[CASE REPORT]

Radiation Pneumonitis with Eosinophilic Alveolitis in a Lung Cancer Patient

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Abstract:
A 59-year-old woman suffering from dry cough and dyspnea was admitted to our hospital. She had undergone concurrent chemo-radiotherapy five months earlier. Chest computed tomography revealed bilateral ground-glass opacities extending outside the irradiated lung field. Her eosinophil numbers were increased in both the peripheral blood and the bronchoalveolar lavage fluid; therefore, she was diagnosed with radiation pneumonitis accompanied by eosinophilic alveolitis. Steroid therapy promptly improved the pneumonitis. Radiation pneumonitis accompanied by eosinophilic alveolitis extending outside the irradiated field is rare. Bronchoalveolar lavage is useful for a diagnosis, and steroid therapy is effective for treatment.

Key words: lung cancer, radiation pneumonitis, bronchoalveolar lavage, eosinophilia, steroid

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Introduction
Thoracic radiotherapy is often performed for lung cancer; however, radiation pneumonitis is an inevitable complication (1). Although the findings of radiation pneumonitis are usually confined to the irradiated lung field, lesions occasionally extend outside the irradiated field (2). The total cell counts and lymphocyte numbers generally increase in the bronchoalveolar lavage fluid (BALF) for radiation pneumonitis; however, the eosinophil numbers only rarely increase (3, 4). Although a few cases of radiation pneumonitis with eosinophilic alveolitis in breast cancer patients have been reported, such reports in lung cancer patients are quite rare. We herein report a case of radiation pneumonitis with eosinophilic alveolitis in a lung cancer patient.

Case Report
A 59-year-old woman was diagnosed with lung adenocarcinoma in the left lower lobe harboring a EGFR gene active mutation 15-base pair deletion in exon 19 of clinical stage IIIA (cT1aN2M0) (Fig. 1A). She had been seeing her doctor regularly at a local hospital for the treatment of bronchial asthma and allergic rhinitis. Her medications were olopatadine hydrochloride, mequitazine, carbocysteine, fluticasone propionate inhalant and fluticasone furoate collumbarium. There had been no change in her medications after the diagnosis of lung cancer. She had no history of smoking or drug allergy. She was treated with 4 cycles of combined chemotherapy consisting of cisplatin and tegafur/gimeracil/oteracil concurrently with a total 60 Gy/30 Fr of thoracic radiotherapy (Fig. 1B). The lung tumor subsequently reached stable disease status with this treatment. However, five months after the end of radiotherapy, chest X-ray showed consolidation within the irradiated field (Fig. 1C). Because of the lack of symptoms, we followed this finding up as mild radiation pneumonitis; however, 12 days later, the patient developed dry cough and dyspnea and was admitted to our hospital again.

Her vital signs were as follows: 98 beats/min pulse rate with a regular rhythm, 127/86 mmHg blood pressure, 36.4°C body temperature, 15 breaths/min respiratory rate and 95% percutaneous oxygen saturation on room air. No
abnormalities were found on a physical examination including auscultation. Laboratory data revealed an extremely elevated peripheral eosinophil count (6,060 cells/μL) and increased C-reactive protein (CRP) level (9.07 mg/dL). Chest computed tomography (CT) revealed straight linear consolidation confined to the irradiated field and ground-glass opacities in the bilateral upper lobes (Fig. 2). The BALF of left B1+2 on the day following administration revealed differential cell counts: macrophages, 2%; lymphocytes, 3%; neutrophils, 1% and eosinophils, 95%. The total cell count was 1.73×10⁶ cells/mL, and the CD4/CD8 ratio of lymphocytes was 2.1. A histopathological examination by a transbronchial lung biopsy of the left upper lobe showed an increased number of eosinophils in the terminal bronchioles and alveoli with no fibrotic changes (Fig. 3). No bacteria, mycobacteria or fungi were detected in the sputum or BALF.
She was diagnosed with radiation pneumonitis accompanied by eosinophilic alveolitis and treated with systemic corticosteroids (500 mg of methylprednisolone) for 3 days (Fig. 4). Four days after the initiation of steroid therapy, her dry cough and dyspnea had markedly improved, and the peripheral eosinophil count had decreased from 6,060 to 130 cells/μL. The ground-glass opacity outside the irradiated field also improved on chest X-ray and chest CT (Fig. 5). She was prescribed 30 mg of oral prednisolone, and the dose was tapered over 8 months before she eventually discontinued steroid therapy.

However, she developed dyspnea again one month after steroid therapy discontinued. Chest X-ray showed a relapse of the ground-glass opacity outside the irradiated field in the left upper lung field, and the peripheral eosinophil count had increased again from 130 to 3,380 cells/μL (Fig. 6). We therefore diagnosed her with relapse of radiation pneumonitis accompanied by eosinophilic alveolitis. Prednisolone (20 mg) was orally re-administered, resulting in the rapid improvement of the pneumonitis.

Figure 4. The clinical course of the present case. Steroid therapy was administered on day 2. The numbers of peripheral eosinophils and the level of C-reactive protein decreased rapidly after steroid administration. CRP: C-reactive protein, Eosino: Eosinophils

Figure 5. (A) Chest X-ray two months after steroid administration showed the disappearance of ground-glass opacity in the left upper lung field. Partial consolidation within the radiation field remained. (B, C) Chest CT two months after steroid administration showed narrow straight linear consolidation in the left lower lobe. Ground-glass opacities in the bilateral upper lobes disappeared.
Most patients receiving thorax radiotherapy over 40 Gy develop radiation pneumonitis (1). Although the findings of radiation pneumonitis are generally confined to the irradiated field, ground-glass opacity or consolidation is occasionally detected outside the treatment area; indeed, Jenkins et al. reported that such events occur at a rate of 24% (2). When opacities are detected outside the irradiated field, BAL is useful for excluding other possible causes, such as infectious pneumonia or cancer relapse. The BALF of radiation pneumonitis usually shows an increased number of total cells and lymphocytes (3, 4). However, in the present case, the eosinophil counts of the lavage fluid were increased. Toma et al. found that 5 out of 65 breast cancer patients with radiation pneumonitis showed opacities outside the irradiated field, while only 1 out of 65 patients showed increased eosinophils in the BALF (5). Radiation pneumonitis with eosinophilic alveolitis is therefore deemed to be quite rare.

We found only one previous report of a lung cancer patient with eosinophilic pneumonia after thoracic irradiation therapy (6). Steroid therapy resulted in the improvement of the infiltrates, just as in our present case. However, whether or not the patient experienced relapse of eosinophilic infiltrates after steroid discontinuation was not mentioned.

To investigate the risk factors, we compared our case with the nine previously reported cases of radiation pneumonitis accompanied by eosinophilic alveolitis (5-9). Seven of the 10 total patients had allergies or histories of bronchial asthma. An association between chronic eosinophilic pneumonia (CEP) and bronchial asthma has been suggested, so a similar relationship may exist between radiation pneumonitis with eosinophilic alveolitis and bronchial asthma (10). The mechanism underlying this relationship remains to be clarified. The pathophysiology of CEP is also unclear, although it has been suggested that increased Th2 inflammation in response to some sort of stimulation recruits eosinophils into the lung airspaces, causing eosinophilic infiltrates (11). Radiation injury has been reported to induce the upregulation of cytokines, including transforming growth factor-β, which activates Th2 inflammation (12). Considering that Th2 inflammation occurs easily among patients with type 1 hypersensitivity diseases, thoracic radiation may cause eosinophilic alveolitis outside of the irradiated area. For this reason, when patients with an allergy or suffering from bronchial asthma undergo thoracic radiotherapy, we should observe their course carefully, considering the possibility of pneumonitis with eosinophilic alveolitis.

The optimum treatment of radiation pneumonitis accompanied by eosinophilic alveolitis has not yet been established. All of the patients reported to date were treated with steroids, the same therapy used for CEP or symptomatic radiation pneumonitis. The initial treatment is prednisolone at 0.5 mg/kg once/day, and at least 6 months of dose tapering is recommended (13). In the present case, however, we administered pulse steroid therapy because of rapid aggravation of the ground-glass opacity. Steroid therapy rapidly improved her respiratory symptoms and peripheral blood eosinophilia. However, she experienced a relapse of radiation pneumonitis one month after steroid discontinuation, and retreatment was needed. Cottin et al. reported five breast cancer patients who had radiation pneumonitis with eosinophilic alveolitis and were treated with steroids, resulting in the rapid improvement of the pneumonitis (7). However, two of the patients experienced relapse of radiation pneumonitis over 14.3 months, and the re-administration of steroids was necessary. Radiation pneumonitis with eosinophilic alveolitis can be improved rapidly with steroid therapy, however the risk of recurrence during tapering of the steroid dose is unignorable.

In conclusion, radiation pneumonitis with opacities outside the irradiation field and increased eosinophil numbers in the BALF is rare. Patients with allergies or a history of bronchial asthma may develop this type of radiation pneumonitis more frequently than others, so such patients require careful observation when receiving thoracic radiotherapy. Steroid therapy is effective, but physicians should be aware of the possibility of relapse during tapering of the steroid dose.

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

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