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Cystoid macular edema secondary to ibrutinib

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ABSTRACT

Purpose: To describe a unique case of cystoid macular edema associated with Ibrutinib treatment for Chronic Lymphocytic Leukemia (CLL).

Observations: A 73-year-old male patient presented to the ophthalmology clinic complaining of decreased vision in his seeing-eye ('only eye', left). Further clinal examination and imaging revealed the presence of a cystoid macular edema (CME). With no apparent cause to this condition, topical treatment with NSAIDS and steroids continued over two years with only partial response and persistent macular edema, resulting in decreased vision. Cessation of Ibrutinib treatment resulted in resolution of the macular edema and improvement in visual acuity over 6 months.

Conclusions and Importance: Several novel oncologic therapies have been associated with CME in recent years. This case demonstrates an association between Ibrutinib an oral, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK), and the development of CME. CME was resistant to topical treatment but resolved after treatment cessation. Along with two previous cases reported, this case suggests that CME is a rare adverse event of Ibrutinib therapy. Screening for CME in Ibrutinib treated patients who report visual symptoms should be considered.

1. Introduction

A possible association has been described between Cystoid Macular Edema (CME) and various systemic and local oncologic medications including tyrosine kinase inhibitors (Imatinib), anti-metabolites (Cytarabine), antimicrotubule agents (Paclitaxel), steroid antagonists (Tamoxifen) and others.[1] This etiology might be overlooked, however, resulting in decreased visual acuity and persistent macular edema which is often unresponsive to treatment. We describe a unique case of cystoid macular edema in the only seeing eye of a 73-year-old male patient treated with Ibrutinib following a diagnosis of Chronic Lymphocytic Leukemia (CLL). Cessation of Ibrutinib treatment resulted in both prompt resolution of the macular edema and improvement in visual acuity.

2. Case report

A 73-year-old male patient presented to the ophthalmology clinic complaining of decreased vision in his seeing-eye ('only eye', left). The patient's ocular history included fusarium infection in his right eye, for which he underwent evisceration 6 years prior to this presentation. Systemic history revealed chronic lymphocytic leukemia (CLL), hypertension and hypercholesterolemia that were well-treated and balanced. He maintains no history of diabetes.

Ocular examination disclosed a Best Corrected Visual Acuity (BCVA) of 6/15 in the left eye. Intraocular pressure was 16 mmHg. Anterior segment was normal except for a mild posterior sub capsular cataract. Ophthalmoscopy revealed a clear vitreous and a normal optic nerve head. Cystoid macular edema with a solitary adjacent microaneurysm was suspected. Optical coherence tomography (OCT; Heidelberg Spectralis, Heidelberg, Germany) demonstrated marked macular edema with a central subfield thickness (CST) of 600 μm (Fig. 1A). OCT angiography (OCTA; 6 × 6 mm area, Zeiss PLEX Elite 9000, Dublin, CA, USA) excluded the presence of choroidal neovascularization, but demonstrated an enlarged foveal avascular zone at the level of the deep capillary plexus. Fluorescein angiography showed petaloid cystoid form of leakage at the macula area and optic disc leakage.

Following the diagnosis of cystoid macular edema (CME), treatment was initiated with topical steroids (prednisolone acetate) at a starting dose of 5 times a day, which was decreased gradually to 3 times a day, and topical NSAIDS (Nepafenac) three times a day. Local treatment continued over two years with only partial response and persistent,

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marked macular edema associated with decreased vision. Since no neovascularization or other pathology amenable to anti-VEGF therapy was identified the patient did not receive intravitreal injections of anti-VEGF compound.

On presentation at our ophthalmological clinic, on being referred for consultation, a review of the patient's medications revealed treatment with Ibrutinib (Imbruvica, Janssen Biotech, PA USA) 420 mg/day over three years. This coincides chronologically with the onset of his symptoms (around 6–7 months after treatment initiation); the dose was then gradually reduced to 140 mg/day. Ibrutinib was thus suspected as causal, and the patient's hematologist discontinued ibrutinib treatment. Topical treatment with NSAIDS and steroids was continued.

A marked improvement of the retinal foveal thickness was observed two months following the cessation of Ibrutinib (from a CST of 600 μm to 315 μm). Six months after Ibrutinib cessation an OCT scan demonstrated complete resolution of the CME (Fig. 1B) and the BCVA improved from 6/15 to 6/12.

3. Discussion

Ibrutinib is a first-in-line-class, oral, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK), a B-cell signaling protein involved in B-cell development, differentiation, proliferation and survival.[2] It is considered standard care for patients with chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders.[3]

Unlike other treatment options that are given in cycle-form, Ibrutinib requires continued treatment; patients may be treated for many years until the occurrence of progressive disease or unacceptable toxicity.[4] Long-term, continuous usage of Ibrutinib makes monitoring the safety profile essential, considering the possible toxicities of this medication.

The most commonly reported adverse systemic effects of Ibrutinib are diarrhea (50%), cough and fatigue.[5] Other adverse events include: atrial fibrillation, low grade bleeding and major hemorrhages, arthralgia and myalgia, hypertension, increased risk of infections (particularly in the respiratory and urinary tracts), rash, peripheral blood lymphocytosis and cytopenia.[3] Ventricular arrhythmias and pneumonitis were also reported in rare cases.[3]

Ocular adverse events were also described among patients treated with ibrutinib. The phase 3 study comparing treatment of ibrutinib with ofatumumab reported that 10% vs 3% of patients complaining of blurred vision, respectively, with an incidence of cataract of 3% and 1%.[6] The etiology of blurred vision was not addressed. Cataract formation was suggested as etiology via tyrosine kinase mediated mechanism.[7] However, it was also shown that the incidence of cataract in a research population of patients over 70 years of age was consistent with its prevalence in an age-matched population.[7] Dry eye and subconjunctival hemorrhage were also reported as adverse effect of treatment.[4,8] A retrospective study reported that 16.1% (5/31) patients treated with ibrutinib suffered from ocular toxicity; the most commonly associated adverse effects in that study were severe dry eyes, irritation and red eye. One patient developed BRAO after 2 years of treatment with ibrutinib.[9] Recently, cases of Ibrutinib related uveitis have also been reported.[10–12]

Macular edema is a well-known complication of numerous systemic and local medications. Cystoid macular edema secondary to Ibrutinib treatment, however, has been described previously in only two cases. Saenz-de-Viteri et al.[13] reported on a 67-year-old man with relapsing CLL presenting with bilateral CME under treatment with 420 mg/day of Ibrutinib. After six weeks of topical treatment with dexamethasone 0.1% and ketorolac, complete resolution of CME was reported. Ibrutinib treatment was continued at a regular dose. Subsequently, 6 and 12 months later, the patient was stable with no recurrence of the edema under topical treatment. Mirgh et al.[14] reported the case of a 62-year-old man with CLL with a diagnosis of bilateral CME after 4 years of treatment with Ibrutinib. Topical steroids, nepafenac eye drops or systemic steroids achieved only temporary improvement. Decreasing Ibrutinib dosage to 140 mg/day resulted in only temporary improvement. There was marked improvement of visual acuity and resolution of the edema only after discontinuing Ibrutinib treatment.

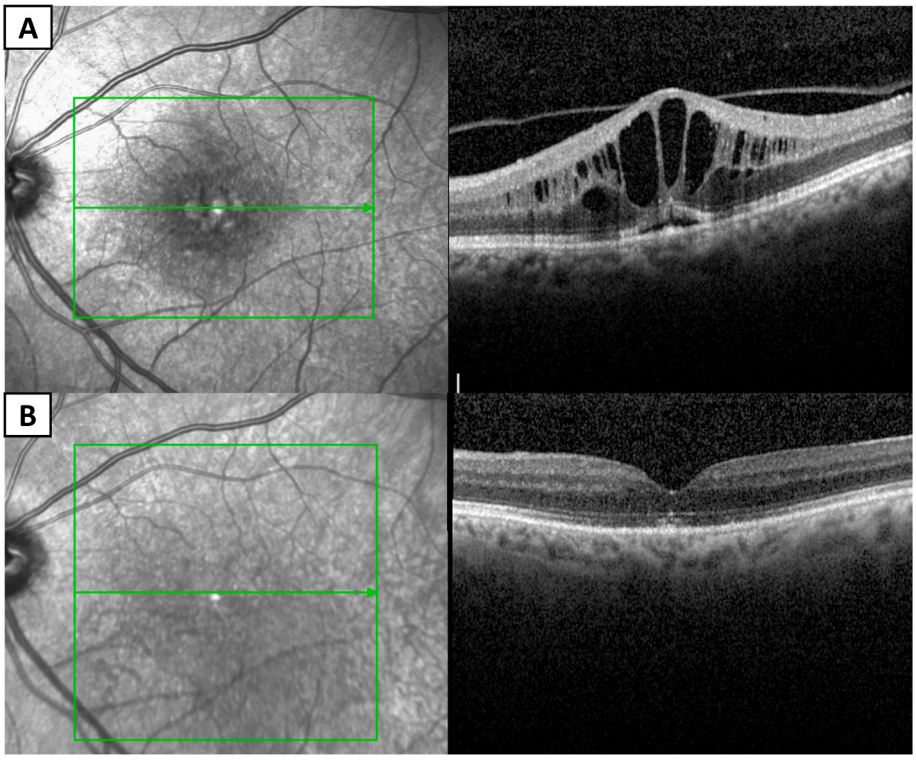

Fig. 1. A Optical coherence tomography (OCT) showing cystoid macular edema in the left eye during ibrutinib treatment. **B.** Optical coherence tomography (OCT) showing resolution of cystoid macular edema in the left eye six months after cessation of ibrutinib treatment. Sub-retinal hyperreflective material can be seen in both [A] and [B].

The present case of the 73-year-old male patient analyzed together with the two cases discussed above suggests that macular edema secondary to ibrutinib appears to be a non-dose dependent phenomenon. In addition, macular edema was reported as early as 4 weeks after treatment commencement.[13] While being diagnosed at an early phase – CME improved solely under local treatment, with no accompanying Ibrutinib cessation. No relapse within one year of follow up was reported, even after discontinuous topical treatment. Yet, the edema diagnosed in the remaining two cases several years after treatment commencement was resolved only following treatment cessation.

Macular edema may be associated with multiple additional conditions. In the current case, diabetic macular edema had been excluded as the patient had no history of diabetes. Other common etiologies - retinal vein occlusion or other vascular disease–did not correlate with the clinical or imaging findings. Perifoveal exudative vascular anomalous complex (PEVAC) was excluded by a lack of PEVAC lesion in OCT, OCTA and FA. There was only one suspected microaneurysm per ophthalmoscopy and FA, but, without meaningful leakage. Clinical appearance and imaging excluded macular telangiectasia type 1. On the other hand, cessation of ibrutinib therapy resulted in resorption of the edema suggesting that the compound was associated with the edema.

OCT images show sub-retinal hyperreflective material under sub-retinal fluid during the acute phase of macular edema that remained after its resolution. The space under the neurosensory retina following its separation from the RPE may contain variable deposits and tissue components such as neovascular tissue, fibrosis, exudation, vitelliform material or hemorrhage.[15] A definitive composition of the material in our case is yet to be known.

The pathophysiological mechanism of Ibrutinib-induced CME is unknown. It has been previously shown to be capable of crossing the blood-brain barrier. Therefore, potentially, ibrutinib induces CME by disruption of blood-retinal-barrier (BRB).[16] Further investigation is indicated to discover the accurate mechanism.

4. Conclusions

A review of the literature shows ours to be the third case report of macular edema secondary to Ibrutinib treatment. In the present case, the edema involved the patient's only remaining eye, naturally having a marked influence on his quality of life. This case contributes to the limited literature on CME secondary to Ibrutinib treatment, and underscores the importance of obtaining a detailed medical history in cases of CME. Moreover, these data suggest that ophthalmic examination and an OCT should be considered for patients who report blurry vision under treatment with Ibrutinib. More evidence is necessary to evaluate the exact prevalence of such adverse events and whether timely ophthalmic evaluation is necessary.

Patient consent

Written informed consent was obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors report no conflict of interest.

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