

## Anti-Cancer Drug Nab-Paclitaxel May Exacerbate Corneal Epithelial Disorder

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### Abstract

**Purpose:** To report 2 cases of corneal disorder after cancer treatment with nab paclitaxel.

**Methods:** Retrospective review of 2 cases.

**Case presentation:** Case 1 was a 55-year-old female who presented with blurred vision. She underwent cancer treatment in the form of combination therapy with nab-paclitaxel, trastuzumab and pertuzumab for breast cancer 2 weeks before. An ophthalmoscopic examination showed an atypical corneal epithelium invasion in both eyes. The corneal disorder was resolved following discontinuation of nab-paclitaxel. Case 2 had a pancreatic cancer and she presented with an atypical corneal epithelium invasion in both eyes after treatment with S-1 and gemcitabine hydrochloride. The corneal disorder might be caused by S-1, so S-1 treatment was replaced by nab-paclitaxel. The corneal disorder improved temporarily, but it worsened 3 months after the administration of nab-paclitaxel. Finally, the corneal disorder was resolved following the discontinuation of nab-paclitaxel as well as in case 1.

**Conclusion:** Our 2 cases suggest that cancer treatment including nab-paclitaxel may cause severe corneal disorders. Clinicians should consider the possibility of the corneal disorder being caused by the cancer therapy.

**Keywords:** Nab-paclitaxel; Corneal epithelial disorder; Anti-cancer agent; S-1

### Introduction

Ocular side effects induced by systemic anti-cancer drugs are common, but less attention is being paid to them, especially ocular surface disorders.

Nanoparticle albumin-bound- (nab-) paclitaxel (ABRAXANE; Abraxis BioScience, Los Angeles, CA, USA) is a taxane-type chemotherapy medicine used to treat various malignancies, such as breast, pancreatic, gastric and non-small-cell lung cancer [1]. Major systemic complications caused by nab-paclitaxel is myelosuppression and peripheral neuropathy. Cystic macular edema is also a known side effect of affecting vision. [2]

Previously, we had reported a case with corneal epithelial disorder caused by nab-paclitaxel [3]. We recently met another case, so corneal disorder may not be a rare side effect induced by this drug. Therefore, in the present study, we report the details of both cases and review cancer drug-induced corneal disorder.

### Case Report

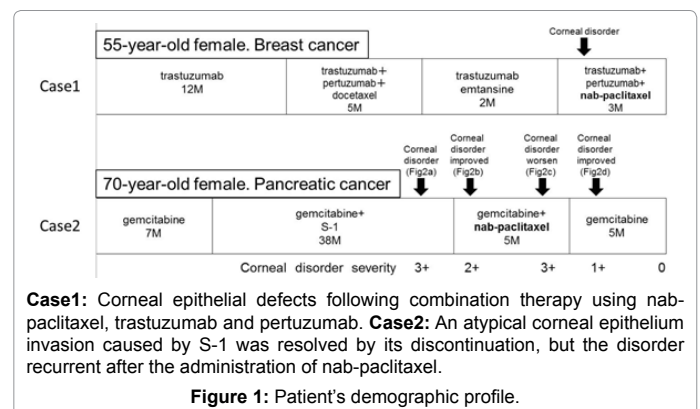
#### Case 1

The corneal epithelial disorder in case 1 had been reported briefly after a short follow-up period [3]. This case was a 55-year-old female who presented with blurred vision bilaterally. Best corrected visual acuity (BCVA) was 20/60 in the right and 20/40 in the left eye. She underwent combination therapy of cancer treatment with nab-paclitaxel (260 mg/m<sup>2</sup>), trastuzumab (6 mg/kg) and pertuzumab (420 mg/day) for breast cancer 2 weeks before. An ophthalmoscopic examination showed an atypical corneal epithelium invasion in both eyes but this was resolved following discontinuation of nab-paclitaxel. BCVA was recovered to 20/15 in the right and 20/20 in the left eye respectively 4 months after the discontinuation [3]. However, the breast cancer worsened and the same therapy including nab-paclitaxel was restarted. Two months after restarting a treatment, similar corneal epithelial disorder was recurrent in both eyes. The vision of each eye was not deteriorated because lesions were localized in the upper cornea but they still remained for more

than 3 months under the continuous administration of nab-paclitaxel (Figure 1).

#### Case 2

A 70-year-old female presented with blurred vision. BCVA was 20/27 in right and 20/50 in left eye. An ophthalmoscopic examination showed an atypical corneal epithelium invasion in both eyes (Figure 2a). She had been treated with gemcitabine hydrochloride (1000 mg/m<sup>2</sup>) and S-1 (40 mg/day to 80 mg/day) for pancreatic cancer for 3 years before. We considered that the corneal disorder might have been caused by S-1, then withdrew the S-1 and nab-paclitaxel (125 mg/m<sup>2</sup>) was administrated instead with the treatment of preservative-free artificial

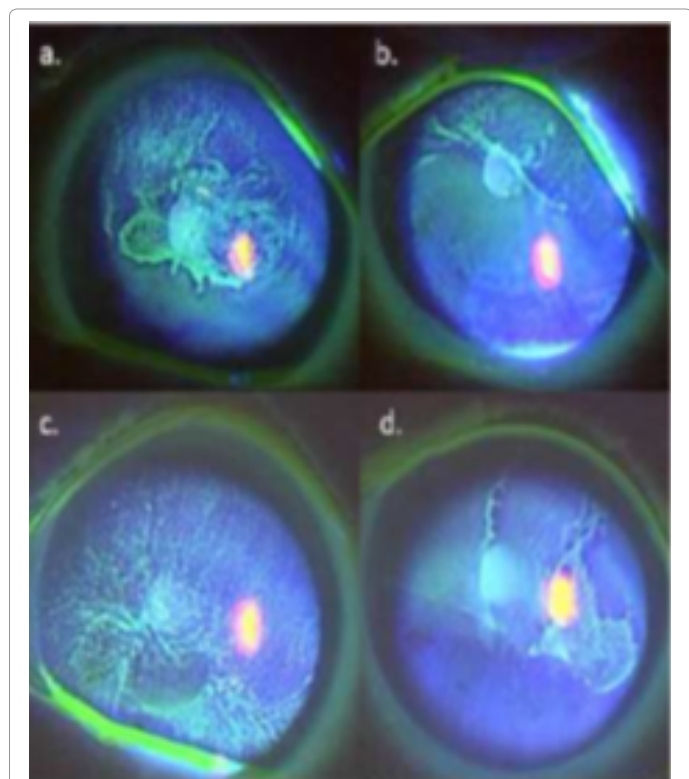


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**Figure 2:** Changes of ocular surface in Case 2.

- a. An atypical corneal epithelium invasion caused by S-1.
- b. Improvement of corneal disorder 1 month after S-1 discontinuation and nab-paclitaxel administration.
- c. Recurrent of corneal disorder 3 months after nab-paclitaxel administration.
- d. Improvement of corneal disorder 1 month after nab-paclitaxel discontinuation.

Agent	Reference	Patients number
Nab-paclitaxel	Hosotani Y et al. [3]	1
Trastuzumab Emtansine	Tsuda M et al. [8]	1
Erlotinib	Hori Y et al. [6]	1
Nivolumab	Nguyen AT et al. [9]	2
S-1	Yamada R et al. [4] and Chikama T et al. [5]	39
		12
Paclitaxel	Lee HS et al. [10]	1
Docetaxel	Goto M et al. [11]	1
Capecitabine		1
Perifosine	Ho WL et al. [7]	Review
Cetuximab		
Gefitinib		

**Table 1:** Summary of available treatment for corneal adverse effects of anti-cancer drugs.

tears, 0.5% levofloxacin and 0.1% fluorometholone OU. The corneal findings improved temporarily (Figure 2b), but the corneal invasion got worsened 3 months after the administration of nab-paclitaxel (Figure 2c). Finally, the corneal disorder was resolved following the discontinuation of nab-paclitaxel and BCVA was recovered to 20/25 in the right and 20/40 in the left eye (Figure 2d).

## Discussion

It has been known that anticancer treatment may induce ocular side effects and S-1 is a representative drug associated with ocular surface

disorder. S-1, an oral antineoplastic agent containing the prodrug 5-fluorouracil (5-FU), is a popularly used cancer drug especially in Japan. Ocular complications of 5-FU include superficial punctate keratitis (SPK), sheet-like appearance, epithelial erosion, epithelial crack lines, lacrimal duct blockage, and conjunctivitis have also been reported [4,5]. One of pharmacological compounds of S-1, tegafur, becomes 5-FU when it is metabolized in the blood. Then 5-FU acts mainly as a thymidylate synthase inhibitor, resulting in impaired DNA synthesis. Otherwise, in the ocular surface, 5-FU in the lacrimal fluid may induce damages to corneal epithelial cells and stem cells. In Table 1, we present another drug that may induce corneal disorders [3-11].

The anticancer treatment in case 1 involved trastuzumab and pertuzumab which were molecular-targeted agents in the form of recombinant humanized monoclonal antibody against the human epidermal growth factor 2 (HER2) and were approved for use in treating HER2-positive breast cancer. HER2 is a receptor tyrosine-protein kinase and a member of the human epidermal growth factor receptor (EGFR) family. Epidermal growth factor can stimulate cell growth, proliferation and differentiation by binding EGFR. Therefore, the antibody against HER2, trastuzumab and pertuzumab, possibly affect the corneal epithelium cells, causing the corneal disorder. Also, Tsuda et al. recently reported that trastuzumab emtansine which is an antibody-drug conjugate combines trastuzumab and emtansine; a tubulin polymerization inhibitor, induced a corneal disorder which was clinically similar to our cases [8].

Each cancer drug used in case 1 had a potential for inducing corneal disorder. The adhesion of corneal epithelium cells might get weakened by using trastuzumab emtansine. Thus, the cancer treatment involving trastuzumab, pertuzumab and nab-paclitaxel might cause a corneal disorder.

## Conclusion

After long-term use of agents that might have negative effects on the corneal epithelium, we conclude that this combination therapy strongly affected the corneal proliferation and differentiation, resulting in a defect of the corneal epithelium cells. Thus, the improvement of corneal disorder following discontinuation of nab-paclitaxel suggested that nab-paclitaxel was a major factor of the anti-cancer drug-induced corneal epithelial disorder. After the restart of nab-paclitaxel, the recurrence of corneal disorder was observed. The fact reinforces our hypothesis; nab-paclitaxel may cause the corneal epithelial disorder.

In case 2, the cancer treatment included gemcitabine, S-1 and nab-paclitaxel. The corneal disorder resolved firstly following the discontinuation of S-1. The recurrent corneal disorder after nab-paclitaxel administration finally resolved following its discontinuation, suggesting that the corneal disorder might be caused by S-1 and nab-paclitaxel mainly but not gemcitabine. Also, there is no report of gemcitabine-induced corneal disorder. Previous report suggested that S-1 could cause damage to the corneal limbal stem cells (CLSCs) [12]. Although there was no corneal limbal stem cell deficiency clinically, over 3 years of use of S-1 might have a significantly negative effect on CLSCs. Therefore, the recurrent corneal disorder after nab-paclitaxel administration occurred due to the CLSCs fragility following long-term use of S-1.

Concerning the ophthalmoscopic examination, our 2 cases showed the same pattern of abnormal corneal epithelial cells invading from the limbs, suggesting that CLSCs might be affected by nab-paclitaxel.

Recent reports support the effectiveness of cancer therapy consisting

of a combination of several anti-cancer agents [13,14]. S-1 is being used increasingly as an adjuvant in general and nab-paclitaxel is used after S-1 such as case 2. In our 2 cases, the causative mechanism of the corneal disorder is considered to be an involvement of nab-paclitaxel directly or the combination cancer therapy involving nab-paclitaxel.

The incidence rates and the timing of development of corneal disorder induced by the cancer therapy including nab-paclitaxel is still unknown. Such disorder can affect vision from several months to several years since the initiation of the therapy. Therefore, we ophthalmologists should consider the association of the cancer drug when examining the case with corneal disorders of uncertain etiology and also check the cornea carefully whenever we examine patients with cancer, especially if they are treated with a combination cancer therapy. In addition, oncologists should be aware of this possible side effects caused by drugs administered systemically and instruct patients to consult ophthalmologists.

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