CASE REPORT

Septic cavernous sinus thrombosis caused by tuberculosis infection

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SUMMARY

We report a rare case of acute, septic cavernous sinus thrombosis (SCST) caused by tuberculosis infection. The diagnosis of SCST was suspected and rapidly confirmed based on high fever, dramatic and typical signs of left cranial nerve paralysis and the result of digital subtraction angiography after the onset of the disease. However, the diagnosis of tuberculosis infection was missed, and the 55-year-old patient was treated with high-dose glucocorticoid, anticoagulants and a series of intravenous antibiotics for bacteria. His symptoms failed to improve, and steroid treatment resulted in serious haematogenous dissemination of *Mycobacterium tuberculosis*, including miliary tuberculosis and tuberculosis verrucosa cutis, which led to the final diagnosis. Then, the patient received a five-agent antituberculosis treatment. He was recently followed up with only the sequelae of left side ptosis and oculomotor weakness.

BACKGROUND

Septic cavernous sinus thrombosis (SCST) is a rare but severe disease that is associated with significant morbidity and mortality.^{1–2} In most cases, SCST occurs secondary to the spread of facial and paranasal sinus or dental infections by veins or direct extension. The microbiology of SCST is well documented. The most commonly isolated organisms are *Staphylococcus aureus* (70%) and *Streptococcus* spp (20%).^{1–2} Tuberculosis (TB) is a common infectious disease predominately prevalent in developing countries. TB infection of the central nervous system (CNS) is also a serious and potentially lethal illness. Meningitis, intracranial tuberculoma and spinal tuberculous arachnoiditis are three major clinical categories of CNS TB.³ However, to the best of our knowledge, SCST caused by TB has not yet been reported.

CASE PRESENTATION

A 55-year-old Chinese man was referred to our department with a 4-month history of headache, high fever, left eye swelling and ptosis. The patient had no significant medical history except type 2 diabetes. On 10 February 2013, he presented with sudden headache, high fever, chills, nausea and vomiting after an 8 h flight from China to Honolulu, Hawaii, USA. He was treated with non-steroidal anti-inflammatory drugs at a local hospital. Subsequently, symptoms of diplopia, left periorbital oedema and left side ptosis developed over the next 5 days. Physical examination showed left eye proptosis, chemosis, dilation and fixation of the

left pupil, hypoaesthesia on the left forehead and cheek with no signs of facial infection. The patient's peripheral white cell count (WCC) was elevated ($14.61\text{--}27.15 \times 10^9/\text{L}$). Subsequent lumbar puncture revealed a slightly elevated protein level but normal WCC in cerebrospinal fluid (CSF). His intracranial pressure was normal and CSF cultures for bacteria were negative. Cerebral MR angiography (MRA), MR venography (MRV) and digital subtraction angiography (DSA) confirmed left cavernous sinus thrombosis and an aneurysm of 4 mm diameter at the intercavernous segment of the left carotid artery. Although the patient had no obvious respiratory symptoms, CT of the chest revealed several thick wall cavities as well as small nodules in bilateral lungs (figure 1A). The diagnosis of cavernous sinus thrombosis secondary to bacteraemia was suspected, and the pulmonary lesions were considered "consistent with the clinical suspicion of septic pulmonary emboli." The patient received high-dose intravenous antibiotics including ceftriaxone, meropenem and moxifloxacin successively. Dexamethasone 4 mg intravenously every 6 h and enoxaparin followed by warfarin was also prescribed. His fever and headache were gradually relieved. The patient returned to China at the end of February and was admitted to a hospital in Shanghai where moxifloxacin was replaced by vancomycin and imipenem and glucocorticoid was tapered gradually to oral prednisone 10 mg/day. Warfarin was continued with international normalised ratios (INR) kept between 2.0 and 3.0. However, the patient's fever and neurological symptoms became worse in April. A repeated CT of the chest seemed to be normalised, and the result of positron emission tomography (PET)-CT scan revealed no signs of tumour. Repeated MRA and MRV demonstrated left cavernous sinus thrombosis and occlusion of the left internal carotid artery. The patient began to present with multiple subcutaneous nodules in upper and lower limbs beginning at the middle of April, and developed exertional dyspnoea.

INVESTIGATIONS

On admission to our department, examination of the patient's eyes and a neurological examination revealed similar findings of dysfunction of the cranial nerves (figure 2). His arterial oxygen saturation at room air was 93%, and arterial blood gas showed a low oxygen tension of 65 mm Hg. He denied cough, haemoptysis and night sweats. He was still on anticoagulants, and blood cultures for bacterial and fungal infection were negative.

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Figure 1 CT of the chest (A) performed in Hawaii, 19 February, showing cavities and small nodules in bilateral lungs, which were thought to be consistent with septic emboli and (B) performed in our department, 21 June, showing randomised distributed fine nodules, which were typical in miliary tuberculosis.

The examinations of the CSF also showed a slightly elevated protein level, normal intracranial pressure and negative acid-fast stain. CSF cultures for bacteria, fungi and acid-fast bacilli were all negative. A biopsy of a subcutaneous nodule was performed, and the pathological results revealed epithelioid granulomas. The smear was positive for acid-fast bacilli, and subsequent culture result was positive for *Mycobacterium tuberculosis*. A repeated CT of the chest suggested pulmonary miliary TB (figure 1B).

DIFFERENTIAL DIAGNOSIS

The cavernous sinus is of great importance for its relations with cranial nerves III–VI and horizontal segment of the internal carotid artery.⁴ So SCST may cause neurological symptoms related with a number of cranial nerve palsies.² Facial infections, sphenoid and/or ethmoid sinus infections, and dental infections are three major sites of primary infections that lead to SCST. The most commonly isolated organisms causing SCST are *S. aureus* (70%) and *Streptococcus* spp (20%). Other reported organisms include *Pneumococcus*, *Bacteroides*, *Fusobacterium*, *Proteus*, *Haemophilus*, *Pseudomonas*, *Corynebacterium* and, occasionally, fungi.^{1 2} *M. tuberculosis* has never been reported as a cause of SCST, to the best of our knowledge, which is one of the reasons why the diagnosis of this case become challenging.

TREATMENT, OUTCOME AND FOLLOW-UP

A five-agent antituberculous chemotherapy including isoniazid, rifampin, ethambutol, pyrazinamide and moxifloxacin was

initiated and glucocorticoid therapy was strengthened with intravenous dexamethasone of 0.2 mg/kg/day. The patient's fever improved and subcutaneous nodules regressed in size over the next 2 weeks. His sputum culture for *M. tuberculosis* was later proved to also be positive and the patient was transferred to a local specialty hospital for communicable diseases. The patient was recently followed up by telephone in September 2014. He has finished a 3-month intensive anti-TB therapy and 9-month prolonged therapy with isoniazid and rifampin. His warfarin was also discontinued in July. Although he still suffered the sequelae of left side ptosis and oculomotor weakness, his subcutaneous nodules were relieved completely and his oxygenation also improved with arterial oxygen saturation 97% at room air. Re-evaluations of CT of the chest also showed it had been normalised.

DISCUSSION

It is estimated that more than two billion people are infected with *M. tuberculosis* in the world, and the highest prevalence is reported in developing countries such as China, sub-Saharan Africa and India. TB infections of the CNS are serious and often fatal diseases with three clinical forms: tuberculous meningitis, tuberculoma and spinal tuberculous arachnoiditis.^{3 5} To the best of our knowledge, SCST as initial and dominant CNS form at the onset of TB infection has never been reported. In this case, the diagnosis of SCST was easily established based on high fever, dramatic and typical signs of left cranial nerve paralysis, high peripheral WCC and the results of DSA soon after the onset of the disease. Imaging, microbiological and pathological results in our hospital confirmed that the patient developed haematogenous dissemination of *M. tuberculosis* including miliary TB and TB verrucosa cutis. However, considering the rarity of TB as a pathogen for SCST and the use of a high-dose steroid, alternative explanations needed to be ruled out to reach the final diagnosis. Whether the patient had latent TB remains unknown. He had type 2 diabetes mellitus and experienced an exhausting long-haul flight. The diagnosis of TB was missed in the hospitals in Honolulu and Shanghai; however, the physical examination records revealed no signs of facial infections, dental abscess, or otitis media. Cultures of blood and CSF were negative for bacteria and fungi. Imaging results failed to demonstrate any sign of paranasal sinusitis or other infections around the cavernous sinus. The only positive finding was from the patient's CT of the chest, which revealed thick wall cavities and small nodules in bilateral lungs (figure 1A). The abnormal manifestations on CT had been considered as small septic pulmonary emboli. His fever, neurological symptoms and the abnormal

Figure 2 On admission to our department, the physical examination revealing left eye ptosis.

findings on CT resolved with an antibiotic regimen containing moxifloxacin, which has been proved to have good CSF penetration and is recommended in the treatment of TB meningitis.^{6 7} Although the empiric antibiotic treatment in Honolulu also included ceftriaxone and meropenem, moxifloxacin was the last prescribed before the relief of symptoms. The patient's symptoms became exacerbated when moxifloxacin was replaced by vancomycin and imipenem in Shanghai. The repeated MRA and MRV results had shown only slow progression when his symptoms became worse again. However, his fever and neurological symptoms improved quickly when he was treated with anti-TB therapy, so did his oxygenation after a 20-day treatment. It would be impossible to explain that the whole course was attributable to bacterial or fungal infection. It has been suggested that bacteria stimulate the formation of a thrombus by the release of a procoagulative substance.⁸ However, whether it was triggered during the reactivation of TB in the case remains unknown.

The usual treatment strategy for TB meningitis was followed in the case.⁵ However, moxifloxacin was also administered as the fifth drug in combination with isoniazid, rifampin, ethambutol and pyrazinamide during the 3-month period of intensive therapy. A susceptibility test was not available in our hospital and was not performed in the specialty hospital for communicable diseases, so we could not get the information on whether there was any resistance to the first-line TB drugs or moxifloxacin. During follow-up, the patient responded well with the regimen. The dysfunction of some cranial nerve palsies did not improve, which might be associated with delayed diagnosis and treatment. How to manage anticoagulation therapy was unclear for us in this case. The role of anticoagulation in the treatment of SCST remained controversial in the literature.¹ Southwick *et al*⁹ retrospectively reviewed 96 cases of SCST and suggested that the use of heparin might reduce mortality in select patients with unilateral involvement. However, Levine *et al*¹⁰ found no statistically significant differences of mortality between combination of anticoagulation with antibiotic therapy and antibiotic therapy alone. Given the rarity of SCST, there is yet no solid evidence on this issue.¹¹ In this case, the low-molecular-weight heparin was initiated and followed by warfarin with INR between 2.0 and 3.0. The early anticoagulation seemed to lead to no serious complications and cavernous sinus thrombosis was initially relatively stable even without appropriate anti-TB therapy. It has been suggested by expert opinions that anticoagulation should be continued until there is radiological resolution of the thrombus. However, the European Federation of Neurological Societies guideline on the treatment of cerebral venous and sinus thrombosis states that oral anticoagulation may be given for 3 months if cerebral venous and sinus thrombosis is secondary to a transient risk factor and longer if there is an underlying thrombophilia.¹² Considering that TB infection may

need a longer duration of treatment, our patient was required to be on warfarin with INR between 2.0 and 3.0 for 12 months until the infection had resolved.

Learning points

- ▶ Septic cavernous sinus thrombosis (SCST) is a severe disease associated with significant morbidity and mortality.
- ▶ Tuberculosis infections of the central nervous system (CNS) are serious and often fatal diseases with three major clinical forms: tuberculous meningitis, tuberculoma and spinal tuberculous arachnoiditis.
- ▶ In acute cases, SCST can rarely be caused by *Mycobacterium tuberculosis*, as in our patient.
- ▶ Moxifloxacin may have stronger drug potency for tuberculosis infections of the CNS and needs to be considered in initial intensive therapy for SCST caused by tuberculosis infection.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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