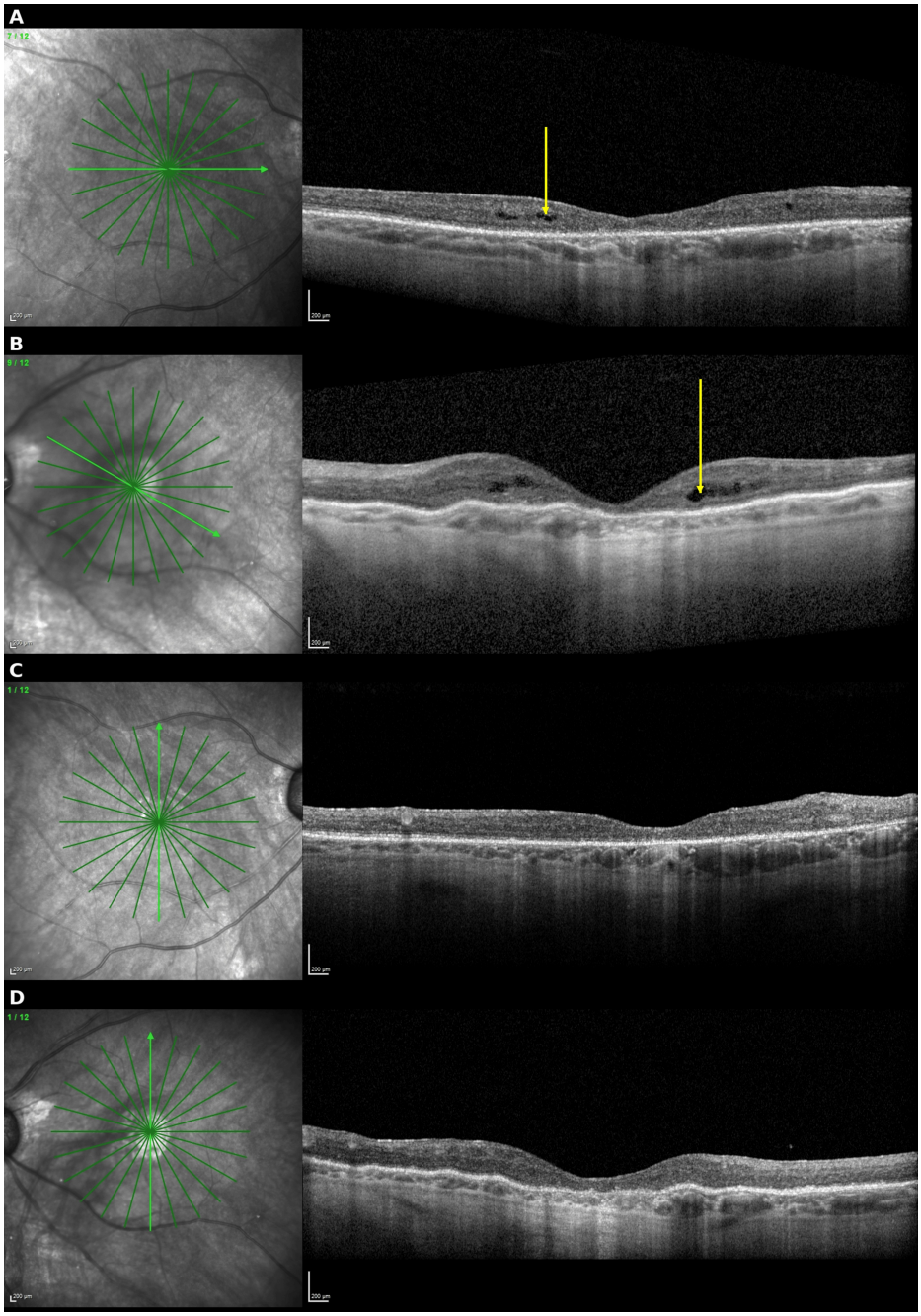



**FIGURE 4: Optical coherence tomography after treatment withdrawal and during subsequent maintenance**

(A) Right eye and (B) left eye in August 2023, showing recurrent intraretinal cysts (yellow arrows). (C) Right eye and (D) left eye in August 2026, showing macular thinning without intraretinal fluid during tocilizumab maintenance. Infrared images show scan locations; scan orientations differ between examinations.

| Period | Treatment and decision | Visual acuity | OCT and inflammatory findings |
|---|---|---|---|
| October 2010 | Initial assessment; follow-up subsequently interrupted | Approximately 0.70 logMAR in each eye | Bilateral cystoid edema; vitritis, venous sheathing, choroidal lesions, and disc edema documented |
| August-November 2015 | Prednisolone 60 mg/day; ciclosporin 5 mg/kg/day added in September | August: right, 1.30 logMAR; left, counting fingers at one meter | Bilateral edema and retinal vascular leakage; edema resolved by November, revealing atrophy |
| 2016 | Prednisolone increased during taper-related recurrence; ciclosporin documented at 200 mg twice daily | Not available | Recurrent macular edema |
| February-June 2017 | Negative tuberculosis evaluation; adalimumab 40 mg every two weeks introduced in June; ciclosporin reduction began | Not available | Initial OCT improvement, more prominent in the right eye |
| January-April 2018 | Prednisolone stopped in January; right-eye dexamethasone implant in April | Not available | Edema recurred in March |
| May-July 2018 | Tuberculin skin test 10 mm with negative IGRA; isoniazid started in July | Not available | No standardized ocular measurements available for this interval |
| November-December 2018 | Second right-eye implant in November; tocilizumab 8 mg/kg every four weeks in December with ciclosporin 150 mg/day | Not available | December: dry, thinned right macula; marked left-eye edema |
| February-May 2019 | Tocilizumab continued; isoniazid completed in April | Not available | Left edema improved in February and resolved by May; atrophy persisted |
| 2020-July 2021 | Cefuroxime for respiratory infection and one-week infusion delay in 2020; ciclosporin stopped in July 2021 | Not available | Sustained clinical stability permitting tapering |
| January-July 2022 | Tocilizumab reduced to 4 mg/kg every four weeks | Not available | No edema; July ICGA reported no hypocyanescent spots |
| April-December 2023 | Tocilizumab stopped in April; restarted at 4 mg/kg every four weeks in August | Visual deterioration reported; numerical acuity unavailable | August: bilateral edema and retinal vascular inflammation; December: no edema documented |
| 2024-May 2025 | Left cataract surgery in 2024; right in 2025 | May: uncorrected right 0.70 logMAR; left counting fingers at 2 m | Macular atrophy without edema |
| January-August 2026 | Infusion interval extended to six weeks in January; right Nd:YAG capsulotomy in August | August: uncorrected right, 1.05 logMAR before capsulotomy; left, counting fingers at 2 m | August: macular thinning without intraretinal fluid in either eye |

**TABLE 2: Clinical timeline with available visual and imaging outcomes**

Not available denotes a measurement not available in the retrospective dataset, not absence of clinical assessment. Early acuity correction status was not consistently documented.

OCT: optical coherence tomography, logMAR: logarithm of the minimum angle of resolution, IGRA: interferon-gamma release assay, ICGA: indocyanine green angiography, Nd:YAG: neodymium-doped yttrium aluminum garnet

## Outcome assessment

For this retrospective report, edema resolution denotes absence of macular edema on the documented OCT examination; recurrence denotes reappearance of intraretinal cysts after a period without edema. Inflammatory activity is reported separately from the available clinical and angiographic assessments. Clinical stability describes the treating clinicians' longitudinal assessment and is not a retrospectively assigned standardized remission score. Numerical acuities were converted from decimal notation using logMAR = -log10 (decimal acuity). Early correction status was not consistently documented; later measurements are explicitly identified as uncorrected. Counting fingers acuity is retained with the testing distance rather than assigned an arbitrary logMAR equivalent.

## Discussion

The principal challenge was sustained disease control through successive phases of recurrent edema, treatment-related morbidity, and irreversible macular damage. The diagnostic combination of bilateral cream-colored lesions, mild vitritis, retinal vasculitis, and HLA-A29 positivity supported birdshot chorioretinopathy. The SUN criteria provide a useful contemporary classification framework but were not prospectively applied at presentation in 2010. Likewise, missing inflammatory grades cannot be reconstructed from a qualitative historical description.

Prednisolone and ciclosporin initially controlled edema, but recurrence during tapering and substantial systemic morbidity limited maintenance. Ciclosporin 5 mg/kg/day is a recommended induction dose for endogenous uveitis; product information advises reduction to the lowest effective dose for maintenance [12]. Its use for approximately two years in this case must therefore be interpreted alongside the documented hypertension, gingival hypertrophy, hirsutism, and renal dysfunction, rather than as evidence that prolonged treatment at this dose is generally well tolerated. Adalimumab introduction allowed an attempt to reduce conventional treatment exposure.

Long-term observational cohorts provide context for this stepwise strategy. Kiss et al. described corticosteroid-sparing systemic immunomodulation in birdshot [5]. In a series of 132 patients, You et al. reported an increase in the proportion without clinically active inflammation from 39.4% after one year to 78.0% after five years [6]. These uncontrolled data support sustained reassessment of efficacy and tolerability but cannot identify a single optimal sequence or establish comparative efficacy between agents.

Adalimumab provided initial anatomical improvement but inadequate sustained control in this patient. In a retrospective series of 19 patients with refractory birdshot, adalimumab was associated with improved acuity and reduced concomitant immunomodulation, although complete remission was rarely achieved [8]. The present course illustrates one reason to change therapeutic mechanism, without implying that tumor necrosis factor inhibition is ineffective for birdshot generally. Right-eye dexamethasone implants offered local edema control while left-eye edema remained substantial.

Tocilizumab was selected after inadequate sustained control with previous treatment. IL-6 receptor blockade offered a different therapeutic mechanism and a rationale grounded in reports of refractory uveitic macular edema [9,10]. Mesquida et al. reported improvement in seven patients, including three with birdshot; edema recurred in two patients after withdrawal and improved after reintroduction [9]. STOP-Uveitis randomized 37 patients with non-infectious uveitis to intravenous tocilizumab 4 or 8 mg/kg and reported improvement in visual acuity, vitreous haze, and central macular thickness at six months [10]. Its open-label design, mixed diagnoses, and absence of a conventional treatment control group limit claims of superiority or birdshot-specific long-term efficacy.

More recently, Zur Bonsen et al. followed eight patients with refractory birdshot treated with tocilizumab. Retinal angiographic inflammation and central retinal thickness improved, whereas choroidal angiographic activity did not show an equivalent sustained reduction [11]. This small retrospective study reinforces the value of assessing retinal and choroidal findings separately. In the present case, follow-up incorporated clinical examination, OCT, fluorescein angiography, and ICGA, including the July 2022 report of no hypocyanescent spots and the angiographically documented retinal vascular recurrence in August 2023. The report therefore reflects multimodal follow-up, although standardized serial angiographic scores were unavailable.

Attribution of the early response remains limited by concomitant treatment. The right macula was already dry after a recent dexamethasone implant when tocilizumab began, and the December 2018 OCT was obtained just after the first infusion. It cannot establish an immediate tocilizumab effect. The subsequent left-eye improvement is temporally informative, but concurrent ciclosporin and the uncontrolled design prevent attribution of the entire response to one agent.

Relapse approximately four months after tocilizumab withdrawal and edema resolution after reintroduction are consistent with treatment-dependent suppression but do not prove causality. Crowell et al. reported sustained drug-free remission in approximately 25% of patients by four years and subsequent relapses in some patients [7]. The present observation adds a prolonged treatment trajectory to that uncertainty. Neither the successful dose reduction nor the later six-week interval establishes a withdrawal rule or maintenance schedule for other patients.

Systemic surveillance accompanied sequential biologic treatment. The tuberculosis clinic record documented a positive tuberculin skin test in 2018 despite a negative IGRA, with isoniazid started before tocilizumab and completed in April 2019. The respiratory infection in 2020 was treated with cefuroxime and prompted a brief infusion delay. These events illustrate the need to integrate systemic findings into treatment decisions; the record does not support a comprehensive comparative safety assessment.

Anatomical improvement and visual recovery diverged. Macular atrophy was evident after edema resolution

in 2015 and persisted thereafter. Cataract and posterior capsule opacification additionally affected acuity, and the latest right-eye measurement preceded capsulotomy. Accordingly, changes in acuity cannot be used as a direct surrogate for inflammatory activity or attributed solely to drug response. This distinction is central to the educational value of the case: treatment decisions continued to address recurrent edema and inflammation despite limited potential for recovery from established damage.

Limitations include the interruption in follow-up between 2010 and 2015, missing clinical measurements, inconsistent correction status during early acuity testing, and the absence of standardized serial visual field, electroretinographic, and angiographic scores. OCT systems and scan orientations varied, and automated foveal localization was unreliable in the most edematous examination. A standardized thickness trajectory or percentage response was therefore not calculated. Table *2* presents the available observations without imputing missing values. These limitations, treatment confounding, and the single-patient design make the findings descriptive and hypothesis-generating.

## Conclusions

This 16-year course illustrates individualized management of birdshot chorioretinopathy through sequential conventional and biologic immunosuppression and local corticosteroid treatment. Recurrent activity and treatment-related morbidity shaped escalation and tapering. Tocilizumab withdrawal was followed by recurrent edema and retinal vascular inflammation, and reintroduction was followed by renewed edema control; these temporal associations do not establish causality or comparative efficacy. Persistent macular atrophy limited visual recovery despite anatomical improvement. The case supports careful distinction between edema control, documented inflammatory activity, and visual function, while highlighting unresolved questions about treatment duration and withdrawal. These observations are hypothesis-generating and do not define a general treatment algorithm.

## Appendices

### Supplementary laboratory results

Tables *3*-*7* reproduce the complete available laboratory panel with the reporting laboratory's reference intervals or qualitative interpretations. Collection dates were not visible on the report copies; values must not be assigned to a treatment phase. Bold numerical results fall outside the supplied reference interval. NR means not reported. A dash denotes a qualitative test without a unit.

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| HLA-A*29 | Positive | - | Not applicable (genotype) |
| HLA-B*5 | Negative | - | Not applicable (genotype) |
| HLA-B27 | Negative | - | NR |
| Antinuclear antibodies (immunofluorescence) | Negative | - | NR |
| Anti-DNA antibodies | Negative | - | NR |
| ENA screen | 0.10 | Index | Negative |
| Anti-PR3 antibodies | 0.10 | U/mL | 0.00-3.00 |
| Anti-MPO antibodies | 0.20 | U/mL | 0.00-5.00 |
| Angiotensin-converting enzyme | 46.7 | U/L | 8.0-52.0 |
| **Lysozyme** | **0.93** | mg/dL | 0.96-1.71 |
| Treponema pallidum total antibodies | <0.10 | Index | Nonreactive |
| HIV-1/2 antigen/antibodies | 0.30 | Index | Nonreactive |
| QuantiFERON-TB Gold | Negative | - | NR |
| Hepatitis B surface antigen | 0.14 | Index | Nonreactive |
| Hepatitis B surface antibodies | <3.1 | mIU/mL | Nonreactive |
| Hepatitis B core antibodies | <0.07 | Index | Negative: <0.5, positive: ≥0.5 |
| Hepatitis C total antibodies | 0.12 | Index | Nonreactive |

**TABLE 3: Immunogenetic autoimmune and infectious investigations**

HLA-B*5 is retained as reported in the molecular typing result; the request page listed HLA-B51.

HLA: human leukocyte antigen, ENA: extractable nuclear antigens, DNA: deoxyribonucleic acid, PR3: proteinase 3, MPO: myeloperoxidase, HIV: human immunodeficiency virus

The negative QuantiFERON result is separate from the May 2018 positive tuberculin skin test.

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| Leukocytes | 9.40 | ×10⁹/L | 4.50-11.50 |
| Neutrophils (relative) | 66.2 | % | NR |
| Neutrophils (absolute) | 6.2 | ×10⁹/L | NR |
| Lymphocytes (relative) | 27.6 | % | NR |
| Lymphocytes (absolute) | 2.6 | ×10⁹/L | NR |
| Monocytes (relative) | 5.2 | % | NR |
| Monocytes (absolute) | 0.5 | ×10⁹/L | NR |
| Eosinophils (relative) | 0.7 | % | NR |
| Eosinophils (absolute) | 0.1 | ×10⁹/L | NR |
| Basophils (relative) | 0.3 | % | NR |
| Basophils (absolute) | 0.0 | ×10⁹/L | NR |
| Erythrocytes | 4.89 | ×10¹²/L | 4.00-5.40 |
| Hemoglobin | 15 | g/dL | 12-15 |
| Hematocrit | 44.3 | % | 35.0-49.0 |
| Mean corpuscular volume | 90.5 | fL | 81.0-97.0 |
| Mean corpuscular hemoglobin | 30.7 | pg | 23.0-32.0 |
| Mean corpuscular hemoglobin concentration | 34 | g/dL | 32-36 |
| Red cell distribution width | 12.6 | % | 11.5-14.5 |
| Erythroblasts | 0 | /100 leukocytes | 0-1 |
| Platelets | 185 | ×10⁹/L | 150-450 |
| Mean platelet volume | 8.7 | fL | 6.8-10.8 |
| Erythrocyte sedimentation rate | 3 | mm at 1 hour | 0-20 |
| Prothrombin time | 11.4 | Seconds | 9.9-12.8 |
| Prothrombin activity | **106** | % | 70-100 |
| International normalized ratio | 0.97 | Ratio | NR |
| Activated partial thromboplastin time | **38.3** | Seconds | 21.9-32.9 |
| Fibrinogen (Clauss) | 2.4 | g/L | 2.4-5.0 |

**TABLE 4: Hematology and coagulation**

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| Glucose | **115** | mg/dL | 74-106 |
| Urea | 30 | mg/dL | 14-42 |
| Creatinine | 0.7 | mg/dL | 0.5-1.2 |
| Sodium | 143 | mEq/L | 136-145 |
| Potassium | 4.2 | mEq/L | 3.4-4.4 |
| Chloride | **107.5** | mEq/L | 98.0-107.0 |
| Total protein | 7.2 | g/dL | 6.6-8.7 |
| Albumin | 4.2 | g/dL | 3.5-5.0 |
| Alkaline phosphatase | 84 | U/L | 25-100 |
| Gamma-glutamyl transferase | 29.1 | U/L | 4.0-32.0 |
| Alanine aminotransferase | 26 | U/L | 3-31 |
| Aspartate aminotransferase | 19 | U/L | 3-31 |
| Total cholesterol | **276** | mg/dL | <200 |
| LDL cholesterol | **182.4** | mg/dL | 100.0-129.0 |
| HDL cholesterol | 79.9 | mg/dL | 33.0-96.0 |
| Triglycerides | 68.5 | mg/dL | <150.0 |
| Uric acid | 5.5 | mg/dL | 2.6-6.0 |
| Immunoglobulin A | **552** | mg/dL | 40-350 |
| Immunoglobulin G | 956 | mg/dL | 650-1600 |
| Immunoglobulin M | 107 | mg/dL | 50-300 |
| Complement C3 | 106.6 | mg/dL | 83.0-177.0 |
| Complement C4 | **37.3** | mg/dL | 12.0-36.0 |
| High-sensitivity C-reactive protein | 0.24 | mg/dL | <0.50 |
| FT4 | 1.1 | ng/dL | 0.9-1.8 |
| Thyroid-stimulating hormone | 2.026 | mIU/L | 0.350-5.500 |

**TABLE 5: Biochemistry immunoglobulins complement and thyroid function**

LDL: low-density lipoprotein, HDL: high-density lipoprotein, FT4: free thyroxine

Hypercholesterolemia is relevant to systemic assessment. Fasting status was not available for glucose interpretation. The record does not establish the significance of the isolated immunoglobulin A, complement C4, and chloride elevations.

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| Total protein | 7.2 | g/dL | 6.6-8.7 |
| Albumin fraction (relative) | 57.8 | % | 55.8-66.1 |
| Albumin fraction (absolute) | 4.18 | g/dL | 4.02-4.76 |
| Alpha-1 fraction (relative) | 4.2 | % | 2.9-4.9 |
| Alpha-1 fraction (absolute) | 0.30 | g/dL | 0.21-0.35 |
| Alpha-2 fraction (relative) | 9.1 | % | 7.1-11.8 |
| Alpha-2 fraction (absolute) | 0.66 | g/dL | 0.51-0.85 |
| Beta fraction (relative) | **14.1** | % | 7.9-13.7 |
| Beta fraction (absolute) | **1.02** | g/dL | 0.57-0.99 |
| Gamma fraction (relative) | 14.8 | % | 11.1-18.8 |
| Gamma fraction (absolute) | 1.07 | g/dL | 0.80-1.35 |
| Albumin/globulin ratio | 1.37 | Ratio | NR |

**TABLE 6: Serum protein electrophoresis**

Relative fractions and absolute concentrations are shown on separate rows. The albumin fraction is distinct from the routine serum albumin assay. The beta fraction exceeded the laboratory reference interval; a specific clinical explanation was not established in the record.

| Test | Result | Unit | Reference or interpretation |
|---|---|---|---|
| pH | 5 | - | NR |
| Specific gravity | 1.024 | - | NR |
| Color | Yellow | - | NR |
| Appearance | Clear | - | NR |
| Protein | Negative | - | NR |
| Glucose | Negative | - | NR |
| Ketones | Negative | - | NR |
| Bilirubin | Negative | - | NR |
| Hemoglobin | Negative | - | NR |
| Nitrites | Negative | - | NR |
| Urobilinogen | 2.0 | mg/dL | NR |
| Deposit | None | - | NR |
| Squamous epithelial cells | **8** | /µL | 0-4 |
| Urothelial cells | Not detected | - | NR |
| Urinary leukocytes | **21** | /µL | 1-10 |
| Erythrocytes | 8 | /µL | 1-24 |
| Non-lysed erythrocytes | Not detected | - | NR |
| Hyaline casts | Not detected | - | NR |
| Pathological casts | Not detected | - | 0.0-0.2 (unit not shown) |
| Crystals | 9 | /µL | 0-27 |
| Yeasts | Not detected | - | NR |
| Dysmorphic erythrocytes | Not detected | - | NR |

**TABLE 7: Urinalysis**

Urinary leukocytes and squamous epithelial cells exceeded the laboratory intervals. Without collection details or contemporaneous urinary symptoms, these findings cannot establish a urinary infection or its cause.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Miguel Ribeiro

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**Drafting of the manuscript:** Miguel Ribeiro

**Critical review of the manuscript for important intellectual content:** Joao P. Costa, Sara Marques, Catarina Almeida, Joao Leandro

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