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CASE REPORT

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Progressive conjunctival invasion of cornea in a child with Warburg-Cinotti Syndrome: a case report

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Abstract

Background Warburg-Cinotti syndrome is a rare syndrome caused by de novo or inherited variants in discoding domain receptor tyrosine kinase 2 (*DDR2*). Only six cases have been reported worldwide and our knowledge of this disease remained sparse especially from an ophthalmological perspective, since previous literature mostly focused on systemic malformations or genetics.

Case presentation A seven-year-old boy developed a gelatinous vascularized conjunctiva-like mass secondary to trauma. The mass enlarged and gradually invaded the cornea. With each surgical intervention, the mass recurred and grew even larger rapidly. The patient ended up with the mass covering the entire cornea along with symblepharon formation. Whole exome sequencing revealed a hemizygous variant in the *DDR2* gene, which is consistent with Warburg-Cinotti syndrome.

Conclusions Considering Warburg-Cinotti syndrome, we should be vigilant of patients exhibiting progressive conjunctival invasion of the cornea, even those without systemic manifestations or a positive family history.

Keywords Warburg-Cinotti syndrome, DDR2, Pseudo pterygium, Corneal neovascularization, Corneal pannus, Keloid formation

Background

Warburg-Cinotti syndrome is a rare condition characterized by corneal vascularization, keloid formation, chronic skin ulcers, wasting of subcutaneous tissue, flexion contractures of the fingers, and acro-osteolysis. Warburg *et al.* first described a 42-year-old white male with deafness, acro-osteolysis, wasting of subcutaneous tissue, and corneal vascularization secondary to ocular surface surgery in 2006 [1]. Later, Cinotti *et al.* reported a case with similar symptoms but mistook it as a variant of Polyfibromatosis [2]. In 2018, Xu and co-workers identified four more patients with similar features and performed exome sequencing for all six patients [3]. They found that all patients share the variants in discoidin domain receptor tyrosine kinase 2 (*DDR2*): c.1829T>C (p.Leu610Pro) or c.2219 A>G(p.Tyr740Cys). Thus, they proposed to name this syndrome Warburg-Cinotti syndrome. Over the years, our knowledge of this disease has remained sparse, as only six cases have been reported worldwide. Herein, we present a new case from an ophthalmological perspective, whereas previous literature has mostly focused on systemic malformations or genetics.

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Case presentation

A seven-year-old boy presented with a symblepharon and a vascularized conjunctiva-like mass covering the entire cornea in his left eye (Fig. 1).

He was initially treated at other centers and was referred to our clinic after undergoing two unsuccessful surgeries. The boy was born healthy and had an unremarkable family history. A review of systemic abnormalities and medical history was negative. His parents told us that it started three years ago when the boy hurt his left eye while playing on the sofa. A local ophthalmologist found a minor corneal limbus injury and prescribed topical antibiotic eye drops and deproteinized calf blood extract eye gel. Two months later, the patient returned with a gelatinous, vascularized mass superior to the limbus. It was initially considered a pseudopterygium; however, the mass continuously enlarged and covered nearly one-third of the cornea a year later. At this stage, the mass was excised, and lamellar keratoplasty was performed simultaneously. However, the mass recurred only three weeks after the surgery; an inferior symblepharon was also detected. A year later, the mass grew to a larger scale than before and invaded the entire cornea. A second surgery was performed, during which only removal of the mass was performed but ended in failure too. Histological examination of the excised mass revealed chronic inflammation, accompanied by fibrous tissue hyperplasia and degeneration. The entire course of the disease is summarized in Fig. 2.

On our advice, the patient underwent whole exome sequencing and found a variant in the *DDR2* gene (Table 1).

According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant was classified as a likely pathogenic variant. The variant was consistent with the previous report of Warburg-Cinotti syndrome [1–3]. Eleven family relatives of the patient, including his parents, sister, grandparents, maternal grandparents and siblings of his parents underwent Sanger sequencing. The *DDR2* variant was not identified in these family members. Considering that the mass might continuously recur, no additional surgical intervention was adopted.

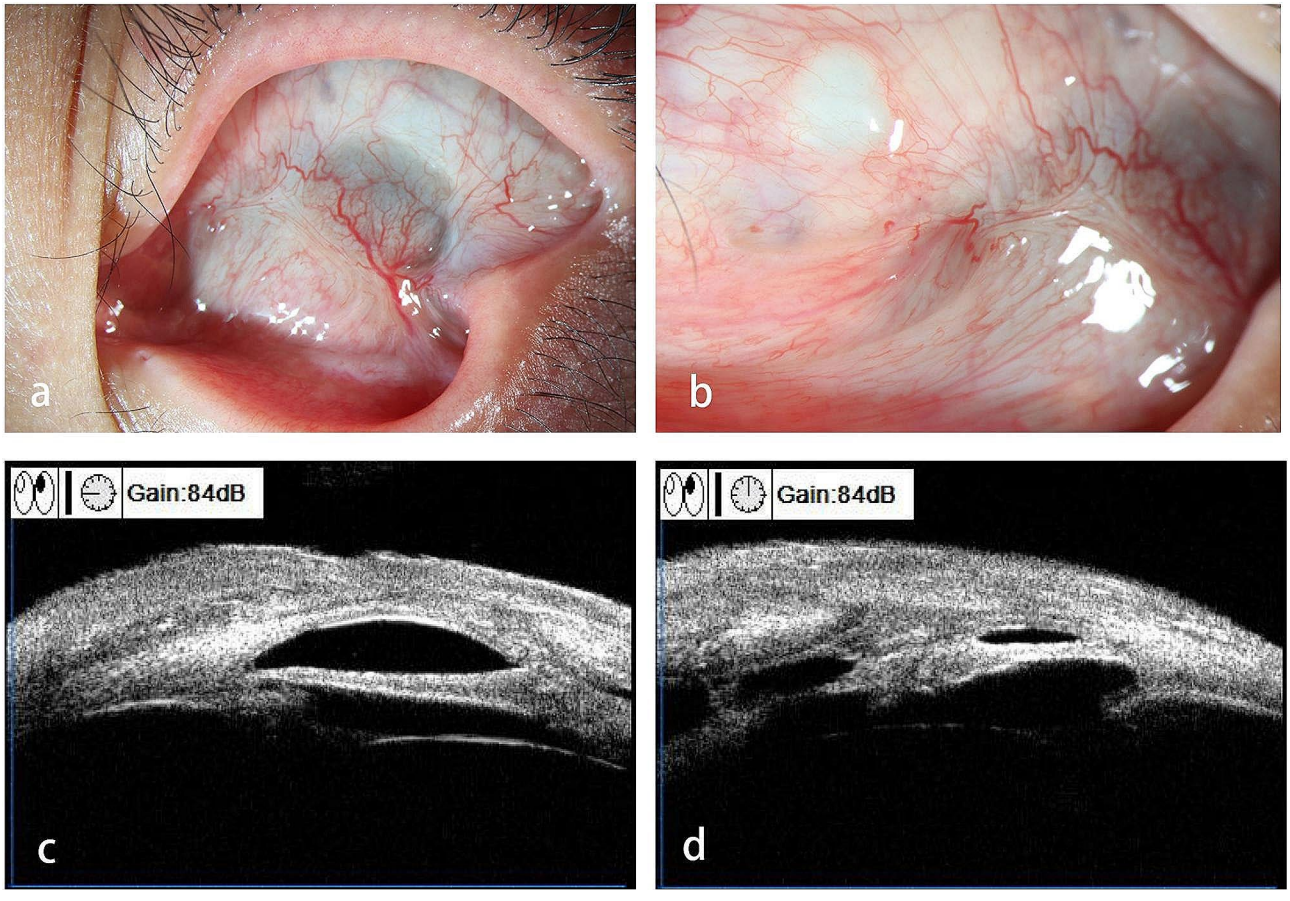

Fig. 1 Clinical manifestations when the patient first presented at our hospital in September 2023. **a**, **b** The vascularized conjunctiva-like mass covered the entire cornea, along with symblepharon formation. **c**, **d** Ultrasound biomicroscope showing that the mass was firmly attached to the corneal surface with blurred boundaries. Corneal opacification and iris synechiae were also observed

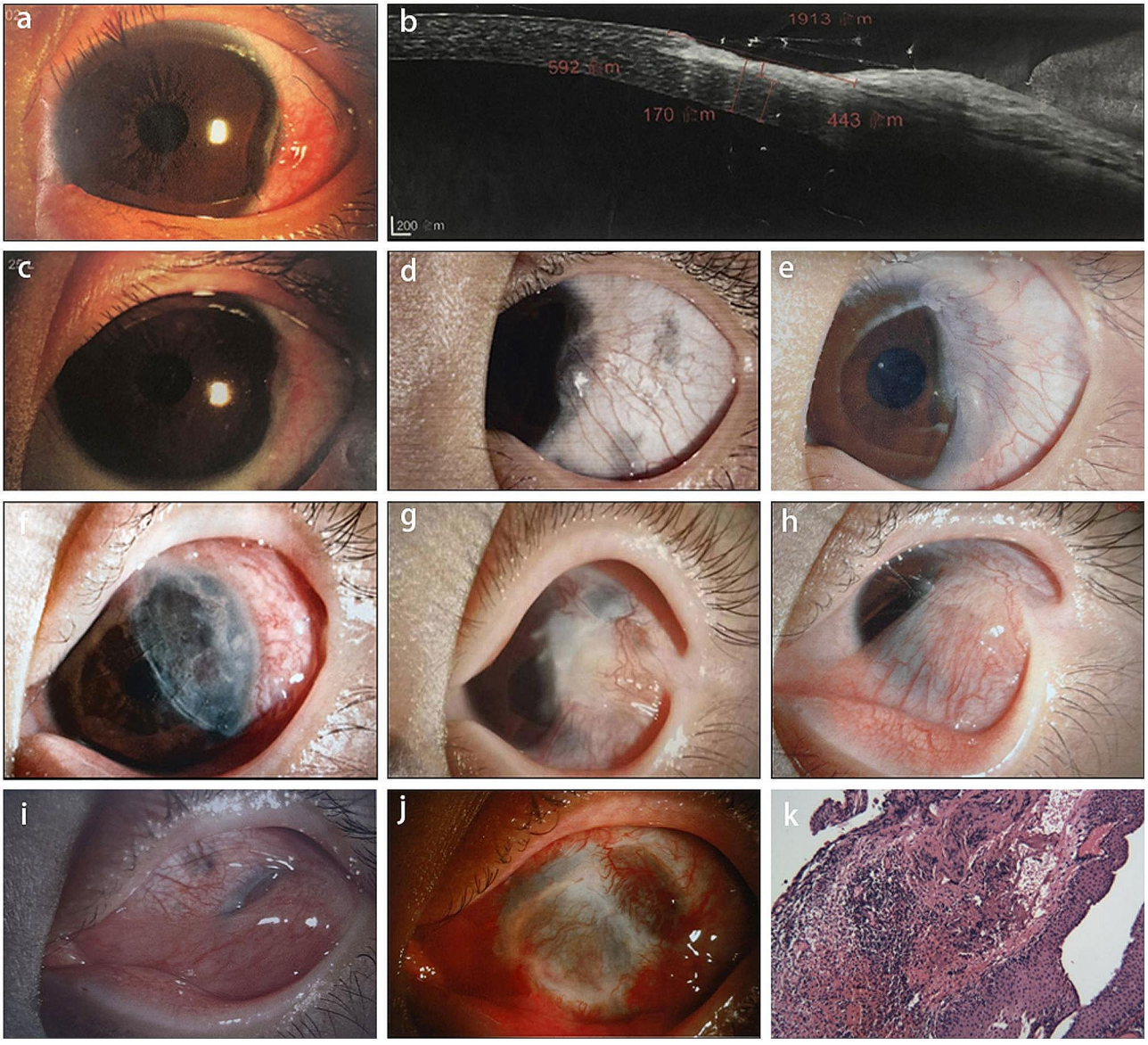

Fig. 2 **a** The boy hurt his left eye and a minor corneal limbus injury was detected *(2020.6)*. **b** Anterior segment optical coherence tomography showed limbal defect ended in the superficial corneal stroma *(2020.6)*. **c**, **d**,**e** The gelatinous, vascularized mass superior to the limbus which kept growing larger. *(2020.8, 2020.11, 2021.4)*. **f** The mass was excised, accompanied by a lamellar keratoplasty *(2021.8)*. **g** The mass recurred and extended onto the opacified corneal graft; symblepharon formed inferiorly *(2022.5)*. **h** The mass gradually covered two third of the cornea, invading the unharmed cornea on nasal side *(2022.9)*. **i** The mass covered the whole cornea *(2023.3)*. **j** A second surgery to excise the mass was performed. Corneal opacity and vascularization became visible after the mass was removed *(2023.6)*. **k** Histological examination found chronic inflammation accompanied by fibrous tissue hyperplasia and degeneration *(2023.6)*. The time of capture was indicated in italics

Table 1 Variant in discoidin domain receptor tyrosine kinase 2 (*DDR2*)

Gene	Transcript ID	Exon	Sequence Change			
DDR2	NM_006182.4	16	chr1:162746096	g.144,934 A > G	c.2219 A > G	p.Tyr740Cys

Discussion and conclusions

Although being one of the main manifestations of Warburg-Cinotti syndrome, ocular abnormalities have not been thoroughly investigated in previous reports in which the term 'corneal vascularization' was usually used. Corneal neovascularization refers to the invasion of blood vessels from the conjunctiva to the normally avascular cornea due to limbal stem cell deficiency (LSCD) or inflammation, primarily caused by infection, burns, and autoimmune disease [4]. We found the case of Warburg-Cinotti syndrome different, for the former is thought to begin with the transition of epithelial type from corneal

to conjunctival, while the latter presents as fibrovascular neoplasm extending onto the cornea, which subsequently disrupts the limbal stem cell barrier.

The child was originally diagnosed with pseudopterygium, given the history of trauma. Pseudopterygium is a non-progressive conjunctival adhesion to the peripheral cornea secondary to trauma or corneal inflammation. Unlike a true pterygium, a probe may be passed at the limbus under a pseudopterygium because there is an interspace between the mass and the underlying corneal epithelium [5, 6]. This diagnosis was later ruled out because the mass showed rapid growth, extending over the unharmed cornea. Ocular surface squamous neoplasia has also been considered a possible diagnosis, but histopathological examination showed no neoplastic cells.

There are other syndromes with similar manifestation described in the literature. Abarca *et al.* reported an entity named Ocular pterygium-digital keloid dysplasia characterized by ocular pterygia and keloids on the digits [7]. They described the ocular abnormality as ingrowth of conjunctival tissue that gradually covered the entire cornea, which is similar to our case. However, the genetic mutation of the two reported families were different with our case, one in *PDGFRB* and the other in *PELI2*; *DDR2* remained normal [8, 9]. Activating variants in *PDGFRB* is associated with a spectrum disorders, notably Penttinen syndrome. The ocular malformations of Penttinen syndrome includes proptosis, abnormal orbital telorism, and pterygium (some described as corneal pannus) presents in adolescence [10–12]. The age of onset clearly distinguishes this pterygium-like abnormality form the conventional pterygium. However, the progression and treatment of the pterygium was not reported in more detail.

According to reported Warburg-Cinotti syndrome cases, surgical removal could worsen the condition and lead to symblepharon formation, which is probably related to *DDR2* 's role in wound healing. DDR2 is a collagen-activated receptor tyrosine kinase that participates in various cellular processes, especially extracellular matrix remodeling [13, 14]. By activating epithelial-mesenchymal transition signaling and expression of matrix metalloproteinases, DDR2 could regulate fibroblasts proliferation and migration [15, 16]. Research has demonstrated that DDR2 is associated with fibrosis and pathological scarring in the skin, liver, and heart [17–20]. It's reported that *DDR2* mRNAs and protein are expressed in the cornea [21]. However, no studies have elucidated the role of DDR2 in ocular diseases. We speculate that *DDR2* mutation may lead to abnormal fibrosis after injury, manifested as cutaneous keloid formation and excessive conjunctival growth in Warburg-Cinotti syndrome. Moreover, it seems that the older the patient, the more severe their clinical manifestations, which may be attributed to the accumulated microtrauma induced by daily dust, wind, or drying. Admittedly, a prospective study on *DDR2* and relevant pathways in corneal and conjunctival diseases is required.

In conclusion, patients with progressive conjunctival invasion of the cornea should cause our alert of systemic syndrome. Surgical excision can induce inflammation and fibrinous exudation, leading to conjunctival hyperplasia and symblepharon formation. Genetic testing is recommended when there is doubt regarding the diagnosis.

Abbreviations

DDR2 Discoding domain receptor tyrosine kinase 2
LSCD limbal stem cell deficiency

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Not applicable.

Author contributions

Jing Hong examined the patient and revised the manuscript. Hanzhi Ben collected the clinical data and wrote the draft of the manuscript. Xiaozhen Liu and Pei Zhang provided professional opinions from genetics and pathology, respectively. All authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Peking University Thid Hospital, and the methods were performed in accordance with the approved guidelines. We have also obtained the informed consent of the patient involved.

Consent for publication

The parent of the study participant gave written consent for clinical details and images to be published in this journal. A copy of the informed consent is available for review by the editor of this journal.

Competing interests

The authors declare no competing interests.

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