CASE REPORT

Mediastinal Seminoma with an Elevated Level of Serum Angiotensin-converting Enzyme

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Abstract

A 22-year-old man was admitted following the detection of right hilar enlargement during a medical checkup. The patient’s serum angiotensin-converting enzyme (ACE) level was abnormally high, and a needle aspiration biopsy showed non-caseating epithelioid cell granulomas. Surgical resection was performed, and the resected specimens showed irregularly shaped seminoma nests with intervening stroma consisting of epithelioid cell granulomas. Furthermore, immunohistochemistry demonstrated ACE expression in the epithelioid cells and some tumor cells. The patient’s serum ACE level declined after the surgery and subsequent systemic chemotherapy, indicating the presence of tumor-induced sarcoid-like reactions rather than the coexistence of seminoma and sarcoidosis.

Key words: angiotensin-converting enzyme, mediastinal tumor, sarcoidosis, sarcoid-like reaction, seminoma

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Introduction

Seminomas account for one-third of testicular germ cell tumors, the most common malignancy in men 15-35 years of age (1); however, primary mediastinal seminoma is rare among extragonadal germ cell tumors (2). Sarcoidosis is a granulomatous disease of unknown etiology characterized by the presence of non-caseating epithelioid cell granulomas, most often located in the lungs or hilar and/or mediastinal lymph nodes, although any organ can be affected. While the detection of an elevated serum angiotensin-converting enzyme (ACE) level may be helpful in the diagnosis of sarcoidosis, the gold-standard is the presence of epithelioid cell granulomas in involved organs. In addition, although there have been several reported cases of testicular seminoma occurring concomitantly with a suspected diagnosis of sarcoidosis, it is unclear whether the granulomas indicate the presence of sarcoidosis or rather reflect sarcoid-like reactions against tumor antigens (3).

We herein describe a rare case of primary mediastinal seminoma with an elevated serum level of ACE.

Case Report

A 22-year-old Japanese non-smoking man without any respiratory symptoms was admitted after right hilar enlargement was detected during a medical checkup (Fig. 1A). The patient had undergone resection of a retroperitoneal teratoma at 4 months of age and resection of a testicular venous aneurysm at 12 years of age and had been found to have mild mental retardation since 6-7 years of age. There were no abnormal findings on a physical examination, including a skin assessment, chest auscultation and SpO₂ measurement. Chest computed tomography (CT) showed an anterior mediastinal mass (Fig. 1B) that was positive (maximum standardized uptake value: SUVmax =8.39) on positron emission tomography (PET) with fluorodeoxyglucose (Fig. 1C); however, no abnormal imaging findings were detected in the other organs. Meanwhile, the laboratory findings indicated a serum ACE level of 72.8 U/L (normal range: 8.3-21.4 U/L), a β subunit of human chorionic gonadotropin (β-HCG) level of 12 mIU/mL (normal range: <5 mIU/mL) and a soluble interleukin-2 receptor level of 671 U/mL (normal range:
cell granulomas suggesting a diagnosis of sarcoidosis. How-

g-needle aspiration biopsy showed non-caseating epithelioid

ranges. A tuberculin skin test was negative. A CT-guided

immunoglobulin-G and calcium were within the normal

122-496 U/mL), whereas the serum levels of lysozyme,
immunoglobulin-G and calcium were within the normal

ranges. A tuberculin skin test was negative. A CT-guided

needle aspiration biopsy showed non-caseating epithelioid

cell granulomas suggesting a diagnosis of sarcoidosis. How-
ever, there were no relevant findings in the lung fields on

high-resolution CT or abnormal results on ophthalmologic

or cardiovascular examinations. In addition, the patient’s se-
rum level of β-HCG was elevated, and the SUVmax of the

mediastinal mass on PET-CT was in the intermediate range

between a benign and malignant lymph node (4). The possi-
bility of a malignant mediastinal tumor could not be ex-
cluded; therefore, surgical resection was performed, which

led to a pathological diagnosis of mediastinal seminoma

with invasion to the right lung. The resected specimens

showed a diffuse proliferation of tumor cells with round to

oval nuclei and intervening stroma consisting of epithelioid

cell granulomas (Fig. 2A), and immunohistochemistry dem-

onstrated ACE expression (anti-ACE antibodies; Atlas Anti-

bodies AB, Stockholm) not only in the cytoplasm of epithe-

lioid cells (Fig. 2B) but also in a portion of the tumor cells

(Fig. 2C). Systemic chemotherapy with cisplatin and
etoposide was performed after the surgery under a diagnosis

of a pathological stage IIIA extragonadal germ cell tumor.
Thereafter, the patient’s serum ACE level declined and the HCG level decreased to within the normal range.

Discussion

We herein describe a patient with mediastinal seminoma who exhibited an elevated serum ACE level which was possibly accompanied by a sarcoid-like reaction. The mediastinal solitary mass detected in the present case was first suspected to be a lesion of a malignant tumor or sarcoidosis due to the elevated serum ACE level, negative tuberculin skin test and positive findings on PET. In addition, a CT-guided needle aspiration biopsy showed only non-caseating epithelioid cell granulomas. Conversely, no evidence of any other organ involvement, an elevated serum β-HCG level and a mediastinal lesion with an intermediate SUVmax on PET-CT (4) suggested the possibility of a diagnosis other than sarcoidosis.

It is known that malignant lymphoma and solid tumors, such as those involving the cervix, liver, lungs, uterus and testicles, are likely to be accompanied by sarcoid-like granulomatous diseases, which are difficult to distinguish from true sarcoidosis (5). Testicular germ cell tumors have been reported to be the most common tumors associated with sarcoid-like granulomatous diseases (5), although the distinct causal relationship between these tumors and sarcoid-like reactions remains unknown. The cumulative incidence of sarcoid-like granulomatous diseases in patients with testicular germ cell tumors has been estimated to be approximately 617.3/100,000, which is higher than that for sarcoidosis among white men (4.0-10.9/100,000) (6). Furthermore, Paparel et al. reported seminoma to be the most frequent anatomopathological type of testicular germ cell tumor coexistent with granulomatous disease (7). Brincker et al. demonstrated immunological differences indicating that B lymphocytes are involved in the pathogenesis of granulomas observed in sarcoid-like reactions but not those associated with sarcoidosis (8), whereas Tjan-Heijnen et al. showed contrary findings (3). Sarcoidosis is essentially a multi-system disease (9), and this diagnosis cannot be made without multi-organ involvement. Therefore, the present case should be classified as a sarcoid-like reaction involving a single organ system, i.e., the regional lymph nodes. As sarcoid lesions may develop in different organs at different times, the definitive diagnosis of a sarcoid-like reaction should be made only after an adequate period of observation. In addition, sarcoid-like reactions may present with various manifestations in regards to the distribution and time course. The adjacent coexistence of tumor cells and sarcoid granulomas in a single organ, as observed in this case, has also been previously reported (3, 10). Furthermore, sarcoid-like reactions may occur simultaneously with the causative tumor as well as paradoxically during or even after tumor resolution (11, 12).

In the present case, the patient’s serum ACE level declined after surgery and the subsequent administration of systemic chemotherapy. The serum levels of ACE are elevated in 30% to 90% in patients with sarcoidosis (13). However, an elevation of the serum ACE level is also noted in other diseases, including mycobacterial and fungal infections, berylliosis and Hodgkin’s lymphoma (13). ACE is normally produced by pulmonary capillary endothelial cells but at a greater rate by activated macrophages in patients with sarcoidal granulomas. ACE is also present in Leydig cells, the endothelium, spermatids and spermatooza in the normal human testis (14). Furthermore, germ cell tumors in which ACE has been detected by immunohistochemistry has been previously reported (14-16). Although the serum levels of ACE are within the normal range in most cases of germ cell tumors (12, 16), there are a few reported cases of ACE elevation (16, 17). In addition, the serum ACE level decreased after surgery in the case reported by Rohner et al. (16) Routine measurement of the serum ACE level is, therefore, of little use for making a diagnosis in patients with germ cell tumors. However, certain germ cell tumors, particularly seminoma with a sarcoid-like reaction, may induce the elevation of serum ACE, and it is possible that the serum ACE level may be a useful tumor marker in such patients.

Further evaluation of the pathogenesis of seminoma using immunohistochemical and serological-based analyses of ACE, in addition to clinical assessments, may be helpful for understanding the mechanisms underlying the development of sarcoid-like reactions.

The authors state that they have no Conflict of Interest (COI).

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