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Enlarging Tuberculous Lymph Node Despite Treatment: Improving or Deteriorating?

LPY ***Lee,*** WK ***Chiu,*** HB ***Chan***

Abstract Tuberculous lymphadenitis is not uncommonly diagnosed in children with cervical lymphadenopathy and fever. Despite effective treatment by anti-tuberculosis therapy, the tuberculous lymph nodes can paradoxically increase in size after initial clinical improvement. This phenomenon of paradoxical reaction during treatment is common among patients with extra-pulmonary tuberculosis. We report a case of tuberculous lymphadenitis, the disease course of which was complicated by paradoxical reaction. The clinical features, pathogenesis, diagnosis and management of paradoxical reaction were highlighted.

Key words Children; Lymphadenitis; Paradoxical reaction; Tuberculosis

Case Report

A 11-year-old boy of 55 kg with 10 days of fever had a right supraclavicular mass of increasing size for three months. Neck examination showed two large right supraclavicular lymph nodes which were matted together. Their sizes were measured 3 cm times 3.5 cm and 3 cm times 3 cm respectively. The lymph nodes were firm, non-tender and were fixed to the underlying structures. There was no overlying skin change. The boy had no BCG scar. Chest X-ray was normal. Fine needle aspiration biopsy yielded positive acid-fast bacilli (AFB) smear and positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*. Histological examination of the lymph node tissue supported the diagnosis of tuberculous lymphadenitis with clusters of granulomatous inflammation and presence of acid-fast bacilli by Ziehl-Neelsen (ZN) stain. The anti-HIV antibody was negative. The boy was treated with isoniazid 300 mg daily, rifampicin 600 mg daily, pyrazinamide 2 g daily and ethambutol 800 mg daily. *Mycobacterium tuberculosis* was isolated from lymph node tissue and was susceptible to isonizid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). His fever subsided in five days and his lymph nodes decreased in size two weeks after treatment. He also showed weight gain within four weeks.

Eight weeks after treatment, the right supraclavicular lymph nodes increased in size again. It ruptured and ulcerated, with pus. Surgical debridement was performed and the pus was both negative for acid-fast bacilli in smear and *Mycobacterium tuberculosis* by PCR. Bacterial culture of the lymph node discharge was negative. Chest X-ray at that time showed prominent right perihilar opacity. Computed tomography of the neck and upper thorax revealed large right superior mediastinal lymph nodes which were matted together (Figures 1 and 2). A diagnosis of paradoxical inflammatory response was made, involving lymph nodes of the original site and another newly identified anatomical site. Oral prednisolone 1 mg/kg/day was given and it was tapered over three months, meanwhile the anti-tuberculosis therapy was continued for a total of 9 months (2 months of HRZE and 7 more months of HR). A prolonged anti-tuberculosis therapy was adopted for extra-pulmonary tuberculosis. Subsequent chest X-rays showed a gradual decrease in size of the right perihilar opacity. The healing process of the suppurative lymph nodes was complete.

Department of Paediatrics and Adolescent Medicine, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Kowloon, Hong Kong, China

LPY **Lee** (李寶儀) *MBBS, MRCPCH*
WK **Chiu** (趙華強) *FHKCPaed, FHKAM (Paed)*
HB **Chan** (陳衍標) *FHKAM (Paed), FRCPCH*

Correspondence to: Dr. LPY **Lee**

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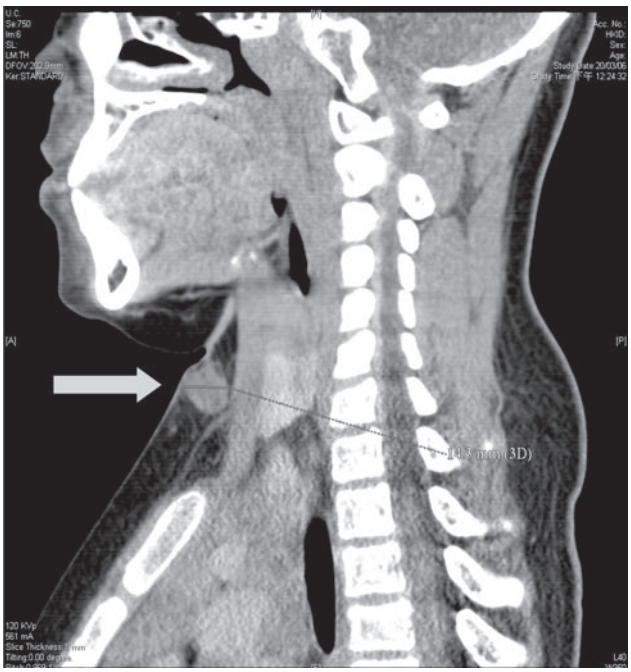

Figure 1 Sagittal view of the computed tomography of the neck showing impingement of the enlarged right supraclavicular lymph node on the overlying skin.

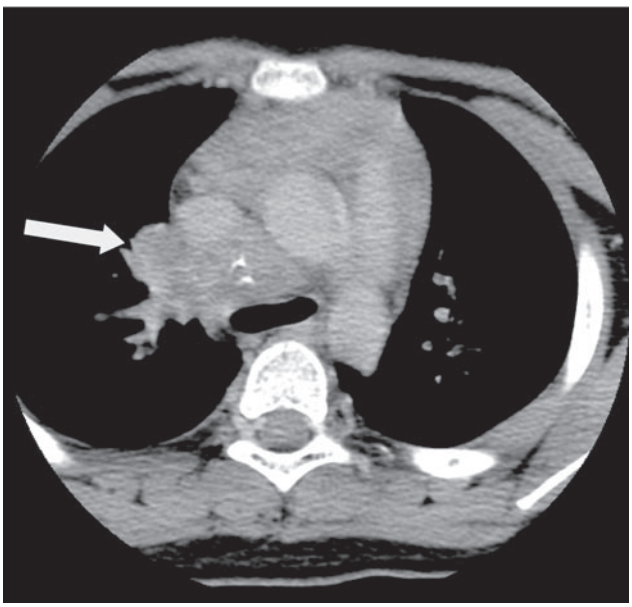

Figure 2 Axial view of computed tomography of the neck showing enlarged right superior mediastinal lymph nodes which appear matted together.

Discussion

Tuberculous lymphadenitis is the most common extra-pulmonary manifestation of tuberculosis. In Hong Kong, from the Annual Report of Tuberculosis & Chest Service in 2004,[1] tuberculous lymphadenitis comprised 39.6% of all extra-pulmonary tuberculosis. Paradoxical reaction during anti-tuberculosis treatment is a well-known phenomenon first described in 1955 by Chloremis,[2] who reported that children receiving anti-tuberculosis treatment occasionally developed exacerbation of fever and worsening X-ray findings. Paradoxical reaction during anti-tuberculosis therapy is defined as the clinical or radiological worsening of pre-existing tuberculous lesions or development of new lesions in a patient who initially improves with anti-tuberculosis therapy,[3] in the absence of disease relapse. It occurred in about 11-15% of patients with tuberculosis.[4] Though occurring commonly among HIV-positive patients, paradoxical reaction can occur in HIV-negative individuals including children.

Paradoxical reaction is seen frequently in those with extra-pulmonary tuberculosis and disseminated tuberculosis.[3-5] In a review of 122 episodes of paradoxical deterioration in HIV-negative patients,[3] 82.8% patients were associated with extra-pulmonary tuberculosis. Another study by Cheng et al[4] showed that age, sex and underlying co-morbidity posed no additional risk to the development of paradoxical reaction. Time of development of paradoxical reaction ranged from 14 to 270 days after initiation of anti-tuberculosis treatment.[3] Paradoxical reaction could manifest in both the initial site of infection and in any other anatomical sites. Central nervous system and respiratory system were commonly involved. Other commonly affected sites were cervical and mediastinal lymph nodes.[3] It was also reported to occur in bone, skin and soft tissue.[6]

Immunorestitution is believed to be a possible mechanism leading to paradoxical reaction.[4] Immunorestitution is defined as an acute symptomatic or paradoxical deterioration of a pre-existing infection that is temporally related to recovery of the immune system.[7] In 1977, Campbell and Dyson[8] proposed the rapid and significant reduction of mycobacterial load with anti-tuberculosis treatment causes release of large amounts of tuberculoprotein and other cell wall products. These materials then initiate a cascade of cellular and cytokine inflammatory response, leading to local tissue damage which can be extensive and severe. The clinical severity of

paradoxical reaction is dependent on the appropriateness of immune recovery.[7] An exaggerated immune recovery can result in excessive tissue damage. Immunorestitution is illustrated by the TB/HIV co-infected patients, who exhibit paradoxical reaction more commonly than the HIV-negative patients. When highly active antiretroviral therapy (HAART) is administered together with anti-tuberculosis treatment, the significant reduction in HIV viral load and the increase in CD4-lymphocyte count reverse the immunosuppressive state,[9] and thus trigger on the cascade of local inflammatory reactions towards the *M. tuberculosis* remnants.

Diagnosis of paradoxical reaction is made by exclusion.[3] This condition often poses diagnostic difficulty to attending physicians. Investigations should be performed to rule out differential diagnosis like secondary infection, inadequate treatment due to drug resistance and poor drug compliance.

In case of secondary local infection with a background history of tuberculosis under treatment, the child should show clinical improvement with improved appetite, weight gain and less fatigue. Detailed history taking on any previous episodes of major infections and family history of similar presentation is important to exclude the possibility of primary immunodeficiencies, which can lead to recurrent cervical lymphadenitis. A thorough physical examination is necessary to look for other causes of cervical lymphadenopathy, in particular any focus of infection at the head and neck region. Pyogenic lymphadenitis should be hot and tender; whereas suppurative tuberculous lymphadenitis gives rise to cold abscess. Elevation of total white cell count and inflammatory markers like erythrocyte-sediment rate (ESR) and C-reactive protein are non-specific because their elevation can be contributed by both secondary infection and paradoxical reaction. Fine needle aspiration (FNA) is indicated to exclude alternative diagnosis. Specimens showing acute suppurative inflammatory changes are suggestive of pyogenic lymphadenitis. The suppurative change can co-exist with residual caseating granuloma which is the feature of tuberculous lymphadenitis.[10] The aspirate from FNA can also be sent for bacterial culture and sensitivity to look for secondary infection.

Chest radiograph and computed tomography of thorax are useful to study the extent of disease because mediastinum and pleura are common site of paradoxical involvement. Imaging study is also helpful to exclude thoracic malignancy that presents with cervical lymphadenopathy.

First-line antituberculosis agents including isoniazid, rifampicin, pyrazinamide and ethambutol are prescribed for children diagnosed of extra-pulmonary tuberculosis. In Hong Kong, the overall prevalence of multi-drug resistant tuberculosis is very low (<1%).[1] Therefore, treatment failure due to drug resistance should be less likely. The prevalence of drug resistance varies among different countries. It takes time to wait for the mycobacterial culture and sensitivity result. A quicker way to assess treatment response is to repeat FNA of the enlarged lymph node for Ziehl-Neelsen staining to look for AFB. Clearing up of AFB in smear indicates positive treatment response. On the contrary, demonstration of AFB does not necessarily mean treatment failure since the organisms may only represent non-viable corpses unless significantly increased AFB count is demonstrated in the presence of unresolving symptoms. Diagnostic accuracy of FNA for smear and culture in tuberculous lymphadenitis is high, with specificity and positive predictive value of both 100% and negative predictive value of 94%.[11] The role of PCR in repeated FNA is not outstanding since the dead mycobacterial material can contribute to positive PCR. Excisional biopsy and FNA are similarly effective in obtaining tissue for cytological and microbiological analysis.[12] Excisional biopsy is not recommended unless FNA examination is inconclusive as it is more invasive, technically demanding if the lymph nodes are matted together, and incomplete evacuation of all infected tissues may result in persistent discharging sinus or poor wound healing.

Provided that drug administration is supervised by a well-informed and responsible adult, drug compliance and hence acquired drug resistance is usually not a great problem in paediatric patients who generally suffer from paucibacillary disease. Nevertheless, enquiry on compliance is needed.

In our patient, the diagnosis of tuberculous lymphadenitis was confirmed by positive AFB smear and culture, and typical pathological finding of tissues obtained by FNA. He showed initial good response to anti-tuberculosis treatment with shrinkage of the cervical lymph nodes and resolution of constitutional symptoms. His compliance to anti-tuberculosis drugs was good. Primary drug resistance was not an issue as the susceptibility result showed that the *M. tuberculosis* isolate was sensitive to the four prescribed anti-tuberculosis agents. Secondary infection was unlikely as the enlarged lymph nodes were non-tender, cold and were matted together. Bacterial culture of the discharge did not yield any pyogenic organism. The cervical lymph nodes and mediastinal lymph nodes enlarged at the same time. Secondary infection seldom affects two anatomical sites. Besides, the onset time and feature of deterioration

after an apparent improvement was compatible with paradoxical reaction.

An interesting observation in Cheng's review[3] may help in making diagnosis of paradoxical reaction. That was the low baseline lymphocyte count and it was followed by an upsurge during paradoxical reaction. This observation concurs with the proposed pathogenesis by immunorestitution. Mounting of inflammatory response involves an increase in number of circulating functional lymphocytes to the killed mycobacteria. However, an absence of lymphocyte upsurge does not exclude the diagnosis. In case of extremely severe immunorestitution, all the lymphocytes migrate to the site of restitution to produce severe tissue damage, leaving the circulating lymphocyte count constant.[4] In our patient, the initial lymphocyte count was normal (2.6×10^9/L) and there was no upsurge in lymphocyte count was noted during paradoxical deterioration (2.7×10^9/L). Further research is required whether serial monitoring of lymphocyte count is useful to predict development of paradoxical reaction.

Mild paradoxical reaction like recurrence of fever and enlargement of superficial lymph nodes does not require specific treatment and no alternation in the anti-tuberculosis regimen is needed.[3] For severe paradoxical reaction such as large intracranial tuberculoma causing obstructive hydrocephalus, massive pleural effusion and development of deep seated abscesses, a combination of medical and surgical treatment should be considered.[3] Medical treatment involves the use of a short course of high dose systemic steroids. However, there is no consensus on the suggested dosage and duration of systemic corticosteroids for treating paradoxical reaction. Clinical response was documented in case reports.[3,13] The use of systemic steroids in the presence of adequate anti-tuberculous drug coverage for the management of paradoxical reaction was safe and there were no reports of steroid-related complications.[3]

Conclusion

Paradoxical reaction is a common condition complicating the disease course of tuberculosis during treatment. It is diagnosed by exclusion, and therefore poses a clinical challenge to the attending physician. One should have a high index of suspicion when there is clinical deterioration, which can occur up to a few months after an initial improvement with anti-tuberculosis treatment, especially in case of extra-pulmonary or disseminated tuberculosis. Treatment is expectant and standard anti-tuberculosis regimen should be continued unless the paradoxical reaction is severe enough to warrant adjunctive medical therapy with or without additional surgical intervention. It is useful to discuss with parents at time of initial diagnosis that there is about 11-15% possibility of paradoxical deterioration despite effective treatment. This helps to relieve doubt and worry when there is deterioration after an apparent clinical improvement.

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