

CASE REPORT

A rare cutaneous adverse effect secondary to cabozantinib therapy

Siona Growcott¹, Alexandra Banner², Adam Bray² and Serena Hilman^{1,3,*}¹Department of Oncology, Bristol Haematology and Oncology Centre, Horfield Road, Bristol BS2 8ED, UK,²Department of Dermatology, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW, UK, and³Department of Oncology, Weston General Hospital, Grange Road, Weston-super-Mare BS23 4TQ, UK

*Correspondence address. Department of Oncology, Bristol Haematology and Oncology Centre, Horfield Road, Bristol BS2 8ED, UK. Tel: +44-117-342-2418; E-mail: serena.hilman@uhbristol.nhs.uk

Abstract

Cabozantinib is a tyrosine kinase inhibitor which is increasingly being used for the treatment of metastatic renal cell cancer. Skin toxicity such as palmar-plantar erythrodysesthesia is not uncommon with such agents. However, bullous skin reactions are not common and we report the case of a patient with metastatic renal cell cancer who experienced such cutaneous toxicity.

INTRODUCTION

Tyrosine kinase inhibitors (TKIs), such as cabozantinib, are a group of oral agents which are increasingly being used to treat cancer. In August 2017, the National Institute for Health and Clinical Excellence (NICE) approved cabozantinib for advanced renal cell carcinoma in adults who have had prior VEGF-targeted therapy [1]. In the UK, cabozantinib is also currently licensed for the treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma [2]. Palmar-plantar erythrodysesthesia (PPES) is a common side effect of TKIs, however, the bullous drug reaction highlighted in this case report is uncommon.

CASE REPORT

A 67-year-old man presented to clinic with a bullous skin reaction confined to both hands after 2 weeks of daily cabozantinib 40 mg for metastatic renal cell carcinoma. Cabozantinib had been commenced as third-line therapy following disease progression on other TKIs: pazopanib and subsequently axitinib, both of which he had tolerated well.

After 7 days of cabozantinib therapy, he began to have tender, pruritic blistering of the palmar surface and fingers of both hands. The bullae were extremely uncomfortable and led to a significant reduction in hand function, predominantly with gripping and writing due to the involvement of the thumbs and index fingers. In particular, the patient reported an inability to brush his teeth or feed himself and therefore required the assistance of a relative. The reaction was also associated with loss of sensation in the fingertips, predominantly in the lateral fingers bilaterally. There were no systemic symptoms or fevers. After stopping cabozantinib, no new bullae developed and the existing lesions began to improve spontaneously.

The patient also had a history of chronic obstructive pulmonary disease, hypertension and hypercholesterolaemia. There was no personal or family history of dermatological conditions. His regular medicines included Zomorph, pregabalin, levomepromazine, amlodipine, tamsulosin, aspirin, ezetimibe, rosuvastatin, salbutamol and Evohaler. Except for cabozantinib, no medications had recently been started, stopped or changed. His performance status was 1.

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Figure 1: Palmar surface of hands: symmetrical bullae with a surrounding well demarcated erythematous border, predominantly affecting the thumbs, index and middle fingers



Figure 2: Palmar surface of hands



Figure 3: Palmar surface of hands

On examination in clinic, there were tense bullae with an erythematous border, predominantly on the medial and lateral aspects of his fingers and thumbs (Figs 1–3), but also on the palmar surfaces and dorsal aspect of the hands (Fig. 4). There was a sensory deficit of the thumbs, ring and little fingers bilaterally. There was no mucous membrane involvement.

His white cell count was 8.24 (reference range: 4.0–11.0 $\times 10^9/L$). Acute phase markers, such as C-reactive protein, were not ordered.

The patient had already stopped cabozantinib prior to attending clinic, which was the correct management. The patient was also assessed by a dermatologist who made a



Figure 4: Dorsum of hands: bullae with surrounding erythema overlying the right third and fifth metacarpophalangeal joint and the thumbs, index, middle and ring fingertips bilaterally

clinical diagnosis of likely bullous erythrodysesthesia or a bullous fixed drug reaction.

A paraffin-based emollient and a potent topical steroid ointment were prescribed. Once the lesions had resolved, cabozantinib was restarted at 20 mg daily. The adverse effect was highlighted to the Medicines and Healthcare Products Regulatory Agency (MHRA) through the 'Yellow Card' scheme.

The patient had complete resolution of the cutaneous lesions within 2 weeks of stopping cabozantinib and starting supportive management. After 3 weeks of taking the lower dose of cabozantinib, 20 mg once daily, the patient reported no recurrence of the bullous drug eruption or any other adverse effects.

DISCUSSION

We believe that our patient's clinical presentation was due to bullous erythrodysesthesia or possibly a bullous fixed drug eruption (FDE). The diagnosis was made on clinical appearance and history. A biopsy could have been helpful to support this, however, the lesions were already starting to improve when cabozantinib was withdrawn, further supporting a likely drug reaction, and so a biopsy would not have changed his management.

Erythrodysesthesia is a well-known side effect of TKIs, however, the bullous aspect of the presentation is more unusual and such a severe response would place our patient into a grade 4 reaction [3]. The pathogenesis of erythrodysesthesia is still not fully understood. Factors involved could be rapid cell division in the palms and soles combined with temperature gradients in the distal extremities and increased drug concentration in the eccrine glands of the palms and soles [4].

The alternative diagnosis is a bullous FDE. The absence of bullae recurring when the drug was restarted does not preclude this diagnosis. FDEs are not uncommon adverse drug reactions, however, the bullous variant is comparatively rare [5]. All FDEs are a form of classical delayed-type hypersensitivity reaction and skin resident T cells are believed to be the key mediators in eliciting FDE [6]. On the first occasion, it begins 1–2 weeks after drug exposure. Once the first exposure has taken place, 'resting' FDE lesions, which contain CD8+ve T cells in the dermal-epidermal junction, are easily reactivated on re-exposure to the drug. With every further exposure, the reaction tends to appear more quickly, is more inflamed, and the residual pigmentation darkens. Post-inflammatory hyperpigmentation can be prominent and persist for several months after the acute episode.

Whilst bullous erythrodysesthesia and bullous FDE are rare manifestations of TKI use, PPES (also known as Hand-foot syndrome), occurs in 42% of patients taking cabozantinib and ~8% of those patients report grade 3–4 toxicity [7]. PPES is characterized by erythema and pain of the palms of the hands and soles of the feet following chemotherapy and TKIs. PPES is by far the most common cutaneous manifestation seen with TKI use [8].

Suwattee et al. [9] described a case of PPES with bullae formation in a patient taking another TKI, sunitinib. Similarly to our case, the lesions resolved after 2 weeks following withdrawal of the drug, topical steroids, zinc oxide and nystatin cream.

Important differentials to rule out include other drug-induced bullous eruptions: erythema multiforme, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Erythema multiforme lesions are targetoid, with a sharp margin, regular round shape and two or three concentric colour zones. Usually the middle zone develops a raised area or blister, and progresses to necrosis in the centre. SJS and TEN are more widespread and severe. All three conditions are more likely to have mucosal surface involvement.

Treatment of bullous drug eruptions involves stopping the offending drug and applying topical corticosteroid. The US Food and Drug Administration advocate withholding cabozantinib until PPES has resolved or minimized to grade 1 toxicity [7]. Systemic corticosteroids may be necessary in patients with multiple lesions. If the TKI must be continued, then cautious introduction at a lower dose is advised, providing that both clinician and patient are aware that a quicker skin reaction may occur. A referral to Dermatology is advised if the patient has widespread bullae, if new blisters are appearing despite stopping the medication or if there is uncertainty regarding the diagnosis and a biopsy is required.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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ETHICAL APPROVAL

No approval required.

CONSENT

Patient consent was obtained.

GUARANTOR

Dr Serena Hilman.

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