LETTER TO THE EDITOR

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Invasive pulmonary aspergillosis in a patient with metastatic non-small cell lung cancer after treatment with gefitinib

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To the Editor,

Gefitinib is an established target agent for advanced non-small cell lung cancer with mutation in the epidermal growth factor receptor (EGFR) gene. The most common adverse effects associated with the use of gefitinib are acneiform skin rashes, diarrhea, and nausea, which are usually mild in severity and manageable [1]. Although interstitial lung disease (ILD) is an infrequent, but severe, adverse effect, gefitinib is better tolerated and less toxic than standard cytotoxic agents and does not typically cause myelosuppression, neuropathy, alopecia, or severe nausea [2]. Invasive pulmonary aspergillosis (IPA) may occur in patients with prolonged neutropenia, recipients of hematopoietic stem-cell transplants or solid-organ transplants, and patients with advanced acquired immunodeficiency syndrome or chronic granulomatous disease [3]. However, it is rare in patients with solid tumors without neutropenia. We describe a case of adenocarcinoma of the lung with multiple metastases, which responded to gefitinib, but developed fatal pneumonia with IPA.

A 49-year-old man admitted to our hospital with posterior neck pain and pain radiating to the left medial upper thigh and right peri-inguinal area, which had persisted for 1 month. He also experienced nausea and poor oral intake and had lost 6 kg in weight. The physical examination showed no specific abnormality. His initial chest radiograph showed multiple nodules in both lung fields, suggesting metastatic lung cancer (Fig. 1A). Chest computed tomography (CT) showed 2.3 cm pulmonary mass in the left lingular segment, with multiple nodules (Fig. 2A and 2B). Additional imaging performed included abdomen CT, brain magnetic resonance imaging, and bone scintigraphy. The findings were consistent with multiple brain, liver metastases, and bone metastases involving the entire spine, both pelvic bones and femurs, the ribs bilaterally, the right tibia and the mandible.

Bronchoscopy revealed stenosis of the lingular segment bronchus of the left upper lobe. The bronchial biopsy showed adenocarcinoma with a missense mutation in exon 21 of EGFR, with negative results for the KRAS mutation and anaplastic lymphoma kinase translocation. Palliative radiotherapy to the whole brain and sacrum was started on hospital day 5. It was completed after 14 days with a total irradiation dose of 3,600 cGy. Intravenous dexamethasone was administered concurrently from

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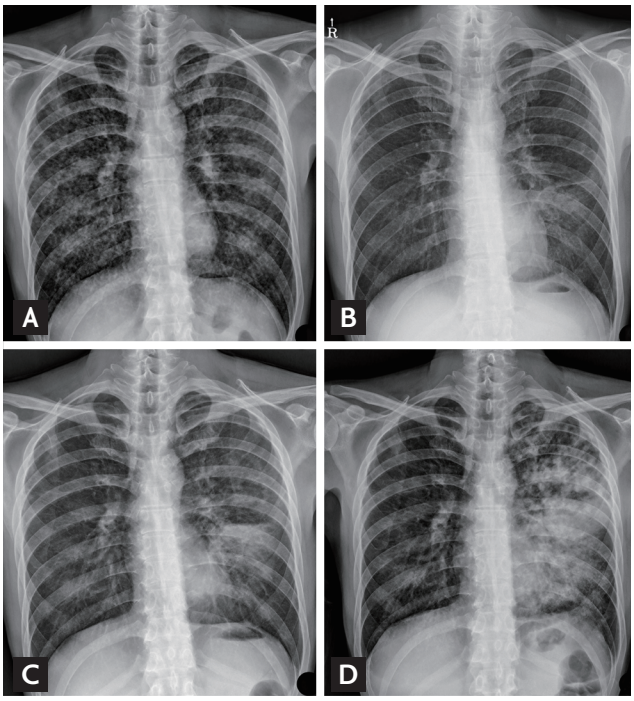

Figure 1. Chest radiographs. (A) Initial findings with multiple nodules in both lung fields. (B) Hospital day 19, showing improvement 12 days after administration of gefitinib. (C) Hospital day 20, showing pneumonic infiltration in the left upper lung field. (D) Hospital day 25, showing aggravation of consolidation on left lung.

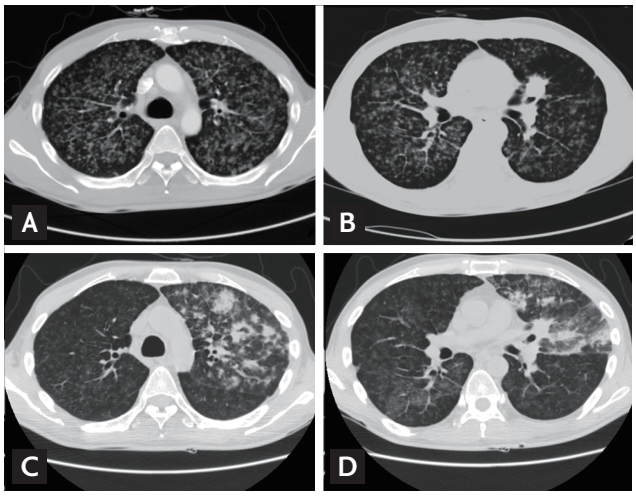

Figure 2. Chest computed tomography. (A, B) Initially multiple small nodules with a 2.3 cm pulmonary mass in the left lingular segment are seen. (C, D) On day 13 of gefitinib patchy ground-glass opacities and mass-like lesions with halo sign are shown, while the lung mass originally seen in the lingular segment has decreased in size.

hospital day 5 at a dose of 5 mg every 6 hours and tapered over 14 days. Oral gefitinib 250 mg per day was initiated on hospital day 7. Follow-up chest X-rays showed a dramatic improvement (Fig. 1B).

On hospital day 20, the patient complained of a cough and purulent sputum without fever or chills. A follow-up posteroanterior chest X-ray showed pneumonic infiltration in the left upper lung (Fig. 1C). Laboratory examinations showed an elevated white blood cell count of 17,450 cells/μL, with a neutrophil count of 97.2%, and C-reactive protein level of 29.81 mg/dL. Neutropenia was not observed at any time while hospitalized. On the same day, antimicrobial therapy with piperacillin/tazobactam was initiated to treat the hospital-acquired pneumonia. The gefitinib was stopped because ILD caused by gefitinib could not be excluded. Follow-up chest CT showed patchy ground-glass opacities and mass-like lesions with a halo sign. The previously noted lung mass in the lingular segment had decreased in size (Fig. 2C and 2D).

On hospital day 23, intravenous levofloxacin was added. On hospital day 25, the antibiotics were switched to vancomycin and meropenem since there was no significant improvement in the pneumonia and the radiographic findings had deteriorated (Fig. 1D). The patient was transferred to the intensive care unit on the same day due to increasing oxygen demands. Despite the broad-spectrum antimicrobial therapy, the infection worsened. Intravenous voriconazole was added empirically on hospital day 27 and the patient was intubated on hospital day 29.

A bronchoscopic biopsy performed on hospital day 29 showed invasive aspergillosis with hyaline hyphae and positive staining for periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) stain. Also, the blood drawn before administering the antifungal agent gave a positive galactomannan antigen test (2.19; reference range < 0.5).

The patient died on hospital day 32 despite hemodynamic support with an interventional lung-assist membrane ventilator device, continuous renal replacement therapy, and administration of high doses of inotropic agents.

Invasive aspergillosis is a severe opportunistic infection typically seen in highly immunocompromised hosts. Classical risk factors of IPA include prolonged neutropenia, hematopoietic stem cell transplantation and solid-organ transplantation, prolonged therapy with

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high-dose corticosteroids, hematological malignancy, cytotoxic chemotherapy, advanced acquired immune deficiency syndrome, and chronic granulomatous disease [3]. The most important risk factor is neutropenia, especially when there is an absolute neutrophil count of less than 500 cells/mm^3, with mortality rate exceeding 50%.

Increasing numbers of reports have documented IPA in patients without classical risk factors. These include patients with severe chronic obstructive pulmonary disease and critically ill patients [3]. According to a retrospective study, 2.6% of patients with lung cancer had invasive aspergillosis [2]. Mortality is devastating in these apparently less immunocompromised patients. Potential explanations of the high mortality of IPA in these patients are older age, poor pulmonary reserve, multiple comorbid illnesses, and a delayed diagnosis secondary to the low index of suspicion of this infection in this patient population. In addition, the nonspecific clinical and radiological presentation in this population and low sensitivity of other diagnostic test leads to underestimation [4]. Therefore, a high index of suspicion is warranted to avoid delay in the diagnosis and management. The isolation of *Aspergillus* species from a specimen from the lower respiratory tract should not be routinely dismissed as colonization, even if these patients are immunocompetent. The value of early diagnostic criteria, such as the galactomannan test, in this population needs to be proven in prospective trials. Development of a novel diagnostic test and adapted clinical diagnostic criteria for critically ill patients might help with the early diagnosis and early initiation of antifungal therapy, which would eventually lead to a better treatment outcome [3].

The risk factors of invasive aspergillosis in the patients with lung cancer were stage IV disease, recent chemotherapy, and corticosteroid use (more than 2 days) in univariate analysis. [2]. Although neutropenia was not observed in our case, the amount of corticosteroid administered with our patient (dexamethasone 20 mg once daily, then tapered) could be a sufficient dose to increase the risk of IPA. Yet, the possible role of gefitinib on development of IPA should not be disregarded. Recent studies reporting immune-modulating actions of gefitinib and other tyrosine kinase inhibitors support this idea. EGFR tyrosine kinase inhibitor such as gefitinib or erlotinib is under investigation in autoimmune disease because it was reported to modulate immune function through inhibition of T cell proliferation and activation [5]. Inhibition of gefitinib and other protein kinase inhibitors might influence immune system since protein kinases are fundamental components of various signaling pathways, including immune cells. Through this case, we suggest that the possibility of IPA should be considered during gefitinib treatment if pneumonic infiltrations persist despite intensive antibiotic therapy. High index of suspicion and an aggressive diagnostic work-up in clinical settings along with further researches estimating incidence of IPA in gefitinib treatment may improve clinical outcomes.

Keywords: Invasive pulmonary aspergillosis; Carcinoma, non-small-cell lung; Gefitinib

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Cersosimo RJ. Gefitinib: an adverse effects profile. Expert Opin Drug Saf 2006;5:469-479.
2. Yan X, Li M, Jiang M, Zou LQ, Luo F, Jiang Y. Clinical characteristics of 45 patients with invasive pulmonary aspergillosis: retrospective analysis of 1711 lung cancer cases. Cancer 2009;115:5018-5025.
3. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. Eur Respir Rev 2011;20:156-174.
4. Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. Clin Infect Dis 2006;43:577-584.
5. Brooks MB. Erlotinib and gefitinib, epidermal growth factor receptor kinase inhibitors, may treat non-cancer-related tumor necrosis factor-α mediated inflammatory diseases. Oncologist 2013;18:e3-e5.