Osimertinib-induced erythromelalgia: A case report

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Abstract. The present study reports a case of osimertinib-induced erythromelalgia in a patient with metastatic lung adenocarcinoma. Osimertinib is an antineoplastic drug that irreversibly inhibits the epidermal growth factor receptor (EGFR) pathway by binding to the intracellular receptor tyrosine kinase site, thus preventing EGFR signal transduction. A 77-year-old female with a lung adenocarcinoma recurrence with secondary metastases was prescribed osimertinib therapy. The patient presented with painful erythema and warmth in the distal phalanges of all fingers on both hands, which worsened with heat and relieved with cold. Based on clinical data, erythromelalgia was diagnosed. Considering the age of onset, a primary erythromelalgia was ruled out. Further investigations excluded other secondary causes of erythromelalgia, therefore osimertinib was suspected as the cause. Although no cases of EGFR inhibitor-induced erythromelalgia have been reported, cutaneous adverse events induced by EGFR inhibitors have been documented. The present case may be the first evidence of osimertinib-induced erythromelalgia and may help clinicians to properly support patients who develop this EGFR inhibitor adverse event.

Introduction

Osimertinib is a third-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). It is widely used as treatment for EGFR mutation-positive non-small cell lung cancer (NSCLC). Cutaneous side effects of EGFR-TKI are well known, and more commonly occur in female patients (1). These include acneiform and papulopustular eruption, pruritus, xerosis, paronychia and fissure/cracks (2). To the best of our knowledge, erythromelalgia has never been reported as a skin-related adverse event of EGFR-TKI. Here, we report the first case of osimertinib-induced erythromelalgia in a 77-year old woman diagnosed with metastatic lung adenocarcinoma. Erythromelalgia is a rare and debilitating disorder characterized by burning pain, redness and increased temperature of the extremities. It is classified as primary and secondary erythromelalgia. Primary erythromelalgia is a hereditary autosomal dominant disorder due to a heterozygous mutation in SCN9A gene, responsible for encoding a voltage-gated sodium channel expressed by neurons. Secondary erythromelalgia is linked with a spectrum of various underlying medical conditions. It may be a consequence of myeloproliferative disorders, including polycythemia vera or essential thrombocythemia, connective tissue disorders such as lupus or rheumatoid arthritis, metabolic conditions such as diabetes, infections, musculoskeletal issues and neurological disorders like multiple sclerosis. Moreover, erythromelalgia can be a paraneoplastic syndrome (3).

Case report

We present the case of a 77-year old woman diagnosed with metastatic lung adenocarcinoma with EGFR L858R mutation in exon 21 treated with osimertinib, a third-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). She presented to the dermatology outpatient clinic due to the onset of painful erythema and warmth in the distal phalanges of all fingers on both hands (Fig. 1). This condition appeared after eight months of therapy with osimertinib, worsened in response to heat and relieved with cold, significantly impacting her quality of life. Additionally, the patient had a history of MRGE, hypertension, diverticulosis of the colon, and hypothyroidism. Moreover, she didn't report recent infective episodes. Alongside osimertinib, she was concurrently receiving bisoprolol, acetylsalicylic acid, ramipril, and levothyroxine. Routine blood tests, encompassing complete blood cell counts, hepatic and renal function assessments, and ion levels, yielded normal results. Furthermore, contrast CT scans showed no signs of cancer progression.

Based on clinical manifestations, erythromelalgia was diagnosed. The patient was prescribed pain relief therapy with a local anesthetic drug (lidocaine 1% cream) once a day as needed, and reported reduction in symptoms. After a couple of months, osimertinib was discontinued by oncologists because of a severe infectious complication (hepatic abscess), with subsequent complete remission of the cutaneous condition in a few weeks.

In this case a primary erythromelalgia, an inherited autosomal dominant disorder due to a heterozygous mutation in SCN9A gene encoding a sodium channel, has been excluded because of the elderly age of onset. Extensive

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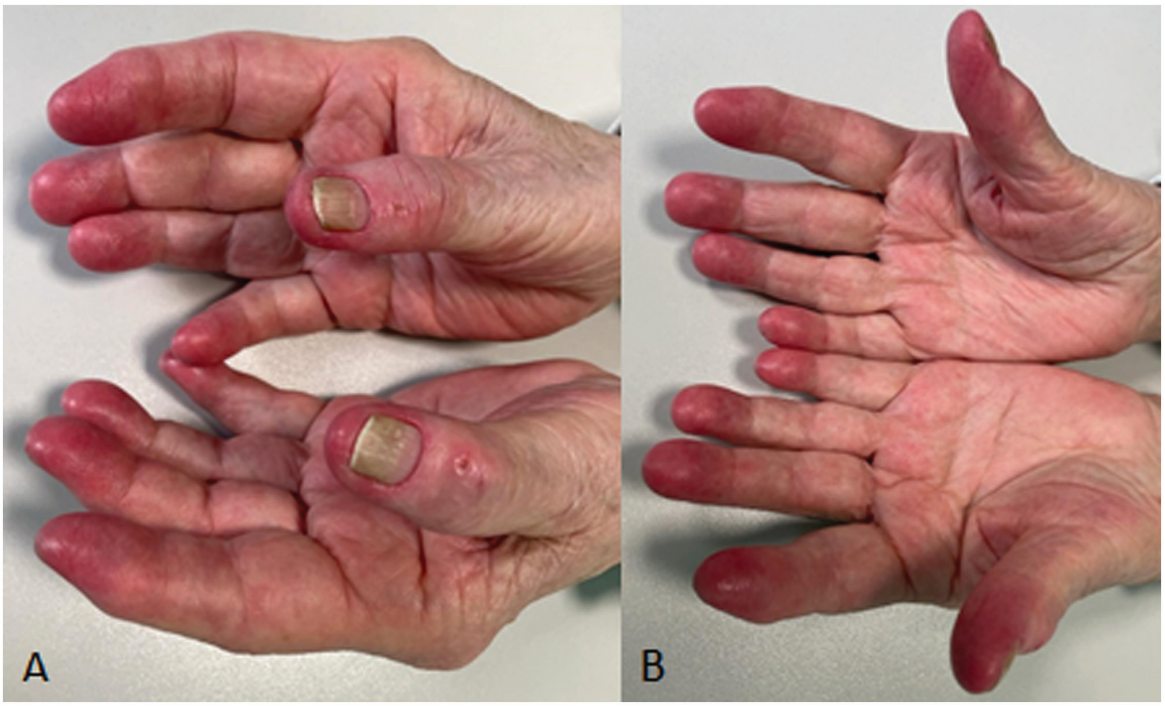

Figure 1. (A and B) Erythema in the distal phalanges of fingers of both hands.

evaluation of the patient including the recent history of the patient, in-range blood exams and CT with contrast, which was negative for cancer progression, ruled out other conditions associated with erythromelalgia, such as myeloproliferative disorders, connective tissue disorders, metabolic disorders, infections, musculoskeletal and neurological conditions, and paraneoplastic erythromelalgia. Given the absence of alternative explanations, the association with osimertinib was considered the most probable diagnosis. Osimertinib, being a life-saving therapy, has not been discontinued. Instead, topical anesthetic was chosen to alleviate the patient's symptoms. During follow-up, the remission of erythromelalgia after discontinuation of osimertinib intake based on the oncologist's recommendation supported the hypothesis of osimertinib-induced erythromelalgia.

Discussion

Erythromelalgia is a rare distressing condition characterized by burning pain of the extremities, erythema and increased temperature of affected skin, exacerbated by warming and relieved by cooling. The diagnosis is made upon clinical signs and symptoms. It is categorized as primary (an inherited autosomal dominant disorder associated with mutations in the SCN9A gene) and secondary, which is linked to underlying medical conditions. Secondary erythromelalgia's pathogenesis is not fully understood, however it has been suggested that erythromelalgia is a disorder of vascular dynamics, with a decrease in capillary perfusion that creates tissue hypoxia, and a simultaneous microvascular arteriovenous deviation within the skin, which then appears erythematous and hot (3). In the skin, EGFR is expressed by basal keratinocytes, sebocytes, the outer root sheath and endothelial cells, and plays a role in the differentiation of keratinocytes and vessels of the dermis. It has been proposed that EFGR inhibition may contribute a vascular impairment (4). We suggest that this may be the primum movens of the vascular dynamics disorder with both decreased perfusion and arteriovenous shunting in skin. Cutaneous side effects of EGFR-TKI reported in literature include acneiform and papulopustular eruption, pruritus, xerosis, paronychia and fissure/cracks (2). Less frequently described EGFR-TKI cutaneous side effects are ashy-dermatosis like hyperpigmentation (5), cutaneous vasculitis (6) and acute onset life-threatening conditions such as severe psoriasis and toxic epidermal necrolysis (7). The dermatological adverse event profile of osimertinib, a third-generation EGFR-TKI, appears to be milder than that found for first and second-generation agents (8). This case study reports the first known instance of erythromelalgia in a patient treated with an EGFR inhibitor, implying that EGFR inhibition may induce vascular dysfunction, potentially leading to arteriovenous shunting in the skin. Despite the significant impact of erythromelalgia on patient's quality of life, discontinuing EGFR inhibitor therapy is discouraged due to its life-saving nature. Instead, symptoms management is recommended in order to avoid discontinuation of this life-sparing therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AB and AG were equally responsible for conceptualization, writing the original draft, reviewing and editing. MASA was responsible for conceptualization and supervision. All authors have read and approved the final manuscript. AB and AG confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient referred in this manuscript gave written informed consent to the publication of the case details.

Competing interests

The authors declare that they have no competing interests.

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