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Uncommon Dermatologic Adverse Effect Related to Afatinib: Case Report and Review of the Literature

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ABSTRACT

Lung cancer is the most lethal neoplasm worldwide, with most patients diagnosed at advanced stages, and without cure attempt possibilities throughout a therapy. Recently, activating mutations have been described as related to epidermal growth factor pathway, which are susceptible of being treated with tyrosine kinase inhibitors from epidermal growth factor receptor. As a drug class, tyrosine kinase inhibitor relates to adverse dermatological effects (acneform eruption, pruritus, skin xerosis, etc.). As an epidermal growth factor receptor tyrosine kinase inhibitor, afatinib has portrayed capability for HER2 and HER4 inhibition. Thus, it is a fact that it shares similar toxicities with other epidermal growth factor receptor tyrosine kinase inhibitors and provokes particular adverse events such as an increase in diarrhea. We report the case of a non-small cells lung cancer male patient treated at third line with afatinib and who has shown an unusual dermatological adverse effect characterized by hyperkeratosis at a subcutaneous trauma site. It is the first case reported in literature as far as we know. (J CANCEROL. 2016;3:125-7)

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INTRODUCTION

Non-small cells lung cancer (NSCLC) is the first cancer-related death worldwide, with an estimated 1.38 million deaths in 2008[1]. Nearly 85% of NSCLC are histologically defined as such and most of the patients portray advanced disease at diagnoses with no hope of cure[2].

Epidermal growth pathway activation (ErbB) promotes tumor growth and progression, enhancing cell proliferation, invasion, and metastasis growth, while inhibiting apoptosis, and creating an optimal therapeutic target. In 2004, three groups described activating metastasis in NSCLC cohorts, and this turns tumors sensitive to EGFR (epidermal growth factor receptor) tyrosine kinases inhibitor treatment[2].

Afatinib, an oral irreversible TKI belongs to the ErbB family and downregulates ErbB signaling through a covalent binding to kinase domains at EGFR in the human epidermal growth factor (HER-2/HER-4), irreversibly inhibiting auto- and transphosphorylation of HER3. Afatanib has been approved as monotherapy of TKI-naive adults with EGFR in locally advanced or metastatic NSCLC with EGFR activating mutations. It has also shown efficacy in EGFR TKI-naive patients receiving no more than one chemotherapy course for advanced NSCLC disease with EGFR-activating mutations[3].

Nevertheless, dermatological adverse effects have been reported as frequent among patients treated with EGFR TKIs (up to 80%). These effects impact more than cosmetically, causing discomfort, pain, and secondary infections, as well as therapeutic detachment, lesser response rates, and mitigating clinical benefit.

As afatinib might cause this type and scope of adverse effects, special strategies would have to be followed in order to avoid such consequences such as acneform rash eruption, pruritus, skin xerosis, paronychia, hypertrichosis, and alopecia, applying particular measures at the patient´s preparation (therapeutic education)[4].

Case report

Male patient; 78 years old; heavy cigarette smoking history, and chronic obstructive pulmonary disease (COPC); oxygen dependent.

The patient was diagnosed with NSCLC in July 2012. Illness was documented by positron emission tomography (PET/CT). Mediastinal masses presented at neck and bilateral pulmonary nodules. Biopsy reports “moderately differentiated adenocarcinoma”. The patient received systemic chemotherapy, based on pemetrexed plus carboplatin for six cycles, achieving clinical improvement, with partial response, and keeping pemetrexed as maintenance therapy. By February 2013, there was progression; thus, it was decided to begin erlotinib therapy at 150 mg once daily, with clinical improvement at small effort dyspnea (dyspnea on exertion, DOE). Computed tomography showed stable disease. The patient was under surveillance due to economical limitations to keep going with TKI.

By August 2013, dyspnea increased as well as thoracic pain, weight loss, and hemoptysis. Illness progression was documented by PET/CT; so, afatinib therapy was re-started as a compassionate measure at 40 mg/day dose, with good tolerance, clinical improvement, dyspnea, and pain reduction. Toxicity showed as eventual grade 1 diarrhea. During afatinib use, there was trauma from a fall from normal height, a product of cutaneous hematoma at the back at follow-up visit, a week after examination, revealed asymptomatic hyperkeratosis process at cutaneous hematoma area (Fig. 1), which is considered as result of afatinib use.

In November 2013, disease showed stable at tomography and clinical improvement lingers through January 2014, with a progression-free period of ≥ 5 months. A second accidental fall from normal height with cranial concussion caused death.

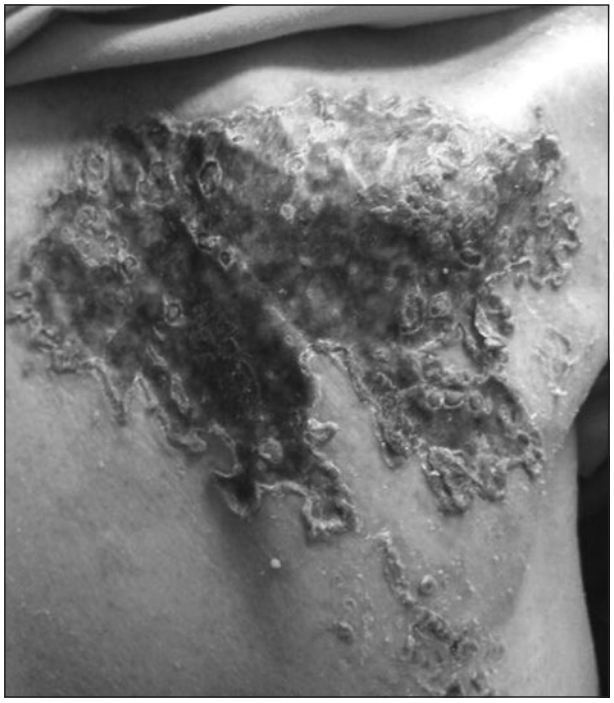

Figure 1. Hyperkeratotic plaques on back skin hematoma developing during afatinib use.

DISCUSSION

The EGFR TKIs, such as gefitinib, erlotinib, and more recently afatinib, are the current standard treatment for patients with EGFR mutations at first-line treatment for NSCLC or metastatic[5]. These molecules have shown benefit in progression-free survival, response rates, and quality of life[6]. Although related adverse events are mild, the proper management is essential in order to attain therapy adherence. This demands good training in the management of the drugs.

Cutaneous adverse effects are frequent and mechanisms related to EGFR TKIs are not yet thoroughly known, but hypothesis points at baseline keratinocytes and to a signaling process disruption of physiological EGFR at skin[4]. This inhibition brings a diminishing/alteration process of baseline keratinocytes, proinflammatory cytokines upregulation, T lymphocytes early infiltration, barrier skin function loss, and secondary infections[7].

Hand-foot like hyperkeratotic lesions are also common with the use of multi-kinase angiogenesis inhibitors like sorafenib, sunitinib, and some other agents targeting against the vascular endothelial growth factor[7], even if not frequent with afatinib, and reported as 7% (all grades) at the LUXD-Lung1[4].

Other proliferative squamous lesions of the skin, like the hyperkeratotic *per se*, and the so-called keratoacanthomas or squamous cell carcinomas have been described with the use of sorafenib or BRAF-selective inhibitors like vemurafenib or dabrafenib[7]. Afatinib monograph reports < 1% of hyperkeratotic lesions as adverse effect.

Evidence of dermatological toxicity in this patient is unusual and can hardly be explained with the current knowledge of physiopathology of toxicities due to EGFR TKIs. The background of a hematoma at the hyperkeratotic region could have had contributed to an interaction of poorly known mechanisms in the development of these changes. As far as we know, this is the first case report with an EGFR TKI.

DECLARATION OF INTEREST

Non-sponsored project, carried out with department's budget.

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