Subacute Cutaneous Lupus as a Paraneoplastic Manifestation of Non-Hodgkin Lymphoma

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Abstract
Malignancies have been associated with paraneoplastic syndromes, such as dermatomyositis. Subacute cutaneous lupus erythematosus (SCLE) can occur due to a wide array of cancers. Paraneoplastic SCLE obeys McLean’s criteria and often regresses after the underlying malignancy has been treated appropriately. Anti-Ro/SSA antibodies are often present in patients with paraneoplastic SCLE; however, there have been many instances where anti-Ro may not be present. We report a case of non-Hodgkin lymphoma causing SCLE, a malignancy not previously known to be associated with paraneoplastic SCLE. We also highlight the importance of perhaps prompt chemotherapy to treat the underlying malignancy, as a failure to do so may lead to worse patient outcomes.

Keywords
subacute cutaneous lupus erythematosus, paraneoplastic syndrome, non-Hodgkin’s lymphoma, follicular B-cell lymphoma

Introduction
Cutaneous lupus erythematosus (CLE) can exist in 2 of 3 patients without systemic lupus erythematosus (SLE).1 Cutaneous lupus erythematosus has 3 subsets, one of which is subacute cutaneous lupus erythematosus (SCLE). The SCLE has been associated with several malignancies as a paraneoplastic syndrome.1-4 The SCLE starts as a small, erythematous, scaly papule that evolves into psoriasiform plaques, which eventually coalesce to form larger plaques.5 Most patients exhibit photosensitivity, with exacerbations upon increased exposure to the sun. Histopathology of SCLE shows prominent suprabasilar lymphocytosis, suprabasilar dyskeratosis, vacuolization in the basement membrane, and mucin deposition in the dermis.5 The treatment of SCLE depends on the cause. Usual first-line therapy are photoprotection and glucocorticoids, topical or systemic.6 However, if an underlying neoplasm is thought to be the cause, then treatment of the neoplasm will lead to regression of the SCLE.7 Here, we report a case of advancing follicular B-cell lymphoma causing SCLE, an occurrence not previously reported in the literature.

Case Presentation
A 64-year-old Caucasian male with a medical history significant for stage II follicular B-cell lymphoma presented to the emergency department with a pruritic, non-painful, erythematous rash. The patient was diagnosed with follicular B-cell lymphoma 3 years prior and underwent radiation and chemotherapy. He achieved partial remission, as positron emission tomography scan after treatment still showed cancer activity in the axillary lymph nodes. His current rash started 1 month before presentation, on his left arm. Subsequently, it spread to his chest and back before covering his entire body (Figure 1). He also reported painful, blistering sores inside his mouth, nose, and on his tongue. The patient denied recent travel or starting new medications. Pertinent laboratory results revealed positive anti-nuclear antibodies (1:160 titer). Rheumatoid factor antibodies, double-stranded DNA antibodies, anti-nuclear cytoplasmic antibodies, and anti-Smith antibodies were negative. Complement 3 and 4 levels were normal. Skin biopsy from the
upper back showed evidence of SCLE with vacuolization along the dermal-epidermal junction and intraepidermal necrotic keratinocytes (Figure 2). Methylprednisolone was started promptly, without adequate resolution of his diffuse SCLE. Computed tomographic scan of the abdomen/pelvis identified a 9.2 × 6.3 cm retroperitoneal mass, with subsequent needle biopsy confirming B-cell lymphoproliferative disorder, indicative of now stage III follicular B-cell lymphoma. Thus, there was high suspicion of paraneoplastic SCLE. There was a plan to start systemic chemotherapy upon hospital discharge to treat the

Figure 1. (A) Initial rash on the left arm, (B) subsequent rash on the upper back, and (C) similar rash appearing on the left leg and (D) right arm.
advancing lymphoma. However, on hospital day 17, the patient developed septic shock due to infected skin wounds and hospital-acquired pneumonia with associated acute hypoxic respiratory failure. He was intubated on day 19 and terminally extubated on day 26.

**Discussion**

The SCLE starts as small, erythematous, scaly psoriasiform plaques that soon coalesce to form larger plaques, and patients can also present with oral ulcers.5 This was the case for our patient whose rash started locally on his left arm and then spread to his chest, back, and eventually his entire body. Our patient also developed oral ulcers. The skin biopsy finds were also incongruent with SCLE.

For a dermatosis to be considered a paraneoplastic manifestation, McLean’s criteria should be satisfied (Table 1).8 In our case, the SCLE presented after the patient’s non-Hodgkin lymphoma (NHL) spread and advanced in stage from II to III, involving lymph nodes on both sides of the diaphragm, axillary and retroperitoneal.9 However, treatment could not be initiated to see whether the dermatosis regresses with adequate therapy of the malignancy. Although SCLE has been associated with drugs such as lisinopril and clopidogrel, both of which are drugs that the patient was taking, they are unlikely culprits as the patient had been on these drugs for several years, even before he was diagnosed with cancer.10 All cases of drug-induced SCLE resolve after withdrawing the drug, although on average it can take 7 weeks for the SCLE to resolve.5 Based on the work of Lowe et al, it was postulated that because the patient had been on both clopidogrel and lisinopril for almost a decade, the drugs were unlikely to be the cause of the patient’s SCLE as such long incubation times for DI-SCLE have not been observed for either drug.10 However, because the patient’s B-cell lymphoma had relapsed and actually spread to the retroperitoneal lymph nodes, it was more likely that the SCLE was in fact a paraneoplastic phenomenon. Cases have been reported of relapse and metastasis of a malignancy causing paraneoplastic SCLE.2,11

The presence of anti-Ro antibodies has been associated with paraneoplastic SCLE; however, there are many reported cases where anti-SSA may not always be present.1,7 It is believed that tumors express certain antigens that are homologous to those in the body. It is these antigens to which body forms antibodies which can then go on to attach to their self-antigen homologs causing autoimmune reactions.12 Antigens such as the Ro antigen can migrate to the surface if the cells are exposed to UV light.13 This effect is seen in keratinocytes and may be the cause of photosensitivity in the presence of tumors causing SCLE.12 It is theorized that this effect can likely occur with other self-antigens also. However, attempts to isolate Ro antigens from resected tumors have been unsuccessful.12 Thus, more research is needed regarding what triggers the SCLE in patients with cancer.

**Conclusion**

This is the first reported case of SCLE as a paraneoplastic syndrome due to NHL. The case demonstrates the importance of keeping progression of malignancy in mind as a possible differential for the appearance of dermatoses such as SCLE, especially in patients with an established history of cancer. We also highlight that it may, at times, be appropriate to promptly start chemotherapy to treatment malignancy-induced dermatoses as a failure to do so may lead to worse patient outcomes, such as in our case. This case further adds to the growing literature that exists regarding SCLE as a paraneoplastic syndrome.

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Informed Consent
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References
1. Gantzer A, Regnier S, Cosnes A, et al. [Subacute cutaneous lupus erythematosus and cancer: two cases and literature review]. Ann Dermatol Venereol. 2011;138(5):409-417. doi:10.1016/j.annder.2011.02.015.
2. Evans KG, Heymann WR. Paraneoplastic subacute cutaneous lupus erythematosus: an underrecognized entity. Cutis. 2013;91(1):25-29.
3. Murad A, O’Donnell B, Rowley H, Mulligan N. Subacute cutaneous lupus erythematosus: a paraneoplastic phenomenon in oropharyngeal squamous cell carcinoma. Clin Exp Dermatol. 2015;40(3):335-337.
4. Jenkins D, McPherson T. Paraneoplastic subacute cutaneous lupus erythematosus associated with cholangiocarcinoma. Australas J Dermatol. 2016;57(1):e5-e7. doi:10.1111/ajd.12251.
5. Stavropoulos PG, Goules AV, Avgerinou G, Katsambas AD. Pathogenesis of subacute cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol. 2008;22(11):1281-1289. doi:10.1111/j.1468-3083.2008.02806.x.
6. Kuhn A, Ruland V, Bonsmann G. Photosensitivity, phototesting, and photoprotection in cutaneous lupus erythematosus. Lupus. 2010;19(9):1036-1046. doi:10.1177/0961203310370344.
7. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. Autoimmun Rev. 2005;4(5):253-263. doi:10.1016/j.autrev.2004.10.003.
8. McLean DI. Cutaneous paraneoplastic syndromes. Arch Dermatol. 1986;122:765-767.
9. Freedman A, Jacobsen E. Follicular lymphoma: 2020 update on diagnosis and management. Am J Hematol. 2020;95(3):316-327. doi:10.1002/ajh.25696.
10. Lowe GC, Henderson CL, Grau RH, Hansen CB, Sontheimer RD. A systematic review of drug-induced subacute cutaneous lupus erythematosus. Br J Dermatol. 2011;164(3):465-472. doi:10.1111/j.1365-2133.2010.10110.x.
11. Shaheen B, Milne G, Shaffrali F. Subacute cutaneous lupus erythematosus associated with breast carcinoma. Clin Exp Dermatol. 2009;34:e480-e481. doi:10.1111/j.1365-2230.2009.03549.x.
12. Szekanecz E, András C, Sándor Z, et al. Malignancies and soluble tumor antigens in rheumatic diseases. Autoimmun Rev. 2006;6(1):42-47. doi:10.1016/j.autrev.2006.03.007.
13. Trüeb RF, Trüeb RM. [Cutaneous paraneoplastic syndrome as an immunologic phenomenon exemplified by paraneoplastic subacute cutaneous lupus erythematosus]. Praxis (Bern 1994). 1999;88:1803-1810.