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Short Communication

Mediastinal Lymphadenopathy due to Mycobacterial Infection

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SUMMARY: Tuberculous lymphadenitis without pulmonary manifestation is an uncommon entity in developed countries, and the possibility of tuberculous infection is usually ignored in the differential diagnosis of lymphadenopathy. Therefore, appropriate treatment may be delayed. Paralysis of the recurrent laryngeal nerve caused by mediastinal lymphadenopathy due to tuberculosis is an extremely rare condition. In this paper, we present a patient who had vocal cord paralysis caused by tuberculous lymphadenopathy of the superior mediastinum. After anti-tuberculosis treatment, vocal cord function was only partially recovered, while the clinical, radiological, and laboratory abnormalities were completely recovered.

Involvement of the mediastinal lymph nodes in tuberculosis (TB) is a common condition in developing countries (1). But, regarding this involvement, recurrent laryngeal nerve (RLN) paralysis and hoarseness is rare (2). Few reports have described this issue since 1966, and according to our knowledge, only four cases have been published in the literature in English.

A 53-year-old housewife visited our clinic in July 2002, due to hoarseness, malaise, night sweats, loss of body weight, and nonproductive cough for 1 month. She had no history of contact with any patient with TB, and had not been vaccinated with bacillus Calmette-Guérin (BCG). She had no history of previous diseases, medication, or exposure to dust or biomass. Lymphadenopathy, 3 to 2 cm in diameter, was found in the left supraclavicular area, and the patient presented with hoarseness on examination. Other examination findings were normal.

Lymphocytosis, elevated erythrocyte sedimentation rate, and anemia were revealed by laboratory investigation. Acid-fast bacilli were negative on three examinations of sputum. There were bilateral hilar and mediastinal enlargement and no parenchymal abnormalities on plain CXR (Fig. 1). Computed axial tomograms (X-Vision Gx, Toshiba Medical Systems Corp., Tochigi, Japan) showed lymph nodes in the subcarinal, periaortic, and aortopulmonary-windows (Fig. 2). In the coronal section the diameters of the lymph nodes were 1.5 and 2.5 cm and showed central low attenuation, suggesting tuberculous lymphadenopathy (3). No parenchymal lesion was seen on computed tomograms. Several lymphadenopathies were shown in the peripancreatic area by abdominal ultrasonography. Fine needle aspiration of the lymph node located in the supra-clavicular area was negative for malignancy and acid-fast bacilli. Flexible bronchoscopy (video-monitorized) revealed no endobronchial lesion, but paralysis of the left vocal cord was observed (Fig. 3). Bronchoalveolar lavage was negative for acid-fast bacilli and pathognomonic organisms, and cytological examination of this lavage was negative for malignancy. Tuberculin skin test was strongly positive, the diameter of enduration was 27 mm, and there was no history of BCG vaccination. There was no finding of HIV-infection. Under local anesthesia, the lymph node in the supraclavicular area was excised. Culture for *Mycobacterium tuberculosis* was made from the biopsy specimens. Granulomatous lesion

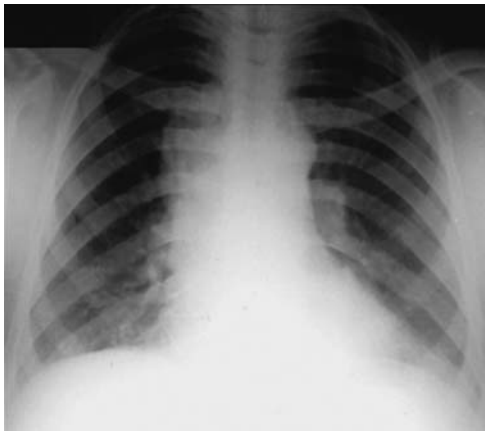

Fig. 1. Before treatment, plain CXR revealed bilateral hilar and mediastinal enlargements.

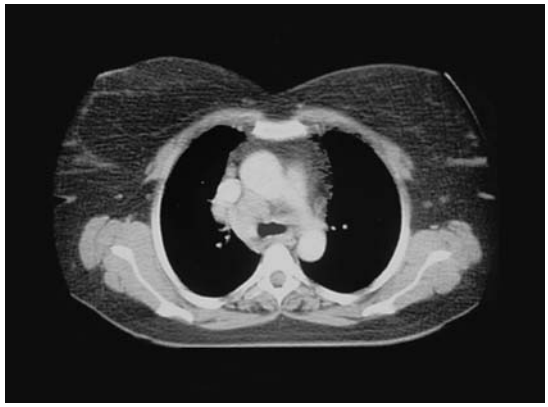

Fig. 2. Before treatment, CT shows lymphadenopathies with low attenuation in the central parts of the aortopulmonary window area.

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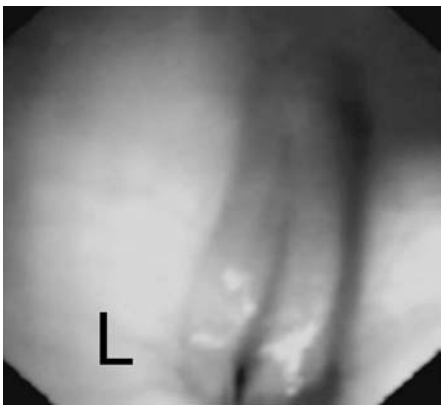

Fig. 3. Bronchofiberscopy revealing left vocal cord paralysis. L: left side.

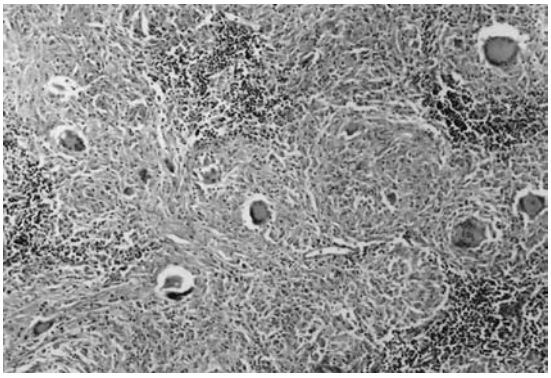

Fig. 4. Histopathologic examination of the lymph node from the supraclavicular area shows a reaction consisting of granulomas formation of epitheloid cells, Langhans' giant cells, and lymphocytic infiltration.

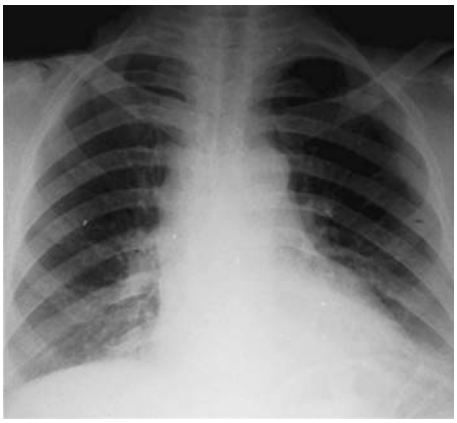

Fig. 5. After treatment, plain CXR of the case showing normalized hilar regions and mediastinum.

without caseous necrosis and with multinucleated giant cells was revealed by histological examination of the lymph node (Fig. 4).

Because granulomatous lesions were shown on the histological examination of the lymph node, and the tuberculin skin test was strongly positive with TB still a prevalent and constant problem in Turkey, anti-TB treatment was administered to the patient, namely, isoniazid, rifampicin, ethambutol, and pyrazinamide. Most of the symptoms subsided after 1 month of treatment. After 4 weeks, the culture was negative. The patients' hoarseness partially recovered after 2 months,

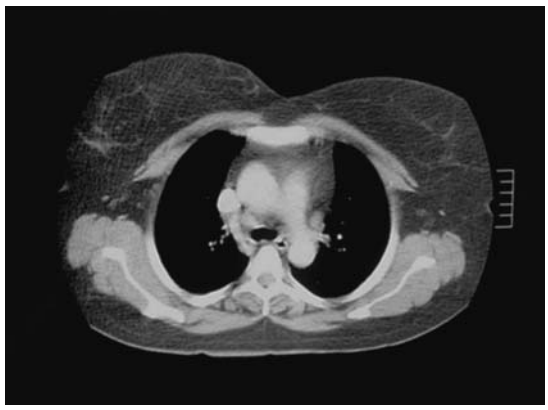

Fig. 6. Completely resolved lymph nodes after treatment in aortopulmonary window area.

but persisted in a mild manner. Four months latter, pathological findings were improved on plain CXR (Fig. 5), and a repeat computed tomography of the chest showed that the mediastinal lymphadenopathies had completely resolved (Fig. 6).

While lymph node swellings are diagnosed, TB as a major possibility is usually not considered. The best approach to the assessment of lymph node TB can be a combination of tuberculin skin testing and histological examination. Cytological and histological examinations show caseous necrosis only in about half of tuberculous lymphadenitis cases (4). We were not able to fully exclude the possibility of other granulomatous diseases before starting the anti-TB chemotherapy. It should be differentiated from other granulomatous diseases. For example, sarcoidosis is a multisystem granulomatous disease and impaires cuteneous response to most antigens bringing out delayed-type hypersensitivity reactions, seen in half of the patients. Because anergy to tuberculin skin test is common in sarcoidosis, active TB must be strongly considered in patients developing a positive tuberculin skin test (5). For Wegener's granulomatosis, three criteria are known as the "Wegener's triad", namely, necrotizing granulomatous inflammation of the upper and lower respiratory tracts, generalized focal necrotizing vasculitis involving both arteries and veins, and focal necrotizing glomerulitis. Also, multiple bilateral pulmonary parenchymal nodules, cavitating in about half of the patients, are the classic radiological findings of Wegener's granulomatosis (6). The patient's past history, occupation, and radiological findings are not suitable for foreign-body granulomas such as pneumoconiosis. On the other hand, fungal diseases are usually opportunistic infections and arise in patients with supressed immune systems such as those with hematological malignancy, HIV infection, or undergoing chemotherapy for cancer.

Also, it should be differentiated from nontuberculous mycobacterial (NTM) disease. Presently, NTM disease usually arises in HIV-infected patients. Causing disease in humans, the most common NTM disease is *Mycobacterium avium* complex. There are some reservoirs of *M. avium* complex such as chickens, other birds, swine, cattle, and several environmental sources (e.g., soil, animal bedding, plants, standing fresh water, and salt water). There was no history of contact with these risk factors in the present patient. Lymphadenitis caused by *M. avium* complex occurs almost solely in children under the age of 5 years (7), and

the best treatment is excision of the infected lymph node, because treatment of this disease is usually very difficult due to the resistance of the organism to first-line antimycobacterial drugs and since chemotherapy is of little utility (7).

Thus, we finally consider that clinical and radiological findings, and the patient's past history, and treatment results are not suitable for the diagnosis of other granulomatous and NTM diseases. Although there was no direct/definite evidence supporting TB before empirical anti-TB chemotherapy, abnormalities in the patient's clinical, radiological, and laboratory findings, such as elevated erythrocyte sedimentation rate, completely recovered and the patient's hoarseness partially recovered after empirical anti-TB chemotherapy.

Chronic pulmonary TB with fibrosis which particularly affects the upper lobes and the entrapment of the RLN in the scar could cause vocal cord paralysis (8). This pathology could also result from entrapment traction neuropathy or compression by enlarged TB nodes (9). Another possible cause is fibrosing and granulomatous mediastinitis usually caused by infection by *Histoplasma capsulatum* and rarely by *M. tuberculosis* (10). When the anatomical location of the RLN is considered, its unique location in the aortopulmonary window and aortic arch, enlarged TB lymph nodes and inflammatory swelling predispose the compression and dysfunction of RLN (11).

M. tuberculosis stimulates T-cell mediated immune response and results in caseous tissue necrosis, and as a rule healing takes the form of fibrosis (11). On the other hand, Fowler and Hetzel (12) have claimed that "direct spread of infection from perforated lymph node abscess damage the RLN rather than mechanical factors alone". In contrast, Rafay (11) reported that RLN paralysis is caused by mechanical compression of swollen lymph nodes. However, the results obtained from the present patient agree with neither those of Rafay nor Fowler and Hetzel. If RLN paralysis depended on mechanical factors, RLN function would improve after anti-TB treatment when mechanical compression disappeared. If the causes of RLN paralysis were the same as those reported by Fowler and Hetzel, partial healing would not be seen and nerve damage would persist completely after anti-TB treatment. Partial improvement of RLN function and hoarseness in the patient showed the formation of nerve paralysis due to both mechanical compression of the lymph nodes and fibrosing mediastinitis. Therefore, we think that fibrosing mediastinitis was a cause of the partial persistence of hoarseness after anti-TB chemotherapy.

Paralysis of the RLN can occur due to superior mediastinal lymphadenopathy which strongly indicated by a malignant process in patients from developed countries and those successfully fighting TB (12). RLN paralysis can also form secondary to radiotherapy (2). Mediastinal lymphadenopathy due to TB is common in developing countries and among immigrants from these countries (1). However, RLN paralysis is an extremely rare condition in mediastinal TB. While most tuberculous infections are located in the lungs, about 15% of are located in extrapulmonary tissues, half of which affect lymph nodes. So, the possibility of TB is often ignored in the differential diagnosis of lymphadenitis, consequently resulting in a significant delay of appropriate treatment (4).

In conclusion, in the investigation of the causes of RLN paralysis, in addition to malignancy, TB should also be taken into consideration especially in patients living in underdeveloped or developing countries and in those emigrating from such countries to industrialized countries.

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