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Two cases of eczematous eruptions caused by everolimus

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Abstract

Objective: Everolimus, an inhibitor of the mammalian target of rapamycin, has been used in the treatment of several types of tumor. Erythematous maculopapular and acneiform rashes are the major dermatological adverse events associated with everolimus therapy, but we encountered two cases of eczematous eruption caused by everolimus.

Method: We assessed the clinical features and laboratory findings of the two cases.

Results: A 52-year-old woman and a 59-year-old man developed pruritic papules and erythema over their entire bodies after initiation of everolimus therapy. Both patients exhibited peripheral eosinophilia and increased serum thymus and activation-regulated chemokine (TARC) levels. A skin biopsy from one patient revealed the features of chronic dermatitis. Both the skin manifestations and the pruritis disappeared rapidly after the discontinuation of everolimus treatment. The peripheral blood eosinophil and serum TARC levels also decreased.

Conclusion: Eczematous eruption associated with an elevated serum TARC level is a dermatological event associated with everolimus therapy.

KEYWORDS

drug eruptions, eczematous, erythema, everolimus, mTOR protein, pruritus

1 | INTRODUCTION

Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), is a targeted drug that induces cell growth arrest and inhibits angiogenesis. Everolimus has been used successfully as both an anticancer and immunosuppressive agent. Dermatological adverse events are commonly reported with everolimus. These skin eruptions have been typically described as erythematous maculopapular or acneiform, but their clinical and histopathologic characteristics have yet to be fully explored. Herein, we report two cases of severe eczematous eruptions as adverse events of everolimus.

2 | CASE REPORTS

2.1 | Case 1

A 52-year-old Japanese woman was treated with everolimus (10 mg/d) and exemestane (25 mg/d) for metastatic breast cancer. The patient had no previous history of atopic dermatitis or any other atopic disease. After approximately 2 months of her chemotherapy regimen, she developed pruritic papules and a rash over her trunk and extremities. The eruption and severe pruritus increased in severity despite application of betamethasone butyrate propionate ointment. Consequently, she was admitted to our hospital. Physical

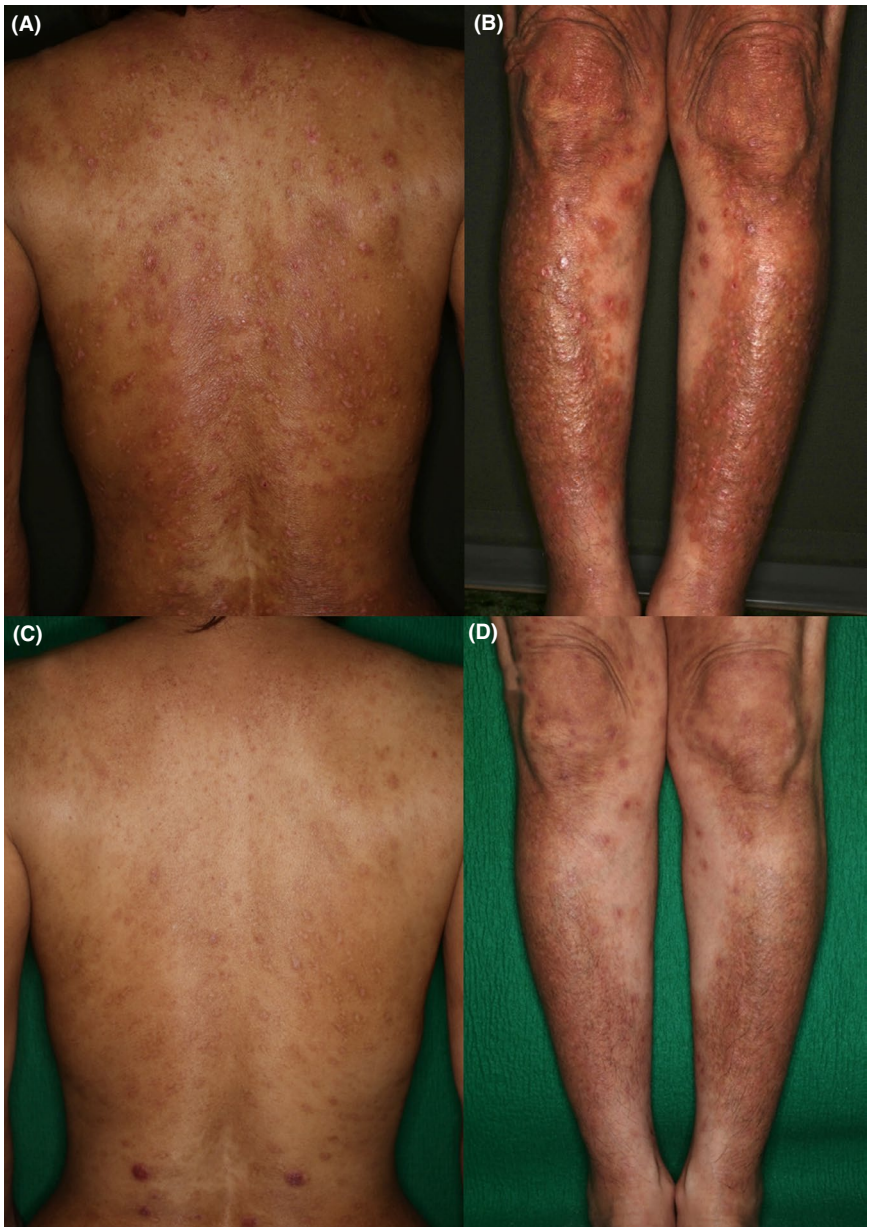

FIGURE 1 Clinical features of Case 1. Papules and nodules on erythema and thick, lichenified plaques were observed on the back (A) and lower extremities (B). The pruritic papules rapidly disappeared, leaving dark brown pigmentation at 2.5 mo after discontinuation of everolimus (C, D)

examination revealed papules, nodules, and thick lichenified plaques over her whole body (Figure 1A,B). Laboratory examination revealed increased numbers of white blood cells (10 500/μL) and eosinophils (4200/μL), as well as elevated lactate dehydrogenase (519 U/L) and thymus and activation-regulated chemokine (TARC) (21 912 pg/mL) levels. Her serum immunoglobulin E (IgE) level was 52 IU/mL.

A skin biopsy was performed on a nodule located on the femur. Histopathologic examination revealed hyperkeratosis, parakeratosis, and acanthosis of the epidermis with spongiosis (Figure 2A). The dermis contained thickened collagen fibers and perivascular infiltration of lymphocytes, eosinophils, and, occasionally, neutrophils (Figure 2B). Together, these findings indicated chronic dermatitis.

We continued the administration of oral antihistamines and topical clobetasol propionate ointment. In addition, the patient was treated with 308-nm excimer light, as well as cryotherapy to improve prurigo-like nodular lesions. The eruption and itching in all areas improved after 2 weeks of treatment. However, we were unable to completely control the appearance of the pruritic papules. Patch testing using a Japanese standard series of allergens was negative, and the cause of the eczematous eruptions remained unclear. We suspected the involvement of everolimus and exemestane because the rashes and itching appeared after the start of chemotherapy. After the discontinuation of everolimus, the pruritic papules rapidly disappeared, leaving dark brown pigmentation (Figure 1C,D). Moreover, the eosinophil count in peripheral blood and serum TARC level decreased to 0/μL and 1554 pg/mL, respectively, at 3 months after discontinuation of everolimus.

The lymphocyte transformation test (LTT) for everolimus and exemestane, which was performed on day 14 of hospitalization, was negative for both. Although everolimus and exemestane had been effective in the treatment of her tumor, the patient did not agree to resume treatment with everolimus and chose instead to receive

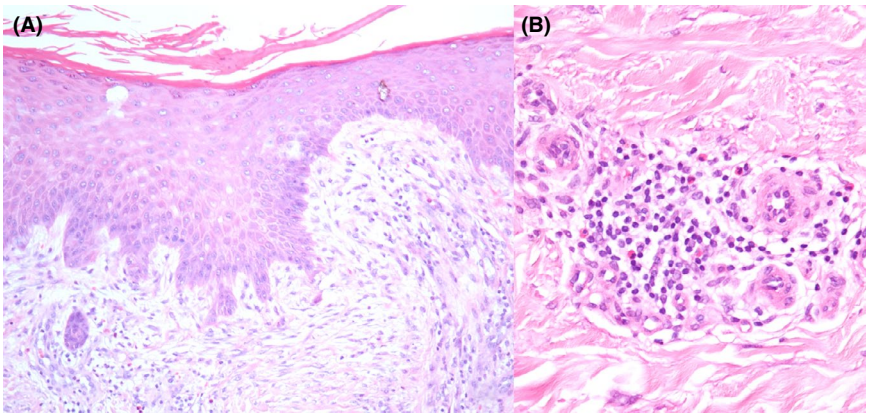

FIGURE 2 Histopathology showed acanthosis of the epidermis with spongiosis and perivascular infiltration (A; hematoxylin-eosin [HE], original magnification: ×40). Infiltrated cells in the dermis included lymphocytes, eosinophils, and a few neutrophils. Increased fibroblasts and fibrosis were observed (B; HE, original magnification: ×100)

paclitaxel and bevacizumab. There was no recurrence of the rash during 6 months of follow-up.

2.2 | Case 2

A 59-year-old Japanese man was treated with everolimus (10 mg/d) for metastatic kidney cancer. The patient had no previous history of atopic dermatitis but did have a history of allergic rhinitis to house dust mites. He had been receiving oral treatment for diabetes mellitus, hypertension, dyslipidemia, and hyperuricemia. After approximately 2 weeks of chemotherapy, the patient developed pruritic papules and a rash over his entire body. He visited the outpatient clinic of the dermatology department after 4 weeks of chemotherapy.

Physical examination revealed serous papules and erythema, with scales seen over his entire body (Figure 3). Laboratory examination revealed a white blood cell count of 4420/μL and an eosinophil count of 840/μL. The IgE level was 54 IU/mL, and TARC level was 8507 pg/mL. Everolimus was discontinued on the day of his initial visit, and he began application of clobetasol propionate ointment. Subsequently, the pruritic papules disappeared over the course of 2 weeks. At 1 month later, the number of eosinophils in peripheral blood and the serum TARC level had decreased to 207/μL and 1016 pg/mL, respectively. Skin biopsy and LTT were not performed. The effectiveness of everolimus for his cancer was unclear because the treatment period was too short to measure this. He refused resumption of everolimus and chose instead to receive Votrient. There was no recurrence of the rash while receiving this treatment.

3 | CONCLUSION

Everolimus is an orally administered inhibitor of mTOR. mTOR is a component of the intracellular signaling pathway that regulates cellular metabolism, growth, proliferation, and angiogenesis. Abnormal functioning of signaling pathways is thought to contribute to the pathogenesis of many malignancies.[1] Therefore, everolimus is used in the treatment of neuroendocrine tumors and malignancies such as renal cell carcinoma and breast cancer.

Excluding oral mucositis, dermatological adverse events related to mTOR inhibitors are generally mild, and the reported incidence of a grade 3-4 rash is 0%-1%.[1–3] The skin manifestations have typically been described as maculopapular rash and acneiform rash.[2]

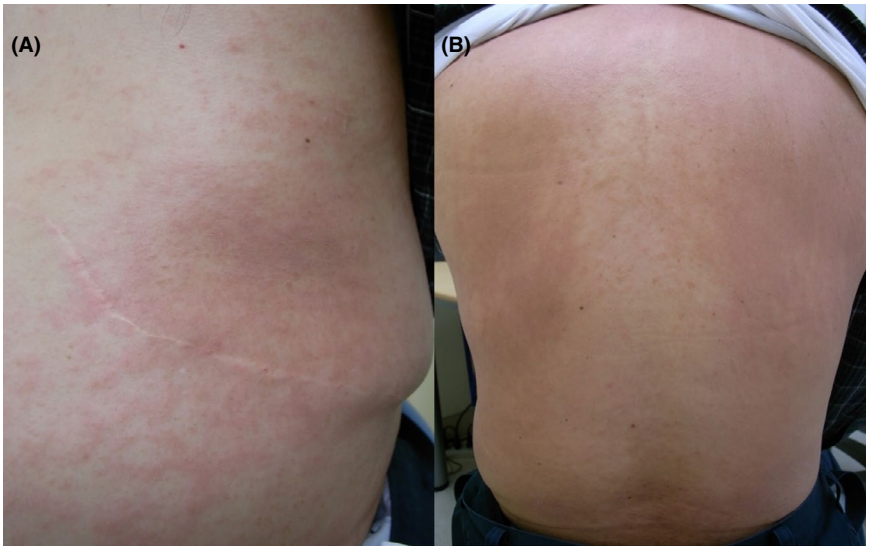

FIGURE 3 Clinical features of Case 2. Serous papules and erythema observed on the left upper abdomen (A) and the back (B)

These are thought to be caused by epidermal growth factor receptor (EGFR) inhibitors, since inhibition of mTOR results in suppression of intracellular signaling from EGFR.[3]

Our report described two cases of severe eczematous eruptions as adverse events of everolimus. Some cases of eczematous eruptions occurring in association with mTOR inhibitors have been reported previously. Raymond et al[3] found that four out of 15 patients who underwent treatment with everolimus developed eczema. Induction of eczematous eruptions by other mTOR inhibitors (eg, temsirolimus and sirolimus) has also been reported.[4,5] Recently, Balagula et al[6] analyzed the clinical and histopathologic features of 13 patients who developed a rash caused by administration of everolimus or temsirolimus. They demonstrated that an erythematous papulopustular rash on the trunk, neck, face, and scalp was the predominant primary lesion morphology and three patients presented with an eczematous or psoriasiform rash mainly on their upper extremities.[6] Skin biopsies were performed in 11 patients, and the most common histopathologic feature was a spongiotic interface and perivascular dermatitis with or without eosinophilic infiltration.[6] Their findings imply that eczematous eruptions are a common feature of rashes caused by mTOR inhibitors.

The mechanism of the development of eczematous eruptions by everolimus remains unclear. We found that the serum TARC levels increased in both our cases and reduced after cessation of everolimus. TARC participates in the type 2 helper T cell (Th2) immune response, and serum TARC levels are related to the activity of eczema in atopic dermatitis.[7] It was reported that everolimus downregulated inflammation caused by Th1 cells in experimental animal models of Crohn's disease and autoimmune uveoretinitis.[8,9] However, Han et al[10] recently demonstrated that although interferon gamma mRNA levels were greatly reduced, interleukin-4 mRNA levels increased in the everolimus-treated splenic mononuclear cells of experimental autoimmune neuritis rats. Everolimus may therefore be able to shift helper T cell responses toward a Th2 cytokine pattern.

Although our patients decided to discontinue everolimus, there may be an option to resume it together with administration of oral steroids. mTOR inhibitors have increased the overall survival of patients with various cancers, and development of a new generation of mTOR inhibitors is ongoing. Since the use of mTOR inhibitors is increasing, it is important to recognize their skin toxicity, which leads to eczematous eruptions, at an early stage. Accumulation of additional cases and investigation of the pathophysiology of this condition are therefore necessary.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

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