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Case report

Negative Mantoux test in a patient with definite pulmonary and ocular tuberculosis

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ABSTRACT

The case is reported of a patient with pulmonary and ocular tuberculosis presenting with blurred vision in both eyes. A 27-year-old well-nourished male nursing-home resident with a previous history of traumatic intracerebral hemorrhage was brought to the ophthalmological clinic due to progressively blurred vision. His best-corrected visual acuity was 20/400 in the right eye with only light perception in the left eye. Fundus examinations revealed retinal segmental periphlebitis and hemorrhagic retinitis in the right eye and dense vitreous hemorrhage in the left eye. The Mantoux test was negative; however, the results of an interferon gamma release assay were positive. Ocular tuberculosis was suspected. Although he had never had any respiratory symptoms, his chest radiograph and computed tomography scan showed a multiple centrilobular glandular and ground-glass appearance with air-space consolidations and atelectasis in both lower lobes. Pulmonary tuberculosis was confirmed by a positive acid-fast stain of a bronchial alveolar lavage sample. A GEN-PROBE amplified *Mycobacterium tuberculosis* direct test of the vitreous fluids was also positive. Ocular tuberculosis was confirmed. After treatment for tuberculosis and vitrectomies, his final best-corrected visual acuity improved to 20/30 in the right eye and 20/200 in the left eye. Ocular tuberculosis is rarely reported as the primary presentation of systemic tuberculosis in young patients. A negative Mantoux test may lead to misdiagnosis and delayed treatment. Doctors should become more familiar with the manifestations of systemic tuberculosis and use advanced diagnostic tools in cases of clinical suspicion.

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1. Introduction

Tuberculosis (TB) usually infects the lungs and is a slowly progressive, chronic, necrotizing or nonnecrotizing, and granulomatous or nongranulomatous infection caused by *Mycobacterium tuberculosis* (MTB). Alveolar macrophages acquire phagocytic and bactericidal functions and may limit the pulmonary infection. However, some organisms may escape through the lymphatic or blood systems or hematogenously, resulting in seeding of the organisms in other organs, including the cardiovascular system, the gastrointestinal system, the musculoskeletal system, the genitourinary tract, the central nervous system, the skin, and the eyes.[1,2] In regions with a naturally high immunity to MTB, reactivation of the latent infection may occur. In developing countries where a high ratio of TB infection and low natural resistance exist, the risk of inhaling bacilli on several occasions is high and may cause reinfection. Ocular TB can be acquired by direct infection or by an indirect immune-mediated hypersensitivity response to mycobacterial antigens; it is a great mimicker of various uveitis entities.[3,4] The Mantoux test (a tuberculin purified protein derivative test) is a screening tool for TB and is one of the major tuberculin skin tests used around the world.

We report the case of a patient with definite pulmonary plus ocular tuberculosis who had a negative Mantoux test result. We also review the currently available laboratory methods for the confirmation of tuberculosis.

Conflicts of interest: The authors do not have any financial conflicts of interest in the subject matter in the manuscript. The authors do not have any commercial or proprietary interest in the product or company.

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2. Case report

The patient presented here was a 27-year-old well-nourished male nursing-home resident with a previous history of traumatic intracerebral hemorrhage. He was mentally and physically disabled. He was brought to the ophthalmological clinic of the local hospital as a result of progressively blurred vision in both eyes for 2 weeks. Based on our impression of branch retinal vein occlusion in the right eye and vitreous hemorrhage in the left eye, an intravitreal bevacizumab injection and laser photocoagualtion were performed in the right eye; however, a vitreous hemorrhage was seen to have developed at the 6-month follow up. He was therefore referred to a tertiary care center for further evaluation and management.

On examination, his best-corrected visual acuity was 20/400 in the right eye with only light perception in the left eye. The intraocular pressure was within the normal range. Slit-lamp examination showed broad-based posterior synechiae in the left eye, which obscured the details of the fundus. Reviewing the presenting fundus photographs revealed retinal segmental phlebitis with perivenous clustering and hemorrhagic retinitis (Fig. 1). Fluorescein angiography revealed occlusive retinal phlebitis with late leakage (Fig. 2). A B-scan examination showed vitreous hemorrhage in his left eye.

The results of his blood investigations, including a complete blood count, random blood sugar, and routine serum biochemistry, were within normal limits. The results for the lupus anticoagulant, anticardiolipin antibody, rapid plasma regain, and HIV Ag/Ab combo tests were negative. A culture of the anterior chamber fluid showed no growth. The Mantoux test was negative, but an interferon gamma release assay (IGRA) was positive. Ocular TB was therefore suspected.

Although the patient had no respiratory problems, his chest radiograph revealed a multiple centrilobular glandular and ground-glass appearance in both lungs (Fig. 3). A chest computed tomography scan showed air-space consolidations and atelectasis in both lower lobes (Fig. 4). Definite pulmonary TB was confirmed due to the positive acid-fast stain from bronchial alveolar lavage by bronchoscope. Drugs for treating TB, including ethambutol, pyrazinamide, rifamycin, and isoniazid, were prescribed.

The vitreous hemorrhage and tractional retinal detachment worsened in both eyes. Small gauge vitrectomies, membrane peeling, and endolaser photocoagulation were performed. Definite ocular TB was confirmed by the positive results of the GEN-PROBE amplified MTB complex (MTBC) direct test of the vitreous humor approximately 1 year after the onset of symptoms. After treatment for TB and surgery, his final best-corrected visual acuity improved to 20/30 in the right eye and 20/200 in the left eye.

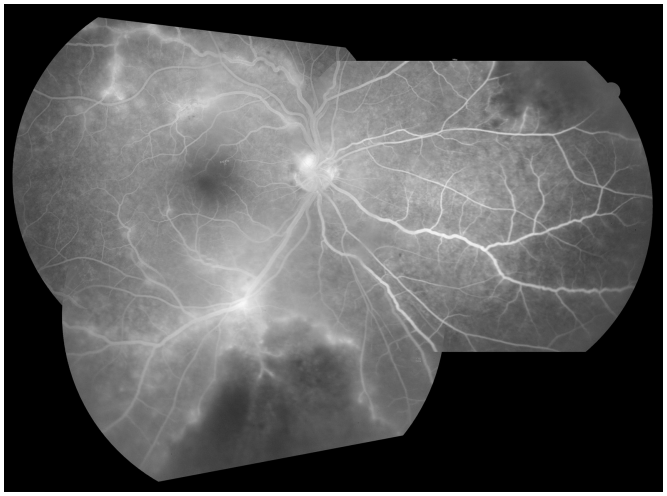

Fig. 2. Fluorescein angiography results showing occlusive retinal phlebitis with late leakage.

3. Discussion

TB is a slowly progressive chronic infection caused by MTB. It mainly affects the lungs, but can also affect other organs and systems, including ocular tissue.[1,2] Ocular TB can be acquired by direct infection or via an indirect immune-mediated hypersensitivity response to MTB antigens. It is a great mimicker of various kinds of uveitis.[3,4] MTB can thrive in the retinal pigment epithelium (RPE), which is similar to the alveolar macrophage environment in which the bacteria normally develop and grow.[5] RPE may serve as a sanctuary for MTB. Reactivation of dormant organisms in the RPE or

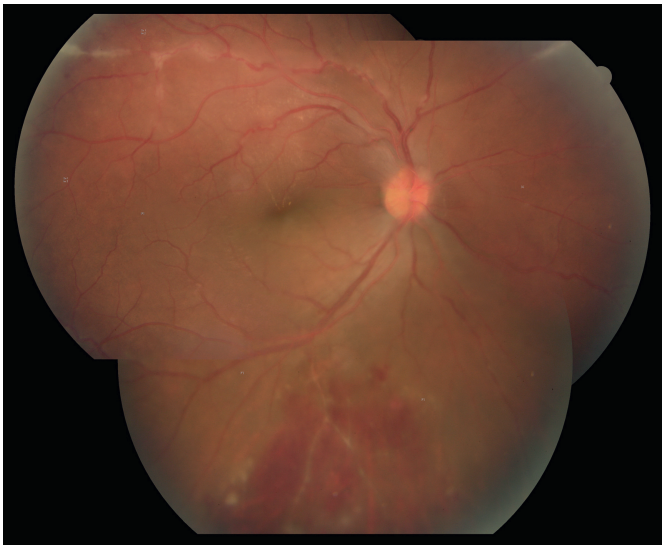

Fig. 1. Fundus photographs showing retinal segmental phlebitis with perivenous clustering and hemorrhagic retinitis.

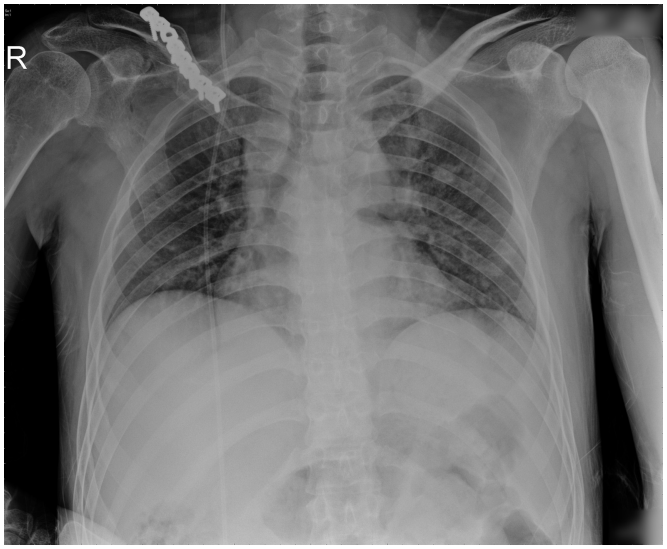

Fig. 3. Chest radiograph of our patient showing a multiple centrilobular glandular and ground-glass appearance in both lungs.

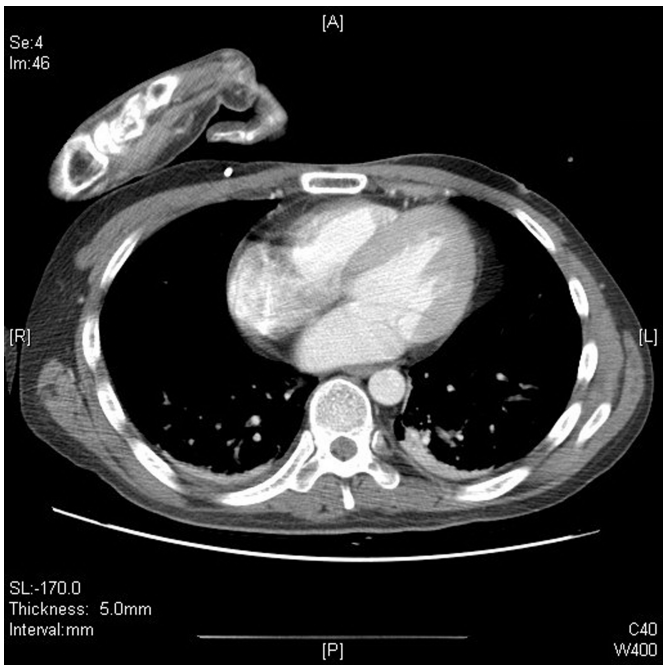

Fig. 4. Chest computed tomography scan of our patient showing air-space consolidations and atelectasis in both lower lobes.

reinfection from a pulmonary origin with the dissemination of microorganisms may cause ocular TB.[6]

The clinical manifestations of ocular TB include necrotizing and nonnecrotizing diffuse or nodular scleritis, episcleritis, peripheral ulcerative keratitis, interstitial keratitis, phlyctenulosis, dacryoadenitis, granulomatous or nongranulomatous acute anterior uveitis, broad-based posterior synechiae, iris nodules, ciliary body tuberculoma, granulomatous or nongranulomatous intermediate uveitis, posterior uveitis, panuveitis, neuroretinitis, and optic neuropathy.[3,4,6] The characteristics of posterior uveitis include choroidal tubercle, subretinal abscess, serpiginous-like posterior pole involvement, and periphlebitis of the retinal vessels with the accumulation of a whitish material around the retinal veins.[7–9] The affected retinal vessels may have pigment along them or RPE depigmentation under previous periphlebitis. Hemorrhagic retinitis and focal choroiditis are usually located adjacent to the affected retinal veins.[10]

Fluorescein angiography is an essential component of the evaluation and management of presumed tuberculous retinal vasculitis. Tuberculous retinal vasculitis is typically an obliterative periphlebitis, which may cause nonperfusion of a substantial portion of the retina. It may lead to proliferative vascular retinopathy. In acute vasculitis, fluorescein angiography may reveal diffuse leakage of dye and staining of the blood vessels. Cystoid macular edema and optic disc leakage have sometimes been noted. Our patient had the characteristic of retinal segmental phlebitis and diffuse late phase vascular leakage on fluorescein angiography.

The diagnosis of ocular TB was difficult due to the inability to demonstrate acid-fast bacilli on a smear sample or histopathology in the ocular specimens. The paucity of available ocular tissue was another issue. Molecular diagnostic techniques such as polymerase chain reaction (PCR) results from the aqueous or vitreous humor have low sensitivities due to the low bacterial load in the ocular fluids and the thick cell wall of MTB.[11,12] For this reason, most previous diagnoses of ocular TB have been presumptive, based on the ocular signs consistent with TB, evidence of systemic TB, and a positive Mantoux test.

The Mantoux test is one of the few investigations dating from the 19th century that is still widely used as an important test for diagnosing TB.[13] A positive Mantoux test result indicates mycobacterial infection with or without manifest clinical disease. However, the Bacillus Calmette–Guérin (BCG) vaccination may induce false-positive results. In Taiwan, the BCG vaccination has been given routinely at birth since 1965 and is repeated in elementary school if the Mantoux test result is negative. According to the data provided by a recent national survey in Taiwan, the BCG vaccination rate is 97% among first-grade students.

False-negative reactions, which are estimated to occur in approximately 5–10% of patients, can be observed early in the infection before hypersensitivity develops, in anergic individuals, in those with severe illness (including active TB), in newborn infants and in infants <3 months of age, and as a result of improper techniques in handling the purified protein derivative solution, administering the intradermal injection, and interpreting the results.[14] The Mantoux test may also show false-negative results in immunosuppressed patients. Nevertheless, the Mantoux test still has an important role in high-risk groups, such as immigrants from regions where TB is endemic.

In the general population in the USA, the sensitivity of the Mantoux test is 0.59–1.0, with a specificity of 0.95–1.0, and a positive predictive value of 0.44–1.0.[15] In a recent study enrolling immunocompetent Asian adults aged from 20 to 29 years old, the Mantoux test was shown to be sufficiently accurate in differentiating active TB from other diseases, with a high sensitivity of up to 94% and a specificity up to 88%, although there were still some patients who had an unexplained negative Mantoux test while presenting with active TB symptoms. From our experience of the patient reported here, a belief in the relatively high sensitivity of the Mantoux test might hinder an accurate diagnosis. Therefore, an adjuvant test such as IGRA is still important in initiating early treatment in highly suspicious clinical situations. This will guarantee the continuous application of such an inexpensive, simple, and widely applied tool, especially in the community and in resource-limited settings.[16]

The change in the Mantoux test result from positive to negative is called “reversion”. This reversion has been reported for decades, but most commonly in the context of isoniazid preventive treatment among healthy mycobacterium contacts. The reported reversion rates vary widely and differences in study design, study populations, and the ability to control for potential confounders, such as the timing of the initial conversion, repeated exposure to mycobacterium, chronic nontuberculous mycobacterium exposure, and receipt of the BCG vaccine, have made it difficult to draw conclusions with respect to the frequency and biological significance of reversion. A recent study showed a Mantoux test reversion of approximately 20% (25 patients from 122 patients with positive Mantoux test results) after isoniazid preventive treatment.[17] An earlier large series of a healthy African population in an area with endemic TB had a reversion rate from 1.39 to 3.72 per 100 patient-years.[18] All these studies involved patients at high risk of TB infection, but without active TB infection. Although some studies included patients in whom the Mantoux test result had reversed after treatment, some studies involved patients in whom the Mantoux test result reversed spontaneously. Thus reversion is possible and may involve multiple factors other than preventive treatment. The patients in these studies with reversion were those who had a milder initial reaction. Based on these results, the possibility of Mantoux test reversion in our patient was very small because it is difficult to explain the disappearance of the immune response during disease progression without any evidence of compromise of the immune system or malnutrition. On the contrary, active TB with an initially negative Mantoux test result has

been reported. Some of these patients became positive for the Mantoux test during disease progression after increasing the dose of tuberculin or repeated testing.[19]

The duration of Mantoux test reversion also varied among different studies, ranging from months to years.[17,18] However, all these studies involved participants at high risk of TB, not patients with active TB infection before treatment. When doctors have a patient with clinically suspected TB infection and a positive Mantoux test result, they do not need to perform the test twice before treatment. Data concerning the duration of Mantoux test reversion in active TB infection before treatment is therefore sparse.

Real-time PCR assays have been used successfully for the detection of the MTB complex in clinical samples.[10–12] An overall sensitivity of 86.3% and 100% specificity in detecting MTB has been reported previously.[11] The low sensitivity is due to the low bacterial load in the ocular fluid and the thick cell wall of the MTB. The sensitivity of the PCR assay could be improved by using different primers and probes, such as primers targeting the MPB64 gene of MTB.[12]

The GEN-PROBE amplified MTB direct test was the first nucleic acid amplification test to obtain US Food and Drug Administration approval in 1996 for the detection of pulmonary TB, followed by the Roche Amplicor MTB Test in 2009.[20] The target RNA is the 16S rRNA of the MTBC. The GEN-PROBE amplified MTBC direct test had higher sensitivity than microscopy (83% vs. 50%), but a similar specificity (95% vs. 96%).[21] Unlike microscopy, the sensitivity of the GEN-PROBE amplified MTBC direct test was not significantly lower in patients with HIV coinfection.[22] However, the performance of this MTBC detection test in a nonpulmonary sample has not been validated with a 5-mL or larger sample. A positive result indicates infection with either both the nontuberculosis mycobacterium and MTB, or MTB alone.

The T-cell IGRA assay (Cellestis Inc., Chadstone, Victoria, Australia) provides a measurement of the interferon gamma produced by T cells in response to stimulation by relatively specific MTB antigens (ESAT-6, CFP-10, TB7.7).[23,24] The advantages of this assay include prompt, same-day results and a greater specificity for the MTB antigen with a decreased response to nontuberculous mycobacterial antigens (e.g., *Mycobacterium avium-intracellulare*). The more mycobacteria that are present, the higher the sensitization, resulting in a higher response in the whole blood test. Extremely high quantiferon levels (mean 7.49 U/mL) were reported in patients with tuberculous uveitis.[25] Active typical ocular inflammation and a positive IGRA result, with or without other systemic signs, are considered as possible TB-associated uveitis. Given that IGRAs enable differentiation between vaccinated and truly infected patients, IGRA is recommended as the first test to be performed in preference to T-SPOT.TB (Oxford Immunotech, Abingdon, Oxfordshire, UK) and the Mantoux test for the diagnosis of tuberculous uveitis.[26]

The guidelines for the diagnosis of ocular TB are as follows: (1) exclusion of other uveitis entities; (2) clinical history and signs consistent with ocular TB; (3) direct evidence from ocular investigations (such as positive acid-fast bacilli smear, MTB culture of ocular specimen, or ocular fluid PCR for MTB) so that a definite diagnosis can be made; (4) systemic investigations (including a positive Mantoux test, IGRA, or a healed or active tubercular lesion on a chest radiograph) are corroborative evidence and a presumed diagnosis can be made; (5) confirmed active extrapulmonary TB with microscopic examination or culture of the affected tissue for MTB; and (6) a therapeutic test with a positive response to four-drug treatment for TB over 4–6 weeks.[4,6,12,24–26]

Our patient was young and well-nourished and should therefore have been in an immunocompetent state at the time of presentation. Although the culture of the anterior chamber fluid showed no growth and the Mantoux test result was negative, his IGRA result was positive. In addition to the bilateral active tubercular lesion in the lungs evidenced by the chest radiograph and computed tomography scan, definite pulmonary TB was also consolidated by a positive acid-fast stain of the bronchial alveolar lavage sample obtained by bronchoscope. In severe cases of ocular TB, vitreous hemorrhage and tractional retinal detachment may develop. Prompt vitreoretinal surgery with coverage by systemic drug treatment is mandatory in these patients. Ocular TB was therefore initially suspected in this patient and was later confirmed by the positive MTBC direct test on the vitreous sample. His best-corrected visual acuity improved from 20/400 to 20/30 in the right eye and his light perception in the left eye improved to 20/1000 after treatment.

It is insufficient to confirm the diagnosis of ocular TB by a positive Mantoux test result and chest radiograph alone. Wroblewski et al[27] reported that only 10 patients out of 17 patients with a positive histopathology had a positive Mantoux test result. In addition, 14 sets of chest radiographic results were submitted and 8/14 (57%) patients had normal chest radiographic results. Both of these findings highlight the unclear reliability of the routine Mantoux test and chest radiographs in ocular TB. The T-cell IGRA may be an alternative choice in helping to diagnose ocular TB. It provides measurement of the interferon gamma produced by T cells in response to stimulation by relatively specific MTB antigens. The advantages of the IGRA over the Mantoux test include prompt, same-day results and a greater specificity for the MTB antigen, given its decreased response to nontuberculous mycobacterial antigens (e.g., *M. avium-intracellulare*).[17] In our patient, the Mantoux test was false-negative, but the IGRA test was positive.

The treatment of ocular tuberculosis includes first-line four-drug treatment for TB and subsequent treatment with steroids. Regular follow up and close monitoring for the development of retinal neovascularization, subsequent vitreous hemorrhage, and tractional retinal detachment are very important. Timely laser treatment and vitrectomy are mandatory. Ocular TB infection is rare in an immunocompetent patient, which may, unfortunately, lead to misdiagnosis and delayed treatment. Ophthalmologists should therefore be familiar with the possible manifestations of this disease.

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