Remission of psoriasis during treatment with sorafenib

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INTRODUCTION

Members of the epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR) families are critical regulators of proliferation of epidermal keratinocytes.[1] These tyrosine kinase receptors activate RAS and downstream RAF, MEK, and ERK proteins of the mitogen-activated protein kinase (MAPK) signaling pathway. Psoriasis is an inflammatory skin disease that, at the level of the epidermis, is characterized by increased keratinocyte proliferation with concomitant altered differentiation.[2] Given its role of transmitting signals from the EGFR and related receptor tyrosine kinases in the MAPK signaling pathway, inhibition of RAF proteins might be efficacious in psoriasis by reducing keratinocyte hyperproliferation.

Abbreviations used:

EGFR:	the epidermal growth factor receptor
FGFR:	fibroblast growth factor receptor
MAPK:	mitogen-activated protein kinase
VEGFR:	vascular endothelial growth factor receptors

CASE REPORT

Here we report the case of a 65-year-old man with chronic plaque psoriasis with unexpected clearance of lesions after treatment with the kinase inhibitor sorafenib for hepatocellular carcinoma. This patient had psoriasis since his 30s and had been treated with (ultra)potent topical corticosteroids and vitamin D analog ointments, which had resulted in only partial regression of skin lesions. Two years earlier, hepatocellular carcinoma was diagnosed, and he was treated with radiofrequency ablation followed by orthotopic liver transplantation. To prevent liver transplant rejection, he received mycophenolate (1000 mg twice a day), tacrolimus (3 mg), and prednisone (2.5 mg) as maintenance immunosuppressants, which had little effect on the psoriasis severity. During follow-up, a solitary metastasis located in the mesorectum was detected and treated surgically. However, a few months later a computed tomography scan of the abdomen and pelvis showed recurrence in the mesorectum and multiple metastases in the left iliacal lymph nodes and left gluteus maximus muscle. Treatment with the kinase inhibitor sorafenib (400 mg twice a day, starting dose 200 mg twice a day for the first 2 weeks) was subsequently initiated. At the start of treatment with sorafenib, the patient had multiple, large, coalescing erythematosquamous plaques covering parts of the upper arms, abdomen, back, and lower legs, covering approximately 10% of the body surface area (Fig 1). There was no nail or joint involvement. Two months after starting sorafenib, almost all psoriatic plaques had regressed completely, with only a few erythematous papules remaining on the upper arms (Fig 2). During resolution of recalcitrant psoriasis, the patient stopped topical treatment with clobetasol ointment and the dose of posttransplant immunosuppressants was not changed. Unfortunately, soon thereafter, the patient showed signs of progression of hepatocellular carcinoma; treatment with sorafenib was discontinued, and the patient died of pulmonary metastases. We were not able to

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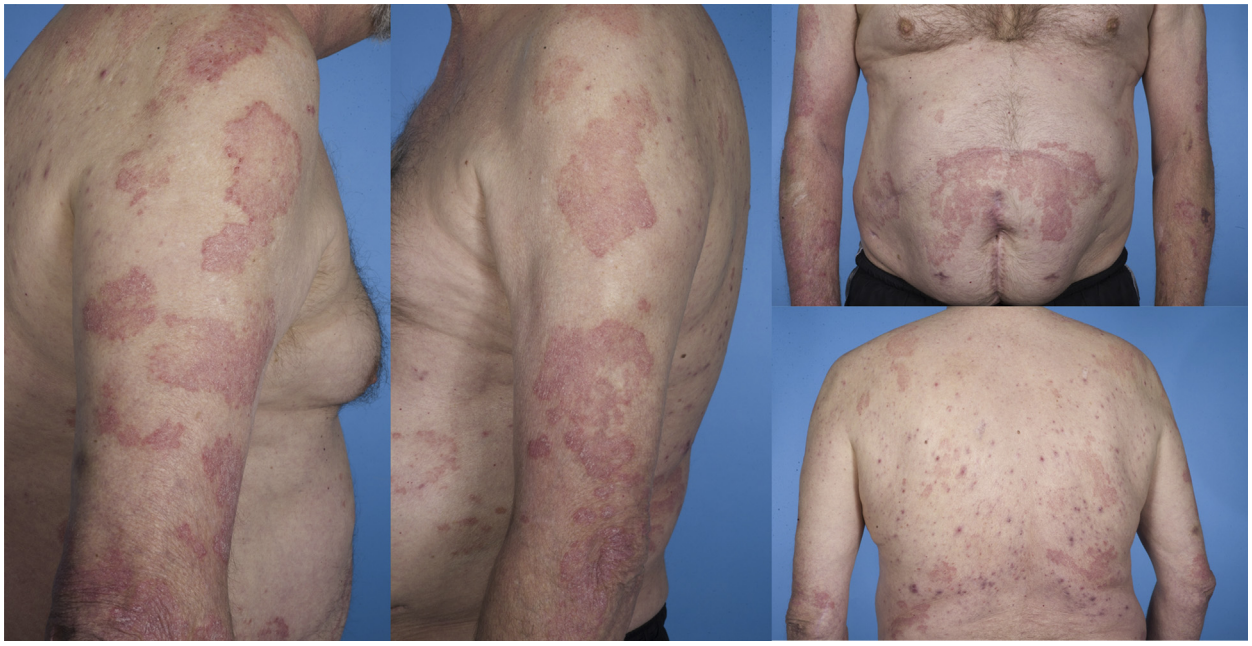

Fig 1. Before treatment with sorafenib.

examine the skin and obtain information regarding recurrence of skin lesions after sorafenib treatment discontinuation.

DISCUSSION

Sorafenib is an inhibitor of multiple kinases including BRAF, CRAF, and vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors.[3] Others have previously reported on modulation of psoriasis severity by sorafenib. Two reported patients similarly experienced clearance of psoriasis skin lesions after treatment with sorafenib.[4,5] However, in 2 sorafenib-treated patients who had no history of psoriasis, induction of a psoriasis-like eruption has been reported.[6,7] In one patient with chronic plaque psoriasis, a pustular eruption appeared during treatment with sorafenib, considered a manifestation of pustular psoriasis or a pustular drug reaction.[8] Others have reported on remission of psoriasis during treatment with the anti-VEGF antibody bevacizumab.[9] In the patient presented here, we assume that inhibition of BRAF, VEGFR, and possibly other kinases is responsible for sorafenib's therapeutic efficacy. Subsequent to the patient described here, we observed 2 patients with remission of psoriasis after treatment with the selective BRAF inhibitor vemurafenib.

Epidermal-specific expression of RAF in mice results in psoriasis-like cutaneous hyperplasia and inflammation.[10] In lesional epidermal keratinocytes of patients with psoriasis, MAPK signaling activity downstream of RAF proteins is increased.[11] This is thought to be induced by elevated expression of EGFR and platelet-derived growth factor receptors by psoriatic keratinocytes and increased abundance of ligands for these tyrosine kinase receptors in lesional skin.[2,12,13] Apparently, inhibition of BRAF in keratinocytes can specifically revert the pathologic hyperproliferation of keratinocytes in psoriasis lesional skin, with little effects on normal epidermis. Additionally, alterations of the superficial dermal microvasculature are a hallmark of psoriasis, induced in part by increased secretion of the angiogenic factor VEGF by lesional keratinocytes.[14] Inhibition of VEGFR on vascular endothelial cells by sorafenib could potentially contribute to its therapeutic effects by attenuating the microvascular changes characteristic of psoriasis.[15]

Most current treatments for severe psoriasis target cytokines and are immunosuppressive, associated with an increased risk of opportunistic infections. By contrast, RAF kinase inhibitors such as sorafenib predominantly act on keratinocytes, regulating their proliferation. If the beneficial effects of RAF kinase inhibition on psoriasis severity are confirmed in larger studies, treatment of psoriasis with sorafenib, vemurafenib, and other chemical inhibitors that attenuate MAPK signaling would constitute a new therapeutic approach. Chemical kinase inhibitors such as sorafenib have the advantage of having a low molecular weight (typically below 1000 Dalton) and could therefore penetrate the epidermis when delivered topically to lesional skin. Studies on the

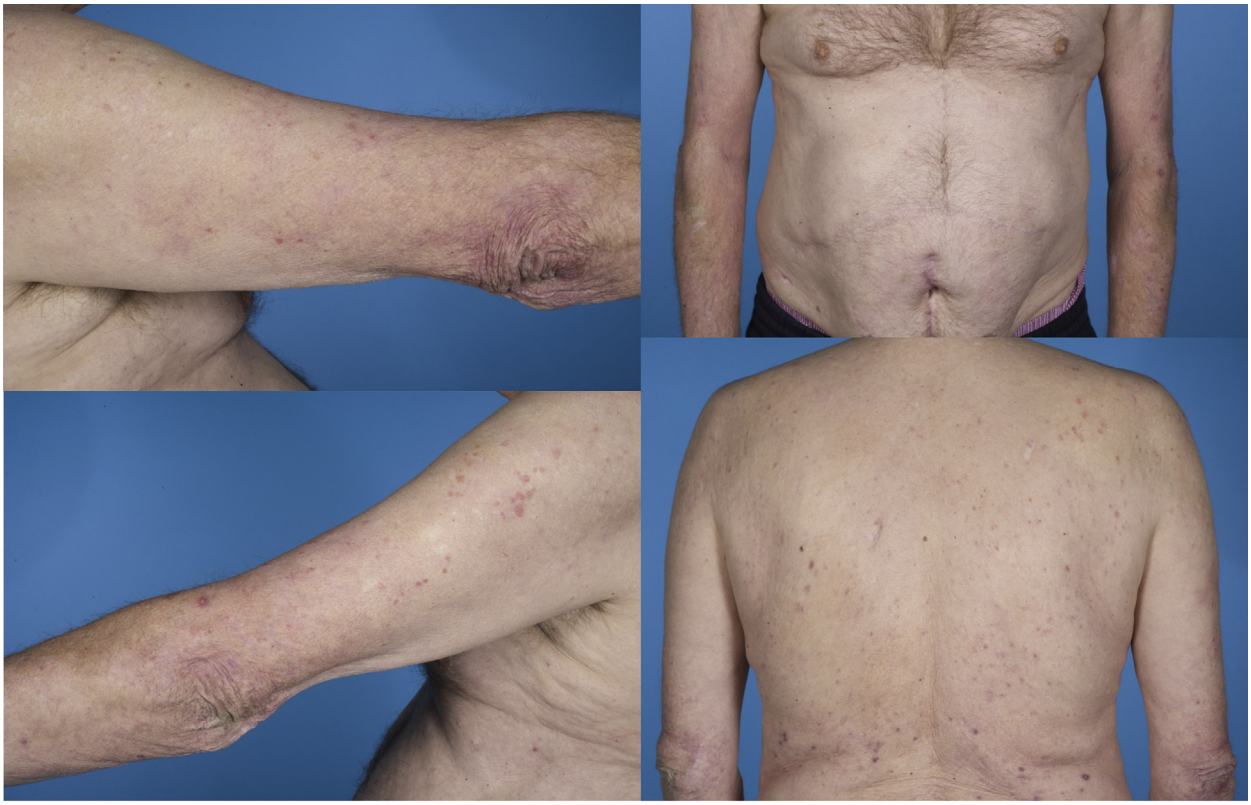

Fig 2. Almost complete clearance during treatment with sorafenib, 6 weeks after cessation of topical treatment.

effects of sorafenib and specific BRAF inhibitors in a larger cohort of psoriasis patients are needed to confirm our observations and ascertain the potential clinical efficacy of these drugs in the treatment of psoriasis.

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