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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

Abbreviations: TB: tuberculosis, PCR: polymerase chain reaction, HAART: highly active antiretroviral therapy

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 23-year-old woman with a high fever was referred to our hospital from a local hospital on 27 December 2000. She worked as a nurse and had contact with a pulmonary tuberculosis patient six months before admission to our hospital. On admission on 30 November 2000, the patient demonstrated a systemic rash and high fever. Plain chest radiograph on admission did not demonstrate any abnormal findings (Fig. 1a). 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 30 mg was administered for two days. Although fever temporarily recovered to the normal range, high fever recurred and she was transferred to another hospital for further examination of miliary shadows on a chest imaging study performed on 22 December. 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 38.7 ℃, pulse rate was 90/min, and respiration rate was 16/min. Blood pressure was 92/70 mmHg. On

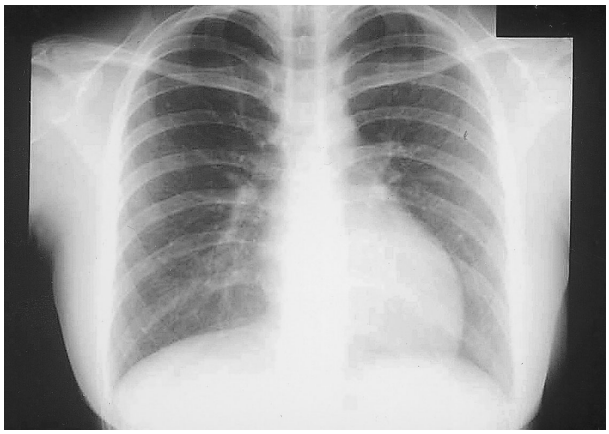

Fig. 1a. Chest radiograph obtained in November 2000 before onset of miliary tuberculosis.

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physical examination, the patient was an underweight woman who appeared fatigued. She had no visible or palpable lymphadenopathy. White blood cell count was 4,300/mm^3. Serum C-reactive protein was 4.2 mg/dl. Urinalysis was negative for protein, occult blood, glucose, cells and casts. Routine bacteriological, fungal, and mycobacterial smears of sputum were negative. PCR (polymerase chain reaction) test for tuberculosis in sputum was positive and sputum culture showed *Mycobacterium* (*M.*) *tuberculosis.* The culture was positive only on admission, and cultures performed thereafter have been negative. Tuberculin skin test (5TU) was positive. Plain chest radiograph demonstrated diffuse miliary shadowing (Fig. 1b). CT scanning of the chest showed diffuse multiple miliary opacities (Fig. 1c). Anti-TB drugs containing rifampicin (450 mg/day), isoniazid (400 mg/day), ethambutol (750 mg/day) and pyrazinamide (1.2 g/day) were administered after admission. Because her general condition deteriorated, prednisolone 20 mg/day was added to anti-TB drugs. Mild liver dysfunction appeared and pyrazinamide was discontinued on 4 January 2001. Her general condition and findings on chest radiograph (Fig. 1d) gradually improved with this treatment. The patient was discharged from our hospital on 24 January. Her prescription at discharge was rifampicin, isoniazid and ethambutol with prednisolone 10 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. 1e). Based on a diagnosis of paradoxical worsening of miliary TB, prednisolone

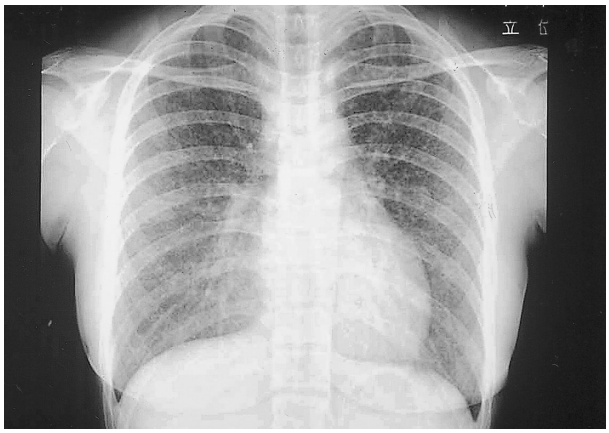

Fig. 1b. Chest radiograph at admission to our hospital.

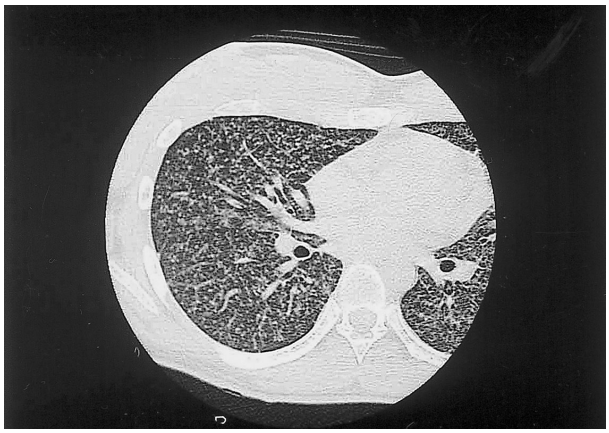

Fig. 1c. CT scan of the thorax showing diffuse multiple nodular lesion.

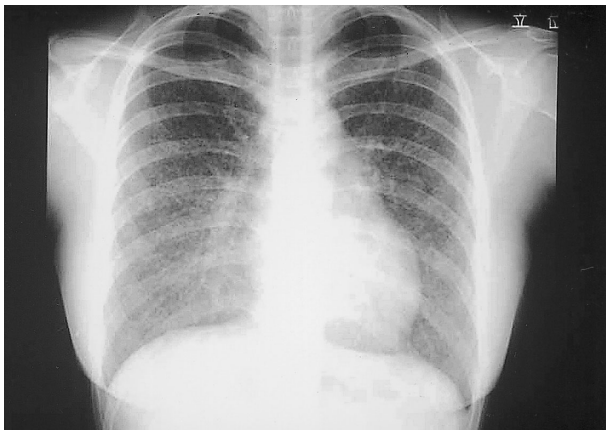

Fig. 1d. Chest radiograph obtained in January 2001 after one month of anti-TB therapy.

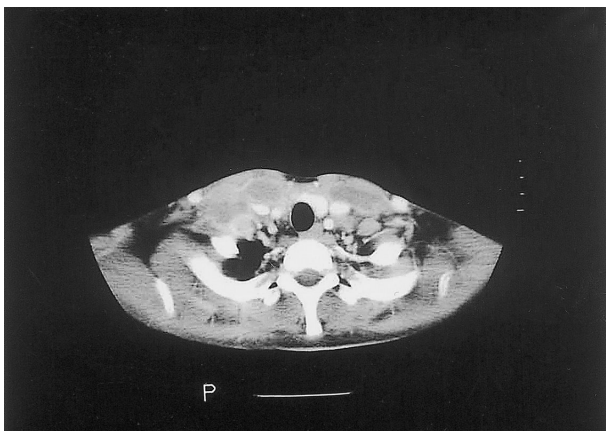

Fig. 1e. CT scan of the neck showing bilateral supraclavicular lymphadenopathy.

was again increased to 20 mg. On 28 April, high grade fever of 38.5 ℃ and progression of bilateral supraclavicular lymphadenopathy developed and she was readmitted to our hospital. Steroid pulse therapy with methylprednisolone 250 mg/day for three days was administered intravenously, followed by prednisolone 20 mg/day. Her symptoms improved and she was discharged again on 26 May. She was followed as an outpatient until 28 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 6 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 15 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 (Fig. 2).

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-

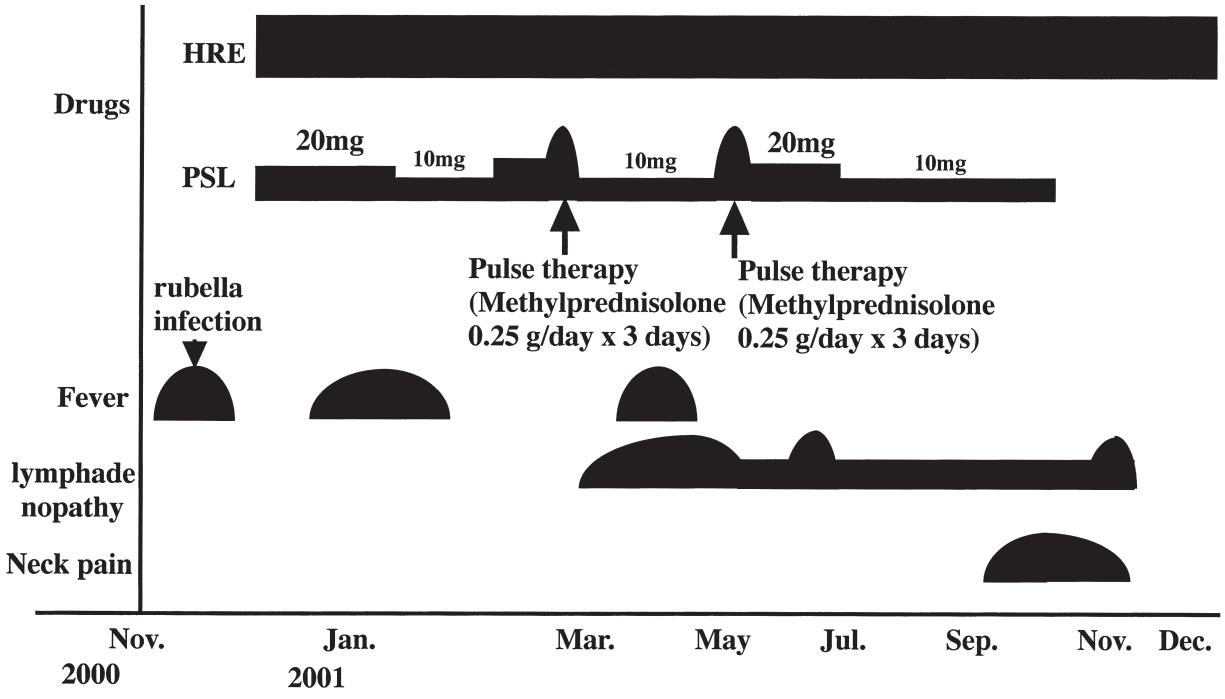

Fig. 2. The clinical course of the patient. HRE: isoniazide, rifampicin and ethambutol. PSL: prednisolone.

mately resulted in cure, malabsorption and adverse drug reaction to these drugs were both denied. During chemotherapy, up to 25% of patients may experience the appearance of new nodes or enlargement, fluctuation, or drainage of existing nodes (1). In this case, the progression of lung opacity or lymph node swelling was not accompanied by an increase in *M. tuberculosis.* 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 (2). 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 (3, 4). Recent work (3) has demonstrated increased proliferation of peripheral blood mononuclear cells and interferon gamma production in response to *M. tuberculosis* antigens after initiating highly active antiretroviral therapy (HAART). Antigen-specific $CD4^+$ lymphocyte responses have also been shown to improve in HIV-infected persons receiving HAART (4). The risk of developing paradoxical worsening of TB has not been associated with a patient's initial CD4 count, viral load, or changes in CD4 count during treatment (2). 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 (5). An increase in memory $CD4^+$ T cells, as defined by $CD45RO^+$, a rapid decrease in the activation markers of $CD8^+$ cells, a slower increase in naive $CD4^+$ cells, as defined by $CD45RA^+$ and recovery of immune function have been demonstrated by tests of recall and specific antigens (6).

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 (German or three-day measles) is an important childhood disease that has historically been wide spread but is now very infrequent. 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-2 receptor alpha ($CD25^+$) $CD45RO^+CD4^+$ T lymphocytes (T-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 (7). In this patient, we suspect that immunological mechanisms were impaired by rubella infection and pulmonary TB rapidly deteriorated thereafter.

Senderovitz *et al.* (8) have reviewed the literature and evaluated its results in relation to our present tuberculosis treatment strategy. In a prospective study (9), 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 (10), prednisolone was given in a daily dose of 20 mg for 3 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 (11). 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.

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