Dermatology Practical & Conceptual

Sorafenib-Induced Acute Generalized Exanthematous Pustulosis

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Introduction

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction (SCAR), with an incidence rate between 1 and 5 cases per million per year. Clinically, AGEP is characterized by the abrupt onset of edematous erythema and widespread small sterile pustules. Fever with leukocytosis generally accompany cutaneous findings and mucous membrane may also be affected; the mortality rate of AGEP is up to 5%. The main differential diagnosis of AGEP with generalized pustular psoriasis is often challenging [1].

Case Presentation

A 62-year-old man with HBV-related chronic hepatitis was referred to our Dermatology Unit for the acute onset of skin and mucosal lesions associated with fever, 7 days since the start of oral sorafenib 400 mg twice daily. for radiation therapy-refractory stage IV hepatocellular carcinoma. Past medical history was negative for psoriasis. On physical examination, numerous disseminated tiny non-follicular pustules were observed overlying confluent erythematous macules on his trunk and limbs, involving about 75% of the body surface area (Figure 1). Furred tongue and desquamation of the lips were also present. Body temperature was 38.5 °C. No enlarged lymph nodes or hepatosplenomegaly were noticed. Complete blood count showed leukocytosis with relative neutrophilia (80%, normal range 50%-75%); serum bilirubin level was increased (3.0 mg/dL, normal range 0.3-1.2 mg/dL). Blood and skin cultures resulted negative. Histological examination of a skin biopsy showed multifocal spongiosis in the epidermis, with intraepidermal pustules containing fibrin and neutrophils. In the superficial dermis, a mixed inflammatory infiltrate composed of scattered neutrophils and lymphocytes was present (Figure 2).

According to the validation score of the EuroSCAR study group [2], a diagnosis of acute generalized exanthematous pustulosis (AGEP) was made; using the Naranjo scale [3] the

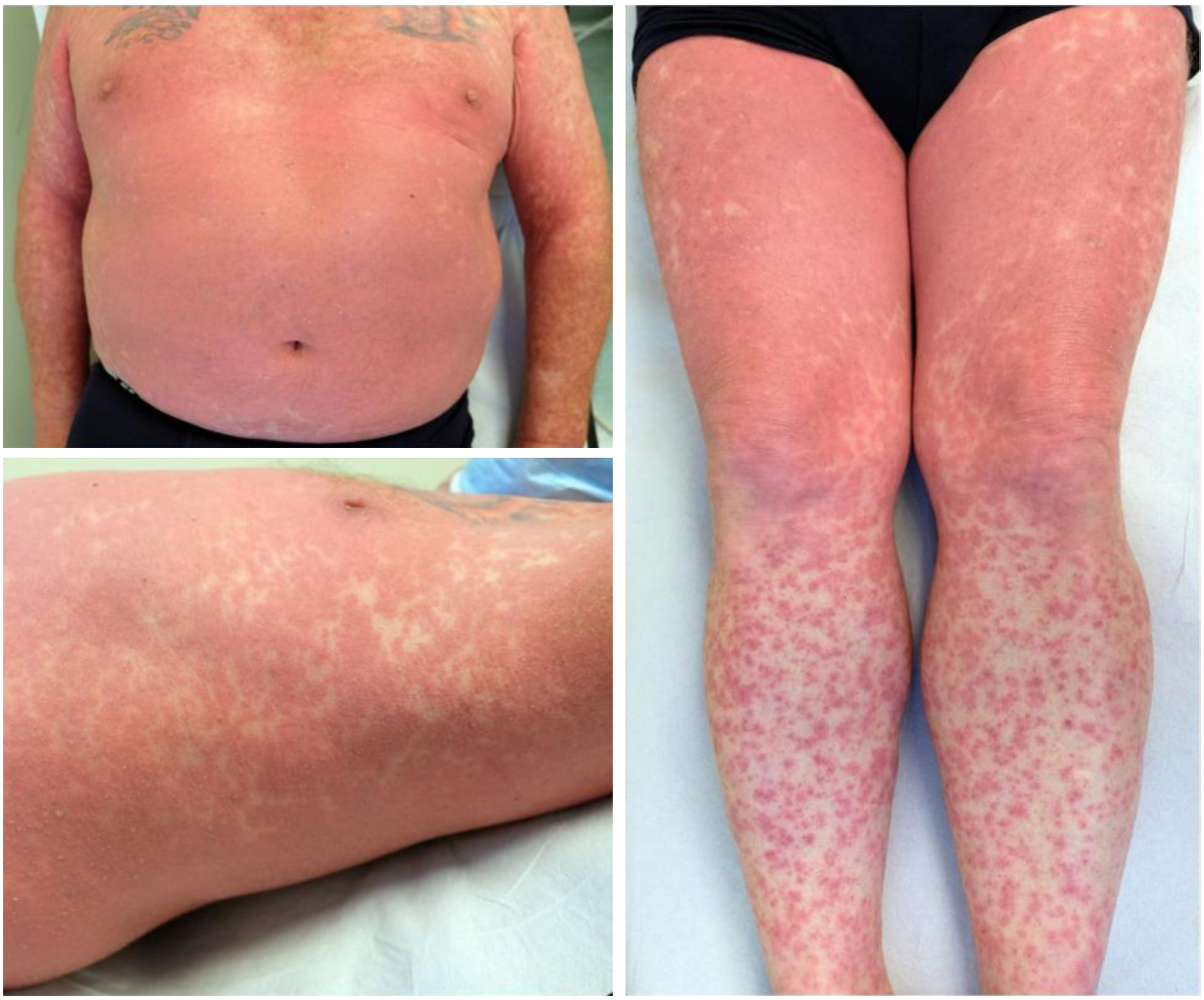

Figure 1. Confluent erythematous macules on his trunk and limbs, involving about 75% of the body surface area, d with overlying disseminated tiny non-follicular pustules.

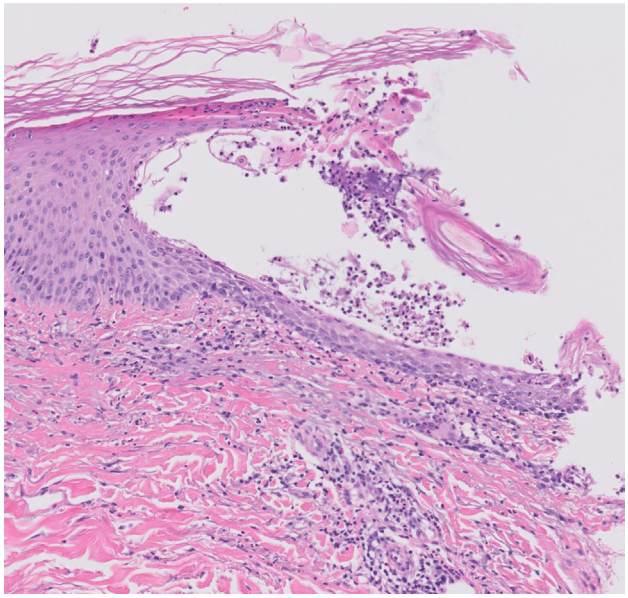

Figure 2. Intraepidermal pustule containing fibrin and neutrophils; in the superficial dermis, a mixed inflammatory infiltrate composed scattered neutrophils and lymphocytes was present.

skin reaction collected six points and was considered probably relate" to sorafenib (Figure 3), so the drug was discontinued with steady improvement in the following days.

Conclusions

Sorafenib is an oral multi-kinase inhibitor that mainly targets C-RAF, B-RAF, vascular endothelial growth factor (VEGF) receptors, and platelet-derived growth factor receptor (PDGFR). The drug is approved for the treatment of both unresectable hepatocellular carcinoma and advanced renal cell carcinoma. Up to 60% patients treated with sorafenib experience cutaneous adverse events, including hand-foot skin reactions, maculo-papular exanthem, pruritus, alopecia, subungual splinter hemorrhages, seborrheic dermatitis-like eruption and erythema multiforme [4]. AGEP has been Most commonly associated with aminopenicillins, quinolones, chloroquine and sulphonamides, and to our knowledge only three cases of sorafenib-induced pustular reactions were

#	Naranjo Questions	Yes	No	Do not know
1.	Are there previous conclusive reports on this reaction?	1	0	0
2.	Did the adverse event occur after the suspected drug was administered?	2	-1	0
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0
4.	Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5.	Are there alternative causes (other than the drug) that could have on their own cause the reaction?	-1	2	0
6.	Did the reaction reappear when a placebo was given?	-1	1	0
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
8.	Was the reaction more severe when the does was increased or less severe when the dose was decreased?	1	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10.	Was the adverse event confirmed by any objective evidence?	1	0	0

Figure 3. Naranjo Adverse Drug Reaction Probability Scale.

published: one of them defined as acute localized exanthematous pustulosis (ALEP) [5], while two reported as AGEP [6,7]. These evidence may suggest an increasing incidence of sorafenib-induced AGEP due to the relatively recent introduction use of this kinase-inhibitor. We therefore underline the importance of early diagnosis of AGEP during sorafenib therapy, in order to promptly withdraw the causative drug and at the same time to consider other therapeutic options for metastatic cancer.

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