Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4237-19
Intern Med 60: 441-444, 2021
http://internmed.jp

【 CASE REPORT 】

Drug-induced Hypersensitivity Syndrome by EGFR-TKI in a Patient with Lung Cancer

Baku Oyama[1], Kei Morikawa[1], Tadashi Sakaguchi[2], Akihito Tsunoda[1], Hirotaka Kida[1], Takeo Inoue[1] and Masamichi Mineshita[1]

Abstract:
An 83-years-old woman diagnosed with advanced Epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma was administered afatinib as a first-line treatment. On Day 17, the patient presented with grade 3 diarrhea and a blood test analysis showed an increased inflammatory response. Afatinib treatment was discontinued on the same day. On Day 26, the patient displayed blepharedema and multiple irregular erythema covering her entire body. Drug-induced hypersensitivity syndrome (DIHS) was suspected, and the systemic administration of 30 mg/day prednisolone was administered. The symptoms subsided thereafter. A blood test analysis 3 weeks after onset revealed a reactivation of Human herpesvirus 6 (HHV-6) and a diagnosis of DIHS due to afatinib therapy was confirmed.

Key words: afatinib, drug-induced hypersensitivity syndrome, HHV-6

(Intern Med 60: 441-444, 2021)
(DOI: 10.2169/internalmedicine.4237-19)

Introduction

Drug-induced hypersensitivity syndrome (DIHS) is a severe drug allergy characterized by fever and a delayed severe rash that can result in multiple organ dysfunction. One main characteristic is the reactivation of human herpesvirus 6 (HHV-6) 10 to 30 days after onset, and in many cases, fever and hepatic impairment are observed with the viral reactivation (1). The drugs known to cause DIHS include; anticonvulsants carbamazepine, phenytoin, phenobarbital, and zonisamide, while occasional cases of antibacterial minocycline have been reported (2). We herein report a case of DIHS in a patient treated with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) afatinib for EGFR-mutant pulmonary adenocarcinoma. This is a first DIHS case report caused by afatinib.

Case Report

An 83-year-old woman with a performance status 1, and a history of hypertension and hyperlipidemia had previously been treated with nifedipine and pitavastatin calcium. The patient had no smoking history or any known allergies. She was referred to our institution for consultation after presenting with a cough. Lung cancer in the lower left lung field was suspected from routine chest radiography. Computed tomography (CT)-guided biopsy, positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI) were performed, revealing adenocarcinoma with multiple metastases at both lungs and for the liver and brain. She was diagnosed with primary pulmonary adenocarcinoma Stage IVB, harbouring an EGFR mutation (exon 19 deletion).

First-line treatment with 40 mg/day afatinib was initiated. On Day 17, the patient had grade 3 diarrhea and a grade 2 fever. Blood test findings showed no elevation of white blood cells (WBC) or eosinophils. However, grade 1 elevation of liver enzymes/lactate dehydrogenase (LDH), and high C-reactive protein (CRP) was seen [WBC 4,600/μL (Seg/Neutro 52%, Lympho 13.5%, Mono 5.5%, Eosino 6.5%, Atypical-lympho 0.5%), Aspartate aminotransferase (AST) 53 IU/L, Alanine aminotransferase (ALT) 45 IU/L, Alkaline phosphatase (ALP) 364 IU/L, LDH 259 IU/L, γ-glutamy transferase 49 IU/L, CRP 6.62 ng/mL]. A physical

[1]Department of Respiratory Medicine, St. Marianna University School of Medicine, Japan and [2]Department of Respiratory Medicine, Matuzaka City Hospital, Japan
Received for publication November 27, 2019; Accepted for publication July 27, 2020
Correspondence to Dr. Baku Oyama, b2oyama@marianna-u.ac.jp

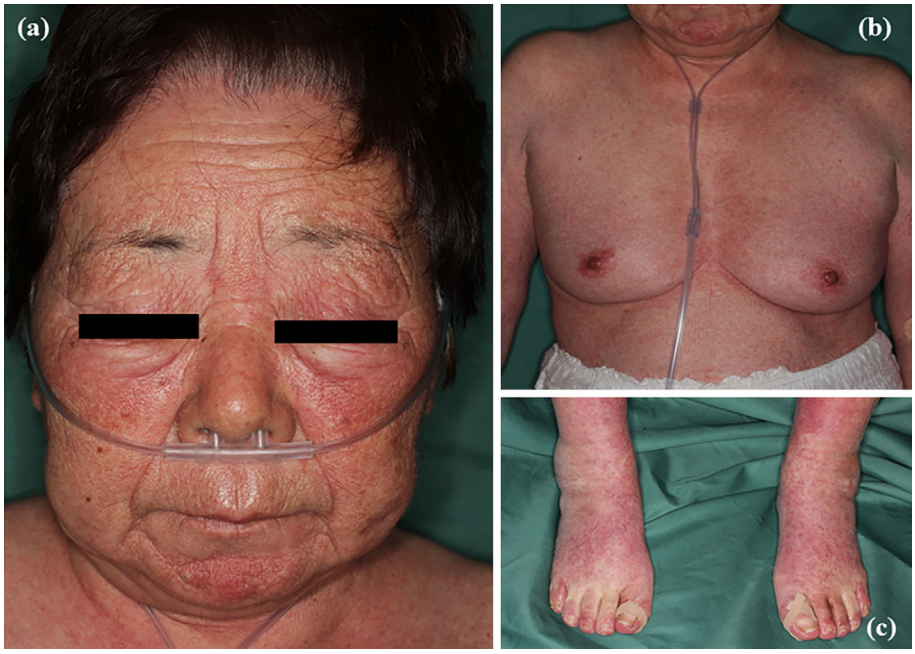

Figure 1. **Blepharedema and erythema.**

examination did not suggest infection, and influenza antigen was negative. Afatinib treatment was discontinued due to treatment-emergent adverse events. The oral administration of loperamide for diarrhea was initiated and the fever was followed-up. On Day 19, the WBC count remained stable, but the eosinophil counts had risen 10%. From Day 23, the results were higher, with grade 2 elevation of biliary enzymes, elevated eosinophils, and the emergence of atypical lymphocytes [WBC 10,400/μL (Seg/Neutro 47%, Lympho 20.0%, Mono 9.5%, Eosino 14.5%, Atypical-lympho 6.5%), AST 74 IU/L, ALT 60 IU/L, ALP 1,005 IU/L]. On Day 26, the patient displayed blepharedema and an exacerbation of multiple irregular erythema covering her entire body (Fig. 1). Due to this severe drug rash, DIHS due to afatinib was suspected. Since the rash worsened with the use of topical steroids, treatment with 30 mg/day prednisolone (PSL) (0.5 mg/kg) was initiated on Day 26 without performing a skin biopsy. After starting PSL, her erythema appeared to subside, and improvements in both liver function and fever were observed. Subsequently, the PSL dosage was gradually reduced. On Day 41, we tested for HHV-DNA, and the patient was discharged on Day 44. We strongly suspected DIHS since the patient experienced rapidly spreading erythema, a delay of at least 2 weeks after withdrawal of the causative drug, a fever of at least 38°C, abnormal liver function, an increase in atypical lymphocytes and eosinophil, and enlarged lymph nodes. HHV-DNA was found to be 250 times the reference level, and HHV-IgG measured at the same time was 640 times the reference. Moreover, paired sera measured approximately 3 weeks later was 640 times the reference. These points made it possible to make a definitive diagnosis of DIHS (Table) (3). The clinical course is shown in Fig. 2.

Discussion

Outside Japan, DIHS is referred to as drug rash with eosinophilia and systemic symptoms (DRESS) (4). In 1998, Suzuki et al. and Tohyama et al. reported that anti-HHV-6 IgG levels become high 3 to 4 weeks after onset (5, 6). The drugs causing DIHS trigger a marked decline in IgG, B cells, and natural killer (NK) cells, and the resulting immunosuppression has been reported to lead to HHV-6 reactivation of the organs in the early stages, followed by the reactivation of HHV-6 in the blood (2). However, the clinical pathology of DIHS is not yet fully understood. DIHS caused by Nivolumab and similar drugs, and the involvement of regulatory T-cells have also been reported (4, 7). Furthermore, it has been reported that HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) reactivation can also cause DIHS (8). One report indicated between 40% and 70% of cases exhibit all four characteristics of DIHS, namely lymph node enlargement, atypical lymphocytes, eosinophilia, and viral reactivation, and that DIHS cannot be ruled out regardless of elevated HHV-6 IgG (9). In this present case, a definitive diagnosis was made since all the diagnostic criteria for DIHS were satisfied (3). Treatment requires systemic steroid administration to suppress hypersensitivity syndrome accompanying HHV-6 reactivation. The use of immunosuppressants like cyclosporine or gamma globulin preparations can also be considered (10). In this case, DIHS treatment was started with PSL 0.5 mg/kg/day, after which an improvement was observed. Subsequently, the steroid dose was gradually decreased. Unlike general drug rashes, a drug-induced lymphocyte stimulation test (DLST) results at 1 month after DIHS onset have been reported. However, we could not perform DLST because the

Table. Japanese Consensus Group Diagnostic Criteria for Drug-induced Hypersensitivity Syndrome (DIHS).

Main findings
1.Maculopapular rash develops 2~3 weeks after start of therapy with a limited number of drugs
2.Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug
3.Fever (>38°C)
4.Liver abnormalities or other organ involvement
5.Leukocyte abnormalities (at least one of the following)
a. Leukocytosis (>11,000/mm^3)
b. Atypical lymphocytosis (>5%)
c. Eosinophilia (>1,500/mm^3)
6. Lymphadenopathy
7. HHV-6 reactivation
Seven criteria needed for diagnosis of DIHS or the first five criteria required for diagnosis of atypical DIHS.

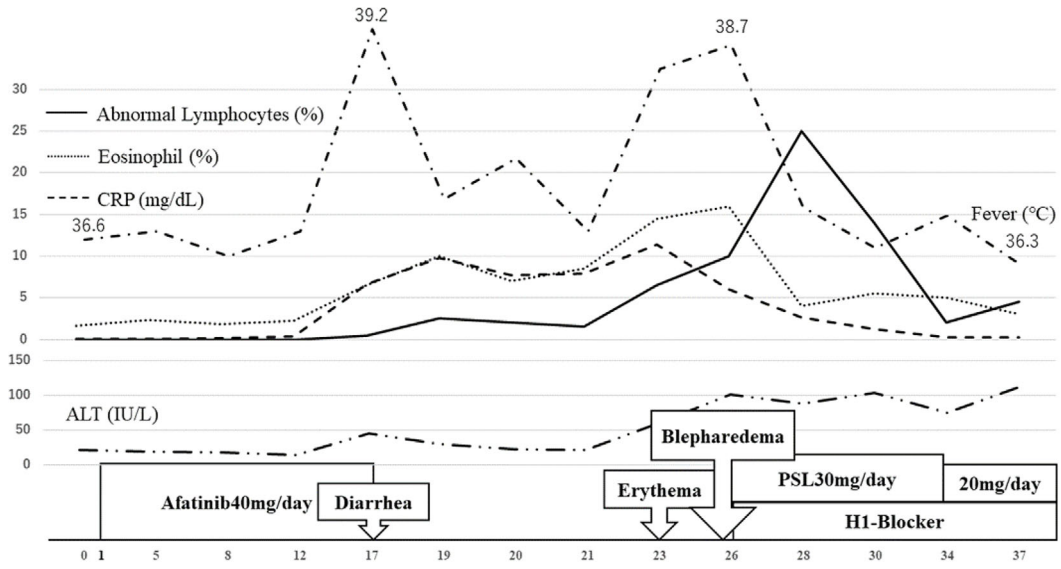

Figure 2. Clinical course.

rash had deteriorated after the PSL dose was reduced to 5 mg. CMV and EBV reactivation had been considered after blood test in this case. On day27, CMV-IgG was elevated to 37.7, however there was no increase seen for CMV-IgM. EBV nuclear antigen and EBV capsid antigen increased to 2.7 and 5.9, respectively. No increase was reported for EBV capsid antigen. On day 49, there was an increase of CMV-IgG to 34.8, but no increased IgM. We considered two reasons why afatinib caused DIHS. First is the time between administration of the drug causing DIHS and onset is thought to be around 2 to 8 weeks, which is clearly longer than the 5 to 14 days seen with other drug rashes. In this case, the rash appeared on Day 26 after afatinib administration. The timing of DIHS onset matches the clinical course for afatinib. In DIHS, fever and eruption do not always occur at the same time. Fever preceded erythema in this case. Second, typical eruptions caused by afatinib are different to erythema in this case. Common skin disorders caused by afatinib are acne (89%), perionychia (61%), dry skin (29%), and latching (18%) (11). On the other hand, blepharedema and erythema are uncommon. The blepharedema and erythema seen in this case are typical but severe drug eruptions. The frequency of skin rashes and flare-ups have been reported during DIHS treatment and occurred twice during the clinical course in our case. Therefore, we believe that this may be the DIHS case caused by afatinib. Anticonvulsants are well-known to cause DIHS. There have also been reports of DIHS caused by the multi-kinase inhibitor sorafenib and the BRAF inhibitor vemurafenib (12, 13). As DIHS can be triggered by drugs used in the field of oncology, doctors should therefore include DIHS in the differential diagnosis and and select appropriate treatments when serious drug rashes occur.

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

References

1. Hashimoto K. Dermatology seminarium 19th drug erupion DIHS. Journal of the Japanese Dermatological Association **116**: 1575-1581, 2006 (in Japanese, Abstract in English).
2. Higashi N, Kano R. A case of drug-induced hypersensitivity syndrome. Journal of the Nippon Medical University Medical Association **4**: 205, 2008 (in Japanese, Abstract in English).
3. Yamamoto Y, Shimizu R, Iwasaki M, et al. A case of acute liver failure due to DIHS. Journal of the Japanese Society of Intensive Case Medicine **22**: 127-131, 2015 (in Japanese, Abstract in English).
4. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): an update in 2019. Allergol Int **68**: 301-308, 2019.
5. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. Arch Dermatol **134**: 1108-1112, 1998.
6. Tohyama M, Yahata Y, Yasukawa M, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. Arch Dermatol **134**: 1113-1137, 1998.
7. Takimoto R, Honda T, Kataoka RT, Ueshima C, Otsuka A, Kabashima K. DIHS/DRESS-like eruption possibly induced by amoxicillin during treatment with nivolumab. Eur J Dermatol **29**: 228-229, 2019.
8. Descamps V, Ranger-Rogez S. DRESS syndrome. Joint Bone Spine **81**: 15-21, 2014.
9. Roujeau JC, Allanore L, Liss Y, Mockenhaupt M. Severe cutaneous adverse reactions to drugs (SCAR): definitions, diagnostic criteria, genetic predisposition. Dermatologica Sinica **27**: 203-209, 2009.
10. Stephanie LK, Matthew SR. Cyclosporine treatment of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a case report and brief review of the literature. Pract Dermatol **2018**: 41-43, 2018.
11. Sequist LV, Yang JCH, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patiients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol **31**: 2013.
12. Salame N, Chow ML, Ochoa MT, Compoginis G, Crew AB. Sorafenib toxicity mimicking drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Drugs Dermatol **18**: 468-469, 2019.
13. Ros J, Muñoz-Couselo E. DRESS syndrome due to vemurafenib treatment: switching BRAF inhibitor to solve a big problem. BMJ Case Rep **2018**: 2018.