A crack in the armor: Wolf isotopic response manifesting as cutaneous lupus

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Abstract

Wolf isotopic response represents the development of skin lesions of one particular morphology occurring at the same site as another morphologically distinct and unrelated skin lesion. Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disorder encompassing a wide range of phenotypes that may be associated with systemic involvement. Although CLE is a well-described entity with a broad spectrum, the occurrence of lesions manifesting as an isotopic response is rare. We present a patient with systemic lupus erythematosus who developed CLE in a dermatomal distribution following herpes zoster. When CLE lesions present in a dermatomal distribution, these cases may be difficult to distinguish from recurrent herpes zoster infection in an immunosuppressed patient. Therefore, they pose a diagnostic challenge and require balancing antiviral therapy with immunosuppression to sufficiently maintain adequate control of the autoimmune disease while addressing possible infections. To avoid treatment delay, clinicians should have elevated suspicion for an isotopic response when disparate lesions erupt in areas previously affected by herpes zoster or in cases of persistent eruptions at sites of prior herpes zoster. We discuss this case within the context of Wolf isotopic response and review the literature for similar cases.

Keywords: cutaneous, erythematosus, herpes, isomorphic, isotopic, Koebner, lupus, response, systemic, Wolf, zoster

Introduction

Areas of skin previously damaged or diseased have an increased predilection to develop other pathology. Wolf isotopic response describes the development of skin lesions of one morphology occurring at the same site as other morphologically distinct and unrelated skin lesions. In contrast to this, an isomorphic response describes the development of lesions of the same morphology occurring at a site of trauma (Koebner phenomenon). Commonly reported cases of Wolf isotopic response include lichen planus, granuloma annulare, and sarcoidosis occurring in areas of previously resolved herpes zoster infections [1]. Limited evidence suggests that long-lasting structural, immunologic, and neurohormonal changes occurring after viral infections of the skin could render the skin more susceptible to a second disease in the same area; however, much remains to be elucidated concerning the pathogenesis of isotopic lesions [2].

Cutaneous lupus erythematosus (CLE) is a well-characterized autoimmune disorder encompassing a wide range of phenotypes that may be associated with systemic involvement. Cutaneous lupus erythematosus involves complex interactions between genetic and various environmental factors. Genes related to major histocompatibility complexes, the complement system, and tumor necrosis factor, amongst others, have been associated with an increased risk of developing CLE. Further downstream, environmental factors appear to contribute to the development of cutaneous lesions by inducing cellular damage and apoptosis,

precipitating autoantigen presentation, and promoting inflammation [3]. Although ultraviolet radiation is believed to be the predominant environmental exposure associated with CLE, a small number of cases of CLE have been reported after herpes zoster infections [4,5]. Although rare, these cases pose a diagnostic challenge and require balancing anti-infective and immunosuppression therapy to sufficiently treat infection while maintaining adequate control of CLE with potentially associated systemic lupus erythematosus (SLE).

Herein, we present a patient with SLE who developed CLE in a dermatomal distribution following a herpes zoster eruption. We discuss this case within the context of Wolf isotopic response and review the literature for similar cases.

A 34-year-old woman with a history of SLE presented with a one-week history of a progressive rash on her back. The patient was diagnosed with SLE at age 26 and had associated oral ulcers, discoid lupus, Raynaud phenomenon, class IV nephritis, and arthritis. Serologies were positive for antinuclear antibodies, anti-double-stranded DNA (dsDNA) antibodies, anti-Smith antibodies, anti-ribonucleoprotein antibodies, and anti-Ro antibodies; low C3 complement level was also detected. The patient's relevant medications included prednisone 20mg daily, mycophenolate mofetil 1000mg twice daily, hydroxychloroquine 300mg daily, and belimumab 200mg subcutaneously once weekly.

One month prior to presentation in the dermatology clinic, the patient was treated in the emergency department for herpes zoster on her right flank. She was treated with a ten-day course of valacyclovir 1000mg thrice daily. She was advised to stop her immunosuppressants, including belimumab and mycophenolate mofetil, and to decrease her prednisone from 20 to 10mg per day. The patient also discontinued hydroxychloroquine. After initial improvement, approximately four weeks later, she noted worsening of the rash in the same site as her resolved herpes zoster associated with significant burning. She had been applying topical lidocaine and aloe vera to the areas. She also noted worsening of her ongoing cutaneous lupus lesions on her hands.

Physical examination revealed pink, edematous papules coalescing into plaques in a dermatomal distribution over the right abdomen and back. Adjacent linear edematous plaques were noted. Underlying the pink papules, also in a dermatomal distribution, were hyperpigmented macules and patches (**Figure 1**). Testing for dermatographism was negative. Laboratory results for anti-dsDNA antibodies and C3 complement levels were stable from the previous year and the complete blood count, basic metabolic panel, erythrocyte sedimentation rate, and C-reactive protein were within normal limits.

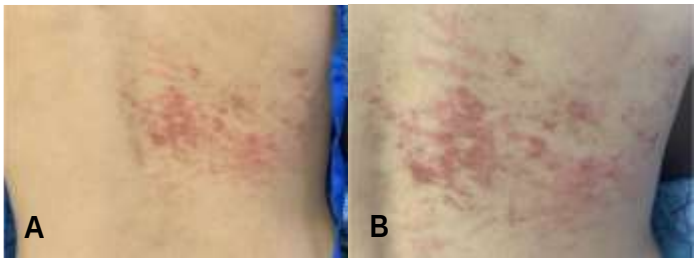

Figure 1. ***A)*** *Far and* ***B)*** *close-up views of the patient's back lesions upon presentation. In a dermatomal distribution over the right abdomen and back were pink, edematous papules coalescing into urticarial plaques. Adjacent linear edematous plaques were noted. Underlying these lesions, also in a dermatomal pattern, were hyperpigmented macules and patches.*

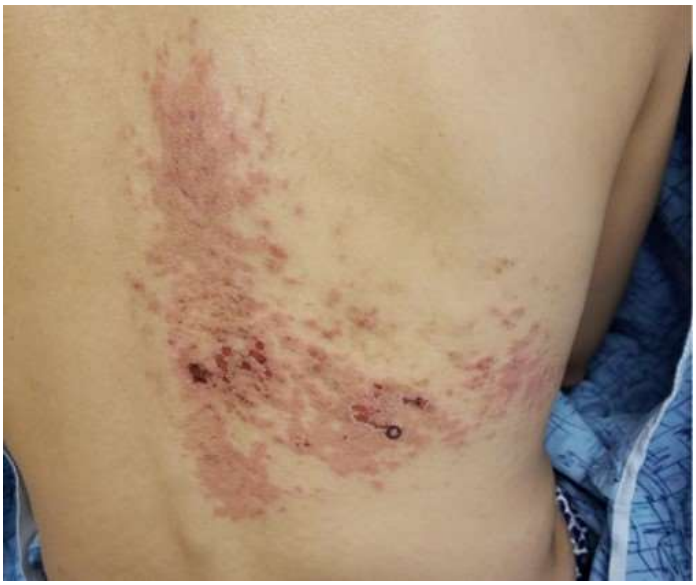

Figure 2. *Appearance of the patient's back lesions two weeks after initial presentation to the clinic and after a second course of valacyclovir. Physical examination showed pink papules coalescing to edematous appearing plaques with erosions and hemorrhagic crusting. Excoriations were secondary to scratching. A punch biopsy was taken.*

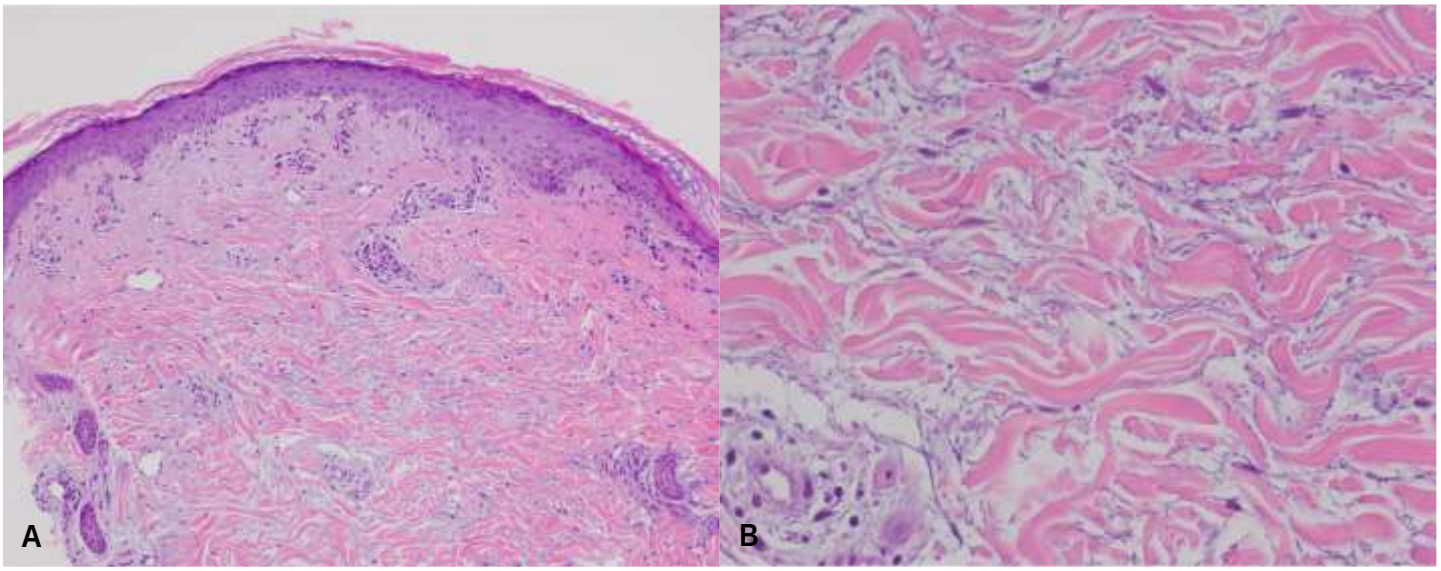

Figure 3. *Histopathology of the isotopic lesion. H&E-stained sections revealing an atrophic vacuolar interface reaction with profound mucin deposition, typical of autoimmune connective tissue disease involving the skin.* ***A)*** *100×,* ***B)*** *200×.*

The patient was prescribed another 10-day course of valacyclovir and told to discontinue all topicals. She returned to clinic two weeks later with no resolution and with increased pruritus. On examination, she was noted to have vertical extension of her rash in the paraspinal region with the development of superficial erosions with hemorrhagic crust (**Figure 2**). A punch biopsy was performed and showed atrophic interface dermatitis with profound mucin deposition, suggestive of an autoimmune connective tissue disease (**Figure 3**).

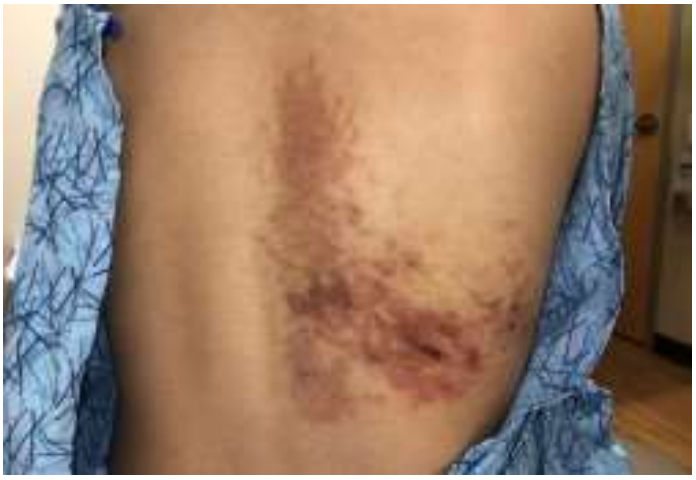

Figure 4. *Appearance of the patient's back lesions one month after initial presentation and after re-initiation of immunosuppressive therapy and treatment with topical fluocinonide. Resolution of lesions with residual post-inflammatory hyperpigmentation is noted. The biopsy site was well-healed.*

The patient was advised to restart her mycophenolate mofetil, weekly belimumab, and hydroxychloroquine and was treated with prednisone taper starting at 40mg by mouth every morning. In addition, she was given topical fluocinonide 0.05% cream to apply to the affected areas.

The patient was diagnosed with Wolf isotopic response manifesting as cutaneous lupus at the site of prior herpes zoster in the setting of flaring discoid lupus and SLE. Within two months, the patient had marked resolution of her pruritus and skin lesions. A significant portion of her skin lesions had resolved with residual post-inflammatory hyperpigmentation (**Figure 4**).

Discussion

The isotopic response, which describes the occurrence of a new skin disease at the site of a prior, healed and unrelated dermatosis, was first coined by Dr. Ronni Wolf et al. in 1995. Cases have been previously reported as early as 1929 [1]. Many dermatoses, including lichen planus, psoriasis, granuloma annulare, and squamous cell carcinoma, have been reported to occur isotopically, frequently after herpes zoster infections [6,7]. However, despite the growing number of reports, the pathogenesis behind Wolf isotopic response remains

uncharacterized. Current theories propose viral, immunologic, neural, vascular, and multifactorial etiologies for the isotopic response, supporting the concept of dermatologic locus minoris resistentiae, in which a congenital or acquired altered defense capacity causes a region of the skin to be more vulnerable to infection, malignancy, and inflammatory diseases [1,8].

Although cutaneous lupus erythematosus is a well-described disease process, the occurrence of CLE at the site of healed, prior dermatoses is rare. We conducted a comprehensive search of the literature through PubMed and only five other cases of isotopic CLE have been described. Our patient is the sixth reported case of CLE as Wolf isotopic response (**Table 1**), [5,8,9,10,11].

Among the six recorded cases of isotopic CLE, five occurred in females, with patient ages ranging from 17 to 70 years old. Three of the six patients had an established diagnosis of SLE prior to their isotopic response and two patients had prior cutaneous lupus. The primary disease was herpes zoster in five out of six cases. In three of the cases with herpes zoster as the primary dermatosis, antiviral therapy was extended beyond the standard course. Three of the six cases were diagnosed with isotopic discoid lupus erythematosus (DLE). The remaining three cases were given the broad diagnosis of CLE, as the patients exhibited significant overlap in the morphology and histopathologic findings of cutaneous lupus subtypes. Of the three patients who had isotopic DLE, none had systemic involvement or a prior diagnosis of cutaneous lupus. Consequently, none of these patients were being treated for CLE at the time of their diagnosis. All cases of isotopic non-discoid CLE occurred in patients with prior systemic involvement.

Our patient (Case 6) is a 34-year-old woman with pre-existing SLE and DLE who presented with lesions consistent with CLE at the site of a prior, healed herpes zoster infection. As our patient's new lesions were different from her pre-existing discoid lesions and occurred in an area that had not been previously affected by cutaneous lupus, her presentation was consistent with Wolf isotopic response. Notably, our patient presented the diagnostic challenge of distinguishing recurrent herpes zoster from CLE. Due to the increased incidence of herpes zoster among patients with SLE [12] and the dermatomal distribution of isotopic CLE lesions after herpes zoster, isotopic CLE can be misdiagnosed as recurrent herpes zoster. Indeed, similarly to Case 2 and Case 5, our patient was treated with a second course of valacyclovir before failed resolution of her symptoms prompted further diagnostic workup. Given the possibility of misdiagnosis and delayed treatment, isotopic CLE should be considered in patients with SLE that develop evolving, persistent, or new dermatomal lesions after herpes zoster infection.

After being correctly diagnosed with isotopic CLE, our patient was restarted on mycophenolate mofetil, belimumab and hydroxychloroquine, and was given an oral prednisone taper and topical fluocinonide. She experienced resolution of her isotopic lesions with post-inflammatory hyperpigmentation. Of note, our patient's immunosuppressive medications were held at the time of her herpes zoster eruption to allow for clearance of the virus, while she independently discontinued hydroxychloroquine therapy. The discontinuation of this immunosuppressive and immunomodulatory regimen likely contributed to the occurrence of the isotopic phenomenon with lesions of CLE. Consistent with this observation, the patient's pre-existing discoid lupus lesions were flaring at the time of her isotopic response. It is difficult to say whether the systemic or topical therapies, or maybe both, were responsible for the resolution of skin lesions.

Although there have only been six reported cases of Wolf isotopic response manifesting as CLE, several articles have reported Koebner isomorphic response manifesting as CLE or DLE in sites of tattooing, scars, burns, intramuscular injections, contact dermatitis, and herpes zoster infections [5]. In 2018, Anyanwu et al. described a 19-year-old woman with pre-existing SLE and DLE who developed DLE lesions in areas previously affected by herpes zoster. After being diagnosed with SLE and DLE, the patient was started on prednisone, mycophenolate mofetil, and tacrolimus. Despite immunosuppressive therapy, the patient continued to develop new discoid lesions of

the face, chest, and arms. After four weeks of immunosuppressive treatment, the patient developed a painful rash consistent with herpes zoster in a T3 to T4 dermatomal distribution. She was treated with a 14-day course of antiviral therapy, which led to resolution of her cutaneous lesions but she developed postherpetic neuralgia. Mycophenolate mofetil was later discontinued due to acute liver toxicity. Upon discontinuation, the patient developed a new pruritic rash in the areas previously affected by herpes zoster. Clinical findings, histopathology, and direct immunofluorescence were together consistent with the development of DLE in areas of previous trauma from herpes zoster. In similarity with the isotopic cases previously described, the authors recommended topical corticosteroids [13]. In this case, it can be contended that the woman exhibited features of an isotopic response, as she developed discoid lesions in an area that was previously unaffected by DLE after having had shingles. A similar assessment was made for a case of an 18-year-old woman with SLE on immunosuppression who developed DLE at the site of prior herpes zoster [14]. However, as the authors classified their patients as having an isomorphic response, these cases were not included in our table.

Indeed, the distinction between isotopic and isomorphic responses has long been a source of debate. For example, it can be argued that, because herpes zoster can cause "trauma" to the skin that may result in increased susceptibility to subsequent lesions, our patient exhibited features of Koebner isomorphic response. However, as her lesions had different morphology than her pre-existing DLE lesions and occurred at the site of a prior, unrelated rash, our patient's presentation was most consistent with Wolf isotopic response. In Case 5, the authors contended that, although their patient's lesions were consistent with pre-existing cutaneous lupus lesions in other areas, qualifying the reaction to be isomorphic, the new lesions also occurred in an area that had previously been unaffected by her cutaneous lupus and in the same site as a herpes zoster eruption, which is consistent with an isotopic reaction [5]. Thus, this case demonstrates the overlap of the two concepts. In both the Koebner isomorphic response and Wolf isotopic response, sources of cutaneous damage give way to subsequent autoimmune cutaneous disease in select individuals. This suggests these preceding events cause local aberrant immune dysregulation in susceptible individuals. Thus, both phenomena embody the concept of locus minoris resistentiae, or an acquired "crack" in the cutaneous armor and may share a similar mechanism.

Conclusion

Cutaneous damage resulting from herpes zoster infection may lead to the development of isotopic CLE lesions. As isotopic CLE lesions present in a dermatomal distribution, these cases may be difficult to distinguish from recurrent herpes zoster infection in an immunosuppressed patient. To avoid treatment delay, diagnostic suspicion should be high for isotopic responses when lesions of different morphology occur in areas previously affected by herpes zoster or other dermatoses or in cases of persistent eruptions at sites of prior herpes zoster. In the event of an isotopic CLE response, topical corticosteroids should be initiated and systemic immunosuppressive therapy may be continued. Given that patients with SLE are at increased risk for herpes zoster infections, varicella zoster vaccination should be considered for this patient population, especially in those taking systemic immunosuppressive medications [12].

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Wolf R, Wolf D, Ruocco V, Ruocco E. Wolf's isotopic response: The first attempt to introduce the concept of vulnerable areas in dermatology. *Clin Dermatol*. 2014;32:557-560. [PMID: 25160096].
2. Mahajan R, De D, Saikia UN. Wolf's Isotopic Response: Report of a Case and Review of Literature. *Indian J Dermatol*. 2014;59:275-282. [PMID: 24891660].

3. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus-an update. *Curr Opin Immunol*. 2012;24:651-657. [PMID: 23131610].
4. Achtman JC, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res Ther*. 2015;17:182. [PMID: 26257198].
5. Lee NY, Daniel AS, Dasher DA, Morrell DS. Cutaneous lupus after herpes zoster: isomorphic, isotopic, or both? *Pediatr Dermatol*. 2013;30:e110-e113. [PMID: 22639953].
6. Patel P, Werth V. Cutaneous lupus erythematosus: a review. *Dermatol Clin*. 2002;20:373-v. [PMID: 12170873].
7. Wolf R, Brenner S, Ruocco V, Filioli FG. Isotopic response. *Int J Dermatol*. 1995;34:341-348. [PMID: 7607796].
8. Storer M, Nazarian RM, Kourosh AS. Nonphoto-exposed initial cutaneous manifestation of lupus after zoster: A case of Wolf's isotopic reaction. *JAAD Case Rep*. 2016;2:425-427. [PMID: 27942574].
9. Bardazzi F, Giacomini F, Savoia F, Misciali C, Patrizi A. Discoid chronic lupus erythematosus at the site of a previously healed cutaneous leishmaniasis: an example of isotopic response. *Dermatol Ther*. 2010;23 Suppl 2:S44-S46. [PMID: 20482569].
10. Hirbod T, Altamura D, Arkoumani E, Stefanato CM, Verdolini R. Discoid lupus erythematosus occurring in an area previously affected by herpes zoster virus: Wolf's isotopic reaction?. *Eur J Dermatol*. 2017;27:186-187. [PMID: 27976613].
11. Parimalam K, Kumar DD, Thomas J. Discoid lupus erythematosis occurring as an isotopic response. *Indian Dermatol Online J*. 2015;6:50-51. [PMID: 25657921].
12. Chakravarty EF, Michaud K, Katz R, Wolfe F. Increased incidence of herpes zoster among patients with systemic lupus erythematosus. *Lupus*. 2013;22:238-244. [PMID: 23257402].
13. Anyanwu CO, Sommer LL, Kuzyshyn H, et al. Discoid lupus erythematosus following herpes zoster. *Cutis*. 2018;101:370-372. [PMID: 29894527].
14. Longhi BS, Centeville M, Marini R, Appenzeller S. Koebner's phenomenon in systemic lupus erythematosus. *Rheumatol Int*. 2012;32:1403-1405. [PMID: 21437691].

Table 1. *Summary of all cases of reported isotopic cutaneous lupus erythematosus.*

Case	Age/ Sex	Systemic Lupus	Prior diagnosis of cutaneous lupus	Primary Disease	Secondary Disease	Biopsy confirmation/final diagnosis	Treatment for prior SLE/CLE at the time of isotopic response	Treatment for isotopic lesions	Follow-up	Ref
1	38 F	N	N	Cutaneous Leishmaniasis	DLE	Perivascular and periadnexial lymphohistiocytic infiltrate in the papillary dermis, thickened basement membrane of epidermis and orthokeratosis, follicular plugs of cornified cells	N	400mg HCQ daily, topical clobetasol ointment, topical tretinoin, sunscreen	Complete healing of lesion with treatment for two months	[9]
2	70 M	N	N	Herpes zoster	DLE	Interface dermatitis, florid lymphocytic infiltrate in the dermis, clear thickening of basal membrane	N	400mg HCQ daily, topical mometasone furoate cream	The rash followed a relapsing-remitting course in the same area during a follow-up period of 28 months	[10]
3	65 F	N	N	Herpes zoster	DLE	Hyperkeratosis, follicular plugging, epidermal atrophy, basal cell degeneration, and perifollicular infiltrate around destroyed follicular structures	N	Topical corticosteroid, zinc, oral antihistamines, oral antioxidants	Outcomes were not recorded	[11]
4	56 F	Y	N	Herpes zoster	CLE	Interface dermatitis with dyskeratosis, superficial perivascular lymphocytic infiltrate, focal red blood cell extravasation, and pigment incontinence	Y; HCQ 400mg daily	Triamcinolone, topical clobetasol ointment twice daily	No response to triamcinolone; lesions improved with clobetasol	[8]
5*	17 F	Y	Y	Herpes zoster	CLE	Hyperkeratosis and vacuolar interface dermatitis	Y; HCQ, oral prednisone, topical steroids, cyclophospha-mide, azathioprine	Topical clobetasol ointment	Prompt resolution with clobetasol	[5]

6	34 F	Y	Y; (DLE)	Herpes zoster	CLE	Atrophic interface dermatitis with profound mucin deposition	N	Re-initiation of MMF, belimumab, HCQ, prednisone, topical fluocinonide	Improvement of lesions within two months with residual post-inflammatory hyperpigmentation	CC

*This case of cutaneous lupus erythematosus was considered by the paper's authors as both an isotopic and an isomorphic response.

ANA, anti-nuclear antibody; CC, current case; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DIF, direct immunofluorescence; dsDNA, double stranded deoxyribonucleic acid; ENA, extractable nuclear antigen; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; Ref, reference; RF, rheumatoid factor; RNP, ribonucleoprotein.