Tyrosine kinase inhibitor-induced severe bullous pemphigoid in a patient with advanced stage of liver cancer: a case report and literature review

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Abstract

Apatinib, a novel vascular endothelial growth factor receptor-2 (VEGFR2) targeted chemotherapy for solid tumors, has revealed promising efficacy in treating liver cancer in China. Although it has been reported to have a high incidence of inducing hand-foot skin reactions, other skin adverse reactions induced by apatinib are rare. Herein, we report a rare case of apatinib-induced severe bullous dermatosis that was successfully treated with methylprednisolone and summarize the dermatologic toxicities of VEGFR tyrosine kinase inhibitor.

Title page

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1 Introduction

Apatinib, a novel tyrosine kinase inhibitor targeted vascular endothelial growth factor receptor-2 (VEGFR2) for solid tumors, has revealed promising efficacy in treating liver cancer in China. Although it has been reported to have a high incidence of inducing hand-foot skin reactions, other skin adverse reactions induced by apatinib are rare. Herein, we report a rare case of apatinib-induced severe bullous dermatosis that was successfully treated with methylprednisolone and summarize the dermatologic toxicities of VEGFR tyrosine kinase inhibitor.

Key words: tyrosine kinase inhibitor, apatinib, drug adverse reaction, bullous dermatosis

2 Case presentation

A 67-year-old man had a one-month history of erythema and multiple bullae with itching and pain over the whole body (Figure 1A). Two years ago, the patient was diagnosed with advanced hepatocellular carcinoma and underwent chemoembolization and systemic treatment, including half-year treatment of sorafenib (0.8 g/d) and one-year treatment of lenvatinib (0.8 mg/d). However, he developed intermittent diarrhea after the systemic treatment. One month prior, the patient began taking apatinib mesylate (850 mg/d). After ten days, the patient presented with patchy erythema, blisters, bullae, and erosion accompanying the oral mucosa, which was affected by itching and pain. He was admitted to local hospital and an initial diagnosis of pemphigus was considered, while discontinuation of apatinib mesylate and symptomatic treatments were ineffective. Then the patient was admitted to our department. Physical examination revealed a few vesicles on the trunk, blood blisters on the hands, and multiple erosions on the trunk, limbs, and scalp, while some were covered with crust. Skin biopsy and immunofluorescence (IF) were obtained from the right waist. The skin biopsy demonstrated subepidermal blisters, individual dyskeratinized cells in the spinous layer, vacuolized focal basal cells, and sparse lymphocyte infiltration around the small vessels in the superficial dermis (Figure 2). Direct IF displayed a basement membrane with linear deposition of IgA, IgG, and C3, with negative indirect IF (Figure 3). His blood pressure was 120-150mmHg/60-90mmHg while fasting blood glucose fluctuates between 8 and 15mmol/L and postprandial blood glucose fluctuates between 5 and 23mmol/L. Furthermore, laboratory investigations depicted mild anemia, hypoproteinemia, abnormal liver function, coagulopathy, fecal occult blood, and urinary tract infection with negative serum autoantibodies including anti-BP180, anti-Dsg1, anti-Dsg3, and anti-nuclear antibody. Staphylococcus squirrels and Corynebacterium striatum were cultured from buttock secretions. Chest CT indicated chronic bronchitis, pneumonectasis, and mild pulmonary infection.

Based on these findings, the patient was diagnosed with apatinib-induced bullous dermatosis (BP). The body weight of the patient was 45 kg. Methylprednisolone (80 mg daily at the initial dose), antibiotics, symptomatic treatments including albumin, niferex, furosemide, fresh frozen plasma, insulun and skin care were initiated. Owing to his multiple underlying diseases, he and his family were discharged after two weeks of treatment (Figure 1A). Methylprednisolone was replaced with oral prednisone 30 mg daily, and recombinant human epidermal growth factor gel was added to promote wound healing. Then the patient took prednisone 30 mg/d for 2 months by himself, the cutaneous and oral erosions mostly healed, with a few

epithelial islands growing. At the 3-month-follow up visit, the skin lesions of the patient completely resolved (Figure 1B).

3 Discussion

Liver cancer, one of the fatal cancers worldwide, is often treated with surgery, chemoembolization and chemotherapy[1]. Sorafenib and lenvatinib are first-line chemotherapy agents for the treatment of hepatocellular carcinoma. However, owing to their unsatisfactory results and numerous adverse side effects, many other chemotherapeutic drugs have been investigated to treat this disease[2]. Apatinib mesylate is a novel tyrosine kinase inhibitor (TKI) launched and approved in China in 2014. It can efficiently and competitively bind to vascular endothelial growth factor receptor-2 (VEGFR2), which inhibits angiogenesis in tumors and inhibits tumor growth and progression[3].

As previously described, VEGFR TKIs have promising therapeutic efficacy for multiple tumors. However, a few skin toxicities have also been elucidated in the literature. In 2015, Massey et al. has revealed that HFS, rash and pruritis were significantly associated with VEGFR TKIs with the incidence of 0-37%, 13-41% and 14%, respetively[4]. Other cutaneous side effects include alopecia, pigmentation, depigmentation, xeroderma, ulcer and erythema multiforme have been reported as well[4,5]. The management of these lesions could refer to previous reviews[6,7]. In terms of apatinib, commonly reported side effects of apatinib to include hematologic toxicity, proteinuria, hypertension, fatigue, nausea, vomiting et al.[8]. Regarding cutaneous lesions, the hand-foot syndrome (HFS) is the most common skin reaction, which may result in a 50.5% incidence[5]. Moreover, some cases have reported skin pigmentation, rashes, and BP induced by apatinib[9,10].

There was only one case reporting that a 62-year-old female patient developed drug-induced BP (DIBP) after taking apatinib (0.5 g/d) for two weeks for breast cancer. In the present case, the patient developed erythema and multiple bullae on the entire body after 10 days of apatinib treatment. The Naranjo score (a tool used to assess the possibility of drug-induced adverse reactions) was 7, which indicated a probable adverse drug reaction of apatinib mesylate. Combined with skin biopsy and DIF, apatinib-induced BP was diagnosed. The therapeutic effect of methylprednisolone was significant. Clinical differential diagnoses at the time of presentation included paraneoplastic pemphigus (PNP). PNP is a rare, autoimmune disease associated with neoplasm. Because the clinical features of PNP are polymorphous, it is sometimes difficult to distinguish it from other bullous diseases. Histopathological examination demonstrated suprabasal acantholysis and dyskeratosis, while DIF demonstrated intercellular IgG and/or C3 deposition in the epidermis, with positive IIF[11]. However, the clinical and pathohistological findings of this patient didn't conform to PNP, thus, the diagnosis of BP induced by apatinib was finally made.

In fact, subepithelial autoimmune bullous dermatosis is a disease spectrum that includes inherited and acquired bullous skin disorders, such as BP, linear IgA bullous dermatosis, and lichen planus pemphigoid. They can be induced either spontaneously or by some drugs[12]. In our case, BP was indicated by the disruption of the basal membrane zone (BMZ) through autoantibodies. The underlying mechanism may be due to drug ingestion acting as an immunological trigger, which stimulates the hyperproduction of autoantibodies, and then the autoantibodies appear to target multiple antigens within BMZ[13]. Referring to treating autoimmune bullous dermatoses, the patient has been prescribed glucocorticoids as initial therapy and achieved satisfactory result[14].

4 Conclusion

VEGFR TKIs are promising therapeutics for multiple solid cancers. However, all these molecular targeting agents are associated with a variety of adverse events that can impact patients' quality of life. Here, we report a rare and severe case of apatinib-induced BP, which demonstrated the effectiveness of glucocorticoid therapy for DIBP.

Ethics statement

The patient provided informed consent.

Fundings

None

Author contributions

LY and WTT designed the study and acquired, analyzed, and interpreted the data. LY wrote the manuscript. WTT and WM critically revised the manuscript for important intellectual content. All authors have contributed to the manuscript and approved the submitted version.

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Legends to the figures

Figure 1. Skin lesions of the patient. (A) Multiple bullae and erosions appeared on the whole body before treatments and improved after two weeks later. (B) At the 3-month-follow up, the skin lesions of the patient completely resolved.

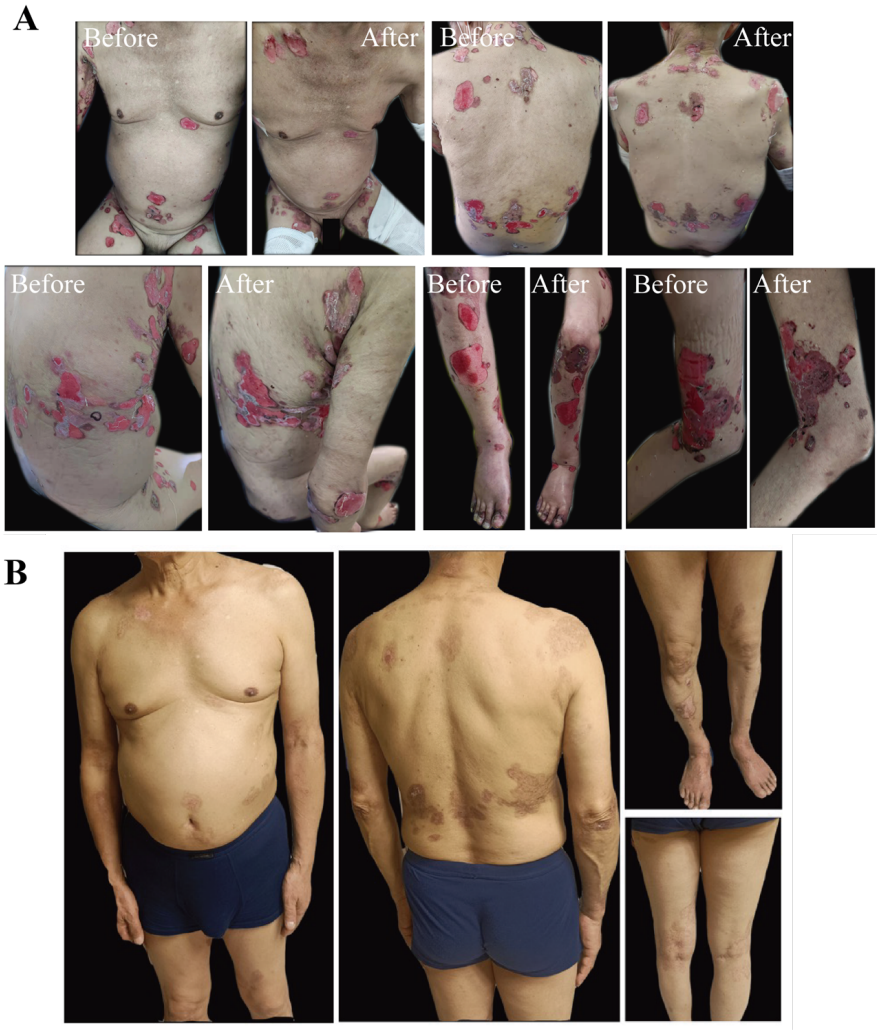

Figure 2. Histopathological images show subepidermal blisters, individual dyskeratinized cells in the spinous layer, focal basal cells vacuolized, and sparse lymphocyte infiltration around small vessels in the superficial dermis. Hematoxylin-eosin stain: (A)×40, (B)×100.

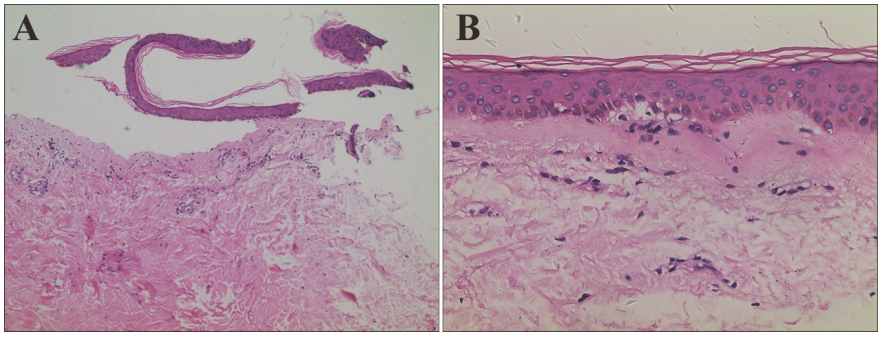

Figure 3. Direct immunofluorescence shows basement membrane with linear deposition of (A) IgA, (B) IgG and (C) C3. Hematoxylin-eosin stain:×40.