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# Case Report 2. Severe erythema multiforme induced by two consecutive anti-angiogenic drugs

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## 1. Introduction

Erythema multiforme (EM) is an abrupt skin reaction with various etiologies characterized by 'target-like' papules. A cell-mediated immune response is involved but the pathogenesis remains unclear.[1] Histopathology consists of the accumulation of mononuclear cells around the superficial dermal blood vessels and keratinocyte necrosis leading to multilocular intraepidermal blisters.[2] The causes of EM include infections (Herpes simplex, Mycoplasma and others), drugs (antibiotics, anti-convulsants, and NSAIDs), hematological disorders and others. About 5% of EM are attributed to drug intake.[2] We report a case of severe cutaneous toxicity including EM with two different anti-angiogenic tyrosine kinase inhibitors.

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## 2. Case Report

A 59-year old patient presented with RCC with pleural metastases to the pleural effusion. Three months following the initial diagnosis, metastatic progression was identified and the patient treated with sorafenib at a dose of 800 mg/day.

On day 7, the patient exhibited a diffuse skin rash involving the face, trunk and limbs and involving approximately 80% of the body surface (Figure 1). There were typical targets with central clearing lesions and raised edematous papules. Minor buccal erosions were detected but corneal membranes were not involved. The patient was febrile with a body temperature of 38.5°C, had asthenia and physical and neurological examinations were normal. EM minor was diagnosed. A cutaneous biopsy on the lesions showed an unspecific cellular infiltrate and spongiotic epidermal lesions. There was no recent history of clinical herpes or cutaneous infection, and no other drug had been prescribed concomitantly with sorafenib. Since the cutaneous event was considered related to sorafenib, treatment was discontinued and the patient was treated with

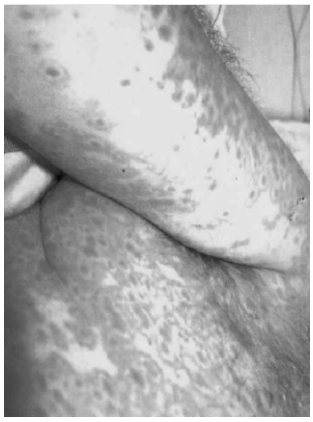

**Fig. 1 – Photograph of erythema multiforme in response to sorafenib therapy in a male patient with metastatic renal cell carcinoma.**

systemic corticosteroids and an oral antihistamine. Clinical improvement was rapid and uneventful.

After 1 month the cutaneous examination was normal. Because of the severity of the cutaneous side effect, treatment was changed to sunitinib. This decision was based on the lower reported frequency of skin toxicities with sunitinib and a prediction of at least a similar level of efficacy as sorafenib. This induced some cutaneous side-effects but fewer than with sorafenib. After 10 days of sunitinib treatment, recurrence of EM minor occurred. Oral corticosteroids and an antihistaminic were given.

Two months after the initial diagnosis, and while the cutaneous examination was normal, a third anti-angiogenic therapy with bevacizumab was started. Three months into this treatment, no cutaneous reaction had been noted.

## 3. Discussion

Sorafenib possesses an acceptable toxicity profile but cutaneous reactions are frequent. Nevertheless, only rash/desquamation (66%), hand-foot skin reaction (62%) and alopecia have been described to date.[3,4] The dose-limiting toxicity of sunitinib is fatigue but various cutaneous side-effects have been recorded, including hair modification, periorbitar edema and subungual hemorrhage.[3,4] Both of these agents have distinct but overlapping mechanisms of action: both inhibit vascular endothelial growth factor receptor (VEGFR), stem cell factor receptor (c-KIT) and Fms-like tyrosine kinase-3 receptor (FLT3). In comparison, bevacizumab, a humanized monoclonal antibody, inhibits only VEGFR.[5] None of these receptors is known to be expressed on keratinocytes. Although the mechanisms remain unclear, the cross-reaction with both compounds rules out a non-specific tablet component-induced EM. The EM observed in this patient was probably due to an overlapping effect on a shared target receptor of both drugs.

## 4. Conclusion

In conclusion, this is the first report of EM occurring during anti-angiogenic therapy, and of a cutaneous cross-reaction with two different anti-angiogenics.

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## Conflict of interest

A. Ravaud: member of the Global, European and/or French advisory boards of Pfizer, Bayer, GSK and Wyeth. Member of RCC clinical trial steering committees for Pfizer and Novartis. Principal investigator for the S-TRAC trial sponsored by Pfizer.

S. Négrier: scientific consultant for Pfizer Europe and Pfizer France, member of scientific advisory boards for Wyeth and Sanofi Aventis.

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