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Remission of Psoriasis in a Patient with Hepatocellular Carcinoma Treated with Sorafenib

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Abstract. *Background: Psoriasis is a chronic, immune-mediated and angiogenesis-dependent disease. Activated keratinocytes in psoriatic lesions produce pro-angiogenic cytokines, including vascular endothelial growth factor (VEGF), which binds to vascular endothelial growth factor receptor (VEGFR) and promotes cell proliferation and angiogenesis. Sorafenib (BAY 43-9006) is a molecular multikinase inhibitor of RAF kinase, platelet-derived growth factor (PDGF), VEGFR-1, -2, -3, platelet-derived growth factor receptor (PDGFR)-β and c-Kit. This molecule inhibits tumor cell proliferation and angiogenesis and it is currently approved for the treatment of hepatocellular carcinoma (HCC). Case Report: We present the complete remission of resistant psoriasis in a hepatitis C virus (HCV)-infected cirrhotic patient who was treated with sorafenib, for recurrent HCC. Conclusion: Several targeted therapies have demonstrated efficacy against psoriasis. More research and well-designed studies, both in novel drugs and those already marketed for other indications, are needed to determine their value as potential novel therapies for psoriasis.*

Psoriasis is a chronic, immune-mediated skin disease, characterized by the presence of symmetrical erythematous plaques covered by scale. Inflammation, epidermal hyperproliferation, abnormal keratinization and local vascular changes are mechanisms involved in psoriasis pathogenesis. Psoriasis is angiogenesis-dependent, with keratinocytes being a major source of pro-angiogenic cytokines. Angiogenesis is tightly regulated by a balance between pro- and anti-angiogenic mediators. Several angiogenic factors have been identified including interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), transforming growth factor-alpha (TGF-α) and vascular endothelial growth factor (VEGF) (1). Platelet-derived growth factor receptors (PDGFRs) are overexpressed in fibroblasts and blood vessels of psoriatic lesions and activated keratinocytes produce pro-angiogentic cytokines, including VEGF. VEGF binds to vascular endothelial growth factor receptor (VEGFR) and promotes cell proliferation and angiogenesis by activating the mitogen-activated protein kinase (MAPK) pathway (also known as Ras/Raf/MEK/ERK pathway) (Figure 1) (2-4).

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related deaths with nearly 600,000 deaths each year worldwide. In addition, its incidence rises in the West. HCC usually develops as a consequence of underlying liver disease and cirrhosis (5). HCC is a hypervascular tumor, with its vascularity being greatly different from normal liver parenchyma. The primary stimulus for tumor angiogenesis is VEGF, an endogenous cytokine that induces capillary endothelial cell proliferation and survival. Other angiogenic factors, such as angiopoietins, PDGF and basic fibroblast growth factor (bFGF), are also expressed in HCC (6). Sorafenib (BAY 43-9006) is a multikinase inhibitor currently approved for the treatment of unresectable HCC and advanced renal cell carcinoma. Sorafenib inhibits tumor cell proliferation and tumor angiogenesis by inhibiting the Raf/MEK/extracellular signal-regulated kinase signaling pathway, VEGFR-1, -2, -3, PDGFR-β and c-Kit. It also inhibits intracellular Raf kinase (Raf-1), which targets the MAPK intracellular signal transduction pathway (Figure 2) (7).

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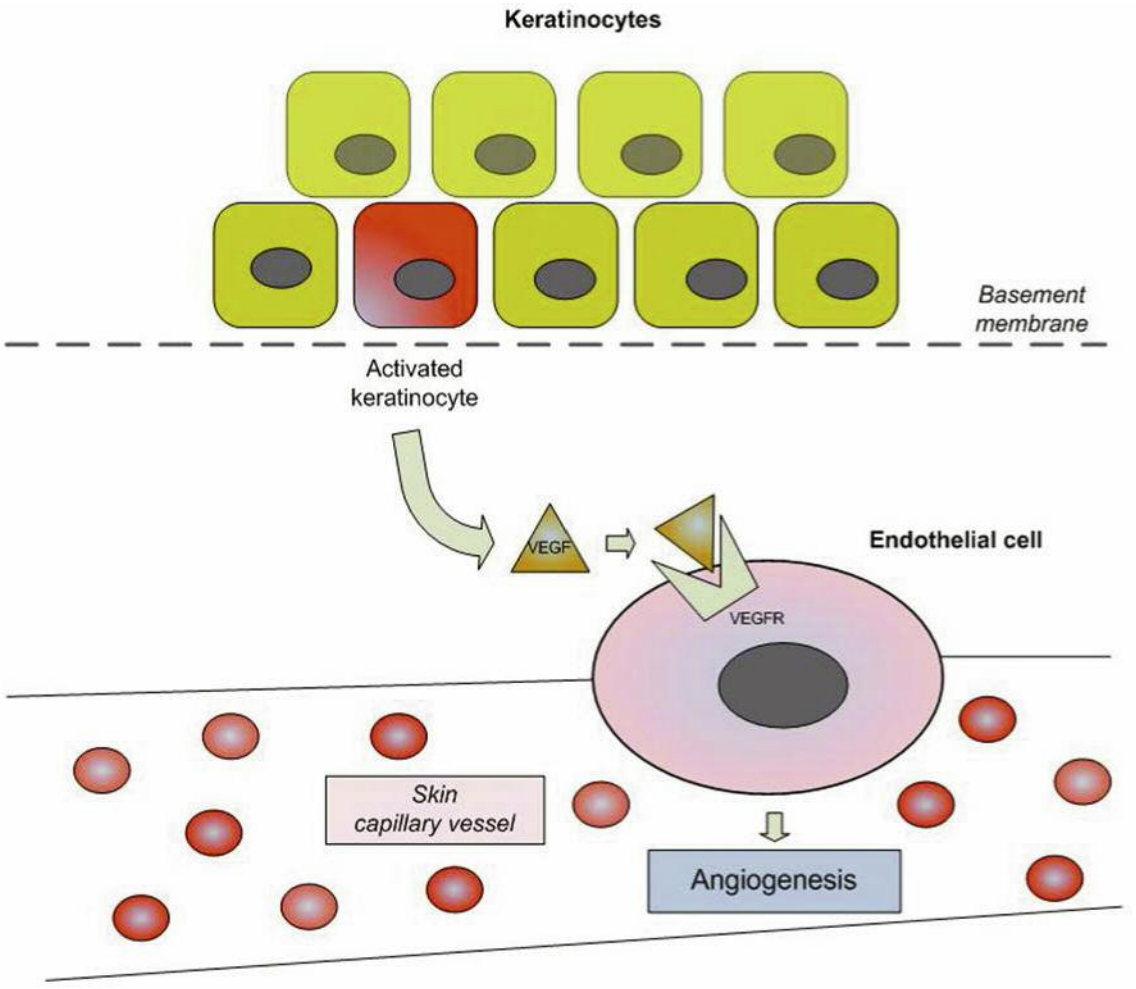

Figure 1. *In psoriasis, vascular endothelial growth factor (VEGF) is produced by keratinocytes after their activation and binds to vascular endothelial growth factor receptor (VEGFR) on skin capillary endothelial cells promoting angiogenesis.*

In this case report, we present the complete remission of resistant psoriasis in an hepatitis C virus (HCV)-infected cirrhotic patient who was treated with sorafenib for recurrent HCC after liver resection for a big (8cm in diameter) HCC.

Case Report

A 71-year-old male presented with a large HCC (8 cm in diameter) at the left lobe of the liver. The patient had been diagnosed with chronic HCV infection seven years ago and psoriasis at his both elbows, knees and anterior lower abdominal wall eight years ago. He had received topical steroids with little efficacy for his psoriasis and anti-viral therapy with no response for his chronic HCV. After a surgical consultation, a left lobectomy was decided and, on 3rd of March, 2008, he underwent a left lobectomy with segment-1 preservation. His post-operative course was uneventful.

However, six months later, during his follow-up computed tomography (CT) examination, multiple liver lesions were found with maximum diameter of 4 cm. He was commenced on sorafenib orally 200 mg daily and gradually increased to 600 mg daily. Attempts for further increasing the dose led to irritating side-effects, including severe hand-foot syndrome, muscle pains and diarrhea; thus he finally stayed with the above mentioned 600 mg daily. A few months later, the patient presented with dramatically regression of his chronic psoriatic lesions and significant remission of liver lesions. Two years later (February 2011, by magnetic resonance imaging (MRI)), after starting sorafenib therapy, liver lesions had completely disappeared and the patient was completely free of any psoriatic lesions and no longer complained of itching or other symptoms. The patient has been on a close follow-up with blood tests every six months and abdominal CT scan yearly. His recent renal and liver function tests, as

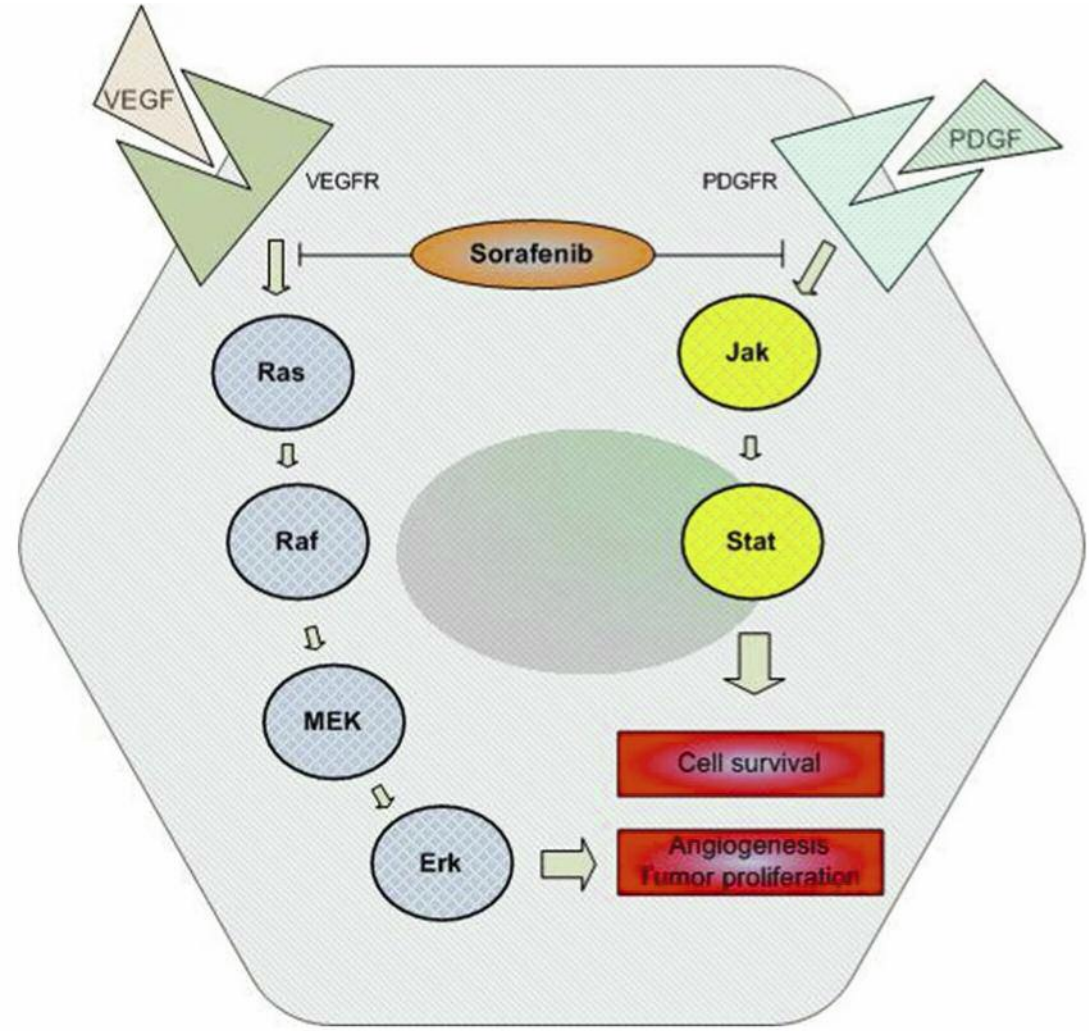

Figure 2. *Sorafenib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) preventing Ras/Raf/MEK/Erk and Jak/Stat pathways activation leading, finally, to inhibition of cell survival and down-regulation of angiogenesis.*

well as his full blood count (FBC) and tumor markers alpha-fetoprotein (a-FP) and carcino-embryonic antigen (CEA), are all completely normal and his CT scan as well. No further anti-psoriatic medication was needed once he was started on sorafenib. He remains on excellent condition with no psoriatic or liver lesions and continues on sorafenib 600 mg (400+200 mg) daily.

Discussion

The overexpression of VEGF on psoriatic keratinocytes and up-regulation of VEGF receptors in microvasculature of psoriatic lesions has now been established as elevated levels of VEGF can be detected in the serum of human psoriasis patients and correlate with disease activity (1). Sorafenib is a multikinase inhibitor, effective in liver and renal cancer, which blocks tumor proliferation and angiogenesis through targeting VEGFR (7). On this basis, drugs against VEGF or its receptor could be considered as future therapies for psoriasis (8). In accordance with our observation, a patient with metastatic hypernephroma treated with sorafenib presented remission of his psoriatic lesions (4). We suggest that inhibition of VEGFR, leading to angiogenesis down-regulation, is the common mechanism in HCC therapy and psoriasis remission induced by sorafenib.

However, cutaneous toxicity is relatively common in patients receiving sorafenib. The most frequent cutaneous side-effect is the hand-foot syndrome, while other described adverse skin reactions include facial and acral erythema, stomatitis, alopecia and pruritus. Less commonly, multiple squamous cell carcinoma, keratoacanthoma and epidermoid cysts have also been described (9). The development of psoriasiform eruptions in patients

treated with sorafenib seems paradoxical, although reported (10-13), since this drug blocks the activity of VEGF, a cytokine whose role in psoriasis pathogenesis is well-documented. A case of sorafenib-related presentation of psoriasis in a HCC patient has been reported. Dysfunctional $CD4^+CD25^+$ T cells, which cause an imbalance between regulatory and effector T-cell functions, are found in patients with psoriasis. According to the authors, tyrosine kinase inhibitors, such as sorafenib, may block the signal transduction pathways in both regulatory and effector T cells (10). In another case, sorafenib was implicated in the development of the psoriasiform eruption in a 59-year-old man diagnosed with nodular HCC secondary to alcoholic liver cirrhosis (11), while another HCC patient developed cutaneous psoriatic lesions following sorafenib therapy (12).

Other biological therapies administered in various advanced cancers have also been involved in psoriasis remission or even exacerbation. Erlotinib inhibits the tyrosine kinase of epidermal growth factor receptor (EGFR) and is successfully used in pancreatic and lung cancer treatment. EGFR is essential in skin development and function and may have a role in the pathogenesis of psoriasis. Although cutaneous side-effects are very common in patients treated with erlotinib, two cases of patients with lung cancer and concomitant psoriasis treated with erlotinib with complete resolution of the skin problems have been reported (14). Bevacizumab, another monoclonal antibody against VEGF, is used for treatment of several cancers and retinopathies. In a report, a patient with metastatic renal cell cancer, psoriasis and psoriatic arthritis, experienced a complete remission of psoriasis during bevacizumab therapy without any other management (15). Finally, among others, the anti-VEGF/anti-TNF-α decoy receptor (Valpha) showed beneficial action against psoriasis (16, 17).

In conclusion, herein, we present the case of a patient with HCC, also suffering from psoriasis, who showed complete remission of his psoriatic lesions after sorafenib administration. Several targeted therapies have demonstrated potential to treat psoriasis as clinical observations of psoriasis remission following administration of bevacizumab, erlotinib, sorafenib and others in cancer patients are encouraging. Contradictory results regarding these drugs' association with psoriasis have also been reported in the literature. More research and well-designed studies, both in novel drugs and those already marketed for other indications, are needed in order to determine their value as potential novel therapies for psoriasis.

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