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Case Report

Optic Nerve Sheath Fenestration as Adjuvant Treatment for Severe Pseudotumor Cerebri Syndrome Induced by All-Trans Retinoic Acid

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Keywords
Pseudotumor cerebri · All-trans-retinoic acid · Acute promyelocytic leukemia · Case report

Abstract
All-trans retinoic acid (ATRA) is a vitamin A derivative which can increase intracranial pressure, causing visual loss and papilledema. Those patients should be treated similarly to others patients with idiopathic intracranial hypertension. We described a case of a 32-year-old woman presenting with severe visual loss and intracranial hypertension induced by ATRA for acute promyelocytic leukemia, which was treated clinically and with optic nerve sheath fenestration. Patients receiving ATRA therapy should be monitored to neurological and ophthalmic signs and symptoms of intracranial hypertension.

Introduction

The pseudotumor cerebri syndrome (PTCS) is a condition characterized by papilledema, normal neurological exam except for cranial nerves abnormalities, neuroimaging criteria of normal brain parenchyma without evidence of hydrocephalus, mass or structural lesion and no abnormal meningeal enhancement on magnetic resonance imaging, normal cerebrospinal fluid (CSF) composition, and elevated lumbar puncture (LP) pressure, defined as greater than or equal to 250 mm H_20 in adults [1]. While some patients may have idiopathic intracranial hypertension (IIH), PTCS may also be secondary to cerebral venous outflow impairment or induced by substances including the consumption of Vitamin A and its analogs [2, 3].

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All-trans retinoic acid (ATRA), a derivative of vitamin A, is an essential component in the treatment of acute promyelocytic leukemia (APL) because it induces remission in 80–94% of such patients [4]. We described a case of a patient with APL and secondary PTCS after the ATRA treatment, which was successfully treated with optic nerve sheath fenestration (ONSF).

Case Report

A 32-year-old woman with APL noticed binocular horizontal diplopia followed by headache and subacute visual loss in both eyes 2 weeks after starting treatment with ATRA (45 mg/m^2). On the examination, her best corrected visual acuity was finger counting in the right eye (OD) and 20/40 in the left eye, there was bilateral abducens paresis and an afferent pupillary defect in OD. Fundus examination showed swollen optic discs in both eyes (Fig. 1). Standard automated perimetry demonstrated a cecocentral scotoma in OD and enlargement of blind spot in the left eye (Fig. 1). Optical coherence tomography showed marked increased peripapillary retinal layer thickness around the disc (Fig. 1). A longitudinal line-scan passing through the optic nerve showed bulging of the posterior scleral indicating elevated pressure at the optic nerve sheath (Fig. 2). Magnetic resonance imaging study was unremarkable with no evidence of optic nerve infiltration or space-occupying lesions. A LP revealed an opening pressure of 42 cm H_2O. The CSF analysis was normal. Her ATRA treatment dosage was halved, and she was given acetazolamide (2 g daily). Because of recent VA loss, an ONSF was performed in OD. Over the following 2 weeks subsequent to the reduction of ATRA, acetazolamide therapy, and ONSF surgery, papilledema and abducens paresis resolved (Fig. 2). After a 6-month period, the best corrected visual acuity was 20/20 and visual fields were normal in both eyes.

Discussion

APL is characterized by a balanced reciprocal translocation involving the retinoic acid receptor α (RARα) on chromosome 17 and promyelocytic leukemia (*PML*) gene on chromosome 15 (t(15:17)) generating the oncogenic PML-RARα fusion protein (PML-RARA). Normally, RARα plays a role in proper differentiation of myeloid precursors, as the receptor interacts with retinoic acid to affect transcriptional of genes required for maturation. However, the t(15:17) mutation causes transcriptional repression and produces an abnormal receptor that is unable to signal for differentiation of myeloid precursors at a physiologic dose of retinoic acid. Clinically, patients present overproduction of promyelocytes and the underproduction of healthy blood cells causing anemia, bleeding, and infections disorders. Treatment with ATRA overcomes this process causing a PLM-RARα proteolysis and stimulates the differentiation of myeloblasts into mature granulocytes. The ATRA treatment induces remission in about 90% of the patients with APL. While ATRA therapy is considered safe, secondary IIH has been described in APL patients [3]. The physiopathology of IIH secondary to ATRA therapy is unclear, but it is hypothesized to be similar to vitamin A overdosage, which presumably increases CSF production at level of choroidal plexus and impairs absorption at level of arachnoid villi or granulations [5]. Since such structures present RARα receptors, they could be stimulated by ATRA therapy.

It is worth noting that patients with PML which present with bilateral optic disc edema should be evaluated for leukemic infiltration of the central nervous system, beyond of other causes of the IIH as cerebral venous sinus thrombosis or intracranial hemorrhage. Therefore, those patients must be undergoing to careful neuroimaging studies and LP establish the correct diagnosis.

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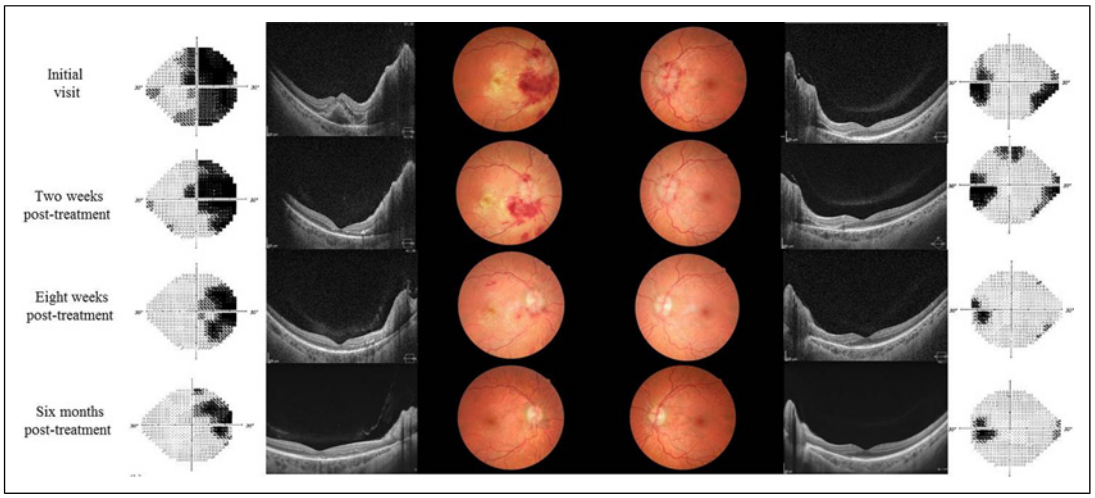

Fig. 1. Standard automated visual field (SAP), fundus photography, and OCT macular scans at the initial visit, at 2 weeks, 8 weeks, and 6 months posttreatment. Optic nerve swelling decreased significantly across visits. In the right eye, the macular edema resolved 2 weeks after the optic nerve sheath fenestration. Six months later, there was no papillary or macular edema. Automated visual field progression demonstrating significant central visual loss in the OD and enlarged blind spot in the OS. OS, left eye.

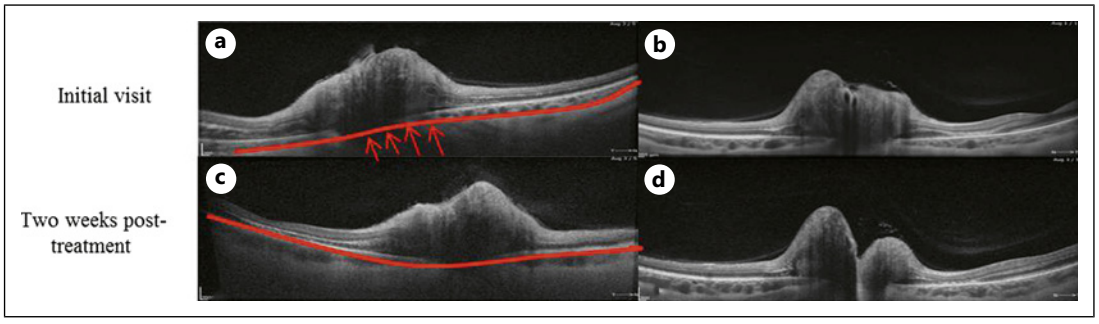

Fig. 2. Line OCT scans in the optic nerve head. Right eye (**a** and **c**) left eye (**b** and **d**). Note the anterior displacement of the optic nerve head in the right eye indicating the posterior polar flattening caused by the intracranial hypertension (**a**), and the improvement 2 weeks after the optic nerve sheath fenestration (**d**).

This case met the diagnostic criteria for PTCS according to the modified Dandy criteria. The criteria state that pseudotumor cerebri is diagnosed if (1) there are symptoms of raised intracranial pressure in the form of headache, nausea, vomiting, transient visual obscurations, or papilledema, (2) no localizing signs with the exception of abducens (sixth) nerve palsy, (3) the patient is awake and alert, (4) normal CT/magnetic resonance imaging findings without evidence of thrombosis, (5) LP opening pressure of more than 25 cm H2 O and normal biochemical and cytological composition of CSF, and (6) no other cause for raised intracranial pressure can be found [1]. Visual acuity is typically normal in ATRA-induced PTCS [6], in contrast to this patient. This patient had count fingers in the OD 2 weeks after beginning ATRA therapy, which suggests a severe form of PTCS.

The treatment of PTCS in patients with PML is similar to other patients with IIH consisting mainly of acetazolamide and topiramate [3, 7]. Depending on the clinical stage ATRA, dosage should be discontinued at least or the dosage reduced. ONSF can be a useful

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surgical treatment for patients with idiopathic IIH who experience progressive vision or visual field loss despite maximally tolerated medical therapy [8]. Our case is interesting because the patient presented severe visual loss in the OD and was demonstrating a good response to ATRA therapy; therefore, we chose to perform an ONSF as adjuvant of ATRA dosage reduction and acetazolamide to preserve the visual function and avoid extensive axonal damage. Adequation of ATRA treatment and continuation of acetazolamide lead to further improvement and complete resolution of papilledema in both eyes. ONSF has not been described previously as a first-line treatment for ATRA-induced PTCS, and this case report serves to suggest ONSF could be an appropriate adjuvant therapy in patients with severe vision loss due to PTCS secondary to ATRA.

In conclusion, our case serves to emphasize that patients with PML receiving ATRA therapy should be monitored for intracranial symptoms such as visual loss, diplopia, and headache. ONSF should be considered as an adjuvant treatment option in patients with significant visual loss of recent onset in order to improve the chances of visual recovery. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531001).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This report does not contain any personal information that could lead to the identification of the patient.

Conflict of Interest Statement

The authors report no conflicts of interest to declare.

Funding Sources

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Author Contributions

Kenzo Hokazono initially examined, followed up the patient's ophthalmologic manifestations, processed OCT images, performed the surgery, and drafted the manuscript. Leonardo Provetti Cunha, Rony Carlos Preti, Leandro Cabral Zacharias, and Mário Luiz Ribeiro Monteiro critically reviewed the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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