Unexpected outcome (positive or negative) including adverse drug reactions

Acute paradoxical reaction of cervical tuberculous lymphadenitis prompted by a misuse of etimicin sulphate

Yang Jiao, Jialin Chen, Xuejun Zeng

Department of General Internal Medicine, Peking Union Medical College Hospital & Chinese Academy of Medical Sciences, Beijing, China

Correspondence to Dr Yang Jiao, peterpumc@hotmail.com

Summary

A 45-year-old HIV-negative man was treated with intravenous etimicin sulphate for an unintentionally found, non-tender neck mass at a local outpatient clinic. His symptoms seemed improved initially. However, the unilateral mass subsequently became enlarged quickly and painful. Spontaneous discharge occurred after admission to our department. The smear of the pus from surgical drainage was positive for acid-fast bacilli and the presence of *Mycobacterium tuberculosis* was confirmed by culture. He was diagnosed with an acute paradoxical reaction (PR) of cervical tuberculous lymphadenitis. Our case was unusual in that acute PR of tuberculosis was caused by receiving single aminoglycoside agent which has not been proven to have therapeutic effect on TB infection and it is also the first case of PR induced by etimicin. The patient recovered well from a 6-month antituberculosis chemotherapy.

BACKGROUND

A paradoxical reaction (PR) is defined as the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions in a patient who initially improves during antituberculosis (TB) treatment.¹ Among non-HIV-infected patients with peripheral tuberculous lymphadenitis, PR may occur in around 20% patients at an average onset time of 2–3.5 months after initiation of standard antiTB therapy.^{2–3} Etimicin sulphate is an ethylisation derivative of gentamicin. It is the newest generation of the aminoglycosides and has a broad-spectrum antibacterium effect.^{4–5} Although selected aminoglycosides, such as streptomycin, are known to have activity against TB infections, no clinical evidence is available on whether etimicin is sensitive on *Mycobacterium tuberculosis*. Here, we report a rare case of acute PR of TB in an HIV-negative patient receiving single aminoglycoside agent and it is also the first case of PR induced by etimicin.

CASE PRESENTATION

In May 2010, a 45-year-old man presented to a local outpatient clinic with an unintentionally found, unilateral neck mass. It was non-tender and located in left submandibular region. The patient also had middle-grade fever and malaise. He denied cough, chills or night sweats. The result of complete blood count showed neutrocyte count was slightly elevated. Intravenous administration of 300 mg of etimicin sulphate once daily was commenced for a week without any other diagnostic investigation at that clinic. For the first 2 days, his fever improved with the peak temperature dropping from 38.8°C to 37.5°C. However, his symptoms got worse subsequently and the neck mass started to become indurated and painful. He presented to our department a week after the antibiotic treatment with the lump enlarging swiftly from original 3×3 to 9×8 cm² in size. The patient had been given BCG

Figure 1 Paradoxical deterioration of cervical tuberculous lymphadenitis with caseous pus discharging.

vaccination. He was a heavy smoker with a good socioeconomic status and reported no other medical history.

INVESTIGATIONS

On admission, physical examination revealed a firm mass fixed to surrounding structures on his left neck and the overlying skin was reddish. No enlarged peripheral lymph nodes elsewhere were found. His neutrocyte and lymphocyte counts were $7.3 \times 10^9/l$ and $2.0 \times 10^9/l$, respectively. Erythrocyte sedimentation rate was 79 mm on 1st h. Blood cultures for bacterial, TB and fungal infection were all negative. Cytomegalovirus, Epstein–Barr virus

(EBV), hepatitis B Virus, hepatitis C virus and HIV-specific antibodies were negative. Cytomegalovirus-DNA and EBV-DNA were undetectable. No atypical lymphocytosis was identified on the peripheral smear. Both tuberculin skin test and interferon γ release assay (TB-spot) were positive. Ultrasonography showed multiple heterogeneously hypoechoic lesions with defined margins in the left submandibular area. CT scanning of the chest showed only apical fibrosis and no evidence of active infection. Fine needle aspirate was obtained. However, the smear was negative for acid-fast bacilli (AFB). His neck mass kept enlarging quickly and broke itself with purulent discharging a week after admission (figure 1). Surgical drainage yielded 20 ml of pus. AFB smear of the pus was positive and subsequent culture result was positive for *M tuberculosis*. *M tuberculosis* antibiotic sensitivity testing was not available in our hospital. The patient was diagnosed with an acute PR of cervical tuberculous lymphadenitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of unilateral cervical lymphadenopathy includes mainly lymphoma, sarcoidosis and other infections, for example, non-tuberculous Mycobacteria infection, viral infection, fungal infection and bacterial infection. Confirmation of the diagnosis depends on histopathologic and microbiological findings.

There is yet no reliable diagnostic tool to predict or substantiate PR during antiTB therapy. To establish the clinical diagnosis will depend on excluding other possible differential diagnoses such as another infection, treatment failure due to resistance or non-compliance, and adverse drug reactions.

TREATMENT

The patient presented to our department with high fever and painful, swollen neck mass. Ultrasonography result suggested the possibility of abscess in the mass. Non-steroidal anti-inflammatory drugs (NSAIDs) were used for the anti-inflammatory and analgesic effects. However, there is no consensus on the use of NSAIDs in the management of PR. After positive smear result was received, the patient was treated with standard antiTB chemotherapy consisting of isoniazid, rifampicin and ethambutol.

OUTCOME AND FOLLOW-UP

The next day after the surgical drainage, the patient's temperature got normalised. He was transferred to a hospital special for communicable diseases and received a 6-month treatment under direct observation. When followed up in October, 2011, he recovered well after entire therapy with no fistula left on the neck.

DISCUSSION

PR has been commonly reported in HIV and TB co-infected patients receiving highly active antiretroviral therapy.⁶

The deterioration of clinical symptoms may also occur in 20~25% of the HIV-uninfected patients undergoing antiTB therapy.^{2,7} The underlying mechanism of PR is still unclear. Researches on immune reconstitution inflammatory syndrome among HIV and TB co-infected cases suggested that the PR might reflect host immunologic reactions to antigens from dying *M tuberculosis* organisms.⁶ Limited information is available on the risk factors for the PR of peripheral tuberculous lymphadenitis in HIV-uninfected patients. Several case-control studies have demonstrated that younger age, male gender, local tenderness of lymph node and higher peripheral blood monocytes at baseline might be predictive for the PR in HIV-negative patients with peripheral tuberculous lymphadenitis.^{2,7} However, none of the factors have been proven clinically useful till date.

Peripheral tuberculous lymphadenitis is one of the most common forms of extrapulmonary TB. Patients with cervical tuberculous lymphadenitis usually present with gradually enlarging, painless and non-tender cervical lymph nodes, which may exist for at most 1 year before diagnosis.⁸ When the PR of peripheral tuberculous lymphadenitis appears during antiTB therapy, worsening symptoms mainly include lymph node enlargement on previously improved lesions or new lesions, or discharging sinus.³ However, it is difficult to carry out the differentiation based only on presenting symptoms. A PR could occur anywhere from several days to many months after the initiation of antiTB chemotherapy. It is still unpredictable in its timing and lack of a reliable diagnostic or predictive tool makes the diagnosis of PR a clinical challenge.

The misuse of antibiotics is very common in Mainland China. The exact reason remained unclear why etimicin was chosen for treatment without any diagnostic investigation results at the very beginning. Selected aminoglycosides have been used in the treatment of TB infection. However, no evidences have shown that etimicin is effective in controlling *M tuberculosis* infection. Hence our case could not be defined as a typical case of PR of TB infection. Acute clinical deterioration occurred before receiving standard antiTB therapy. Cervical tuberculous lymphadenitis could be diagnosed based on the positive microbiological findings. However, the patient's symptoms and the course of disease could not be fully explained by TB infection. The possibility of antiTB treatment failure due to drug resistance or non-compliance could be obviously excluded. Microbiological evaluation excluded the possibility of other infection and temporal correlation in clinical features helped to exclude the flare of TB infection and adverse drug reactions. Clinical symptoms, the result of ultrasonography and the prognosis strongly suggested that it was a course of PR. It is unknown whether higher potency of chemotherapy predisposes patients to the development of PR or which factors are associated with the severity of PR. The mechanism on how the acute PR in our case was triggered by etimicin remains unclear. However, our unintentional finding may indicate that etimicin might have potential therapeutic effect on TB infection.

Learning points

- ▶ No reliable test is available to predict or substantiate the diagnosis of PR. To establish the clinical diagnosis will depend on excluding other possible differential diagnoses.
- ▶ The PR of TB has been commonly reported in HIV and TB co-infected patients receiving highly active antiretroviral therapy. It may also occur in around 20% non-HIV-infected patients with peripheral tuberculous lymphadenitis during antiTB therapy.
- ▶ Although no clinical evidence demonstrated that the drug potency of antiTB therapy was related with the incidence or severity of PR, the finding of our case may hinted that as the newest generation of the aminoglycosides, etimicin sulphate may have activity against TB infection, which will be worth further exploring.

Acknowledgements This work was supported by Beijing Nova Program (grant number. 2008B49).

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Cheng VC**, Ho PL, Lee RA, *et al*. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002;**21**:803–9.
2. **Cho OH**, Park KH, Kim T, *et al*. Paradoxical responses in non-HIV-infected patients with peripheral lymph node tuberculosis. *J Infect* 2009;**59**:56–61.
3. **Polesky A**, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. *Medicine (Baltimore)* 2005;**84**:350–62.
4. **Xi L**, Wu G, Zhu Y. Analysis of etimicin sulfate by liquid chromatography with pulsed amperometric detection. *J Chromatogr A* 2006;**1115**:202–7.
5. **Zhao C**, Li J, Hou J, *et al*. A randomized controlled clinical trial on etimicin, a new aminoglycoside antibiotic, versus netilmicin in the treatment of bacterial infections. *Chin Med J* 2000;**113**:1026–30.
6. **Breen RA**, Smith CJ, Bettinson H, *et al*. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004;**59**:704–7.
7. **Hawkey CR**, Yap T, Pereira J, *et al*. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. *Clin Infect Dis* 2005;**40**:1368–71.
8. **Mert A**, Tabak F, Ozaras R, *et al*. Tuberculous lymphadenopathy in adults: a review of 35 cases. *Acta Chir Belg* 2002;**102**:118–21.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Jiao Y, Chen J, Zeng X. Acute paradoxical reaction of cervical tuberculous lymphadenitis prompted by a misuse of etimicin sulphate.

BMJ Case Reports 2012;10.1136/bcr.12.2011.5458, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow

Keep up to date with all published cases by signing up for an alert (all we need is your email address) <http://casereports.bmj.com/cgi/alerts/etoc>