

## Case Research

# Toxic epidermal necrolysis related to AP (pemetrexed plus cisplatin) and gefitinib combination therapy in a patient with metastatic non-small cell lung cancer

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## Abstract

Toxic epidermal necrolysis (TEN) is a rare acute life-threatening mucocutaneous disorder that is mostly drug-related (80%–95%). It is clinically characterized as a widespread sloughing of the skin and mucosa. AP regimen (pemetrexed plus cisplatin) has been the preferred first-line chemotherapy for metastatic non-squamous non-small cell lung cancer (NSCLC). Gefitinib, a small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has already been recommended as a first-line treatment in *EGFR*-mutant metastatic NSCLC. We report rare presentation of TEN involving adverse effects of AP and gefitinib combination treatment in a 42-year-old woman diagnosed with metastatic NSCLC harboring an *EGFR* mutation. On the 21st day after administration of the first cycle of AP regimen and the 8th day after the initiation of gefitinib treatment, she developed an acne-like rash, oral ulcer, and conjunctivitis, which later became blisters and ultimately denuded. The characteristic clinical courses were decisive for the diagnosis of TEN. Treatment with systemic steroids and immunoglobulin as well as supportive treatment led to an improvement of her general condition and a remarkable recovery.

**Key words** Toxic epidermal necrolysis, pemetrexed, gefitinib, non-small cell lung cancer, drug-related bullous disease

Toxic epidermal necrolysis (TEN) is an acute life-threatening mucocutaneous disorder with an estimated incidence of 0.4–1.9/1,000,000 and a mortality higher than 20%–40% and is mostly drug-related (80%–95%)<sup>[1]</sup>. It is clinically characterized as a widespread sloughing of the skin and mucosa on both external and internal surfaces. Histologically, the denuded areas show full thickness epidermal necrosis.

Pemetrexed is a multitargeted antifolate drug approved for use in metastatic non-small cell lung cancer (NSCLC). AP regimen (pemetrexed plus cisplatin) is the preferred first-line chemotherapy

for non-squamous NSCLC. The most common adverse events of pemetrexed include myelosuppression and gastrointestinal toxicity; cutaneous toxicity usually occurs as grades 1–2 rash. There also exist some severe cases that present acute generalized exanthematous pustulosis (AGEP), painful generalized erythematous patches, urticarial vasculitis<sup>[2-4]</sup>, and TEN. To our knowledge, TEN related to pemetrexed has been described in only 4 other cases to date<sup>[5-8]</sup>.

Gefitinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) extensively used as the first-line treatment for *EGFR*-mutant metastatic NSCLC. The most common adverse effects include acne-like rash, diarrhea, and nausea, most of which are mild (grade 1/2) and reversible, and predominantly begin within the first treatment cycle. The acne-like rash (folliculitis) has been described variously as acne, rash, macropapular rash, pustular rash, vesiculobullous rash, or urticaria. Thus far, there have been no reports of TEN related to gefitinib toxicity.

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## Case Report

A 42-year-old woman diagnosed with stage IV NSCLC (adenocarcinoma) was admitted to our hospital in August 2013 and given an AP regimen (pemetrexed 500 mg/m<sup>2</sup> on day 1, cisplatin 75 mg/m<sup>2</sup> on days 1 to 3, repeated every 3 weeks) as initial chemotherapy on August 2nd, 2013. She received folate, vitamin B12, and corticosteroids as recommended. Several days later, her *EGFR* genetic test results demonstrated an exon 19 mutation (L747-T751>P); thus, she started taking gefitinib (250 mg once daily) on August 15th. On August 23th, which was 21 days after AP chemotherapy and 8 days after gefitinib treatment, the patient suddenly developed a widespread eruption including acne-like rash on the face, erythema papules on the trunk and limbs, oral ulcer, and conjunctivitis (**Figure 1A and 1B**), followed by a fever of 39°C. The rash gradually increased and aggravated, accompanied with blisters, pruritus, and ulceration. Twelve days after gefitinib treatment, the patient was hospitalized. Gefitinib was immediately stopped, and imipenem, amikacin, and fluconazole were administered intravenously as prophylaxis, and diphenhydramine and loratadine were given as an anti-allergy treatment. On the 13th day, the patient's condition deteriorated further with a fever of 42°C, fused mucocutaneous rash as well as diffuse vesicles and bullae (**Figure 1C and 1D**), which coalesced and then sloughed, presenting a scalded appearance. A positive Nikolsky sign was present on her back and feet (**Figure**

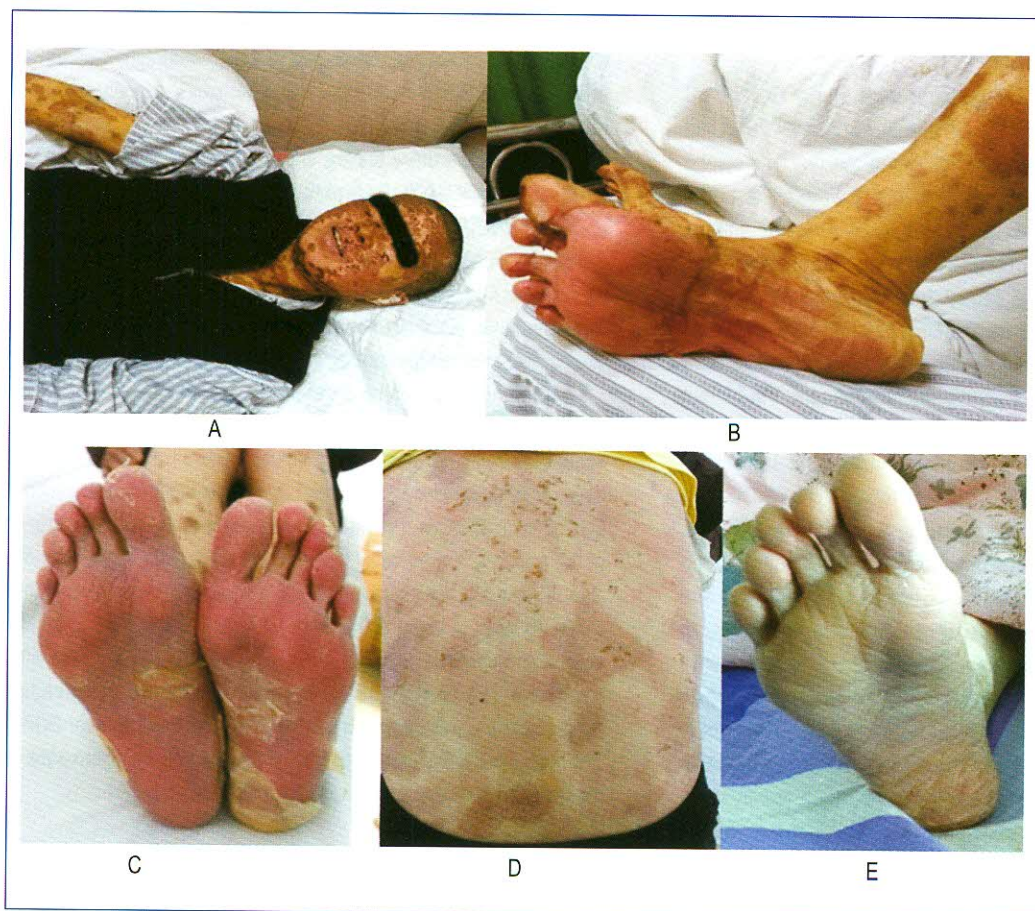
**1E and 1F**). After consulting dermatology doctors, the patient was diagnosed with TEN and transferred to the Dermatology Department at the Second Affiliated Hospital of Sun Yat-sen University for further treatment.

Routine laboratory testing showed a white blood cell (WBC) count of  $6.26 \times 10^9/L$  [reference value:  $(3.69-9.16) \times 10^9/L$ ], neutrophil (NEU) proportion of 73.1% (reference: 50%–70%), and C-reactive protein (CRP) level of 16.36 mg/L (reference: 0–8.2 mg/L); both the *Mycoplasma pneumoniae* IgM antibody and Mac strains were negative. No suspicious fungus was found in the oral swab examination, nor did bacteria grow in the skin secretion culture.

Immunosuppressive treatment was started with 100 mg methylprednisolone (daily injection) for 9 days and intravenous immunoglobulin (20 g/day) for 5 days, followed by 10 g/day for 5 days, accompanied with imipenem and teicoplanin for anti-infection and other supportive treatment. This treatment led to a recurrence of the rash and the mucosal lesions, reepithelization of the denuded skin (**Figure 2**), and improvement of the patient's general condition within 40 days. A chest computed tomography (CT) scan and brain magnetic resonance imaging (MRI) showed partial remission after treatment. The combination of AP and gefitinib was suspended; accordingly, the patient began treatment with icotinib (another EGFR-TKI made in China) after recovery, without exfoliative dermatitis or other similar toxicities. Stable disease was later achieved.



**Figure 1.** The widespread eruption of toxic epidermal necrolysis (TEN) in a 42-year-old woman with stage IV non-small cell lung cancer (NSCLC) after AP regimen (pemetrexed plus cisplatin) and gefitinib treatment. On the 8th day after gefitinib treatment, diffuse erythema papules were observed on the trunk (A) and palms (B); on the 13th day, fused skin rash and diffuse vesicles and bullae (C) as well as erosive lip mucosa (D) were observed; on the 16th day, fused and sloughed systematic herpes (E) and plantar blister (F) were observed.



**Figure 2. Recovery of the patient from TEN.** The systematic rash gradually crusted and desquamated (A and B); reepithelization of the denuded skin and ultimate healing were observed (C–E).

## Discussion

Most TEN cases result from hypersensitive reaction to drugs, and sulfonamides, pyrazolones, barbiturates, and antiepileptics are the most frequent triggers<sup>[9]</sup>. TEN usually occurs between 7 days to 8 weeks after drug administration. Upon readministration of the implicated drugs, it may develop within hours.

TEN is a T-cell-mediated disease with CD8<sup>+</sup> T cells acting as the major mediator of keratinocyte death. Drug-induced CD8<sup>+</sup> T-cell activation is highly specific for particular human leukocyte antigen (HLA) allotypes, placing certain populations at a greater risk of developing TEN. Granulysin is the main mediator of apoptosis, and soluble Fas ligand (sFasL), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and granzyme B/perforin are important in the pathogenesis of TEN<sup>[10]</sup>.

The diagnosis of TEN is made based on clinical and histological findings. Schwartz *et al.*<sup>[11]</sup> put forward that the clinical features of TEN include (1) constitutional symptoms such as fever, malaise, anorexia, and pharyngitis; (2) erythematous, dusky, violaceous macules, morbilliform, or atypical targetoid macules starting on the trunk and spreading distally, confluence on the face, trunk, and elsewhere [the skin lesion area of TEN is greater than that of

Stevens-Johnson syndrome (SJS)]; (3) manifests in flaccid bullae, epidermal sloughing, and necrosis with gray hue; (4) exfoliation of the epidermis involving 10% of body surface area for SJS, 10%–30% for SJS/TEN overlap, and >30% for TEN; (5) oral, genital, and ocular mucositis in nearly all patients; (6) tender skin and painful mucosal erosions; (7) positive Nikolsky sign; (8) positive Asboe-Hansen sign; (9) systemic symptoms always present in SJS/TEN overlap and TEN; and (10) respiratory tract epithelial involvement in 25% of patients with TEN. Histological features were described as follows: (1) full thickness epidermal necrosis; (2) subepidermal split, lymphocytic infiltrate at the dermoepidermal junction, CD4<sup>+</sup> T cells in the dermis, and CD8<sup>+</sup> T cells in the epidermis; and (3) endothelial apoptosis<sup>[11]</sup>.

For mild and early stage TEN, the main differential diagnoses includes SJS, acute generalized exanthematous pustulosis (AGEP), erythema multiforme major (EMM), staphylococcal scalded skin syndrome (SSSS), drug-induced linear immunoglobulin A (IgA) dermatosis, acute graft versus host disease (GVHD), and a generalized morbilliform drug eruption, among other conditions<sup>[12,13]</sup>. Our patient's clinical characteristics were consistent with the above criteria except items (8) and (10). Because the patient's exfoliation was almost systemic, SJS and EMM were excluded; SSSS were

excluded due to negative blood and rash cultures for bacteria and fungus as well as the presence of conjunctiva and oral mucosa damage. In addition, the patient's rash mainly appeared as blisters and bullae due to erythema in the beginning stage, without pustules. Accordingly, AGEP and other diseases were also excluded.

Therefore, the patient was diagnosed with TEN according to typical clinical features. After treatment with glucocorticoids combined with immunoglobulin, her condition gradually improved, which verified the diagnosis of TEN. However, there also exists some deficiency in the diagnosis of this case, primarily the lack of mucocutaneous biopsy and immunologic examination to aid in the diagnosis.

There is currently no standardized treatment for TEN. An effective treatment requires early diagnosis, immediate discontinuation of the causative drugs, and supportive and specific treatment. Recently, the systematic application of glucocorticoids has been the major therapeutic regimen, and glucocorticoids combined with immunoglobulin can quickly control symptoms and shorten hospitalization time and is especially suitable for patients with concurrent infection<sup>[11]</sup>.

Because this case of TEN occurred after AP and gefitinib sequential combination treatment, it is difficult to determine which drug was responsible for this toxicity. Thus far, there has been no report of TEN induced by cisplatin, whereas there has only been one case of SJS related to bleomycin-cisplatin combination treatment<sup>[14]</sup> and another case of exfoliative dermatitis associated with cyclophosphamide-cisplatin combination treatment<sup>[15]</sup>. To the best of our knowledge, 4 cases of TEN due to pemetrexed have been reported thus far: 1 due to pemetrexed alone, 1 related to pemetrexed

plus carboplatin, and the other 2 related to pemetrexed plus cisplatin. The mucocutaneous disorder occurs between 2 days after the first cycle and 15 days after the second cycle of drug administration. Pemetrexed seems to be the most likely cause for our TEN case. Although our patient received gefitinib after AP chemotherapy, TEN occurred at the expected time and the patient did not develop mucocutaneous disorder after readministration of another EGFR-TKI, which supports pemetrexed as the initiator.

Although there is no report of EGFR-TKI-induced TEN thus far, gefitinib could not be ruled out for the cause of this case as EGFR-TKIs alter keratinocyte proliferation, differentiation, migration, and attachment, and cutaneous toxicity occurs in more than 50% of patients. Meanwhile, TEN occurring after 8 days of gefitinib administration has also increased the suspicion of gefitinib as the initiator. Another possible mechanism may be the synergistic effect on dermal toxicity for pemetrexed and gefitinib combination therapy. The basic skin toxicity of EGFR-TKIs may facilitate the occurrence of TEN induced by pemetrexed. Meanwhile, is there any possibility for the enhancement of EGFR-TKI-induced mucocutaneous disorder based on the alternation of folic acid metabolism of epithelial cells by pemetrexed? It is still unknown.

In summary, we report this case with the intent to further understand the potential rare mucocutaneous adverse effects of AP with gefitinib combination therapy. This case report also warns of the possibility of gefitinib as a potential initiator agent of TEN.

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