Increased Serum Thymidine Kinase Activity in Acute Sarcoidosis

Syunji Tajima, Yoshichika Sando, Toshitaka Maeno, Naoki Sagawa, Mami Nara, Yuri Maeno, Junichi Nakagawa, Toshio Ito, Yoichi Hoshino, Tatsuo Suga, Masashi Arai and Masahiko Kurabayashi

Abstract

This is the first case report of acute sarcoidosis with increased serum thymidine kinase (TK) activity. A 43-year-old male presented fever, swelling of parotid glands, lymphadenopathy, and peripheral neuropathy. Sarcoidosis was pathologically diagnosed by lung and parotid gland biopsy. His serum TK, which was increased to 11.2 U/l at diagnosis (normal <5 U/l), normalized after glucocorticoid therapy. Serum TK has been considered as a good marker of the proliferative activity of various types of neoplasms. Its rise in sarcoidosis has, however, not been described. Because acute sarcoidosis sometimes resembles malignant lymphoma, the possible rise of serum TK in sarcoidosis may be worthy of note.

(Key words: malignant lymphoma, soluble interleukin 2 receptor, parotid gland, neuropathy

Introduction

Thymidine kinase (TK) is a cellular enzyme, which is involved in a “salvage pathway” of deoxyribonucleic acid (DNA) synthesis. Because TK is activated in the cell division cycle, its serum level has been considered as a good marker for proliferative activity of hematologic malignancies and some solid tumors. It is also known that serum TK is increased in patients with viral infections. There has been, however, no previous report on the serum TK level in sarcoidosis. Here, we report a case of acute sarcoidosis with high serum TK activity, which normalized after glucocorticoid steroid therapy.

Case Report

A 43-year-old man visited to our hospital because of fever, painless swelling of the parotid glands, and bilateral hilar lymphadenopathy. He had been well until the beginning of April 2000, when he began to have a low-grade fever every evening.

He visited a medical practitioner on April 12, and bilateral hilar lymphadenopathy was noted on his chest radiograph. Both parotid glands swelled without pain on April 28. Subsequently, back pain and right facial nerve palsy emerged, and he was admitted to our hospital on May 15.

His medical history was unremarkable except for hypertension, which had been treated with quinapril, an angiotensin-converting enzyme inhibitor and ferodipine, a calcium antagonist. He did not smoke, but he drank about one-half liter of beer a day. His son was suffering from atrial septal defect.

On admission, he was alert and ambulatory, but he complained about severe back pain. He was 162 cm tall, and weighed 55 kg. Vital signs were as follows: body temperature 36.5°C, blood pressure 140/70 mmHg, pulse 100/min, regular, respiration 15/min. The bilateral parotid glands were swollen and elastic-hard without pain; the right was 3 cm, and the left was 6 cm large. He coughed occasionally, and expectorated a small amount of white sputum. Auscultation of the chest was unremarkable. In the abdomen, the liver was palpable 5 cm below the right costal arch. Superficial lymph nodes were not palpable. Skin eruption, clubbing of fingers, and pretibial edema were not found. Neurological examination revealed anisocoria (the right pupil was larger than the left), right facial nerve palsy, enhanced left patellar and bilateral Achilles’ tendon reflex, and neuralgia on his back, although motor and sensory function were preserved in the limbs.

Laboratory data on admission showed normal hemogram and blood chemistry, except for a slight increase of lactate dehydrogenase (LDH) to 426 IU/l (normal <420 IU/l), and a marked rise of amylase to 1,026 IU/l (normal <200 IU/l). Blood sedimentation rate was 13 mm in 1 hour, and C-reactive protein was 0.4 mg/dl. Autoantibodies including anti-nuclear antigen, SS-A, SS-B, rheumatoid factor were negative. Serum angiotensin-converting enzyme (ACE) activity measured 7 days after the cessation of quinapril was 17.4 IU/l at 37°C, which was within the normal range. Both soluble interleukin 2 receptor (sIL2R) and thymidine kinase (TK) were increased to 1,740 U/ml (normal range 246–742) and 11.2 U/l (normal <5 U/l), respectively. Urinalyses were normal. Arterial blood gas analyses breathing ambient air showed pH 7.426, partial pressure of carbon dioxide (CO2) 37.3 Torr, that of oxygen (O2) 74.0 Torr.

From the Second Department of Internal Medicine, Gunma University, Maebashi
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Reprint requests should be addressed to Dr. Yoshichika Sando, the Second Department of Internal Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511

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The results of pulmonary function tests were as follows; vital capacity (VC) 3.73 l (100.5% of predicted vital capacity), forced expiratory volume in 1.0 second 2.42 l (65.1% of forced vital capacity), diffusion capacity of carbon monoxide 98.9% of predicted value. The electrocardiogram and the ultrasonic echocardiography were normal. Tuberculin skin test was negative.

The chest radiograph on admission showed prominent bilateral hilar lymphadenopathy (Fig. 1), although that taken in January 1998 was unremarkable. Computed tomography of the chest revealed massive swelling of mediastinal and hilar lymph nodes (Fig. 2A, B) along with tufting and irregular thickening of bronchovascular bundles (Fig. 2C, D). Gallium-67 scintigraphy showed strong abnormal accumulation of radiotracers in bilateral hilar, parotid and orbital regions, in addition to the less intensive uptake in the mediastinum and the supraclavicular areas (Fig. 3). From the above findings, malignant lymphoma and sarcoidosis were listed as differential diagnoses,

Figure 1. Chest radiograph on admission suggested prominent swelling of bilateral hilar lymph nodes.

Figure 2. Computed tomography of chest depicted massive swelling of mediastinal and hilar lymph nodes (A, B), and tufting and irregular thickening of bronchovascular bundles (C, D).
Serum Thymidine Kinase in Sarcoidosis

and several procedures were performed to determine the diagnosis.

Videobronchoscope disclosed edematous change and dilatation of the small vessels in tracheobronchial mucosa. Bronchoalveolar lavage (BAL) was carried out by instilling 150 ml of isotonic saline solution in the lateral bronchus of the right middle lobe, and 64 ml (42.7%) was recovered. Total cell count was increased to 5.8x10⁵/ml, consisting of 33.6% macrophages, 66.0% lymphocytes, 0.4% neutrophils. The ratio of CD4 positive to CD8 positive lymphocytes was 4.87. Microscopic examination of lung specimens obtained by transbronchial approach revealed epitheloid cell granuloma with multinucleated giant cells (Fig. 4A). Similar pathological findings were also observed in bilateral parotid glands (Fig. 4B). Therefore, the diagnosis of sarcoidosis was confirmed. Electrophysiological study of the peripheral nerves disclosed impaired conduction velocity in the lower limbs. His neurological findings such as anisocoria, facial nerve palsy, hyperreflexia, and back neuralgia were attributed to polyneuropathy due to neurosarcoidosis. Ophthalmologic examination was unremarkable.

Oral prednisolone was commenced and continued for 3 weeks at a dose of 50 mg a day for treatment. Thereafter, prednisolone was tapered at the rate of 5 mg per week. Soon after the start of treatment, he became afebrile and felt better with the alleviation of back pain and parotid gland swelling. The facial nerve palsy recovered within a month. One month after the initiation of oral glucocorticoid, both serum sIL2R and TK were normalized from 1,740 to 346 U/ml and from 11.2 to 1.7 U/l, respectively.

Discussion

This is the first case report of sarcoidosis, in which serum thymidine kinase (TK) activity was initially high, but was normalized after glucocorticoid steroid therapy.

Thymidine kinase is a cellular enzyme that is involved in DNA synthesis. It catalyses the phosphorylation of exogenous, alimentary or endogenous deoxythymidine to deoxythymidine monophosphate (dTMP) in the "salvage pathway", which is further utilized in the synthesis of DNA. Because TK is formed in the cells prior to cell division, serum TK levels correlate with the proliferative activity of various types of tumor cells.

Figure 3. Gallium-67 scintigraphy showed strong abnormal accumulation of radiotracers in bilateral hilar, parotid and orbital regions, along with less intensive uptake in mediastinum and supraclavicular areas.

Figure 4. A) Specimen of transbronchial lung biopsy showed epitheloid cell granuloma with multinucleated giant cells (HE stain, ×400, scale bar=50 μm). B) Parotid glands also showed epitheloid cell granuloma with multinucleated giant cells (HE stain, ×400, scale bar=50 μm).
including malignant lymphoma (ML) (1), multiple myeloma (2), leukemia (3), breast cancer (4), and small cell lung carcinoma (5). Especially in cases of non-Hodgkin’s lymphoma, the serum TK level correlates well with clinical staging and has prognostic value (1). In addition to neoplasias, serum TK becomes elevated in patients with viral infection (6) or vitamin B12 deficiency (7). There has been, however, no previous report on the serum TK level in sarcoidosis.

The present case showed fever, parotid gland swelling, thoracic lymphadenopathy, and polyneuropathy. We considered sarcoidosis as the most plausible diagnosis, but could not initially rule out ML, because ML can also present all of the above findings; Fever and lymphadenopathy are the most common signs of ML. ML can affect the salivary glands, especially in patients with Sjögren’s syndrome (8) and it has been reported that ML has involved bilateral parotid glands (8, 9). ML can present a variety of neurological signs (10). Consequently, we measured serum ACE, sIL2R and TK, the markers of sarcoidosis and/or ML.

Both serum sIL2R and TK were increased in this patient, but serum ACE level was within the normal range. Serum sIL2R has been used as a sensitive and prognostic marker of non-Hodgkin’s lymphoma (11, 12), however, as it is also elevated in sarcoidosis, reflecting disease activity (13, 14), the serum sIL2R level is not useful to differentiate sarcoidosis from ML. The combination of lymphadenopathy and high serum TK is suggestive of ML rather than sarcoidosis.

Here, both the lung and parotid gland biopsy revealed epitheloid cell granulomas with multinucleated giant cells, which pathologically confirmed the diagnosis of sarcoidosis. The negative tuberculin skin reaction and increased lymphocyte counts with high ratio of CD4 positive to CD8 positive cells in the BAL fluid supported this diagnosis. The patient was treated with oral prednisolone, which induced a good clinical response and achieved normalization of both serum sIL2R and TK levels. Since no relapse was observed after tapering off of the steroid regimen, it was very unlikely that ML was concomitant with sarcoidosis. Therefore, high serum TK levels in the present case should be attributed to active sarcoidosis.

Why does the serum TK activity rise in sarcoidosis? It might be due to the release of TK into the blood stream during extensive replication of T cells. However, the mechanism by which TK is released from dividing cells is not fully understood. It is thought that TK is an intracellular enzyme, and is probably not released into circulation by normal dividing cells (15). What does high serum TK imply in sarcoidosis? It might reflect some disease activity of sarcoidosis. However, it is an open question whether it relates to the prognosis, the BAL fluid findings, or the involvement of specific organs such as lung. We have preliminarily measured serum TK and ACE activities in another ten patients with sarcoidosis, and found that both TK and ACE were high in 3, only ACE was high in 3, only TK was high in 2, and neither ACE nor TK was high in 2 of these 10 cases. The elevation of serum TK seems to be a relatively common finding in sarcoidosis, and is not always correlated with ACE levels. Further studies are needed to determine the clinical significance of serum TK in sarcoidosis.

In conclusion, we first reported the rise of serum TK in sarcoidosis. Since acute sarcoidosis and ML share many clinical symptoms and signs, it is important to note that serum TK may be elevated in patients with sarcoidosis.

References