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Case Report

Optic neuropathy secondary to dasatinib in the treatment of a chronic myeloid leukemia case

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Abstract

The drug dasatinib is a new therapeutic option for patients with chronic myeloid leukemia (CML) as well as acute lymphocytic lymphoblastic leukemia (ALL). However, the scientific literature has not reached a consensus regarding the types of secondary ophthalmologic effects that this drug may have. In this study, we present the case of a 36-year-old male patient who was treated with dasatinib. Two and a half months later, this patient began to experience progressive visual loss in the superior visual field of both eyes.

After ruling out various diagnostic options and performing extensive complementary tests, the suspected diagnosis was compatible with optic neuropathy secondary to dasatinib. The patient partially improved after stopping this medication and receiving oral corticosteroid treatment.

Although secondary ophthalmological effects related to dasatinib are practically non-existent, our case is the first to report optic neuropathy secondary to this drug.

Keywords: Dasatinib, Imatinib, Nilotinib, Optic neuropathy, Chronic myeloid leukemia, Visual campimetry/perimetry

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Introduction

The etiology of chronic myeloid leukemia (CML) remains unknown. However, recent studies have shown that this condition is closely related to activation of a tyrosine kinase that is produced as a result of rearrangement of the break point cluster region (BCR) and Abelson murine leukemia (ABL) genes, which are located on chromosomes 22 and 9, respectively. This type of rearrangement creates the Philadelphia translocation in CML.[1]

Tyrosine kinase inhibitors (TKI) are the treatment of choice for CML. Imatinib was the first drug approved for the treatment of CML, and it was originally used as the treatment of choice, with an estimated 5-year survival rate of 89%.[1]

However, it has been recently demonstrated that dasatinib is more effective than imatinib as treatment for the chronic phase of CML.[5] Therefore, dasatinib, a second generation TKI used as treatment for patients intolerant or non-responsive to imatinib, has become a first-line treatment in patients with a recent diagnosis of CML. This superiority over imatinib has also been demonstrated for another second-generation TKI named nilotinib.[2,3,22,23]

Dasatinib has the ability to join the inactive form (similar to imatinib) as well as the active form of the BCR/ABL tyrosine

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kinase. This translates into a more potent and effective inhibition of the tyrosine kinase in comparison to imatinib,[4,5] and this also explains why dasatinib is effective against certain types of CML that are resistant to imatinib.[6,7] Without a doubt, dasatinib represents a new treatment option for patients with secondary effects or an ineffective response to imatinib.[2–4]

Phase I and Phase II clinical studies have demonstrated that the use of dasatinib is safe in patients with CML.[8–11] The most frequent secondary effects in patients treated with dasatinib are the following: headache (34%), diarrhea (30%), fatigue (28%), skin rash (22%), nausea (19%), pleural effusion (19%), and peripheral edema (18%). In addition, reversible myelosuppression is one of the most important and severe side effects associated with this drug.[12–14]

However, the ophthalmological secondary effects of dasatinib, according to studies published to date, are practically non-existent or trivial. Periorbital edema secondary to fluid retention has been reported, although to a lesser degree than that produced by imatinib.[15–17]

Herein, we present the case of a patient with optic neuropathy possibly related to dasatinib exposure. To the best of our knowledge, this is the first case of optic neuropathy secondary to dasatinib to be published.

Case report

Here, we present the case of a 36-year-old male patient, who worked as a bus driver and was involved in a traffic accident in September 2008. As a consequence, he suffered a spleen laceration that did not require surgical treatment. In this accident, the patient did not suffer head trauma or loss of consciousness. However, incidentally, the patient was diagnosed with CML due to hematological alterations observed in the requested complementary tests obtained during his stay in the emergency room.

After obtaining informed consent, he was included in a clinical trial for patients with CML to compare dasatinib versus imatinib as a first-line treatment. The patient was randomly assigned to the group that received 100 mg daily of dasatinib, and he obtained a complete hematological response after 4 weeks of treatment and a complete cytogenetic response after 3 months of treatment. These data were compatible with a totally satisfactory and optimal response to treatment.

However, 2.5 months after initiating treatment, the patient began to notice a loss in his visual field, which was subjectively perceived by the patient as a scotoma located in the superior region of both eyes.

For this reason, the patient was referred for neuro-ophthalmology consultation to evaluate this visual field defect. In the neuro-ophthalmological examination, the patient demonstrated a visual acuity of 20/100 in the right eye (RE) and 20/20 in the left eye (LE). The presence of a relative afferent pupillary defect in the RE was observed. Through the Ishihara test, color vision was noted to be altered in the RE, where the patient was unable to identify any of the plates; the LE was normal.

The patient's visual field, as assessed through campimetry by confrontation, presented a supero-temporal defect in the RE and a normal left eye. Through Humphrey visual field testing (HVF) 24-2, the existence of a superior arcuate defect was observed in the RE [mean deviation (MD) of −15.47 dB], and a superior arcuate defect was observed in the LE (MD of −5.39 dB) (Fig. 1).

Slit lamp examination did not show any abnormalities, although fundus examination showed slight temporal pallor in the optic nerve in the RE and a normal optic nerve in the LE (Fig. 2).

The study was completed by performing a global electroretinogram (ERG), which demonstrated normal results, and obtained visually evoked potentials (VEP), which showed axonal loss in both optic nerves (more marked in the RE) (Fig. 3).

Extensive laboratory tests were obtained, including serology for common infectious diseases (syphilis, HIV, Herpes virus, cytomegalovirus, Epstein Barr virus, Adenovirus, Brucella, Hepatitis A-B-C, and Bartonella), immunologic diseases (ANA, Anti-DNA, Anti-Ro, Anti-La, c-ANCA, and rheumatoid factor), and vitamins (B6, B1, B12, and folic acid). All of these results were within the normal limits. A lumbar puncture with an opening pressure of 19 cm of H2O was also conducted, and all biochemical, microbiological, and cytological analyses were within the normal limits.

Head and orbital magnetic resonance imaging (MRI) was also normal.

After conducting all complementary evaluations, it was suspected that dasatinib could be the cause of the optical neuropathy, and treatment with this drug was suspended. Treatment with oral prednisone, at 100 mg daily, was initiated for 3 weeks, followed by a progressive decrease in the dose until its suspension 1 month after initiation.

Two months later, the ophthalmologic examination was repeated, at which time the patient demonstrated a VA of 20/50 in the RE and 20/20 in the LE. The HVF was repeated, and it showed improvement with a decrease in the size and density of the visual field defects in both eyes. We cannot rule out completely that this improvement can be explained by a learning effect doing the visual field. Fig. 4 shows the presence of a superior arcuate defect in the RE (MD −13.2 dB) and a residual paracentral scotoma in the LE (MD −1.94 dB). Six months later, the patient's VA improved to 20/30 in the RE and 20/20 in the LE. However, the defects in the visual field remained without significant changes; these included the presence of a superior arcuate defect in the RE (MD −11.94 dB) and a residual paracentral scotoma in the LE (MD −1.44 dB).

Lastly, the VEPs were repeated 1 year later, showing a slight improvement of the P100 wave in the RE, but with continued asymmetry of the amplitude in the LE.

After improvement of visual function and considering the good hematological response to initial treatment with dasatinib, the Hematology service proposed to initiate treatment with nilotinib, a drug that differs from dasatinib but is within the same family. After patient agreement, this treatment was initiated with good tolerance. However, after 2 months of treatment, the patient began to note photopsia in the area of the residual scotoma of the RE, which spontaneously went into remission after several days. After repeat neuro-ophthalmological evaluation, it was confirmed that the VA, as well as the HVF, remained without changes in both eyes compared to the patient's situation prior to the initiation of treatment with nilotinib. Taking into account that these visual symptoms were very transient, it was decided to continue treatment with nilotinib, and to this date, the patient remains asymptomatic.

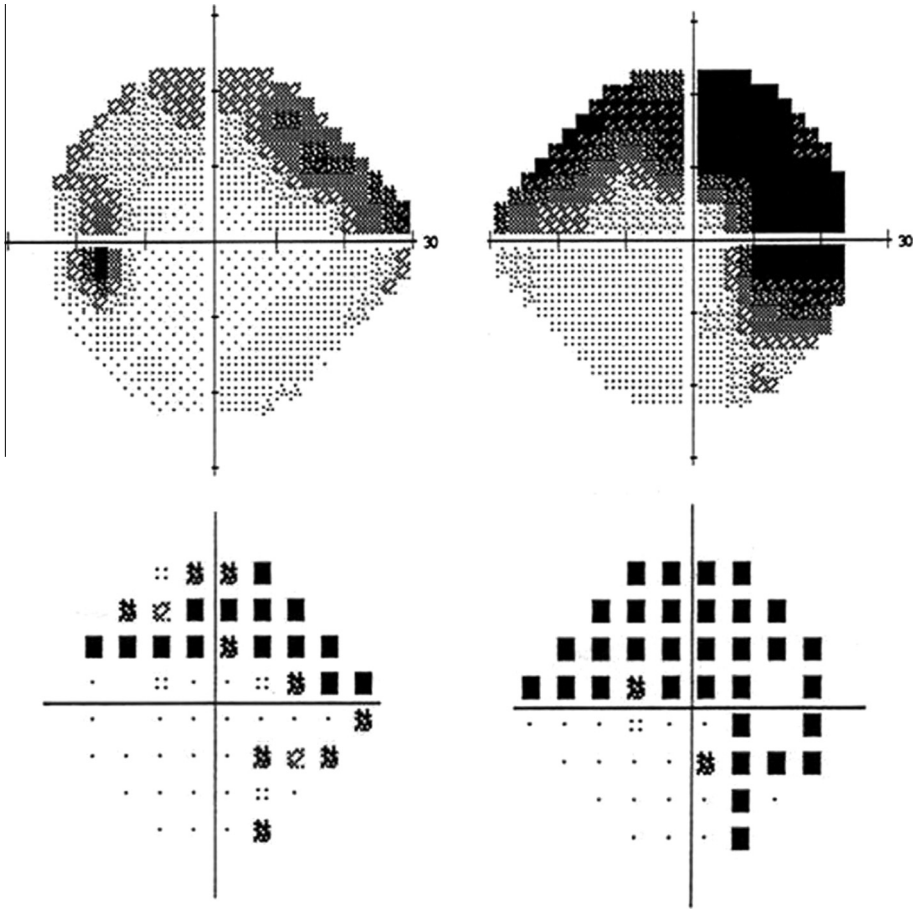

Figure 1. HVF testing 24-2. LE (represented to the left): Presence of a superior arcuate defect (MD −5.39 dB). RE (represented to the right): Presence of a superior arcuate defect (MD −15.47 dB).

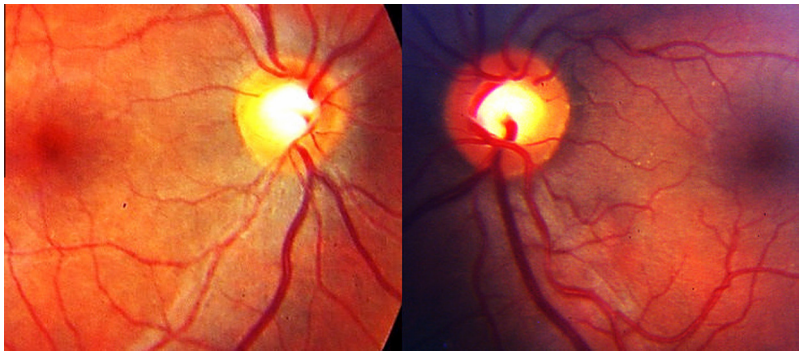

Figure 2. Fundus examination of the eye showing mild pallor in the temporal area of the RE and a normal appearance in the LE.

Discussion

TKIs are the treatment of choice for patients with CML. [10,14,22,23] Trivial ophthalmological secondary (side) effects like periorbital edema have been described in patients who received treatment with imatinib.[18,19]

In the reviewed scientific literature, we found a case of a patient who, 26 days after initiating treatment with imatinib, suffered from progressive bilateral visual loss. This report suggests the role of imatinib as a cause of optic neuropathy.[20]

In another study, Breccia et al. studied ophthalmological secondary effects in 250 CML patients treated with imatinib. Of these 250 patients, only a single patient developed optic neuritis. This patient demonstrated a complete recovery of visual function upon stopping the treatment and receiving vitamin supplements (B complex) and oral corticosteroids. Imatinib was re-initiated 14 days later without any reoccurrence of toxicity.[19]

Our patient, after receiving dasatinib, presented with an optic neuropathy that was manifested clinically as VA loss in the RE and bilateral visual field involvement. After suspension

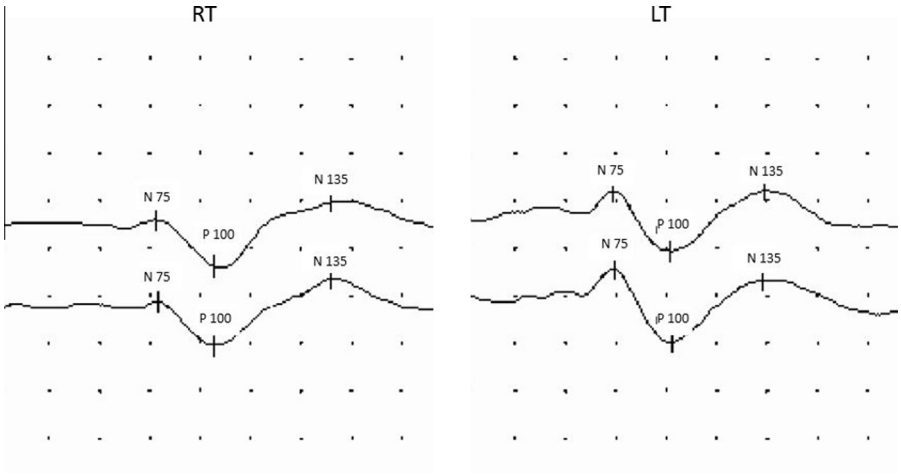

Figure 3. Consistent simultaneous monocular visual stimulus in a 30–60 inverse pattern applied to obtain macular and pattern-evoked potentials. The result was compatible with axonal loss in the optic nerve. There was discrete asymmetry in the amplitude of the cortical responses (P 100), where the wave in the RE was slightly smaller. The responses of both eyes showed waves below the normal range. The latencies were bilateral without asymmetry between both eyes.

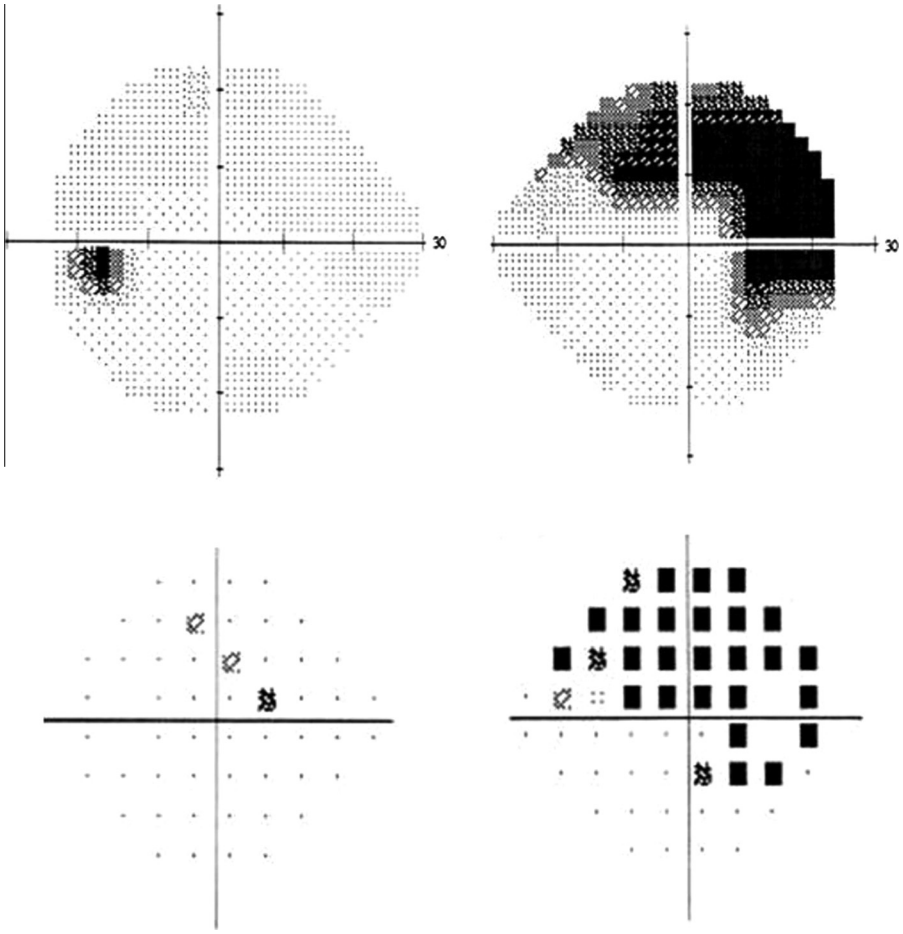

Figure 4. HVF testing 24.2 (obtained 2 months after the first examination). LE (represented to the left): Presence of a residual paracentral scotoma (MD −1.44 dB). RE (represented to the right): There is improvement in the density of the superior arcuate defect (MD −11.94 dB).

of dasatinib and oral corticosteroid treatment, there was a clear improvement in VA (with recovery back to normal).

Given that our patient was a bus driver, he was very concerned with his visual function in order to maintain his profession. For this reason, he opposed the re-introduction of dasatinib. However, this patient did agree to initiating therapy with nilotinib (a second-line TKI that belongs to the same family as dasatinib).

After beginning treatment with nilotinib, the patient experienced mild photopsia in the area of the previous residual scotomas. Given that the symptoms were very mild and his VA and visual campimetry were not affected,

it was decided to continue with this treatment. After several days, these symptoms went into remission, and the patient remained asymptomatic after several months of treatment.

Although this relapse in visual symptoms was much more mild and occurred following exposure to a drug within the same family, we can assume that these symptoms were identical secondary effects to those observed with dasatinib.

The World Health Organization (WHO) has established a series of criteria to obtain evidence of the cause-effect relationship between a certain pharmaceutical principal and a secondary effect. These criteria include temporal association, relationship with the dosage, improvement after discontinuation, worsening after re-introduction, possible pathophysiological mechanism, similar effects after introduction of drugs in the same family, and absence of alternative mechanisms that may explain the secondary effect.[21]

Applying these criteria to our patient, we identified the following: a temporal association; a relationship with the dosage (progressive worsening with dosage increase); improvement after removal of the drug and worsening after re-introduction of nilotinib (drug within the same family); and the lack of an alternative pathophysiologic mechanisms that could explain the optic neuropathy (after extensive diagnostic tests). Taking into account the WHO classification, we therefore define the relationship of causality between dasatinib and optic neuropathy in our patient as probable.

In summary, to the best of our knowledge, this is the first case of toxic optic neuropathy related to exposure to dasatinib. Despite suspending this medication, the visual field defects in our patient persisted, which suggests an irreversibility of this toxicity. However, the mechanisms by which TKIs produce optic neuropathy remain unclear. Moreover, although we cannot be sure that there is similar toxicity for other TKIs, the fact that reintroduction of nilotinib in our patient led to a mild and transient reoccurrence of symptoms indicates that this secondary effect could also occur for TKIs of the same family.

Conflict of interest

The authors declared that there is no conflict of interest.

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