LYMPHADENOPATHY DUE TO PARADOXICAL WORSENING OF MILIARY TUBERCULOSIS FOLLOWING RUBELLA INFECTION

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This is the first report of paradoxical worsening of miliary tuberculosis following rubella infection. We suspect that immunological mechanisms were impaired by rubella infection and pulmonary TB rapidly deteriorated thereafter. This paradoxical worsening of lymphadenopathy was refractory to antituberculous therapy without drug resistance.

Key words: paradoxical worsening, miliary tuberculosis (TB), rubella

INTRODUCTION

Tuberculosis (TB) of the lymph nodes is one of the most common forms of extrapulmonary TB. Transient worsening of tuberculous symptomatology and lesions in response to anti-TB therapy has previously been reported. Recently, paradoxical worsening of TB following antiretroviral therapy in AIDS patients was reported. We reported a case that some immunological deficiency due to a previous rubella infection might affect the paradoxical worsening of TB.

CASE REPORT

A 31-year-old woman with a high fever was referred to our hospital from a local hospital on December 21. She worked as a nurse and had contact with a pulmonary tuberculosis patient six months before admission to our hospital. On admission on November 27, the patient demonstrated a systemic rash and high fever. Plain chest radiograph on admission did not demonstrate any abnormal findings (Fig. a). The patient was diagnosed as having rubella based on an increase of rubella IgM antibody and characteristic symptoms. As she did not recover from high fever, prednisolone 40 mg was administered for two days. Although fever temporarily recovered to the normal range, high fever reoccurred and she was transferred to another hospital for further examination of miliary shadows on a chest imaging study performed on December 3. Transbronchial biopsy performed at the second hospital did not show any specific findings. However, since the possibility of miliary tuberculosis was very high, she was transferred to our hospital for diagnosis and treatment of pulmonary tuberculosis (TB). On admission to our hospital, temperature was 38.6°C, pulse rate was 88/min, and respiration rate was 18/min. Blood pressure was 110/70 mmHg. On December 5, she was diagnosed with miliary tuberculosis. She was treated with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) as first-line drugs. She received 6 months of treatment with HRZE. On December 15, she was discharged with no symptoms and with a good response to treatment.
physical examination, the patient was an underweight woman who appeared fatigued. She had no visible or palpable lymphadenopathy. White blood cell count was $\text{WBC} = 4,500 \, \text{cells/mm}^3$. Serum C-reactive protein was $\text{CRP} = 5.2 \, \text{mg/dl}$. Urinalysis was negative for protein, occult blood, glucose, cells and casts. Routine bacteriological, fungal, and mycobacteriological smears of sputum were negative. PCR polymerase chain reaction test for tuberculosis in sputum was positive and sputum culture showed *Mycobacterium tuberculosis*. The culture was positive only on admission, and cultures performed thereafter have been negative. Tuberculin skin test was positive. Plain chest radiograph demonstrated diffuse miliary shadowing [Fig. 1b]. CT scanning of the chest showed diffuse multiple miliary opacities [Fig. 1e]. Anti-TB drugs containing rifampicin $200 \, \text{mg/day}$, isoniazid $300 \, \text{mg/day}$, ethambutol $300 \, \text{mg/day}$ and pyrazinamide $500 \, \text{mg/day}$ were administered after admission. Because her general condition deteriorated, prednisolone $20 \, \text{mg/day}$ was added to anti-TB drugs. Mild liver dysfunction appeared and pyrazinamide was discontinued on January 1. Her general condition and findings on chest radiograph [Fig. 1d] gradually improved with this treatment. The patient was discharged from our hospital on January 1. Her prescription at discharge was rifampicin, isoniazid and ethambutol with prednisolone $20 \, \text{mg}$. After discharge, she remained in excellent good condition until March, when she began to experience general malaise and bilateral supraclavicular lymphadenopathy. Chest radiograph demonstrated progression of bilateral lung nodules and computed tomographic scan of the neck demonstrated bilateral supraclavicular lymphadenopathy [Fig. 1f]. Based on a diagnosis of paradoxical worsening of miliary TB, prednisolone...
was again increased to 250 mg. On 1 April, high grade fever of 39°C and progression of bilateral supraclavicular lymphadenopathy developed and she was readmitted to our hospital. Steroid pulse therapy with methylprednisolone 500 mg/day for three days was administered intravenously, followed by prednisolone 50 mg/day. Her symptoms improved and she was discharged again on 5 May. She was followed as an outpatient until 7 June, when bilateral supraclavicular lymphadenopathy showed severe swelling. She was readmitted and given steroid pulse therapy of methylprednisolone 250 mg/day for three days followed by prednisolone 20 mg. Neck swelling was improved and she was discharged on 7 July. After three months, her neck again became swollen with fluctuant fluid storage in the midportion of the neck, although bilateral supraclavicular lymphadenopathy had regressed. As the patient complained of neck pain, needle aspiration was performed. The effusion was 10 ml of moderately turbid and slightly viscous yellow fluid. Microscopic examination of stained fluid specimens demonstrated abundant neutrophils and moderate numbers of lymphocytes with no acid-fast bacilli or other microorganisms. PCR test for TB was positive, but culture of the effusion was negative. The neck swelling decreased with scar formation after spontaneous rupture of the tumor. She was treated with rifampicin, isoniazid and ethambutol for one year until December 2001.

DISCUSSION

Worsening of lymphadenopathy is the most commonly reported exacerbation after anti-TB therapy. These episodes of unexpected exacerbation of the disease under appropriate therapy have been called “paradoxical response” or “paradoxical worsening” by some investigators. Although such paradoxical worsening frequently arouses concerns of uncontrolled TB due to drug resistance and/or noncompliance, drug fever, or alternative diagnosis, these cases are distinct from such complications and may represent an enhanced anti-TB immune response after the initiation of anti-TB therapy. This patient was consistently treated with rifampicin, isoniazid and ethambutol, which were sensitive for *M. tuberculosis*. Her compliance for these drugs was also good and the other diagnoses such as the lymphoma were denied cytologically. As the continued therapy ulti-

![Diagram](image-url)
mately resulted in cure, malabsorption and adverse drug reaction to these drugs were both denied. During chemotherapy, up to % of patients may experience the appearance of new nodes or enlargement, fluctuation, or drainage of existing nodes . In this case, the progression of lung opacity or lymph node swelling was not accompanied by an increase in . Therefore, we thought this progression was paradoxical worsening of TB.

The pathogenesis of paradoxical worsening of TB is not well understood. Paradoxical worsening is thought to represent an improvement in the host’s immune response to mycobacterial antigens during the course of treatment, leading to more intense inflammation at sites of TB infection. Treatment of TB is associated with increased host immune responses to mycobacterial antigens. In addition, paradoxical worsening of TB following antiretroviral therapy in AIDS patients has been reported. Recent work has demonstrated increased proliferation of peripheral blood mononuclear cells and interferon gamma production in response to . Antigen-specific CD lymphocyte responses have also been shown to improve in HIV-infected persons receiving HAART. The risk of developing paradoxical worsening of TB has not been associated with a patient’s initial CD count, viral load, or changes in CD count during treatment. One report showed that in TB patients treated with anti-TB therapy and antiretroviral therapy, those who developed paradoxical worsening had a slightly though not significantly larger drop in viral load after combination antiretroviral therapy compared to that in those who did not develop paradoxical worsening. An increase in memory CD T cells, as defined by CD RO, a rapid decrease in the activation markers of CD cells, a slower increase in naive CD cells, as defined by CD RA and recovery of immune function have been demonstrated by tests of recall and specific antigens.

In this case, the patient had rubella one month before the onset of miliary TB, which was diagnosed by a characteristic rash and increased rubella IgM antibody. Rubella is an acute viral infection ordinarily characterized by mild constitutional symptoms, a rash similar to that of mild rubeola or scarlet fever, and enlargement and tenderness of the postoccipital, retroauricular, and posterior cervical lymph nodes. The pathogenesis of T-cell activation by rubella virus is not well understood. The expression of interleukin receptor alpha CD RO CD T lymphocytes -cell activation in response to the rubella virus antigen has been demonstrated in healthy children who had received either monovalent or measles-mumps-rubella vaccine. In this patient, we suspect that immunological mechanisms were impaired by rubella infection and pulmonary TB rapidly deteriorated thereafter.

Senderovitz et al. have reviewed the literature and evaluated its results in relation to our present tuberculosis treatment strategy. In a prospective study, a more rapid decrease in temperature in febrile patients, a quicker normalization of the clinical state, a quicker normalization of anemia, and a more rapid normalization of the X-ray was seen in the corticosteroid treated group. In another prospective study, prednisolone was given in a daily dose of mg for months particularly in the severely ill patients. In this case, paradoxical worsening occurred repeatedly, and steroid pulse therapy was used each time. Though steroids are considered effective for the improvement of paradoxical worsening, the dosage and term of steroid therapy was not sufficient to cure in this case.

Before the advent of anti-TB medication, surgical excision was the primary mode of treatment for scrofula. The rate of recurrence in the early studies was often high and was frequently associated with the size of the lymph node. Chemotherapy has also been used alone with some degree of success. It is currently accepted that the best therapeutic strategy is a combination of surgery and medication. Surgical excision for initial diagnosis before chemotherapy has been recommended for the last three decades. Many physicians have suggested that clinical diagnosis alone followed by chemotherapy is appropriate. Surgical intervention is reserved for those with a poor response to therapy or obvious discomfort due to enlarged lymph nodes. In this case, excision of both bilateral supraclavicular and mediastinal
lymphadenopathy was thought to be technically difficult since chronic inflammation in and around the nodes might have caused distortion of the anatomy and it was thought that there was some risk of injuring the tissue around the nodes. Therefore, we only continued the anti-TB drugs. There is no way to determine whether this was the optimal choice.

In summary, we reported the first case of paradoxical worsening of miliary TB associated with prior rubella infection. Prior infection with rubella may have activated T cell function promoting subsequent rapid worsening of miliary TB.

REFERENCES