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Letter to the Editor

Pathogenetic Mechanism of Macular Edema During Treatment with Ibrutinib

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To the editor.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are low-grade non-Hodgkin lymphomas characterized by monoclonal B lymphocytes. Bruton tyrosine kinase inhibitors (BTKis) represent the first-line treatment for symptomatic CLL/SLL. Here we report a case of a patient with SLL treated with ibrutinib who developed macular edema as confirmed by optical coherence tomography (OCT). Tyrosine kinase inhibitors have been linked to macular edema, but it is a very rare adverse event, and the pathogenic mechanism underlying it remains uncertain. Reviewing the literature, we sought to identify possible off-target effects of ibrutinib that could contribute to this condition. Although some kinases are involved in inflammation, this does not explain the link between ibrutinib and macular edema. However, only the inhibition of one kinase, Fyn tyrosine kinase, may play a role by altering adhesions between retina cells and the extracellular matrix when deficient.

Introduction. Chronic lymphocytic leukemia (CLL) is characterized by the presence of >5.000/mmc monoclonal B lymphocytes expressing CD5, CD23, CD19, CD20 and kappa or lambda immunoglobulin light chains in the peripheral blood, while small lymphocytic lymphoma (SLL) diagnosis is made if these B lymphocytes in peripheral blood are <5.000/mmc and confirmed by a lymph node biopsy.[1] Only patients who develop symptoms or signs of active disease need to start treatment with Bruton tyrosine kinase inhibitors (BTKis), the B-cell lymphoma 2 inhibitor venetoclax, or anti-CD20 monoclonal antibodies.[1] BTKis bind to a kinase involved in the signaling cascade of the B-cell receptor, reducing cell proliferation and survival. The main side effects of BTKis are cardiotoxicity, bleeding, myelosuppression, infections, diarrhoea, and fatigue.[2] The aim of this paper is to describe a case of macular edema in a patient treated with ibrutinib and to explore possible pathogenetic mechanisms linking BTKi therapy to this rare ocular complication.

Clinical Presentation. A 73-year-old male patient was diagnosed with SLL by bone marrow biopsy and flow cytometry on peripheral venous blood showing a B lymphoid population equal to 18% of the sample (about 1.600/mmc). Molecular biology tests reported 11q22 deletion and immunoglobulin heavy chain variable region gene mutation. Regarding his past medical history, the patient reported left eye cataract surgery combined with pars plana vitrectomy with inner limiting membrane peeling. The patient underwent a total-body computed tomography and positron emission tomography (TBCT/PET) scan, with evidence of multiple supradiaphragmatic and subdiaphragmatic lymphadenopathies (maximum diameter 8 cm at the para-aortic station) and a standardized uptake value (SUV) below 3. So, he started immune chemotherapy with rituximab (375 mg/m^2 at day 1 of every cycle) and bendamustine (90 mg/m^2 at day 1 and 2 of every cycle) for 6 cycles with a good response. However, one year later, disease relapse occurred with renewed subdiaphragmatic lymphadenopathy. Therefore, the patient started second-line therapy with ibrutinib (420 mg per day), which was complicated by an episode of atrial fibrillation, so treatment was discontinued. Concurrently, he complained of worsening visual blurring. Fundus examination revealed the presence of bilateral macular edema, which was then confirmed by optical coherence tomography (OCT) scans (**Figure 1 A** and **B**). The visual symptoms and macular edema began to resolve one month after ibrutinib was interrupted, without requiring any specific treatment (**Figure 1 C** and **D**). Due to another disease progression, the patient started third-line therapy with Zanubrutinib, with no further visual or cardiac adverse events.

Discussion. Ophthalmic adverse events are very rare during treatment with ibrutinib. In a study of ibrutinib's

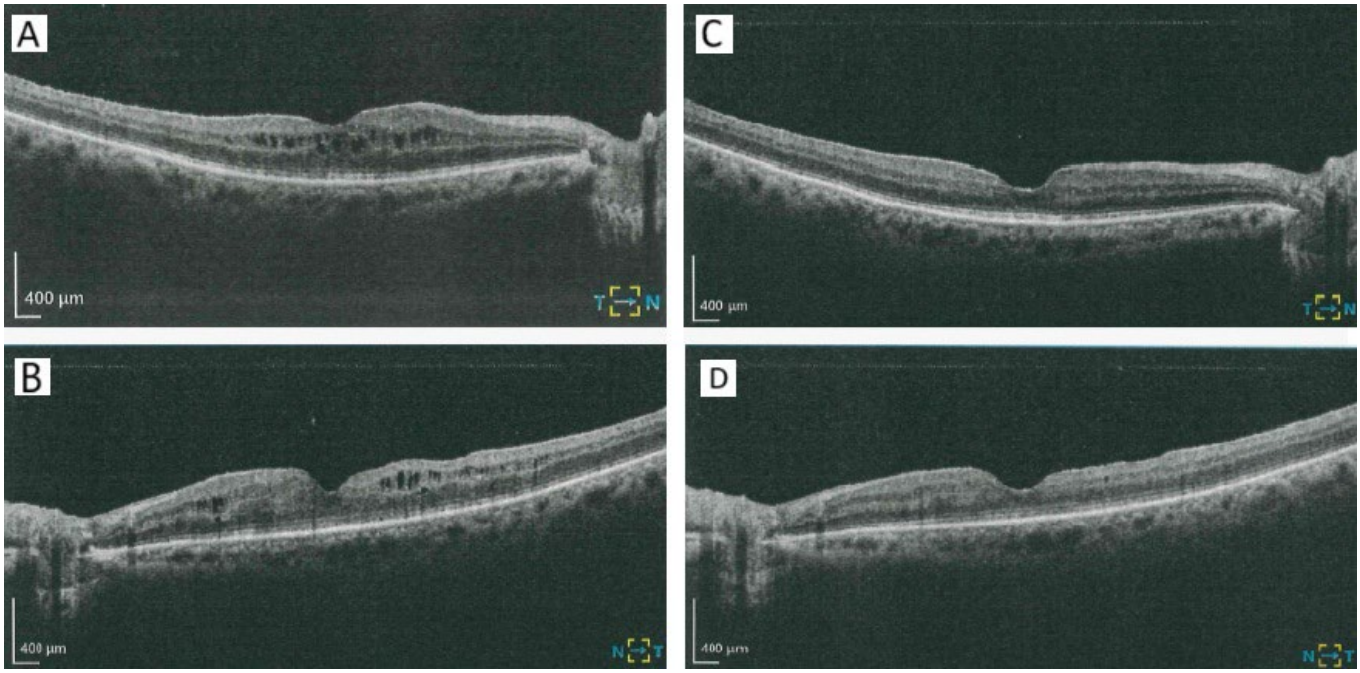

Figure 1 Macular edema after one year of treatment with ibrutinib. (A: right eye; B: left eye) and resolution of macular edema after one month discontinuation of ibrutinib (C: right eye; D: left eye).

safety profile, Allouchery et al. found that 0.64% of patients experienced serious ocular adverse events.[3] In contrast, the RESONATE study reported that 10% of patients taking ibrutinib experienced blurred vision.[4] Mirgh et al. described a case of a CLL patient who underwent third-line ibrutinib treatment and developed cystoid macular edema (CME). Despite topical and systemic anti-inflammatory drugs and a dose reduction of ibrutinib, the macular edema did not resolve until ibrutinib was discontinued.[5] On the other hand, Saenz-de-Viteri et al. reported a patient treated with ibrutinib for CLL who was diagnosed with CME by an OCT scan and improved with topical steroids without discontinuing the BTKi.[6] The peculiarity of our patient's case is that he developed these side effects together with cardiac adverse events, while the other patients developed them as the only side effect. Furthermore, his symptoms resolved without any topical or systemic ophthalmologic therapy.

We reviewed the off-target kinase-inhibition profile of ibrutinib to identify potential mechanisms underlying macular edema. Ibrutinib crosses the blood–brain barrier and can likely reach retinal tissues.[7] Lipsky et al. and Xiao et al.'s studies demonstrated ibrutinib off-target effects on other kinases, such as interleukin-2–inducible T-cell kinase (ITK), tyrosine-protein kinase (TEC), endothelial growth factor receptor (EGFR), FYN tyrosine kinase (FYN), mitogen-activated protein kinase 5 (MEK5), C-terminal c-Src kinase (CSK), and Receptor-interacting serine/threonine-protein kinase 3 (RIPK3).[8,9] They do not seem likely to cause or predispose macular edema, except for FYN tyrosine kinase.[10,11,12,13] Chavez-Solano et al. investigated the functional role of FYN tyrosine kinase in the postnatal neural retina, focusing on Müller cells, a specialized glial cell type that maintains retinal homeostasis and integrity through cytokine and chemokine secretion. They found that Fyn-deficient retinas exhibit distinct alterations, including zones devoid of cells in the inner and outer nuclear layers, increased immunoreactivity, reduced cell proliferation, and impaired focal adhesion formation.[11] This may be related to our research because inadequate retinal architecture and increased immunoreactivity, with higher levels of cytokines and chemokines, could lead to edema; however, this hypothesis needs to be tested in experimental studies.

Conclusions. We report a rare case of reversible macular edema associated with ibrutinib therapy in a patient with SLL. The temporal relationship between drug exposure and symptom resolution after discontinuation, without any ophthalmologic-specific therapy, strongly supports a causal link. Only a few reports have described BTKis as causing macular edema, and none have provided a pathogenic mechanism. Therefore, the pathogenesis of this side effect remains uncertain and may be linked to ibrutinib's off-target effects on other tyrosine kinases. The one we identify is Fyn tyrosine kinase, whose deficiency alters the retina's structure and induces the production of cytokines. Surely, this hypothesis is speculative, and further reports and clinical experimental studies are required to confirm the correlation between ibrutinib and macular edema.

Author contributions. C.M., A.N. and L.C. wrote the main manuscript text; C.M. e M.L. prepared figure 1; F.E., E.B., L.P., M.L., M.C. and M.P. made the principal

corrections; A.V. and MI.DP. supervised and made the final corrections.

Ethical approval Ethical approval was obtained from the Territorial Ethic Committee (R.S.3.25CS).

Consent to publish. Informed consent was obtained from the patient at the patient's first hospital admission in accordance with the protocols approved by the Institutional Review Board and the ethical principles set forth by the Declaration of Helsinki.

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Competing interests: The authors declare no conflict of Interest.

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