CASE REPORT

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Lung Carcinoma Developing Afatinib-Associated Skin Reactions

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ABSTRACT Afatinib is an irreversible second-generation tyrosine kinase inhibitor. It is used to treat epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma. The most well-known side effects associated with afatinib are diarrhea, rashes or acne and stomatitis. Herein, we present a case of skin toxicity that developed in the late phase of afatinib treatment. A 51-year-old, non-smoker woman diagnosed with EGFR deletion-19 mutant advanced lung adenocarcinoma. Afatinib was initiated as the first-line treatment. At the twelfth treatment month, Grade-2 acneiform dermatitis, paronychia, and hand-foot syndrome developed. Despite the interruption or discontinuation of afatinib treatment and local/systemic steroid treatments, the lesions did not regress. The patient was responsive to afatinib; however, the treatment was discontinued in the eighteenth month of treatment. The treatment response may be predicted by the severity of skin toxicities owing to afatinib. They occur in the early treatment phase and are commonly observed at the Grade 1-2 level.

Keywords: Afatinib; epidermal growth factor receptor; hand-foot syndrome; lung adenocarcinoma; paronychia

An integral component of non-small cell lung carcinoma (NSCLC) is the lung adenocarcinoma. In 40-80% of NSCLCs, epidermal growth factor receptor (EGFR) is overexpressed. EGFR mutation is commonly detected in women, individuals of East Asian descent, and non-smokers.[1]

Afatinib, an oral tyrosine kinase inhibitor (TKI), is utilized in EGFR exon 19 deletions and exon 21 mutations in advanced NSCLCs. Additionally, its effectiveness in rare EGFR mutations has expanded its application compared to other TKIs.[2] Diarrhea is the most well-established side effect, which occurs in 17-22% of patients and can reach Grade 3.[3] The commonly occurring skin toxicities in the early treatment period are rashes or acne, stomatitis, and paronychia, particularly observed on the face and trunk and can be easily controlled. The lesions are painful, itchy, prone to infection, and may negatively affect quality of life. Skin toxicities, which develop owing to strong expression of EGFR, positively affect patient survival.[4,5] Herein, we present a case of advanced lung adenocarcinoma responding to afatinib treatment, where uncontrolled skin toxicities were developed despite local and systemic steroid treatments.

CASE REPORT

A 51-year-old non-smoker female patient with no known history of chronic disease developed a cough and shortness of breath that was initiated two weeks back. A mass was observed in the right mediastinum and upper lobe of the lung in the posteroanterior radiograph. Fluoro-D-glucose-positron emission tomography/computed tomography (FDG-PET CT) imaging was performed for the patient who was suspected of having malignancy in the foreground. FDG-PET CT images demonstrated a hypermetabolic mass (SUV_{max} 8.6), originating in the middle part of the right lung, covering the upper lobe anterior segment,

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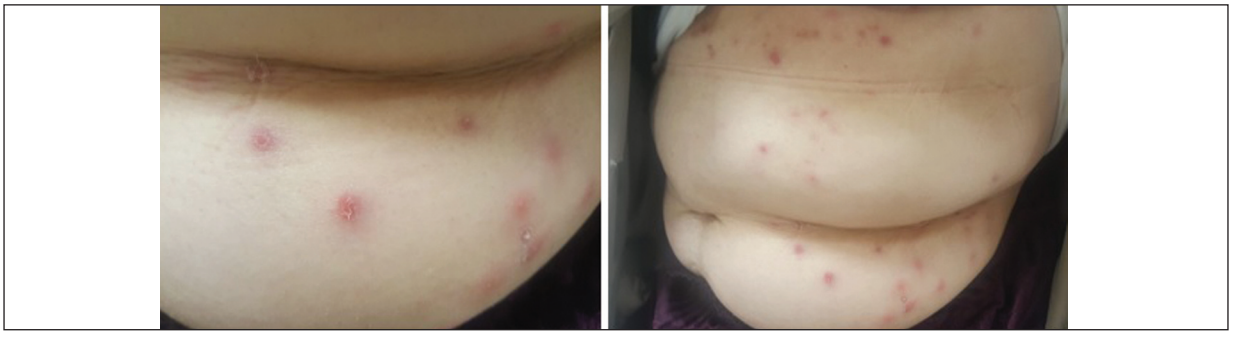

FIGURE 1: Itchy skin lesions with a papulopustular appearance on the patient's abdominal skin.

and accompanied by ground-glass weakening areas. Additionally, hilar, mediastinal, and left supraclavicular lymph node metastases, were observed. Lytic hypermetabolic bone metastases were observed in many bones, including the pelvis and vertebrae. Bronchoscopy was performed for tissue diagnosis. A malignant mass was observed obliterating the main bronchus of the right lung upper lobe. The pathology results of a patient who underwent bronchoscopic lavage and brushing biopsy revealed lung adenocarcinoma. The cranial magnetic resonance imaging performed to determine the presence of brain metastases did not reveal any pathological involvement. Additionally, mutation analysis was planned. Zoledronic acid 4 mg was initiated intravenously for the treatment of lytic bone metastases with pelvic and vertebral involvement. EGFR exon-19 deletion was detected in the next-generation sequencing analysis.

Afatinib 40 mg/day was initiated for a patient with metastatic EGFR mutant lung adenocarcinoma in the first-line treatment. According to Response Evaluation Criteria in Solid Tumours criteria, partial response was observed under afatinib treatment. However, Grade 1 acneiform dermatitis, paronychia, and hand-foot syndrome (HFS) developed in the twelfth month of treatment (Figure 1, Figure 2). The dose of afatinib was titrated (from 40 mg/day to 30 mg/day); however, side effects persisted. When Grade 2 skin toxicities were observed, the patient was referred to a dermatologist. The skin lesions regressed partially when the patient was treated with topical steroids (hydrocortisone 1% cream) and antibiotics (tetracycline-based) for 3 months; however, they did not disappear completely. The patient's skin

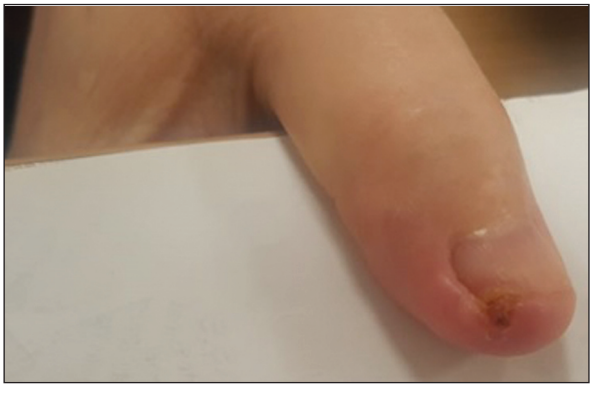

FIGURE 2: Paronychia appearance on the right-hand first finger.

lesions regressed one month after the drug was discontinued; however, the skin toxicities flared up when the drug was reinitiated at a low dose. Computed tomography images recorded to evaluate the treatment response of the patient demonstrated stable disease. Afatinib was continued at 30 mg/day. Based on the extent and severity of the skin lesions, topical steroids, antibiotherapy, and oral steroids were administered intermittently with dermatologist consultation. Treatments were continued until the skin lesions regressed to Grade-1 or disappeared. However, skin toxicity reached Grade-3 in the eighteenth month of afatinib treatment. The patient was hospitalized, and intravenous steroids and supportive treatment were administered. However, afatinib was discontinued. In the fourth month after discontinuation of afatinib, tumor progression and healing of skin lesions was observed . The biopsy taken from the progressive lesion revealed EGFR T790M mutations. Osimertinib, a third-generation TKI, was initiated as second-line therapy. The patient has been stable for 22 months with minimal residual disease under osimertinib therapy (Figure 3).

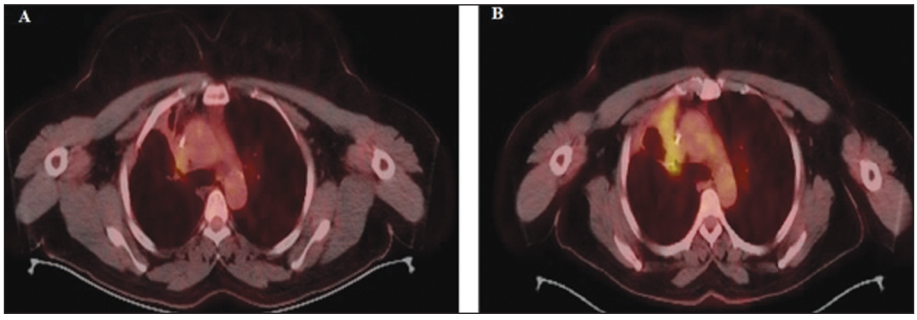

FIGURE 3: A) FDG-PET/CT sections showing lung carcinoma in remission at 12 months of afatinib therapy. **B)** FDG-PET/CT section showing progressive lung carcinoma four months after discontinuation of afatinib therapy. FDG-PET/CT: Fluoro-D-glucose-positron emission tomography/computed tomog.

ETHICAL STATEMENT

All procedures, including the informed consent, were conducted based on the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2000. The authors obtained all appropriate patient consent forms. The patient gave consent for the presentation of her images and other clinical information in the journal. The patient comprehended that all due efforts will be made to conceal her identity.

DISCUSSION

EGFRs are the most frequently detected mutations in NSCLCs.[1,6] Approximately 85% of EGFR-related mutations are exon 19 deletions or exon 21 L858R point mutations.[7] EGFR TKIs have been used in lung cancer treatment since the 2000s. The possibility of oral use and significant survival advantage has led to these drugs being recommended as the first-line therapy in patients with mutations.

Afatinib is a second-generation EGFR TKI that irreversibly blocks pan-ErbB. Studies have demonstrated that afatinib is superior to chemotherapy.[8] In the LUX-Lung 7 study, afatinib had a superior progression-free survival outcome than that of gefitinib (hazard ratio, 0.73; 95% confidence interval, 0.57 to 0.95).[9] Although the overall toxicity rates of EGFR TKIs are comparable, afatinib had a higher Grade 3-4 toxicity than that of the first-generation EGFR TKIs gefitinib or erlotinib. In 2013, afatinib was approved by the Food and Drug Administration for use in patients with EGFR exon 19 deletions or exon 21 (L858R) mutations in advanced/metastatic NSCLCs. Afatinib demonstrates the maximum survival benefit, particularly in patients with del-19 mutants, as in our case.[10]

The most common adverse events related to afatinib are rashes/acne, diarrhea, paronychia, and stomatitis/mucositis.[1,11] The most common and earliest adverse events in TKIs are skin toxicities. They can be observed as papulopustular rashes, xerosis, paronychia, mucositis, pruritus, alopecia, or eyelash growth.[12,13] HFS or palmar-plantar erythrodysesthesia are highly rare afatinib-related skin toxicities.[14,15] Nail changes such as paronychia, painful fissures, swelling, and granulomas, commonly in the big toe, may be observed in 4-56.8% of patients.[16] In our case, papulopustular eruptions on the abdominal skin, HFS, and paronychia developed owing to afatinib treatment. Additionally, as reported in the literature, the severity of skin reactions occurring with TKI treatment was observed to be associated with treatment response.[4,5]

The etiology of skin toxicities is still ambiguous; however, it occurs owing to the involvement of basal keratinocytes in the skin and the disruption of physiological EGFR signaling processes in the epidermis.[17] It generally begins as a rash one or two weeks after treatment and resolves spontaneously one month after TKI treatment is discontinued.[15] The duration and severity of symptoms may vary depending on the treatment dose. Contrary to expectations, skin toxicity in our case developed one year after the treatment. The patient had minimal exposure to sunlight, and skin toxicity developed late owing to taking protec-

tive measures. Additionally, the skin lesions of the patient who underwent afatinib dose titration and medical treatment for six months improved only when afatinib treatment was interrupted. Although there is no clear information regarding the pathophysiology of afatinib-related skin reactions, it was related to T lymphocytes.[17,18] In our patient, a more severe skin reaction developed when afatinib treatment was reinitiated, even at a low dose. A delayed type-4 hypersensitivity reaction, which is known to be associated with T lymphocytes, may have caused this situation.

Skin toxicities can cause infection, pain, and itching and adversely affect the quality of life, as observed in our patient. Additionally, it may cause depression, sleep disorders, treatment non-compliance, and increased costs owing to supportive treatments. Clinically, Grade 3-4 adverse effects may lead to dose reduction or treatment discontinuation.[15] In previous studies, 2.1-8% of patients required discontinuation of therapy owing to afatinib-related toxicities.[11,19] Owing to the development of Grade 3 skin toxicity in our case, afatinib treatment was permanently discontinued.

The primary treatment for adverse skin toxicities is based on inflammatory cell-reducing drugs.[20] Medical treatments comprise topical moisturizers, topical corticosteroid creams, tetracycline-based antibiotic treatments, and oral/intravenous steroids.[15] Moreover, sun protection, use of sunscreen, use of non-irritating skin products, and use of comfortable clothing/shoes may be recommended for prophylactic purposes.

In conclusion, the severity of skin reactions owing to TKIs can be associated with treatment response and survival benefits. Lesions can develop at any time of the treatment in a wide spectrum. Early detection and appropriate management of adverse events will increase treatment adherence, ultimately improving patients' quality of life and clinical outcomes.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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