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Diagnosis of tuberculous uveitis by macrogenome of intraocular fluid: A case report and review of literature

Zhang YK *et al*. Diagnosis of tuberculous uveitis by macrogenome

Abstract

BACKGROUND

Tuberculous uveitis caused by tuberculosis infection factors is common, but tuberculous uveitis caused by *Mycobacterium tuberculosis* can be found in the intraocular fluid is rare. This paper discusses the application of intraocular fluid detection in the diagnosis of tuberculous uveitis through case report and review of relevant literature.

CASE SUMMARY

A 24-year-old woman with 31 wk of pregnancy visited Hebei Chest Hospital due to the intermittent chest pain, fever, decreased vision for 3 mo, hydrothorax test suggests "tuberculous pleurisy", giving the chest tube and extract yellow effusion 2 times, total about 800 mL. The patient chose to continue the pregnancy without treatment, and was hospitalized for high fever again. After 2 mo of anti-tuberculosis treatment, a healthy boy was delivered by cesarean section. Tuberculous uveitis was diagnosed with tuberculosis Xpert, tested for intraocular infection by second-generation gene. After systematic treatment, the body condition gradually improved, and the corrected visual acuity of the left eye gradually increased from 0.08 to 1.0.

CONCLUSION

The etiology of uveitis is complex, and it is necessary to combine the general situation of the whole body and apply molecular biology methods, to explore the pathogenesis and guide precise treatment, so as to improve the vigilant awareness of clinicians and standardized treatment of the disease.

Key Words: Tuberculous uveitis; Metagenomic next-generation sequencing; Xpert; Case report

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Core Tip: Tuberculous uveitis caused by tuberculosis infection factors is common, but tuberculous uveitis caused by *Mycobacterium tuberculosis* can be found in the intraocular fluid is rare. This article describes a 24-year-old pregnant patient who was diagnosed with tuberculosis Xpert and ophthalmologic multimodal imaging after 2 mo of anti-tuberculosis treatment and cesarean delivery of a healthy baby boy. Detection of intraocular infections by second-generation genetics. After systemic treatment, the vision was recovered.

INTRODUCTION

Uveitis is a common ophthalmic disease, which is one of the important causes of visual impairment in humans, accounting for 10% of blindness in the world[1]. Tuberculous ocular lesions account for 1.40%-5.74% of systemic tuberculosis[2], among which tuberculous uveitis caused by tuberculosis infection is common. However, tuberculous uveitis in which *Mycobacterium tuberculosis* can be found in intraocular fluid is clinically rare. A case was recently discovered in our hospital, and a summary report and literature review are made to analyze the results of tuberculosis-related testing, in order to improve clinicians' vigilant cognition and standardized treatment of the disease.

CASE PRESENTATION

Chief complaints

A 24-year-old woman with 31 wk of pregnancy visited Hebei Chest Hospital due to the intermittent chest pain, fever, decreased vision for 3 mo, temperature up to 39.4 °C, with chills, dizziness, headache, fatigue and other symptoms, occasional cough, dry cough, with shortness of breath, aggravated after activity, The local fever clinic considered "pneumonia", and was given "cephalosporin" for 10 d, but the symptoms

were not significantly relieved. Further examination of the thoracic cavity revealed "left pleural effusion", a pleural tube was placed and the yellow effusion was extracted twice, with a total volume of about 800 mL. The pleural effusion test showed "tuberculosis pleurisy", and the temperature was better than before, fluctuating at about 37.5 °C. Because the patient chose to continue the pregnancy without treatment, the patient was admitted to our hospital again with high fever.

History of present illness

The patient developed pain at the left costal margin without obvious inducement 3 mo ago, which was prick-like pain, aggravated by deep inspiratory coughing and vomiting. There was no posterior sternal pressing sensation and radiating pain in the left shoulder. Electrocardiogram examination in the local hospital showed no abnormality.

History of past illness

No history of disease.

Personal and family history

No family history of disease.

Physical examination

The body temperature was 38.9 °C, the superficial lymph nodes were small, the left lower lung had percussion dullness, the breath sounds were decreased on auscultation, and no wet or dry rales were heard. Ophthalmic physical examination: Corrected visual acuity was 1.0 in right eye, 0.08 in left eye, no hyperemia in bulbar conjunctiva of right eye, transparent cornea, a little Keratic precipitate (KP) in posterior cornea, good depth of anterior chamber, normal pupil size, sensitive light reflex, clear lens, clear edge of optic disc of fundus, yellow and white exudation and linear bleeding were seen below the center of macula. Left eye bulbar conjunctival hyperemia, corneal transparency, KP (+++), aqueous humor opacification, drug-induced pupil dilation, clear lens, vitreous

opacification, fundus invisibility. Intraocular pressure: 16 mmHg in right eye, 17 mmHg in left eye.

Laboratory examinations

Routine blood test: White blood cell: 8.93 × 10^9/L, neutrophil 85.7%; C-reactive protein: 51.7 ng/mL; T-spot: 277; *Mycobacterium tuberculosis* 31.52; Procalcitonin: 0.370 ng/mL; Erythrocyte sedimentation rate: 87 MM/H; metagenomic pathogen detection (mNGS) was sent for Xpert examination. The result of *Mycobacterium tuberculosis* detected by Xpert was positive; PPT test: 10 mm × 10 mm positive.

Imaging examinations

Chest computed tomography showed hematogenous disseminated pulmonary tuberculosis.

FINAL DIAGNOSIS

A healthy baby boy (37 wk of intrauterine gestation) was delivered by cesarean section in the Department of Obstetrics and Gynecology of our hospital. Examination: Placenta Xpert: *Mycobacterium tuberculosis* was detected, containing very low bacteria. At this time, the patient had been treated with anti-tuberculosis therapy for 2 mo, and his general condition was improved, and the ocular aqueous humor turbidity was aggravated. Considering that the drug could not pass through the blood-eye barrier, the second-generation gene test of the left ocular aqueous humor was performed to understand the intraocular infection, and four sequences of "*Mycobacterium tuberculosis*" were found in the aqueous humor test.

The destruction of the blood-eye barrier is often accompanied by the destruction of the blood-brain barrier. Further brain magnetic resonance imaging (MRI) examination revealed the intracranial conditions, and the results suggested that multiple abnormal signal shadows in the brain parenchyma were enhanced punctate and nodular, and miliary tuberculosis was considered.

Systemic diagnosis: Acute hematogenous disseminated pulmonary tuberculosis; tuberculous pleurisy; tuberculous encephalitis; left tuberculous meningitis. ophthalmologic diagnosis: Tuberculous uveitis in both eyes; retinal vasculitis in both eyes. Determine the cause of diagnosis through a variety of molecular biological detection methods.

TREATMENT

With the cooperation of the Department of Tuberculosis, Obstetrics and Ophthalmology, the patients were given isoniazid 0.3 g orally 1/ d, rifampicin 0.45 g orally 1/d, pyrazinamide capsule 0.5 g orally 3/d, ethambutol 0.75 g orally 1/d, the ophthalmology department was given local anti-inflammatory mydriasis, dexamethasone sodium phosphate 5 mg by peribulbar injection, twice a week. Tobramycin dexamethasone eye drops on the left eye 6/d, pranoprofen eye drops on the left eye 4/d, and compound tropicamide eye drops on the left eye three times before bed.

OUTCOME AND FOLLOW-UP

After systematic treatment, the general condition gradually improved, and the corrected vision of the left eye gradually increased from 0.08 to 1.0. According to uveitis standard working group (Standardization of Uveitis Nomenclature, SUN) standard assessment, the grade of anterior chamber cells and vitreous opacity was evaluated. The patient's anterior chamber aqueous was from three grades: the anterior chamber had 21 to 50 cells/field of vision, and the iris and lens were difficult to recognize gradually to grade 1: The aqueous humor had no anterior chamber flash or weak anterior chamber flash, and no inflammatory cells. Vitreous opacity gradually changed from 4 + to 0.5 +. The fundus photography is shown in Figures 1A-F, and the changes of ocular B-ultrasound are shown in Figures 2A-D. The changes of anterior segment photography are shown in Figures 3A-B.

DISCUSSION

About one-third of the world's population is infected with *Mycobacterium tuberculosis*[3], but only 10% of those infected have clinical manifestations. Tuberculosis is most common in the lungs, but it can actually affect other organs, of which 16%-27% are extrapulmonary infections. Extrapulmonary tuberculosis can involve multiple systems and organs such as skin, eye, cardiovascular, digestive system, bone and joint, urinary system and central nervous system. Intraocular tuberculosis is a unique form of extrapulmonary tuberculosis. All eye tissues except the lens can be infected with *Mycobacterium tuberculosis*[4]. The uvea is rich in blood vessels, containing 96% of the blood flow of the eyeball, and the flow rate in the eye is slow. Previous studies have shown that ocular tuberculosis is relatively rare, mostly secondary to tuberculosis foci in other parts of the body[5]. With the deepening of diagnosis doctors' understanding of the disease, the improvement of imaging and laboratory testing methods, the detection rate of ocular tuberculosis disease is increasing. Tuberculous uveitis accounts for 6.9%-10.5% of unexplained uveitis, and 1.4%-6.8% of active tuberculosis patients are complicated with ocular tuberculosis[6-9]. Eye TB pathophysiology mechanisms include: (1) Active *Mycobacterium tuberculosis* infection - blood line spread and *Mycobacterium tuberculosis* directly into local eye tissue, such as choroid granuloma; and (2) The immune response, has nothing to do with copying an infected, is extrapulmonary organs (eye) of *Mycobacterium tuberculosis* late-onset allergic reactions, such as stomach morphic choroiditis.

Ocular tuberculosis is monocular come on commonly, also have binocular case. The left eye has a higher incidence than the right eye. It is because of anatomical position, left common carotid artery is given out directly from aortic arch, tuberculous bacterium goes up with blood flow *via* aortic arch directly into left ocular artery, and right side needs to pass innominate artery.

In this case, tuberculin skin test [postpartum depression (PPD)] was strongly positive, tuberculosis infection T-cell positive T-spot: 277 increased, and three positive findings were found. Brain MRI showed multiple intracranial nodules and diffuse miliary

nodules, and chest computed tomography (CT) showed miliary nodules in both lungs, which supported the diagnosis of blood group disseminated pulmonary tuberculosis. Diagnostic criteria for tuberculous uveitis: (1) History of systemic tuberculosis or previous history of tuberculosis; (2) Detection of tuberculous bacilli in body fluids or tissues; (3) Ocular lesions consistent with tuberculosis manifestations; (4) Strong PPD positive tuberculin skin test; (5) Effective anti-tuberculosis therapy; and (6) Differential diagnosis: Choroidal inflammation caused by syphilis, toxoplasmosis and other systemic diseases was excluded by laboratory examination. At present, in terms of diagnosis, aqueous humor or vitreous fluid sampling from intraocular fluid is performed under topical anesthesia, which is easier to obtain than other tissue fluid such as lumbar puncture for cerebrospinal fluid and thoracic puncture for pleural effusion. The incidence of intraocular tuberculosis in patients with uveitis has been reported in the literature, including 6.9% in Japan, 4% in China, 10.5% in Saudi Arabia and 20% in India[7,8,10]. The detection method in this report uses molecular biology technology, and the proportion of intraocular tuberculosis diagnosed by polymerase chain reaction (PCR) detection of intraocular fluid is up to 20%. This indicates that the proportion of intraocular tuberculosis in uveitis infection increases with the improvement of examination methods.

Previous studies have found that the positive rate of tuberculin skin test and chest X-ray in patients with confirmed ocular tuberculosis is only 40% and 57%, respectively[11]. The positive detection rate of chest CT was 68.6%, which was higher. Therefore, it is necessary to consider the general condition of suspected cases. In the general population, the infection rate of latent tuberculosis is very high. Under the existing conditions, the correct interpretation of tuberculate-related test results can improve the correct diagnosis rate of systemic tuberculosis and reduce the chance of missing the cause of tuberculosis in “idiopathic uveitis”[12]. PPD rhzomorph skin test and tuberculosis infected T cells are the two most basic method of confirmed previous tuberculosis[13], tuberculin test is a kind of cellular immune response, low immunity will be false positives, tuberculosis infected T cells is a means of immunology examination,

is not affected by immunity, positive show once injected BCG vaccine or previously had been infected with tuberculosis, Or in the state of tuberculosis infection, its simple positive significance is not big, should be based on the size of the value, combined with the patient's own and other imaging examination indicators comprehensive analysis.

Intraocular fluid Xpert and metagenomic sequencing as emerging detection methods can also help in the diagnosis of tuberculous uveitis. Which inspection is a kind of detection techniques of molecular biology, polymerase reaction technology, able to quickly detect *Mycobacterium tuberculosis* and rifampicin resistance of new test, it can trace the tissue fluid in patients with tuberculosis DNA extraction, amplification ropB genes, more than 95% rifampicin resistant strains ropB gene mutations, most rifampicin resistant strains of isoniazid resistance at the same time. Therefore, this test can not only detect rifampicin resistant strains, but also indicate whether there are multiple drug-resistant strains to a certain extent. In this case, tuberculosis bacillus DNA was detected in sputum and placenta by this method. mNGS in the intraocular fluid of this case, Xpert is not only used to check sputum and placental tissue, but also used to extract anterior chamber aqueous from intraocular fluid. Because there are few samples, only mNGS was sent for examination. which is a next-generation sequencing technology based on metagenomics directly extracts the DNA or RNA of all microorganisms from clinical samples, and studies the genetic composition and community functions of all microorganisms contained in the samples using genomic research strategies. The positive rate of *Mycobacterium tuberculosis* in patients with systemic active tuberculosis complicated with uveitis is relatively high. *Mycobacterium tuberculosis* is an intracellular bacterium with thick cell wall, which is difficult to be detected by conventional detection. In this case, the cell-FreedNA extraction and library construction process was used to reduce the loss and contamination in the process of wall breaking genome extraction and enzyme digestion interruption, and also reduce the contamination of human sequence, effectively improving the detection rate of difficult-to-detect pathogens[14]. In this case, four sequences of *Mycobacterium tuberculosis* were detected by aqueous humor detection. Zhou *et al*[15] reported that the sensitivity of mNGS for the

diagnosis of active tuberculosis was 44%. They proposed that intracellular bacteria release less extracellular nucleic acids, resulting in a high false-negative rate of mNGS results. Biswas *et al*[16] reported that the sensitivity of intraocular fluid PCR detection was 33.33% in tuberculous retinal vasculitis and 66.67% in granulomatous uveitis. In this case, sputum and placental tissue were detected by Xpert, and intraocular fluid was detected by metagenomic sequencing. At present, the sensitivity of Xpert and metagenomic sequencing for intraocular fluid samples remains to be studied. The study showed that the detection sensitivity of metagenomic sequencing for all active tuberculosis cases was 44%, which was similar to that of Xpert (42%). The sensitivity can be increased to 60%[15].

For the purpose of the intraocular fluid detection of this patient, on the one hand, it was clear whether there were pathogens in the eye, and on the other hand, the turbid inflammatory cells were directly sucked out by the extraction of aqueous humor, and the new aqueous humor was generated by itself to achieve the purpose of replacement. The positive rate of mNGS tuberculosis is high in patients with ocular manifestations of vitreous haze and endophthalmitis, and extraocular manifestations of hematogenous disseminated tuberculosis. The positive rate of mNGS tuberculosis was relatively low in patients with ischemic retinal vasculitis, choroidal tuberculoma, and prostrate choroidal choritis. Speculated reasons: (1) There is no active replication of *Mycobacterium tuberculosis* in the eye, and the disease manifestation is caused by delayed hypersensitivity reaction of *Mycobacterium tuberculosis*; and (2) The pathogen is located in the chororetinal level and not released into the vitreous body[17]. The aqueous humor or vitreous fluid with planktonic cells should be selected to improve the positive rate of intraocular fluid detection.

This article could remind tuberculous physicians that when systemic problems such as blood type disseminated tuberculous lesions and tuberculous meningitis were found, should pay attention to the diagnosis of possible tuberculous eye diseases, so as to avoid missing diagnosis and delayed treatment, resulting in blindness, and comprehensively consider the infection of other parts of the body in the diagnosis and

treatment of tuberculous eye disease, and use molecular biological detection methods to improve detection rate, and give patients early diagnosis and standardized treatment.

CONCLUSION

This article introduces the application of intraocular fluid detection in the diagnosis of tuberculous uveitis, the application of molecular biology methods for diagnosis, and the recovery of visual acuity through treatment, which illustrates the importance of intraocular fluid detection for the diagnosis of uveitis.

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