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CASE REPORT

Gefitinib-induced Toxic Epidermal Necrolysis 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 condition that is usually caused by a reaction to drugs (80-95%). It is characterised by widespread sloughing of the skin and mucosa. Gefitinib, a small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is a standard first-line treatment for EGFR-mutated metastatic non–small cell lung cancer. We report a case of TEN complicating gefitinib treatment in a 65-year-old woman with metastatic pulmonary adenocarcinoma. She developed skin eruptions on day 5 of treatment that rapidly evolved to TEN on day 8. This case report highlights the rapidly evolving course of gefitinib-induced TEN and the importance of early diagnosis, prompt withdrawal of the drug, and intensive care.

Key Words: *Carcinoma, non-small-cell lung; Receptor, epidermal growth factor; Stevens-Johnson syndrome*

中文摘要

在一名轉移性非小細胞肺癌患者中吉非替尼誘發中毒性表皮壞死鬆解

楊利、林嘉安、李浩勳、李詠梅

中毒性表皮壞死鬆解（TEN）是罕見的急性危及生命的皮膚病並通常由藥物反應引致（80-95%）。它的特點是皮膚和粘膜廣泛脱落。吉非替尼是一種小分子表皮生長因子受體（EGFR）酪氨酸激酶抑製劑，是*EGFR*突變轉移性非小細胞肺癌的標準一線治療。我們報告一例65歲轉移性肺腺癌女性患者因吉非替尼治療誘發TEN。她在治療開始後第5天皮膚出疹，第8天迅速發展為TEN。本病例報告突出了吉非替尼誘發TEN的快速發展過程以及早期診斷、及時中止藥物和重症監護的重要性。

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare life-threatening mucocutaneous condition mostly triggered by drug treatment (80-95%).[1] It is characterised by extensive epidermal detachment, erosion of the mucous membranes, and severe systemic symptoms. The estimated incidence of TEN is 0.4 to 1.9 per 1,000,000 people and the mortality rate ranges between 20% and 40%, according to a study of antiepileptic therapy.[2]

Gefitinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor widely used for *EGFR*-mutated

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metastatic non–small cell lung cancer. The common cutaneous adverse reactions induced by gefitinib are acneiform eruptions on the face, anterior trunk, and back (39%), followed by xerosis or desquamation of the face, body or distal parts of the fingers or toes (36%), urticarial and small ulcers of the oral mucosa or nasal mucosa,[3] and severe bullous, blistering or exfoliating conditions. The development of TEN in a patient treated with high-dose (1000 mg daily) gefitinib has been reported.[4] We report a case of TEN secondary to gefitinib treatment at a regular dose of 250 mg daily.

CASE PRESENTATION

In May 2015, a 65-year-old woman presented with headache, right-sided weakness, and shortness of breath to the University of Hong Kong–Shenzhen Hospital. She was diagnosed with stage IV adenocarcinoma of the lung with pericardial effusion and multiple brain metastases. Pericardiocentesis was performed and adenocarcinoma cells were detected in the pericardial fluid. Dexamethasone was given at a dose of 3.75 mg 4 times per day initially and tapered to 3.75 mg 3 times per day on day 10, 3.75 mg twice a day on day 19, and 3.75 mg daily on day 22. Palliative whole brain radiotherapy (20 Gy in 5 daily fractions) was given with lateral opposing cranial fields from days 7 to 13. These resulted in improvement in headache and limb weakness.

EGFR exon 19 deletion was detected in the cancer cells from pericardial effusion and thus gefitinib 250 mg daily was started on day 21. Gefitinib was well tolerated in the first 4 days. On day 5 of gefitinib treatment, she developed some sporadic acneiform rashes on the face and neck that progressed rapidly with painful blisters and ulcers despite the use of topical emollient and macrolide. On day 8 of gefitinib treatment, she developed a high fever and severe skin rash. She presented with signs of septicaemia with a body temperature of 40°C and a pulse rate of 130 beats per minute. Diffuse mucocutaneous rashes and bullae were noted over 80% of her body surface area, mainly involving the face and trunk, with some of them coalesced and sloughed (Figure). There were also oral ulcers, conjunctivitis, and mucositis of the anorectal region. The Nikolsky sign was positive (exfoliation of the outermost layer of skin when rubbed slightly). She was clinically diagnosed with TEN and gefitinib was promptly stopped. She was admitted to the intensive care unit for further treatment.

Blood tests revealed a white blood cell count of 8.8 (reference range, 3.89-9.93) × 10^9/l and a neutrophil proportion of 74.4% (reference range, 44.0%-72.0%). Liver function was deranged with a raised alanine aminotransferase level of 174 (reference range, 9-52) U/l and aspartate aminotransferase level of 156 (reference range, 14-36) U/l. Renal function and blood electrolytes were unremarkable. Blood and urine cultures were negative. Carcinoembryonic antigen was 132.7 (reference range, 0-3) ng/ml, carbohydrate antigen 125 was 2297.4 (reference range, 0-35) U/ml, and carbohydrate antigen 15-3 was 106.1 (reference range, 0-25) U/ml. Chest radiograph showed no evidence of pneumonitis or consolidation and the right lung nodule was stable in size.

Three days later, the patient deteriorated rapidly and died despite vigorous fluid resuscitation and administration of anti-allergy agents, corticosteroids, empirical topical antibiotics (including erythromycin

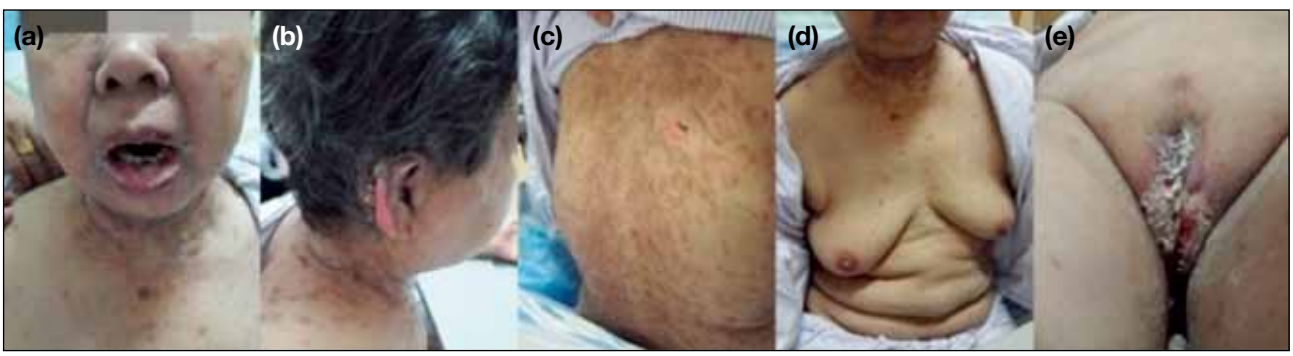

Figure. A 65-year-old woman with toxic epidermal necrolysis 8 days after gefitinib treatment showing skin rashes with vesicles and bullae over a large area of the body: (a) face and lip; (b) scalp and neck; (c) back; (d) anterior chest; and (e) vulva. Whitish materials shown in (a), (b), and (e) were topical tobramycin applied to the affected areas.

ointment, sulfadiazine silver cream, fusidic acid cream, tobramycin, and dexamethasone eye drops), and eye ointment.

DISCUSSION

Both TEN and Stevens-Johnson syndrome (SJS) are characterised by widespread sloughing of the skin and mucosa on both external and internal surfaces. TEN refers to epidermal detachment of >30% of the body surface area; SJS refers to <10% of body surface area involvement; and SJS / TEN overlap refers to 10% to 30% body surface area involvement.[5]

Most SJS / TEN cases are severe cutaneous hypersensitivity reactions to medication[1] that includes antibiotics (sulfonamides and beta-lactams), antiepileptics (phenobarbital, phenytoin, and valproate), and non-steroidal anti-inflammatory drugs (allopurinol and quinolones).[6] Some cytotoxic agents and targeted therapies (including methotrexate,[7] pemetrexed plus cisplatin and gefitinib combination treatment,[8] and rituximab[9]) have also been reported (Table 1).

The pathogenesis of SJS / TEN has not been fully elucidated. The detachment of the epidermis in TEN is caused by necrosis of keratinocytes following apoptosis.[10] It is proposed that cytotoxic $CD8^+$ T cells become overactive when stimulated by drugs or drug metabolites. The cells then mediate keratinocyte cell apoptosis through the release of a number of molecules including perforin, granzyme B, granulysin, soluble Fas ligand, and tumour necrosis factor alpha.[11] Genetic predisposition related to the human leukocyte antigen may influence the incidence of SJS / TEN.

The diagnosis of TEN relies on clinical symptoms and supplementary histological features.[12] Initial manifestations include erythema and macules on the face and trunk with positive Nikolsky sign, followed by epidermal detachment and development of blisters within minutes to hours. Mucosal, ocular, and sexual organs can be involved shortly before or simultaneously with the cutaneous signs. As TEN progresses, patients become susceptible to sepsis, acute renal injury, liver failure, respiratory failure, or myocarditis.[11] Histological findings of widespread necrotic epidermis involving all layers are pathognomonic. Direct immune fluorescence staining is recommended in order to rule out auto-immune-related blistering diseases.[12] Despite the lack of histological and immunological confirmation, our patient presented with the typical clinical features diagnostic of TEN.

Gefitinib is the standard of care for patients with advanced or metastatic non–small cell lung cancer associated with *EGFR* mutations.[13] It is generally well tolerated. Although acneiform skin rashes may occur in up to two-thirds of patients during the course of treatment, very rarely is cutaneous inflammation so pronounced that skin necrosis and ulceration occur.[3] The incidence of skin rash may increase with the dose: from approximately 30% at 150 mg daily to approximately 80% at 1000 mg daily.[13] In a phase I trial of high-dose gefitinib, one patient presented with TEN at the 1000 mg daily dose level.[4] The skin disorders can be explained by the fact that EGFR is also expressed in the basal layer of the epidermis. The roles of EGFR include stimulation of epidermal growth, inhibition of differentiation, and acceleration of wound healing. Thus, EGFR inhibition results in impaired growth and migration of keratinocytes, and inflammatory chemokine expression by these cells. These lead to inflammatory cell recruitment and subsequent cutaneous injury, which account for most symptoms including tenderness, papulopustules, and periungual inflammation. Furthermore, overactive cytotoxic $CD8^+$ T cells may respond to stimulation from drugs or drug metabolites mediating keratinocyte cell apoptosis.

Table 1. Cases of Stevens-Johnson syndrome / toxic epidermal necrolysis.

Study	Sex / age, y	Disease	Drug	Time of onset, d	Treatment	Outcome
Cuthbert et al,[7] 1993	M / 54	Lymphoma	Methotrexate	8	Antibiotics	Recovered
Huang et al,[8] 2015	F / 42	Non–small cell lung cancer	Pemetrexed plus cisplatin followed by gefitinib	21 (After pemetrexed plus cisplatin) and 8 (after gefitinib)	Antibiotics, anti-allergy, corticosteroids, immunoglobulin	Recovered
Lowndes et al,[9] 2002	M / 36	Lymphoma	Rituximab	14	Antibiotics, corticosteroids, cyclosporine	Deteriorated

Table 2. A severity-of-illness score for toxic epidermal necrolysis (SCORTEN).[14]

Risk factor (1 score for each)*
Age ≥40 years
Heart rate ≥120 per minute
Concomitant malignancy
Epidermal detachment >10% of body surface
Serum urea level >10 mmol/l
Serum bicarbonate level <20 mmol/l
Serum glucose level >14 mmol/l

* Mortality rates of a SCORTEN score 0-1, 2, 3, 4, and ≥5 are 3.2%, 12.2%, 35.5%, 58.3%, and 90.0%, respectively.

There is no standard treatment for SJS / TEN and the mortality rate is high.[11] Early diagnosis, immediate withdrawal of the causative agent, and supportive care have been shown to decrease mortality.[11] The prognosis of TEN is poor with mortality rates ranging between 20% and 40%.[2] In 2000, the severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was introduced to evaluate the risk of death among patients with SJS / TEN (Table 2).[14] The SCORTEN of our patient was at least 4 and the expected mortality rate was 58.3%. Despite intensive care, our patient developed multi-organ failure and died 3 days later.

Cutaneous adverse events have been reported to correlate with good tumour response.[15] However, there is no significant correlation between pharmacodynamic effects of gefitinib and skin toxicity.[13] In our patient, serum tumour markers increased over the 8 days of treatment, with an increase in carcinoembryonic antigen from 76.9 to 132.7 ng/ml, carbohydrate antigen 125 from 1089.3 to 2297.4 U/ml, and carbohydrate antigen 15-3 from 59.2 to 106.1 U/ml. An initial transient flare of tumour markers is not uncommon. The size of the primary lung tumour was stable on serial chest radiographs. Improvement in headache and limb weakness may have been due to whole brain radiotherapy and steroids.

CONCLUSION

Gefitinib is a common medication for metastatic *EGFR*-mutated pulmonary adenocarcinoma. It can give rise to life-threatening cutaneous complications. Oncologists should be aware of the possibility of TEN following gefitinib treatment. Early diagnosis, prompt withdrawal of the drug, and intensive care are the keys to improve outcome.

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