Fever, Hypercalcemia and Tuberculosis

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Key words: miliary tuberculosis, sarcoidosis, hypercalcemia

(DOI: 10.2169/internalmedicine.46.0176)

Since the “Tuberculosis Emergency Declaration” issued by the Ministry of Public Welfare of Japan in 1999, the incidence of newly registered active tuberculosis has decreased from 32.4 to 23.3 per 100,000 (1). However, the figure is relatively high among developed countries, defining Japan as the region of intermediate risk for tuberculosis (2). The high incidence owes much to that of elderly persons, constituting more than half of all patients in the last 10 years (1). The background for the high incidence of the disease in elderly persons is the high rate of infection with Mycobacterium tuberculosis; more than half of the people over the age of 60 years old are infected with the organism, and there is an increased chance of risk factors for tuberculosis such as diabetes mellitus, malignant tumors and corticosteroid therapy in these generations. Early diagnosis is important in tuberculosis to avoid the exacerbation of the disease and the spread of the organism, but the annual report shows that a period of more than 3 months is required to establish the diagnosis in about one-quarter of the patients (1). The delay is not rare in elderly patients, because of the absence of characteristic symptoms or due to the lack of typical chest x-ray findings. The report by Uchiyama-Tanaka and Mori of this journal describes this type of clinical problem (3).

The patient was a 69-year-old man with interstitial pneumonia for which the maintenance dose of corticosteroid had been given. He was diagnosed as having abdominal aortic aneurysm and underwent surgical resection that revealed necrotic tissue suggestive of infectious origin. After the operation he developed night fever, and blood tests showed hypercalcemia with an albumin-adjusted calcium level of 12.3 mg/dl. Increased levels of serum soluble IL-2 receptor and lysozyme were also noted and with a negative tuberculin skin test, the diagnosis of sarcoidosis was suggested. Corticosteroid therapy was started but brought no apparent effects, and bone marrow study was performed to reveal acid-fast bacilli with a positive PCR test for M. tuberculosis and non-caseating granulomas. Although chest x-ray findings were not characteristic, the diagnosis of miliary tuberculosis was made. Antituberculous treatment was initiated and showed the improvement of clinical findings.

Miliary tuberculosis represents the unchecked hematogenous dissemination of M. tuberculosis, constituting about 1% of tuberculosis (4). The diagnosis is sometimes difficult because of the low ratio of positive sputum smear tests of about 50%, negative tuberculin skin test and lack of abnormal findings on chest x-ray films. The last is due to the fact that it requires about one month before the scattered pulmonary lesions grow and show apparent nodules on chest x-ray films. Furthermore, corticosteroid therapy depresses the granuloma formation, resulting in the inconspicuous chest x-ray findings as was the case in this patient. It should therefore be noted that normal chest x-ray film does not necessarily contradict the diagnosis of miliary tuberculosis.

From the viewpoint of problem solving, the key factors in the case were high fever and hypercalcemia. Lymphoma, tuberculosis and sarcoidosis would be the candidate of differential diagnosis in these circumstances, and bone marrow studies were helpful to establish the diagnosis in this patient. In granulomatous diseases such as tuberculosis and sarcoidosis, hypercalcemia is caused by an overproduction of calcitriol, the active form of vitamin D3, most likely in granulomas by activated macrophages (5, 6). Although it is a rare manifestation in patients with these diseases in Japan, albumin-adjusted hypercalcemia has been detected in about 25% of Greek patients with tuberculosis (7).

Another characteristic feature that complicated the course of the disease in this case was the change in the abdominal aorta. This seems to be due to invasion of the bacilli to the internal surface of the vessel wall, which is again a rare complication in a Japanese patient with tuberculosis. The case shows the diversity of tuberculosis and stresses the necessity of considering the disease in cases with unexplained data.
References


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