

found in many preservatives, and ferulic acid is found in citrus and tomato.⁴ Coniferin alcohol is a fermentation product of brewer's yeast and thus may be present in alcoholic beverages.⁴ In one study in which oral challenges with balsam of Peru were used, dietary restriction resulted in improvement of dermatitis in half of the patients within 1 month.⁶ In another study, 28 of 46 patients who had initial (within 1–2 months) improvement in dermatitis with a restricted diet continued to have longer-term improvement after 1 to 3 years of the diet.⁷

The exact immunologic mechanism of balsam of Peru–induced contact dermatitis is unknown. Allergic contact dermatitis is a delayed, cell-mediated hypersensitivity reaction that involves sensitized CD4 helper T cells.³ One study found that balsam of Peru is a CD1_a antigen that activates T cells via lipid antigens.⁸ Contact urticaria syndrome due to patch testing with balsam of Peru has also been reported in a patient with chronic urticaria.⁹

In conclusion, we present a patient with balsam of Peru allergic contact dermatitis. Fragrance and cosmetic exposures are obvious sources of sensitization. However, balsam of Peru components are also found in many common foods. Many patients present with dermatitis and are subjected to an ineffective restricted diet with no documented justification (as in our patient with wheat). A thorough history and examination should prompt targeted testing (including the use of patch testing) for patients who present with dermatitis. Balsam of Peru should be considered in the differential diagnosis of any patient with a suspected dermatitis.

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Severe adverse skin reaction and desensitization to sorafenib



Sorafenib is a multikinase inhibitor that targets various receptor tyrosine kinases and RAF kinases (serine/threonine kinases) associated with tumor growth. The most common adverse reactions ($\geq 20\%$) for sorafenib are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage. Severe skin reactions may require dose reduction or even discontinuation of the therapy.¹ We report a case of a patient in whom continuation of sorafenib treatment was required despite suspected sorafenib-induced fever and generalized urticaria.

A 21-year-old woman presented with febrile fever and generalized urticaria that appeared on the legs and spread on the whole skin, including the face. The patient was diagnosed as having a metastatic lamellar hepatocellular carcinoma and started treatment with 800 mg/d of oral sorafenib. Skin lesions and febrile fever developed 10 days after the start of the treatment. Because the patient was suspected of having sorafenib-related reactions, the treatment was stopped, and systemic glucocorticoids and oral antihistamines were prescribed. Urticaria disappeared within 5 days. Because sorafenib was the only treatment possible for this patient, it was decided to induce oral tolerance. We used the modified protocol for oral tolerance induction described by Bauer et al² (Table 1).

From the eighth day, treatment with 400 mg twice daily of sorafenib was started. Eight hours after the evening dose urticaria developed on the face and neck. Sorafenib dose was reduced (400 mg in the morning and 200 mg in the evening) and continued for

more than 6 months without any adverse effects. There were no signs of the disease progression after 6 months.

Immune disorders (including generalized urticaria) are uncommon ($\geq 0.1\%$ to $< 1\%$) during sorafenib therapy. According to the National Cancer Institute, the common toxicity criteria of urticaria and febrile fever constitute a grade 2 allergic reaction. Because skin toxic effects are considered to be a sign of sorafenib effectiveness,^{1,3} an allergological workup is usually not performed in clinical practice. There are no published data describing skin test reactions to multikinase inhibitors. Allergic mechanisms of skin toxic effects should also be considered⁴ because this requires different approach.

We consider this case to represent an allergic reaction to sorafenib. An acute upper respiratory tract infection was not confirmed because no febrile fever was registered once sorafenib treatment was stopped and the blood cell count and C-reactive protein level were normal. No increase of absolute eosinophil or lymphocyte counts were registered in repeatedly performed blood tests. In addition, after 5 days of intravenous prednisolone and oral antihistamine treatment, the skin cleared.

Tolerance induction appears to be suitable to reintroduce sorafenib therapy if symptoms are considered to be allergic. We assessed urticaria, which appeared on the second day of desensitization, as a positive reaction, indicating the causal relationship between the previous urticaria and sorafenib. We selected bilastine for premedication because it is effective in treating urticaria and is not metabolized by the liver or kidneys.^{5,6} Glucocorticoids, such as prednisolone, are widely applied in patients with cancer during antitumor therapy, although glucocorticoids induce pro-survival and pro-proliferative effects in vitro in several different tumor types.^{7,8}

Table 1

The Protocol of the Tolerance Induction to Sorafenib

Treatment	Time, min	Dose, mg	Reaction	Treatment
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 1	0–60 60–120 120–180	0.4/0.8/1.6/3.2 6/12/24/50 100/200/400	No No No	No No No
Cumulative Dose of 798 mg (Every 15 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 2	0 180 300	100 100 200	30 min later: pruritus, face and neck urticaria No 180 min later: pruritus, face and neck urticaria	20 mg of bilastine, symptoms reduced within 30 min No 20 mg of bilastine, symptoms reduced within 30 min
Cumulative Dose of 400 mg (Every 180 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 3	0 120 240	100 200 200	No No 5 hours later: pruritus, face and neck urticaria	No No 30 mg of bilastine
Cumulative Dose of 500 mg (Every 120 Minutes)				
Oral premedication with 30 mg of prednisolone and 20 mg of bilastine on day 4	0 120 240	200 200 200	No No 12 hours later: pruritus, face and neck urticaria	No No 20 mg of bilastine
Cumulative Dose of 600 mg (Every 120 Minutes)				
Oral premedication with 20 mg of bilastine on days 5–7	Every 120 min	200	No	No
Cumulative Dose of 800 mg (Every 120 Minutes)				

We then changed the tolerance induction protocol and discontinued premedication with prednisolone, although theoretically it could be beneficial in alleviating late skin reactions appearing 5 to 12 hours after the last dose.

Induction of drug tolerance consists of the progressive administration of increasing doses of a particular drug to render immune effector cells less reactive. Immunologic mechanisms, including IgE-mediated and/or cell-mediated mechanisms, or even nonimmunologic unknown mechanisms are involved in this process. The resulting state is temporary, and continuous administration of particular drugs is required to maintain the tolerance. Case reports of successful oral tolerance induction in patients with severe cutaneous reactions have been presented in literature, including reports on 2 multikinase inhibitors, sorafenib (in metastatic renal cancer)² and imatinib (in chronic myeloid leukemia).⁹ Unfortunately, we could not measure the tumor necrosis factor for the patient. Others who use this protocol might want to measure tumor necrosis factor before and after the desensitization because it might play a role in such situation. We conclude that the induction of tolerance to sorafenib is possible, allowing highly efficient treatment to be continued.

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Paracetamol-induced fixed drug eruption in a patient with recurrent fever and rash



We describe a 3-year-old boy with recurrent fever and rashes on the same areas of his body and diagnosed multiple fixed drug eruption (FDE) induced by paracetamol. The boy was admitted to a pediatrics clinic with recurrent fever (39°C–40°C) and rash attacks every 2 to 3 months during last year. The skin lesions were painless, without itching above the mouth, around both eyes, above chin and

nose, and on the right elbow and right knee. The lesions were red at the beginning and then turned purple in 2 to 3 weeks, leaving hyperpigmentation. The patient was hospitalized for a differential diagnosis of periodic fever syndromes, autoinflammatory syndromes, and dermatomyositis. He presented with hyperpigmentation on the periorbital and perioral area, on the second and fifth fingers, and at the abdominal region. Blood cell count, kidney and liver function test results, and muscle enzyme, serum electrolyte,