Imiquimod-Induced Subacute Cutaneous Lupus Erythematosus–like Changes

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Practice Points

- Subacute cutaneous lupus erythematosus has been reported in association with multiple systemic medications; however, association of this disorder with topical agents has not been widely reported.
- The use of topical imiquimod in patients with a personal or family history of lupus erythematosus should be undertaken with caution until more is known.

Imiquimod is a topical immunomodulator used to treat genital warts and cutaneous malignancies that exerts its effects via induction of proinflammatory cytokines through activation of toll-like receptor (TLR) 7. Although subacute cutaneous lupus erythematosus (SCLE) has been reported in association with multiple systemic medications, SCLE in patients treated with topical agents has not been widely reported. We report the case of a 50-year-old woman with local induction of lesions that clinically and histologically resembled SCLE following treatment with topical imiquimod.

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Drug-induced lupus accounts for up to 10% of lupus erythematosus cases. Subacute cutaneous lupus erythematosus (SCLE) is a distinct clinical variant of lupus erythematosus that typically presents as annular, often scaly, erythematous plaques in photodistributed areas. Subacute cutaneous lupus erythematosus has been reported in association with multiple systemic medications including docetaxel, terbinafine, leuprolide acetate, etanercept, and efalizumab[1-5]; however, the induction of SCLE by topical agents has not been widely reported. We report a case of local induction of lesions that clinically and histologically resembled SCLE in a 50-year-old woman following treatment with topical imiquimod.

Case Report

A 50-year-old woman presented with an adverse inflammatory reaction on the right side of the upper chest secondary to application of topical imiquimod. Prior to the current presentation the patient was diagnosed with a biopsy-proven superficial basal cell carcinoma (BCC) on the sun-exposed area of the upper right breast, and topical imiquimod therapy was initiated. Several days after starting treatment, the patient began applying imiquimod on areas of clinically normal skin on the upper chest as advised by her dermatologist. After 7 to 10 days of application the patient reported intense erythema, pain, and crusting in the treated area on the right side of the upper chest. She also experienced systemic symptoms including fatigue, arthralgia, malaise, and fever.

Clinical examination revealed erythematous to violaceous annular and polycyclic plaques on the upper chest (Figure 1). Erythema and scaling were noted at the site of the superficial BCC. A biopsy showed a superficial and mid-dermal perivascular and periadnexal lymphocytic infiltrate with

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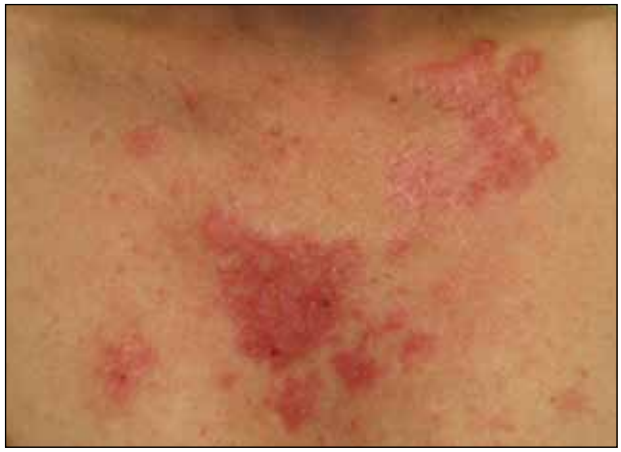

Figure 1. Annular plaques on the upper chest with overlying scale and focal central clearing.

overlying vacuolar interface dermatitis and scattered necrotic keratinocytes (Figures 2A and 2B). There was slightly increased dermal edema and mucin. Anti-CD123 immunohistochemical staining revealed nodular aggregates of plasmacytoid dendritic cells (pDCs) accompanying lymphocytes around dermal vessels and adnexa (Figure 2C). The patient's family history was remarkable for SCLE in her daughter. Antinuclear antibody, anti-Ro (Sjögren syndrome antigen A), and anti-La (Sjögren syndrome antigen B) were negative. On follow-up examination 1 month after discontinuation of imiquimod, the patient's skin lesions had completely cleared. Two years later, the patient continued to be free of skin lesions.

Comment

Imiquimod is a topical immunomodulator used for the treatment of genital warts and cutaneous malignancies. It exerts its effect via induction of proinflammatory cytokines (eg, IFN-α, tumor necrosis factor α [TNF-α]) through activation of toll-like receptor (TLR) 7, an intracytoplasmic receptor that is found on several cell types including pDCs and B cells. When the cell surface receptor is bound by activating ligands (eg, single-stranded RNA, imiquimod), downstream signaling is initiated, resulting in the production of large amounts of IFN-α and TNF-α.[6,7] Both IFN-α and TNF-α are upregulated in patient serum and lesional skin in SCLE.[8,9] Additionally, pDCs have been shown to accumulate in lesions of cutaneous lupus erythematosus (CLE) in a distinct dermal pattern, as demonstrated by CD123 staining.[9,10] This pattern is identical to the one seen in our case. Although pDCs also are present

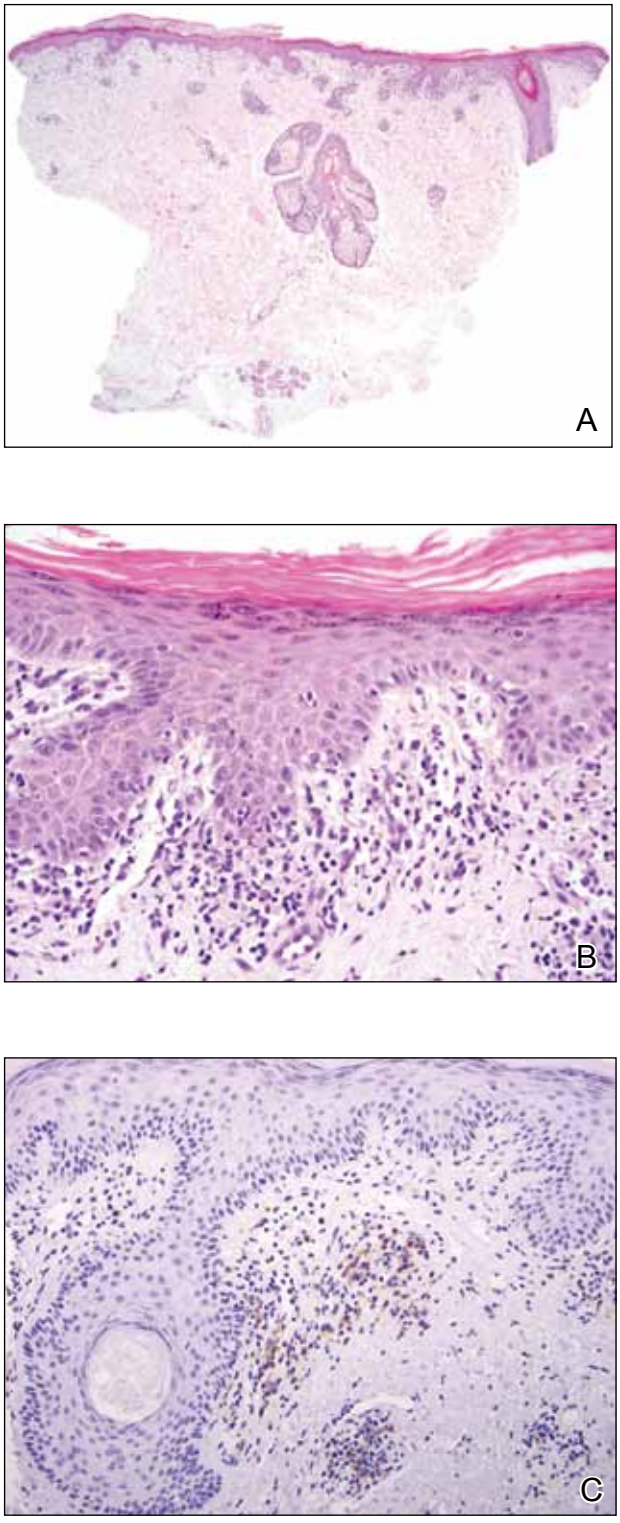

Figure 2. Vacuolar interface dermatitis with a perivascular and periadnexal lymphocytic infiltrate (A)(H&E, original magnification ×40). Scattered necrotic keratinocytes were evident (B)(H&E, original magnification ×400). Anti-CD123 immunohistochemical staining revealed nodular aggregates of plasmacytoid dendritic cells with accompanying lymphocytes centered around dermal vessels and adnexa (C)(original magnification ×200).

in cutaneous dermatomyositis lesions, the pattern is distinct from CLE.[10] These findings indicate that IFN-α produced by pDCs may play an integral role in the pathogenesis of CLE. Several observations implicating TLR signaling in the pathogenesis of lupus have been described. In a lupus-prone mouse model of lupus erythematosus, transgenic overexpression of TLR-7 resulted in increased severity of clinical disease and accelerated mortality. Antimalarials improve lupus erythematosus via blockade of TLR-7 and TLR-9 signaling.[11]

Imiquimod, which acts as an inducer of IFN-α expression through TLR-7 signaling, may have been an inciting factor in the development of SCLE-like lesions in this genetically predisposed patient. Histopathology of cutaneous malignancies treated with topical imiquimod typically does not show lupuslike features.[12] It is possible that a subset of predisposed patients have increased numbers of pDCs primed in their skin or that they exhibit a more robust TLR-7 reaction to imiquimod, resulting in abundant IFN-α production. Other autoimmune diseases, such as pemphigus foliaceus and vitiligo, also have been reported to occur locally after the application of imiquimod,[13,14] which suggests that a localized autoimmune reaction can be induced by activation of TLR-7; however, a case of chronic discoid lupus erythematosus of the scalp improving after treatment with imiquimod has been reported.[15]

The use of imiquimod in patients with a personal or family history of lupus erythematosus or those with a personal history of an autoimmune blistering disorder should be undertaken with caution until more is known.

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