Corticosteroid Refractory Radiation Pneumonitis that Remarkably Responded to Cyclosporin A

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Abstract

Radiation therapy is commonly used for the treatment of lung cancer. However, radiation pneumonitis frequently occurs as a complication of the radiation therapy. Although corticosteroids are widely used for the treatment of radiation pneumonitis, they are not always effective. In this report, we used cyclosporin A in the treatment of a patient suffering from steroid-refractory radiation pneumonitis. To our knowledge, this is the first report in which cyclosporin A was successfully used in the treatment of radiation pneumonitis.

Introduction

Radiotherapy is commonly used for the treatment of intrathoracic neoplastic diseases. It has been reported that radiation pneumonitis occurs in approximately 5 to 15% of patients who have received radiation therapy for lung cancer (1, 2). It is usually recognized between 2 to 6 months from the end of radiotherapy (3). Clinical symptoms are characterized by the development of cough, shortness of breath, and fever. Arterial blood gases often show hypoxemia and an increased alveolar-arterial gradient of oxygen. Of all diagnostic tests, the chest radiograph is undoubtedly the most crucial test. The hallmark of radiation pneumonitis is the straight, sharp edge of the infiltrate, corresponding to the boundary of the irradiated areas (3, 4). No definite therapy has been established to improve radiation pneumonitis. In severe cases, however, most clinicians agree with steroid usage (3).

Currently, immunosuppressive agents are used in some patients who do not respond to corticosteroids. Since an immunologically mediated mechanism is suggested by many investigators as the cause of radiation pneumonitis, the combination of a corticosteroid and immunosuppressive agents may be effective in patients with severe radiation pneumonitis (5).

In this paper, we report a patient with steroid-refractory radiation pneumonitis who was successfully treated with cyclosporin A.

Case Report

A 76-year-old man was admitted to our hospital in June 2001. He had a medical history of smoking. One month prior to hospitalization, he had experienced hemoptysis and right chest pain. Physical and laboratory examinations disclosed no abnormalities. Arterial blood gases while breathing room air showed an arterial oxygen tension of 77 mmHg and arterial carbon dioxide tension of 37 mmHg. Lung function studies showed a vital capacity of 86.8% and forced expiratory volume in 1s was (FEV1) 57.8%. Chest radiograph and a computed tomography (CT) scan of the thorax revealed a 4x2x2-cm mass in the right hilar area with right hilar lymphadenopathy (Fig. 1A, B). Fiberoptic bronchoscopy showed an extrabronchial compression of the right B3 and cytologic findings were positive for small cell carcinoma. The staging of lung carcinoma was consistent with a limited disease (stage T2N1M0). The patient was treated with carboplatin, doxorubicin, and etoposide with concomitant radiotherapy. Four cycles of chemotherapy with the same agents were given. The patient received a total of 55.2 gray (Gy) radiation using 10-MV X-ray to a field encompassing the primary tumor with a 12x11-cm field size. Radiotherapy was given over 5 weeks. Finally, he achieved clinical complete response (CR).

Two months after completion of radiotherapy, the patient developed a non productive cough, high-grade fever, and arterial blood gases examined while breathing room air showed an arterial oxygen tension of 65 mmHg and arterial carbon dioxide tension of 32 mmHg. The chest radiograph revealed shaggy infiltrates, corresponding to the previous irradiated areas (Fig. 2A) and the CT scan of the thorax revealed ground glass opacities (Fig. 2B), suggesting the development of radiation pneumonitis.
Radiation Pneumonitis Treated with Cyclosporin A

Figure 1. Chest X-ray and computed tomography (CT) findings on admission. A) Chest X-ray shows a right hilar mass shadow. B) CT scan shows a 4×2×2-cm mass in the right hilar area with the right hilar lymphadenopathy.

monitis. He was treated with 500 mg of methylprednisolone drip per day for three days, and the symptoms and pulmonary infiltrates resolved gradually. During the period maintenance prednisolone at the dosage of 60 mg per day was beneficial, but decreasing to a dose of 30 mg per day led to increased symptoms and worsening of the chest radiograph. Since “re-bound” pneumonitis following the withdrawal of steroid therapy was suspected, steroid pulse therapy was reinstituted. However, there was no apparent clinical or radiological improvement at that time. Finally, 30 mg of oral prednisolone per day with 150 mg (3 mg/kg) of oral CsA, per day was initiated. Over the ensuing month, we decreased the dosage of prednisolone successively. Accordingly, a gradual improvement in dyspnea with stabilization of radiologic findings was observed. Presently, the patient is well and shows no evidence of recurrent lung carcinoma.

Figure 2. Chest X-ray and CT findings obtained 2 months after completion of radiotherapy. A) Chest X-ray shows extensive infiltrates in right upper lobe, corresponding to the previous irradiated areas. B) Chest CT demonstrates extensive interstitial shadow in the right upper lobe and superior segment of the right lower lobe.
During the treatments, we successively measured his serum CRP, surfactant protein A (SP-A), surfactant protein D (SP-D) and Interleukin-6 (IL-6) levels as markers of the activity of radiation pneumonitis (6, 7). In this patient, these markers increased even after steroid pulse therapy, compared with the baseline levels before radiotherapy. However, they decreased remarkably after the CsA administration (Fig. 3).

Discussion

Explanations for radiation pneumonitis have focused on direct damage to type II pneumocytes and endothelial cells leading to the release of a “cascade of cytokines” including growth factors (8–10). In turn, growth factor receptors on fibroblasts may be activated and result in collagen production and fibrosis. Another proposed mechanism of lung injury attributable to irradiation postulates that radiation treatment results in increasing alveolar-capillary permeability and, in turn, leads to decreased alveolar stability and loss of airspace protection (11). Other investigators have suggested that lung injury results from the production of free radicals that could cause damage to structural macromolecules and leaky cell membranes (12, 13). The aforementioned mechanisms presume the direct damage to lung tissues caused by irradiation. None of these theories, however, can adequately account for the occurrence of injury outside the field of irradiation.

Currently, an immunologically mediated mechanism seems to be most plausible. One suggestion has been that the initial local radiation damage may cause the release of autoantigens that are recognized by activated pulmonary lymphocytes. The action of these lymphocytes leads to the development of a diffuse bilateral lymphocytic alveolitis (14, 15). In addition, Gibson et al reported that an immunologically mediated mechanism such as hypersensitivity pneumonitis may explain the injury both in irradiated and unirradiated lung (16). They performed bronchoalveolar lavage and found intense alveolar lymphocytosis not only in the irradiated lung but also in the contralateral lung. This finding suggests that radiotherapy causes immunologically mediated mechanisms. In fact, McCarty et al reported the successful use of azathioprine as an immunosuppressive agent in a patient with severe radiation pneumonitis (5). Under this immunological background, we used CsA in a patient with steroid-refractory radiation pneumonitis.

CsA is a well-established immunosuppressant that acts on CD4+ T cells by blocking transcription of the interleukin-2 gene. This agent has been applied to patients with autoimmune connective tissue disease in addition to organ transplantation (17–20). The efficacy of this agent for several diseases combined with interstitial pneumonitis is recognized. CsA reduces the humoral and cellular immune response and may have a
role in the treatment of cryptogenic fibrosing alveolitis (21).

In contrast to other immunosuppressive agents, such as azathio- 
prine, CsA appears to be free from myelotoxicity and does not 
impair the level or proliferative capacity of hematopoietic 
stem cells (22). In addition, CsA is a fairly safe drug, because 
no rebound phenomenon is observed after discontinuation, and 
the frequency of side effects seems to be low if the serum con-
centration is monitored carefully (17). Elderly patients with 
steroid-dependent radiation pneumonitis can have severe side 
effects including immune suppression, weight gain, osteoporo-
sis, and endocrine dysfunction. Therefore, we treated our pa-
tient with CsA, and succeeded in improving his lung involve-
ment and symptoms without any complications due to corti-
costeroids.

The fundamental question in the present case is whether CsA 
affects the growth of residual carcinoma or not. Because we 
know that immunosuppressive therapy has the potential for 
increasing the incidence of certain malignancies. Hojo et al 
reported that CsA can promote cancer progression by a direct 
cellular effect that is independent of its effect on the host’s 
immune cells, and that cyclosporine-induced TGF-β produc-
tion is involved in this mechanism (23). Several conflicting 
data are presented in this field, however, the bulk of the evi-
dence suggests that immunosuppression favors the growth of 
existing cancer cells (24). Therefore, the administration of CsA 
should be limited to patients who suffer from uncontrollable 
radiation pneumonitis with corticosteroids. In addition, CsA 
should not be used for a long period after improvement of the 
radiation pneumonitis.

In conclusion, CsA is worthy of being applied for progressed 
radiation pneumonitis. It offers a safe, well-tolerated option in 
the treatment of patients with radiation pneumonitis. Additional 
patients at our institution will be treated with CsA combined 
with corticosteroids to further elucidate its role in the manage-
ment of severe radiation pneumonitis.

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