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Successful Treatment of Ocular Chronic Lymphocytic Leukemia with Ibrutinib: Case Report and Review of the Literature

Ayushi F Chauhan[a,*,#], Narine Viruni[b,#], T.Y. Alvin Liu[c], J Fernando Arevalo[c], Bruce D Cheson[d]

[a] Department of Hematology and Oncology, MedStar Georgetown University Hospital, Washington, DC
[b] Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland
[c] Department of Ophthalmology, Retina Division, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland
[d] Department of Hematology and Oncology, MedStar Georgetown University Hospital, Washington, DC

Introduction

Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by a progressive accumulation of monoclonal B-lymphocytes. It is the most common adult leukemia in Western countries, accounting for approximately 30 percent of all leukemias in the United States [1]. Presenting findings are heterogeneous and range from incidental detection on routine laboratory studies to disease-related symptoms, infection, anemia or other non-specific findings.

Clinically apparent neurological involvement by CLL, especially ocular manifestation, is rare [2]. There are few case reports describing orbital, lacrimal, conjunctival, and/or scleral involvement. To date, we have found only two reports of ocular CLL: one report describing retinal and another describing choroidal leukemic infiltration due to CLL [3,4].

Ibrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor, with significant activity in a number of B-cell malignancies, including CLL, mantle cell lymphoma (MCL), those with CNS localization and primary central nervous system lymphoma (PCNSL) [5]. Here we present the first case of ocular relapse of CLL with leukemic retinopathy successfully treated with Ibrutinib.

Case discussion

A 66-year-old male was diagnosed with CLL in 2009 based on the incidental detection of lymphocytosis on routine laboratory studies. Peripheral blood flow cytometry showed a monoclonal B-cell population expressing CD19, CD20, CD5, and CD23. CD20 was dimly expressed. The cells were negative for CD10, ZAP70, and CD38. FISH analysis did not show CCND1-IGH fusion, extra signals or deletions of ATM, trisomy 12, 13q, 17p deletion, or TP53 aberrancies. Bone marrow biopsy showed 45% involvement by CLL. He was maintained on observation, with monthly infusions of intravenous immunoglobulin due to hypogammaglobulinemia accompanied by frequent infections. Six years after diagnosis, systemic treatment was indicated because of progressively worsening lymphadenopathy, fatigue, unintentional weight loss, and splenomegaly. Absolute lymphocyte count was 13,300/μL, hemoglobin 15 g/dl, and platelet count was 243/μL. He was enrolled on a clinical trial comparing Bendamustine-Rituximab (BR) with or without the class I phosphoinositol-3-kinase delta inhibitor idelalisib. Cytogenetics were repeated as part of trial enrolment and PCR analysis showed unmutated IgHV and absence of TP53 aberrations. A repeat FISH analysis was similar to prior. He was randomized to the idelalisib arm however study drug was discontinued after four weeks due to grade 3 diarrhea and rash. He completed six cycles of BR with resolution of leukocytosis and lymphadenopathy.

Two years after treatment completion, his disease recurred with development of fatigue, worsening lymphocytosis, and lymphadenopathy. Concomitantly he also complained of decreased vision in his right eye. He did not have any pre-existing ocular abnormalities.

Initial visual acuity examination was counting fingers at one foot for the right eye and 20/25 for the left eye. Intraocular tensions and ocular motility were normal. Confrontational visual fields revealed a right partial outer temporal visual field deficit. Slit lamp bio-microscopy of both eyes showed trace keratic precipitates, moderate anterior chamber inflammation, and sheets of vitreous cells. Funduscopic examination of the right eye revealed vitreous haze, blurred disc margins, diffuse vascular sheathing in the posterior pole, and multiple creamy lesions in the nasal macula and inferonasal to the optic nerve (Figure 1B). Exam of the left eye was notable for a small, subtle, creamy lesion nasal to the optic disc, and otherwise normal appearing optic nerve, macula, and vessels. Optical coherence tomography (OCT) images of the right eye showed full thickness retinal infiltration by a hyperreflective material corresponding to the inferonasal lesion on fundus photographs (Figure 2A) with a sharp demarcation between normal and abnormal retina at the edge of the lesion. OCT images of the macula showed multiple retinal pigment epithelial detachments (PEDs) (Figure 2B). Wide field fluorescein angiography (FA) revealed leakage in nasal macula and inferonasal to the disc on late frames (Figure 1A). FA of the

* Corresponding author.
E-mail addresses: ayushi.chauhan@gunet.georgetown.edu (A.F. Chauhan), nabgary1@jhmi.edu (N. Viruni).
# Both authors contributed equally to the creation and conception of this manuscript and share first authorship.

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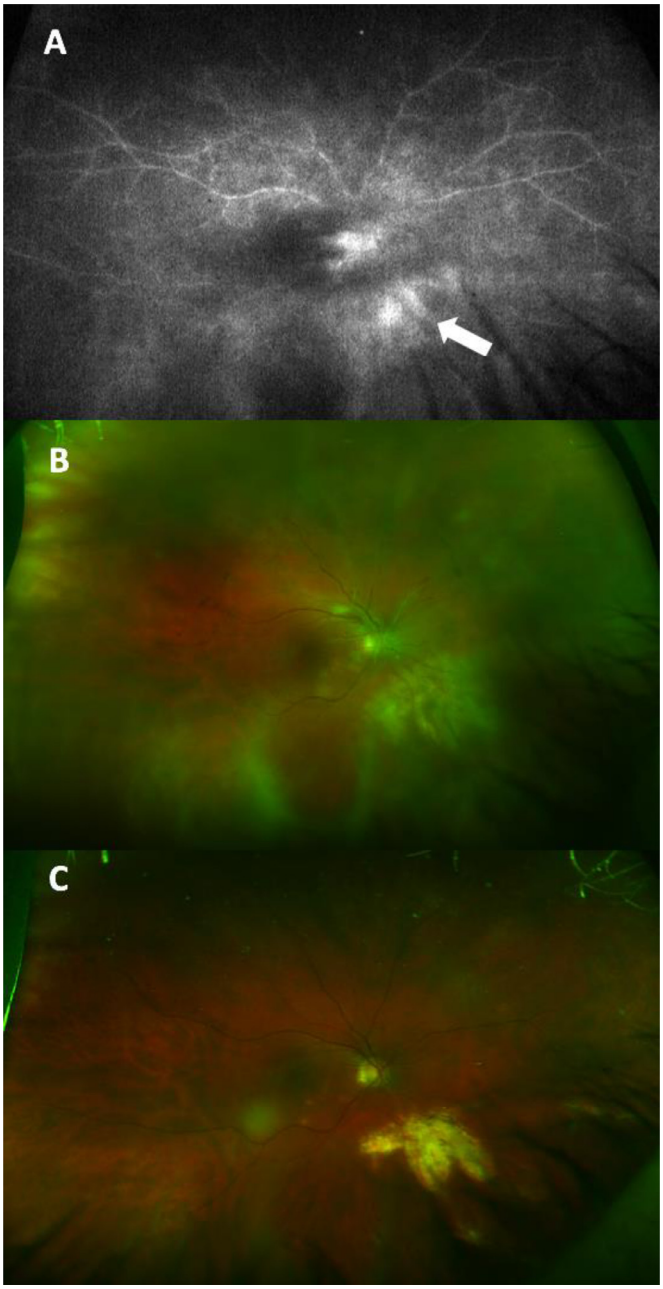

Figure 1. Wide field fluorescein angiography of the right eye reveals retinal vascular leakage inferonasal to the optic nerve (arrow) corresponding to the infiltrative retinal lesion on fundus photographs (A). Wide field fundus photograph of the right eye shows vitritis and multiple creamy lesions in the nasal macula and inferonasal to the optic nerve on presentation (B), and subsequent resolution of retinal lesions with residual scarring, atrophy, and hypopigmentation at 8 months follow up (C).

left eye revealed trace leakage corresponding to the lesion nasal to the disc, but without a corresponding PED or retinal infiltrate on OCT.

A focused uveitis workup was negative for syphilis, tuberculosis, toxoplasmosis, or sarcoidosis. MRI of the brain and orbits with and without contrast revealed diffuse leptomeningeal enhancement. Patient underwent a pars plana vitrectomy with vitreous biopsy, which was inconclusive. A lumbar puncture [LP] was done with the cerebrospinal fluid (CSF) showing an atypical lymphoid infiltrate. CSF flow cytometry was positive for involvement by a small population (3% total cells) of CLL/SLL cells, expressing CD19, CD5, Cd23, CD20 (dim), and SIG-lambda (negative for FMC7), confirming CNS relapse. He received two

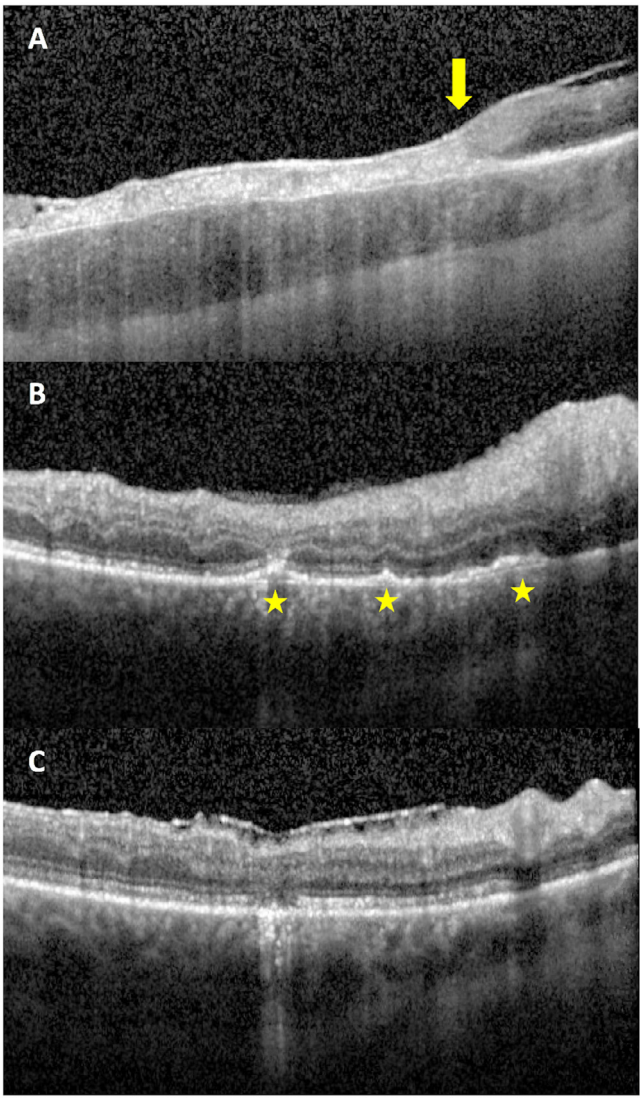

Figure 2. Optical coherence tomography (OCT) images of the right eye at initial presentation show a transition zone (arrow) from a normal retina nasally to a full thickness retinal infiltration by a hyperreflective material temporally (A); multiple retinal pigment epithelium detachments (PEDs) in the inferior macula (star) (B); and resolution of PEDs with resultant retinal atrophy at a two year follow up (C).

cycles of intrathecal cytarabine.

Concurrently, the patient also experienced vertigo, muscle spasms, imbalance, and seizures which were treated successfully with levetiracetam.

In September 2017, he was started on Ibrutinib at a dose of 560 mg daily for CNS penetration. Within 4 weeks, the patient reported a significant improvement in vision in both eyes except for some peripheral visual field defect, tunnel vision and scotomatas in the right eye. He did not experience any further seizures. A repeat MRI brain showed resolution of leptomeningeal enhancement, and CSF flow cytometry showed 1% involvement by CLL/SLL cells, thought to be peripheral blood contamination. Best corrected visual acuity at 8 months follow up improved to 20/40 and 20/20 in right and left eyes, respectively. Biomicroscopy was notable for resolution of vitritis, decrease in the size of the retinal lesions with resultant focal retinal atrophy and scarring on the right (Figure 1C and 2C).

He subsequently developed intolerance to ibrutinib, manifested by grade 3 diarrhea with urgency and fecal incontinence, unresponsive to supportive measures, and extensive bruising. He was switched to the

second generation BTK inhibitor, acalabrutinib at a dose of 100 mg twice daily. He has tolerated that drug extremely well and, after a year, remains asymptomatic and in a clinical remission. His vision, including peripheral, continues to improve, such that he is now able to drive and ride a bicycle. He no longer requires anti-seizure medications. Physical examination reveals no lymphadenopathy or splenomegaly. Latest CBC shows a WBC of 5100/ul including 1200 lymphocytes, hemoglobin of 13.8 g/dl, and platelets of 222,000/ul.

Conclusions

In earlier case series, the incidence of neurological complications in CLL was reported to be 4-11.3%; however, direct CNS localization occurred in only 0.4-0.8% of cases [2,6]. Post-mortem studies have reported an incidence of 7-20%, indicating underdiagnosis, difficulty in diagnosis or a high occurrence of sub-clinical disease [7,8].

Ocular involvement in CLL may be either direct via leukemic infiltration or indirect due to immune compromise, hyperviscosity, thrombocytopenia, anemia, or treatment. Whereas ocular involvement is rare [9–11] it may be the first and sole site of disease relapse. In a retrospective cohort of 30 CLL patients with ocular or CNS involvement, less than half had progressive CLL and 20 had never been treated for CLL [12]. There was no apparent correlation between Rai/Binet stage and occurrence of neurological or ocular disease [12,13].

Varied ophthalmological anomalies have been noted, including subcapsular cataracts, conjunctival anomalies, ophthalmoplegia, extraocular muscle infiltration, ptosis, optic nerve infiltration, optic neuropathy, [11,12,14–17] eyelid and orbital soft tissue masses, [18] bilateral lacrimal gland infiltration, episcleral infiltration, [19] and bilateral posterior scleritis [20]. Anterior segment pathology included one case of anterior uveitis with hypopyon. [18] Vitreous involvement has been documented in a patient with CLL, who developed intraocular Richter transformation. [9] Other secondary ocular complications of CLL include fungal endophthalmitis [10,21] and acute retinal necrosis. [11]. However, there are only two other case reports describing leukemic retinal [4] or choroidal [22] infiltrates due to CLL.

The current case is the first to present OCT findings in this condition. OCT images of the macula in our patient showed several focal PEDs with subsequent resolution of hyperreflective lesions in the inferonasal macula following treatment, with persistent focal photoreceptor disruption. OCT images through the retinal lesion inferonasal to the optic nerve corresponding to the area of retinal vascular leakage on fluorescein angiography, showed hyperreflectivity and disruption of all retinal layers that persisted following treatment and was associated with choroidal thinning. OCT findings of retinal leukemic infiltration have been described in one other case report; however, the patient had chronic myelogenous leukemia. Herein, OCT revealed lesions of uniform reflectivity involving all layers of the retina with subsequent resolution of hyperreflective lesions at 3 months without consecutive atrophy of the inner retinal layers upon resolution. This case too demonstrated persistent focal disruption of the photoreceptor outer segments where there was initial leukemic involvement. [23]

Diagnostic work-up typically involves neuroimaging; however, MRI has a lower sensitivity for detection of meningeal involvement in primary CNS lymphoma [20-37.5%] compared to solid tumors [24,25] and the absence of MRI abnormalities may not rule out CNS CLL. CSF examination, while important, is challenging, because of the low burden of CLL cells in the CSF as well as the risk of peripheral blood contamination during the procedures, increasing false-positive rates. Flow cytometry significantly increases the sensitivity of detection [26]. In anecdotal case reports leptomeningeal biopsy has been used for diagnosis [27], a procedure not usually performed. Ultimately, CSF flow cytometry remains the gold standard, and diagnosis of CNS localization can be made despite a low percentage of malignant cells in the CSF, especially in the presence of symptoms. Given rarity of intraocular CLL involvement, the yield of vitreous biopsy is unknown however, data from primary intraocular lymphoma show high false negative rates of vitreal biopsy with the diagnostic yield dependent on collection technique, prompt cytopathologic analysis, and appropriate fixative agent [28,29]. Ophthalmoscopic exam may also be of low yield as optic neuropathy may not be accompanied by concomitant optic disc edema. Hence, despite the negative vitreal biopsy in our case, the concordance of OCT, CSF, and clinical findings align with diagnosis of ocular CLL and underscore the need for a high clinical index of suspicion.

No specific guideline-based recommendations for treatment of patients with CNS involvement of CLL exist [30] and combinations of systemic and intrathecal chemotherapies, rituximab monotherapy, localized radiotherapy or ibrutinib have been used in case reports [12,13]. Prognosis appears to be determined by the underlying CLL characteristics rather than neurological/ocular involvement [12].

Ibrutinib has changed the landscape of CLL treatment in recent years with better progression-free survival, overall response rates, and overall survival than standard chemo-immunotherapy. Ibrutinib provides benefit regardless of adverse prognostic factors, such as del(17p)/TP53 mutation and del(11q) [31]. Pre-clinical data with Ibrutinib has shown a high level of brain distribution, and correlates with plasma concentrations [32] providing the justification for the dose used in the current patient of 560 mg rather than the standard 420 mg typically administered in CLL. Ibrutinib has shown promising results in treatment of CNS involvement with histologic subtypes of non-Hodgkin lymphoma including MCL [33,34],Waldenström macroglobulinemia (WM) [35–37], and, relapsed/refractory primary CNS lymphoma. In relapsed/refractory primary CNS lymphoma, response rates as high as 68% have been reported, albeit relatively short-lived [5]. Unfortunately, one of the more serious complication of its administration is spontaneous bruising or bleeding, which may involve the central nervous system or eye.

This case represents a rare presentation of intraocular CLL with retinal and choroidal infiltration, successfully treated with Ibrutinib monotherapy, highlighting the safety and efficacy of this agent regardless of site or type of relapse. Clinical benefit persists despite switching to acalabrutinib. This BTK inhibitor has demonstrated efficacy similar to that reported with ibrutinib in relapsed and refractory CLL, and has been shown to be of benefit in patients intolerant to ibrutinib [38]. Clinicians should be aware of the possibility of ocular involvement in CLL in patients with prior history of this disease and complaints of neurologic or ocular abnormalities. Administration of ibrutinib should be considered for rapid and sustained clinical benefit.

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