Editorial

Update on cutaneous lupus erythematosus

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The skin is the second most frequently involved organ in lupus erythematosus (LE). Although cutaneous involvement is rarely life threatening, it is associated with major morbidity.[1] Cutaneous lupus erythematosus (CLE) can be associated with systemic lupus erythematosus (SLE), can precede SLE, or occur on its own. Central to the pathogenesis is loss of immune tolerance and upregulation of the interferon-α (IFN-α) signaling. The clinical spectrum of CLE is wide and includes both specific and nonspecific lesions. These have varying pathologies ranging from primary interface involvement, dermal involvement, or involvement of the subcutis. Disease burden has been quantified by many tools. Cutaneous lupus area severity index (CLASI) is a validated tool for CLE which has been used in numerous studies. The mainstay of treatment is photoprotection, antimalarials, corticosteroids, and calcineurin inhibitors.[1] Indeed, with the advances made in CLE, it is difficult to keep abreast of the latest advances. This article attempts to highlight the recent updates in the field in the past year.

PATHOGENESIS

Patients with subacute cutaneous lupus erythematosus (SCLE) and discoid lupus erythematosus (DLE) were found to have elevated IFN scores as compared to healthy controls regardless of concomitant SLE. This was found to correlate with the CLASI score. It has also been seen that active CLE is associated with a systemic type I IFN effect that appears to induce a shift toward a Th1-associated chemokine receptor profile.[2] Upregulation of the IFN-inducible antiviral protein Myxovirus A (MxA) in CLE has also been found. This expression was mainly seen in the epidermis and the upper dermis in DLE and SCLE, while in rare cases of lupus tumidus and lupus profundus, MxA was mainly detected in perivascular and subcutaneous areas, respectively, reflecting the distribution of the inflammatory infiltrate in different subsets of CLE.[3] Recently, various cytokines have been found to be involved in CLE. Interleukin (IL)-18 and the overexpression of IL-18 receptor in keratinocytes was found to induce the apoptosis of keratinocytes via increased tumor necrosis factor (TNF)-α and decreased IL-12 production.[4] This apoptotic death was reported to be due to the strong expression of TNF-related apoptosis-inducing ligand (TRAIL) in the skin and the blood of patients with CLE.[5] Some CLE lesions showed increased levels of IL-17, but the precise role of IL-17 is uncertain[4] Moreover, transforming growth factor (TGF)-β serum levels were found to be significantly lower in patients with DLE as compared to the levels in patients with psoriasis and in healthy controls. This downregulation of TGF-β and IL-10 in DLE may lead to defective immune suppression and thus to the generation of the tissue injury that is found in lupus patients.[6] It has been seen that patients with CLE have a low prevalence of skin infections. Kreuter *et al*.[7] reported that human β-defensin (hBD) 2 and 3, cathelicidin LL-37, and psoriasin were significantly more highly expressed in CLE as compared with healthy controls.

CLINICAL FEATURES

Patients with active discoid lupus rarely have progressive renal insufficiency. The development of

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discoid lupus may involve an immunologic mechanism that differs from that which produces severe organ involvement.[8] Overlap of toxic epidermal necrolysis (TEN) and LE is very difficult to diagnose and manage. Ziemer *et al*.[9] studied patients with TEN like LE. Acute cutaneous manifestations of SLE and Stevens Johnson syndrome (SJS)/TEN can be phenotypically similar. A combination of recent SLE exacerbation, photo-distribution, annular lesions, and absent or only mild focal erosive mucosal involvement may favor LE over SJS/TEN clinically. Histopathologically, junctional vacuolar alteration, presence of solitary necrotic keratinocytes at lower epidermal levels combined with moderate to dense periadnexal and perivascular lymphocytic infiltrates with variable presence of melanophages and mucin point at an LE-related origin.

Some authors feel that Rowell's syndrome does not qualify as a separate entity. Antiga *et al*.[10] in their report suggested that LE with erythema multiforme (EM)-like rashes represents a subset of SCLE with targetoid lesions rather than a distinct entity. A real association between DLE and EM was present only in a minority of cases (about 20 patients) and could be considered a mere coincidence without any immunopathological implication or unusual characteristic to either illness. Another big challenge is to differentiate drug-induced SCLE from idiopathic SCLE. Marzano *et al*.[11] reported that drug induced-SCLE differs from idiopathic SCLE by virtue of distinctive cutaneous features, particularly the widespread presentation and the frequent occurrence of malar rash and bullous, EM-like, and vasculitic manifestations.

There were multiple reports of interesting clinical presentations like linear CLE,[12] linear sclerodermoid LE,[13] comedonal DLE,[14] nonbullous neutrophilic LE,[15] neutrophilic dermatosis in conjunction with LE,[16] and CLE of the elbows.[17]

The clinical presentations of nonbullous neutrophilic LE included urticarial papules, plaques, and subcutaneous nodules. Histopathological findings in all patients included an interstitial and perivascular neutrophilic infiltrate with leukocytoclasia, and variable vacuolar alteration along the dermo-epidermal junction.

CUTANEOUS LUPUS ERYTHEMATOSUS AND CANCER

In a Swedish national cohort study which compared 3663 patients diagnosed with CLE in Sweden with a control cohort without CLE, a fourfold increase in risk was seen for buccal cancer, lymphomas, respiratory cancer, and non-melanoma skin cancers. This increase remained when excluding patients also diagnosed with SLE. The authors stressed the importance of non-smoking and sun avoidance and specialized monitoring among these patients.[18]

OUTCOME MEASURES

CLASI can be used to classify patients into groups according to disease severity and to identify clinically significant improvements in disease activity.[19] It has also been seen that quality of life in CLE was severely impaired, particularly with respect to emotional well-being. Patients with CLE have worse quality of life than those with other common dermatologic conditions such as acne, nonmelanoma skin cancer, and alopecia. Factors related to poor quality of life include female gender, generalized disease, severe disease, distribution of lesions, and younger age.[20]

THERAPY

Topical calcineurin inhibitors were found to be efficacious either as monotherapy or in combination with hydroxychloroquine. Tacrolimus 0.1% was found to be efficacious in a randomized, double-blind, vehicle-controlled trial of 30 patients of CLE, especially in acute, edematous, non-hyperkeratotic lesions of CLE patients.[21]

Wahie *et al*.,[22] in their multicenter observational and pharmacology study, investigated the effects of disease attributes and metabolizing cytochrome P450 (CYP) polymorphisms on clinical outcome of DLE. Although the majority of patients responded to hydroxychloroquine, a significant proportion (39%) either failed to respond or were intolerant to the drug. Cigarette smoking and CYP genotype did not have any significant influence on the response to hydroxychloroquine. Moreover, multivariate analysis indicated that disseminated disease and concomitant SLE were significantly associated with lack of response to hydroxychloroquine. Antimalarials were found to be efficacious in a study of 11 cases of reticular erythematosus mucinosis. It has also been reported that current smokers with LE had worse disease, worse quality of life, and were more often treated with a combination of hydroxychloroquine and quinacrine than were nonsmokers.[23]

Low-dose thalidomide (100 mg daily) was found to effective in a study of 60 consecutive cases of refractory CLE. Complete response occurred in 50 patients (85%). Clinical relapse was frequent (70%) and usually occurred 5 months after withdrawal or reduction of thalidomide. Whereas DLE forms tended to relapse and required a long-term maintenance dose of thalidomide, SCLE forms showed a sustained remission after withdrawal.[24] In a small, open label study of five cases, the authors reported that lenalidomide may have usefulness as therapy for severe, treatment-refractory CLE However, their preliminary data also suggest that lenalidomide may activate T cells and trigger systemic disease in some patients with CLE.[25]

The combination of methotrexate (MTX) and cyclosporine (CsA) might offer a good treatment strategy with potentially additive effects for the durable control of recalcitrant CLE, including SCLE. After an initial phase of combined standard immunosuppressive doses (3 mg/kg/d CsA, 22.5–30 mg MTX per week) the dosage of both agents could be reduced to a maintenance level and no significant side effects were observed in a report of two cases.[26]

Mycophenolate mofetil was also found to be efficacious in the treatment of refractory cutaneous lupus. The mean treatment time to initial response was found to be 2.76 months. The average final dose was 2750 mg/day.[27] Ustekinumab has been used in one case of SCLE. The dramatic and sustained clinical improvement after ustekinumab therapy suggested that either TH1 or TH17 differentiation pathways play a central role in the pathogenesis of SCLE.[28]

LASERS

Pulse dye laser[29] and long pulse Nd:YAG laser[30] were found to be effective in LE tumidus and refractory DLE in two reports. Active features of the lupus lesions responded better as compared to atrophic changes. The selective destruction of cutaneous microvasculature, which may modulate the inflammatory network, leading to regression of DLE lesions, was thought to be the main mechanism of action.

REFERENCES

1. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus 2010;19:1050-70.
2. Braunstein I, Klein R, Okawa J, Werth VP. The IFN-regulated gene signature is elevated in SCLE and DLE and correlates with CLASI score. Br J Dermatol 2012. [In press]
3. Karageorgas TP, Tseronis DD, Mavragani CP. Activation of type I interferon pathway in systemic lupus erythematosus: Association with distinct clinical phenotypes. J Biomed Biotechnol 2011;2011:273907.
4. Mikita N, Ikeda T, Ishiguro M, Furukawa F. Recent advances in cytokines in cutaneous and systemic lupus erythematosus. J Dermatol 2011;38:839-49.
5. Zahn S, Rehkämper C, Ferring-Schmitt S, Bieber T, Tüting T, Wenzel J. Interferon-α stimulates TRAIL expression in human keratinocytes and peripheral blood mononuclear cells: Implications for the pathogenesis of cutaneous lupus erythematosus. Br J Dermatol 2011;165:1118-23.
6. Antiga E, Del Bianco E, Difonzo E, Fabbri P, Caproni M. Serum levels of the regulatory cytokines transforming growth factor-β and interleukin-10 are reduced in patients with discoid lupus erythematosus. Lupus 2011;20:556-60.
7. Kreuter A, Jaouhar M, Skrygan M, Tigges C, Stücker M, Altmeyer P, *et al*. Expression of antimicrobial peptides in different subtypes of cutaneous lupus erythematosus. J Am Acad Dermatol 2011;65:125-33.
8. Merola JF, Chang CA, Sanchez MR, Prystowsky SD. Is chronic cutaneous discoid lupus protective against severe renal disease in patients with systemic lupus erythematosus? J Drugs Dermatol 2011;10:1413-20.
9. Ziemer M, Kardaun SH, Liss Y, Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: A descriptive study of 17 cases from a national registry and review of the literature. Br J Dermatol 2011. [In press]
10. Antiga E, Caproni M, Bonciani D, Bonciolini V, Fabbri P. The last word on the so-called "Rowell's syndrome"? Lupus 2011. [In press]
11. Marzano AV, Lazzari R, Polloni I, Crosti C, Fabbri P, Cugno M. Drug-induced subacute cutaneous lupus erythematosus: Evidence for differences from its idiopathic counterpart. Br J Dermatol 2011;165:335-41.
12. Kim J, Lee SH, Roh MR. Linear cutaneous lupus erythematosus on the midline of the face. J Dermatol 2011;38:609-12.
13. Khelifa E, Masouye I, Pham HC, Parmentier L, Borradori L. Linear sclerodermic lupus erythematosus, a distinct variant of linear morphea and chronic cutaneous lupus erythematous. Int J Dermatol 2011;50:1491-5.
14. Farias DF, Gondim RM, Redighieri IP, Muller H, Petri V. Comedonic lupus: A rare presentation of discoid lupus erythematosus. An Bras Dermatol 2011;86:89-91.
15. Brinster NK, Nunley J, Pariser R, Horvath B. Nonbullous neutrophilic lupus erythematosus: A newly recognized variant of cutaneous lupus erythematosus. J Am Acad Dermatol 2012;66:92-7.
16. Pavlidakey P, Mills O, Bradley S, Casey J, Morgan MB. Neutrophilic dermatosis revisited: An initial presentation of lupus? J Am Acad Dermatol 2011. [In press].
17. Bielsa I, Guinovart R, Fernández-Figueras M, Rodríguez C, Ferrándiz C. Cutaneous lupus erythematosus on the elbows: A peculiar localization. Lupus 2012;21:84-8.
18. Grönhagen CM, Fored CM, Granath F, Nyberg F. Increased risk of cancer among 3,663 patients with cutaneous lupus erythematosus- A Swedish nationwide cohort study. Br J Dermatol 2011. [In press]
19. Klein R, Moghadam-Kia S, LoMonico J, Okawa J, Coley C, Taylor L, *et al*. Development of the CLASI as a tool to measure disease severity and responsiveness to therapy in cutaneous lupus erythematosus. Arch Dermatol 2011;147:203-8.
20. Klein R, Moghadam-Kia S, Taylor L, Coley C, Okawa J, LoMonico J, *et al*. Quality of life in cutaneous lupus erythematosus. J Am Acad Dermatol 2011;64:849-58.

21. Avgerinou G, Papafragkaki DK, Nasiopoulou A, Arapaki A, Katsambas A, Stavropoulos PG. Effectiveness of topical calcineurin inhibitors as monotherapy or in combination with hydroxychloroquine in cutaneous lupus erythematosus. J Eur Acad Dermatol Venereol 2011. [In press]
22. Wahie S, Daly AK, Cordell HJ, Goodfield MJ, Jones SK, Lovell CR, *et al*. Clinical and pharmacogenetic influences on response to hydroxychloroquine in discoid lupus erythematosus: A retrospective cohort study. J Invest Dermatol 2011;131:1981-6.
23. Piette EW, Foering KP, Chang AY, Okawa J, Ten Have TR, Feng R, *et al*. Impact of smoking in cutaneous lupus erythematosus. Arch Dermatol 2011. [In press]
24. Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, Vilardell-Tarres M, Ordi-Ros J. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: Prognostic factors of clinical outcome. Br J Dermatol 2011. [In press]
25. Braunstein I, Goodman NG, Rosenbach M, Okawa J, Shah A, Krathen M, *et al*. Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: Histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. J Am Acad Dermatol 2011.
26. Klein A, Vogt T, Wenzel SM, Fleck M, Landthaler M. Cyclosporin combined with methotrexate in two patients with recalcitrant subacute cutaneous lupus erythematosus. Australas J Dermatol 2011;52:43-7.
27. Gammon B, Hansen C, Costner MI. A comment on mycophenolate mofetil and hydroxychloroquine: An effective treatment for recalcitrant cutaneous lupus erythematosus. J Am Acad Dermatol 2012;66:161-2.
28. De Souza A, Ali-Shaw T, Strober BE, Franks AG Jr. Successful treatment of subacute lupus erythematosus with ustekinumab. Arch Dermatol 2011;147:896-8.
29. Truchuelo MT, Boixeda P, Alcántara J, Moreno C, de Las Heras E, Olasolo PJ. Pulsed dye laser as an excellent choice of treatment for lupus tumidus: A prospective study. J Eur Acad Dermatol Venereol 2011. [In press]
30. Park KY, Lee JW, Li K, Seo SJ, Hong CK. Treatment of refractory discoid lupus erythematosus using 1,064-nm long-pulse neodymium-doped yttrium aluminum garnet laser. Dermatol Surg 2011;37:1055-6.