Comparative analysis of rosacea and cutaneous lupus erythematosus: Histopathologic features, T-cell subsets, and plasmacytoid dendritic cells

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Background: Distinction of rosacea and cutaneous lupus erythematosus (LE) can be challenging because of significant clinical and histologic overlap. A controlled study comparing these conditions is lacking.

Objective: We compared the histologic features, T-cell subsets, and plasmacytoid dendritic cells in rosacea and LE.

Methods: Biopsy specimens of rosacea (n = 27) and facial LE (n = 30) were retrospectively reviewed and reacted with Alcian blue and periodic acid—Schiff stains, and CD4, CD8, CD25, and CD123 immunostains.

Results: LE demonstrates a lower CD4:CD8 ratio (1.74 vs 2.80, $P = .0064$), fewer $CD4^+CD25^+$ regulatory T cells (13% vs 31%, $P < .0001$), and more $CD123^+$ plasmacytoid dendritic cells (18% vs 6%, $P = .0137$) than rosacea. The plasmacytoid dendritic cells in LE are more likely to form clusters ($P = .0137$) and comprise at least 20% of the infiltrate ($P = .0340$). Also associated with LE are follicular plugging ($P = .0039$), perineural lymphocytic infiltrate ($P = .0211$), abundant mucin deposition ($P = .0031$), and conspicuous basement membrane thickening ($P = .0073$), whereas Demodex infestation ($P = .0064$) and sebaceous hyperplasia ($P = .0029$) are significantly associated with rosacea.

Limitations: Although statistically significant, the immunophenotypic differences are rather small and limited for routine use.

Conclusion: The infiltrates in rosacea and LE differ immunophenotypically, and may aid in their distinction in addition to conventional histologic examination. (J Am Acad Dermatol 2014;71:100-7.)

Key words: CD123; CD25; CD4:CD8 ratio; immunophenotype; lupus erythematosus; plasmacytoid dendritic cells; regulatory T cells; rosacea.

Differentiation between rosacea and cutaneous lupus erythematosus (LE) can be extremely challenging because of significant clinical and histologic overlap. Correct diagnosis is crucial in guiding therapy and prompting appropriate workup, especially in LE. Clinically, both conditions may present as facial erythema or inflammatory papules.[1-4] A subset of patients with rosacea may also present with positive antinuclear antibodies,[5] albeit at lower titers than typically seen in LE. Histologically, both rosacea and cutaneous LE are characterized by perifollicular and perivascular lymphocytic infiltrates. Although interface dermatitis

Abbreviations used:

LE:	lupus erythematosus
PAS:	periodic acid—Schiff
PDC:	plasmacytoid dendritic cell
Treg:	regulatory T cell

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would speak strongly for LE, its absence does not exclude this diagnosis. Furthermore, it is not uncommon to find rare necrotic keratinocytes on sun-exposed skin[6] and focal lymphocyte exocytosis in rosacea, which may mimic interface dermatitis. Scant dermal mucin may also be observed in chronically sun-damaged skin, thus limiting its specificity for LE.

The lymphocytic infiltrates in both rosacea and LE are composed of predominantly T cells. To our knowledge, the CD4:CD8 ratio in rosacea has only been examined in 2 series of cutaneous and ocular rosacea, both of which reported an increased CD4:CD8 ratio.[7,8] In contrast, the CD4:CD8 ratio tends to be lower than normal in discoid LE and subacute cutaneous LE,[9] or even reversed (CD8>CD4) in systemic LE.[10,11] No study has yet compared the CD4:CD8 ratios in rosacea versus cutaneous LE. $CD4^+CD25^+$ regulatory T cells (Tregs) are a specific subset of T cells that normally suppress autoreactivity and have been implicated in autoimmune diseases.[12] Although reduction in Tregs has been described in cutaneous LE,[13] the number of Tregs in rosacea has never been reported to our knowledge.

Plasmacytoid dendritic cells (PDCs) are interferon-α/β-producing cells that are also believed to play an important role in autoimmune diseases. Few studies have shown the accumulation of $CD123^+$ PDCs in cutaneous LE.[14-16] Of these, only 1 study has included 7 cases of rosacea in its extensive list of non-LE conditions for comparison. The PDCs were present in only 3 of those 7 rosacea cases, in which the clusters were fewer in number and showed weaker CD123 staining compared with the 106 cases of LE.[16]

Our objective was to explore the diagnostic value of various histologic features and ancillary studies, including immunohistochemistry and special stains, in the differential diagnosis of rosacea and facial LE.

CAPSULE SUMMARY

- The histopathologic differential diagnosis between rosacea and lupus erythematosus may be difficult yet is rarely addressed in the literature.
- We found statistically significant differences in the proportions of $CD4^+$, $CD8^+$, $CD25^+$, and $CD123^+$ cells in rosacea and lupus erythematosus.
- Immunophenotyping may aid in the differential diagnosis of rosacea and lupus erythematosus when routine histology is inconclusive.

METHODS

After approval by the institutional review board, the surgical pathology database at the University of Michigan was searched for "rosacea" and "lupus erythematosus" between the years 2000 and 2012. Cases in which a differential diagnosis of "rosacea versus lupus" was rendered either by the clinician or the pathologist were eliminated because of diagnostic uncertainty. Cases of pustular or granulomatous rosacea were also excluded, as they are seldom confused with LE. Only facial lesions were included, as rosacea rarely occurs outside of the face. The final series consisted of 27 cases of rosacea and 30 cases of facial LE in which the diagnoses were confirmed by careful clinicopathologic correlation.

Microscopic review was conducted by 2 contributing authors blinded to the original diagnoses. Hematoxylin-eosin slides were evaluated for the presence or absence of the following: intraepidermal lymphocytes, necrotic epidermal keratinocytes, necrotic follicular epithelial cells, follicular plugging, perineural lymphocytic infiltrate, telangiectasia, fibrosis, Demodex infestation, and sebaceous hyperplasia. Alcian blue stain was performed to evaluate for dermal mucin (0, absent; 1+, scant; 2+, abundant). Periodic acid—Schiff (PAS) stain was performed to evaluate for basement membrane thickening (0, normal; 1+, slight/focal; 2+, conspicuous).

Formalin-fixed paraffin-embedded tissue sections from all cases were immunolabeled with CD4 (clone BC/1F6, BioCare Medical, Concord, CA), CD8 (clone BC/1A5, BioCare Medical, Concord, CA), CD25 (clone 4C9, Leica Biosystems, Newcastle, UK), and CD123 (clone 7G3, BD Biosciences, San Diego, CA) mouse antibodies using Envision+ (DAKO Corp, Carpinteria, CA) and diaminobenzidine as chromogen. Digital images were taken of at least 1 representative lymphoid aggregate in each case, in which the numbers of $CD4^+$, $CD8^+$, and $CD25^+$ cells were counted. The CD4:CD8 ratio was calculated using the corresponding CD4 and CD8 counts. The percentage of T cells representing Tregs was estimated by dividing the CD25 count by the CD4 count. The percentage of $CD123^+$ PDCs of the entire infiltrate was estimated in a semiquantitative manner from 0% to 100% in 10% increments. The presence of clusters consisting of more than 20 $CD123^+$ PDCs and intraepidermal $CD123^+$ PDCs were also noted.

Histologic features were compared between rosacea and LE by χ^2 tests. The CD4:CD8 ratios, CD25/CD4 percentages, and CD123 percentages were compared by 2-sample t tests. A P value of less than .05 was considered statistically significant.