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LETTER

Staphylococcus aureus Bacteremia Related with Erlotinib Skin Toxicity in a Patient with Pancreatic Cancer

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Summary

Erlotinib, a small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor has been approved by FDA for patients with pancreatic cancer and non-small cell lung cancer. Skin rash is a well-known side effect related with all EGFR blocking agents. It has been suggested that rash could be used as a surrogate marker for response and possibly be associated with prolonged survival. There is scant data reporting bacteremia secondary to severe erlotinib skin toxicity. In this letter, we report a case that developed systemic bacteremia while on erlotinib for treatment of advanced pancreatic cancer due to development of severe rash. This case underlines the significance of potential severe/systemic infection associated with erlotinib. Previously there are many reports describing various skin toxicity manifestation, however, this is the second case in English literature which had systemic *Staphylococcus aureus* bacteremia arising from erlotinib skin toxicity. Monitor patients closely after starting EGFR blocking agents and initiate immediate skin care based on general guideline are highly recommended.

Treating pancreatic cancer, the fourth leading cause of cancer-related deaths in the United States has always been a challenge [1]. Gemcitabine remains the standard of care in this field since 1990s, the addition of a second cytotoxic agent (cisplatin, oxaliplatin) demonstrated advantage in terms of response rates and progression free survival, but did not achieve a significant overall survival benefit [2, 3]. A phase III randomized controlled trial by National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) has shown a statistically significant survival benefit of gemcitabine plus erlotinib compared with gemcitabine alone [4]. Based on these data, the US Food and Drug Administration (FDA) approved erlotinib to be used with gemcitabine as first line treatment for advanced pancreatic cancer.

Erlotinib is a small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor [5]. In addition to pancreatic cancer and non-small cell lung cancer, Erlotinib has also potential use in hematological malignancies including polycythemia vera, idiopathic myelofibrosis and essential thrombocythemia [6]. Skin rash is a well-known side effect related with all EGFR blocking agents. It has been suggested that rash could be used as a surrogate marker for response and possibly be associated with prolonged survival [7]. There are very few cases reporting any bacteremia secondary to severe erlotinib skin toxicity [8]. In this letter, we report a case that developed systemic bacteremia while on erlotinib for treatment of advanced pancreatic cancer and we believe the occurrence of bacteremia is precipitated by the use of erlotinib.

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Key words erlotinib; Exanthema; Fever; Infection; Pancreatic Neoplasms; Sepsis

Abbreviations NCIC-CTG: National Cancer Institute of Canada Clinical Trials Group

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Case Report

The patient we are presenting here is a 56-year-old white female with medical history of insulin dependent diabetes, hypothyroidism, and dyslipidemia who initially presented with intermittent abdominal pain for months associated with 18 kg weight loss in early 2008; she was subsequently diagnosed with locally advanced pancreatic adenocarcinoma involving the celiac axis and superior mesenteric artery. She was started on palliative chemotherapy with a combination of gemcitabine and oxaliplatin based on GERCOR/GISCAD study [3]. Disease was controlled for almost 5 months, and then new pulmonary nodules were found on restaging CT scan. Treatment was changed to bFOL regimen (oxaliplatin: 85 mg/m^2 on days 1 and 15; bolus 5-FU: 400 mg/m^2; leucovorin: 20 mg/m^2 on days 1, 8 and 15 every 28 days) [9]; unfortunately, the patient did not derive any benefit on following imaging studies, nor the symptoms or performance status. Erlotinib was considered based on

NCIC-CTG study since October 2008. Four days after initiation of erlotinib at 100 mg daily, the patient returned to clinic with a papulopustular acneiform rash on face, neck, back, predominantly on face (Figure 1). The rash was erythematic, associated with dryness, pruritis and tenderness. The scalp, arms, and lower body were uninvolved. Clindamycin 3% gel and oral minocycline at 100 mg daily were given for treating the rash [10]. Meanwhile, erlotinib was dose reduced to 100 mg every other day; however, the rash continued to get worse despite of dose reduction of erlotinib. Therefore, erlotinib was completely discontinued after a total of 11 days of use. A week after discontinuation of erlotinib, the patient developed shaking chills with rigors. Her temperature is only 36.8ºC, with heart rate of 114/min, and respiration rate of 20/min; clinically, she was highly suspicious for systemic infection. A complete blood count revealed leukocytosis with total white cell count of 12,200 μL^{-1} (reference range: 4,000-10,000 μL^{-1}) with neutrophils of 77% (reference range: 38-81%). Pan-culture was performed from peripheral line and double-lumen port-a-cath. The patient was admitted to hospital and treated with intravenous antibiotics for broad-coverage with vancomycin and Zosyn® (piperacillin and tazobactam) initially, then narrowed to vancomycin after 5 out of 6 bottles grew penicillin and clindamycin resistant but vancomycin-sensitive *Staphylococcus aureus*. Port-a-cath was removed during that hospitalization, and temporary peripherally inserted central catheter line was inserted for antibiotics administration. Port-a-cath tip culture grew out mixed gram positive flora of 3 varieties consistent with skin flora. She was treated with intravenous vancomycin for a total of 10 days. Repeated peripheral blood culture and culture from the newly inserted peripherally inserted central catheter in two days and five days were all negative. Her skin rash gradually subsided after we discontinued erlotinib, and eventually disappeared after two weeks of skin care with topical clindamycin gel.

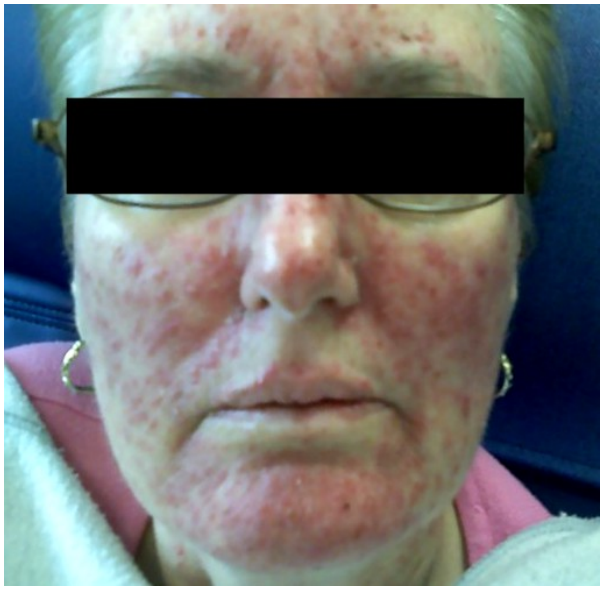

Figure 1. Severe rash associated with erlotinib in a patient with pancreatic cancer.

Discussion

Skin eruption is a common adverse reaction in patients receiving erlotinib and other EGFR inhibitors [11, 12]. The incidence rate is up to almost 80% of patients receiving erlotinib [4]. It usually develops within two weeks of commencement of treatment with median of eight days, but it could occur as early as three days after therapy. The eruption commonly consists of follicular, erythematous papules and pustules on the face, chest, and upper back.

Pathogenesis of EGFR inhibitor-associated rash is not fully understood, but interference with the follicular and interfollicular epidermal-growth signaling pathway is hypothesized to play an important role. EGFRs are widely present in epidermal keratinocytes in skin as well as in hair follicles [13]. Erlotinib inhibits the EGFR tyrosine kinase and leads to growth arrest of keratinocyte and follicular obstruction with subsequent inflammation leading to rash development [14]. Microbiologic stains and cultures from most cases of skin rash usually do not show an infectious cause. Superimposed secondary bacterial infection has been reported as cases [8].

The case we report here developed a severe papulopustular rash four days after initiation of erlotinib, predominantly on face, neck, chest and upper back, areas rich of pilosebaceous units. Treatment with topical clindamycin gel as well as oral antibiotics was immediately started given the clinical severity of the case, erlotinib was dose reduced as per general guideline. The patient only tolerated 7 more days, erlotinib was eventually held due to persistently worsening skin rash. Bacteremia with *Staphylococcus aureus* occurred subsequently. We believe the chronological relationship between starting an EFGR inhibitor and the occurrence of *Staphylococcus aureus* bacteremia is very critical, especially in the setting of severe skin rash. It is very likely the patient had superimposed *Staphylococcus aureus* skin infection precipitated by erlotinib led to a systemic infection.

Grenader *et al.* have also reported a patient with non-small-cell lung cancer who developed *Staphylococcus aureus* bacteremia secondary to severe erlotinib skin toxicity [8].

We report this case to remind oncologists in practice to be aware of potential severe/systemic infection associated with erlotinib. Previously there are many reports describing various skin toxicity manifestation, however, this is the second case in English literature which had systemic *Staphylococcus aureus* bacteremia arising from erlotinib skin toxicity. Monitor patients closely after starting EGFR blocking agents and initiate immediate skin care based on general guideline are highly recommended.

Conflict of interest The authors have no potential conflicts of interest

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