Monocular visual impairment in a patient undergoing cisplatin-based chemotherapy: a case report and clinical findings

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Abstract

Background

Visual impairment occurred as an infrequent form of chemotherapeutic toxicity and was often underestimated despite of several reports. We described a case of acute monocular visual impairment after one cycle of intravenous cisplatin-based chemotherapy of normal dose, aimed at raising attention to chemotherapy-induced ocular toxicity.

Case presentation

The patient consulted to an ophthalmologist, and during her follow-up period we documented the ophthalmologic examinations including visual acuity, visual field (VF), visual evoked potential (VEP), electroretinogram (ERG), fundus photograph (FP), fundus fluorescein angiography (FFA) and optical coherence tomography (OCT). During chemotherapy, the patient developed progressive vision loss in the right eye. No evidence of ocular infiltration was observed from the cerebral magnetic resonance imaging (MRI). Ophthalmoscope examination and fundus photograph showed optic disc edema, fuzzy boundary and linear hemorrhages in the right eye. Fundus fluorescein angiography (FFA) revealed capillary underdevelopment at the nasal and superior temporal area of optic disc in the early phase and capillary fluorescein leakage in the late phase. The result of VEP test suggested that the function of optic nerve was impaired. A diagnosis of nonarteritic anterior ischemic optic neuropathy (NAION) was made by an ophthalmologist and the patient received prednisone combined with neuroprotective drugs, which did not work. After cessation of chemotherapy, her impaired vision gradually improved.

Conclusions

This is the first reported case of acute visual impairment in a patient undergoing cisplatin-based chemotherapy of normal dose. It is warranted that cancer patients benefiting from chemotherapy simultaneously suffer from the risk of vision loss.
Background

Many patients with malignancies benefit from advances in chemotherapeutic treatments; however, in parallel chemotherapeutic agents present a wide spectrum of toxic effects. Visual impairment occurred as an infrequent form of chemotherapeutic toxicity, and chemotherapy reportedly induces irreversible or reversible visual loss in recent years. As reported in one study, a male patient suffered from acute unilateral blindness after 5 cycles of cisplatin/gemcitabine (cisplatin 80 mg/m2, gemcitabine 1250 mg/m2) for lung cancer [1]. Visual complications related to chemotherapy might come to light when vision loss occurred after receiving chemotherapy and it is imperative to consult at ophthalmology department.

Case Presentation

A 48-year-old woman developed tinnitus and enlarged cervical lymph nodes. Nasopharyngoscopy examination and biopsy confirmed nasopharyngeal squamous cell carcinoma; thus, she received anti-tumor therapy of TPF (docetaxel d1 at 75mg/m2, cisplatin d1-2 at 75mg/m2 and fluorouracil d1-5 at 500mg/m2) which was repeated every four weeks. The patient complained of visual loss in the right eye two weeks after the first cycle of chemotherapy, and she received the second cycle of chemotherapy as planned. One week later, she made the first visit to an ophthalmologist because of progressive vision loss. Visual acuity was determined as VOD 0.4 which was much worse than before as she said and the presence of relative afferent pupillary defect (RAPD) was measured in the right eye. Since she had a history of high myopia and amblyopia in her left eye evidenced by the determined visual acuity (VOS CF/25cm), the current vision impairment in her right eye seriously affected her quality of life. Ophthalmoscope examination and fundus photograph showed optic disc edema, fuzzy boundary and linear hemorrhages in
the right eye (Fig. 1a). Typical fundus changes of high myopia were observed in the left eye, such as atrophic arc around optic disc, fuchs spot and tigroid fundus (Fig. 1b). MRI of brain provided evidence of no tumor involvement in orbits and central visual pathways (Fig. 1c and 1d). The long optic axis of the left eye is a typical feature of high myopia eyeball (Fig. 1d). The patient received neurotrophic drug treatment. Three weeks later, the visual acuity in the right eye decreased to 0.3 and the signs of optic disc mentioned above also existed.

About one week after the third cycle of chemotherapy, she made the third visit to the ophthalmologist. The VOD was determined to be 0.3. The optic disc edema subsided, the upper part of the optic disc became gray and residual retinal hemorrhage was located on the inferior rim. Creases, depigmented macules and hard exudate were observed in the macular area creases (Fig. 2a). The optic disc optical coherence tomography (OCT) of the right eye showed that the thickness of ILM-RPE at the superior side and nasal side was thinner than that in normal eyes (Fig. 2b). Visual field (VF) examination of the right eye indicated severe visual field defects (Fig. 2c). Fundus fluorescein angiography (FFA) as the most important assistant examination revealed capillary underdevelopment at the nasal and superior temporal area of the optic disc in the early phase and capillary fluorescein leakage in the late phase (Fig. 2d-2f). Thus, the doctor arrived at the diagnosis of NAION to the right eye, and gradually reduced high-dose oral prednisone along with neuroprotective drugs were used for treatment. Meanwhile, retrobulbar injection of Compound Betamethasone (1 ml) was given to the right eye, combined with eye drops of ocular hypotensive agents.

One month after finishing three cycles of induction chemotherapy, concomitant intravenous antitumor therapy with radiotherapy was started. Due to the suspicious ocular toxicities of cisplatin, a targeted agent Nimotuzumab was recommended for alternative
treatment. The patient made the fourth visit to the ophthalmologist and VOD of the right eye was determined to be 0.4. The optic disc edema subsided with clear boundary, but the color of optic disc was still gray (Fig. 3a). OCT showed the secondary macular epiretinal membrane (Fig. 3b). The VF improved obviously compared with the image three weeks ago, which meant the function of the optic nerve was partially repaired (Fig. 3c). The ERG from the right eye showed that the amplitudes of a-type wave and b-type wave at light adaptation 3.0 test were almost normal, and the amplitude of P1-type wave at light adaptation 30Hz Flicker test was also normal, which indicated that the function of the retina was normal (Fig. 3d). The incubation period of P100-type wave in P-VEP test was lengthened, suggesting that the function of optic nerve was partially impaired (Fig. 3e).

On finishing radiotherapy, the patient had not been treated with chemotherapy for 3 months and she made her follow-up visit at the ophthalmic clinic. The VOD improved to be 0.5. The color of optic disc was not so gray as before while the macular epiretinal membrane still existed (Fig. 4a and 4b). The amplitude and incubation period of P2-type wave from the right eye were almost normal in F-VEP-1HZ test, which meant the function of the optic nerve was mostly repaired (Fig. 4c). About 7.5 months after chemotherapy, the visual acuity remained at VOD 0.5. The VF of the right eye improved dramatically (Fig. 4d). The results of ophthalmologic examinations during her follow-up period are presented in Table 1.

Discussion And Conclusions

NAION is the most common cause of acute visual loss in people aged over 50, resulting from non-inflammatory small vessel ischemic damage to the anterior portion of the optic nerve. The cause and pathogenesis of this disorder remains unclear [2, 3]. Symptoms was noticed over several hours to days and patients usually complained of acute, unilateral and painless visual loss [2]. Neuroprotective drugs or agents acting on the disc edema are
often included in the treatment of NAION, however, currently no therapy has been yet proved to be effective [4]. Given the temporal relationship between chemotherapy and vision loss of the patient, we considered that the onset of NAION might be attributed to the intravenous chemotherapy. Because of a combination of drugs, it is difficult to identify the specific agent accounting for the followed vision loss. Ototoxicity represents a widely recognized form of cisplatin-induced neurotoxicity, also, visual impairment has been reported in several studies. Evidence from clinical and experimental studies revealed that cisplatin-based chemotherapy presented retinal toxicity [1, 5, 6]. Thus, we suspected that NAION of the patient was closely related to cisplatin. The ERG showed diminished a-wave and b-wave in the previous report on cisplatin [5]; however, abnormal outcomes of VEP and VF examinations were observed in our case report, not changed ERG. Since the toxic effect on retinal or optic nerve might result in irreversible vision loss, early detection of ocular toxicity and cessation of anti-cancer therapy are required. However, sometimes it is a trade-off for clinicians and patients between the risk of permanent visual damage and the effectiveness of anti-cancer therapy.

Neck mass constitutes the most common presenting symptom of patients with nasopharyngeal carcinoma (NPC) [7]. Impaired vision as the initial presentation due to optic nerve involvement was rarely reported. Concomitant chemoradiotherapy and adjuvant chemotherapy were accepted as the standard in the treatment of patients with stage III and IV NPC [8, 9]. Neoadjuvant chemotherapy was currently reported to reduce local-regional recurrences and distant metastases [10]. Fluorouracil and cisplatin are commonly used, and the major toxicities include myelo-suppression and vomiting. Ocular toxicities have not been widely recognized and are difficult to be detected, which might turn out to be severe and permanent. NPC has a favorable prognosis and, thanks to the advance in anti-cancer therapies the patients live a longer life. Vision represents an
important part of life quality. Here we reported the case aimed at raising attention to chemotherapy-induced ocular toxicity in the treatment of NPC.

Chemotherapy-induced ocular toxic effects include eyelid inflammation, cataracts, glaucoma, conjunctivitis, dry eye or watery eye syndromes, keratitis, blurred vision and itchy eyes [11]. Vision loss related to cisplatin, docetaxel and fluorine has been reported in several studies. Cisplatin-associated retinal toxicity was dose-dependent or unique to high doses, including blurred vision, color vision defects, and electroretinographic (ERG) changes. A patient received five cycles of cisplatin/gemcitabine (gemcitabine 1,250 mg/m2 on days 1, 8 and 15 and cisplatin 80 mg/m2 on day 8 monthly) treatment for lung cancer. Unfortunately, the patient was admitted to the emergency room complaining of acute blindness in his left eye. Fundus examination were normal in both eyes, and the MRI of the left optic nerve and orbit did not reveal any relevant findings. A diagnosis of left retrobulbar optic neuritis was made [1]. A 55-year-old man planned to receive a 4-day continuous infusion of cisplatin at a dose of 25 mg/m2 daily as part of a chemotherapeutic salvage regimen for non-Hodgkin lymphoma. Inadvertently, the actual cisplatin dose was 100 mg/m2 daily for 4 days. Immediately after treatment, except anorexia, nausea and tinnitus, he developed bilateral decreased vision. The ERG showed diminished a-wave and missed b-wave [5]. A clinical study of 52 patients determined the prevalence rates of 5-FU-associated ocular abnormalities [12]. The results showed that the most common presentation was tearing (26.9%), followed by blurred vision (11.5%). After receiving 12 courses of intravenous 5-FU for metastatic breast cancer, a 72-year-old woman complained of a sudden visual loss. MRI (orbits and optic nerves) was normal and the discontinuation of anti-cancer agent resulted in the improvement of the vision. A deficiency of dihydropyrimidine dehydrogenase (DPD) was detected and it was considered that 5-FU was responsible for the visual loss, associated with DPD deficiency [13]. A 53-
A 55-year-old female received monthly intravenous infusion of docetaxel 100 mg/m² for metastatic breast cancer, and 2 months later she complained of blurred vision in both eyes. Thus, docetaxel was replaced by Xeloda, and her vision improved [14].

Many diseases are manifested by visual acuity impairment including eye problems and systemic disorders, posing challenges to the etiological diagnosis. Based on the MRI images of the patient, we firstly ruled out the possibility of vision loss caused by orbital tumor invasion. On the first admission, the patient informed her history of hypertension and adequate blood pressure control was achieved with antihypertension medication. She did not complain of dizziness, headache and vomit when vision loss occurred. The prevalence of NAION, as a vascular disease, was considered to be associated with systemic disorders such as hypertension, diabetes mellitus and arteriosclerotic heart disease. However, none of them are reported to be firmly associated with NAION except diabetes mellitus [15]. Due to sharp decrease of visual acuity, the patient consulted to ophthalmology clinic for etiological diagnosis and potential therapy. Glaucoma, cataracts, macular degeneration and other eye diseases were excluded and the right optic disk edema was observed by funduscopic examination, and a diagnosis of NAION was made with etiology unknown. Chemotherapy-induced NAION should be considered when patients receiving cancer chemotherapy suddenly developed vision loss. Most ophthalmic complications are readily reversible if recognized early. Dosage reduction or agent cessation could rescue patients from vision loss. However, if optic nerve or retinal was involved, patients might develop irreversible vision loss. Given the evidence from previous reports of chemotherapy-associated vision loss, we communicated with the patient about benefits and side effects of her chemotherapy before conducting the second cycle. After a discussion, a decision was made to receive two more cycles of induction chemotherapy for ensuring the efficiency of anti-cancer therapy. During the following two cycles of induction
chemotherapy, the patient's vision was stably poor. An additional one month of radiation was included in her therapy schedule. Given cisplatin-associated ophthalmic complications, a targeted agent Nimotuzumab was recommended to combine with radiation, replacing chemotherapeutics. On finishing radiotherapy, she had not been treated with chemotherapy for 3 months and there was obvious improvement in the vision of her right eye. Induction chemotherapy plays an important role in the therapy of local advanced nasopharyngeal carcinoma, and presented here was one case of severe visual impairment induced by chemotherapy. It is warranted that cancer patients benefiting from chemotherapy simultaneously suffer from the risk of vision loss. Although it has been reported that intravenous chemotherapy of cisplatin and docetaxel caused retinal toxicity, this is the first case in which intravenous administration of chemotherapy (TPF) for NPC induced NAION, enough causing irreversible vision loss. This reported case suggests that ophthalmic complications should be considered when patients receiving chemotherapy suddenly develop visual impairment. As soon as symptoms are recognized, the patient should be scheduled for a follow-up examination in ophthalmology clinic. Oncologists and ophthalmologists should work together for subsequent treatment.

List Of Abbreviations
VF-visual field; VEP-visual evoked potential; ERG-electroretinogram; FP-fundus photograph; FFA-fundus fluorescein angiography; OCT-optical coherence tomography; FFA-fundus fluorescein angiography; NAION-nonarteritic anterior ischemic optic neuropathy; NPC-nasopharyngeal carcinoma.

Declarations
Ethics approval and consent to participate
The report of patient data was approved by the Institutional Animal Care and Use Committee.
and Ethics Committee.

Consent for publication

Written consent was obtained from the patient for the publication of the patient's details.

Availability of data and material

The data supporting the conclusions of this article are included within the article.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors' contributions

M.L. conceived the idea, participated in information gathering, literature search and data analysis. X.Y. participated in information gathering, literature search, data analysis and drafting the final manuscript. Y.F. performed the ophthalmologic examination and composed this manuscript. D.L participated in drafting the final manuscript and editing the figures. All authors read and approved the final manuscript.

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Table 1

Table 1. The results of ophthalmologic examinations in the right eye during the follow-up period.
| Time points                          | Eye symptoms                        | Visual field | ERG | VEP | OCT | Ophthalmoscopy examination | Fundus fluorescein angiography | Visual acuity |
|-------------------------------------|-------------------------------------|--------------|-----|-----|-----|----------------------------|-------------------------------|---------------|
| December 6th, 2017 (during chemothe rapy) | Progressive visual loss             | —            | —   | —   | —   | Optic disc edema, fuzzy boundary and linear hemorrhages. | —                            | 0.4           |
| December 29th, 2017 (during chemothe rapy) | Progressive visual loss             | —            | —   | —   | —   | Optic disc edema, fuzzy boundary and linear hemorrhages. | —                            | 0.3           |
| January 5th, 2018 (1 week after chemothe rapy) | Progressive visual loss             | Severe visual field defects | —   | —   | Thinner ILM-RPE at superior side and nasal side | The upper part of the optic disc becoming gray, optic disc edema subsiding and residual retinal hemorrhage on the inferior rim; creases, depigmented macules and hard exudate in the macular area. | —             | 0.3           |
| January 25th, 2018 (1 month after chemothe rapy) | Improved vision                    | Obviously improved visual field. | Normal amplitude of a-type wave, b-type wave and P1-type wave. | —   | —   |  | Capillary underdevelopment at the nasal and superior temporal area of optic disc in the early phase and capillary fluorescein leakage in the late phase | —             | 0.4           |
| March 28th, 2018 (3 months after chemothe rapy) | Improved vision                    | —            | —   | —   | Normal incubation period of P2-type wave. | Secondar y macular epiretinal membran e | The optic disc becoming not so gray as before. | —             | 0.5           |
| August 13th, 2018 (7.5 months after chemothe rapy) | Improved vision                    | Dramatically improved visual field. | —   | —   | —   | — | — | — | — | 0.5 |
Note: On October 31st, 2017 the patient received the first cycle of chemotherapy. On November 30th, 2017, she received the second cycle of chemotherapy. On December 29th, 2017, she received the third cycle of chemotherapy. From January 26th, 2018 to March 22th, 2018, she received radiotherapy combined with targeted therapy. VEP: visual evoked potential; ERG: electroretinogram; OCT: optical coherence tomography.

Figures

Figure 1

Ophthalmoscope examination and MRI images of orbits during chemotherapy. a: fundus photo of the right eye, b: fundus photo of the left eye (December 6th, 2017), c: MRI images of skull base invasion in nasopharyngeal carcinoma, d: MRI images of orbits (December 26th, 2017).

Figure 2

Ophthalmologic examinations of the right eye one week after chemotherapy ends. a: ophthalmoscope examination, b: optic disc OCT, c: visual field examination, d-f: fundus fluorescein angiography (January 5th, 2018).

Figure 3

Ophthalmologic examinations of the right eye one month after chemotherapy ends. a: ophthalmoscope examination, b: macula OCT, c: visual field examination, d: ERG test, e: P-VEP test (January 25th, 2018).
Figure 4

Ophthalmologic examinations of the right eye at follow-up visits to ophthalmology.

a: ophthalmoscope examination, b: macula OCT, c: F-VEP (March 28th, 2018), d: visual field examination (August 13th, 2018).

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