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Unusually Severe Bullous Skin Reaction to Sorafenib: A Case Report

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1. Abstract

Sorafenib is a multikinase inhibitor widely used in advanced malignancies and is commonly associated with dermatologic adverse effects, particularly hand–foot skin reaction (HFSR). We report a 66-year-old man with metastatic renal cell carcinoma who developed a severe, painful bullous eruption confined to the fingertips after six weeks of sorafenib therapy. Infectious causes were excluded, and clinical improvement followed drug discontinuation. Histopathology supported a drug-induced process. This case highlights an atypical, severe presentation of HFSR with significant functional impairment and absence of plantar involvement, emphasizing the need for early recognition and management.

2. Keywords

Sorafenib, hand–foot skin reaction, bullous eruption, adverse drug reaction

3. Introduction

Sorafenib is an oral multikinase inhibitor targeting RAF kinases and multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors. It is approved for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid carcinoma.

Cutaneous adverse effects are among the most frequent toxicities associated with sorafenib. These include rash, erythema, xerosis, alopecia, and the characteristic hand–foot skin reaction (HFSR). HFSR typically presents as painful hyperkeratotic lesions on pressure-bearing areas of the palms and soles. Although usually mild to moderate, severe and atypical presentations can occur and may necessitate treatment modification.

We describe a case of an unusually severe bullous variant of HFSR with predominant fingertip involvement and marked functional impairment.

4. Case Report

A 66-year-old man with metastatic renal cell carcinoma involving the lungs presented with fever, fatigue, anorexia, and a two-day history of painful discoloration of the fingertips.

He had been receiving sorafenib for six weeks, after switching from sunitinib due to pancreatitis. A similar but milder episode two weeks earlier had prompted dose reduction.

4.1. Medical History

His comorbidities included diabetes mellitus, hypertension, dyslipidemia, and stage 3 chronic kidney disease. He had undergone right nephrectomy two years earlier.

4.2. Examination

On admission, the patient was afebrile with stable hemodynamics. Examination revealed:

- Swollen, tender fingertips with violaceous discoloration
- Bullous lesions along the lateral aspects of the fingers
- Cyanotic nodules on the dorsal fingertips
- Acneiform eruptions over the upper back
- Eyelid edema with crusting

Systemic examination was otherwise unremarkable.

4.3. Investigations

Laboratory findings showed mild anemia, hyponatremia, hypoalbuminemia, and elevated creatinine. White blood cell count was within normal limits. Chest radiography was unremarkable, and blood cultures were negative.

During hospitalization, the lesions progressed to large, tense bullae associated with severe pain, significantly limiting hand function. Some bullae ruptured spontaneously, followed by dark discoloration and gradual reduction in pain.

A skin biopsy from the back lesions demonstrated neutrophilic dermatosis, consistent with a drug-induced reaction.

4.4. Management and Outcome

Empirical antibiotics were initiated initially but discontinued after negative infectious workup. Sorafenib was withheld, and analgesia was provided with opioids.

Following discontinuation of sorafenib, the lesions gradually resolved, with improvement in pain and functional status. The patient was discharged with outpatient oncology follow-up for alternative therapy.

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5. Discussion

HFSR is a well-recognized adverse effect of sorafenib, occurring in approximately one-third of treated patients. It is clinically distinct from classic chemotherapy-induced hand–foot syndrome and is characterized by localized, pressure-related lesions.

Severity is graded as:

- Grade 1: Minimal skin changes without pain
- Grade 2: Painful lesions not interfering with function
- Grade 3: Severe pain with functional impairment

This patient exhibited a grade 3 reaction, with debilitating pain and inability to perform daily activities.

The pathogenesis of HFSR remains incompletely understood. Proposed mechanisms include:

- Direct cytotoxic effects on keratinocytes
- Increased drug concentration in eccrine gland–rich areas
- Inhibition of angiogenic pathways (e.g., VEGF, PDGF)

This case is notable for several atypical features:

- Predominant bullous morphology, rather than hyperkeratosis
- Exclusive involvement of the hands, sparing the feet
- Severe pain leading to functional disability

The diagnosis was supported by:

- Temporal association with sorafenib use
- Exclusion of infection
- Histopathological findings
- Clinical improvement after drug withdrawal

Management of severe HFSR includes dose reduction or discontinuation of the offending agent, along with symptomatic treatment. Early recognition is crucial to prevent morbidity and maintain treatment adherence.

6. Conclusion

This case illustrates a rare and severe bullous variant of sorafenib-induced hand–foot skin reaction. Clinicians should be aware of atypical presentations, including isolated hand involvement and significant functional impairment. Prompt identification and appropriate management, including drug cessation when necessary, are essential to optimize patient outcomes.

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