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CASE REPORT

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Drug eruption due to bosentan in a patient with systemic sclerosis

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Abstract We present the case of a 60-year-old female patient with systemic sclerosis complicated by pulmonary hypertension. Ten days after the initiation of treatment with bosentan, high fever and skin eruptions were noted. In the previous reports, the frequency of drug-induced skin eruptions has not been well documented. Since the use of bosentan is expected to increase, we should be aware of the previously unknown adverse effects as well as skin eruptions.

Key words Bosentan · Drug eruption · Endothelin-receptor antagonist · Pulmonary arterial hypertension (PAH) · Systemic sclerosis (SSc)

Introduction

It is recognized that severe pulmonary arterial hypertension (PAH) sometimes develops in patients with systemic sclerosis (SSc).[1] Because the prognosis of patients with PAH is substantially worse than that of patients without this complication, intensive efforts are underway to develop sensitive screening methods and effective treatments. Bosentan, a dual endothelin-receptor antagonist, has been proven to be effective for PAH associated with SSc, and was approved for the treatment of PAH in Japan in 2005. The frequency of drug-induced skin eruptions, however, has not been well documented. We herein report on a patient with drug eruption due to bosentan.

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Case report

A 60 year-old woman first visited our hospital in 1978 with a 2-year history of Raynaud's phenomenon. She presented with skin sclerosis on her fingers, forearms, chest, and upper back. Macular telangiectasial spots on her face and digital pitting scars were also observed. She was diagnosed as having diffuse cutaneous systemic sclerosis (dcSSc), and oral treatment with vitamin E and pronase was initiated. In 1998, her case was complicated by reflux esophagitis, for which treatment with omeprazole was started. Shortness of breath developed. Secondary PAH was diagnosed in 2002, and treatments with fulosemide and barapesorim sodium were initiated.

In November 2003, she was hospitalized in our dermatology department due to her digital ulcers and gangrene. Despite hyperbaric oxygen treatment, sympathetic blockade, and a debridement of gangrenous tissues, her right fourth finger was amputated.

As dyspnea had gradually worsened, she was hospitalized again on September 6, 2005. At that time, slightly elevated levels of C-reactive protein (2.2 mg/ml), blood urea nitrogen (41 mg/ml), and serum creatinine (1.3 mg/ml) were noted. The other abnormal serological findings included anti-nuclear antibody 1:640 (speckled nuclear pattern), anti SS-A antibody 140.4 index, and anti SS-B antibody 29.9 index. Anti Scl-70 and anti RNP antibodies were negative. A right heart catheterization revealed mean pulmonary arterial pressure of 60 mmHg. Oral administration of bosentan 62.5 mg/day was initiated on September 6, and after 10 days was increased to 125 mg/day. Her dyspnea improved. On September 16, she developed a high fever of up to 38.5°C with generalized skin rashes. Physical examination revealed pruritic bean-sized erythemas disseminated on her face, trunk, arms, and thighs (Fig. 1a,b). Eosinophilia (13.4%) was noted at that time, but no liver dysfunction developed. We suspected drug eruption due to bosentan. Histologically, a biopsy specimen taken from the erythema of the thigh showed mild liquefaction degeneration and slight infiltration of lymphocytes around the vessels in the

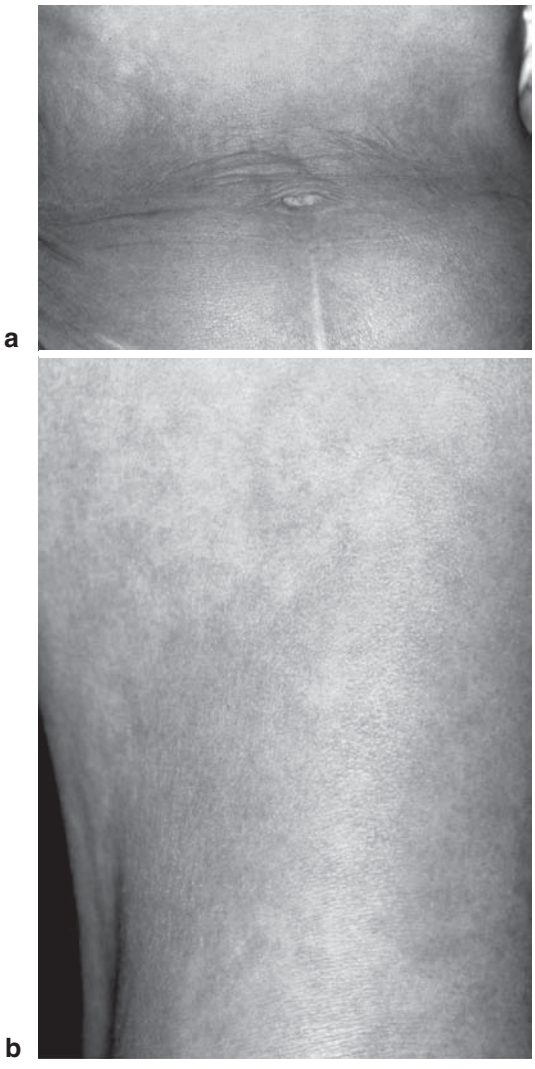

Fig. 1a,b. Generalized light-red colored skin rashes were noted on the trunk and extremities

upper dermis (Fig. 2). The withdrawal of bosentan was not enough to reduce the symptoms, so prednisolone (PSL), 30 mg/day orally, was initiated. The treatment was effective so her skin rashes improved gradually and the number of eosinophilis was normalized. However, after the discontinuation of PSL, mild fever and skin rashes with eosinophilia (12.4%) recurred and continued for about 1 month without PSL. Other drugs including furosemide, famotidine, barapesorim sodium, spironolactone, and allopurinol were continued. Patch testing with bosentan 5%, 10%, and 20% in vaseline were negative. The stimulation index of the drug-induced lymphocyte stimulation test (DLST) for bosentan was also negative (i.e., less than 180%). Provocation test with 6.25 mg of bosentan twice a day was performed on October 31. The next day, 12.5 mg of bosentan twice a day induced a slight fever and skin eruption. An elevated proportion of eosinophils of up to 13% was observed, along with skin eruptions and fever.

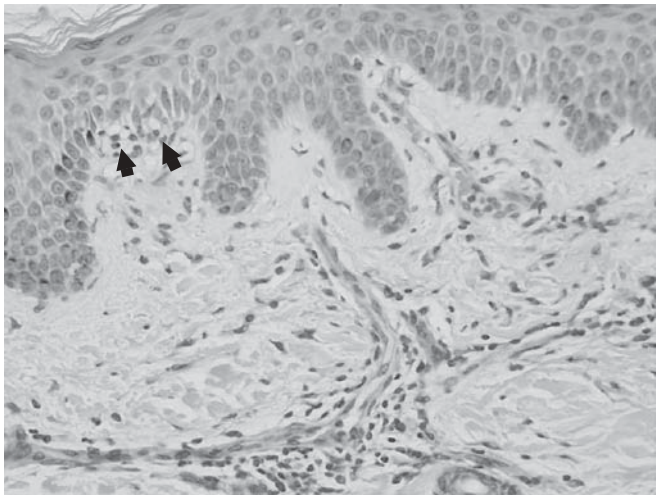

Fig. 2. Histological findings showed liquefaction degeneration (*arrows*) and slight lymphocytic infiltration around small vessels in the upper dermis

Discussion

Bosentan is the first endothelin receptor antagonist (ERA), which blocks endothelin receptor A and B, and has been approved in Europe and the United States for the treatment of PAH and PAH associated with systemic rheumatic diseases.[1–3] The drug is considered a first-line oral treatment for PAH, a devastating orphan disease with a poor prognosis. Bosentan improved exercise capacity and cardiopulmonary hemodynamics in patients with PAH,[4] and its long-term effect has also been reported.[5]

In patients with SSc, elevated endothelin levels in plasma, and higher levels in patients with dcSSc as compared with those with limited cutaneous SSc (lcSSc), have been demonstrated.[6] Endothelial cell damage leading to increased endothelin production may influence the early stage of the disease such as Raynaud's phenomenon, and sustained increase in endothelin levels may play an important role in organ fibrosis of the subsequent stage. Endothelin levels in plasma are elevated in scleroderma patients with pulmonary disease, including PAH, and a positive correlation between the increased endothelin levels and the severity of PAH supports the concept that endothelin dysfunction may be involved in the development of PAH.[2]

Pulmonary arterial hypertension associated with SSc is now one of the leading causes of mortality. Although patients with lcSSc are more likely to develop PAH than those with dcSSc,[7,8] the true prevalence of PAH and its risk factors are not yet known.[1] The prevalence of PAH in patients with SSc appears to be no higher than 15%; however, histopathological evidence of pulmonary arteriopathy is found in up to 50%–65% of patients with lcSSc, suggesting that much greater numbers of patients may be at a risk of developing PAH if followed up long enough.[2] The development of treatments with proven efficacy for PAH is a major medical advance and a milestone for SSc management.

As the main adverse event of bosentan is a moderate and usually transient increase of transaminase levels, liver enzyme monitoring is required to prevent hepatic injury.[2] It has been reported that liver dysfunction is dose dependent, and inhibition of the hepatocanalicular bile salt export pump is implicated.[9] Other adverse events include headache, dizziness, worsening of symptoms of PAH, cough, and flushing; however, the frequency of drug eruption has not been well documented.[2] Regardless of the wide use of bosentan in Europe and the United States, we found only one case report with necrotizing leukocytoclastic vasculitis due to bosentan.[10] Therefore, the frequency of drug eruption might not be so high. Our patient presented generalized confluent erythemas on the whole body and a prolonged disease course. It is uncertain whether the clinical course of our patient is exceptional. Further reports will elucidate the characteristic features of adverse skin eruption during bosentan treatment.

Bosentan has been reported to be also effective for Raynaud's phenomenon and digital ulcers in SSc patients.[11–14] Since the use of bosentan is expected to increase, we should be aware of potential previously unknown adverse effects as well as skin eruptions.

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