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Case Report

Cystoid Macular Edema following Treatment with Nanoparticle Albumin-Bound Paclitaxel and Atezolizumab for Metastatic Breast Cancer

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Keywords
Atezolizumab · Breast cancer · Cystoid macular edema · Nanoparticle albumin-bound paclitaxel

Abstract
Cystoid macular edema (CME) is a rare side effect associated with chemotherapy. Although the development of CME has been reported to occur following treatment with taxane drugs, such as nanoparticle albumin-bound paclitaxel (Nab-PTX), the occurrence of CME with treatment with atezolizumab has not yet been reported. Here, we report the case of a 49-year-old woman who developed CME 19 months into chemotherapy with Nab-PTX and atezolizumab. Improvement was not achieved with steroid injections into the Tenon's sac, and Nab-PTX and atezolizumab treatments were ceased. One month later, there was subjective improvement in her symptoms. Although many reports have indicated that cessation of chemotherapy has successfully improved CME, a specific treatment for CME has not yet been established. Clinicians should be aware of the ophthalmologic side effects and offer immediate treatment if symptoms develop.

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Introduction

Recently, the treatment of metastatic breast cancer has involved not only systemic chemotherapy but the addition of immune checkpoint inhibitors is now recognized as useful for treatment. Some chemotherapeutic agents reportedly induce immunogenic cell death through a number of diverse pathways and mechanisms [1, 2]. Moreover, chemotherapy plus immunotherapy combinations cause myeloid-derived suppressor cells and regulatory T cells depletion [3]. Based on the hypothesis that there is a synergistic action with the use of chemotherapy plus immunotherapy, important trials using these combinations, such as the IMpassion130 and KEYNOTE-355 trials, were announced for the treatment of triple-negative breast cancer. The IMpassion130 trial demonstrated an improvement in progression-free survival by adding atezolizumab plus nanoparticle albumin-bound paclitaxel (Nab-PTX) treatment in patients diagnosed with unresectable advanced or metastatic recurrent triple-negative breast cancer. Improvement in prognosis was observed, especially in the programmed cell death ligand 1 (PD-L1)-positive population [4].

Nab-PTX, a taxane-type anticancer drug, is a formulation of paclitaxel bound to human serum albumin. It is associated with known side effects, such as peripheral neuropathy, myelosuppression, interstitial pneumonia, and ophthalmologic adverse events, which have been reported in approximately 10% of patients treated with paclitaxel and Nab-PTX [5]. These ophthalmologic adverse events include visual impairment, ocular dryness, conjunctivitis, and cystoid macular edema (CME), which is a rare but serious adverse side effect. The macula is the site responsible for central vision, and dysfunction of the macula leads to immediate vision loss and may lead to irreversible changes if treatment is delayed.

Atezolizumab is a humanized monoclonal antibody that targets PD-L1. It is approved for use in many carcinomas, but a wide variety of side effects have also been reported with its use. Ophthalmologic adverse events have been reported in approximately 1.5% of cases treated with atezolizumab. However, until now, CME has not been reported [6]. This report describes a case of CME experienced during treatment with atezolizumab and Nab-PTX.

Case Report

A 49-year-old patient consulted a local doctor due to pain in her right breast. She had previously undergone preoperative chemotherapy (paclitaxel and trastuzumab), a partial mastectomy, fat valve revision, conservative breast irradiation, postoperative chemotherapy (epirubicin and cyclophosphamide), and treatment with tamoxifen citrate at 33 years old for right breast cancer.

Upon examination at our hospital, we palpated a hard, poorly mobile, painful mass in the right C region. Positron emission tomography scanning showed significant accumulation of a 4.9-cm mass in the right CD region and an enlarged left axillary lymph node. A biopsy of the left axillary lymph node was performed, and a diagnosis of invasive ductal carcinoma was made. The diagnosis was T4aN3cM1, stage IV (nuclear grade 3, ER <1%, PgR <1%, HER2 score 2, Ki67 80%, MSI negative, PD-L1/SP142 positive, BRCA2 mutation positive 6415del).

A treatment regimen of atezolizumab (840 mg/body, days 1 and 15) and Nab-PTX (100 mg/m^2, days 1, 8, and 15) every 4 weeks was prescribed. After a total of 6 courses, the right primary tumor was enlarged (24–35 mm) and the bilateral axillary lymph nodes were reduced. A right mastectomy was performed and histopathology showed recurrent breast cancer (pT4a, 2.5 cm, NG3, ly3, v1, grade 1b). Postoperative complications included delayed wound healing that required 4 months of chemotherapy withdrawal.

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Computed tomography showed an enlarged left axillary lymph node, so a seventh course of Nab-PTX and atezolizumab treatment was started (Table 1). Nineteen months after the start of this round of Nab-PTX and atezolizumab treatment, the patient reported vision loss in her left eye and visited an ophthalmologist. Her visual acuity was 0.03 on the right and 0.05 on the left. Optical coherence tomography (OCT) confirmed bilateral edema in the macula (Fig. 1a, b). Based on the above, the patient was diagnosed with bilateral CME and she received an injection of triamcinolone in her Tenon sac. There was a lack of improvement in the patient's CME with this injection. Therefore, in collaboration with our hospital and ophthalmologist, treatment with Nab-PTX and atezolizumab were ceased 20 months after the start of chemotherapy. Two months later, the patient's visual symptoms had improved (right 0.06; left 0.08), as did the bilateral CME as observed on OCT (Fig. 1c, d). She was then scheduled to begin treatment with olaparib (600 mg per day).

Discussion

CME is seen in various pathologies and diseases through fluorescence leakage, generally observed on fluorescein fluorescence fundus angiography due to disruption of the medial vascular retinal barrier and leakage of fluorescein out of the retinal vessels. However, CME caused by taxane-based anticancer drugs is thought to be due to toxicity to Müller cells and fluorescence leakage or fluorescence retention tends not to be observed with OCT [7]. It is assumed that the toxic taxane drugs cause intracellular fluid retention and an increase in extracellular fluid in Müller cells, resulting in the disruption of the intracellular structure of Müller cells and the formation of cysts in the outer reticular and inner granular layers, leading to the formation of CME [8]. In this case, age-related CME was suspected, but the lack of improvement with steroid treatment suggested a possible association with chemotherapy treatment. Cases of Nab-PTX-induced CME have been rarely reported in breast cancer patients. A total of 14 cases, including our case, were identified in a search of PubMed using the keywords "Nab-PTX," "breast cancer," and "CME" (Table 2). The time to onset of CME after the initiation of Nab-PTX ranged from 1.5 to 27 months, with an average of 9.3 months. In 12 cases, Nab-PTX was discontinued and visual improvement was achieved in an average of 2.7 months. In our case, a sub-Tenon's injection of triamcinolone only resulted in limited symptom improvement, and visual improvement was achieved only after discontinuation of chemotherapy. Ham et al. [9] reported that an intravitreal bevacizumab injection was effective for CME induced by paclitaxel. Although various treatments, such as steroid administration, have been attempted in previous reports, the therapeutic effects have been limited. While there is no established treatment for CME, the prompt discontinuation of Nab-PTX is considered to be the first choice.

Atezolizumab is a humanized monoclonal antibody that targets PD-L1. The benefit of atezolizumab plus Nab-PTX compared with placebo plus Nab-PTX in unresectable, locally advanced, or metastatic triple-negative breast cancer was demonstrated in the IMpassion130 trial. Although it was not formally tested, patients with PD-L1-positive disease experienced a 2.5-month progression-free survival improvement and a 7.5-month overall survival increase when treated with atezolizumab plus Nab-PTX [4, 22]. Based on results from IMpassion130, atezolizumab plus Nab-PTX was recommended in international treatment guidelines for this group of patients [23]. In regards to the safety profile, the IMpassion130 trial reported alopecia in 56.4% of patients, nausea in 46.0% of patients, and cough in 24.8% of patients, but no ocular adverse events similar to the present case were reported. On the other hand, several reports of ophthalmologic side effects, such as CME, caused by the administration and completion of treatment with immune checkpoint inhibitors have been reported as

Table 1. Patient treatment timeline summary

Time order	Treatment details
	Nab-PTX+Atezo was started
After 6 months	Logo-regional therapy was performed due to the presence of an enlarged primary tumor
After 10 months	Nab-PTX+Atezo was reopened
After 18 months	CME developed and STT was administered, but there was no improvement of symptoms
After 19 months	Nab-PTX+Atezo was discontinued
After 20 months	Symptoms improved

Atezo, atezolizumab; Nab-PTX, nanoparticle albumin-bound paclitaxel; STTA, sub-Tenon triamcinolone acetonide injection.

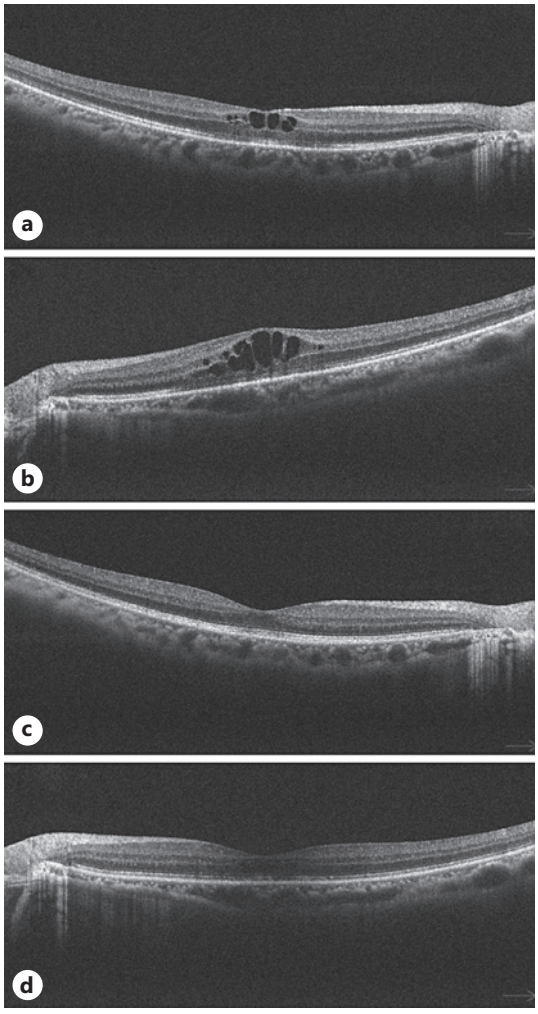

Fig. 1. Spectral domain OCT imaging revealing bilateral CME during the initial visit to the ophthalmologist (right side (**a**), left side (**b**)). Improvement in the bilateral CME is observed 2 months following cessation of chemotherapy treatment (right side (**c**), left side (**d**)).

immune-related adverse events [24, 25]. This suggests that regular follow-up is necessary even after completion of treatment with immune checkpoint inhibitors. As atezolizumab plus Nab-PTX is widely used as a standard treatment, there is a need to examine ophthalmologic side effects among cases.

Table 2. The characteristics of CME in patients with breast cancer treated with Nab-PTX in published reports

Author	Age, years	Affected side	Onset, months	Other drugs	Treatment	Time to recovery, months
Smith et al. [10] 2008	56	Bilateral	27	Trastuzumab	Observation	3
Murhy et al. [11] 2010	65	Bilateral	1.5	Bevacizumab	Steroid and NSAID medication	0.75
Murhy et al. [11] 2010	58	Bilateral	11	Bevacizumab	Observation	3
Baskin and Garg [12] 2011	40	Bilateral	6	Bevacizumab, zoledronic acid, and goserelin	i.v. P and NSAID medication	4
Ehlers et al. [13] 2013	59	Bilateral	ND	Nothing	Dorzolamide	1
Tanaka et al. [14] 2015	47	Bilateral	4	Zoledronic acid	Observation	2
Rahimy and Sarraf [15] 2013	32	Bilateral	10	ND	Observation	0.7
Rahman et al. [16] 2013	73	Bilateral	3	Bevacizumab	i.v. B and continuous Nab-PTX	lost
Matsuokaet al. [17] 2015	39	Bilateral	4	Nothing	STTA	11
Park et al. [18] 2016	69	Bilateral	6	Nothing	Observation	2
Rao and Choudhry [19] 2016	45	Bilateral	ND	Nothing	Observation	Death
Otsubo et al. [20] 2021	72	Bilateral	2	Nothing	Dorzolamide	1.5
Ye et al. [21] 2021	45	Bilateral	18	Nothing	i.v. R	1.25
Our case	49	Bilateral	19	Atezolizumab	STTA	2

i.v. B, intravitreal bevacizumab; i.v. P, intravitreal prednisolone; i.v. R, intravitreal ranibizumab; Nab-PTX, nanoparticle albumin-bound paclitaxel; ND, not described; NSAID, non-steroidal anti-inflammatory drug; STTA, sub-Tenon triamcinolone acetonide injection.

There are a variety of treatment options for metastatic breast cancer, and each case should be considered on a case-by-case basis [26, 27]. The standard treatment for stage IV breast cancer is systemic therapy without resection of the primary tumor [28]. However, in prospective randomized controlled trials, the impact of surgery for the primary tumor on overall survival had been already evaluated in patients with stage IV breast cancer. Therefore, no survival advantage was obtained for surgery [29, 30]. On the other hand, utility of loco-

regional treatment is controversial. Thoracic tumors with local invasion cause various adverse events such as ulceration, bleeding, and dysbiosis, which diminish the patient's quality of life. According to a previous report, a patient's quality of life may be improved with local control surgery in these cases [28]. In this case, local control surgery was performed on a primary tumor that had grown without progression of distant metastasis during chemotherapy. Although there was a postoperative complication of delayed wound healing, chemotherapy was resumed, and the disease was controlled. Since control of the primary tumor is directly related to the patient's quality of life, a detailed examination of each case is necessary.

The indication of immune checkpoint inhibitors for treatment is expected to expand to include patients with early-stage triple-negative breast cancer [31]. To prevent vision loss and maintain quality of life, it is important to be aware of the potential side effects involving the eye with immune checkpoint inhibitor treatments. Research is currently being conducted on the use of artificial intelligence for automatic analysis of OCT [32], which is expected to make it easier to perform regular ophthalmologic examinations in the future. 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/10.1159/000533999).

Conclusion

Here, we describe a case in which chemotherapy-related CME resolved with discontinued use of nab-PTX and atezolizumab. Clinical oncologists should be aware that CME can develop not only with treatment with nab-PTX but also with atezolizumab treatment. This case highlights the importance of prompt ophthalmic examination for decreased vision in patients being treated with nab-PTX and atezolizumab therapy. Collaboration between oncology and ophthalmology teams is crucial for the treatment of patients with similar conditions.

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Statement of Ethics

Ethics approval was not required in accordance with local guidelines for this retrospective, unplanned study. Written informed consent was obtained from the patient for treatment and for the publication and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.Y. wrote the draft and critically revised the manuscript for important intellectual content. H.Y., T.I., K.K., Y.Ko, Y.Ka, and M.O. contributed to the conception of the work. Y.Ko diagnosed and treated this patient with C.M.E. Y.Ko interpreted and revised the results of the optical coherence tomography included in this report. H.Y. and M.O. confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

Data Availability Statement

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

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