


## Osimertinib-induced cutaneous vasculitis: A case report and review of the literature

### *Vasculite cutânea associada ao osimertinib: Relato de caso e revisão da literatura*

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#### RESUMO

Doente de 77 anos, com adenocarcinoma pulmonar estadio IVa (cT4N3M1a) sob osimertinib 80 mg/dia. Nove dias após o início do tratamento desenvolveu lesões de púrpura palpável. A biopsia cutânea revelou vasculite leucocitoclástica. Uma revisão clínica e um estudo analítico completos permitiram excluir atingimento sistémico. O fármaco foi suspenso e a doente iniciou metilprednisolona 1mg/Kg/dia, com melhoria paulatina das lesões. Ao fim de quatro semanas, reiniciou osimertinib 40 mg/dia e desmame progressivo de prednisolona até 0.5 mg/Kg/dia sem recidiva da vasculite. Boa tolerância ao osimertinib ao fim de 5 meses de seguimento. Na primeira avaliação de resposta ao tratamento apresenta resposta parcial. Trata-se do primeiro caso de vasculite cutânea induzida pelo osimertinib descrito em Portugal e o quarto a nível mundial. É, ainda, o primeiro caso de reintrodução do fármaco em metade da dose, em associação a corticoide.

**Palavras-chave:** Cancro do pulmão; Osimertinib; Vasculite leucocitoclástica.

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#### ABSTRACT

A 77-year-old patient with a history of stage IVa (cT4N3M1a) lung adenocarcinoma, treated with osimertinib 80 mg/day, developed palpable purpura nine days after starting therapy. Skin biopsy revealed leukocytoclastic vasculitis. A complete clinical and lab workup for systemic involvement was unremarkable. The patient suspended osimertinib and started on methylprednisone 1mg/Kg/day. Skin lesions gradually improved. Four weeks apart, the patient resumed

osimertinib 40 mg/day along with prednisolone in a slow tapering down scheme until 0.5 mg/Kg/day, without vasculitis relapse. After five months of follow-up, there is a good tolerance and a partial response to treatment. This is the first reported case of cutaneous vasculitis induced by osimertinib described in Portugal and the fourth case reported worldwide. Furthermore, this is the first report in which the osimertinib at a dose of 40 mg daily was rechallenged along with corticosteroid therapy.

**Key-words:** Lung cancer; Osimertinib; Leukocytoclastic Vasculitis

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## INTRODUCTION

Epidermal growth factor receptor (EGFR) mutations are one of the targetable driver mutations in lung cancer. The most common sensitizing EGFR mutations are the exon 19 deletion and exon 21 L858R point mutation.<sup>1,2</sup> Osimertinib is a third-generation irreversible tyrosine kinase inhibitor (TKI) of EGFR that is approved for first-line treatment of metastatic EGFR-mutant non-small cell lung cancer according to FLAURA clinical trial.<sup>1,2</sup>

Skin rash and paronychia are the most reported cutaneous adverse events (AEs). Cutaneous vasculitis is a rare AE.<sup>3,4</sup>

We present a case of grade 3 leukocytoclastic cutaneous vasculitis induced by osimertinib in a patient with lung adenocarcinoma. Lesions were completely resolved after TKI suspension and starting corticosteroids. The patient restarted medication with no relapsing lesions after a five-month follow-up.

## CASE DESCRIPTION

We report the case of a 77-year-old Caucasian, non-smoker woman, with a history of hypertension, atrial fibrillation and a pacemaker for

bradycardia. The patient was being treated with osimertinib at 80 mg/day for a stage IVa (cT4N-3M1a) lung adenocarcinoma with EGFR exon 19 mutation. Nine days after starting osimertinib, multiple petechiae appeared on the anterior aspect of both legs. There was no history of trauma or recent change in medication. Lesions were non-blanching, painless, and neither pruritic nor hemorrhagic. In the following days, lesions evolved into palpable purpura, affecting all the extension of lower limbs (Figure 1), dorsal (Figure 2) and abdominal regions. Purpura spared palmar, plantar and mucosal surfaces, face and chest. There was no fever or other clinical or laboratory evidence of systemic vasculitis. A complete workup revealed normal renal and liver function, a blood count of 158.000 platelets/ $\mu$ L, a normal coagulation study, and fibrinogen dosing. There was no hemolysis. Urinalysis was negative. The antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative, IgA was in reference ranges, and there was no complement consumption. There is no viral or bacterial infection detected. Cutaneous biopsy revealed leukocytoclastic vasculitis (Figure 3).

Paraneoplastic vasculitis was excluded. Lesions did not occur within (or before) the lung cancer diagnosis but during treatment with osimertinib. No other inciting factors were found.

**Figure 1.** palpable purpura affecting the anterior and posterior aspects of lower limbs

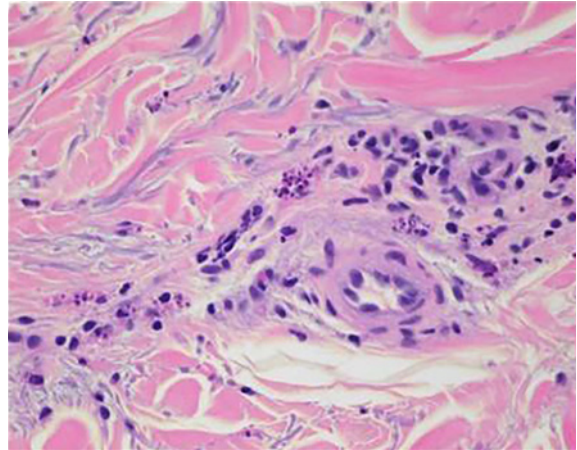


**Figure 2.** palpable purpura affecting the dorsal region



Therefore, the diagnosis was grade 3 osimertinib-induced leukocytoclastic vasculitis. TKI was suspended, and 1 mg/Kg/day of methylprednisolone was started. In one week, the lesions improved. After a follow-up of four weeks, medication

**Figure 3.** Leukocytoclastic vasculitis: perivascular inflammation with neutrophils and nuclear debris (HE)



was resumed at 40 mg/day, in association with 0.5 mg/Kg/day of prednisolone. Steroid dosing was slowly tapered off until the dose of 5 mg/day. After six weeks lesions completely resolved.

After a five-month follow-up, the patient presented with partial response to osimertinib, with no vasculitis relapse.

## DISCUSSION

The mechanism of osimertinib-induced vasculitis might be explained by the inflammatory response that EGFR-TKIs create on endothelial cells of cutaneous blood vessels. Vasculitis affects predominantly the lower extremities and typically spares the palmar, plantar, and mucosal surfaces.<sup>3,4</sup>

Iriarte C., *et al* summarized all reported cases of cutaneous vasculitis induced by EGFR-TKIs in patients with lung cancer. There were nine reported cases, of which two (including theirs) were related to osimertinib.<sup>5,6</sup> It is worth noting that both

are from post-marketing data. Three cases of cutaneous vasculitis were reported in the AURA, FLAURA, and ADAURA trials, but none of them were of leukocytoclastic origin.<sup>7</sup>

We performed a thorough review of the literature using an international database search to provide up-to-date information about Osimertinib-induced cutaneous vasculitis. Three case reports were available, one of them is a review article. All patients, including ours, were female, with ages ranging from 45 to 86 years old, and with no history of autoimmune disease. In all cases, the clinical aspect was vasculitis. The onset occurred between nine days (that is our case) to five months after initiating osimertinib. In two cases (including ours) the treatment was suspended and restarted after lesion resolution. In the case of Hamada K., *et al*, osimertinib was rechallenged at 80 mg/day with oral prednisolone (started with 25 mg/day and subsequently reduced to 7.5 mg/day).<sup>6</sup> The case reported by Iriarte C., *et al* is the first one reporting resolution of cutaneous vasculitis with local treatment with dapsone, without treatment interruption.<sup>5</sup> Lastly, the case reported by Calderon B., *et al.* is the only one describing a severe cutaneous vasculitis, with necrotic skin lesions, that progressed to systemic involvement. Osimertinib was permanently discontinued, and cyclophosphamide was started.<sup>3</sup> It is noteworthy that vasculitis has not relapsed in any of the cases.

Concerning our case, the decision of resuming osimertinib was based on a multidisciplinary discussion. Vasculitis clinical evolution, tumour response to osimertinib, and the available information in the literature were considered. Regarding the severity of the lesions, treatment was restarted at half-dose with corticosteroid. Local treatment was not pondered, since this a grade 3 event with major involvement of body surface area. Furthermore,

there are recommendations that grade  $\geq 2$  events should lead to medication interruption for at least three weeks. Medication could be resumed after lesion improvement for grade  $< 2$ .<sup>7</sup>

AE has not relapsed in any of the described cases, independently of the suspension of the TKI. Therefore, a dose-dependent phenomenon cannot be assumed. Alternatively, a tolerance effect to the drug may be hypothesized, as the osimertinib rechallenge at either half or full dose did not cause vasculitis.<sup>3,5,6</sup> Likewise, it is not possible to infer if this is early or late toxicity because the timing of developing vasculitis ranged from days to months.<sup>3,5,6</sup> Lastly, the pertinence of the use of systemic corticosteroids should be discussed since they could act as a confounding factor in vasculitis prognosis. More importantly, the impact of vasculitis on malignancy response to EGFR inhibitors is still controversial.<sup>3,4,8</sup>

Clinicians must be aware of cutaneous vasculitis as a possible, though rare, adverse event. If not diagnosed and treated on time, it can progress to systemic involvement.<sup>6</sup>

The scarce information available precludes any meaningful interpretation of data on osimertinib-induced cutaneous vasculitis. Further investigation is needed to characterize this AE, as well as its implications on tumor response. A complete and regular skin exam should be mandatory for all patients. Likewise, periodic assessment of tumor progression risk versus toxicity is strongly recommended.

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