

Unusual Tuberculosis Mimicking Connective Tissue Disease: A Pediatric Case Report

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Abstract:

We reported a child with unusual extrapulmonary tuberculosis (TB) who was misdiagnosed with a connective tissue disease leading to treatment delay. A 13-year-old boy presented with subacute joint pain, headache and diplopia. The examination revealed swelling in the right knee, cervical lymphadenopathy, impaired abduction of right eye and multiple groups of follicular papules at right forearm, cheeks and buttocks. Blood tests showed mild anemia, thrombocytosis and high erythrocyte sedimentation rate. Serological tests including antinuclear antibody, rheumatoid factor, anti-double stranded deoxyribonucleic acid and anti-human immunodeficiency virus were negative. Brain magnetic resonance imaging (MRI) illustrated multiple lobulated dural thickening areas and a small infarction of left cerebellum. Chest film and tuberculin test were normal. Joint fluid analysis suggested reactive arthritis. Cultures for TB and fungus from cervical lymph node and forearm skin lesion were negative. After an extensive investigation, the presumptive diagnosis was non-specific connective tissue disorder. The arthritis and ophthalmoparesis initially responded to prednisolone, but arthritis relapsed at the third week of treatment, and intravenous cyclophosphamide was added. Three months later, left facial palsy had developed and ophthalmoparesis increased. New skin lesions also appeared over his axillae and groins. Axilla skin biopsy showed granulomatous abscesses with caseous necrosis leading to TB diagnosis. After treatment with anti-TB agents, clinical signs and brain MRI were completely resolved at 6-month-follow-up. Our report addressed that TB may mimic connective tissue diseases and temporarily respond to immunosuppressants. Because idiopathic pachymeningitis is rare in children, TB must be excluded in cases with meningeal thickening. Re-evaluation of TB is highly recommended in atypical systemic illnesses.

Keywords: arthritis, connective tissue diseases, meningeal, mycobacterium tuberculosis infection

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Introduction

Tuberculosis (TB) is common in developing countries. Thai TB figures from 2005–2006 showed that pediatric TB accounted for 2.0% of all 14,487 cases.¹ The extra-pulmonary form of TB occurs in almost 30.0% of pediatric cases. Of extrapulmonary cases, TB lymph node and meningitis are the most two common forms which account for 50.0% and 25.0%, respectively.¹ We reported a pediatric case of TB presenting with uncommon extra-pulmonary manifestations such as reactive arthritis, pachymeningitis, cerebellar infarction and cutaneous lesions. These atypical manifestations led to misdiagnosis and treatment delay.

This case report received clearance from the ethics committees of Faculty of Medicine, Prince of Songkla University (REC 58-103-19-1).

Case report

A 13-year-old boy was admitted due to right knee swelling, severe headache and diplopia which had developed over 1 week. He was afebrile during the entire course of the illness. Physical examination revealed a cooperative, adolescent boy with normal growth and development. His right knee showed positive ballottement and mild tenderness and the only positive neurological examination was an impaired abduction of his right eye. His skin showed multiple clusters of erythematous papules over his cheeks and buttocks and a violaceous patch surrounded by erythematous follicular papules on his right forearm. All skin lesions were painless. There was a 2-centimetre-firm, movable lymph node at each anterior cervical area.

Complete blood count showed mild leukocytosis (white blood cells (WBC) 16,610/microlitre) with lymphocytic predominance, mild anemia (hemoglobin 9.6 grams/decilitre), thrombocytosis (platelet 710,000/microlitre) and an elevated erythrocyte sedimentation

rate at 104 millimetres/hour. Serological tests including antinuclear antibody, rheumatoid factor, anti-double stranded deoxyribonucleic acid (anti-dsDNA) and anti-human immunodeficiency virus (anti-HIV) showed negative results. Knee joint fluid analysis showed WBC 2,650/microlitre (lymphocytes 66.0% and red blood cells 14,400/microlitre) with negative bacteria and TB culture. Brain magnetic resonance imaging (MRI) illustrated multi-focal lobulated hypointense dural thickening along the right cerebral convexity, left parietal convexity, right tentorial cerebelli, right Meckel's cave, and right posterior cavernous sinus. These lesions were enhanced after gadolinium injection (Figures 1A–B). There were also several hyperintense wedge-shaped lesions with fluid restriction on diffusion weighted imaging at the left cerebellar hemisphere, suggesting a cerebellar infarction (Figure 1C). Brain magnetic resonance angiography was unremarkable. Cerebrospinal fluid (CSF) analysis showed elevated increased intracranial pressure (opening pressure 19 centimetre water) and mild lymphocytic pleocytosis. CSF findings included mononuclear cells 15/microlitre, protein 39 milligrams/decilitre and sugar 55 milligrams/decilitre (blood sugar 72 milligrams/decilitre). Blood and CSF were negative for aerobic cultures.

We tried to exclude TB in the patient. Chest x-ray and tuberculin test were negative (0 millimetre). Fine needle aspiration of a right cervical lymph node was consistent with a non-specific inflammation. Lymph node culture for TB and fungus were negative. Histopathological report of full thickness skin biopsy from the papular lesions of his right forearm was not specific for TB. It showed focal epidermal and dermal necrosis, cell debris, lymphohistocytic infiltration into the perivascular layers and periadnexa. Additional immunofluorescent study found a weakly positive immunoglobulin M at the dermo-epidermal junction and periadnexa. Parents did not give their consent for a meningeal biopsy of the patient.

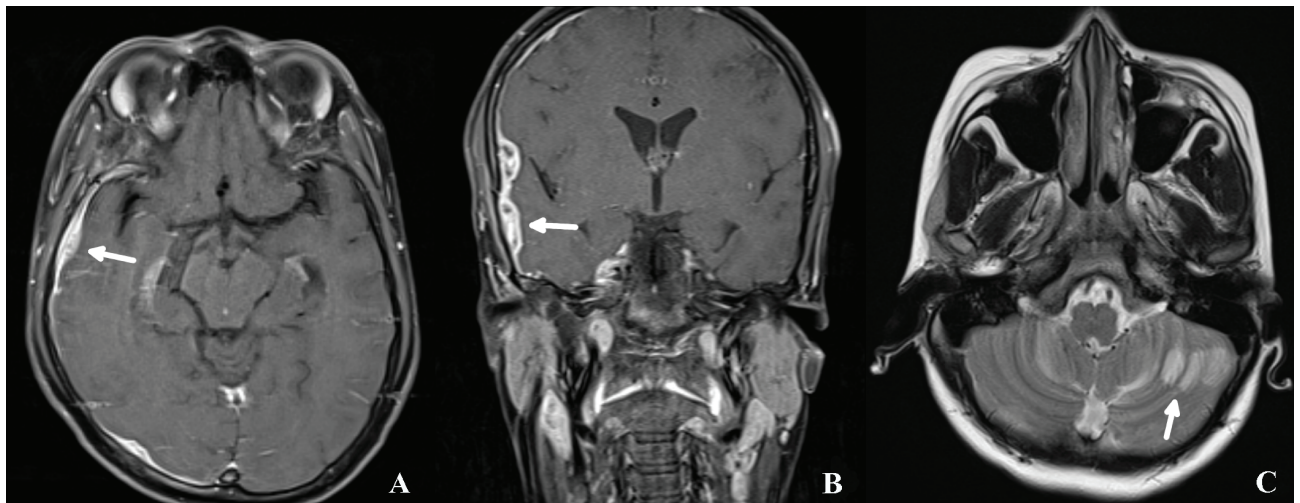


Figure 1 Brain magnetic resonance imaging (T1 with gadolinium) shows enhanced dural thickening along the bilateral cerebral convexities (A–B). Axial magnetic resonance imaging (Fluid-attenuated inversion recovery technique) shows asymmetrical small cerebellar infarctions (C).

After extensive investigation to exclude infections, presumptive diagnosis was non-specific connective tissue disorder with central nervous system involvement. Oral prednisolone 2 milligrams/kilogram/day was administered, and all symptoms disappeared in two weeks. However, arthritis of the right knee reoccurred in the third week of steroid treatment. Intravenous cyclophosphamide (500 milligrams/square meter) was added to the prednisolone resulting in an improvement of arthritis after seven days. Monthly intravenous cyclophosphamide was subsequently given while prednisolone was being tapered. Three months later, his sixth nerve palsy became worse and he developed lower motor neuron facial palsy on the left side of his face. The brain MRI illustrated lobulated enhanced dural thickening along the right cerebral convexities, Meckel's cave and cavernous sinus. No hydrocephalus or new infarction were noted. Relapse of the connective tissue disease was suspected, so a 3-day-course of pulse methylprednisolone followed by 2 milligrams/kilogram/day of oral prednisolone were given. This time, his

neurological deficits did not improve. Two months later, new skin lesions characterized by erythematous vesiculo-papular rashes appeared at both axillae and groins.

A skin biopsy was carried out from the new lesion at his right axilla. Pathological report showed granulomatous abscess with caseous necrosis. Skin tissue for acid-fast bacilli and giemsa stains were negative. We repeated the tuberculin test and found a positive reaction at 20 millimetres. He had no history of TB contact from adults. Chest x-rays of the patient and family members were unremarkable. The patient was treated with 2 months of combined anti-tuberculous drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol), followed by 4 months of isoniazid and rifampicin. Cyclophosphamide was discontinued, and prednisolone was tapered off over 1 month. All clinical signs were resolved at 1 month of follow-up. A repeated brain MRI after six months of treatment illustrated a complete resolution of abnormal dural thickening.

Discussion

TB in our patient was presumably diagnosed with evidence of caseous necrosis of skin lesion, with tuberculin skin test conversion and its complete resolution after treatment with anti-TB drugs.

Manifestations of extrapulmonary TB may result from a direct infection or an inflammatory reaction. Our patient presented with uncommon forms of extrapulmonary TB such as reactive arthritis, pachymeningitis, brain infarction and cutaneous lesions. These unusual presentations as well as the negative initial results for TB investigations led to a delay in diagnosis and treatment.

The sites of extrapulmonary TB seen in our patient were rarely reported in children. The most common sites of extrapulmonary TB in Thai children were lymph node and meninges.¹ Reactive arthritis from TB or Poncet's disease is the third most common extrapulmonary TB found in about 10.0–19.0% of extrapulmonary TB.^{2–5} Poncet's disease is usually oligoarticular or polyarticular affecting weight-bearing joints. It is difficult to differentiate Poncet's disease from other reactive arthritis causes including connective tissue diseases.^{2–4} Our patient had negative cultures and polymerase chain reaction for TB of joint fluid. However, the gold standard for diagnosis of tubercular arthritis is synovial biopsy, with positive results in 80.0% of cases. Thus, the diagnosis of reactive arthritis in this patient was inconclusive.^{6–7}

Cutaneous lesion is also uncommon in TB.⁸ The asymptomatic lichenoid eruption of minute papules seen in our patient was compatible with a tuberculid called lichen scrofulosorum. Histopathological findings in tuberculid are epithelioid cell granulomas in upper dermis and around dermal appendages. This lesion is usually negative for TB stain and culture, making it harder to diagnose TB.⁸

Multi-focal dural thickening on MRI and mild CSF pleocytosis in the patient were suggestive for pachymeningitis. Pachymeningitis is an inflammation of the

dura mater which can cause headache, cranial nerve neuropathies and cerebellar dysfunction.⁹ Granulomatous diseases, vasculitis, connective tissue diseases (e.g. rheumatoid arthritis) and malignancies must be ruled out first. In idiopathic pachymeningitis, dural thickening is usually located at the posterior falx and tentorium.¹⁰ Our patient had multiple dural lesions which also involved the tentorial area. Although CSF culture for TB was negative, we were not assured that the dural thickening was either sterile pachymeningitis or a direct infiltrative lesion of mycobacterium species due to the lack of meningeal tissue biopsy. Brain infarction can be seen in a generalized form of TB meningitis^{11,12}, but it is rarely reported in a localized meningeal inflammation. Tubercular protein induced hypersensitivity and vasculitis may result in the small cerebellar infarctions seen in our patient.¹³

Our case report illustrated the real-life difficulty in definitively diagnosing extrapulmonary TB. Indirect supportive evidence, such as imaging, tuberculin test or even therapeutic trial, may be required to diagnose atypical TB. Tuberculin test is useful supporting evidence in children, but it is not sensitive or specific. The test result depends on the individual's cellular immunity and sites of TB infection. It may be worth considering a repeat of the tuberculin test even in a patient who is on steroid treatment, although it may represent either a recent TB infection or just a booster effect.

A negative culture for TB and a temporary response to drugs may lead some physicians to the wrong diagnosis. In addition, a physician may hesitate to give a patient long-term administration of anti-TB drugs without proving a definitive diagnosis due to the known adverse effects. Anti-inflammatory drugs usually temporarily ameliorate the symptoms, but TB will eventually flare up. Hence, close monitoring after immunosuppressant therapy is crucial.

Conclusion

Our report addressed that tuberculous manifestations may mimic connective tissue diseases and temporarily respond to immunosuppressants. Since idiopathic pachymeningitis is rare in children, TB should always be excluded in subacute or chronic meningeal thickening. In countries where TB is common, it should be ranked high in the differential diagnosis of pachymeningitis. Re-evaluation of TB is highly recommended in patients presenting with atypical systemic illnesses.

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Conflict of interest

There are no potential conflicts of interest to declare.

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