Paradoxical Development of a Sarcoid-Like Reaction during Successful Chemotherapy for Seminoma

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Abstract

Although the association between seminoma and sarcoidosis or a sarcoid-like reaction has been well recognized, a paradoxical case during chemotherapy for seminoma has not been reported. We report the first case of a sarcoid-like reaction that developed paradoxically during successful chemotherapy for recurrent seminoma. A 36-year-old Japanese man had recurrent seminoma in abdominal lymph nodes four years after left orchiectomy. Chemotherapy consisting of bleomycin, etoposide and cisplatin had reduced the abdominal mass, but mediastinal and bilateral hilar lymphadenopathy newly appeared. Surgical biopsy of the mediastinal lymph nodes and left nephrectomy and retroperitoneal lymphadenectomy revealed noncaseating granulomas only in mediastinal lymph nodes and confirmed complete remission of seminoma. Nine months later the thoracic lymphadenopathy had resolved spontaneously.

Key words: sarcoid-like reaction, seminoma, chemotherapy, lymphadenopathy

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Introduction

Sarcoid-like reaction refers to the development of noncaseating granulomas in no more than one organ in neoplastic patients (1). According to a recent study using integrated 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography and computed tomography (PET/CT) a sarcoid-like reaction was suspected in 1.1% of cancer patients, with confirmation of the diagnosis in 0.6% (2). A sarcoid-like reaction is often indistinguishable from metastases on radiological studies (3). We report a case with a sarcoid-like reaction with a paradoxical and unusual course during successful chemotherapy for recurrent seminoma.

Case Report

A 32-year-old Japanese man underwent left orchiectomy, resulting in the pathological diagnosis of stage 1 testicular seminoma. Four years later he experienced left back pain and was diagnosed as having recurrent seminoma in the abdominal lymph nodes. He received three cycles of chemotherapy consisting of bleomycin, etoposide and cisplatin, but an abdominal lesion remained, although reduced in size. He was referred to our hospital for resection of the residual tumor. Vital signs were normal. The lungs were clear and no superficial lymphadenopathy was detected. Laboratory studies showed normal titers of LDH, HCG-β and AFP, all of which had been elevated at the onset of disease four years previously. Soluble interleukin-2 receptor was elevated at 867 U/dL and the angiotensin-converting enzyme (ACE) value was normal. Enhanced CT of the abdomen before chemotherapy showed prominent lymphadenopathy in the abdomen. After three courses of chemotherapy at another hospital, lymphadenopathy in the abdomen was reduced but did not completely resolve. Enhanced CT of the chest revealed mediastinal and bilateral hilar lymphadenopathy, which had been absent before the treatment but which developed newly during successful chemotherapy (Figs. 1A, 1B). Thoracic lymphadenopathy suggested the possibility of a metastatic tumor, and histopathological examination was performed. Examination of mediastinoscopic biopsied lymph nodes

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showed only multiple noncaseating granulomas with no evidence of malignancy (Figs. 2A, 2B). Thereafter, left nephrectomy and retroperitoneal lymphadenectomy were performed for the purpose of curable resection. Histopathological examination of the resected kidney and retroperitoneal lymph nodes revealed no residual tumor or granulomatous lesion but only fibrous tissue, which was considered to be a burned-out seminoma (Fig. 2C). No mycobacterium was detected by acid-fast staining or culture of the resected specimens. Electrocardiography, echocardiogram and ocular examination showed no evidence of sarcoidosis. A sarcoid-like reaction, not systemic sarcoidosis, was diagnosed because no other granulomatous lesions were detected other than mediastinal and hilar lymphadenopathy. Seminoma was in complete remission, and the patient received no adjuvant therapy. Nine months after surgery, enhanced CT of the chest revealed spontaneous remission of the mediastinal and bilateral hilar lymphadenopathy (Fig. 1C). In the subsequent four years, he has had no recurrence of seminoma or sarcoid-like lymphadenopathy and has not had any additional treatment.

**Discussion**

Sarcoid-like reaction is thought to be an immunological hypersensitivity to tumor-associated antigens, although the precise pathogenesis is unknown (1, 3). It may be an anti-neoplastic immune phenomenon that represents a host defense against the spread of tumor. Indeed, a sarcoid-like reaction is associated with a better prognosis in patients with gastric lymphoma and Hodgkin’s lymphoma (4, 5). Support for this view is that a sarcoid-like reaction is more commonly found during restaging PET/CT examinations in patients with suspected recurrence than in those undergoing PET/CT for primary tumor staging (2).

Sarcoid-like reaction is usually found in regional lymph nodes and tumor stroma itself (1, 3). The causative antigens may be shed from tumor cells or released during tumor necrosis and induce a host’s immune response in the tumor tissue itself or after transportation to regional lymph nodes. This reaction also has been detected in sites not involved with the tumor, as in the present case. A more distant or systemic reaction may be mediated by humoral and T cell-mediated factors, resulting in the recruitment and activation of macrophages. Possibly, a sarcoid-like reaction at distant sites may represent micrometastases. Tjan-Heijnen et al reported a case of sarcoid-like reaction in mediastinal lymph nodes that was accompanied by a microscopic relapse of seminoma, which was detected not by the initial histopathological examination but by an additional immunohistochemical analysis (6). In such a case, the sarcoid-like reaction may have been protective against the spread of tumor. Sieber and Duggan reported a case of mixed embryonal seminomatous testicular cancer with a bilateral hilar sarcoid-like reaction (7). During the observation period, the elevated alpha-fetoprotein returned to normal without antitumor treatment, indicating a spontaneous remission of the testicular tumor through the sarcoid-like reaction.

The paradoxical development of systemic sarcoidosis or a sarcoid-like reaction during chemotherapy is very rare, and
Figure 2. Biopsy specimen. A. Multiple noncaseating granulomas without any residual tumor cells in the mediastinal lymph node (Hematoxylin and Eosin staining). B. Noncaseating granulomas with multinucleated giant cells in the mediastinal lymph node (Hematoxylin and Eosin staining). C. No residual tumor cells or granulomatous lesions, only fibrous tissue in the paraaortic lymph node (Hematoxylin and Eosin staining).

has been reported only in limited numbers of cases of malignant lymphoma, osteosarcoma and solid tumors (8-10). Although the association between seminoma and sarcoidosis or a sarcoid-like reaction has been well recognized, a paradoxical case during chemotherapy for seminoma has not been reported (2). Yao et al described a paradoxical case of sarcoid-like reaction developing during CDDP monotherapy and radiation for squamous cell carcinoma of the tongue (11). Among the chemotherapeutic agents used in the present case, CDDP may have induced the reaction, while chemotherapy can suppress immune responses in most cases.

In the current case, the chemotherapy-induced breakdown of tumor cells might have produced the causative antigens, resulting in the formation of noncaseating granulomas during the treatment. However, it is more difficult to explain why the reaction developed not in tumor tissue or regional lymph nodes but only in distant lymph nodes, while there was no evidence of systemic sarcoidosis.

The distinction between a sarcoid-like reaction and a metastasis is often difficult. Chowdhury et al noted that semi-quantification using the maximum standardized uptake value (SUVmax) in FDG-PET/CT examinations was unlikely to be of discriminatory value (2). Rather, the distribution of lesions is more valuable. Solely mediastino-pulmonary localization with an absence of retroperitoneal lymphadenopathy is unusual in metastatic testicular cancer, especially if the patient has not undergone retroperitoneal lymph node dissection (3). Of the 510 patients treated with chemotherapy for metastatic testicular cancer at Memorial Sloan-Kettering Cancer Center, only four patients (0.8%) had exclusively mediastinal metastatic localization (12). The present case was more unusual because of lack of preceding abdominal recurrence and the paradoxical clinical course.

In conclusion, when a paradoxical lymphadenopathy occurs in spite of otherwise successful chemotherapy for a neoplastic disease, we should consider the possibility of a sarcoid-like reaction even if it occurs during or immediately after treatment. Histopathological examinations can be useful for a precise diagnosis and appropriate decision making.

References


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