Delayed-onset cutaneous eruption associated with lenalidomide in a setting of multiple myeloma

Michele Buonomo[1] BA, Gowri Kabbur[2,3] MD, Najla El Jurdi[4] MD, Alessio Giubellino[5] MD PhD, Brittney Schultz[2,3] MD

Affiliations: [1]University of Minnesota Medical School, Minneapolis, Minnesota, USA, [2]Department of Dermatology, University of Minnesota, Minneapolis, Minnesota, USA, [2]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA, [4]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA, [5]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA

Corresponding Author: Brittney Schultz MD, Department of Dermatology, University of Minnesota, 515 Delaware Street SE, MMC 98, Phillips-Wangensteen Building, Suite 4240, Minneapolis, MN 55455, Tel: 612-625-8625, Email: bschultz@umn.edu

Abstract

Lenalidomide (LEN) is increasingly being used for the treatment of multiple myeloma. Adverse cutaneous reactions to LEN are common and present almost exclusively within one month of initiating therapy. We report a case of delayed-onset LEN-associated eruption presenting over three years after starting treatment. Histopathologic findings are also described, which are infrequently reported for LEN-associated eruptions. Our case serves as a reminder that proper recognition and management of LEN-associated eruption is important in the treatment of multiple myeloma. Dermatologists should be aware of the potential for delayed presentations of adverse cutaneous reactions to LEN, even years after initiation.

Keywords: dermatopathology, drug, hematology, hypersensitivity, lenalidomide, oncology, reaction

Introduction

Lenalidomide (LEN) is one of several immunomodulatory drugs (IMiDs) used for treatment of multiple myeloma (MM) and other hematologic malignancies. Adverse dermatologic effects to IMiDs are a frequent complication, especially with LEN [1]. Existing data suggests that LEN-associated eruptions almost exclusively present within one month of initiating therapy; onset beyond 3-4 months is rare [1-4]. Herein, we describe a case of delayed-onset LEN-associated eruption developing over three years after starting treatment, well beyond the expected time period of occurrence. We also present histopathologic findings which have been infrequently reported for LEN-associated eruptions.

Case Synopsis

A 73-year-old woman presented to dermatology clinic in February 2020 with a pruritic eruption that evolved over the preceding nine months. Her medical history was notable for IgG kappa MM diagnosed in 2010, followed by autologous stem cell transplant in March 2011. She subsequently relapsed in 2015, at which time she received reinduction therapy with bortezomib/dexamethasone followed by two cycles of cyclophosphamide, bortezomib, and dexamethasone. Following a second autologous stem cell transplant in January 2016, she began maintenance therapy with LEN 10mg/day. Due to cytopenias, the dose was reduced to 10mg every three days in June 2016. She was previously on dexamethasone but discontinued in 2016.

Physical examination demonstrated innumerable pink papules and thin plaques over the extensor arms, abdomen, and back (**Figure 1**). The patient had no history of childhood eczema, similar eruption, or recent medication changes. She had been on a stable

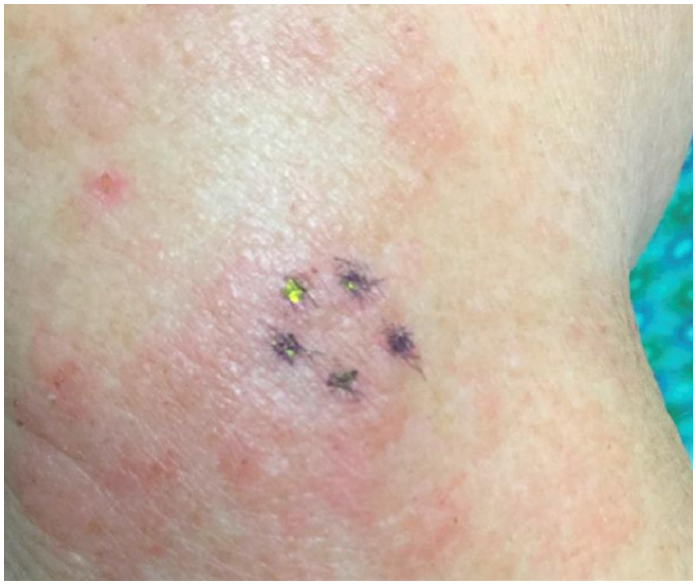

Figure 1. *Close-up view of eruption on patient's arm at site of punch biopsy demonstrated scattered thin light pink plaques with occasional excoriation.*

dose of LEN for more than three years, as well as losartan and metoprolol for nine years.

She failed oral antihistamines and potent topical corticosteroids. Punch biopsy showed a mild superficial and mid-dermal inflammatory infiltrate with perivascular and interstitial eosinophils, consistent with a dermal hypersensitivity reaction (**Figure 2**). Given concern LEN was contributing to her symptoms, it was discontinued. Her eruption resolved completely within two weeks of medication cessation and has not recurred since discontinuing LEN.

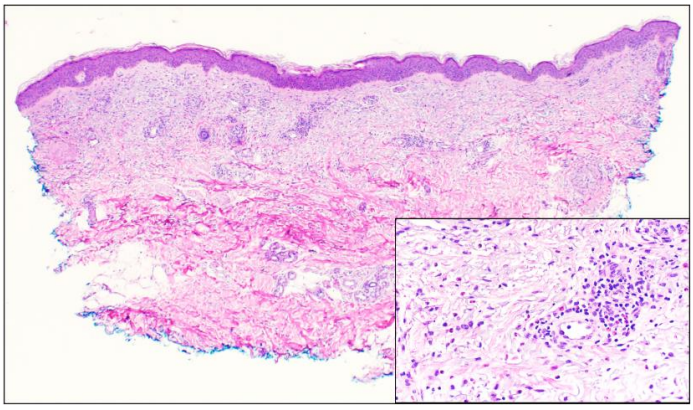

Figure 2. *Low power view shows a mild inflammatory infiltrate involving papillary and upper reticular dermis. H&E, 2×. Inset: at higher power a perivascular and sparse interstitial infiltrate with eosinophils is appreciated, 20×.*

Case Discussion

Lenalidomide is increasingly used in the treatment of multiple myeloma (MM) and other hematologic malignancies. Although generally well tolerated, adverse cutaneous reactions have been reported. In patients with MM or myelodysplastic syndrome (MDS) receiving LEN as monotherapy or in combination with dexamethasone, there was a 27% incidence of all-grade rash and a 3.6% incidence of high-grade rash [2]. Eruptions commonly occurred within two weeks of initiating therapy,and were said to occur no later than four weeks after beginning therapy [2]. Onset of LEN-associated eruption beyond 3-4 months has only rarely been reported [1,4]. In one series, 15% of patients developed eruptions over 12 weeks after IMiD initiation, but with a maximum range of 45 weeks [1]. In another series, only 5% had onset of eruption beyond four months after LEN initiation, but details of timing beyond four months were not specified [4]. Additionally, all patients with onset beyond four months had been on combination therapy with dexamethasone, which authors suggested may have delayed onset of cutaneous eruption [4]. Our patient was not on dexamethasone at the time of eruption.

Most LEN-associated eruptions are morbilliform, although acneiform, urticarial, vascular, and exfoliative-type patterns have been described [3]. Pruritus can occur. Eruptions are usually mild, but importantly, are a frequent cause of early medication discontinuation [3]. Although only 2-3% of rash adverse events secondary to LEN in patients with MDS led to permanent discontinuation in clinical trials, post-marketing analysis showed that 72% of non-serious rash adverse events led to early (within two cycles) permanent discontinuation and non-serious rash was the leading cause of permanent early discontinuation of LEN [5]. Considering that indicators of treatment response, such as red blood cell transfusion independence, may take three or more cycles of treatment [6], early recognition and appropriate management of rash is necessary in allowing patients to sustain therapy and maximize treatment response.

Histopathology manifestations of drug eruptions are protean, varying not only across drug classes but also

within the same medication group. Histopathology reports of LEN-associated eruptions are scant in the literature. One prior case report of a patient who presented with Steven-Johnsons syndrome thought to be secondary to LEN detailed histopathologic findings of spongiotic, vacuolar, and lichenoid changes with a lymphocyte-predominant infiltrate and few eosinophils [7]. In our patient, who presented with a morbilliform eruption, histologic features were consistent with a dermal hypersensitivity reaction. Dermal hypersensitivity reaction is a relatively common reaction pattern of drug eruption and refers to the presence of a superficial and mid-dermal perivascular and interstitial inflammatory infiltrate with eosinophils, mostly with sparing or minimal changes in the epidermis [8]. However, it is important to remember that dermal hypersensitivity reaction is a non-specific pattern of cutaneous inflammation that always requires clinicopathological correlation to reach a definite diagnosis. In our case, attentive correlation of the patient's clinical history with particular attention to drug history helped to define this histologic pattern as a drug eruption. Although the mechanism by which LEN induces a cutaneous eruption is unknown, IMiDs have been shown to induce a Th2 response [9].

Management of LEN-associated eruption is based on severity [3]. For mild to moderate eruptions, topical corticosteroids and antihistamines are recommended. If more severe, oral corticosteroids and antihistamines can be utilized. Dose interruption for 7–14 days or permanent discontinuation may be considered. A desensitization protocol has also been described, which allowed patients to resume LEN without adverse effects and achieve remission [10]. Drug rechallenge was not pursued in our case according to patient preference.

Had our patient failed to improve with drug elimination, the clinical presentation and pathology could also be consistent with hematologic-related malignancy-induced eosinophilic dermatosis (*He Remained*), a new nomenclature used to describe the eosinophilic dermatosis observed in patients with hematologic malignancies [11]. Multiple morphologies of *He Remained* skin lesions have been described, associated with a chronic and relapsing clinical course [11,12]. Some have reported prompt resolution of *He Remained* with dupilumab [13,14]. Although the discontinuation of LEN and resolution of symptoms in our case supports a diagnosis of drug reaction, dupilumab may have enabled our patient to continue LEN therapy.

Conclusion

We present a rare case of dermal hypersensitivity reaction to LEN developing three years and two months after initiating therapy, far beyond the expected timeline for an eruption to occur. LEN-associated eruptions are often mild and managed conservatively but persistent and/or severe presentations may necessitate treatment discontinuation. Our case serves as a reminder that proper recognition and management of LEN-associated eruption is important in the treatment of MM. Dermatologists should be aware of the potential for delayed presentations of adverse cutaneous reactions to LEN, even years after initiation.

Potential conflicts of interest

The authors declare no conflicts of interest.

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