Primary Lung Cancer Associated with Diffuse Granulomatous Lesions in the Pulmonary Parenchyma


A 60-year-old man was admitted to our hospital for productive cough. Chest roentgenography and CT scan disclosed a left hilar tumor invading the mediastinum with mediastinal lymphadenopathy and diffuse micronodular shadows in both lung fields. A biopsied sample of the tumor revealed squamous cell carcinoma, while noncaseating epithelioid cell granulomas were observed in the samples obtained by transbronchial lung biopsy. The granulomas in the pulmonary parenchyma were determined to be sarcoid reactions secondary to lung cancer, since there was no evidence of sarcoidosis. Combination chemotherapy was effective for the tumor, and the granulomas disappeared after completion of the chemotherapy. These findings suggest the presence of a relationship between sarcoid reactions and lung cancer in this case.

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Introduction

Noncaseating epithelioid cell granulomas are observed in patients with malignant disease as sarcoid reactions without sarcoidosis. Sarcoid reactions in malignant disease appear in close association with tumors, in regional lymph nodes with or without associated tumor infiltration, or in more distant locations. These reactions occur with a wide range of malignant tumors, and their overall frequency in patients with cancer has been reported to be 4.4% (1). We report here an interesting case of primary lung cancer simultaneously accompanied by diffuse noncaseating epithelioid cell granulomas in the pulmonary parenchyma.

Case Report

A 60-year-old man was admitted to our hospital on April 22, 1994 for productive cough. He had been a civil engineer for about 40 years. He was a heavy smoker (Brinkman index, 1,200) and had a history of hypertension and gastric ulcer from the ages of 54 and 55, respectively. However, he had been quite healthy with no respiratory symptoms until 3 months prior to admission, when he noted progressive productive cough and visited a local clinic, and was informed of an abnormal shadow on chest X-ray for the first time. No pulmonary disease had been detected in the medical checks he had undergone on a yearly basis.

On physical examination, he was alert, with normal body habitus. Body temperature on admission was 36.3°C, blood pressure 130/70 mmHg, pulse regular at 96 bpm, and respiratory rate 16 breaths per minute. Breath sounds were diminished in the left upper lung field, heart sounds were clear, and no abnormality was found in the head, neck, or abdomen.

The complete blood count was normal except for mild eosinophilia (6%). The erythrocyte sedimentation rate was moderately increased (45 mm/h). Blood chemistry tests including serum Ca level (10.0 mg/dl) disclosed no abnormal findings, and tumor markers including CEA and SCC were normal, but an increased level of angiotensin-converting enzyme (ACE) (42.2 IU/l; normal range, 7.7–29.4 IU/l) was noted. Pulmonary function testing demonstrated a mild restrictive pattern of disturbance (%VC, 75.5%; FEV1.0%, 75.1%), with decreased diffusion capacity (%DLCO, 59.7%). Arterial blood gas analysis also demonstrated mild hypoxemia (PaO2, 74.6 Torr; PaCO2, 39.1 Torr). The PPD skin test was negative.

A chest roentgenogram obtained on admission revealed a left hilar mass shadow with a normal-sized right hilum and bilateral diffuse micronodular shadows (Fig. 1). These shadows...
were not present at the patient's previous medical check.

A computed tomogram (CT) of the chest revealed a tumor attached to the left pulmonary trunk with disappearance of the fat plane, suggesting direct mediastinal invasion by the tumor. Mediastinal lymphadenopathy (#1, 2, 4, 6, and 7) was noted. Micronodular lesions were present in both lung fields, and an especially large nodule (1 cm in diameter) was observed in right S3 (Fig. 2A).

Bronchofiberscopic examination demonstrated an obstruction by the tumor of the left upper bronchus. A biopsied sample of the tumor contained poorly differentiated squamous cell carcinoma (Fig. 3A). In addition, transbronchial lung biopsy samples from right S3, S4, and S8 contained noncaseating epithelioid cell granulomas with Langhans'-type giant cells (Fig. 3B). In addition, a CT-guided needle biopsy sample from the right S3 nodule revealed metastasis of squamous cell carcinoma surrounded by a similar granulomatous lesion. Several sections of the sample from primary tumor were further examined in order to check carefully for concomitant granulomatous lesions; however, there were no components of such lesions in the tumor. The patient's lung cancer was therefore T2N2M1, stage IV. 67Ga scintigraphy revealed accumulation in tumor and both lung fields, and ophthalmologic examination disclosed no findings of sarcoidosis.

Combination chemotherapy consisting of ifosfamide (1,300 mg/m², days 1 to 5), cisplatin (20 mg/m², days 1 to 5), and vindesine (3 mg/m², days 1 and 8) was begun on May 24, 1994 (2). This combination chemotherapy was effective and was repeated every 4 weeks without severe toxicity. The percent reduction of primary tumor remained about 30%, but the mediastinal lymphadenopathy and metastatic right S3 nodule were both remarkably reduced in size. The micronodular shadow on chest CT became unclear after one cycle of chemotherapy, and almost disappeared by October 27 (Fig. 2B). At that time, the serum level of ACE had decreased to within normal range (22.7 IU/l).

He was discharged from our hospital on November 28, 1994. However, he was readmitted 2 months later due to rapid recurrence of the primary tumor, and underwent 60 Gy radiation therapy from January 25 to February 21, 1995. The tumor responded to the therapy briefly, but he died 19 months after the initiation of chemotherapy. The micronodular shadow never recurred after recurrence of the tumor.

Figure 1. Chest roentgenogram on admission revealing a left hilar mass shadow. Bilateral diffuse micronodular shadows are also noted.

Figure 2. Chest CT scans. A) On admission. Left hilar tumor, metastatic nodule in right S3, and bilateral diffuse micronodular lesions are shown. B) After completion of chemotherapy, the percent reduction of the primary tumor remained at about 30%; however, the metastatic lesion exhibited a marked response. The micronodular lesions also disappeared.
Discussion

Sarcoidosis is a multisystem disorder of unknown etiology. It can affect all organs, and commonly presents with bilateral hilar lymphadenopathy and pulmonary infiltrates. Frequently observed immunological features of sarcoidosis include depression of cutaneous delayed-type hypersensitivity and activation of helper T lymphocytes at sites of involvement (3). Localized groups of epithelioid cell tubercles of sarcoid type may be observed in a variety of tissues as a response both to foreign bodies and to such infiltrative processes as malignant disease. Such histological changes, which are not indicative of systemic sarcoidosis, have been termed “sarcoid reaction”. Tumor-related sarcoid reactions may be found in lymph nodes draining an area containing malignant tumor, in the tumor itself, and even in nonregional tissues. They have been reported to occur in a variety of malignant diseases, with particularly high incidences in lymphoproliferative disorders such as Hodgkin’s disease (13.8%) and non-Hodgkin’s lymphoma (7.3%) (1). The overall incidence of this condition in patients with carcinoma has been reported to be 5.8% (4), 5.6% (5), and 0.26% (6) in three independent studies. The average incidence in these reports is 4.4%, as reviewed and summarized by Brincker (1). In a lung cancer series, Jepsen reported that sarcoid reactions in regional lymph nodes were observed in 11 (3.4%) of 325 cases (7), and Laurberg reported a similar incidence of 3.2% in 630 cases (8).

The cause of sarcoid reactions has remained unclear, although hypotheses have been advanced that sarcoid reactions are associated with a host-versus-tumor response (9), and that these reactions are caused by degradative substances released by tumor cells and/or their metabolites (10). However, as described by Brincker (1), sarcoid reactions seem not to be a result of direct interaction between malignant tumors and lymph nodes, since such reactions are more commonly observed in lymph nodes without metastases than in nodes with metastases. Therefore, sarcoid reactions might be caused by soluble factors from tumor cells. The exact nature of such factors has not been determined; however, experimental models have demonstrated that many noninfectious agents such as immune complexes, peptides, and modified cells can serve as granuloma-inducing agents (11).

It is usually difficult to determine whether noncaseating epithelioid cell granulomas coexisting with malignant disease represent sarcoid reaction or true systemic sarcoidosis. In the present case, the patient’s pulmonary granulomatous lesions were considered sarcoid reactions secondary to lung cancer, for the following reasons: 1) there was no clear evidence of hilar lymphadenopathy in sites unaffected by lung cancer; 2) there were no extrathoracic lesions suggestive of sarcoidosis; 3) noncaseating epithelioid cell granulomas were demonstrated adjacent to the site of metastasis; 4) the granulomas and lung cancer were simultaneously detected in this patient, who had been undergoing annual medical checks; and 5) the granulomatous lesions of the pulmonary parenchyma disappeared as the tumor became smaller. To meet the diagnostic criteria for sarcoidosis, it is necessary to confirm the presence of granulomatous lesions in at least two different organs. Although mediastinal lymphadenopathy was observed in addition to the granulomatous lesions in the pulmonary parenchyma in this case, it is unclear whether it was due to the development of noncaseating epithelioid cell granulomas, since histological examination of it was not performed. Given the disease stage of this patient, invasive examination with mediastinoscopy appeared to be contraindicated. The finding that granulomatous lesions disappeared with a decrease of tumor load by chemotherapy may not be generally acceptable as a criterion distinguishing between sarcoid reaction and true systemic sarcoidosis. However, to our knowledge, there have been no reports of the improvement of true sarcoidosis by chemotherapy for complicated cancer. This
indirect evidence appears to support the diagnosis of sarcoid reaction in this case. In addition, the elevated serum ACE level observed in this case is not necessarily indicative of sarcoidosis, since ACE is thought to be produced by epithelioid granuloma cells (12), and the serum level of ACE may be increased simply if large numbers of epithelioid granuloma cells are present. Concerning differences in histological classification between sarcoid reactions and true sarcoidosis, Symmers reported that the noncaseating epithelioid granulomas observed in sarcoid reactions have unclear borders with adjacent lymph node tissues and a more scattered pattern of distribution than those in sarcoidosis (13). However, in practice it appears to be difficult to distinguish the two lesions by histological examination alone. Brincker reviewed 41 cases of sarcoidosis occurring before or concurrent with a solid tumor, up to 16 (39%) of which were reported to be sarcoidosis occurring simultaneously with tumor (14). It is possible that these cases included those of sarcoid reactions secondary to tumors; therefore, distinctive criteria for sarcoidosis coexisting with a malignant disease are necessary.

Notably, in the present case the noncaseating epithelioid cell granuloma lesions in the pulmonary parenchyma disappeared after chemotherapy. Primary tumor response occurred simultaneously with near disappearance of both mediastinal lymphadenopathy and metastatic tumor. In addition, this is the first report that the serum level of ACE was demonstrated to decrease to within normal range in serial measurements during chemotherapy. These findings suggest the presence of a relationship between sarcoid reactions and lung cancer in this case, and appear compatible with the hypothesis of Brincker that sarcoid reactions are caused by soluble factors released from tumor cells. However, sarcoid reactions did not recur after regrowth of the tumor in our patient. We have no clear explanation for these findings. The latter finding may have been due to immune depression, which often develops in patients with tumor progression.

The relationship between sarcoidosis (or sarcoid reactions) and malignant disease should be considered briefly. Cases of sarcoidosis have been reported to complicate a variety of malignant diseases to a significant extent, especially lymphoproliferative disorders and lung cancer (15–17). On the other hand, cases of malignant disease associated with sarcoid reactions have been reported to have a better prognosis than those without sarcoid reactions (1). These findings may provide important clues for determining the cause of sarcoidosis.

References