유방암 환자에서 발생한 파클리탁셀 망막병증

Paclitaxel-associated Retinopathy in a Female Patient with Breast Cancer

강혜민

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Purpose: To report a case of paclitaxel-associated retinopathy in a 53-year-old female patient with breast cancer, and describe the treatment response to intravitreal bevacizumab injection.

Case summary: A 53-year-old female patient visited our Ophthalmology Clinic with a complaint of visual deterioration in both eyes. She had undergone paclitaxel chemotherapy for breast cancer with multiple metastases. Her ophthalmologic history included visual acuity 20/30 in each eye and normal ophthalmologic findings 2 years prior to visual deterioration. At the time of examination, her vision was 20/50 in each eye, and fundus examination showed macular thickening in both eyes. Fluorescein angiography showed faint petaloid dye pooling at the fovea, and spectral domain optical coherence tomography showed intraretinal cysts with macular thickening in each eye. Fundus autofluorescence images showed hypo-autofluorescent petaloid patterns involving the fovea in both eyes. She was diagnosed with paclitaxel-associated retinopathy, but the oncologist refused to stop paclitaxel chemotherapy. We performed intravitreal bevacizumab injection in each eye, which did not result in improvement of macular edema.

Conclusions: We report a case of paclitaxel-associated retinopathy that presented with a form of cystoid macular edema, and that did not respond to intravitreal bevacizumab injection. If a patient undergoing paclitaxel chemotherapy complains of visual deterioration, further ophthalmologic evaluation is recommended.

Keywords: Breast cancer; Macular edema; Paclitaxel

Introduction

Paclitaxel (Taxol; Bristol-Meyers Squibb Co., New York, NY, USA) is an anti-tubule agent preventing mitotic cellular functions that is used as an anti-neoplastic agent for breast cancer, ovarian cancer, head and neck cancer, and advanced forms of Kaposi's sarcoma. Paclitaxel is chemically similar

to docetaxel. In addition to systemic side effects such as fatigue, nausea, bone marrow suppression, alopecia, peripheral neuropathy, arthralgia, and myalgia, ocular side effects can occur. These include mild conjunctival chemosis, corneal epitheliopathy, corneal edema, and keratitis [1-5]. In addition to these anterior segment complications, several case reports have reported paclitaxel-associated retinopathy [6-15].

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Although it is rare, paclitaxel-associated retinopathy can lead to visual deterioration. The exact mechanism of paclitaxel-associated retinopathy is unclear, and currently the best treatment is cessation of paclitaxel [6-15]. Other adjuvant treatments have been reported, such as intravitreal bevacizumab injection [12], topical or intraocular steroid treatment, oral acetazolamide [13], topical non-steroidal anti-inflammatory drugs [10], and topical dorzolamide [14]. Here, we describe a case of paclitaxel-associated retinopathy in a 53-year-old female patient with breast cancer who could not stop paclitaxel.

Case Report

A 53-year-old female patient visited the ophthalmology clinic with a complaint of visual deterioration in both eyes. She was undergoing paclitaxel chemotherapy for breast cancer with multiple metastases. Two years prior to visual deterioration, her visual acuity was 20/30 in each eye without any significant ophthalmologic findings. At the time of examination, her best-corrected visual acuity (BCVA) was 20/50 in each eye, and fundus examination showed mild macular thickening in both eyes (Fig. 1A, B). Fluorescein angiography (FA) showed petalloid dye pooling at the fovea in both eyes (Fig. 1C, D),

and spectral domain optical coherence tomography (SD-OCT) showed intraretinal cysts with macular thickening and photoreceptor ellipsoid zone disruption in both eyes (Fig. 1E, F). Fundus autofluorescence (FAF) images showed a hypo-autofluorescent petalloid pattern at the macula (Fig. 1G, 1H), which was much more distinct than the petalloid pattern on FA. Under the impression of paclitaxel-associated retinopathy in both eyes, we consulted her surgeon and oncologist regarding whether the chemotherapy regimen could be changed. However, it was impossible to replace paclitaxel with another agent because the patient had already changed chemotherapy regimens several times due to multiple metastases, including brain and bone metastases. Thus, we decided to perform intravitreal bevacizumab injections in an effort to reduce the cystoid macular edema (CME). Three days after intravitreal bevacizumab injection in both eyes, her intraretinal cysts and central macular thickness were reduced compared to baseline (Fig. 2), although there was no significant change in vision. One month after the first injection, the CME in both eyes became aggravated, and her BCVA was 20/63 in both eyes (Fig. 3). We tried intravitreal bevacizumab injections again in both eyes, but there was no significant improvement after 3 days. One month after the second injection, the CME in both eyes was aggravated further, with more photoreceptor ellipsoid zone disruption (Fig. 4),

Figure 1. Multi-modal imaging analysis of a patient with paclitaxel-associated retinopathy. Fundus photography of the right eye (A) and left eye (B) show mild macular thickening. Fluorescein angiography shows faint petalloid dye pooling at the fovea in the right eye (C) and left eye (D). Spectral domain optical coherence tomography shows intraretinal fluid cysts with macular thickening in the right eye (E) and left eye (F). The mean central macular thickness is 544 μm in the right eye, and 509 μm in the left eye. Fundus autofluorescence images show distinct hypo-autofluorescent petalloid patterns at the macula in the right eye (G) and left eye (H).

Figure 2. Three days after the first intravitreal bevacizumab injections, cystoid macular edema slightly improves in the right eye (A) and left eye (B). The mean central macular thickness is 357 μm in the right eye, and 295 μm in the left eye.

Figure 3. One month after the first intravitreal bevacizumab injections, cystoid macular edema is aggravated in each eye (right eye, A; left eye, B). The mean central macular thickness is 555 μm in the right eye, and 451 μm in the left eye.

Figure 4. One month after the second intravitreal bevacizumab injections, we observe significant cystoid macular edema (right eye, A; left eye, B). The central macular thickness is 640 μm in the right eye, and 580 μm in the left eye.

but without any change in BCVA. We planned to perform intravitreal steroid injections and prescribed topical ketololac eyedrops. However, the patient was unable to undergo further treatment due to poor general condition.

Discussion

Although the exact pathogenesis is not clearly identified, there are several lines of evidence indicating that paclitaxel-associated retinopathy does not involve vascular-endothelial growth factor (VEGF)-mediated mechanisms of CME. Paclitaxel-associated retinopathy presents as a form of CME, but there is usually minimal leakage or staining on

FA [6,11,12,15]. In addition, paclitaxel-associated retinopathy has appeared in patients who underwent concomitant chemotherapy with paclitaxel and bevacizumab [10]. Intravitreal bevacizumab injections were not effective for reducing CME in previous cases either, although vision was preserved [12]. Our case is consistent with previous case reports, showing faint petalloid dye pooling on FA and limited response to intravitreal bevacizumab injections for CME.

Several theories have been suggested for the pathogenesis of paclitaxel-associated maculopathy [6-9]. One theory is the engorgement of Müller cells [6]. Because Müller cells are responsible for maintaining osmotic gradients within the neurosensory retina, degeneration of Müller cells can lead to intraretinal fluid cysts and subsequent CME [6]. A recent case report suggests that the functional failure of aquaporin-mediated water transportation at the level of retinal intermediate and deep capillary plexuses, and to a lesser extent at the level of the retinal pigment epithelium (RPE), is responsible for CME [7]. Another case report suggests that paclitaxel-associated retinopathy may result from intraretinal accumulation of intracellular fluid due to impaired polarized microtubule-dependent transport by RPE cells. Paclitaxel-induced disruption of cytoskeletal structures such as microtubules may trigger protein and fluid accumulation in the retina [8]. Further studies are needed to define the exact pathophysiology of paclitaxel-associated retinopathy and would be helpful for planning patient management.

Although large case series regarding treatment are lacking, discontinuation of paclitaxel is generally accepted as the treatment of choice for paclitaxel-associated retinopathy. Several adjunctive therapies have also been suggested, including topical steroids and non-steroidal anti-inflammatory drugs, oral acetazolamide, and topical dorzolamide [10,12-14]. In our case, the first intravitreal bevacizumab injection resulted in significant improvement of CME at 3 days, but this improvement did not persist over 1 month. The second intravitreal bevacizumab injection, did not result in improvement in CME in either eye at 3 days. Furthermore, we observed CME aggravation 1 month after the second injections. Thus, anti-VEGF agents such as bevacizumab do not seem to be effective for the treatment of paclitaxel-associated retinopathy. If discontinuation of paclitaxel is not allowed, clinicians should seek alternative treatments for paclitaxel-associated retinopathy. Our case adds to the evidence that intravitreal bevacizumab injection is not effective

for paclitaxel-associated retinopathy, and other treatments should be considered as first-line therapy if paclitaxel cannot be replaced. If we elucidate the precise mechanism underlying paclitaxel-associated retinopathy, we can manage patients better and hopefully prevent visual deterioration.

After resolution or improvement of CME, most previous cases reported visual improvement compared to baseline [6-14], but some cases did not [15]. Limited visual recovery after paclitaxel-associated retinopathy may be due to photoreceptor ellipsoid zone disruption caused by CME or toxic damage to the photoreceptor ellipsoid zone. In our case, CME and photoreceptor ellipsoid zone disruption were noted on SD-OCT at the time of presentation. CME persisted despite intravitreal bevacizumab injections, and concurrent photoreceptor ellipsoid zone disruption led to gradual visual deterioration. Thus, prompt diagnosis and changes of chemotherapy regimen if possible seem essential for patients with paclitaxel-associated retinopathy. Currently, routine ophthalmologic screening for paclitaxel-associated retinopathy is not considered or recommended due to its rarity, however, it should be suspected when patients undergoing paclitaxel chemotherapy complain of visual deterioration. Prompt discontinuation of paclitaxel may prevent further visual deterioration due to paclitaxel-associated retinopathy.

In conclusion, if a patient undergoing paclitaxel chemotherapy complains of visual deterioration, further ophthalmologic evaluation is recommended. If paclitaxel-associated retinopathy is diagnosed, intravitreal bevacizumab injection is not effective for the reduction of CME, and discontinuation of paclitaxel is recommended if possible.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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