

Disseminated non-tuberculous mycobacterial infection induced by localized acupuncture and infection: a report of four cases.

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Abstract

This study reported four cases of disseminated non-tuberculous mycobacterial (NTM) infection caused by local puncture, and elaborated the pathway of infection, their clinical manifestations, the process of diagnosis and treatment. The study aimed to improve the clinicians' recognition on the sterilization of acupuncture, and prevent the iatrogenic infection. Both the 4 cases had a history of local puncture, and diagnosed as disseminated NTM infection. They recovered to a better situation after receiving the anti-NTM infection treatment. Recently, there were few reports about disseminated NTM infection caused by local puncture. The clinical manifestation is not obvious, it usually misdiagnosed as tuberculosis mycobacteria. Thus, it's necessary to improve the recognition of infection routes and clinical manifestations of NTM, and establish a standard operational disinfection procedure.

Keywords: Puncture, Non-tuberculous mycobacteria, Tuberculosis, Mycobacteria.

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Introduction

Except for *Mycobacterium tuberculosis* complex (including *M. tuberculosis*, *Mycobacterium bovis*, Africa mycobacterium) and *Mycobacterium leprae*, non-tuberculosis mycobacteria (NTM, non-tuberculous mycobacteria) are pathogenic bacteria or conditioned pathogens which can invade cervical lymph nodes, skin, tissues and organs. Disseminated non-tuberculosis mycobacterial disease (disease of disseminated non-tuberculous mycobacteria, DDNTM) [1] is defined in the condition that the bacterium is found in more than two lesions or in blood. Many factors contributed to the occurrence of DDNTM, such as the immunosuppressive conditions, organ transplantation and pulmonary disease [2]. Until now, due to the complicated and nonspecific clinical/histologic manifestations of DDNTM [3-5], it was easily to be misdiagnosed and was rarely reported, the diagnosis and treatment of DDNTM infection was still a challenge. Previous studies found that the patients with anti-TNF therapy had a higher risk of DDNTM [6,7], and females were more likely to be infected than males.

The present study described [4] DDNTM cases who were caused by local puncture, which were little reported. Resort to this study, we aimed to improve the awareness of protection against mycobacterium tuberculosis infection caused by

various ways, and also provided some information on the diagnosis, treatment and prevention of DDNTM.

Patients and case reports

Between November 2011 and May 2012, 4 patients suffered from disseminated mycobacterium infections which caused by local acupuncture and treated at The First Affiliated Hospital of Wenzhou Medical University were reported. Written informed consent was obtained from each patient. All of them were treated with acupuncture and local injection of medicine in the same clinic several months ago before they were hospitalized. Their demographic and clinical characteristics were summarized in Table 1.

Case 1

An otherwise healthy 40-year-old woman, she felt "uncomfortable and painful in waist" and diagnosed as "lumbar disc herniation" 5 months ago before being hospitalized. Her symptoms were relieved after acupuncture and local injection of drugs. A painful mass in the left side of lower waist was noted. MRI showed "abnormal signal in L4-S1 psoas and adjacent subcutaneous soft tissue, infection should be considered". Positive acid fast bacilli was detected in the smear of pus pumped from mass (Figure 1A), while

bacteria and fungi was negative. After admission to orthopedics department, the pus culture revealed “fast-growing mycobacteria”. Then she was received a combined regimen of

rifampicin/isoniazid/pyrazinamide/ethambutol (RHZE) therapy and hepatic-protective therapy (utilize the mild proprietary Chinese medicine as a preventive mediation).

Table 1. The demographic and clinical characteristics of the 4 patients.

	Case 1	Case 2	Case 3	Case 4
Gender	Female	Female	Male	Female
Age (years)	40	53	54	73
Epidemiology	Local acupuncture and drug injection (Angelica extract + vitamin B12) in lumbar	Local acupuncture and drug injection (Angelica extract +vitamin B12) in knee-joint	Local acupuncture and drug injection (Angelica extract +vitamin B12) in knee-joint	Local acupuncture and drug injection (Angelica extract +vitamin B12) in knee-joint
Fever	38	39~40°C	39~40°C	38~39.2°C
Arthralgia	Inflammation and pain in lumbar vertebra	Confined left knee with pain	Local pain in both knees	Swelling and pain in left knee
Headache	No	Yes	Yes	No
Involvement of tissues and organs	Lumbar vertebra, lung	Left knee, lung, brain	Both knees, lung, brain	Left knee, lung
Erythrocyte sedimentation rate (ESR, mm/h)	36-45	21-25	14-20	58-69
White blood count (WBC, ×10 ⁹)	4.7-7.4	4.0-6.3	9.2-12.9	8.3-13.9
Cerebrospinal fluid (CSF) examination	Not done	Pressure>400 mmHg, Mycobacterial culture (+)	Pressure>200 mmHg, Mycobacterial culture (-)	Pressure>200 mmHg, Mycobacterial culture (-)
C-reactive protein (CRP, mg/L)	21	29.2	13	178
Other tests	Normal liver function	Abnormal liver function, normal by Bronchoscope examination	Abnormal liver function, normal by Bronchoscope examination	BALF culture: Staphylococcus epidermidis MDRO. Analysis of blood gas: PaO ₂ 55.6 mmHg; PaCO ₂ 30.8 mmHg
Chest CT scan	Diffuse, miliary lesions in both lungs	Diffuse, miliary lesions in both lungs	Diffuse miliary lesions in both lungs	Diffuse, ground-glass lesions in both lungs
Coronal MRI	Normal	Multiple low density lesions	Lacunar infarction in both sides of the frontal lobe and brainstem, softening	Normal
T-spot test	Positive	Positive	Positive	Positive
Acid fast stain of puncture fluid	(+) for 3 times	(++++) for 4 times	(+) for 3 times	(+) for 3 times
Acid fast stain of sputum smear	(+)	(-)	(-)	(+)
Mycobacterial culture	Rapid-growing Non-tuberculous Mycobacteria	Rapid-growing Non-tuberculous Mycobacteria	Rapid-growing tuberculous Mycobacteria	Non-tuberculous Mycobacteria
Pathology	Granulomatous lesions associated with obvious necrosis, Tuberculosis should be considered first	Granulomatous lesions in synovium of joint	Granulomatous inflammation of synovial tissue, tuberculosis should be considered	None
Drug therapy	Cefoxitin+Clarithromycin +Rifampicin+Pyrazinamide +Ethambutol	Cefoxitin+Rifabutin +Azithromycin+Ethambutol +Pyrazinamide+Moxifloxacin	Cefoxitin+Rifabutin +Azithromycin+Ethambutol +Isoniazid+Clarithromycin	Isoniazid+Ethambutol+Rifabutin +Pyrazinamide+Levofloxacin
Surgical treatment	Removal of abscess	Knee arthroscopy	Knee arthroscopy	None
Course and outcome	19 M; Better	19 M; Better	18 M; Better	19 M; Better

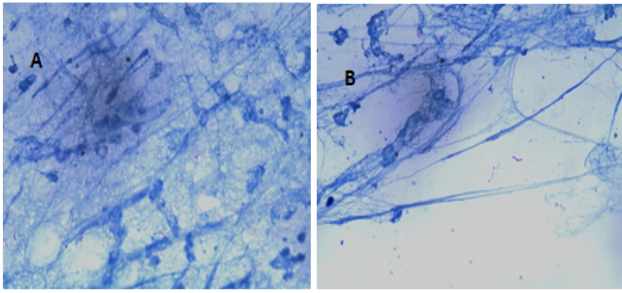


Figure 1. (A) Smear of hip pus by acid-fast stain $\times 1000$; (B) Smear of pus from left knee joint by acid-fast stain $\times 1000$.

Debridement of abscess in left hip was performed, the acid fast stain from pus was detected positive again and also with a positive culture of fast-growing mycobacteria. Pathological examination showed “granulomatous lesion with obvious necrosis in the left hip, tuberculosis should be given more consideration” (Figure 2A). Fever was occurred and the temperature was fluctuated between 37.5 to 38 after operation, the chest CT displayed “diffuse distribution of miliary nodules in both lungs”. Positive result of acid fast stain was detected from joint puncture fluid. Since she was allergic to isoniazide, RZE regimen was used instead of RHZE regimen. However, the wound healing was affected by sustained leaking of pus, then cefoxitin (6 g/d) and clarithromycin (1 g/d) were added. The patient was finally discharged from hospital when the secretions from wound were greatly reduced. “Lesions are absorbed” was proved by chest CT 4 months later.

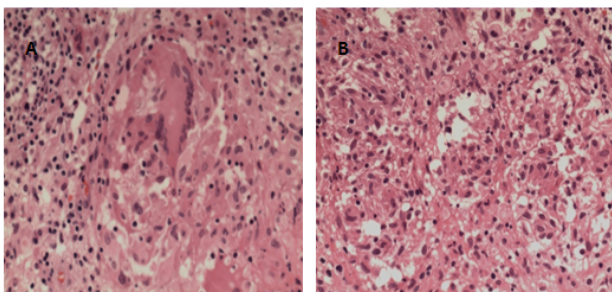


Figure 2. (A) Granulomatous lesions accompanied with obvious necrosis in left hip, tuberculosis should be considered, HE $\times 400$; (B) Granulomatous lesions accompanied with necrosis in soft tissue of left knee, HE $\times 400$.

Case 2

A 53-year-old woman, without history of heart or lung disease. She felt swelling, aching and confined activity in the left knee joint with unexplained reasons for 2.5 months. The puncture and injection of drugs achieved little improvement. “Lesions in and around the left knee joint” was showed by MRI, then she was admitted to orthopedics department with admitting diagnosis of “synovitis and infection in left knee joint”. Slight pressing pain in the left knee joint and confined movements was noted. Her temperature was raised to 39°C on the 2nd day after admission. Ceftriaxone (2.0 g/d) was given to resist

infection. Her chest CT scan displayed “miliary nodules are diffused in both lungs”. Miliary tuberculosis could not be ruled out, thus the patient was transferred to respiratory department. However, her temperature still fluctuated at 37-39°C when azithromycin (0.5 g/d) was added. Then it was replaced by the combination injection of isoniazid (0.6 g/d), rifampin (0.6 g/d), ethambutol (0.75 g/d), pyrazinamide (1.5 g/d) and ofloxacin (0.5 g/d), but the regimen showed little effect. After that, positive acid-fast stain was detected in smear of puncture fluid and the culture showed positive in mycobacteria.

The patients complained headache and dizziness, so lumbar puncture was given on the 5th day after admission. Cerebrospinal fluid examination revealed protein 853 mg/L, glucose 2.2 mmol/L, chloride 110 ml/L, 9 WBC/ μ l, 1 RBC/ μ l, cryptococcus was negative and pressure higher than 400 mmHg. Brain MRI showed “multiple lesions, infectious disease should be considered and tuberculosis is more likely”. T-spot test was positive. Acid fast stain of sputum, smear of fiberoptic bronchoscope-lung-brush and alveolar lavage fluid as well as the detection of *Mycobacterium tuberculosis* was all negative.

As it turned out that both case 1 and 2 received same treatment in the same clinic prior to admission, so the iatrogenic and disseminated infection of NTM had a higher possibility. Treatment regimen was changed into the combination of rifabutin (0.15 g/d), cefoxitin (6.0 g/d), azithromycin (0.5 g/d) and moxifloxacin (0.4 g/d), and her temperature was dropped to normal 0.5 month later. Reexamination of cerebrospinal fluid showed pressure was 200 mmHg, protein 706 mg/L, glucose 2.8 mmol/L, chloride 114 mmol/L. When headache and arthralgia were relieved, she was discharged from hospital. 6 days later, fast-growing mycobacteria was detected in the culture of CSF. Treatment regimen of Isoniazid (0.4 g/d), ethambutol (0.75 g/d), pyrazinamide (1.5 g/d), moxifloxacin (0.4 g/d), rifabutin (0.3 g/d) was continued. A follow-up chest CT showed “obvious absorption of lesions” 4 months after her discharge.

Case 3

A 54-year-old man who was suffered from repeated pain in both knees caused by trauma, he received acupuncture and intracavitary injection of drugs in a local clinic for 2 months but without obvious improvement. Swelling and pain in joints were reoccurred after the end of the course. MRI indicated “injury and swelling of soft tissue in medial collateral ligament and medial retinaculum of left knee joint, marked effusion existed in suprapatellar bursa”, he was diagnosed as arthroedema and treated with articular cavity puncture. The remove of bloody fluid did slight improvement. High fever (40) accompanied with chills, headache, slightly cough and sputum were occurred 1 month prior to admission. Pulmonary CT scan showed “diffuse lesion in both lungs” (Figure 3A). The patient was admitted under the circumstances of persistent fever and suppuration in left knee.

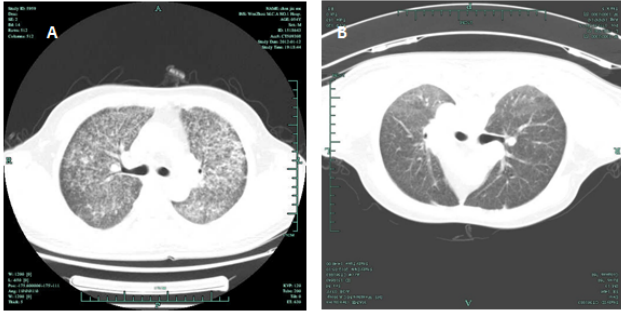


Figure 3. (A) Diffuse lesions in middle lobe and posterior segment of lower lobe in lungs; (B) Obvious absorption of diffuse lesions after treatment.

Physical examination revealed that both knees appeared swelling and redness, the left knee joint also with purulent secretion (Figure 4). Linezolid (1.2 g/d) and levofloxacin (0.5 g/d) were used, and yellow pus was cleaned, positive by acid fast stain. T-spot test showed positive. Since he received local acupuncture and injection in the same clinic with previous two patients, coupled with his chest CT scan result, negative in sputum acid-fast stain and positive in synovial fluid acid-fast stain, it could be suspected that the infection was caused by hematogenous dissemination after infection of NTM in knees. Then, he was further treated with azithromycin (0.5 g/d), isoniazid (0.6 g/d, injection 1 day later), ethambutol (1.0 g/d) and cefoxitin (6.0 g/d). Rifabutin (0.3 g/d) were added based on the smear results of paracentesis fluid. His temperature was gradually dropped to normal while sinus was still existed in the right knee. The continued combination treatment of cefoxitin (4.0 g/d), clarithromycin, rifabutin, isoniazid and ethambutol was used. Then he received arthroscopic treatment, obvious absorption of diffuse lesions in both lungs was observed by chest CT (Figure 3B).

Case 4

A 73-year-old women, she had suffered from osteoarthritis for more than 10 years and received irregular acupuncture and moxibustion as well as local injection of drugs in a local clinic. The anti-infective therapy was ineffective, and then she was admitted to hospital and diagnosed as "pulmonary infection, tuberculosis, acute respiratory distress syndrome (ARDS), respiratory failure". She was given ventilation assisted by bilevel positive airway pressure and meropenem (2.0 g/d). At the 11th day after admission, she developed fever and swelling, pressing pain in the left knee. Meropenem was replaced by sulperazone based on the culture result of baumannii in sputum, but it was stopped due to the allergic reaction. T-spot result was positive, fiberoptic bronchoscope brushing examination and culture result of bronchial lavage were negative. At the 18th day after admission, her temperature recovered to normal, puncture of the left knee joint was preformed again and the acid fast stain was positive. Then, the combination of isoniazid (0.6 g/d), pyrazinamide (1.5 g/d), ethambutol (0.75 g/d), rifampicin (0.45 g/d) and levofloxacin (0.5 g/d) was given. The patient's symptoms have improved evidently. Chest CT

indicated a partial absorption of diffuse lesions in both lungs. Treatment was lasted for 19 months with HRZE regimen and levofloxacin (0.5 g/d) (Figure 4).

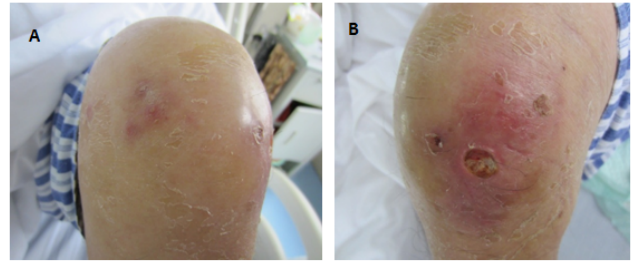


Figure 4. (A) Local redness and swelling in left knee joint; (B) Local redness and swelling accompanied with ulceration in left knee joint, and fistula was formed.

Discussion

Though more attentions were paid to NTM infection, its diagnosis and treatment were still difficult [8]. NTM infection mainly occurred in lungs and lymph nodes, rarely in soft tissues, bones, joints and skin [9]. It was pathogenic to human body regardless the status of immune system [10]. Water, soil and aerosols were the primary routes of NTM infection, and there were multiple transmission routes. Chronic respiratory tract infection commonly occurred by *M. abscessus*, *M. avium complex*, *M. kansasii*, *M. simiae*, etc, meanwhile the traumatic and iatrogenic infection were usually occurred by *M. fortuitum*, *M. neoaurum*, etc [11].

Both the 4 patients had a medical history of local skin puncture and received pre-hospital treatment in the same clinic. It could be speculated that the unqualified sterilization before puncture might be the source of NTM infection and contribute to the progression of DDNTM. As there were few studies reported the outbreaks of NTM caused by acupuncture, this study will arouse the concerns of clinicians on the sterilization of acupuncture.

For patients who were suffered from NTM infection, their symptoms were inconspicuous or un-obvious, and often accompanied with chronic cough, sputum even hemoptysis. 30%-50% patients had low fever, night sweats and weight loss which the symptoms were similar with that of tuberculosis infection. Take the low sensitivity and specificity of NTM clinical symptoms into consideration, their medical history and medical image reports were essential for the diagnosis of NTM infection.

From this report, the patients mentioned above had the following characteristics, (i) all of them were treated with local puncture and intracavitary injection in the same local clinic during the same time period; (ii) all of them suffered from fever, inflamed hot pain and abscess in skin, soft tissue, muscle or joint, and conventional antibiotic therapy obtained a poor effect; (iii) diffuse lesions in lungs were observed. Miliary nodules existed in 3 cases, the other one was diagnosed as diffuse ground-glass opacity, her manifestations including bronchiectasis with multiple nodules and "tree-in-bud" in

ligule or middle lobe, as well as cavity-like changes and isolated nodular shadows; (iv) both of them had abscess and partial necrosis in the position of local puncture and joint, their pathological results revealed caseous necrosis and granuloma-like changes (Figure 2); (v) T-spot tests were positive; (vi) Acid-fast bacilli (1-3 +); (vii) positive in fast-growing mycobacteria for the secretions of injury site. The anti-tuberculous therapy was used as the first-line treatment, but the effect was unsatisfactory, and their temperatures were stayed high.

After the diagnosis of Case 1, more attentions were paid to the medical record collections and epidemiological characteristics of Case 2-4. Their situations were greatly improved when the treatment was changed and aimed at NTM infection. The following performances and clues were helpful in their diagnosis, (i) acid-fast stain assay of secretion and sputum was positive, the clinical manifestations were different from pulmonary tuberculosis; (ii) the shape of acid-fast bacillus might help to differentiate NTM from other mycobacterium tuberculosis after culturing, bead type or curved and short rod-like shaped were common in the former (Figure 1); (iii) the fast growing of NTM was different from the complex of mycobacterium tuberculosis; (iv) delayed healing of injury in soft tissue or surgical postoperative wound for a long time without definite reasons.

There were no effective and specific drugs to resist NTM infection currently. Many NTM had natural resistance to first-line anti-tuberculosis drugs and the resistance rate was up to 100% [11]. For most patients suffered from pulmonary disease caused by *Mycobacterium avium-intracellulare* complex with nodules or bronchiectasis, clarithromycin 1000 mg/kg or azithromycin 500 mg/kg or the combination of rifampicin 600 mg/kg and ethambutol 25 mg/kg 3 times a week was recommended. For pulmonary disease caused by *Kansas mycobacterium*, isoniazid 300 mg·kg⁻¹·d⁻¹, rifampicin 600 mg·kg⁻¹·d⁻¹ combined with ethambutol 15 mg·kg⁻¹·d⁻¹ was recommended until sputum culture converted for 1 year. The therapy for non-pulmonary disease caused by fast-growing mycobacteria (including *M. Abscessus* and *M. chelonae*) should base on the sensitive test *in vitro*. Surgical debridement should be performed as soon as possible [12], it gained better effect than simple medication. In the absence of effective treatment to NTM, early surgical intervention was necessary if local abscess or dead space was occurred [13].

NTM infection has been reported in cosmetic surgery and folk therapy previously [14]. Disseminated NTM infection caused by local puncture in a patient without immunodeficiency was little reported [15]. The clinical manifestation of NTM infection is atypical, it usually misdiagnosed as tuberculosis mycobacteria [6,16]. In this study, relaxed disinfection during the operation caused the iatrogenic infection and further led to the serious systemic dissemination, as well as persistent refractory, which brought great pain and economic burden to patients. Strict disinfection and standard operating procedures should be paid great attentions in the process of clinical diagnosis and treatment, health authorities should strengthen

management and hospitals should prevent the iatrogenic infection of NTM.

Competing Interest

The authors indicated no potential conflicts of interest.

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