BMC Ophthalmology

CASE REPORT Open Access

# CDK4/6 inhibitor-associated vortex keratopathy: a case report

Lian Shu[1], Xinhan Cui[1], Yan Wang[1] and Xinghuai Sun[1,2*]

## Abstract

**Background** Cyclin-dependent kinase (CDK) 4/6 inhibitors are novel anticancer drugs that can arrest the cell cycle and halt the progression of cancers. This study presents a rare case of vortex keratopathy associated with the use of a cyclin-dependent kinase (CDK) 4/6 inhibitor for breast cancer treatment.

**Patient presentation** A 60-year-old female patient with a one-year history of eye irritation presented at our hospital. She had been diagnosed with metastatic breast cancer two years prior and received treatment with tiremciclib (a novel CDK4/6 inhibitor) in combination with fulvestrant at the same time. After slit-lamp examination, anterior segment optical coherence tomography (AS-OCT), and corneal confocal microscopy, the patient was diagnosed with vortex keratopathy. The ocular symptoms of the patient improved slightly after the use of artificial lubricating eye drops.

**Conclusions** This case demonstrates the ocular characteristics and novel findings of corneal confocal microscopy of CDK4/6 inhibitor-related vortex keratopathy. Our findings increase the understanding of the pathophysiological mechanisms of drug-induced vortex keratopathy and increase our awareness of ocular manifestations in patients receiving novel anticancer drugs.

**Keywords** Vortex keratopathy, Corneal verticillate, CDK4/6 inhibitor, Corneal confocal microscopy

## Background

Cyclin-dependent kinases (CDKs), a class of serine/threonine protein kinases, are involved in the regulation of the cell cycle, transcription initiation, and control of certain metabolic cascades. Among these, CDK4/6 is a key factor in cell cycle regulation and can trigger the transition of the cell cycle from the G1 phase (growth phase) to the S phase (DNA replication phase). Inhibitors targeting CDK4/6 are an important class of targeted anticancer drugs that can arrest the cell cycle at the G1 phase and halt the progression of various cancers, especially breast cancer [1, 2]. According to previous studies, common adverse reactions to CDK4/6 inhibitors primarily include bone marrow suppression, gastrointestinal discomfort, and liver function abnormalities [2].

Vortex keratopathy, also called corneal verticillate, is a rare form of corneal degeneration characterized by whorl-like opacity in the corneal epithelium. Although the specific mechanism remains unclear, it might result from dysfunctional lipid storage in the lysosomes of corneal epithelial cells, leading to abnormal accumulation of intracellular lipid complexes [3]. Primary lysosomal storage diseases include Fabry disease, a rare genetic

*Correspondence:
Xinghuai Sun
xhsun@shmu.edu.cn
[1]Department of Ophthalmology & Visual Science, Eye & ENT Hospital, Shanghai Medical College, Fudan University, No.83 Fenyang Road, Shanghai 200031, China
[2]State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institutes of Brain Science, Fudan University, Shanghai, China

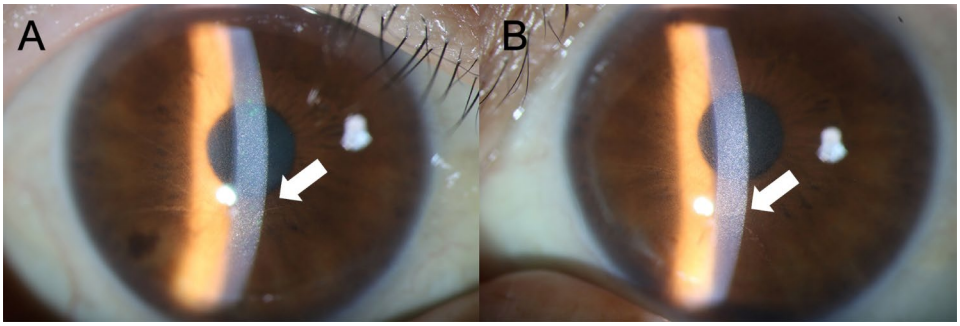


**Fig. 1** **A**, Slit lamp photograph of the right eye. **B**, Slit lamp photograph of the left eye. Bilateral symmetric crystalline-like golden brown deposits are observed within the corneal epithelium and anterior stroma, with arrows highlighting the vortex-patterned epithelial lesions

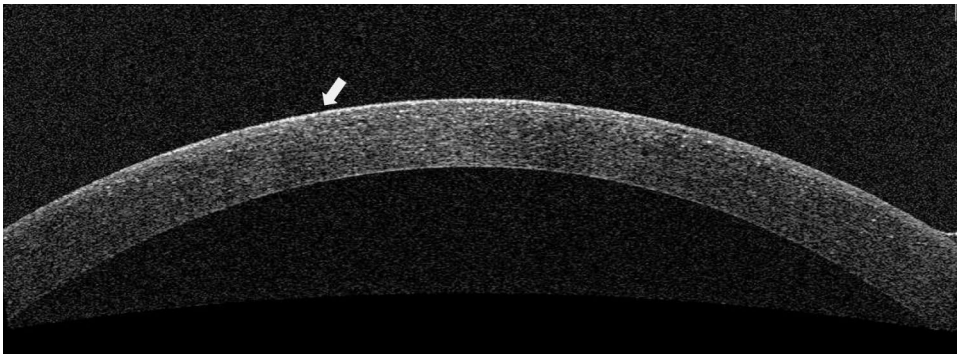

**Fig. 2** Anterior segment optical coherence tomography (AS-OCT) of the right eye. Normal corneal morphology with unsmooth tear film (arrows)

disorder caused by a deficiency of the α-galactosidase enzyme. Characteristic vortex keratopathy is observed in approximately 80% of patients with Fabry disease [4]. Cationic amphiphilic drugs, such as amiodarone, chloroquine, and chlorpromazine, are the most common agents that induce secondary vortex keratopathy [5, 6]. These drugs can penetrate lysosomes and bind to cellular lipids to form drug–lipid complexes, which are resistant to degradation by lysosomal enzymes. Additionally, drug-induced vortex keratopathy is commonly able to be gradually reduced upon discontinuation of drugs. This report describes a rare case of vortex keratopathy induced by a novel CDK4/6 inhibitor.

## Case presentation

A 60-year-old Asian female patient presented to our clinic with bilateral eye irritation, including dryness, sensitivity to light, and occasional epiphora for one year. She claimed that she had been diagnosed with advanced breast cancer with liver metastasis two years prior, which was confirmed by histopathological examination and immunohistochemistry as hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2-). Subsequently, the patient received a combined therapeutic regimen consisting of tiremciclib (400 mg administered orally once daily) and fulvestrant (500 mg administered via intramuscular injection every 28 days) for a duration of 18 months, and her tumor status was stable with regular follow-up. The patient denied any history of other systemic diseases, ophthalmic family history, or use of other medications, including eye drops.

Ophthalmic examination revealed a best-corrected visual acuity (BCVA) of 18/20 and normal intraocular pressure (IOP). Slit-lamp examination did not reveal apparent corneal edema or opacity; however, bilateral symmetric crystalline-like golden brown deposits were observed in the corneal epithelium and partial stroma. Additionally, lesions located inferiorly in the central corneal epithelium displayed a characteristic spiral or radiating distribution (Fig. 1). Furthermore, no abnormalities were found in the rest of the examinations of the anterior and posterior segments, except for a slightly increased lens density. The fluorescein staining test was negative, and nasolacrimal duct examination suggested patency.

The anterior segment optical coherence tomography (AS-OCT) revealed that the tear film did not appear smooth, but no significant corneal morphological abnormalities were detected (Fig. 2). Corneal confocal microscopy revealed a widespread distribution of dot-like or patchy deposits with high reflection, involving almost all layers of the cornea (Fig. 3). However, the intensity of the deposits gradually decreased toward the deeper corneal layers, whereas the endothelium remained unaffected. Notably, a small number of deposits accumulated as a

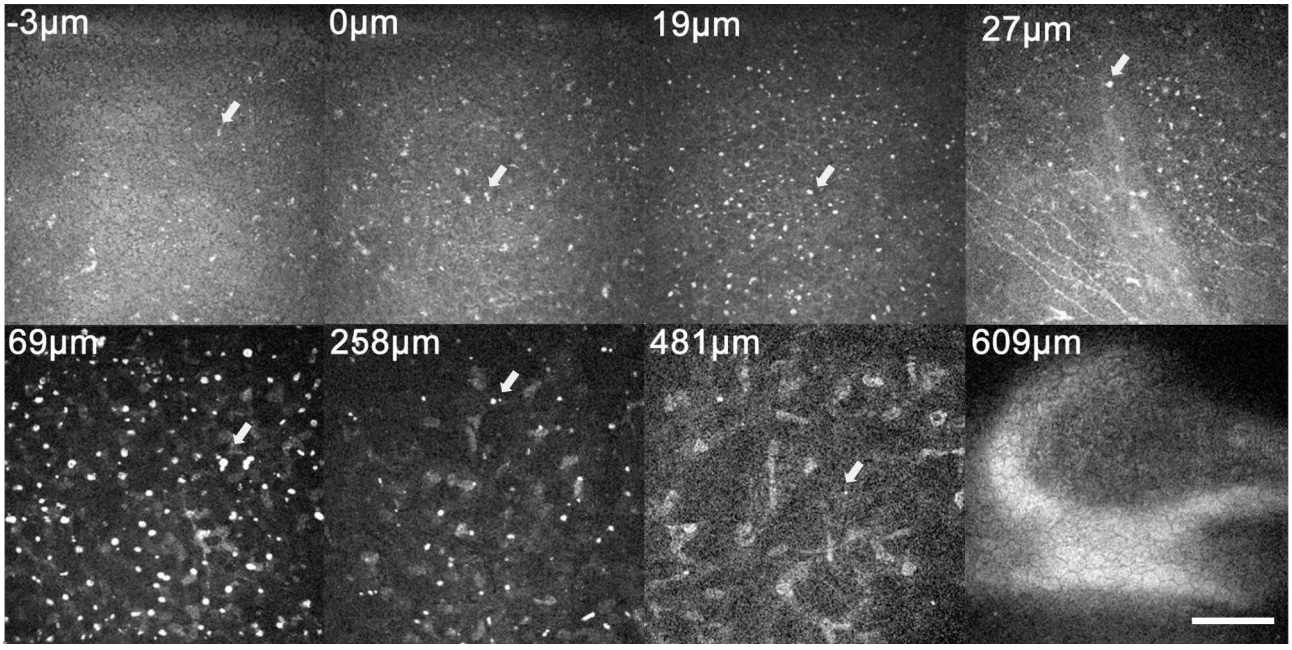


**Fig. 3** Corneal confocal microscopy of the right eye. Depth-encoded map demonstrates corneal stratification, and arrows indicate intracellular hyperreflective deposits. -3 μm: anterior to epithelial layer; 0, 19 and 27 μm: corneal epithelial layers; 69, 258 and 481 μm: corneal stromal layers; 609 μm: corneal endothelial layer. Bar represents 100 μm

thin layer and protruded above the outer corneal epithelial surface at -3 μm. After examination with a slit lamp, AS-OCT, and corneal confocal microscopy, the patient was diagnosed with bilateral corneal verticillate. Symptomatic treatment was provided via preservative-free 0.3% sodium hyaluronate eye drops (Santen, Japan) three times a day, leading to a slight improvement in her ocular symptoms without any changes in keratopathy in the following two weeks. Finally, regular follow-up ophthalmic treatment was advised.

## Discussion and conclusions

We describe a case of corneal verticillate in a patient treated with a combination of tiremciclib and fulvestrant. Tibremciclib is currently a novel CDK4/6 inhibitor under phase III clinical trials [7], and fulvestrant is a selective estrogen receptor modulator (SERM). The combination of these two drugs has synergistic effects on reversing endocrine resistance, particularly in HR+/HER2- advanced or metastatic breast cancer [8]. Only three cases of corneal verticillate induced by ribociclib—another CDK4/6 inhibitor—have been reported worldwide. The patients in these two cases presented similar complaints and ocular manifestations to those in our study but without further examination for keratopathy [9–11].

The morphological characteristics of vortex keratopathy have a high degree of similarity, making it difficult to differentiate between specific types through direct examination via slit lamps. Additionally, due to resolution limitations, AS-OCT often fails to detect significant corneal abnormalities like vortex keratopathy caused by tiny intracellular deposits. Studies have suggested that corneal confocal microscopy may help distinguish Fabry disease-related and amiodarone-induced vortex keratopathy [12, 13]. The corneal confocal microscopy findings in our study revealed the presence of extremely thin deposits on the surface of the corneal epithelium (at -3 μm in Fig. 3), which may result in ocular symptoms of eye irritation in patients. In addition, we observed that the intracorneal deposits were predominantly intracellular and smaller than normal with low heterogeneity in size and morphology. These findings are highly consistent with previous confocal microscopy studies of amiodarone-induced vortex keratopathy, while hyperreflective structures commonly completely fill the cellular cytoplasm in Fabry disease [13]. However, corneal deposits can involve the endothelium in patients with long-term use of amiodarone [13], which was not observed in the present case. We suppose that this may be may be due to corneal absorption through the tear film, and that the severity of keratopathy is related to the drug concentration levels in vivo. Thus, the possibility of finding endothelial involvement cannot be excluded in the later follow-up for this patient. In summary, this case study provides novel insights into the pathological mechanisms of CDK4/6 inhibitor-related vortex keratopathy via corneal confocal microscopy.

Previous studies have shown that CDK4/6 inhibitors share a common characteristic of lysosomal trapping

[14]. These findings suggest that tibiremciclib may directly interfere with phospholipid metabolism within lysosomes, leading to abnormal lipid accumulation. Additionally, tibiremciclib may be involved in the development of vortex keratopathy by interfering with the growth and renewal of normal corneal cells, in which the CDK4/6 pathway plays an essential role [15]. Although it is necessary to reduce the dose of CDK4/6 inhibitors and observe the subsequent changes in keratopathy to establish a convincing causal relationship, it is still reasonable that vortex keratopathy is induced by the use of CDK4/6 inhibitors at present, considering the mild ocular symptoms and the status of malignant tumors in this patient. Additionally, although no cases of keratopathy have been reported with fulvestrant monotherapy to date, it is clinically significant that fulvestrant was concurrently administered in another case of CDK4/6 inhibitor-induced vortex keratopathy in breast cancer management [10]. Given the existing clinical evidence, the potential involvement of fulvestrant in the pathogenesis of CDK4/6 inhibitor-associated vortex keratopathy cannot be definitively excluded, requiring further investigation through well-designed preclinical studies or animal experiments to elucidate its potential role. Currently, there are no specific treatments for vortex keratopathy, and we only provide symptomatic treatment to patients. Regular ophthalmic follow-up is also recommended because some known drugs that cause vortex keratopathy can also induce retinal or optic nerve injuries [16].

Indeed, dry eye disease is the most common ocular adverse event observed in patients receiving novel anticancer drugs and may be associated with hormonal imbalance or cytotoxicity induced by immune suppression [17]. Vortex keratopathy shares striking similarities with normal dry eye disease in terms of clinical manifestations, leading to a potential underdiagnosis. Therefore, We strongly recommend that patients receiving novel anticancer agents, particularly CDK4/6 inhibitors, should undergo immediate slit-lamp examination and comprehensive ophthalmic assessment for early detection and management of potential vortex keratopathy, particularly when presenting with ocular irritation symptoms.

**Abbreviations**

| | |
|---|---|
| CDK4/6 | Cyclin-dependent kinases 4/6 |
| AS-OCT | Anterior segment optical coherence tomography |
| HR+/HER2- | Hormone receptor-positive and human epidermal growth factor receptor 2-negative |
| BCVA | Best-corrected visual acuity |
| SERM | Selective estrogen receptor modulator |

**Acknowledgements**
Not applicable.

**Author contributions**
LS and XC contributed to manuscript writing. YW and XS performed the ophthalmological examination and data acquisition. All authors read and approved the final manuscript.

**Funding**
Not applicable.

**Data availability**
All the data generated or analyzed during this study are included in this published article.

## Declarations

**Ethics approval and consent to participate**
No ethical approval was needed.

**Consent for publication**
Written informed consent was obtained for publication from the patient in our case report.

**Competing interests**
The authors declare no competing interests.

Received: 13 September 2024 / Accepted: 7 April 2025
Published online: 14 April 2025

**References**

1. Reddy S, Barkhane Z, Elmadi J, Satish Kumar L, Pugalenthi LS, Ahmad M. Cyclin-Dependent kinase 4 and 6 inhibitors: A quantum leap in the treatment of advanced breast cancers. Cureus. 2022;14(4):e23901. https://doi.org/10.7759/cureus.23901.
2. Spring LM, Zangardi ML, Moy B, Bardia A. Clinical management of potential toxicities and drug interactions related to Cyclin-Dependent kinase 4/6 inhibitors in breast cancer: practical considerations and recommendations. Oncologist. 2017;22(9):1039–48. https://doi.org/10.1634/theoncologist.2017-0142.
3. Raizman MB, Hamrah P, Holland EJ, Kim T, Mah FS, Rapuano CJ, et al. Drug-Induced corneal epithelial changes. Surv Ophthalmol. 2017;62(3):286–301. https://doi.org/10.1016/j.survophthal.2016.11.008.
4. Wu Y, Zhang W, Yao X, Song W, Zhao Y, Yuan Y, et al. Investigation of ocular involvement in patients with Fabry disease. Ann Med. 2023;55(1):2226909. https://doi.org/10.1080/07853890.2023.2226909.
5. Shayman JA, Abe A. Drug induced phospholipidosis: an acquired lysosomal storage disorder. Biochim Biophys Acta. 2013;1831(3):602–11. https://doi.org/10.1016/j.bbalip.2012.08.013.
6. Alshehri M, Joury A. Ocular adverse effects of Amiodarone: A systematic review of case reports. Optometry Vis Science: Official Publication Am Acad Optometry. 2020;97(7):536–42. https://doi.org/10.1097/opx.0000000000001534.
7. Zhang J, Liu R, Gao S, Chen W, Han X, Ma Y et al. Bpi-16350, a novel promising Cdk4/6 inhibitor for Hr+/Her2- metastatic breast cancer (Mbc): results from a phase I study. (2023) 41(16_suppl):e13051–e.https://doi.org/10.1200/JCO.2023.41.16_suppl.e13051
8. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective Estrogen receptor modulators: tissue specificity and clinical utility. Clin Interv Aging. 2014;9:1437–52. https://doi.org/10.2147/cia.S66690.
9. Saeed D, Hussain A. Ribociclib-Associated vortex keratopathy. Can J Ophthalmol J Canadien D'ophtalmologie. 2020;55(4):e140–2. https://doi.org/10.1016/j.jcjo.2019.11.003.
10. Türkel A, Özdoğan S, Yekedüz E, Şeyran E, Karaçin C, Ateş Ö. Vortex keratopathy associated with ribociclib. J Oncol Pharm Practice: Official Publication Int Soc Oncol Pharm Practitioners. 2023;29(1):230–2. https://doi.org/10.1177/10781552221101799.
11. Bilen NB, Tarım B, Hamurcu M, Ulusoy DM. Bilateral epithelial keratopathy and punctate keratitis due to ribociclib. J Oncol Pharm Practice: Official Publication Int Soc Oncol Pharm Practitioners. 2024;10781552241301406. https://doi.org/10.1177/10781552241301406.
12. Falke K, Büttner A, Schittkowski M, Stachs O, Kraak R, Zhivov A, et al. The microstructure of cornea verticillata in Fabry disease and Amiodarone-Induced keratopathy: A confocal Laser-Scanning microscopy study. Graefe's Archive Clin Experimental Ophthalmol = Albrecht Von Graefes Archiv fur Klinische Und Experimentelle Ophthalmologie. 2009;247(4):523–34. https://doi.org/10.1007/s00417-008-0962-9.

13. Wasielica-Poslednik J, Pfeiffer N, Reinke J, Pitz S. Confocal Laser-Scanning microscopy allows differentiation between Fabry disease and Amiodarone-Induced keratopathy. Graefes Arch Clin Exp Ophthalmol. 2011;249(11):1689–96. https://doi.org/10.1007/s00417-011-1726-5.
14. Llanos S, Megias D, Blanco-Aparicio C, Hernández-Encinas E, Rovira M, Pietrocola F, et al. Lysosomal trapping of Palbociclib and its functional implications. Oncogene. 2019;38(20):3886–902. https://doi.org/10.1038/s41388-019-0695-8.
15. Swamynathan S, Campbell G, Tiwari A, Swamynathan SK. Secreted Ly-6/Upar-Related Protein-1 (Slurp1) Is a Pro-Differentiation Factor That Stalls G1-S Transition During Corneal Epithelial Cell Cycle Progression. *The ocular surface* (2022) 24:1–11.https://doi.org/10.1016/j.jtos.2021.12.006
16. Sahyoun JY, Sabeti S, Robert MC. Drug-Induced corneal deposits: an up-to-Date review. BMJ Open Ophthalmol. 2022;7(1):e000943. https://doi.org/10.1136/bmjophth-2021-000943.
17. Vitiello L, Lixi F, Coco G, Giannaccare G. Ocular surface side effects of novel anticancer drugs. Cancers. 2024;16(2). https://doi.org/10.3390/cancers16020344.

## Publisher's note