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Exacerbation of Psoriasis after Alectinib Treatment

*Qiuyang Xu[1], Yangyang Li[2], Yang N[1], Chen L[1] and Wang J[1]**

[1]Department of Dermatology and Venereology, The First Affiliated Hospital of Wenzhou Medical University, China

[2]Department of Pathology, The First Affiliated Hospital of Wenzhou Medical University, China

Abstract

Alectinib, a highly selective tyrosine kinase inhibitor of Anaplastic Lymphoma Kinase (ALK), has shown significant efficacy in the treatment of ALK-positive Non-Small Cell Lung Cancer (NSCLC). Skin and subcutaneous tissue disorders induced by alectinib have been reported, including rash, maculopapular rash and more. Psoriasis is a chronic, systemic, inflammatory disorder, in which an increased release of pro-inflammatory cytokines and chronic activation of the innate and adaptive immune systems can cause cutaneous and systemic manifestations and significant negative effects on patient quality of life. However, little is known about the effect of alectinib on aggravating psoriasis. Here, we report a 59-year-old male whose pre-existing psoriasis was exacerbated following the administration of alectinib to treat metastatic lung adenocarcinoma.

Keywords: Alectinib; ALK Inhibitor; Drug reaction; Psoriasis

Abbreviations

ALK: Anaplastic Lymphoma Kinase; NSCLC: Non-Small Cell Lung Cancer; QOL: Quality of Life; CNS: Central Nervous System; ADRs: Adverse Drug Reactions

Introduction

Non-Small Cell Lung Cancer (NSCLC) with Anaplastic Lymphoma Kinase (ALK) fusion gene rearrangement occurs in approximately 5% of advanced adenocarcinoma cases. Alectinib, as a second-generation highly selective tyrosine kinase inhibitor, has shown significant efficacy in the treatment of ALK-positive NSCLC [1,2], which is approved by the US Food and Drug Administration and the European Medicines Agency and recommended as a preferred first-line treatment option in the NCCN guidelines. Several adverse effects have been reported, including increased blood creatinine, increased Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), anemia, hepatic function abnormalities, constipation, and more. Skin and subcutaneous tissue disorders induced by alectinib including rash, maculopapular rash and more [3]. Psoriasis primarily affects the skin and joints and has substantial negative effects on patient Quality of Life (QOL), with an estimated global prevalence of 2% to 3% [4]. However, a drug reaction involving the exacerbation of psoriasis has not been previously reporter. Moreover, the diagnosis and subsequent treatment of the disease is particularly critical.

Case Presentation

A 59-year-old male was diagnosed as having metastatic lung adenocarcinoma in 2017 and began receiving chemotherapy consisting of carboplatin, pemetrexed, and bevacizumab. The patient was successively treated with crizotinib and alectinib after tumor studies showed positivity for the ALK mutation. Another significant medical condition was a 10-year history of mild psoriasis, which only affected the scale and nails. He presented fascicular hairs and typical psoriatic nail dystrophy such as nail plate thickening, crumbling, pitting, onycholysis, and subungual hyperkeratosis. The condition of psoriasis was stable without any regular treatment. From November 2018 to July 2020, the patient had been treated with crizotinib daily for about 2 years, and his pre-existing psoriasis did not develop any exacerbation. In July 2020, examination of skull MR indicated nodules in the left frontal lobe and the right parietal lobe, and metastasis was considered. Therefore, crizotinib was replaced with alectinib in September 2020. After 1 month of oral alectinib therapy (600 mg twice daily), he presented with multiple erythematous scaly plaques over his trunk and extremities. The lesions had gradually increased in size and number and spread from the scalp and nails to the whole body with severe itching. Physical examination disclosed multiple bilaterally symmetrical erythematous plaques of different sizes with characteristic silvery-white scales over the whole body (Figure 1). The scales could be peeled in layers, which were looser toward the periphery and

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Correspondence:
Jingying Wang, Department of Dermatology and Venereology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China,
E-mail: wangjingying@wmu.edu.cn

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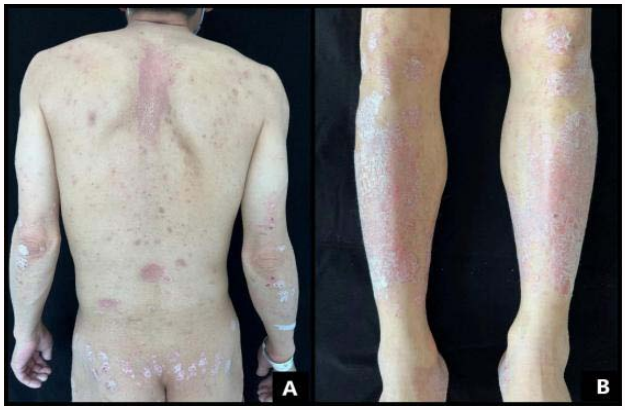

Figure 1: Photographs show the multiple bilaterally symmetrical erythematous plaques with characteristic silvery-white scales over extremities and trunk.

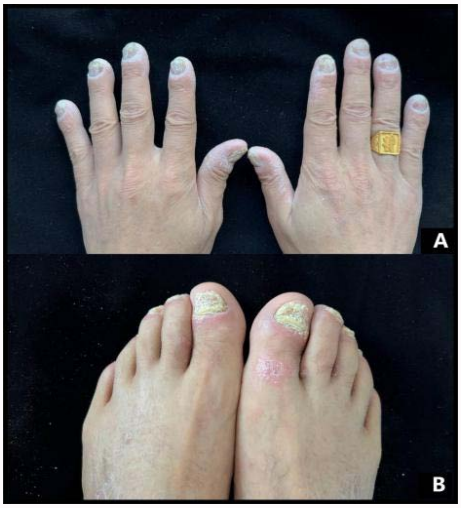

Figure 2: Photographs show typical features of psoriatic nail dystrophy, such as nail plate thickening, crumbling, pitting, onycholysis, and subungual hyperkeratosis.

adherent centrally. When scales were removed, bleeding points appear (Auspitz sign). He simultaneously presented typical features of psoriatic nail dystrophy (Figure 2). We performed a skin biopsy for the left lower limb. Histopathological examination reported hyperkeratosis, parakeratosis, loss of granular layer, acanthosis, superficial perivascular lymphocytes and microabscess, consistent with psoriasis vulgaris (Figure 3), which suggested the exacerbation of underlying psoriasis. At that time, the patient complained of no previous history of exposure to special medicines and chemicals except for cancer therapy; neither did he have any clinical findings indicating that the skin rash was associated with an infectious disease or prior history of allergies. The patient's autoimmune antibodies and other indicators were not significantly abnormal. Initial diagnostic tests had ruled out additional causes of exacerbation of psoriasis. Therefore, we suspected the exacerbation of psoriasis might be an adverse effect of alectinib.

In consideration of the metastasis of his lung adenocarcinoma, biologics could not be administered to alleviate psoriasis eruption, and alectinib was continued without any change in the dose to control the cancer metabolism. Treatment with compound glycyrrhizin injection, ebastine, loratadine, topical halometasone cream and

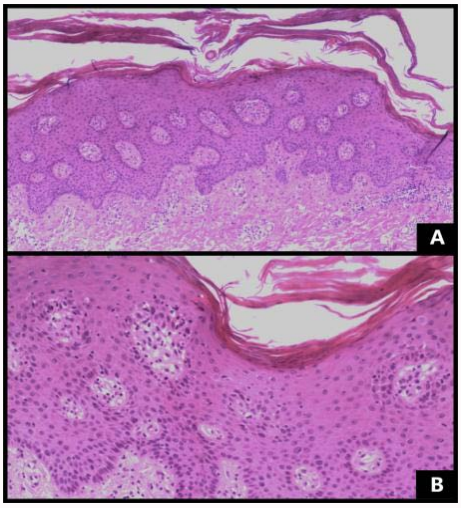

Figure 3: Biopsy specimen from the left lower limb demonstrates hyperkeratosis, acanthosis, loss of granular layer, parakeratosis, superficial perivascular lymphocytes and microabscess, consistent with psoriasis vulgaris. (H&E). A 100x. B 200x).

topical calcitriol betamethasone ointment was initiated to improve psoriatic skin lesions. In the continued clinical follow-up, his psoriasis gradually recovered and was controlled to a moderate degree with regular oral compound glycyrrhizin and topical steroid ointments.

Discussion

The current standard first-line therapy for patients with advanced-stage ALK-positive NSCLC is alectinib. Advanced ALK-positive NSCLC is characterized by a high lifetime risk of Central Nervous System (CNS) metastases. Unlike crizotinib, alectinib as a second-generation tyrosine kinase inhibitor, is a CNS penetrant, which is active in the CNS in both preclinical and clinical investigations [5]. Rash was one of the common Adverse Drug Reactions (ADRs) of alectinib in clinical trials, including macular rash, popular rash, maculopapular rash, dermatitis acneiform, erythema, exfoliative rash, and pruritic rash [6]. However, a drug reaction involving the exacerbation of psoriasis, to our knowledge, has not been previously reported. Several reports had described aggravation or development of psoriasis with the first-generation tyrosine kinase inhibitors, such as imatinib and nilotinib. Shim et al. reported a case of exacerbation of psoriasis in a patient diagnosed with metastatic melanoma, who was administered 400 mg imatinib. Psoriatic skin lesions were gradually improved after good treatment, imatinib administration was then reinitiated at the reduced dose of 200 mg daily; the skin lesions remain well-controlled [7]. Several other cases also observed an association between the dose of imatinib and psoriasis, which suggested that the disturbance of psoriasis may be related to a pharmacological effect of imatinib rather than to a hypersensitivity reaction [8-10]. Kaunda et al. presented a patient with chronic myeloid leukemia who acquired psoriasis while using nilotinib, a second-generation tyrosine kinase inhibitor. Improved with methotrexate and topical fluticasone propionate 0.05% cream, nilotinib therapy could be maintained without dosage decrease [11]. Alectinib, as a kind of tyrosine kinase inhibitor, might promote the development of psoriasis as well.

In the present case, an adverse skin reaction developed after administration of the alectinib, at that time, he was not taking any other prescribed medicines except for cancer therapy and there were

no clinical findings indicating that the skin rash was associated with an infectious disease or prior history of allergies. According to the Naranjo ARDs probability scale, the probability of ADR induced by alectinib is possible [12]. The mechanism behind alectinib-exacerbated psoriasis remains unknown. Psoriasis is a disorder of both the innate and adaptive immune systems. Keratinocytes, dendritic cells and T cells play central roles in the pathogenesis of psoriasis, especially type 1 and type 17 cytokine-producing cells, which are modulated by regulatory T cells (Tregs). Expression of ALK was also found in skin, alectinib probably impairs the function of Treg cells by inhibiting the tyrosine kinase, and ultimately leads to altered Th17/Treg balance [13]. Further studies are required to establish the effects of alectinib on the evolution of psoriasis.

The patient had a strong willingness to administrate psoriasis biologics (adalimumab or scoochiumab) to treat psoriasis. Malignancies are not included in the contraindications. Biologic therapy can be given to patients with a history of malignancy if the malignancy has been excised more than 5 years previously and where the absence of recurrent or metastatic malignancy has been confirmed [14]. Due attention should be paid to the occurrence of new malignancies during the treatment with biologics. In this case, alectinib was continued for new CNS metastases. According to the guidelines, priority should be given to treatment for the malignancy, therefore biologics was not recommended [15]. Systemic antihistamine and topical steroid therapy mildly improved psoriatic skin lesions.

Conclusion

Psoriasis mainly affects the skin and joints and has well-described negative effects on patient QOL. The knowledge of drugs that trigger or exacerbate psoriasis could be of great importance in individuals' prophylaxis. This case perhaps indicates that the pharmacological effects of alectinib may play a pathological role in the exacerbation of psoriasis. Further studies are required to elucidate the precise mechanism by which alectinib induces this adverse cutaneous effect. While alectinib is the current standard first-line therapy for patients with advanced-stage ALK-positive NSCLC, optimal management of adverse effects requires constant observation and collaboration between dermatologists and oncologists, especially in patients with previous skin disorders.

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