

Paradoxical response as a cervical lymph node enlargement after termination of anti-tuberculosis treatment in a patient with pulmonary tuberculosis

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A paradoxical response is not uncommon in non-HIV-infected patients, particularly those with extra-pulmonary tuberculosis. It is defined as the radiological and clinical worsening of a previous lesion or the development of new lesion during anti-tuberculosis therapy. The paradoxical response has been attributed to host immunologic reactions, such as a delayed hypersensitivity or a response to mycobacterial antigens. In most reports of paradoxical response, these responses occurred in the same location as a previous lesion. In this patient with pulmonary tuberculosis, cervical lymph node enlargement occurred as a paradoxical response after the completion of anti-tuberculosis treatment. Although the new lesion developed in another location, it could be considered as a paradoxical response based on the negative culture result of acid fast bacilli from the new lesion and drug sensitivity result from initial bronchoalveolar lavage specimen. Therefore we were able to decide on the termination of unnecessary anti-tuberculous treatment. Based on our case, we can conclude that paradoxical response can occur after the termination of anti-tuberculosis therapy even in new site.

Key Words: Diagnosis, Extra-pulmonary tuberculosis, Paradoxical response

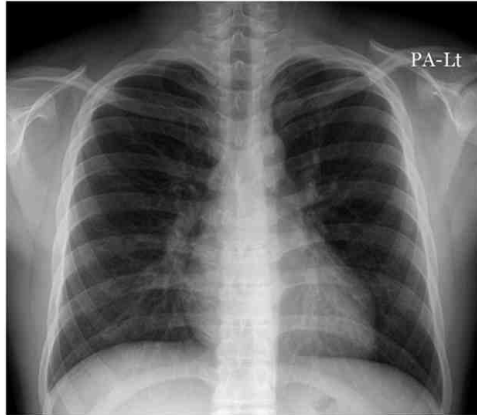
Paradoxical response in patients with tuberculosis refers to the occurrence of a new lesion or deterioration of the former lesion with no evidence of treatment failure and other secondary infection aside from tuberculosis.¹⁻⁴ Paradoxical response occurs in 20-30% of patients receiving tuberculosis treatment, and its cause has not yet been clearly revealed. But in general, it is accepted as a cell-mediated re-

sponse that occurs when the repressed immunity of the antigen removed from tubercle bacilli is recovered, activating a host reaction.¹⁻⁵ Paradoxical response usually occurs in the early stage of treatment, and is naturally recovered as the treatment continues. But paradoxical response sometimes occurs after treatment, which is often mistaken for deterioration related to tuberculosis.^{2,4} In particular, if paradoxical re-

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(A)



(B)



Fig. 1. Posteroanterior (A) and left lateral (B) chest radiograph shows irregular linear opacities in left upper lung field.

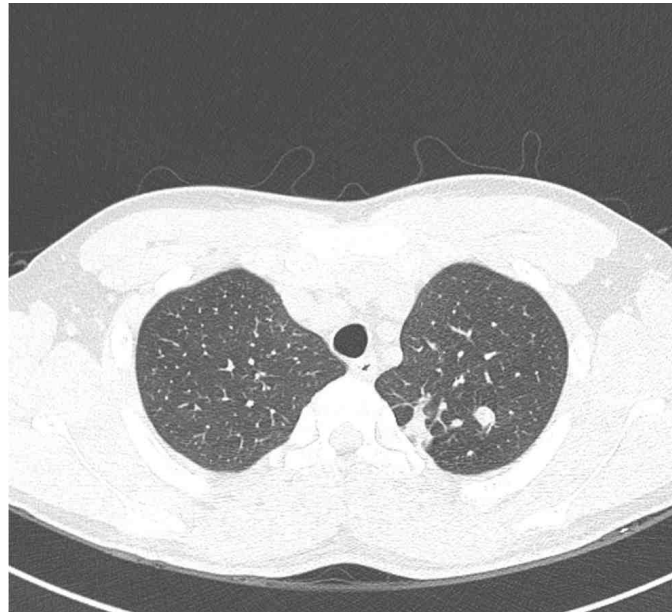


Fig. 2. High-resolution CT image (1.0-mm section thickness) shows irregular fibronodular opacities in apicopost. segment of the left upper lobe. In high-resolution CT image, mediastinal lymph node enlargement is not observed.

sponse occurs in other areas after terminating anti-tuberculosis treatment, it is difficult to clinically determine. The authors have experienced a case in which paradoxical response occurred in the form of cervical lymph node enlargement after anti-tuberculosis treatment.

CASE

A 19-year-old male patient visited the hospital after showing signs of tuberculosis in a plain chest

radiograph during contact investigation at another hospital (Fig. 1). He had no unusual past medical history, and no symptoms of pulmonary diseases. There were also no abnormalities in physical examination. His mother was diagnosed with tuberculosis and was in treatment. There were no other abnormalities aside from the shading in the form of irregular fiber tubercle on the left upper lobe in chest CT. Bronchoalveolar lavage was performed on this area (Fig. 2). A month later, tubercle bacilli grew on the liquid medium, and the patient was given isoniazid, rifampin, ethambutol and pyrazinamide. The result of the drug sensitivity test performed later showed that the patient was sensitive to all drugs for tuberculosis. After 2

months of treatment, the drugs were changed to isoniazid and rifampin according to the drug sensitivity test result, after which there were no drug side effects, and the treatment was terminated after 4 months. Tubercle bacilli did not grow on the sputum examination that was in longitudinal tracking.

A month after the termination of the treatment, enlargement of the right cervical lymph node was observed, and the patient complained of pain and oppressive pain on the cervical lymph node. A cervical lymph node biopsy was performed in the department of otolaryngology, and chronic granulomatous inflammation accompanied by caseous necrosis was observed (Fig.

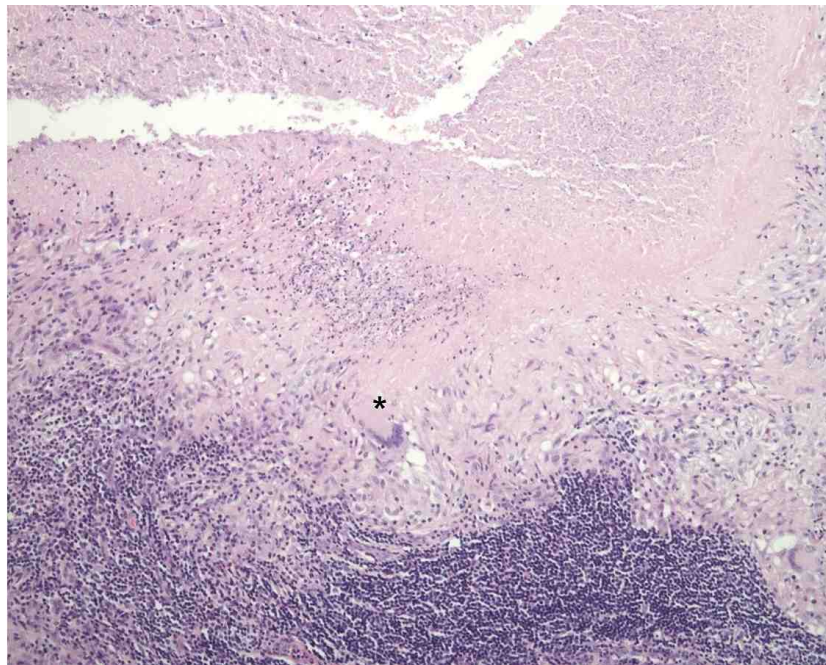


Fig. 3. Postoperative histopathology. Chronic granulomatous inflammation with central caseous necrosis (upper half) is noted which is surrounded by epithelioid histiocytes with Langhans giant cell (*) and lymphocytes in outermost layer. (H&E, x 200)

3). The test of the acid fast bacilli smear from the tissue showed a negative result, and tuberculosis polymerase chain reaction was positive. Isoniazid, rifampin, ethambutol, and pyrazinamide were given again as there is a possibility of tuberculosis recurrence, and continuation of drug treatment was to be determined by the result of the tissue culture test. A month later, there was constant drainage in the cervical lymph node biopsy and no improvement, so lymphadenectomy was performed again on this area. The lymphadenectomy result was equivalent to the biopsy result. Two months after the retreatment, the result of the tuberculosis culture test performed on the tissues obtained from cervical lymph node biopsy and lymphadenectomy showed that there were no tubercle bacilli growing. The patient was diagnosed with paradoxical response, and all anti-tuberculosis treatment was terminated.

There was no recurrence in the longitudinal tracking of chest x-ray, and also no recurrence of extrapulmonary tuberculosis such as lymph node enlargement; thus, the patient is in longitudinal tracking without medication.

DISCUSSION

Paradoxical response is the deterioration of a

former lesion or the creation of a new lesion during anti-tuberculosis treatment. The cause for this has not yet been clearly revealed, but generally it is considered an immune response of the host to tuberculosis antigen generated by the recovery of immunity after anti-tuberculosis treatment.¹⁻⁵ It occurs mostly in tuberculosis of patients with human immunodeficiency virus, or in extrapulmonary tuberculosis if the patient is not immunodeficient.¹⁻⁴ Paradoxical response commonly occurs during anti-tuberculosis treatment, but also in rare cases can occur after the termination of treatment.^{4,6-8} The clinical significance of paradoxical response is that it can bring confusion to anti-tuberculosis treatment.⁹⁻¹² The prevalence rate of multidrug-resistant tuberculosis in Korea is as high as 2.9% in new tuberculosis, and considering that it takes weeks and even months to obtain the results of drug sensitivity tests, it is not easy to identify the failure of treatment due to paradoxical response and drug-resistant tuberculosis when there is paradoxical response.^{13,14} In particular, if paradoxical response occurs after treatment, it is difficult to determine whether it is a recurrence of tuberculosis or a paradoxical response. This case also showed a deterioration of the lesion after anti-tuberculosis treatment and could not exclude the possibility of tuberculosis recurrence, and thus a biopsy was performed. It is necessary to perform

germiculture again in the lesion in order to verify paradoxical response.^{1-2,4} This case also performed tissue culture in cervical lymph node enlargement, and was diagnosed as paradoxical response since tubercle bacilli were not identified in the tissue culture.

In this case, paradoxical response occurred in the form of a lymph node enlargement after anti-tuberculosis treatment. Most paradoxical responses occur in the same area. For example, there is enlargement in other lymph nodes in the case of lymph node tuberculosis, or an increase in pleural fluids in the case of tuberculous pleurisy. But in this case, paradoxical response occurred in the form of extrapulmonary tuberculosis after anti-tuberculosis treatment. Tuberculosis may occur in the form of miliary tuberculosis, in which countless tubercles are observed in lungs or other organs as tubercle bacilli are spread to the whole body through blood circulation, or in the form of disseminated tuberculosis, in which tuberculosis occurs in two or more nonadjacent organs.^{15,16} Considering that tuberculosis polymerase chain reaction was positive, there is a possibility that a small amount of bacteria may have been in the lymph node when there was pulmonary tuberculosis. However, mediastinal lymph node enlargement was not observed in the chest CT in diagnosis, and cervical lymph node enlargement was also

not observed in the physical examination, which suggests that there were not enough bacteria to cause lymph node tuberculosis. In this case, tuberculosis polymerase chain reaction may be positive for a certain period of time, even after treatment. Thus, the remarks on lymph node biopsy in this case showed that tuberculosis polymerase chain reaction was positive, but mycobacterial smear and tubercle bacilli culture were negative. Of course, there was chronic granulomatous inflammation accompanied by caseous necrosis in the biopsy, but considering that this may be due to the powerful immune reaction of macrophage to a small quantity of bacteria, this case shall be diagnosed as a paradoxical response on cervical lymph node after termination of the anti-tuberculosis treatment. Previous studies also showed the same test results as this case.^{2,4,8} However, it is not easy to clinically determine this as a paradoxical response, and thus biopsy and culture were also performed to distinguish whether it is a tuberculosis recurrence or paradoxical response, and it was diagnosed as a paradoxical response as there were no bacteria growing in the tissue culture test. However, considering that it takes 1-2 months to obtain the result of the tissue culture test, it is not easy to discontinue anti-tuberculosis treatment and observe the progress. In particular, most paradoxical responses occur at the

early stage of anti-tuberculosis treatment, and thus it is difficult to discontinue anti-tuberculosis treatment and observe the progress if the paradoxical response occurred after the termination of the treatment, as shown in this case.¹⁻⁹ Thus, the authors also began anti-tuberculosis treatment again until the tissue culture test result was obtained, and could only discontinue the treatment after verifying from the test result that tubercle bacilli were not growing.

Considering that paradoxical response may occur in various forms, it is important to identify the tubercle bacilli when starting the first anti-tuberculosis treatment and obtain the drug sensitivity test results for the identified tubercle bacilli. Patients with tuberculosis that are sensitive to all anti-tuberculosis drugs are likely to show a paradoxical response to a new lesion that occurs later if they are properly treated with the four standard drugs. But if bacteria are not identified when the treatment first begins and thus there are no drug sensitivity test results, it is not easy to discontinue drugs in paradoxical response even if bacteria are not identified. As such, there is a need for efforts to identify bacteria in anti-tuberculosis treatment. In this case, anti-tuberculosis treatment was also provided again when the paradoxical response occurred since there was a possibility of tuberculosis recurrence, but bacteria were identified during anti-tuberculosis

treatment and it was verified that there was sensitivity to all drugs; thus, it was possible to discontinue the drugs immediately after checking the result that did not identify tubercle bacilli in the cervical lymph node. Moreover, while there are studies on risk factors for paradoxical response, the number of subjects is small and the risk factors varied slightly among the studies, and thus there are no clear risk factors revealed thus far.¹⁻⁴ A large-scale study on the risk factors of paradoxical response in the future will be helpful for clinical determination.

There are reports that steroids are helpful for treating paradoxical response, but in most cases it will improve naturally. In a study on patients with lymph node tuberculosis in Korea, 33 (91.7%) out of 36 patients showing paradoxical response improved naturally.⁴ It was reported that steroids are helpful for paradoxical response in some patients with tuberculous meningitis; thus, the use of steroids can be determined based on clinical aspects and area.¹⁷

Diseases that must be identified in cervical lymph node enlargement include virus diseases other than tuberculosis such as infectious mononucleosis, toxoplasmosis, Epstein-Barr virus, and cytomegalovirus diseases, as well as autoimmune diseases such as Kikuchi disease and Boeck's sarcoid. Therefore, biopsy is essential for diagnosis. In this case, it was easy to perform

a biopsy as it was a cervical lymph node enlargement, but it is difficult to test mediastinal lymph node enlargement. With the recent development of endobronchial ultrasounds, there are more and more tests for mediastinal lymph node enlargement but it is still not easy to decide to do the test considering its high cost.¹⁸ From that perspective, this case may provide evidentiary material for observation of progress without anti-tuberculosis treatment according to the area and degree of paradoxical response, since paradoxical response may occur in areas other than the lungs for patients with pulmonary tuberculosis.

In conclusion, paradoxical response may occur not only during but also after anti-tuberculosis treatment, and may occur in areas other than the lungs. Therefore, even if a new lesion occurs after the termination of treatment, it is necessary to perform an additional test considering the possibility of paradoxical response, rather than hastily judging it as a tuberculosis recurrence. Moreover, drug sensitivity test and drug compliance obtained in the first anti-tuberculosis treatment can be checked to help determine whether it is a recurrence or a paradoxical response.

REFERENCES

1. Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2007;11:1290-5.
2. Cho OH, Park KH, Kim T, Song EH, Jang EY, Lee EJ, et al. Paradoxical responses in non-HIV-infected patients with peripheral lymph node tuberculosis. *J Infect* 2009;59:56-61.
3. Jeon K, Choi WI, An JS, Lim SY, Kim WJ, Park GM, et al. Paradoxical response in HIV-negative patients with pleural tuberculosis: a retrospective multicentre study. *Int J Tuberc Lung Dis* 2012;16:846-51.
4. Park KH, Lee MS, Lee SO, Choi SH, Kim YS, Woo JH, et al. Incidence and outcomes of paradoxical lymph node enlargement after anti-tuberculosis therapy in non-HIV patients. *J Infect* 2013;67:408-15.
5. Marshall BG, Chambers MA. Central nervous system tuberculosis--the paradox of the host immune response. *J Infect* 1998;36:3-4.
6. Hawkey CR, Yap T, Pereira J, Moore DA, Davidson RN, Pasvol G, et al. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. *Clin Infect Dis* 2005;40:1368-71.
7. Polesky A, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. *Medicine* 2005;84:350-62.

8. Carter EJ, Mates S. Sudden enlargement of a deep cervical lymph node during and after treatment for pulmonary tuberculosis. *Chest* 1994;106:1896-98.
9. Kim JK, Jung TY, Lee KH, Kim SK. Radiological follow-up of a cerebral tuberculoma with a Paradoxical response mimicking a brain tumor. *J Korean Neurosurg Soc* 2015;57:307-10.
10. Park JH, Kim YH, Kwon CH, Shin HI. Paralysis developing as a paradoxical response during the treatment for tuberculous spondylitis: a case report. *Ann Rehabil Med* 2014;38:405-9.
11. Ruvinsky S, Rowenstein H, Taicz M, Paolillo A, Arroyo H, Rugilo C, et al. [Paradoxical reaction during tuberculosis treatment in immunocompetent children: case report]. *Rev Chilena Infectol* 2013;30:673-5.
12. Medina-Franco H, Pimienta-Ibarra AS, Dorantes-Heredia R, Nuñez-Gómez J, Pastor-Sifuentes FU. Paradoxical response to tuberculosis treatment producing bowel obstruction. *Int J Colorectal Dis* 2015;30:1749-50.
13. Park YS, Hong SJ, Boo YK, Hwang ES, Kim HJ, Cho SH, et al. The national status of tuberculosis using nationwide medical records survey of patients with tuberculosis in Korea. *Tuberc Respir Dis (Seoul)* 2012;73:48-55.
14. Joh JS, Lee CH, Lee JE, Park YK, Bai GH, Kim EC, et al. The interval between initiation of anti-tuberculosis treatment in patients with culture-positive pulmonary tuberculosis and receipt of drug-susceptibility test results. *J Korean Med Sci* 2007;22:26-9.
15. Sharma SK, Mohan A, Sharma A, Mitra DK. Miliary tuberculosis: new insights into an old disease. *Lancet Infect Dis* 2005;5:415-30.
16. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. *Tuberc Respir Dis (Seoul)* 2015;78:47-55.
17. Nema N, Verma A, Singh K, Mehar V. Management of paradoxical response in pediatric tubercular meningitis with methylprednisolone. *Middle East Afr J Ophthalmol* 2014;21:189-92.
18. Ko Y, Lee HY, Lee YS, Kim MY, Lee YM, Seon Kang M, et al. Esophagomediastinal fistula secondary to multidrug-resistant tuberculous mediastinal lymphadenitis. *Intern Med* 2014;53:1819-24.