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Case Report

Trachoma is Coming Back to Ukraine: Two Case Reports

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Abstract

Introduction: Trachoma has been absent in Europe and Ukraine for a long time. We encountered two clinical cases of trachoma in a teenager and an adult woman in Ukraine, which are of great concern. This report aims to analyze the clinical presentation, diagnostic procedures, and outcomes of trachoma treatment.

Case Presentation: This report describes two trachoma patients: a 12.8-year-old girl and a 46-year-old woman, both experiencing lacrimation, photophobia, and redness in both eyes. In case 1, the onset of the disease occurred in July 2020 after the patient engaged in swimming in a local lake. The patient was diagnosed with a herpes virus infection in both eyes at the regional medical center. Despite antibacterial and antiviral therapy, the patient did not exhibit any signs of improvement. The patient in case 2 had recently traveled to Africa and Southwest Asia. In both patients, laboratory examination of the conjunctival scrapings revealed intracellular Prowazek bodies. Specific antibacterial therapy administered to the patients included instillations of 1.5% azithromycin (a first-line drug with a broad spectrum of action, without preservatives), tetracycline ointment, parabular injections of amikacin, and oral azithromycin.

Conclusion: The occurrence of trachoma should alert the ophthalmologists in Ukraine. The diagnostic «gold standard» for trachoma is the detection of intracellular Prowazek bodies in conjunctival scrapings. For the treatment of trachoma, a novel topical 1.5% azithromycin ocular solution has been developed; in combination with systemic therapy, it was proven to be highly effective in our clinical cases.

Keywords: *Trachoma; Diagnostic; Treatment; Azithromycin; Case Report*

Introduction

Trachoma, an anthroponotic disease, has been recognized since antiquity. *Chlamydia trachomatis* (*C. trachomatis*), the causative agent of trachoma, was identified in 1907 by the Czech scientist S. Prowazek. *C. trachomatis* is classified as an intermediary species, situated between viruses and rickettsiae. The pathogen can be preserved at a temperature of +20°C for up to 7 days, in non-chlorinated water for up to 5 days, and in lakes for up to 60 hours. The organism exhibits inadequate immunogenic activity, as evidenced by the recurrent nature

of reinfections and the unsuccessful outcomes of vaccine attempts. There is no specific immunity. A sick individual is the primary source of infection; the patient's conjunctiva serves as the reservoir. Transmission may occur either directly or indirectly (through hands, clothes, or secretions). The incubation period is 5 - 8 days [11] in developed nations; its prevalence is highest in regions inhabited by the poorest segments of society, where access to healthcare and fundamental sanitation is inadequate. Trachoma is a severe problem in impoverished nations across the Indian subcontinent, Africa, some regions of the Middle East, Southeast Asia, and South America, where its prevalence is currently the highest [1,12].

For a long time, preventive measures and the general improvement in living standards have rendered trachoma-associated morbidity non-existent in Europe and Ukraine. Hence, the detection of two clinical cases of trachoma by us, one in a teenager and the other in an adult woman in Ukraine, is cause for concern.

Purpose of the Study

To analyze the clinical picture, diagnostic measures, and outcomes of trachoma treatment.

Case Presentation

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

This report details two patients: a 12.8-year-old girl and a 46-year-old woman, who both presented with complaints of lacrimation, photophobia, and redness in both eyes.

Medical history: The patient in case 1, developed the disease in July 2020 after swimming in the local lake. The patient was diagnosed with a herpes virus infection affecting both eyes at the regional medical center. The patient was treated with antibiotics and antiviral medication but did not show improvement. In case 2, the patient had recently traveled to Africa and Southwest Asia.

Clinical picture

Case 1: The patient experienced blepharospasm, photophobia, lagophthalmos, and increased thickness of eyelid margins in both eyes. Upon slit-lamp examination, the upper eyelid tarsal conjunctiva exhibited cicatricial changes with yellow-pink elevations typical of trachoma. Hyperemia of the bulbar conjunctiva was also identified (Figure 1). Additionally, circumferential neovascularization at the limbus with corneal vascularization extending from the corneal lower half up to its center was also observed on slit-lamp examination. There was corneal edema, along with total superficial corneal staining (Figure 2a). All the signs were more pronounced in the left eye (Figure 2b). The anterior chamber was of medium depth; the aqueous humor and deep optical media were transparent. The corneal alterations hindered visibility of the fundus during slit-lamp examination with a panretinal lens; no pathology was detected. The uncorrected visual acuity (VA) in the right and left eyes was 0.85 and 0.5 logMAR units, respectively. The intraocular pressure was within the normal range in both eyes.

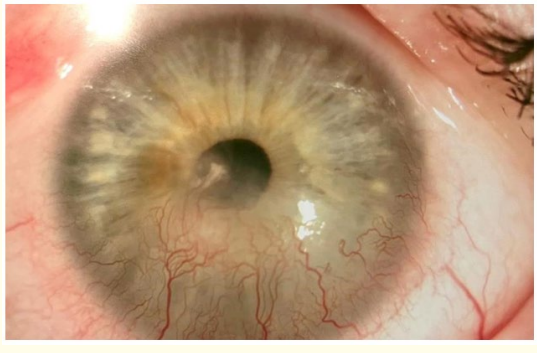


Figure 1: *Case 1: The edge of the eyelids is unevenly thickened in both eyes. The conjunctiva of the upper eyelid is hyperemic, with cicatricial changes and yellow-pink trachomatous conjunctival follicles.*

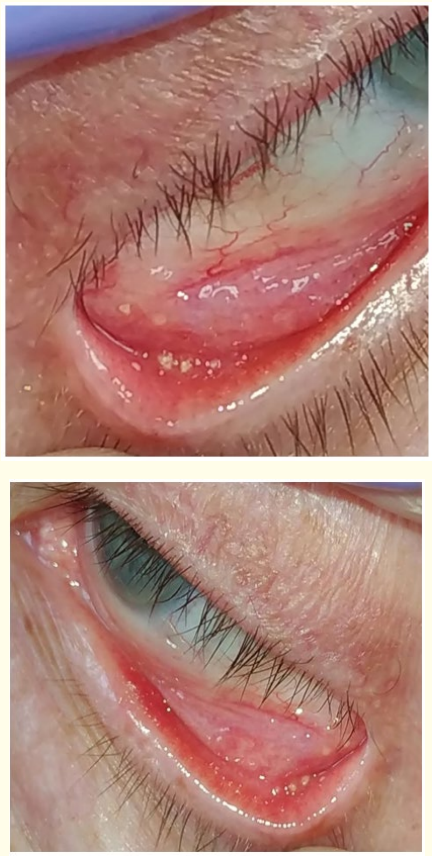
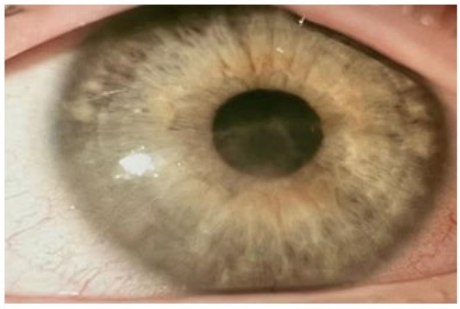


Figure 2: *a. OD B. OS. Case 1: OD, bulbar conjunctival injection is observed and is more prominent on the OS. Figure 2b: Circumferential neovascularization of the limbus can be observed with pannus formation in the lower half to the middle portion of the cornea. The cornea is swollen, cloudy in the lower half, and stained in the upper half. Deeper structures did not exhibit focal changes (it is more noticeable in the left eye, figure 2b, with corneal opacification in the upper part).*

Case 2: Slit-lamp examinations revealed hyperemia, edema, and infiltration of the lower eyelid conjunctiva, as well as the presence of follicles (Figure 3). The slit-lamp examination revealed normal anterior and posterior parts of both eyes, as well as transparent media. The uncorrected VA in both eyes was 1.0 logMAR.



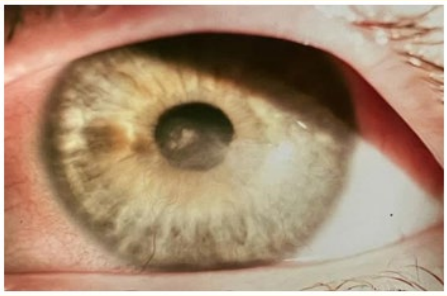


Figure 3: *a. OD, 3. b. OS. Case 2: In OU, the lower eyelid conjunctiva is hyperemic, with yellow-pink trachomatous conjunctival follicles.*

Trachoma of both eyes was suspected in both patients.

Laboratory tests: To elucidate the etiology of the inflammatory process of the conjunctiva, due to the suspicion of trachoma, laboratory examinations were undertaken in both patients, including the bacterial culture test to determine the microflora and the conjunctival scraping test to identify Prowazek bodies. In case 1, enzyme-linked immunosorbent assay (ELISA) was performed to detect IgG and IgM antibodies against ToRCH (Toxoplasmosis, Rubella, CMV and Herpes I/II).

The specimen for culture (bacteriological examination of a smear from the conjunctiva) was collected from both patients using the following method. The discharge from each patient's eye was taken in the morning before "eyewash". The lower eyelid of the patient was pulled down to expose the conjunctiva. A sterile flocked swab was gently moved toward the inner corner of the palpebral fissure to collect any discharge. The swab was immediately placed into a sterile test tube following aseptic protocols. The swab was placed into a sterile test tube following aseptic protocols. Then, swabbed samples were seeded on Petri dishes with 5% blood agar and with a "sterility control medium" (a meat-peptone broth with the addition of 0.2% glucose, i.e. a growth medium) and placed in a incubator at a constant temperature of 37°C. On the second day, we observed growth in the growth medium, analyzed the growth patterns, and performed Gram staining. Depending on the morphology of the microorganisms, plating on selective nutrient media was performed to isolate pure cultures, followed by identification and sensitivity testing. In the presence of growth on 5% blood agar, the tinctorial properties of the grown colonies were studied morphologically by bacterioscopy with Gram staining. The bacterial growth was assessed both qualitatively and quantitatively. Individual colonies were isolated on selective media for identification and sensitivity testing. *S. epidermidis* growth was detected in both eyes of our patients.

To perform the conjunctival scraping test, a blunted eye scalpel was used to scrape the surface of the tarsal conjunctiva of both eyelids after anesthetic instillation. Immediately after sampling, the collected material was placed on the surface of a clean, degreased glass slide to form a thin smear. The smear was air-dried at ambient temperature for 20 - 30 minutes.

Detecting *Chlamydia* in cells entails identifying cytoplasmic inclusions generated by the pathogen through staining with the Romanowsky-Giemsa method, a conventional method used for diagnosing *Chlamydia*. According to this method, a 1:10 dilution of azure-eosin dye with distilled water was applied to the specimen and left for 30 minutes. The stained specimen was rinsed with running water, differentiated for 5 - 10 seconds (under visual control) with acidified ethanol (3 - 5 drops of ice-cold acetic acid per 15 - 20 ml of alcohol), rinsed again with water, air-dried, and examined by immersion microscopy.

Prowazek bodies were identified in the conjunctival cells obtained from the scraping, confirming the presence of trachoma in both patients (Figure 4).

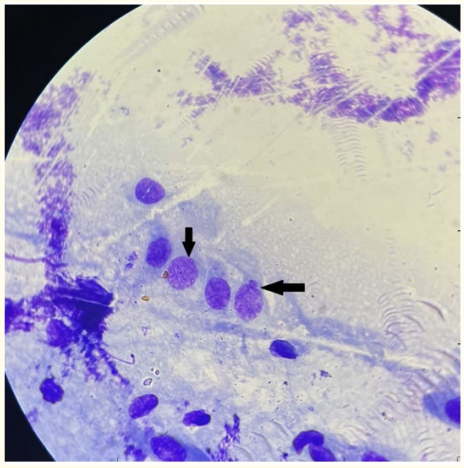


Figure 4: *Cytologic examination of the patient's conjunctival scraping. Small early inclusions contain large reticular bodies and display a blue-violet color. Romanowski-Giemsa stain. Magnification x100 (immersion). Chlamydia, conjunctival scraping, Giemsa stain. The cytoplasmic inclusion body (asterisk), composed of chlamydial organisms, can be seen capping the nucleus (N). A distinct space separates the inclusion body from the nuclear chromatin.*

ELISA in case 1 revealed a minor increase in titers of IgG to a virus of the herpes group (IgG antibodies to the herpes virus to HSV 1/2 and IgG antibodies to CMV were 4.06 CP and 1.22 CP, respectively).

Diagnosis: The patient in case 1 was diagnosed with stage III trachoma, blepharitis, keratoconjunctivitis, and trachomatous pannus of the cornea in both eyes.

The patient in case 2 was diagnosed with stage I trachoma and blepharoconjunctivitis in both eyes.

Treatment: Specific antibacterial therapy included instillations of 1.5% azithromycin (a first-line drug with a broad spectrum of action, without preservatives), tetracycline ointment, parabulbar injections of amikacin, and oral systemic azithromycin. The patients also received a massage of the eyelids with the removal of trachomatous grains by extrusion. Resorptive therapy, in the form of parabulbar injections of heparin and emoxipin, was administered after the resolution of inflammation.

Outcomes: The cartilage plates of the upper eyelids were shortened. The conjunctiva of the upper eyelids showed alterations, but no follicles were present. No evidence of active inflammation was observed in the eyes. A small amount of residual neovascularization of the limbus was observed in the lower part. The left eye's central cornea exhibited opacification, ghost vessels, and areas of thinning. At the two-month follow-up, there were no indications of inflammation on the eyelids, which had improved significantly. There was deformation and shortening of the cartilaginous plates of the upper eyelids, resulting in a minor lagophthalmos of 1 - 2 mm. The conjunctiva of the upper eyelids exhibited cicatricial changes without any follicles. The eyes were quiet and showed no signs of persistent inflammation. A slight residual neovascularization of the limbus was observed in the lower part. The central opacification of the cornea in the left eye was significantly resolved. The fundus exhibited no signs of any pathology (Figure 5a and 5b). The uncorrected VA was 0.85 logMAR in the right eye and 0.7 logMAR in the left eye.

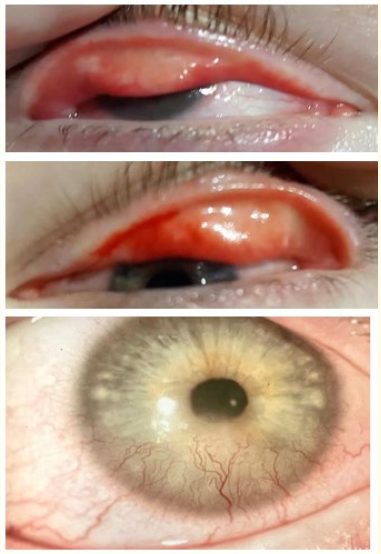


Figure 5: *a. OD, b. OS. Case 1: Outcomes of treatment. Congestion in the eyes was resolved. Insignificant residual limbal neovascularization is seen in the lower part. Centrally opacified corneas have ghost vessels and partial thinning that was significantly diminished through treatment.*

The follow-up laboratory examination revealed no intracellular Prowazek bodies, indicating the elimination of the causative agent and suppression of the active infectious process.

Discussion

Trachoma emerged as a major medical problem for Europeans in 1798 when Napoleon Bonaparte's army invaded Egypt. Soldiers returning from Egypt to Europe became a source for the spread of an unknown infectious disease. Trachoma rapidly spread from Europe to various parts of the world, including the Russian Empire. At the time, the disease was referred to as «military» or «Egyptian» ophthalmia. Over several decades, trachoma has affected a significant portion of the population. As quoted by Filatov V.P., at the beginning of the 20th century, Prof. Golovin S.S. found that trachoma was the primary (21%) cause of blindness, having examined 65,724 blind individuals in tsarist Russia [8]. Prof. Bellyarmynov L.G., Ochapovsky S.V., Danilov D.N., *et al*. established "flying eye squads" to combat trachoma-related blindness [6,9]. Ophthalmologists from the flying eye squads traveled to epidemic areas, provided direct assistance to the sick, trained medical personnel, and contributed to the establishment of outpatient clinics in the field. During their twenty years of professional practice, 527 "flying units" ophthalmologists treated more than 1 million patients and performed more than 300,000 follicle expressions using Belyarminov's forceps [2]. Academician Filatov V.P. made a significant contribution to the diagnosis and treatment of trachoma in Ukraine from 1936 to 1956; he introduced clinical measures to eliminate the consequences of trachoma, including scarring changes, stricture and obliteration of lacrimal points and tubules, and symblepharon, through tissue therapy and transposition of the Stenon's duct [7,13]. Consequently, trachoma was eliminated in Ukraine. Chirkovsky V.V. and Mac Callan A.F. identified four phases of trachoma progression in 1935-1936. Trachoma stage I is characterized by hyperemia, the appearance of follicles in the tarsal conjunctiva, vascularization of the upper part of the limbus, and corneal subepithelial infiltrates. Trachoma stage II is accompanied by papillary hyperplasia of follicles in the forniceal and tarsal conjunctiva, corneal infiltrates and pannus formation, and the onset of trachomatous conjunctival scarring. Trachoma stage III is complicated by scarring of the conjunctiva of the eyelids with persistent inflammation. In trachoma Stage IV, follicles and infiltrates are entirely replaced by scar tissue [10].

In 1987, the World Health Organization proposed a new classification to distinguish follicular trachomatous inflammation, intense trachomatous inflammation, trachomatous scarring, trachomatous trichiasis, and corneal clouding.

A definitive diagnosis of trachoma can be made if the cytological examination of conjunctival scrapings reveals the presence of specific cytoplasmic inclusions, known as Prowazek bodies, in the conjunctival epithelial cells. Contemporary laboratory diagnostic methods for trachoma include ELISA (detection of specific antibodies to *Chlamydia* in the blood serum), RIF (detection of *Chlamydia* antigens in epithelial cells), PCR examination of scrapings, and the culture method (bacteriological examination of a smear from the conjunctiva) [1]. Since the pathogen has low immunogenicity, serological tests do not detect antibodies to it in many patients. Hence, as previously stated, the identification of Prowazek inclusion bodies within the conjunctival epithelial cells is of decisive importance.

Antibiotic-based attempts to control trachoma failed to produce satisfactory outcomes until the 1990s. Mass administration of oral sulfonamides in North America in the 1930s and 1940s was associated with an unacceptably high incidence of severe adverse reactions, including the Stevens-Johnson syndrome. In the 1950s and 1960s, the mass distribution of tetracycline eye ointment (subsequently referred to as tetracycline) in several countries was also ultimately unsuccessful. Compliance was poor because tetracycline is unpleasant to apply and requires many weeks of use to be effective [14].

In our clinical cases, the application of topical azithromycin 1.5% eye drops combined with systemic therapy proved highly effective. Azyter is the world's first azalide eye drop. It was developed in response to a WHO directive to eliminate trachoma and has undergone large-scale clinical trials in Asia, Africa, and Europe. Over 2,160,000 doses were administered in Cameroon under the WHO program for the treatment of trachoma in its first year of production alone.

The safety profile of azithromycin 1.5% eye drops has been substantiated by the research conducted by Bremond-Gignac D [3] as well as by Cochereau I [4] in the trachoma study involving 670 children aged 1 - 10 years with active trachoma. In contrast to oral azithromycin, Cochereau I. evaluated the safety and efficacy of azithromycin 1.5% for the treatment of active trachoma over the course of two to three days. The results indicated that topical 1.5% azithromycin was not inferior to oral azithromycin.

Denis F [5] and Bremond-Gignac D [3] have reported that following azithromycin eye drop application, sustained antibiotic concentrations in tears and conjunctival cells were usually much higher than the plasma concentrations reached after oral administration of azithromycin. This may explain why even microorganisms that are resistant to azithromycin plasma concentrations are susceptible to azithromycin eye drop treatment. Because of its significant intracellular concentration and long half-life, azithromycin is more effective for topical treatment of *C. trachomatis*, which can only replicate intracellularly. It has been demonstrated that a three-day treatment regimen can sustainably enhance concentration in the cornea and conjunctiva for over two weeks [3-5].

Conclusion

First, ophthalmologists should be alarmed by the recent emergence of trachoma in Ukraine, which suggests that the causative agent of trachoma can rapidly spread from epidemic to non-epidemic regions as a result of population migration and deteriorating hygienic practices and regulations. Second, the diagnosis of trachoma is based on the clinical picture assessment, cytological examination of conjunctival scrapings, and intracellular detection of Prowazek bodies, which is the "gold standard" of trachoma diagnosis. Finally, topical azithromycin has been specially developed for trachoma treatment, and its efficacy has been demonstrated by virtue of its novel intracellular action mechanism. Azyter, the topical form of 1.5% azithromycin, has been extensively implemented in clinical settings due to its broad spectrum of action, especially on the causative agent of trachoma, *C. trachomatis*.

Study Approval Statement

The present case report was conducted in accordance with the principles laid out in the Declaration of Helsinki. This study protocol was reviewed and approved by the Bioethics Committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" at its meeting (protocol № 1 dated December 08, 2022).

Consent to Publish Statement

Written informed consent was obtained from the parent of the patient in case 1 and the patient in case 2 for the publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nadia Bobrova: conception, design, data interpretation, data collection and analysis, drafting, and revision. Tetiana Sorochinska: conception, design, data collection and interpretation, and paper revision. Tetiana Romanova: conception, design, data collection and interpretation. Alina Shylyk: conception, design, data collection, and interpretation. Olga Dovgan: design, data collection. Oksana Linchevska: microscopic examination analysis, data collection and interpretation. All authors: final approval of the manuscript to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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