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Case report

Anaphylaxis preceded by erythema multiforme with sorafenib: First case report

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ABSTRACT

A 63-year-old female patient with recent diagnosis of hepatitis C and cirrhosis and no other comorbidities, on no medications, was found to have Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma and began systemic therapy with sorafenib 400 mg twice daily. Five days after starting treatment, the patient went to an emergency department with pruritic, target-shaped, erythematous papules compatible with erythema multiforme, painful oral aphthous ulcers, and fever. Sorafenib was suspended and the patient underwent oral corticosteroid treatment for 5 days, showing significant improvement of the lesions. One month after discharge, the patient was reassessed at an outpatient clinic. As she was asymptomatic and had no skin lesions, sorafenib was resumed at a lower dose (200 mg daily). Three hours after ingesting a single dose of sorafenib, the patient experienced chills, fever, rash, angioedema and stridor. She immediately sought the emergency department and was diagnosed with anaphylaxis. The patient received intravenous corticosteroid therapy, which improved her respiratory and cutaneous symptoms in 72 h. Sorafenib was permanently suspended, and regorafenib could not be prescribed as second-line therapy. This is the first description of anaphylaxis to sorafenib.

1. Introduction

Sorafenib is a well-known multikinase inhibitor and the first-line medication, along with lenvatinib [1], for advanced hepatocellular carcinoma Barcelona Clinic Liver Cancer (BCLC) stage C. Two major trials have demonstrated that sorafenib use can increase the overall survival by 3 months when compared to the placebo [2,3] and in a recent real-life study, performed at our center, patients who received sorafenib had a mean overall survival of 32.5 months, while patients who did not receive the medication, 10.4 months [4].

Diarrhea, abdominal pain and nausea are the most common adverse effects associated with sorafenib [2,5] and usually become more tolerable with time of use. Skin toxicity, such as hand-foot skin reaction, is also a common adverse effect and – despite being a beneficial indicator of therapy response [5,6] – is one of the leading causes of dose reduction or discontinuation of the drug. Sorafenib-induced erythema multiforme, however, is rare [7], and there are no case reports in the literature of anaphylaxis associated with this medication.

2. Case report

A 63-year-old female patient with recent diagnosis of hepatitis C and cirrhosis and no other comorbidities, on no medications and no history of any allergies, was found by abdominal computerized tomography to have five solid lesions, the largest of which was 5.2 × 4.1 × 3.1 cm. All lesions were classified as Liver Imaging Reporting and Data System (LI-RADS) category 5, with invasion of the median hepatic vein. Imaging was compatible with BCLC stage C hepatocellular carcinoma, for which systemic therapy with sorafenib 400 mg twice daily is indicated. Five days after starting the medication, the patient presented pruritic, target-shaped, erythematous papules compatible with erythema multiforme (EM). Papules occurred initially on the torso and spread to the abdomen, neck, arms, legs, and palmoplantar regions in two days. In addition to skin lesions, the patient had painful oral aphthous ulcers and fever, which led her to seek medical care in an emergency department. Her laboratory exams showed an increase in aminotransferases, AST = 224 IU/L (previously 118 IU/L) and ALT = 264 IU/L (previously 144 IU/L), as well as albumin = 3.2 g/dL,

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total bilirubin = 0.8 mg/dL, direct bilirubin = 0.4 mg/dL, prothrombin time = 15 s (control = 13.7 s), no leukocytosis (6000/mm^3) and no important eosinophilia (198/mm^3). She was prescribed 5 days of prednisone 40 mg daily and, because of the prior occurrence of vesicular lesions of the oral cavity, acyclovir 400 mg three times daily for 7 days. Sorafenib was suspended, and the patient was discharged after 4 days with significant cutaneous improvement.

One month later, the patient was reassessed at the outpatient clinic. She was asymptomatic and had no skin lesions. As sorafenib is the only therapeutic choice approved in Brazil for this clinical scenario, the medication was resumed at a lower dose, 200 mg daily. The patient was recommended to seek the emergency department if lesions reappeared.

Three hours after ingesting a single sorafenib tablet, the patient developed chills, fever (38.3 °C), a rash on the legs, angioedema and stridor. She immediately presented to the emergency department. Anaphylaxis was diagnosed, and the patient was managed with intravenous corticosteroid therapy and ventilatory support via a Hudson mask. Within 72 h, her respiratory and cutaneous symptoms resolved; skin lesions cleared completely, breathing was effortless, and she did not require oxygen supplementation. She was prescribed oral prednisone 40 mg daily for 7 days and discharged. Sorafenib was permanently discontinued. As regorafenib is a sorafenib analog, it could not be used as a second-line therapy. Two weeks after discharge, the patient was re-evaluated at the outpatient clinic. She was asymptomatic, had no skin lesions, and received a prescription for nivolumab. This is the first description of anaphylaxis induced by sorafenib.

3. Discussion

Cutaneous adverse events associated with sorafenib are common: more than 90% of patients experience a skin reaction and 60–70% of patients report hand-foot skin reaction (HFSR). However, delayed cutaneous hypersensitivity reactions, such as EM, and severe cutaneous adverse reactions, such as Stevens–Johnson Syndrome, are very rare [8].

In a Japanese study by Ikeda et al. [9] 36 patients receiving sorafenib were followed up; 28 (78%) patients experienced a skin reaction of any grade and 9 (25%) patients developed EM. Diagnoses were biopsy-confirmed. The authors concluded that sorafenib-induced EM in Japanese patients might not be as rare as previously estimated and recommended permanent discontinuation of sorafenib in patients with biopsy-proven EM.

There is a reported case of biopsy-confirmed EM induced by sorafenib in which the patient was able to restart treatment without recurrence of the eruption during 3 months of follow-up [10], but the vast majority of studies either report that patients were not rechallenged or that skin eruptions recurred upon retreatment [9,11,12].

In another case report, a patient treated with sorafenib had skin lesions suggestive of EM. Punch biopsies were performed, and histological results showed that lesions were more compatible with medication-induced hypersensitivity reaction rather than EM. Sorafenib was then resumed in a lower dose without recurrence of cutaneous lesions. In this paper, there is a recommendation for biopsy of any suspected EM lesions to avoid unnecessary discontinuation of sorafenib [13].

The patient in our case report unfortunately did not have a biopsy, but was rechallenged with the drug. Rechallenge led to a more severe reaction than the first adverse reaction. Different from HFSR, in which hyperkeratotic plaques develop over areas of pressure or friction, EM and anaphylaxis are idiosyncratic, IgE-mediated (type 1) hypersensitivity reactions involving the release of numerous chemical mediators from basophils and mast cells after re-exposure to a specific antigen [14]. The terminology was revised in the last International Consensus on Anaphylaxis in 2014, with preferential use of anaphylaxis, instead of other terms such as anaphylactoid reaction, for example, due to the difficulty in differentiating between their mechanisms (immunologic or non-immunologic anaphylaxis) or their simultaneity [15].

In this case, we could not confirm the lesions to be EM, but we can affirm that the patient suffered a hypersensitivity reaction. In the rechallenge, we confirmed that the patient had anaphylaxis, which therefore precluded the use of sorafenib or regorafenib, the second-line drug. Our literature search did not reveal any cases of sorafenib-related anaphylaxis. Such severe reactions have not been reported even in cases of rechallenge, which have been shown to lead to EM, at most.

4. Conclusions

With this case report, we aim to emphasize two important aspects: (1) a lesion suggestive of EM should be biopsied to confirm its histological identity, and, if an EM diagnosis is confirmed, sorafenib should be permanently discontinued; and (2) great caution must be taken in rechallenging patients who had a hypersensitivity reaction to sorafenib, which should preferably be performed in a hospital setting because the effects of re-exposure to the drug can be more severe, as observed in the present case.

Abbreviations

BCLC	Barcelona Clinic Liver Cancer
LI-RADS	Liver Imaging Reporting and Data System
EM	erythema multiforme
AST	aspartate aminotransferase
ALT	alanine aminotransferase
HFSR	hand–foot skin reaction

Authors' contributions

Both AM and MRA write and review the whole manuscript.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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