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Extra-pulmonary Tuberculosis with Mediastinal Lymphadenopathy and Ocular Involvement: A Case Report

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Abstract

Extrapulmonary tuberculosis has variable clinical manifestations, and the infection sites can be anywhere in the body. Owing to the difficulty in obtaining a microbiological diagnosis, it is common to make a presumptive diagnosis using laboratory data, imaging studies, and pathological examination as indirect evidence. In addition, the treatment response to the empirical antituberculosis regimen indicates whether tuberculosis is the correct answer. Here, we present a case of extrapulmonary tuberculosis with multiple mediastinal lymphadenopathies and ocular involvement. The diagnosis was made based on the relevant clinical presentations and typical pathological reports. The patient recovered well after empirical antitubercular treatment. A comprehensive study should be attempted and would provide further help to build the diagnosis. (J Intern Med Taiwan 2022; 33: 227-232)

Key Words: Ocular tuberculosis, Extra-pulmonary tuberculosis, Necrotizing granulomatous inflammation, Mediastinal lymphadenopathy

Introduction

Tuberculosis is an airborne infectious disease that is endemic to numerous developing and underdeveloped countries worldwide. Taiwan once had a high disease burden of tuberculosis, but the incidence rate of the disease has steadily decreased in recent decades. Tuberculosis typically presents with pulmonary symptoms and occasionally with extrapulmonary involvement[2]. Among those patients with an extrapulmonary presentation, tuberculous lymphadenitis is the most common, but ocular tuberculosis is rare. One study in India demonstrated ocular involvement in only 1.2% of patients with pulmonary tuberculosis. For patients with uveitis, 0.2–10.5% are diagnosed with ocular tuberculosis, which is higher in endemic areas[3]. Delayed or missed diagnosis is common because physicians are often unfamiliar with extrapulmonary tuberculosis[3]. The average delay from the onset of symptoms to the initiation of antitubercular treatment would be more than 800 days among patients with ocular tuberculosis. In the present report, we present a case of a patient who developed both tuberculous

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lymphadenitis and ocular tuberculosis.

Case presentation

A 45-year-old woman without any underlying disease presented to our outpatient clinic after experiencing headache with blurred vision for 1 week.

The patient had been well until 1 month prior when she started to experience generalized joint pain and bilateral leg edema. The symptoms were mild and intermittent, and the patient did not seek medical help. One week prior, the patient developed progressive headache, photophobia in both eyes, and floaters in the left eye. No nausea, vomiting, double vision, neck stiffness, or pain with eye movement was reported. She also denied any history of recent travel or contact with sick individuals. She first visited our ophthalmology clinic. Fundoscopic examination revealed retinal vasculitis with hemorrhage in the right eye (Figure 1a) and vitreous hemorrhage in the left eye (Figure 1d). A complete blood count revealed the presence of leukocytosis (white blood cell count: 18,220 per μL, reference range: 3,500–11,000 per μL) and microcytic anemia (hemoglobin count: 8.3 g/dL, reference range: 12.0–16.0 per dL; mean corpuscular volume: 66.9 fL, reference range: 80.0–100.0 fL). Her serum albumin level was low (2.5 g/dL, reference range, 3.5–5.0 g/dL), and her renal and liver function results were within the normal range. Because the patient was suspected of having a systemic infectious disease or hematological disorder, she was referred to our infectious disease clinic, where her body temperature of 38.7°C was recorded. The patient was admitted to the hospital on the same day for further observation.

Upon admission, a physical examination revealed that the patient had cachexia. Neurological examination results were normal. No nuchal rigidity and no Brudzinski's or Kernig's signs were recorded. Chest radiography revealed an absence of active lesions. A survey of the infectious etiology revealed negative results for bacterial blood culture, syphilis, and human immunodeficiency virus. Three sets of sputum specimens were collected, and the staining results for acid-fast bacilli

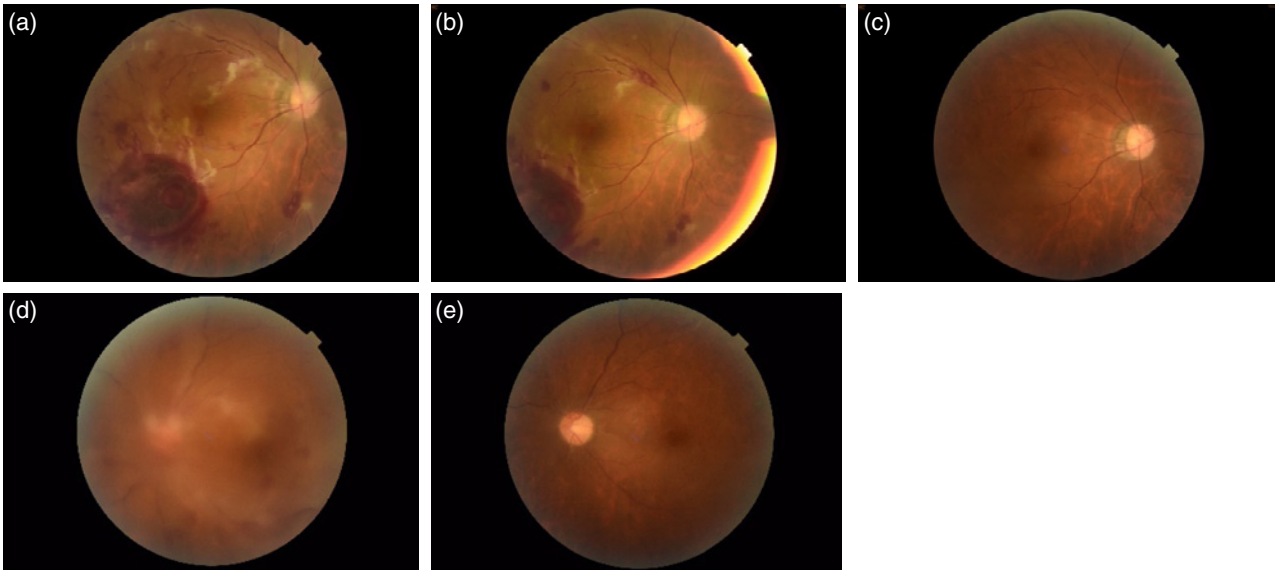

Figure 1. Serial fundoscopic examination of the right eye (1a, 1b, 1c) and left eye (1d, 1e). 1a: Initial presentation: retinal vasculitis with periphlebitis, cotton wax exudates, retinal and vitreous hemorrhage; 1b: One month later under standard anti-tuberculosis regimen and steroid management: partial resolution of vasculitis and hemorrhage; 1c: Nine months later under standard anti-tuberculosis regimen: retinal vasculitis has mostly resolved leaving attenuated vessels; (1d) vitreous hemorrhage; (1e) Nine months later under standard anti-tuberculosis regimen: vitreous hemorrhage has mostly resolved.

were negative. The survey results for microcytic anemia indicated anemia due to chronic inflammation. Both fibrinogen and D-dimer levels were elevated and chronic disseminated intravascular coagulopathy was observed. A cerebrospinal fluid study showed only mild lymphomonocytic pleocytosis without elevation of the total protein concentration, and the bacterial, fungal, and mycobacterial cultures were all negative. We initiated empirical antibiotic therapy with ceftriaxone; however, the spiking fever persisted. On the 3rd day of hospitalization, computed tomography (CT) from the chest to the pelvis was performed after administration of intravenous contrast material, which revealed multiple mediastinal confluent lymphadenopathies (Figure 2). Lymphoma and metastatic malignancy were also considered. CT-guided biopsy of the left anterior mediastinal lymph node was performed, and a pathological examination of the biopsy specimen revealed caseous necrosis and focal epithelioid histiocytes. The staining results for acid-fast bacilli were negative, and no malignancy was detected (Figure 3). Given her clinical presentation, persistent fever under empirical antibacterial therapy, and necrotizing granulomatous inflammation (revealed through pathological examination), extrapulmonary tuberculosis with mediastinal and ocular involvement was highly suspected. We initiated standard antitubercular treatment with isoniazid, ethambutol, rifampin, and pyrazinamide (HERZ) on the 6th

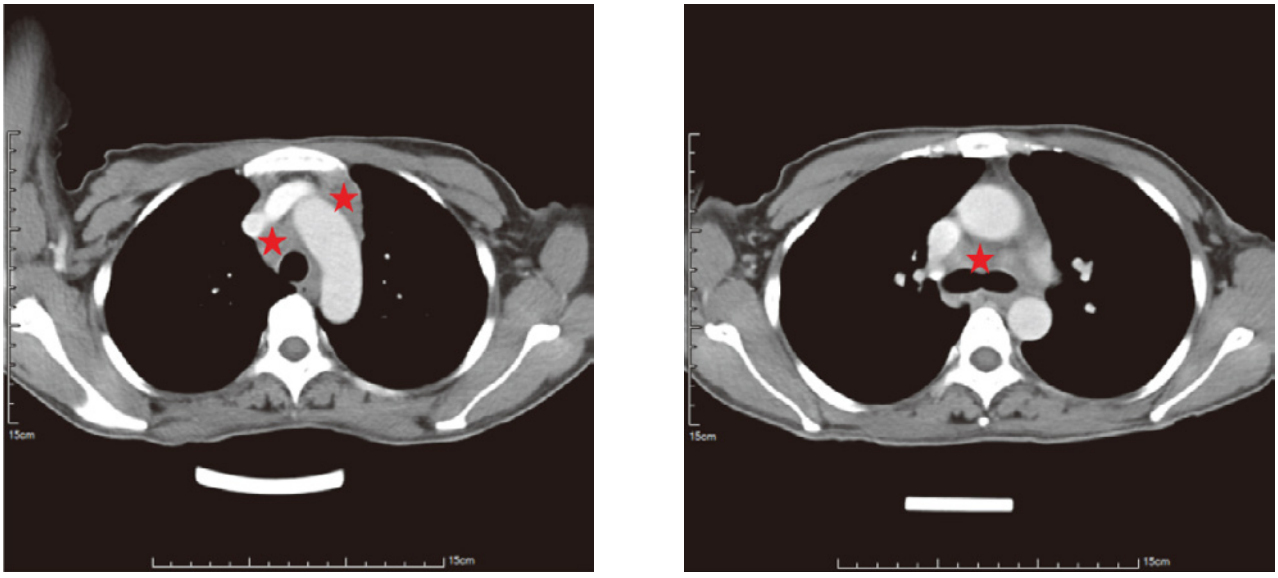

Figure 2. Contrast-enhanced computed tomography (CT) showed multiple mediastinal lymphadenopathies (asterisks).

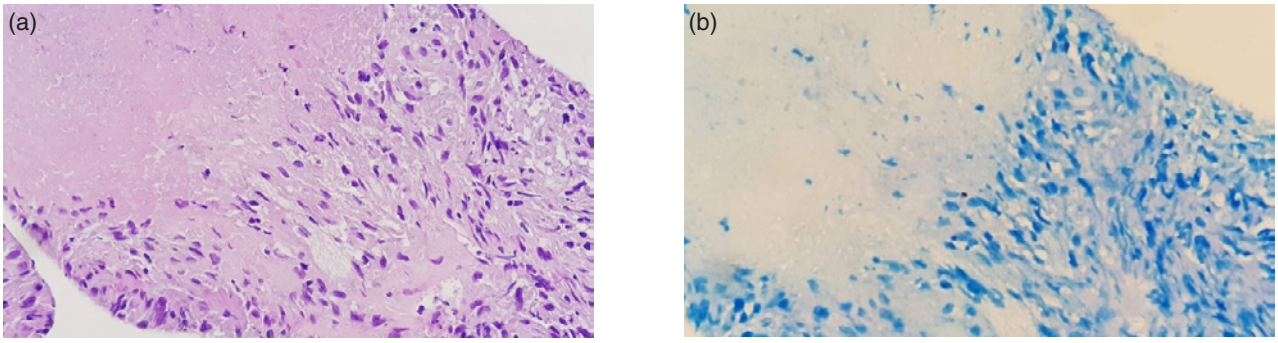

Figure 3. (3a) H & E stains, 40X. It showed granulomatous inflammation (right side) with caseous necrosis (left side); (3b) Acid-fast stain, 40X. No acid-fast bacilli was found.

day of hospitalization. The patient's fever subsided within 2 days, and leukocytosis improved. The blurred vision and leg edema resolved gradually. The patient was discharged on the 22nd day of hospitalization and returned home. Serial fundus examinations indicated improvement in retinal vasculitis and hemorrhage (Figure 1b).

During outpatient follow-up, an antitubercular regimen with HERZ was maintained. Oral steroids (prednisolone starting at 30 mg/day) were administered 3 weeks after HERZ was initiated to treat the remaining retinal vasculitis; her retinal vasculitis subsided gradually over 5 months of follow-up. Mycobacterial cultures of the sputum specimens collected initially and during follow-up were negative. The HERZ regimen was maintained for 9 months. Chest CT performed in the 9th month revealed resolution of mediastinal lymphadenopathies. No further episodes of fever were recorded, and her microcytic anemia improved. Subsequent follow-up at the ophthalmology outpatient clinic revealed that the patient's ocular condition and visual acuity had improved (Figure 1c, 1e). However, vitreous opacities were noted in both eyes, and the patient complained of persistent floaters; this was thought to be the sequela of retinal and vitreous hemorrhages.

Discussion

Tuberculosis has a high, albeit decreasing, incidence; 6,936 new disease cases were reported in Taiwan in 2021[4]. The lungs are the main target organ of *Mycobacterium tuberculosis*; however, this ancient pathogen can also cause disease in almost any organ and has a variable clinical presentation. The bones and lymph nodes are also commonly involved in extrapulmonary tuberculosis, and other infection sites (e.g., joints, eyes, genitourinary tract, and meninges) have been reported[5,6]. The diagnosis of pulmonary tuberculosis usually depends on sputum examination and typical findings on chest radiography. However, for extrapulmonary tuberculosis, diagnosis tends to be more challenging because the yield rate of mycobacterial culture is considerably lower for other body fluids than for sputum. Tissue biopsy is often required, and the detection of granulomatous inflammation with caseous necrosis through pathological examination strongly supports the diagnosis of tuberculosis but is not pathognomonic. In numerous clinical scenarios, empirical treatment with an antitubercular regimen is an alternative option when a microbiological or pathological diagnosis cannot be achieved[6]. The recommended treatment course for extrapulmonary tuberculosis is between 6 and 9 months, which can be extended to 12 months for specific situations (e.g., tuberculous meningitis)[7].

Tuberculous lymphadenitis presenting as mediastinal lymphadenopathy is common, especially among children in developing countries. According to reports, a patient can have leukocytosis and anemia but no respiratory symptoms[7,8]. For patients with mediastinal lymphadenopathy but without pulmonary involvement, the differential diagnosis is broad. For example, sarcoidosis, lymphoma, chronic fungal infection, and Wegener's granulomatosis can have similar clinical manifestations[9]. A lymph node biopsy is often required to establish a diagnosis, but even typical caseous necrosis can only be identified in approximately half of the patients with tuberculous lymphadenitis[10].

Conversely, ocular tuberculosis is a rare presentation of extrapulmonary tuberculosis. In most cases, the eyes are infected through the hematogenous spread, but primary exogenous infection of the eyelids or conjunctiva or secondary infections through contact with sputum containing *M. tuberculosis* have all been documented[11]. Essentially, any part of the eye can be involved, and the variable presentations include but are not limited to uveitis, keratitis, scleritis, retinitis (with or without retinal hemorrhage), panophthalmitis, and optic neuropathy[11,12]. Without early effective treatment, vision

impairment or blindness are common[12]. Ocular tuberculosis is usually a presumptive diagnosis because of the difficulties in acquiring the required specimens for culture or biopsy and the low sensitivity of these examinations because intraocular specimens are small in volume[11]. Current recommended criteria for the diagnosis of presumed ocular tuberculosis include 1. clinical signs suggestive of ocular tuberculosis; 2. at least one of the following: (a) histological confirmation of *M. tuberculosis* from an extraocular sample, (b) positive tuberculin skin test or interferon-gamma release assay results, and (c) chest radiograph or CT findings consistent with tuberculosis infection; 3. positive response to trialed antitubercular treatment; and 4. exclusion of other differentials such as sarcoidosis or autoimmune disorders[3,13]. An empirical treatment with a standard antitubercular regimen is warranted for high clinical suspicion[9,10,14]. Usually, the HERZ regimen would be used for the first 2 months, followed by isoniazid and rifampicin for at least 4 months[3]. The recommended treatment course is between 6 and 9 months, and it is extended to up to 19 months in some studies depending on the clinical response[9]. Oral or topical steroids are commonly added to improve a patient's prognosis[14,15]. According to recent studies, more than 70% of patients achieved clinical remission at the end of antitubercular treatment[16,17]. In our case, the HERZ regimen was maintained throughout the 9-month-course due to the lack of drug susceptibility reports, and no adverse effects were observed. However, the risk of hyperuricemia and optic neuropathy is higher, and the additional benefits are limited.

Our patient presented with blurred vision and mediastinal lymphadenopathy but without any pulmonary symptoms; for such cases, tuberculosis is seldom at the top of the list of differential diagnoses for ophthalmologists and internists. Furthermore, no microbiological evidence of tuberculosis infection was obtained even after a mediastinal lymph node biopsy was performed. However, anemia, chronic disseminated intravascular coagulopathy, and low albumin levels suggest a chronic inflammatory or infectious process, and tuberculosis should not be ruled out when this scenario occurs in an endemic area. Later, a definite retrospective diagnosis was made confidently because of the patient's favorable response to empirical antitubercular treatment. This case report highlights the challenges of managing a patient with a rare presentation of extrapulmonary tuberculosis. A more comprehensive study might provide further help in this case, especially if the response to empirical antitubercular treatment is unsatisfactory. For example, the interferon-gamma release assay can be tested, and the possibility of tuberculosis infection is lower if the result is negative. Tissue from mediastinal lymph node biopsy can be used for mycobacterial culture and tuberculous polymerase chain reaction. Finally, ocular fluid aspiration or intraocular tissue biopsy are still options; however, they should be considered if the diagnostic potential outweighs the risk[3].

Conclusion

Ocular tuberculosis is a rare presentation of extrapulmonary tuberculosis, and its diagnosis is challenging. However, empirical antitubercular treatment is often used, and the response to the therapy is itself supportive evidence for the diagnosis. Besides, a comprehensive study should be attempted to build the diagnosis and exclude other differentials.

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肺外結核併縱膈腔淋巴腺病變及眼結核：個案報告

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摘　要

肺外結核感染在臨床上有多種不同的表現，感染部位可遍及全身。由於難以獲得微生物進行診斷，通常使用實驗室檢查、影像學檢查及病理檢驗作為間接證據進行推論診斷；此外，經驗性抗結核桿菌藥物治療的成效也是診斷的線索之一。本篇文章介紹一位肺外結核感染併縱膈腔淋巴腺病變及眼結核之患者，其診斷有賴臨床判斷及病理檢查，介入標準結核病治療，病患得到良好的預後。