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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.