A case of necrotizing vasculitis with panniculitis, during sorafenib treatment for hepatocellular carcinoma, appeared in disease progression

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Abstract: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and is the third most common cause of death from cancer (1). Sorafenib is the only drug which improves survival in first line advanced HCC. Sorafenib has been associated with several dermatologic toxicities and toxic effects have been related to a better treatment response. We report the case of a well-circumscribed panniculitis and necrotizing vasculitis due to sorafenib, appeared in disease progression in a man affected by advanced HCC.

Keywords: Sorafenib; hepatocellular carcinoma (HCC); panniculitis

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Case Report

We report a case of panniculitis and necrotizing vasculitis due to sorafenib, appeared in disease progression in an 80-year-old white man affected by HCC, HCV-related.

The patient had a clinical history of arterial hypertension, idiopathic myelofibrosis in treatment with oncocarbide from 2008 and chronic obstructive pulmonary disease (COPD); HCC was diagnosed in December 2012 and treated with radiofrequency ablation in January 2013.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer (1).

When diagnosed in early stages, HCC is amenable to potentially curative treatments such as surgery (resection or liver transplantation), or loco-regional procedures like radiofrequency ablation (2). Unfortunately, a dismal prognosis is reserved for HCC when an advanced stage has been diagnosed or after progression to loco-regional therapies, in part due to the lack of effective treatment options and in part due to the underlying liver disease (2–4). Before sorafenib, no systemic therapy has improved survival in patients with advanced HCC (5).

Sorafenib (Nexavar, Bayer AG) is a small molecule that inhibits the serine-threonine kinases Raf-1 and B-Raf and the tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR-β) (6,7).

Sorafenib inhibits tumour-cell proliferation, tumour angiogenesis and increases the rate of apoptosis in a wide range of tumour models (6,7). Sorafenib is approved for advanced renal carcinoma treatment (8) and for advanced HCC (9).

In advanced HCC, sorafenib was superior, when compared to placebo, in terms of overall survival (10.7 vs 7.9 months, hazard ratio 0.69; 95% confidence interval, 0.55 to 0.87; P<0.001) (9).

Like all tyrosine kinase inhibitors (TKI), sorafenib has been associated with several dermatologic toxicities (10). Development of skin toxic effects with EGFR inhibitors has been related with a better treatment response (11).
In October 2013, a CT scan showed local progression with multiple hepatic lesions and an alpha fetoprotein (AFP) value of 1,362 ng/mL.

In December 2013, sorafenib 400 mg twice daily was started; after 7 days, due to asthenia G3 and significant abdominal pain, treatment was discontinued. After the regression of symptoms, sorafenib was restarted with daily dose reduction to 600 mg, with good tolerance.

In February 2014, after three months of therapy, patient complained left leg pain and edema. Clinical examination showed several harsh and painful skin lesions on palpation (Figure 1A,B); AFP was 3,179 ng/mL, doubled compared to baseline.

A skin biopsy revealed a perivascular lympho-granulocytic inflammatory infiltrate involving dermal and subcutaneous tissue. Epidermis was slightly hyperplastic. Inflammatory infiltrate was heavier in subcutaneous fat than in superficial dermis and it was associated with lobular panniculitis and necrotizing vasculitis. At this level, the blood vessels showed fibrinoid necrosis and thrombosis. The periodic acid Schiff (PAS) staining method, performed to detect fungal infection, resulted negative. The morphological findings were consistent with a panniculitis associated with necrotizing vasculitis (Figure 2).

Sorafenib was interrupted with the resolution of cutaneous lesions in 2 weeks. A CT scan confirmed the progression of liver lesions.

Discussion

Cutaneous reactions are frequent in patients treated with TKI and some cases of vasculitis have been described in literature. Maculopapular rash, papulopustular rash, bullous dermatitis, vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS) or panniculitis have been observed during sorafenib treatment (10). Three different hypotheses have been generated to explain the development of cutaneous toxicity. The first hypothesis concerns the inhibition of mitogen-activated protein kinase, stress-activated protein kinase, and VEGF pathways. This leads to keratinocyte proliferation and focal apoptosis carrying to keratosis pilaris, epidermal inclusion cysts and keratoacanthomas. The second hypothesis is that of the inhibition of c-kit or RAF kinase resulting in keratinocyte injury. Histopathologically, cutaneous lesion is seen as a focal epithelial damage with dyskeratotic keratinocytes and reactive epithelial changes in the basal layer of the epidermis and in eccrine sweat ducts. The last and third hypothesis is that of apoptosis induction in endothelial-cells due to direct anti-VEGFR or anti-PDGFR effects on dermal endothelial cells (12).
Figure 2 (A) Dermal and subcutaneous inflammation (2x); (B) epidermis is unaffected. Superficial dermal inflammatory infiltrate is moderate and numerous granulocyte neutrophils are evident (10x); (C) subcutaneous fat shows a heavy inflammatory infiltrate consistent with panniculitis; (D) necrotizing vasculitis with vessels wall fibrinoid necrosis (arrows) and (E) vascular thrombosis (arrow) (20x; 40x).

Vascular lesions have been also described in patients with HCC, but they are more frequent in HBV-related HCC (13) and seem related to an autoimmune mechanism.

Other cases of vascular lesions have been described during treatment with sorafenib (13) but only a few have been documented histologically.

In our case, skin lesions were located only on the left leg, without other cutaneous lesions; biopsy described lobular panniculitis and necrotizing vasculitis.

Our case, like other clinical cases described in literature, shows the extreme variability of skin lesions that may occur during treatment with sorafenib and other TKIs.

Very interesting the lack of correlation between response and toxicity; diversely than other cases reported with other TKI, we found, indeed at the same time, progression disease and skin toxicity. Liver and renal function was normal so there was no reason for suspecting a drug accumulation.

To our knowledge, this is the first case of localized vasculitis histologically confirmed, due to a TKI and appeared during progression disease. It seems that vascular
lesions can appear during every sorafenib treatment phase regardless of the effectiveness and that toxicity is rapidly reversible with TKI suspension.

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**References**