Milia en plaque manifesting as a post-herpetic isotopic response

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Abstract

Isotopic response in dermatology refers to the development of a new primary dermatosis at the site of a previous reaction such as cutaneous herpes virus infection. We report a 63-year-old woman with a recent history of a bullous drug eruption treated with prednisone who presented with herpetic dermatitis and subsequent milia en plaque. This unique case represents a novel presentation of milia en plaque manifesting as a complication from post-herpetic isotopic response and highlights the wide array of isotopic responses that can occur following a cutaneous herpes simplex infection.

Keywords: herpes simplex, isotopic response, milia en plaque, virus, Wolf post-herpetic

Introduction

Isotopic response, coined by Wolf et al., refers to the presence of a dermatologic condition at the site of a previous healed, unrelated dermatologic condition [1]. The term Wolf post-herpetic isotopic response (PHIR) was later published in a review describing the occurrence of the phenomenon after healed herpes virus infections [2]. Post-herpetic isotopic response classically occurs with herpes zoster as the primary condition. To date, there have been 193 cases of PHIR subsequent to herpes zoster, but only 20 cases subsequent to herpes simplex [3,4]. Milia en plaque is a rare condition that presents clinically as an erythematous plaque containing clusters of white-yellow cysts [5,6]. Both PHIR and milia en plaque are relatively rare entities. To our knowledge, we report the first case of milia en plaque manifesting as a post-herpetic isotopic response following a herpes simplex infection.

Case Synopsis

A 63-year-old woman with hypertension, hyperlipidemia, hypothyroidism, and seronegative rheumatoid arthritis with 6 weeks of hydroxychloroquine therapy with cessation two days before presentation developed a generalized tense, blistering rash sparing the mucous membranes, palms and soles. Her hospital course included facial edema, hyponatremia, and fevers. A 4mm punch biopsy of the left neck at the edge of a vesicle revealed a subepidermal blister with neutrophils and eosinophils. Direct immunofluorescence was negative for an autoimmune-mediated bullous process and she did not meet diagnostic criteria for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Bullous drug eruption secondary to hydroxychloroquine was the favored diagnosis and the patient was started on high-dose prednisone with improvement in the rash.

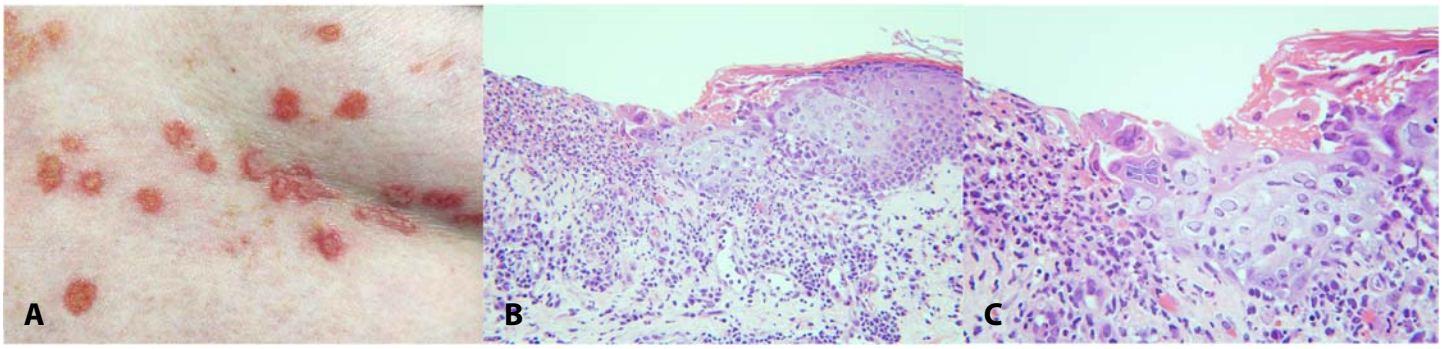

Figure 1. ***A)*** *Clinical image. Punched out superficial ulcerations with a fibrinous base were seen on the inframammary region and left lateral chest wall.* ***B)*** *A low power view of the edge of the ulcer bed with a lip of acantholytic and spongiotic skin. Keratinocytes demonstrate "steel-gray nuclei." Acute inflammation is present, but a brisk dermal lymphoplasmacytic response predominates. H&E, 200×.* ***C)*** *A high-power view of the edge of the ulcer bed revealed scattered keratinocytes exhibiting features of viral cytopathic change including multinucleation, margination, and nuclear molding. H&E, 400×.*

One month later, she presented with a one-week history of punched-out ulcerations with a fibrinous base localized to the inframammary region and lateral chest wall (**Figure 1A**), different in appearance from the previous eruption. A 4mm punch biopsy of the lesion on the left chest wall was obtained. Histopathologic sections revealed ulcerated skin with focal acantholysis and spongiosis. Keratinocytes with steel-gray or ground glass nuclei were noted at the ulcer edge (**Figure 1B**). Scattered, enlarged keratinocytes exhibiting multinucleation, nuclear margination, and molding were seen, suggesting herpetic dermatitis (**Figure 1B, C**). Herpes simplex virus 1 and 2 nucleic acid amplification test results were positive for HSV1. Though her past medical history included herpes labialis eruption in the past, she did not have a history of herpes simplex or herpes zoster infection at this site. The patient was started on a 10-day course of valacyclovir, one gram twice daily, with resolution of the infection following completion of the medication.

At her follow-up visit three weeks later, the area previously biopsied had evolved and now exhibited erythematous pinpoint papules and cysts both grouped and annular, located on the abdomen, lateral chest wall, and anterior neck (**Figure 2A**). A 1.0×1.0 ×0.2cm shave biopsy of a cluster of lesions on the left lateral abdomen was performed. Histopathologic sections reveal multiple small

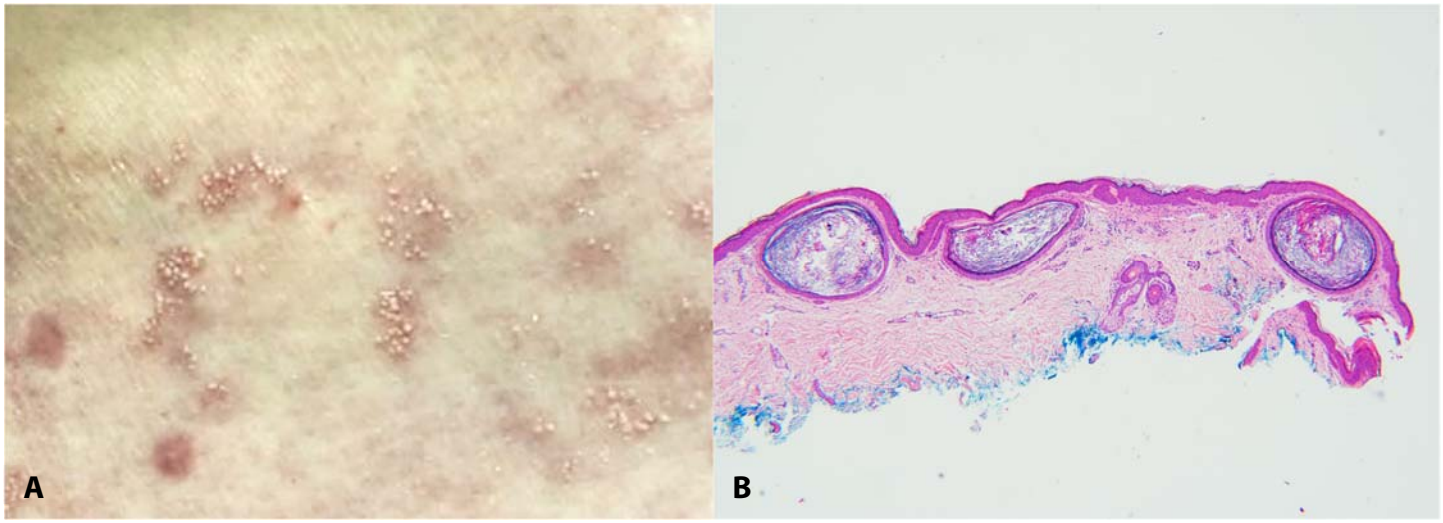

Figure 2. ***A)*** *Clinical image. Pinpoint white papules grouped on an erythematous base were seen on the lateral abdomen in the same location and distribution as the previous herpetic rash.* ***B)*** *A low power view of the skin with multiple, superficial, keratin-filled cysts which are histologically reminiscent of small epidermoid cysts. H&E, 40×.*

keratin-filled cysts situated superficially within the dermis. The cyst lining was composed of stratified squamous epithelium, histologically identical to that of a small follicular cyst. Minimal lymphocytic inflammation was present surrounding each milium. These features, in conjunction with the clinical description, were consistent with a diagnosis of milia en plaque (**Figure 2B**). The patient was started empirically on topical triamcinolone with no improvement.

Case Discussion

Post-herpetic isotopic response is a rare phenomenon that classically occurs after healed herpes zoster infection. Less frequently, it has been reported to develop after healed herpes simplex infection, as in our case. The second dermatosis presenting after the healed herpes infection varies, but reports include malignancies, inflammatory dermatoses, and infections [3,4]. Furthermore, milia en plaque is a rare entity with fewer than 60 cases described in the literature [7]. It has a predilection for the postauricular area in adults, though occurrence at other locations such as the earlobes, eyelids, nose, lip, and supraclavicular areas have been described [8].

Two cases of milia developing at the site of a previous herpes zoster infection have been reported [9,10]. However, the unique entity milia en plaque has yet to be described as a manifestation of PHIR. In addition, a review of the literature did not reveal any case reports of herpes simplex virus and milia en plaque as the primary and secondary, respectively, skin conditions of PHIR.

The pathogenesis of PHIR is not completely understood. However, a proposed mechanism involves local immune dysregulation at the site of herpes virus infections mediated by neuromediators released after sensory nerve damage caused by the virus [3]. In this case, the patient's course of prednisone after the initial bullous drug eruption likely induced an immunosuppressed state, increasing the patient's susceptibility to herpetic dermatitis and subsequent isotopic response.

The pathogenesis of milia en plaque is unknown. Beutler et al. describe a case of cryotherapy-induced milia en plaque and review cases of milia en plaque arising at the site of previous trauma, such as blistering disorders, suggesting that the pathogenesis of milia en plaque is related to tissue trauma [11]. The possibility of our patient's milia en plaque occurring as a result of tissue trauma can be considered. In previous reports of milia presenting after herpes zoster, Lee et al. attributed the presentation of milia in herpes zoster scars to trauma to the area [9]. However, Oh et al. describe a case of PHIR in which multiple milia developed on the right shoulder four months after herpes zoster infection of the same area. They also suggested that the use of immunosuppressive drugs increases the susceptibility to milia [10]. Our patient's history of herpes simplex leading to dysregulated immunity of the affected area in addition to the patient's history of immunosuppressive medication use allows us to consider the patient's milia en plaque as a result of PHIR.

Although PHIR has come to be regarded as usually an inflammatory process arising at the site of prior herpetic infection, Wolf and colleague's initial report included a broad range of both neoplastic, infectious, and inflammatory conditions arising in a healed site of prior disease [1]. As such, the definitive mechanism by which the milia develop following herpetic infection does not preclude considering it to be a PHIR as initially described.

Treatment in this case included antivirals, which successfully resolved the patient's HSV1 infection. However, the milia en plaque persisted despite treatment with topical triamcinolone. There are limited pharmacologic treatment options for milia en plaque. Topical tretinoin, oral minocycline, oral etretinate, and photodynamic therapy with topical aminolevulinic acid have been used with variable response. Surgical techniques such as dermabrasion, electrodessication, CO_2 laser vaporization, and radiosurgery have been documented to be successful in improving the aesthetic appearance of milia en plaque [12-14]. However, not all treatments induced complete remission and there is not

consensus as to the optimal treatment method of milia en plaque.

Conclusion

Milia en plaque is a relatively rare entity that, to our knowledge, has not yet been reported as an isotopic response subsequent to herpetic dermatitis. Our patient, initially presenting with a bullous drug eruption related to hydroxychloroquine. She was treated with prednisone, which precipitated a herpetic infection, diagnosed by biopsy showing viral changes and confirmed by PCR. The development of subsequent milia en plaque further exemplifies the wide array of isotopic responses that can occur following a cutaneous HSV infection.

Potential conflicts of interest

The authors declare no conflicts of interest.

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