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Case Report

Glasdegib (DAURISMO™) As A Cause of Optic Disc Edema in A Patient with Glioblastoma

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Abstract

A case of a 50-year-old female with glioblastoma who developed optic disk edema after starting treatment with Glasdegib is described. She referred a 2-days history of blurred vision in the left eye and was diagnosed with glioblastoma and treated with exeresis of the tumor and concomitant treatment with radiotherapy, Temozolamide and Glasdegib 6 months before the ophthalmic symptoms started. Ophthalmological examination showed a decreased BVCA with optic disk edema in the left eye without other findings. The patient was diagnosed with optic disk edema in left eye as a related side effect of the toxicity from Glasdegib and consequently Glasdegib was discontinued with complete resolution of the optic disc edema, developing later optic disc atrophy. To our knowledge, there are no published reports of optic disc edema as a complication related to the treatment with Glasdegib.

Keywords: Glasdegib; Optic Disc Edema

Introduction

Glasdegib (DAURISMO™) is an oral inhibitor of the Hedgehog signaling pathway, by binding to and inhibiting the transmembrane protein Smoothened, downregulating the expression of GLI [1]. (a Hedgehog signaling pathway target gene), the activation of which is associated with a number of malignancies [1]. It is the first Hedgehog pathway inhibitor to be approved, in November 2018, for Acute Myeloid Leukemia (AML) in the USA, where it is indicated for use in combination with low-dose cytarabine for the treatment of newly-diagnosed AML in patients aged ≥ 75 years or those who have comorbidities that preclude use of intensive induction chemotherapy [1]. A phase I/II clinical trial of Glasdegib in combination with Temozolamide is being performed in Spain for treating glioblastoma [1]. The most frequently reported adverse events are anemia, febrile neutropenia, thrombocytopenia, pneumonia and fatigue. Elevated alanine aminotransferase, aspartate aminotransferase and/or total bilirubin levels and mean QTcF interval of> 480 ms and/or a mean increase from baseline in QTcF of > 60 ms have also been described [1]. To our knowledge, there are no published reports of optic disc edema as a complication related to the treatment with Glasdegib.

Case Report

A 50-year-old female patient was referred on the 14th of November of 2018 to ophthalmology for a 2-days history of blurred vision in the left eye. Following the diagnosis of glioblastoma, it was treated with a complete exeresis of the tumor and concomitant treatment with radiotherapy, Temozolamide (75mg/m^2/day) and Glasdegib (3 dose levels are being evaluated: 100mg QD, 150mg QD and 200mg QD, or 75-50mg) 6 months before the ophthalmic symptoms started (Figure 1). Total duration of both chemotherapeutic regimens was since the 28th of May of 2018 to the 14th of November of 2018. During this time, the only adverse effects that occurred were dysgeusia grade I, myalgia in lower limbs grade I (which began on 7/08/2018 and persisted unchanged without clinical relevance) and cramps in lower limbs (since 10/30/2018 without clinical relevance).

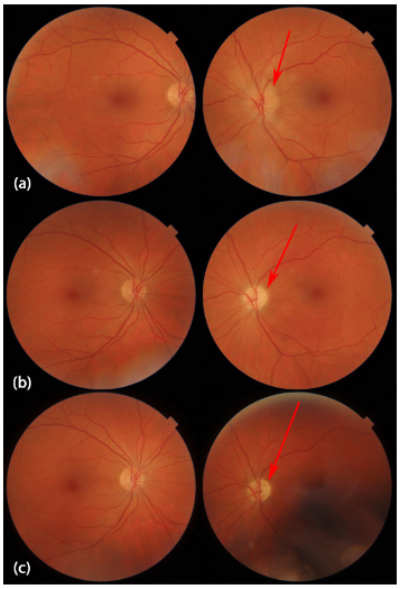

Figure 1: MRI of glioblastoma before treatment.

At the initial exam, Best Corrected Visual Acuity (BCVA) was 20/20 in the right eye and 20/40 in the left eye. Fundoscopy showed optic disc edema in left eye that was confirmed with Optical Coherence Tomography (OCT) of optic nerve head (Figure 2 (a), Figure 3 (a)). No other signs in the fundus; macular OCT showed normal macular architecture without edema and/or thickening and the posterior poles and peripheral retina of both eyes were normal. Visual field 30 -2 examination confirmed a significant inferonasal arcuate defect and blind spot enlargement in the left eye and normal field in the right eye (Figure 4 (a)). The rest of the examination was normal.

In the possible causes of optic disk, we included intracranial hypertension direct or indirectly related to the tumour and secondary effects of the co-adjuvant treatments.

With these findings and taking into account the differential diagnosis, complete analytics were carried out, which showed a stable hematologic status (only lymphopenia related to treatment with Temozolamida and Glasdegib without clinical relevance). Magnetic Resonance Imaging (MRI) of spine and brain was carried out, with stability according to previous findings and without any evidence of tumour recurrence in the central nervous system or retrobulbar compression of the left optic nerve or in the tissues of the left orbit or intracranial hypertension. After ruling out all other causes, the patient was diagnosed with optic disk edema in the left eye as a related side effect of the toxicity from Glasdegib and the oncologist discontinued Glasdegib treatment permanently. In addition, Acetazolamide 250 mg/12 hours was initiated.

2 weeks after stopping Glasdegib treatment, although decreased BVCA in the left eye persisted, the optic disc edema and the visual field improved. At the first month visit after treatment discontinuation, BVCA was 0.7 in the left eye and optic disc edema has disappeared and the visual field has improved, thus, Acetazolamide was stopped. However, OCT of optic nerve head began to show peripapillary Retinal Nerve Fiber Layer (RNFL) thickness decreased in the inferior quadrant (Figure 2 (b), Figure 3 (b), Figure 4 (b)). In successive ophthalmic examinations, the visual field progressively improved, BVCA of 0.7 in left eye remained stable, but retinography showed optic disc atrophy and OCT of optic nerve head showed a progressive optic disc atrophy with temporal, superior and inferior fibre reduction until today (Figure 2 (c), Figure 3 (c), Figure 4 (c)).

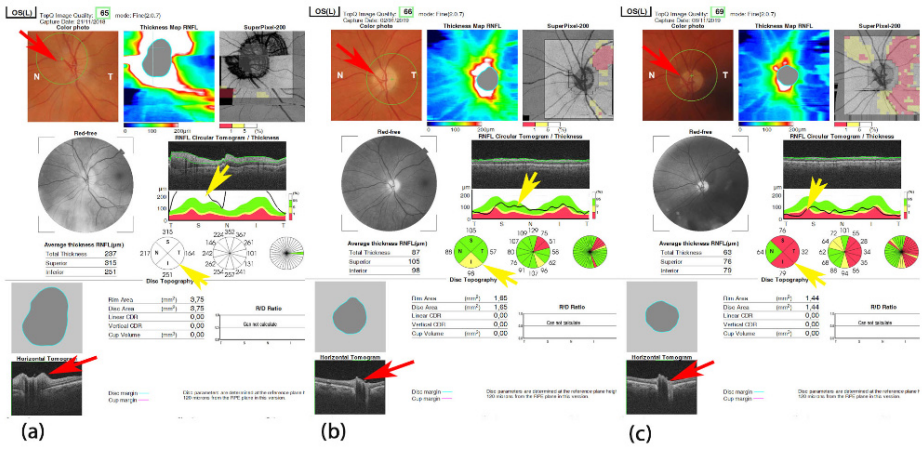

Figure 2: Retinography. **(a)** Retinography showed optic disc edema with blurred disc margin (red arrow) at the initial exam in the left eye. **(b)** After 1 month of Glasdegib discontinuation, retinography showed the resolved swelling (red arrow) of the optic nerve. **(c)** After 1 year of Glasdegib discontinuation, retinography showed increased pallor and atrophy (red arrow) of the optic disc.

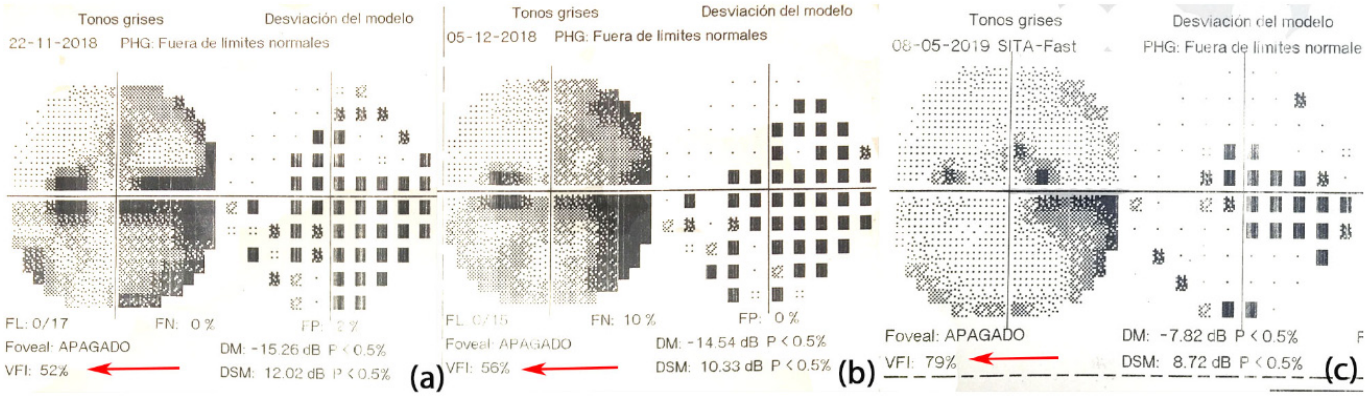

Figure 3: OCT of optic nerve head. **(a)** Optic disc edema (red arrow) and peripapillary RNFL thickness (yellow arrow) increased on OCT at the initial exam in the left eye. **(b)** After 1 month of Glasdegib discontinuation, optic disc edema is resolved (red arrow) and peripapillary RNFL thickness is decreased in the inferior quadrant (yellow arrow) on OCT. **(c)** After 1 year of Glasdegib discontinuation, OCT showed atrophy of the optic disc (red arrow) and the RNFL is decreased in the superior, inferior and temporal quadrants (yellow arrow) on OCT.

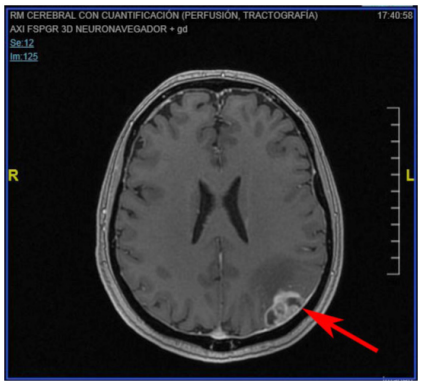

Figure 4: Pattern deviation for the left eye from a visual field 30-2. **(a)** Visual field showed a significant inferonasal arcuate defect and blind spot enlargement in the left eye at the initial exam **(b)** After 1 month of Glasdegib discontinuation, the visual field improved **(c)** After 6 months of Glasdegib discontinuation, the visual field continued improving.

Discussion

Optic disc edema has been described as a related side effect of other drugs used in some malignancies, such as Imatinib (a selective inhibitor of BCR-ABL tyrosine kinase) or Dasatinib (a second generation tyrosine kinase inhibitor) [2-4]. Most complications of tyrosine kinase inhibitors are related to fluid retention in the connective tissue and extracellular matrix, due to inhibition of the platelet-derived growth factor receptor, including optic disc edema [2-4]. Other possible chemotherapeutic regimens with optic disc edema as a side effect are summarized in (Table 1).

Drug	Context	Mechanism
BCR-ABL tyrosine kinase inhibitors	A patient with chronic myeloid leukemia developed cystoid macular edema and optic disc edema after starting treatment with imatinib mesylate [3].	Most complications of tyrosine kinase inhibitors are related to fluid retention in the connective tissue and extracellular matrix, due to inhibition of the platelet-derived growth factor receptor, included optic disc edema [2-4].
Bevacizumab	6 patients with glioblastoma treated with Bevacizumab in addition to fractionated radiation therapy and temozolamide developed severe optic neuropathy [5].	Proposed mechanisms may involve arterial thrombosis or upregulation of VEGF and subsequent neovascularization after radiotherapy with delayed ischemia following bevacizumab [5].

Trastuzumab	Some cases of papilledema after trastuzumab treatment have been reported [6].	Proposed mechanisms are toxic optic neuropathy [6].
Docetaxel	A patient with HER2 positive breast cáncer who received docetaxel and trastuzumab chemoterapy who developed bilateral optic neuropathy with normal opening pressure in the LP that improved after oral corticosteroids treatment and docetaxel discontinuation [7].	Proposed mechanism is that this toxic neuropathy is most likely caused by an underlying ischemic or neurotoxic insult to the optic nerve retinal ganglion axons [7].
Paclitaxel	14 breast cáncer patients treated with cetaxel and 16 patients treated with paclitaxel and adriamycin who developed electrophysiological changes and visual symptoms [8].	The most likely mechanism of visual symptoms and electrophysiological changes during paclitaxel administration are ischemic mechanisms when the optic nerve is involved [8].
Vincristine	A 6-year-old boy diagnosed with frontotemporal primitive neuroectodermal tumor with bilateral optic nerve toxicity after treatment with placitaxel [9].	Results of ophthalmologic assessment were suggestive of selective impairment to parvocellular pathways which were consistent with a diagnosis of vincristine-induced toxic optic neuropathy [9]. It has been suggested that vincristine-induced optic neuropathy may be more likely in those who have also received cranial irradiation [9]. Tissue injury to the blood-brain barrier following irradiation, or mechanical disruption following tumor invasion or surgery, is also likely to facilitate central nervous system penetration of vincristine [9].
Ipilimumab	Papillitis in the setting of VKH and thyroid eye disease due to Graves' disease have been described with ipilimumab treatment [10].	The ocular adverse effects of ipilimumab seem to be mediated by loss of immune tolerance; Vogt-Koyanagi-Harada syndrome and Grave's disease have been associated with inherited polymorphisms in the CTLA-4 gene [10].
Mitogen-activated protein kinase kinase inhibitors (Trametinib and cobimetinib)	Optic disc neuropathy have been described in a few reports [5, 11].	Mechanism remains unknown [5, 11].
Anaplastic lymphoma kinase inhibitors	Optic neuritis and optic neuropathy have been described in patients with non-small cell lung cancer treated with crizotinib [12].	Mechanism remains unknown [12].
Carboplatin	A case of a 48-year-old woman was diagnosed with stage 3b high-grade ovarian endometrioid carcinoma and she was treated with adjuvant carboplatin who developed unilateral disc edema and a case of bilateral papilloedema in the context of treatment for stage 3c ovarian carcinoma with carboplatin have been reported [13].	The postulated mechanism is neurotoxicity from the agent crossing the blood-brain barrier [13].
Cisplatin	Toxic neuropathy is found in the literature in around 5-6% of patients treated with cisplatin and some cases of optic disc neuropathy have been described [14].	The postulated mechanism is neurotoxicity and it is known that the coniocellular system (yellow-blue-antagonistic fields) is most affected [14].

Table 1: Chemotherapeutic regimens with optic disc edema as a side effect.

There are no published reports of optic disc edema as a complication of Glasdegib and the mechanism by which this adverse effect could have occurred is still unknown. A common mechanism in the origin of the optic disc edema could be present in hedgehog pathway inhibitors that should be studied. Before establishing diagnosis of optic disc edema as a related side effect of the toxicity from Glasdegib, other causes should be ruled out, such as retrobulbar compression of the optic nerve or intracranial hypertension [15]. MRI is a simple way to rule out all these causes. For this reason, an MRI should be done in all patients with optic disc edema and treatment with Glasdebib before assuming a toxicity mechanism.

Conclusion

Optic disc edema should be considered one of the adverse events associated with Glasdegib. Thus, we propose performing ophthalmic examinations in all patients treated with Glasdegib before starting the therapy to have a reference in case of any visual symptom could appear; discontinuation of Glasdegib should be considered in case of developing this adverse event. Further studies are necessary in order to establish the mechanism and toxicity level of Glasdegib and whether to reinitiate treatment or not after its discontinuation.

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Authors declare no conflict of interest.

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