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Case Report

Thalidomide-induced rash in patients with multiple myeloma

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Abstract: Allergic reactions triggered by thalidomide were rarely reported. We described two cases of thalidomide-induced morbilliform rash in patients with multiple myeloma, reviewed the related literature, and summarized the clinical manifestations, possible mechanisms, diagnostic methods and treatment options. The erythra of our cases were under control after methylprednisolone 1 mg/kg/day 5 to 7 doses intervention. Steroids seems to be effective during the acute phase of allergic reaction. Desensitization therapy may be suitable for re-taking of thalidomide.

Keywords: Thalidomide, rash, multiple myeloma, hypersensitivity reaction

Introduction

Due to the superior anti-angiogenic and anti-inflammatory capability, thalidomide is widely administrated in patients with multiple myeloma either alone or in combination with other drugs [1, 2]. Likewise, its potential adverse reactions should not be ignored. The most common adverse reactions of thalidomide are constipation, fatigue, neurotoxicity and deep venous thrombosis [3], however, cutaneous drug reactions (CDR) were reported relatively rare in China. Severe CDR may lead a interception of therapy. Here, we reported two cases of CDR caused by thalidomide to deepen the recognition of the rare adverse reactions and explore the approach to diagnosis and treatment.

Case report

Case 1

A 60-year-old man was diagnosed with multiple myeloma in June 2015. He received the first course of VDT (bortezomib (Velcade, Janssen) 1.3 mg/m^2. days 1, 4, 8, 11, dexamethasone 40 mg, days 1, 4, 8, 11, plus thalidomide (Fanyingting, Changzhou pharmaceutical factory) 100 mg continuously taking orally, repeated every 28 days) as the primary therapy. Twenty-five days after starting on 100 mg of thalidomide, he suffered from morbilliform rash on his trunk. At that time, bortezomib and dexamethasone had been withdrawn for 11 days. Given to the activity of anti-myeloma therapy, we didn't suspend thalidomide, adding anti-histamine drugs, vitamin C and calcium as the anti-anaphylactic treatment. Two days later, his papula expanded to the limbs instead of remission (**Figure 1**), and his temperature rose to 38 degrees which suggesting the systemic syndrome. His white blood cell count were normal, however, the percentage of eosinophils was 15% which was 2.5 folds of the upper baseline. Skin pathological examination was recommended, but the patient refused. We had to broke off the intake of thalidomide, prescribing methylprednisolone 1 mg/kg venous infusion once daily. Subsequently, his rash subsided, and temperature turned to normal range within 7 days. Three weeks after that, he undertook a patch test, and the results were strong positive.

Case 2

A 76-year-old woman was diagnosed with multiple myeloma in December 2014. After 6 cycles of VD therapy (bortezomib 1.3 mg/m^2, days 1, 4, 8, 11 plus dexamethasone 40 mg, days 1, 4, 8, 11, every cycle), she achieved

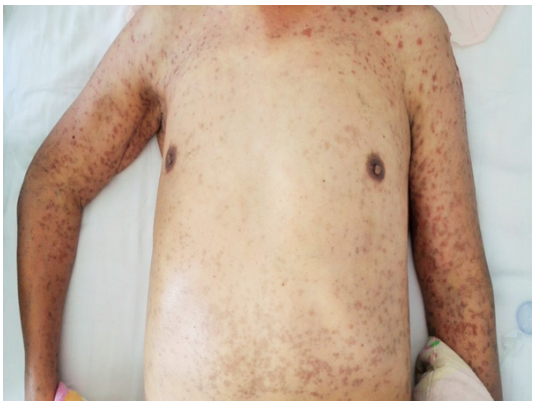

Figure 1. Morbilliform Rash on trunk and limbs induced by thalidomide.

complete remission. Then, therapeutic regimen was followed by 100 mg of thalidomide daily as maintenance treatment. Thirteen days after being on 100 mg of thalidomide, she experienced itchy morbilliform rash on her trunk and lower extremities. Her white blood cell count were normal, however, the percentage of eosinophils was 12%, two folds of the reference range. Thalidomide was stopped, she started on methylprednisolone 1 mg/kg orally once daily. Five days later, the rash faded away significantly. After a half months, she came back to the clinic without complaint. We made a patch test for her, and the results were positive. Given the necessity for maintenance therapy, she was restarted on s small dose of thalidomide, 50 mg daily, without recurrence of the CDR.

Discussion

Thalidomide was initially taken as antiemetic and sedative drug for the pregnant woman in 1954 and withdrawn from market in the 1960s because of its teratogenicity. Short after, it was found to have immunoregulation and anti-angiogenesis properties. Thalidomide was rediscovered and proved to be effective in the management of multiple myeloma, solid tumor and many rheumatosis [4]. Combining with bortezomib and dexamethasone, it can be used as first-line choice for multiple myeloma [5]. Also, when used alone, it is strongly recommended during the maintenance therapy [6]. Compared with constipation and fatigue, CDR of thalidomide presents a lower incidence. Studies have shown that thalidomide induced rash is usually pruritic and maculopapular, beginning on the skin of trunk and spreading to limbs [7]. Only a mild rash can be seen in more than 40% of patients taking thalidomide alone or thalidomide with dexamethasone, urticaria and bullous eruptions are reported in 3% and 5% respectively in a small sample study [8]. In addition, other rare thalidomide-induced CDR include morbilliform rashes, erythroderma, exfoliative dermatitis, hemorrhagic rash and so on [9-11]. Most CDRs occurred in the first 10-14 days after the initially treatment, what is more, several cases appeared in 30 days or even longer as much as 1 year later [7, 10]. The two cases we reported suffered CDRs in the 13 and 25 days after starting thalidomide respectively. Considering the site and clinical characteristics of skin rash, our two cases are coincide with the features described above.

Thalidomide induced CDR can be divided into two categories, dose related and non dose related. Most CDR cases were non dose related, interestingly, multiple myeloma cases seem to be an exception. A study on relapsed myeloma treatment showed that when the dosage of thalidomide increased from 200 mg/d to 400 mg/d, the incidence of CDR was rising from 26% to 16% [12]. In these cases, as our case 2, it seemed feasible to reduce the dosage of the thalidomide when CDR was in remission. Nevertheless, other cases concern a hypersensitivity reaction with systemic involvement, such as rash, fever, tachycardia, hypereosinophilia, may result in termination of treatment.

The pathogenesis of CDR induced by thalidomide is still unknown, nevertheless, the time from our stimulation till immune response occurred reveals a delayed hypersensitivity reaction. Certain components of thalidomide combining with the skin protein or some functions of thalidomide changing the structure of skin protein, may trigger a group of sensitive T cells, which can not only damage the skin directly but release inflammatory cytokines (e.g. IL-5, IL-4 and IL-13) [13].

The optimal diagnostic criteria for CDR induced by thalidomide may be as follows: ① thalidomide taking history; ② clinical manifestations of allergic dermatitis; ③ patch tests and/or prick tests positive [14]; ④ skin biopsy revealed eosinophilic infiltration; ⑤ laboratory examination, including the abnormal increase of eosino-

phils in peripheral blood and cytokines (e.g. IL-5, IL-4 and IL-13) in serum. In our case 1, during the first cycle of VDT, he continuously took thalidomide at a dose of 100 mg/d, however, other agents, such as bortezomib and dexamethasone, had been suspended for 14 days. His CDR appeared on the 25th day. Without any other drugs exposure history, thalidomide was suspected as the sensibiligen. Taking into account the need for anti-myeloma, anti-histamine drug, vitamin C and calcium were given without discontinuation of thalidomide. Subsequently, his rash was spreading from the trunk to the extremities, accompanied by fever and blisters. Thus, our conjecture was confirmed. Peripheral blood eosinophils were significantly elevated and patch tests were positive, all of which provided the indirect evidences for diagnosis of CDR caused by thalidomide. Likewise, case 2 had experienced the same diagnostic process. Lack of pathological evidences may be the defects of our cases.

Corticosteroids showed a ideal effort in administrating most of the CDR cases [9, 10], especially in the acute phase of allergic reactions. Consistent with the reports described above, the rash in our cases were subsided after treated with methylprednisolone 1 mg/kg/day 5-7 days. Even more convincing, another patient with multiple myeloma was prescribed methylprednisolone with thalidomide after presented to be a morbilliform rash, interestingly, his CDR was successfully suppressed [10]. In addition, taking the essence into account, thalidomide related CDR may be a type IV delayed-hypersensitivity reaction, thereby, some scholars tried to implement desensitization therapy [15]. Five cases allergic to lenalidomide, an analogue of thalidomide, was retreated with a small doses and gradually increasing doses of the sensitinogen. They had been well tolerated. Continuous re-exposure to the relatively low doses of thalidomide may induce immune tolerance. Our case 2 also provided a robust evidence. Thus, either steroids or desensitization therapy can be used as a treatment choice for CDR. Significantly, if the allergy reactions are more serious, starting with fever, heart palpitations and other systemic symptoms, stopping taking thalidomide immediately and accepting glucocorticoid therapy instantly seems to be necessary.

In conclusion, we have reported 2 CDR cases caused by thalidomide, meanwhile, we reviewed the related literature, summarized the clinical manifestations, possible mechanisms, diagnostic methods and treatment options. Although it was rarely reported in China, CDR need to be a profound understanding. The possible strategies for overcoming CDR were discussed, that may lead to a better tolerance in myeloma and other patients during the continuously exposure to thalidomide.

Disclosure of conflict of interest

None.

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