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CASE REPORT

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Successful erlotinib rechallenge in an *EGFR*-mutant metastatic non-small cell lung cancer patient with afatinib-induced drug rash with eosinophilia and systemic symptoms: A case report

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Abstract

Tyrosine kinase inhibitors (TKIs) are the standard treatment for epidermal growth factor receptor (EGFR)-mutant advanced-stage non-small cell lung cancer (NSCLC). However, TKIs can cause some severe adverse events, which are more prevalent within first-generation EGFR-TKI use than with second-generation inhibitors. Herein, we report a case of a patient with advanced-stage *EGFR*-mutant NSCLC who developed drug reaction with eosinophilia and systemic symptoms (DRESS) after receiving treatment with afatinib. The patient was successfully rechallenged with erlotinib, without manifestations of skin rash in the following 6 months. Hence, erlotinib may be considered a potential substitute for other EGFR-TKIs following DRESS occurrence.

KEYWORDS

adenocarcinoma, drug reaction with eosinophilia and systemic symptoms, epidermal growth factor receptor, tyrosine kinase inhibitor

INTRODUCTION

Epidermal growth factor receptor (EGFR) mutations are the most common oncogenic driver events in non-small cell lung cancer (NSCLC).[1] Administration of tyrosine kinase inhibitors (TKIs) provides better progression-free survival and objective response rates than chemotherapy for patients with *EGFR*-mutant advanced-stage NSCLC.[2] However, EGFR-TKIs are associated with some adverse events including pneumonitis, hepatitis, diarrhea, and nail or skin disorders. Herein, we present a case of severe dermatological toxicity after afatinib use, which was successfully rechallenged with erlotinib.

CASE REPORT

A 53-year-old woman, with no history of allergies, presented to our outpatient department with a primary complaint of chronic cough for more than 6 months. Computed tomography findings were suggestive of left upper lung cancer with bone and contralateral lung metastases. A bronchoscopic biopsy confirmed adenocarcinoma diagnosis, and further genomic testing revealed an EGFR L858R substitution. For advanced-stage *EGFR*-mutant NSCLC, targeted therapy with afatinib (40 mg once daily) was prescribed. Three weeks after the first afatinib dose, the patient developed rashes with itching sensation on the trunk and limbs. Systemic prednisolone (20 mg/day) and topical steroids administration were ineffective. Thus, afatinib was discontinued and the patient was admitted for high-dose steroid treatment.

Physical examination revealed that the patient was febrile (38.8°C) with a heart rate of 111 beats/min, respiratory rate of 20 breaths/min, and blood pressure of 115/84 mmHg. Multiple confluent erythematous maculopapular rashes were observed on the face, trunk, and upper and lower extremities, with facial swelling and periorbital sparing (Figure 1A–D), which affected more than 50% of the body surface area (BSA). Multiple yellowish crusts and scales were observed on the face. Enlarged lymphadenopathy was palpable in the cervical and axillary areas. Laboratory test results revealed a white blood

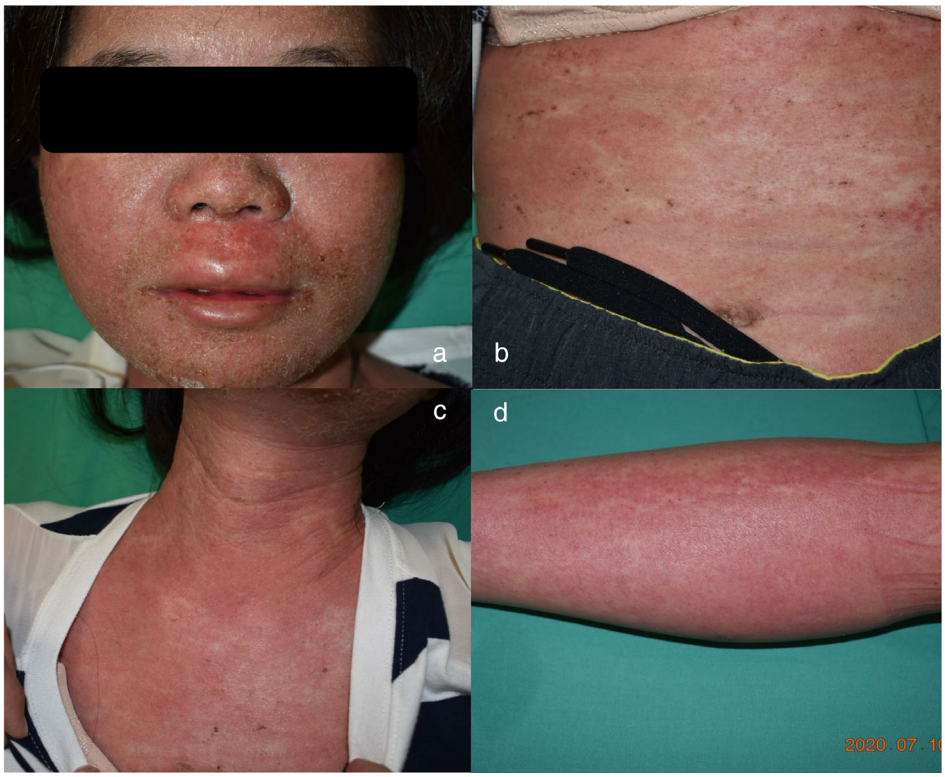

FIGURE 1 Cutaneous manifestation of drug rash with eosinophilia and systemic symptoms including (a) facial swelling and confluent erythematous maculopapular rash on the (b) abdomen, (c) chest, and (d) right thigh

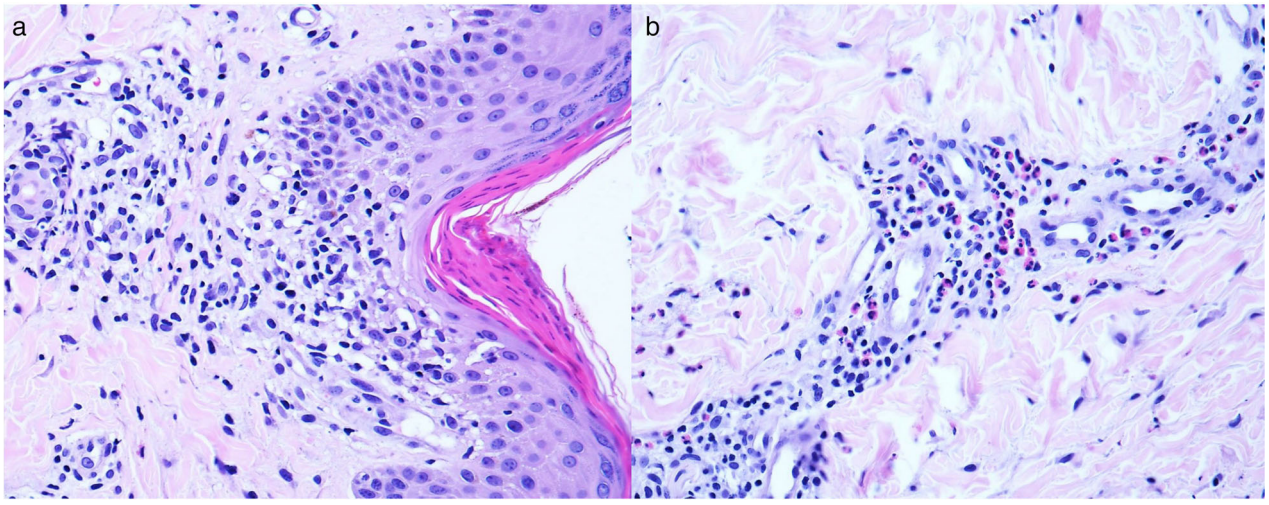

FIGURE 2 Hematoxylin and eosin staining of a skin biopsy from the right thigh. (a) Vacuolar alteration at the dermoepidermal interface. (b) Superficial perivascular infiltration of lymphocytes and eosinophils. Magnification: ×400

cell count of 21 300 cells/mm^3, with 33% eosinophils (absolute count: 7029 cells/mm^3) and 1% atypical lymphocytes. Alanine aminotransferase level was 45 U/l, and serum creatinine level was 0.9 mg/dl. The patient was negative for hepatitis B and C viruses, and human herpesvirus 6. Blood and urine cultures showed no evidence of bacterial infection. After consultation with a dermatologist, a diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) secondary to afatinib was considered. Further skin biopsy demonstrated interface dermatitis with superficial perivascular infiltration of lymphocytes and eosinophils, confirming DRESS diagnosis (Figure 2).

After admission, the patient received intravenous methylprednisolone (1 mg/kg/day). Although the rashes appeared sporadically, they gradually improved. The intravenous methylprednisolone dose was tapered to 0.5 mg/kg/day 2 weeks after admission and further tapered 1 week later. One month after steroid treatment, a rechallenge with erlotinib was initiated without recurrence of rash in the following 6 months.

DISCUSSION

DRESS is a potentially life-threatening drug reaction with atypical and diverse manifestations, including skin eruption, fever, hematological abnormalities, lymphadenopathy, and internal organ damage.[3] According to the RegiSCAR-Group Diagnosis Score for DRESS,[4] our patient had a final score of 7 (indicative of a definite case of DRESS) based on fever, enlarged lymph nodes, presence of atypical lymphocytes and eosinophilia in the blood differential test, presence of rash affecting more than 50% BSA with edema and scaling, and resolution of skin rashes lasting for more than 15 days.

EGFR plays an important role in maintaining normal epithelial cells. Thus, EGFR-TKIs may interrupt keratinocyte growth, migration, and chemokine expression, leading to inflammation and skin toxicity.[5] However, DRESS caused by TKIs is rare, being more commonly associated with aromatic antiepileptic drugs, allopurinol, antimicrobial sulfonamides, and dapsone.[6] In the U.S. Food and Drug Administration received a total of 6 106 629 drug adverse event reports from January 2004 to March 2018, among which afatinib-induced DRESS only accounted for 0.0087% ($n = 535$).[7] In addition, the scaling of DRESS observed in our case was uncommon (~10%).[6]

Although the incidence of DRESS was similar between afatinib (odds ratio: 2.29, 95% confidence interval [CI]: 2.22–2.35) and erlotinib (OR: 2.41, 95% CI: 2.17–2.67),[7] the rashes did not recur in our patient after erlotinib rechallenge. To the best of our knowledge, there is no literature regarding the EGFR-TKI rechallenge in cases of EGFR-TKI-induced severe skin adverse events (ex. Stevens-Johnson syndrome or DRESS). In contrast, there are other case reports regarding EGFR-TKI rechallenge in other rare adverse events. Kashiwabara et al. reported three lung adenocarcinoma cases who had gefitinib or erlotinib induced interstitial lung disease (ILD) and were rechallenged with another first-generation EGFR-TKI without the recurrence of ILD.[8] Further, Nishima et al. also described a lung adenocarcinoma patient with osimertinib-induced ILD who was rechallenged with afatinib successfully.[9] These studies suggest that different generations of TKIs may have interclass differences concerning adverse effects. Different substituents linked to the quinazoline and anilino rings may contribute to diverse toxicological profiles.

In conclusion, although the first-generation EGFR-TKI erlotinib was reported to be associated with a relatively higher incidence of DRESS, it could possibly be considered an alternative substitute for other EGFR-TKIs following DRESS occurrence. However, the evidence of this treatment strategy was still limited, further prospective studies are warranted to validate the result.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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REFERENCES

1. Recondo G, Facchinetti F, Olaussen KA, Besse B, Friboulet L. Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? Nat Rev Clin Oncol. 2018;15:694–708.
2. Lee CK, Davies L, Wu YL, Mitsudomi T, Inoue A, Rosell R, et al. Gefitinib or erlotinib vs chemotherapy for *EGFR* mutation-positive lung cancer: individual patient data meta-analysis of overall survival. J Natl Cancer Inst. 2017;109:djw279.
3. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med. 2011;124:588–97.
4. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156:609–11.
5. Mascia F, Mariani V, Girolomoni G, Pastore S. Blockade of the EGF receptor induces a deranged chemokine expression in keratinocytes leading to enhanced skin inflammation. Am J Pathol. 2003;163:303–12.
6. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169:1071–80.
7. Huang J, Meng L, Yang B, Sun S, Luo Z, Chen H. Safety profile of epidermal growth factor receptor tyrosine kinase inhibitors: a disproportionality analysis of FDA adverse event reporting system. Sci Rep. 2020;10:4803.
8. Kashiwabara K, Semba H, Fujii S, Tsumura S. Outcome in advanced non-small cell lung cancer patients with successful rechallenge after recovery from epidermal growth factor receptor tyrosine kinase inhibitor-induced interstitial lung disease. Cancer Chemother Pharmacol. 2017;79:705–10.
9. Nishima S, Miyanaga A, Saito S, Yuasa M, Takahashi S, Kashiwada T, et al. Successful treatment with Afatinib after Osimertinib-induced interstitial lung disease in a patient with EGFR-mutant non-small-cell lung cancer. Intern Med. 2021;60:591–4.

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