A Case of Persistent Erythema Multiforme Treated with Dapsone

Senay Agirgol[1,2], Kamer Faruk Coşkun[2], Ceyda Caytemel[2], Nazli Caf[2,3], Zafer Turkoglu[1], Betül Aytekin[2]

[1]Haseki Training and Research Hospital, Istanbul, Turkey; [2]Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey; [3]Istanbul Atlas University, Istanbul, Turkey

Corresponding author:
Senay Agirgol
Haseki Training and Research Hospital
Millet Caddesi Aksaray, Istanbul, Turkey
senayagirgol@hotmail.com

Received: March 24, 2024
Accepted: October 24, 2024

ABSTRACT
Erythema multiforme is a clinical entity that presents in three different clinical forms, namely classic, recurrent, or persistent. Persistent erythema multiforme (PEM) is a rare variant that may be localized in different regions compared with the classical erythema multiforme, has a continuous course, and can present in inflammatory clinical forms. PEM was defined as the uninterrupted persistence of typical or atypical target-like lesions. Data about its etiology and treatment is obtained from case reports. Herein, we present the case of a 37-year-old male patient who presented to our outpatient clinic with palmar lesions and with the presence severe oral bullae and ulcers treated with systemic steroids and dapsone. Due to the rarity of the disease, reporting this case is expected contribute to the literature and provide evidence that 50 mg dapsone treatment may be used to control PEM.

KEY WORDS: erythema multiforme, persistent, dapsone, treatment

INTRODUCTION

Erythema multiforme (EM) is an immune-mediated disease. EM clinically progresses with typical target-like lesions on the extremities and is then termed EM minor. If the skin lesions are accompanied by one or more locations with mucosal involvement, it is called erythema multiforme major (1). Mucosal involvement is classified into three groups: classical, recurrent, and persistent. Recurrent EM usually occurs following herpes virus 1 (HSV-1) infection and resolves in 1-6 weeks. Persistent erythema multiforme (PEM) is rare and has been defined as the uninterrupted persistence of typical or atypical lesions (2-4). Information on the etiology of PEM is based on case reports, and cases associated with viral infections, drugs, and malignancies have been reported in the literature (5,6). Although the pathogenesis of the disease has not been fully clarified, it is thought to be a hypersensitivity reaction against infections, vaccines, menstruation, autoimmune diseases, and malignancies (1,4) While systemic steroids are preferred in treating the disease, antiviral therapy, immunomodulatory treatments, and Janus kinase inhibitors have been used in some patients (7).

Herein we will describe the clinical course and treatment approach in a case of PEM in a 37-year-old male patient with typical-atypical lesions on the oral-genital mucosa, extremities, and trunk, who responded to systemic steroid and dapsone treatment, without any established etiology for the disease.

CASE REPORT

A 37-year-old male patient was admitted to the dermatology outpatient clinic with a non-healing wound in his palms persisting for two months. The patient stated that his complaint began as a single papular lesion on the palm and gradually spread throughout the palm. The patient stated that the

Acta Dermatovenerol Croat
2024;32(3):163-167

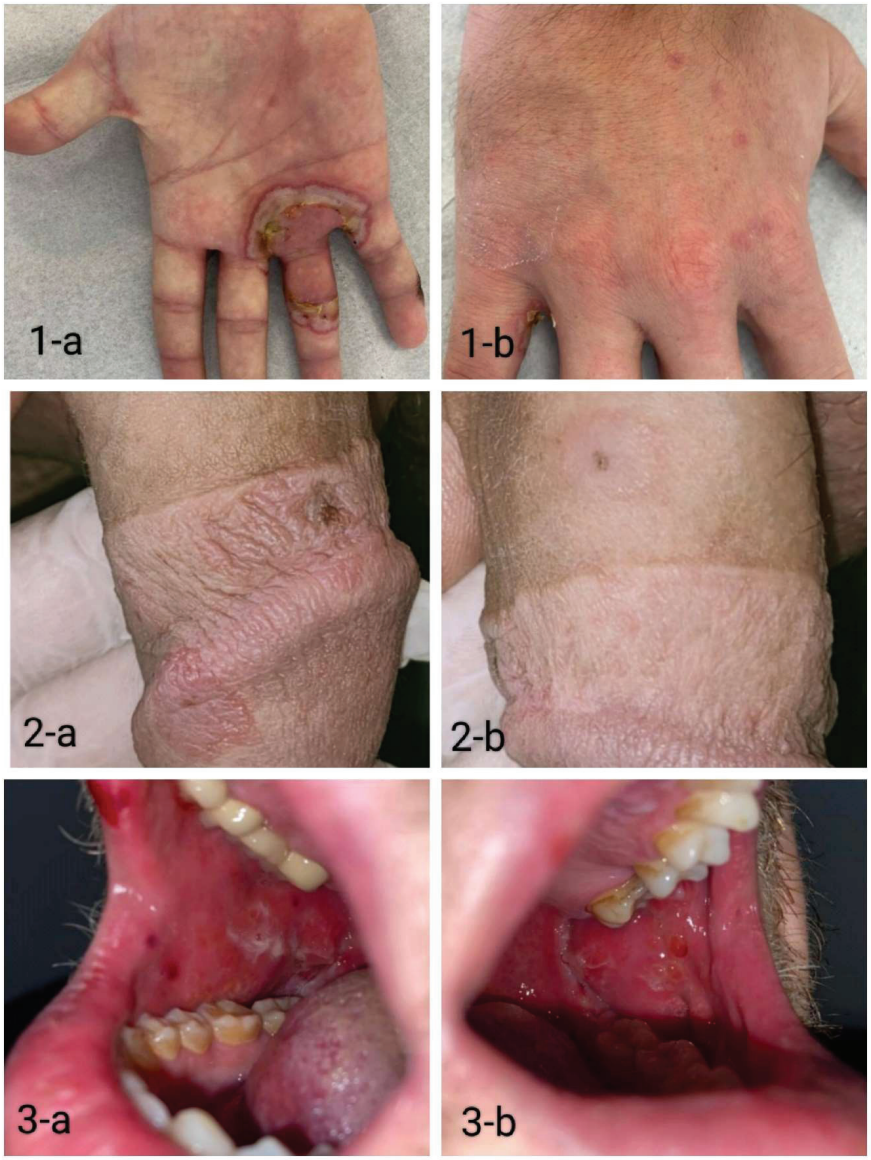

Figure (1a): An ovaloid ulcerated plaque of approximately 10 cm in diameter, extending from the proximal interphalangeal area of the fourth finger to the palmar region, with a bulla residue anda erythematous border on the margin, and pale red erythema on the mid-palmar region. (**1b,2a,b):** Classical atypical lesions on the hand, oral ulcers, and typical target-like lesions in the genital area.**(3a,b)**: Intact bullae and eroded areas in the oral mucosa

lesion did not show any regression with the use of topical antibiotics and epithelializing creams. Dermatological examination of the patient revealed an ovaloid ulcerated plaque of approximately 10 cm in diameter, extending from the proximal interphalangeal area of the 4th finger to the palmar region, with a bulla remnant and an erythematous border on the edge, and a pale erythematous papule 3 mm in diameter on the dorsal side of the fifth finger (Figure 1, a). The patient had no subjective symptoms. Biopsy was taken both from papular and ulcerated lesions, with the preliminary diagnoses of pyoderma gangrenosum, neutrophilic dermatosis of the hand, fixed drug eruption, sweet syndrome, and erythema multiforme. During the follow-up of the patient, it was observed that 5-6 papular lesions developed on the hand after 1-2 days, and these papules took on a typical target-like appearance within two days (Figure 1, b). The histopathological findings of the biopsies were similar: hyperkeratosis, parakeratosis, lymphocyte exocytosis in the epidermis, spongiosis, suprabasal separation, apoptotic keratinocyte, basal vacuolar change, and lymphocytic infiltration accompanied by neutrophils extending from the superficial dermis to the mid-dermis were observed. Additionally, subepidermal edema and focal separation were observed (Figure

Acta Dermatovenerol Croat
2024;32(3):163-167

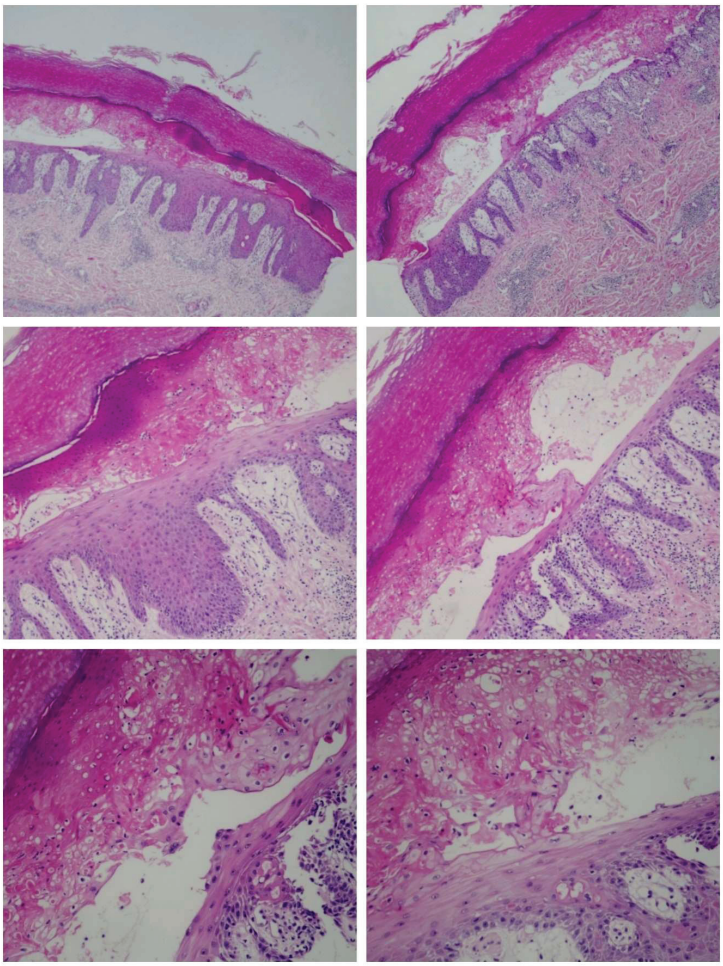

Figure 2: Hyperkeratosis, parakeratosis, lymphocyte exocytosis in the epidermis, spongiosis, suprabasal separation, apoptotic keratinocyte, basal vacuolar change, lymphocytic infiltration accompanied by neutrophils extending from the superficial dermis to the middle dermis in the histopathologic specimen. In addition, subepidermal edema and focal separation are observed.

2). The patient was diagnosed with erythema multiforme in light of these findings.

Routine laboratory results for the patient were normal, whereas viral serology was as follows: herpes simplex virus-1 IgM negative and IgG positive; cytomegalovirus IgM and IgG negative; toxoplasma IgM and IgG negative, Epstein-Barr virus (EBV) IgM negative and IgG positive. There was no known frequent herpes labialis in the patient's medical history. Topical clobetasol propionate ointment and steroids 40 mg/day were administered. Treatment response was observed rapidly, and the dose was reduced and stopped within three weeks. During follow-up, shortly after the steroid treatment was discontinued, multiple target-like lesions were observed on the genital area (Figure 2, a, b). Severe oral erosions, ulcerated areas, and hemorrhagic bullae suddenly developed one month later (Figure 2, a, b). The patient was hospitalized due to fever, weakness, and poor general condition, and systemic 1 mg/kg/day prednisolone treatment was initiated. The patient's subjective complaints were addressed with systemic steroid treatment, and dapsone 50 mg/day in addition to valacyclovir 500 mg/day for herpes simplex prophylaxis were administered. Since the patient did not experience any events for four months under the above-mentioned treatment, he discontinued the treatment, thinking that he had fully recovered. Two weeks after stopping the treatment, similarly to the first event, the patient was re-hospitalized due to severe oral ulcers, bullae, fever, and deterioration of his general condition; systemic steroid and dapsone treatments were consequently administered. After the second hospitalization, the prednisolone dose was gradually tapered and discontinued. The patient has been in follow-up for 24 months at our clinic since

the onset of the disease. In his current state, he has no symptoms under treatment with valaciclovir 500 mg/day and dapsone 50 mg/day. The treatment plan is as follows: we initially stopped treatment with valaciclovir, and, in the absence of reactivation, cessation of dapsone therapy is planned.

DISCUSSION

Persistent erythema multiforme has been rarely reported in the available literature. According to the literature, clinically typical EM lesions can be observed in the course of PEM along with papulonecrotic, bullous, or atypical lesions (2,4). Our patient presented with an ulcerated lesion in the palmar region that did not regress, and typical-atypical target-like lesions, bullae on the oral mucosa, ulcers and fever, as well as poor general condition were observed during the follow-up period. It was previously reported that HSV, EBV, malignancies, drugs, inflammatory bowel diseases, and contact allergens may be involved in the etiology of PEM (1,4,8). In the present case, no etiology could be identified, but it was assumed that the potential triggering HSV infection may have been be difficult to detect due to the severe oral lesions, and the patient was given HSV suppression therapy with valacyclovir. In the literature, it has been reported that antiviral treatment may be beneficial in some patients (4).

Erythema multiforme is thought to be an immune-mediated cutaneous disease. A cytotoxic response against keratinocytes and IL-15 has been reported, and interferon-gamma plays a role in cytotoxic effects (7). In some cases, low levels of immune complexes may be detected (4,8), and disease duration may last for months or years (5,7). It has also been noted in the literature that immunosuppressive therapies, systemic steroids, dapsone, thalidomide, azathioprine, mycophenolate, and antivirals can be used in the treatment of PEM in addition to the treatment for the underlying etiology (5). In the reviewed literature, recurrence and erythroderma have been reported following steroid therapy in previously presented cases (3). In our patient, severe activation was observed shortly after the first steroid treatment. Based on this, adding a steroid-sparing agent may be recommended when systemic steroids are given to patients with PEM. In the present case, the symptoms started with an atypical, persistent ulcerated lesion. Over time, oral bullae, ulcers, and both typical and atypical target lesions were observed throughout the body. No viral cause could be detected in the patient, the immunocomplex level was average, and herpes PCR was negative when taken from acute ulcerated lesions. Despite this, herpes prophylaxis was given to the patient, since HSV is the most common etiology. The patient has been treated with dapsone for two years. It would seem that dapsone may be effective in the treatment of PEM and has been used at a dose of 25-200 mg/day and for 468 weeks in cases reported in the available literature (4,9). In the present case, 50 mg daily dapsone was administered due to treatment resistance, and treatment response was obtained with the above-mentioned dosage. There were no activations after the third month of dapsone treatment, except for occasional individual papular lesions. Valacyclovir treatment was discontinued at the end of the sixth month.

As a result, our patient was treated with dapsone 50 mg/day concomitantly with a systemic steroid, valacyclovir (6 months), at the time of the disease event. The patient is currently undergoing follow-up with dapsone treatment 50 mg/day without any lesions.

CONCLUSION

Persistent erythema multiforme is a rare entity, and it should be kept in mind that the disease may occur in different locations and clinical forms. We believe that dapsone can be used in the treatment of PEM due to the positive outcome achieved in the presented case.

References:

1. Badavanis G, Pasmatzi E, Kapranos N, Monastirli A, Tsambaos D. Golimumab-associated persistent erythema multiforme in a patient with ulcerative colitis in full remission. Dermatol Online J. 2018;24.
2. Pavlovic MD, Karadaglic DM, Kandolf LO, Mijuskovic ZP. Persistent erythema multiforme: a report of three cases. J Eur Acad Dermatol Venereol. 2001;15:54-8.
3. Chen CW, Tsai TF, Chen YF, Hung CM. Persistent erythema multiforme treated with thalidomide. Am J Clin Dermatol. 2008;9:123-7.
4. Mahendran R, Grant JW, Norris PG. Dapsone-responsive persistent erythema multiforme. Dermatology. 2000;200:281-2.
5. Turnbull N, Hawkins D, Atkins M, Francis N, Roberts N. Persistent erythema multiforme associated with Epstein-Barr virus infection. Clin Exp Dermatol. 2014;39:154-7.
6. Wetter DA, Davis MDP. Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. J Am Acad Dermatol. 2010;62:45-53.

Acta Dermatovenerol Croat
2024;32(3):163-167

7. Murphy MJ, Gruenstein D, Wang A, Peterson D, Levitt J, King B, *et al.* Treatment of Persistent Erythema Multiforme With Janus Kinase Inhibition and the Role of Interferon Gamma and Interleukin 15 in Its Pathogenesis. JAMA Dermatol. 2021;157:1477-82.
8. Leigh IM, Mowbray JF, Levene GM, Sutherland S. Recurrent and continuous erythema multiforme--a clinical and immunological study. Clin Exp Dermatol. 1985;10:58-67.
9. Oak AS, Seminario-Vidal L, Sami N. Treatment of antiviral-resistant recurrent erythema multiforme with dapsone. Dermatol Ther. 2017;30.