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Utility of CD123 immunohistochemistry in differentiating lupus erythematosus from cutaneous T-cell lymphoma

(Running title: CD123 in lupus and cutaneous T-cell lymphoma)

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Abstract

Aims: Histopathologic overlap between lupus erythematosus and certain types of cutaneous T-cell lymphoma (CTCL) is well documented. CD123+ plasmacytoid dendritic cells (PDCs) are typically increased in lupus erythematosus, but have not been well studied in CTCL. We aimed to compare CD123 immunostaining and histopathologic features in these conditions.

Methods and Results: Skin biopsies of cutaneous lupus erythematosus (CLE, n=18), lupus erythematosus panniculitis (LEP, n=17), mycosis fungoides (MF, n=25) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL, n=9) were retrospectively reviewed and immunostained with CD123. Percentage, distribution, and clustering of CD123+ cells were compared between CLE and MF, and between LEP and SPTCL, using Chi-square and two-tailed t tests. A higher percentage of CD123+ cells was observed in CLE than MF ($p<0.01$), more frequently comprising ≥20% of the entire infiltrate ($p<0.01$) and forming clusters ($p<0.01$). Similarly, LEP showed a higher percentage of CD123+ cells than SPTCL ($p=0.01$), more frequently comprising ≥20% of the infiltrate ($p=0.04$) and forming clusters ($p=0.01$). Basal vacuolar change or dyskeratosis was observed in all CLE cases and in 48% cases of MF cases ($p=0.05$). Plasma cells were readily identified in 76% cases of LEP but in none of the SPTCL cases ($p=0.01$). Adipocyte rimming by lymphocytes, hyaline fat necrosis, and fibrinoid/grungy necrosis did not significantly differ between LEP and SPTCL. Dermal mucin also failed to distinguish between groups.

Conclusions: CD123 immunostaining is helpful in differentiating CLE from MF and LEP from SPTCL, but should be interpreted in conjunction with clinicopathologic features and other ancillary studies to ensure accurate diagnosis.

Keywords: CD123, cutaneous T-cell lymphoma, lupus erythematosus, mycosis fungoides, plasmacytoid dendritic cells, subcutaneous panniculitis-like T-cell lymphoma

Introduction

Histopathologic overlap between cutaneous/subcutaneous lupus erythematosus and cutaneous T-cell lymphoma (CTCL) is well recognized and may present a diagnostic challenge. Although mycosis fungoides (MF) is readily diagnosed when fully developed, classic features such as Pautrier microabscesses are often lacking in early cases.(1-3) Such cases may mimic various inflammatory dermatoses such as eczematous dermatitis, connective tissue disease, pigmented purpuric dermatosis, and lichen sclerosus.(4-6) Of these, cutaneous lupus erythematosus (CLE) may enter the differential diagnosis of MF when interface changes(1-3, 7-10) or dyskeratotic keratinocytes(2, 3, 8) are present. Conversely, some cases of CLE may show a robust lymphomatoid infiltrate at the dermoepidermal junction and around blood vessels, potentially raising concern for MF.(6, 10, 11)

Even more notoriously challenging is the distinction between lupus erythematosus panniculitis (LEP) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL).(12-19) Several authors have reported misdiagnosis of LEP as SPTCL and vice versa.(14, 15, 20, 21) Specifically, interface changes and other classic features of LEP have been reported in SPTCL.(13, 18, 22, 23)

The striking similarities of LEP and SPTCL have led some authors to propose that these entities may belong on a spectrum of T-cell dyscrasia.(12, 16) A European Organization for Research and Treatment of Cancer study group reported that 19% of the patients with SPTCL had an associated autoimmune disease, with one third of those having systemic lupus erythematosus.(15) These findings further support a possible link between LEP and SPTCL.

Plasmacytoid dendritic cells (PDCs), most commonly stained with CD123, are rarely present in normal skin.(24-26) The distribution and quantification of CD123+ PDCs have been studied in a variety of inflammatory dermatoses.(18, 26-33) Increased density and clustering of PDCs have been noted in all forms of lupus erythematosus(24, 26-28, 30, 31, 34, 35) including LEP.(18, 29, 36) In contrast, their density and distribution have been less rigorously studied in CTCL. Only 3 prior studies have examined PDCs in SPTCL, all of which found PDC clusters in significantly fewer cases of SPTCL than in LEP.(18, 29, 37) Another 2 studies have utilized the BDCA2/CD303 antibody to detect PDCs, in addition to other dendritic cell types, in various stages of MF and Sezary syndrome.(38, 39)

The goal of this study was to compare CD123 immunostaining and various histopathologic features in lupus erythematosus (CLE and LEP) and CTCL (MF and SPTCL).

Materials and Methods

After approval by the Institutional Review Board, the pathology database at University of Michigan was searched for skin biopsies diagnosed as CLE (discoid, subacute cutaneous, or systemic), LEP, MF, and SPTCL between years 2000 and 2017. An additional case of SPTCL was obtained from Tufts Medical Center. All cases were diagnosed originally based on clinicopathologic correlation, with supporting immunohistochemical and T-cell receptor (TCR) gene rearrangement studies as needed. Clinical data were obtained from electronic medical records.

Hematoxylin and eosin (H&E) stained sections of CLE and MF cases were evaluated for the following features: basal vacuolation with associated lymphocytes and/or dyskeratotic keratinocytes, Pautrier microabscesses, melanin incontinence, increased dermal mucin, and readily identifiable plasma cells. For LEP and SPTCL the following were evaluated: basal vacuolation with associated lymphocytes and/or dyskeratotic keratinocytes, increased dermal mucin, adipocyte "rimming" by lymphocytes, readily identifiable plasma cells, hyaline fat necrosis, and fibrinoid/grungy fat necrosis (fibrinoid necrosis containing karyorrhectic debris).

CD123 immunohistochemistry was performed on all cases. The majority of cases were immunostained at the University of Michigan research laboratory using the following protocol: 4-µm thick sections were deparaffinized and heat-induced epitope retrieval was performed using the Dako PT Link with a proprietary Tris-EDTA buffer pH 9 from Dako (FLEX retrieval solution, high pH). After blocking endogenous peroxidase activity, the slides were incubated for 120 minutes at room temperature with a mouse monoclonal CD123 antibody (7G3, BD Pharmingen, Franklin Lakes, New Jersey) and subsequently detected on the EnVision FLEX+ Mouse DAB detection system (Dako). A small subset of cases was immunostained at the time of original diagnosis using the same antibody on the BenchMark ULTRA slide staining platform (Ventana Medical Systems, Tucson, AZ) according to standard protocols validated in our clinical immunohistochemistry laboratory. Protein expression was detected using the ultraView Universal DAB Detection Kit (Ventana).

Plasmacytoid dendritic cells were identified by strong and crisp CD123 staining of small, round to oval cells outside of blood vessels. The percentage of CD123+ PDCs of the entire infiltrate was assessed semi-quantitatively from 0% to 100%. Clusters of CD123+ PDCs were defined as tight aggregates of ≥15 CD123+ PDCs. Subcutaneous location of PDC clusters and intraepidermal PDCs were additionally recorded. Other immunohistochemical findings were recorded from the original pathology reports.

Histopathologic and CD123 immunohistochemical findings were compared between groups: CLE vs. MF, and LEP vs. SPTCL. Chi-square and two-tailed t-tests were used for categorical and continuous data, respectively. A p-value of ≤ 0.05 was considered statistically significant.

Results

Eighteen CLE biopsies from 18 patients, 25 MF biopsies from 23 patients, 17 LEP biopsies from 14 patients, and 9 SPTCL biopsies from 9 patients were identified. Patients with CTCL (mean age, 66 years) were generally older than those with lupus erythematosus (mean, 45 years) ($p<0.01$). Female predominance was observed in the lupus group (male-to-female ratio, 1:2.5), whereas the reverse was seen the CTCL group (male-to-female ratio, 2:1). Anti-nuclear antibody serologies were available in a subset of cases and were positive in 9/11 CLE patients, 9/12 LEP patients, 0/3 MF patients, and 1/2 SPTCL patients. Follow-up data were available for 8 CLE patients and 11 LEP patients, none of whom developed lymphoma over a mean follow-up period of 4 and 5 years, respectively.

The histopathologic and immunohistochemical findings in CLE and MF are summarized in Table 1. Basal vacuolar changes and/or dyskeratotic cells were more frequently seen in CLE than in MF ($p=0.05$) (Fig 1A-B). Pautrier microabscesses were found exclusively in MF ($p<0.01$). Increased dermal mucin, melanin incontinence, and plasma cells did not show significant differences between these groups. The mean percentage of CD123+ PDCs was higher in CLE (21%; Fig 1C) than in MF (4%; Fig 1D) ($p<0.01$). These cells more frequently comprised ≥20% of the entire infiltrate ($p<0.01$) and formed clusters ($p<0.01$) in CLE (Fig 1E) compared to MF (Fig 1F). Intraepidermal CD123+ PDCs were common in both groups.

The histopathologic and immunohistochemical findings in LEP and SPTCL are summarized in Table 2. Plasma cells were readily identified only in LEP (Fig 2A) and not in SPTCL (Fig 2B) ($p=0.01$). All other examined histopathologic features failed to distinguish between groups (Fig 2C-D). The mean percentage of CD123+ PDCs was significantly higher in LEP (17%) than in SPTCL (2%) ($p=0.01$). About half of the LEP cases consisted of ≥20% CD123+ PDCs (Fig 2E), while none of the SPTCL cases did (Fig 2F) ($p=0.04$). The majority of LEP cases contained clusters of PDCs (Fig 2G), which was consistently absent in SPTCL (Fig 2H) ($p=0.01$). Intraepidermal CD123+ cells were similarly common in both groups. Nonspecific, weak and "fluffy" CD123 staining was noted in the subcutaneous fat in both LEP and SPTCL cases with significant fat necrosis (Fig 3). Such staining appeared to be located in histiocytes and/or extracellular matrix.

Additional immunohistochemical stains were performed on 2 CLE cases, 7 LEP cases, and all CTCL cases at the time of diagnosis. All examined lupus cases showed a normal T-cell immunophenotype except for 1 LEP case. This latter case displayed a reversed CD4:CD8 ratio (1:3) but otherwise classic histomorphologic features of LEP including vacuolar interface changes, hyaline fat necrosis, increased dermal mucin, and increased plasma cells. All MF and SPTCL cases revealed aberrant T-cell immunophenotypes.

Results of TCR gene rearrangement studies (performed at time of diagnosis) were available for a subset of MF, LEP, and SPTCL cases. A T-cell clone was identified in 4/5 (80%) MF cases, 0/5 (0%) LEP cases, and 4/4 (100%) SPTCL cases.

Discussion

Although most cases of CLE are readily distinguishable from MF, this differential diagnosis can be challenging at times. For example, mild basal vacuolar changes and occasional dyskeratotic keratinocytes in MF may raise consideration for CLE, whereas CLE with a robust lymphocytic infiltrate at the dermoepidermal junction may simulate epidermotropism in MF. Likewise, histopathologic overlap between LEP and SPTCL is well recognized(12-14, 16-19, 22, 23, 29) and has led to a proposed spectrum of subcutaneous T-cell dyscrasia encompassing both entities. As distinction between cutaneous/subcutaneous lupus erythematosus and CTCL is crucial for guiding appropriate clinical workup and treatment, we aimed to assess the utility of CD123 immunostain in addition to various histopathologic features in differentiating these entities.

Plasmacytoid dendritic cells are a subtype of dendritic cells that produce type I interferons (alpha/beta). These cells can be highlighted by immunohistochemistry for CD123 (interleukin-3 receptor α chain) or BDCA-2/CD303. The quantity and distribution of PDCs vary in different inflammatory and neoplastic conditions. Increased number and clustering of PDCs have been described as common findings in CLE(24, 26-28, 30, 31, 34, 35) and LEP,(18, 29) and these cells are thought to play an important role in the pathogenesis of lupus erythematosus.(26)

Only 2 previous studies have assessed the quantity and distribution of PDCs in MF, neither of which has compared their results with CLE or other inflammatory dermatoses.(38, 39) Schwingshackl *et al* noted an increased number of single and loosely aggregated PDCs in MF compared with normal skin, and concluded that their number was dependent on the intensity of the infiltrate.(38) Pileri *et al* also observed rare loose aggregates of PDCs in MF, and that their number was significantly higher in stage IIB compared to stage IA/B disease.(39) While these results offered insight into the microenvironment of MF, the utility of CD123+ PDCs in distinguishing MF from CLE remained to be investigated.

Of all histopathologic parameters compared between CLE and MF, basal vacuolar changes and dyskeratotic cells were of particular interest given their potential to masquerade MF as an interface dermatitis.(6, 8, 9) In our cohort, although these changes were more frequently seen in CLE, the difference barely reached statistical significance ($p=0.05$). The specificity of these changes was poor (52%), as nearly half of our MF cases showed these features. Other series have reported interface changes in 59-76% of MF cases.(2, 3) These findings should caution pathologists against using basal vacuolation and dyskeratotic keratinocytes alone to exclude a diagnosis of MF. Although the presence of Pautrier microabscesses was highly specific (100%) for MF, its sensitivity was low (48%). This is in keeping with previous reports of Pautrier microabscesses in less than half of MF cases.(2, 3, 7, 40) Plasma cells are commonly present in connective tissue diseases including lupus erythematosus. Although less well described in MF, plasma cells have been reported in 9% of MF/Sezary syndrome cases.(41) We found modest amount of plasma cells in 24% of our MF cases, where they were readily identified and failed to distinguish between CLE and MF. Lastly, both increased dermal mucin and melanin incontinence (a common consequence of interface dermatitis) were slightly more common in CLE, but the associations fell short of statistical significance ($p=0.06$). Together, these findings indicate that histopathologic distinction between CLE and MF has its limitations, and ancillary tools are needed in challenging cases.

The percentage of PDCs and their tendency to form clusters in our CLE cases was similar to that reported previously.(28, 30, 31, 35) We found that a cut-off of 20% PDCs separated CLE and MF reasonably well. Furthermore, presence of PDC cluster(s) was both highly sensitive (94%) and specific (100%) for the diagnosis of CLE when compared with MF, rendering CD123 a superior diagnostic tool in distinguishing these conditions. The percentage of CLE cases with intraepidermal CD123+ cells (100%) was higher than reported previously,(35) yet this feature was also common in MF and thus was not helpful.

With regard to the comparison between LEP and SPTCL, the only reliable discriminative histopathologic feature in our study was the presence of readily identifiable plasma cells, seen exclusively in LEP. Other histopathologic features deemed helpful in previous studies failed to show significant differences in ours. Hyaline fat necrosis was more common in LEP but was observed in less than half of these cases. Fibrinoid/grungy necrosis, previously reported to be supportive of SPTCL,(29) was seen at almost equal frequency in both groups. Adipocyte rimming by atypical lymphocytes was another useful feature according to previous reports.(18, 29) In our experience, however, evaluation for lymphocytic atypia tends to be subjective, as it was not uncommon to find slightly hyperchromatic and irregular lymphocytes in LEP. We therefore assessed for adipocyte rimming by lymphocytes regardless of the degree of atypia, and found no association with either group. While the limited utility of histopathologic features in this differential diagnosis may be in part attributable to the small sample size of SPTCL in this cohort, our findings again highlight a significant need for additional tools to help distinguish these conditions.

The presence of PDCs has been examined in SPTCL in comparison with LEP in 3 previous studies. All of these studies found that PDC clusters were more common in LEP but were also present in a smaller subset of SPTCL cases.(18, 29, 37) This feature must therefore be interpreted in the context of clinical, histopathologic, immunophenotypic and molecular findings. As none of our SPTCL cases showed ≥20% PDCs or PDC clusters, we consider these findings highly specific for a diagnosis of LEP. Of note, we observed that cases with fat necrosis tended to show weak, “fluffy” CD123 staining of histiocytes and/or extracellular matrix in the subcutis. Such nonspecific staining could lead to overinterpretation of PDC clusters. Recognition of the strong and crisp staining of true PDCs, which are typically small and round to oval in shape, would avoid this pitfall. Also, a strict requirement of ≥15 touching CD123+ PDCs in a PDC cluster will likely improve the specificity of this finding.

Interestingly, 1 LEP case demonstrated a reversed CD4:CD8 ratio. While this case was classified as LEP based on a history of systemic lupus erythematosus and classic histopathologic features, CD123+ PDCs were notably absent. We therefore speculate that the loss of PDCs could represent an early sign of progression on the LEP-SPTCL spectrum. Unfortunately this patient was lost to follow-up a year after the biopsy, precluding further assessment.

A major limitation of this study is the small sample size, especially of the SPTCL group, due to relative rarity of this condition and over-representation of consult cases from outside facilities (hence limited access to tissue blocks). Another limitation is that only a small subset of cases has been studied by TCR gene rearrangement at the time of diagnosis; however, lack of evidence of progression to lymphoma in patients diagnosed with CLE and LEP provided additional support for their diagnoses.

In conclusion, our study confirms that CD123 immunostain is a useful ancillary tool in differentiating CLE from MF, and LEP from SPTCL. In particular, CD123+ PDC clusters are highly specific for CLE and LEP in these contexts. Although CD123 immunohistochemistry shows superior sensitivity and specificity compared to most histopathologic features examined in this study, it should be interpreted in conjunction with clinical history, histopathologic examination, other immunohistochemical findings, and gene rearrangement studies (when necessary) to ensure accurate diagnosis.

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S. J. T. Chen and M. P. Chan designed the research study. S. J. T. Chen, J. Y. Tse and M. P. Chan obtained the data. S. J. T. Chen and M. P. Chan analysed the data. S. J. T. Chen and M. P. Chan wrote the paper. All authors performed critical review of the manuscript.

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Figure Legends

Figure 1. Selected histopathologic features and CD123 immunostaining in cutaneous lupus erythematosus (CLE) and mycosis fungoides (MF). A, An example of CLE shows an interface dermatitis with aggregates of lymphocytes at the dermoepidermal junction (hematoxylin and eosin [H&E], ×200). B, An example of MF shows lymphocyte tagging and mild vacuolation of the basal layer (H&E, ×200). C and D, This case of CLE demonstrates many CD123+ plasmacytoid dendritic cells (PDCs) constituting 30% of the entire inflammatory cell infiltrate and forming prominent clusters (CD123 immunohistochemistry, ×40 [C] and ×100 [D]). E and F, This example of MF shows fewer CD123+ PDCs constituting 10% of the entire infiltrate without clustering (CD123 immunohistochemistry, ×40 [E] and ×100 [F]).

Figure 2. Selected histopathologic features and CD123 immunostaining in lupus erythematosus panniculitis (LEP) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL). A, Plasma cells and adipocyte rimming by lymphocytes in a case of LEP (hematoxylin-eosin [H&E], ×400). B, Fibrinoid/grungy necrosis in LEP (H&E, ×200). C, A subcutaneous lymphoid infiltrate in SPTCL lacks plasma cells (H&E, ×400). D, Increased dermal mucin in a case of SPTCL (H&E, ×200). E and F, An example of LEP contains 40% CD123+ plasmacytoid dendritic cells (PDCs) with formation of several clusters, including some in the subcutaneous fat (CD123 immunohistochemistry, ×20 [E] and ×200 [F]). G and H, This case of SPTCL shows a few scattered CD123+ PDCs constituting less than 10% of the infiltrate, without formation of clusters (CD123 immunohistochemistry, ×20 [G] and ×200 [H]).

Figure 3. Nonspecific CD123 immunostaining. An example of subcutaneous panniculitis-like T-cell lymphoma with prominent fat necrosis demonstrates weak and “fluffy” CD123 staining in the subcutaneous fat, mostly within histiocytes (solid arrows). This type of nonspecific staining contrasts with the strong and crisp staining of the small ovoid plasmacytoid dendritic cells (empty arrows) (CD123 immunohistochemistry, ×400).

Tables

Table 1. Comparison of clinical, histopathologic, and immunohistochemical (CD123) findings in cutaneous lupus erythematosus (CLE) and mycosis fungoides (MF)

	CLE (n=18)	MF (n=25)	p-value
Mean age (years)	47	70	**<0.01**
Male-to-female ratio	1:2.6	3:1	**0.04**
Basal vacuolar changes or dyskeratosis	18 (100%)	12 (48%)	**0.05**
Pautrier microabscesses	0 (0%)	12 (48%)	**<0.01**
Increased dermal mucin	13 (72%)	8 (32%)	0.06
Melanin incontinence	11 (61%)	6 (24%)	0.06
Readily identifiable plasma cells	7 (39%)	6 (24%)	0.37
Mean % CD123+ cells	21%	4%	**<0.01**
≥20% CD123+ cells	12 (67%)	3 (12%)	**<0.01**
Intraepidermal CD123+ cells	18 (100%)	19 (76%)	0.40
CD123+ cluster(s)	17 (94%)	0 (0%)	**<0.01**

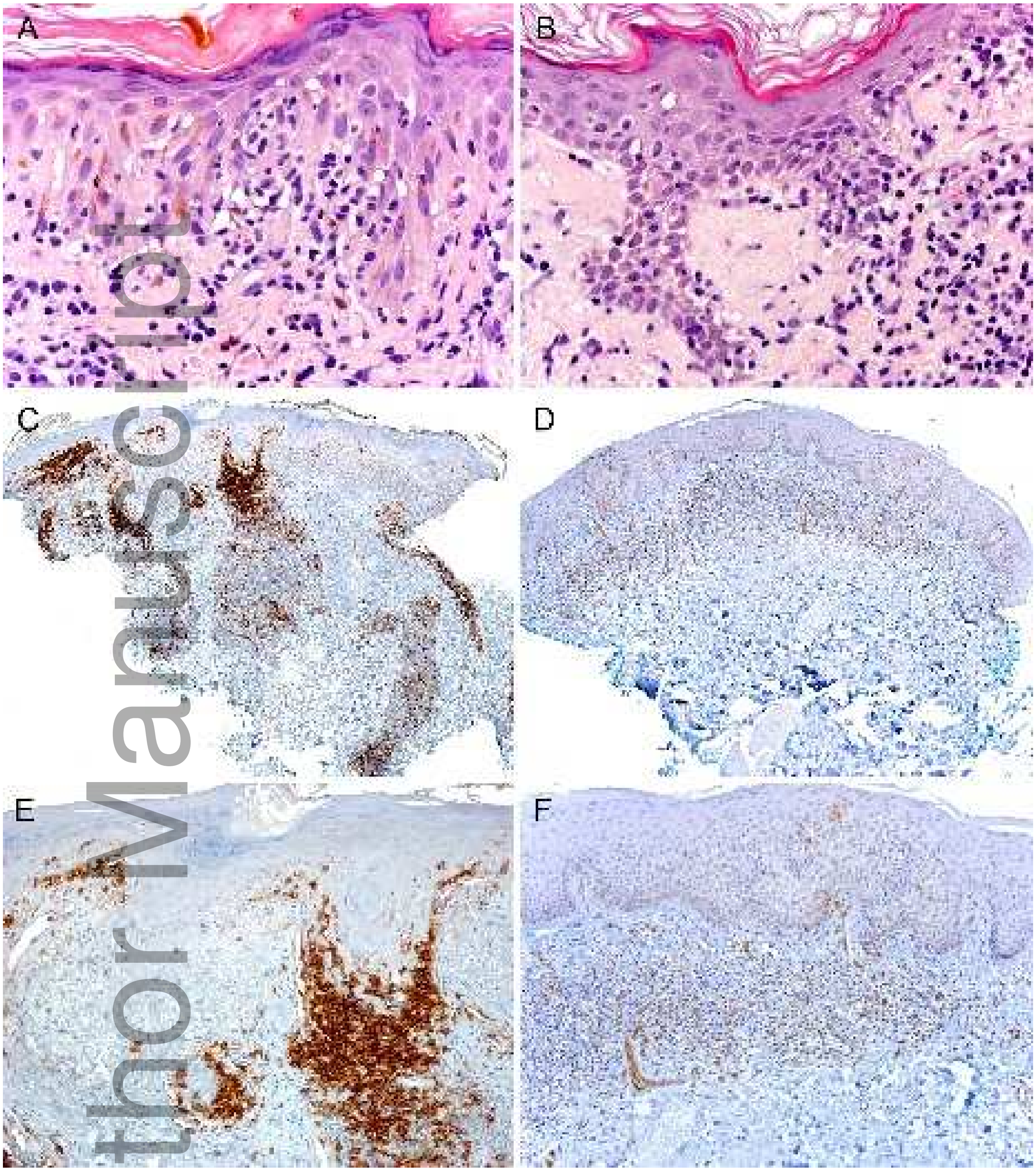
Boldface indicates statistical significance.

Table 2. Comparison of clinical, histopathologic, and immunohistochemical (CD123) findings in lupus erythematosus panniculitis (LEP) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

	LEP (n=17)	SPTCL (n=9)	p-value
Mean age (years)	43	54	0.20
Male-to-female ratio	1:2.4	1:1.3	0.65
Basal vacuolar changes or dyskeratosis	10/16 (63%)[a]	2/7 (29%)[a]	0.29
Increased dermal mucin	12 (71%)	4/7 (57%)[a]	0.70
Adipocyte rimming by lymphocytes	12 (71%)	8 (89%)	0.60
Readily identifiable plasma cells	13 (76%)	0 (0%)	**0.01**
Hyaline fat necrosis	8 (47%)	1 (11%)	0.14
Fibrinoid/grungy necrosis	5 (29%)	3 (33%)	0.88
Mean % CD123+ cells	17%	2%	**0.01**
≥20% CD123+ cells	8 (47%)	0 (0%)	**0.04**
Intraepidermal CD123+ cells	4/16 (25%)[a]	2/7 (29%)[a]	0.86
CD123+ cluster(s) in any location	12 (71%)	0 (0%)	**0.01**
CD123+ cluster(s) in fat	7 (41%)	0 (0%)	0.06

[a]Absence of epidermis and/or dermis precluded evaluation of these features in some cases.

Boldface indicates statistical significance.



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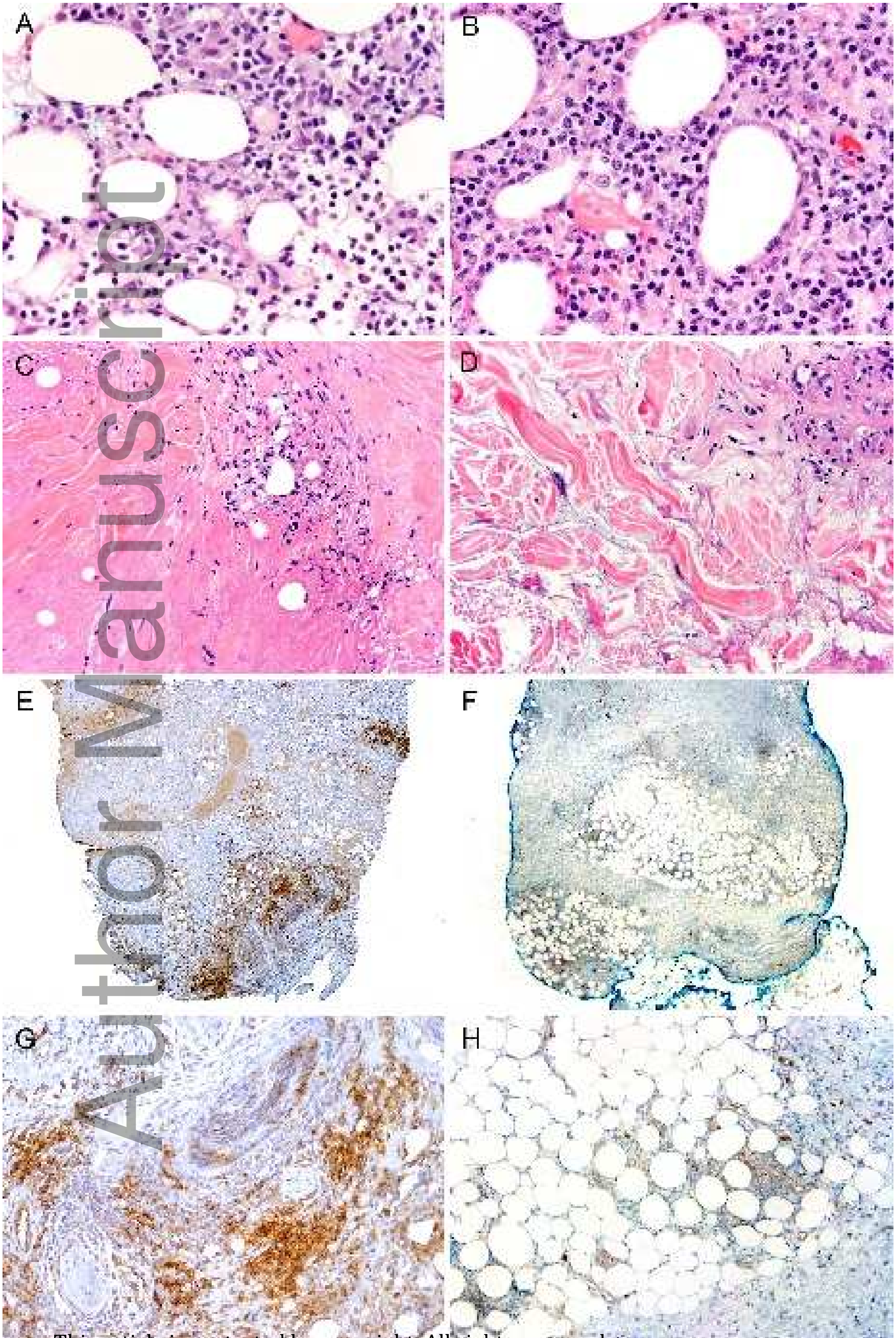

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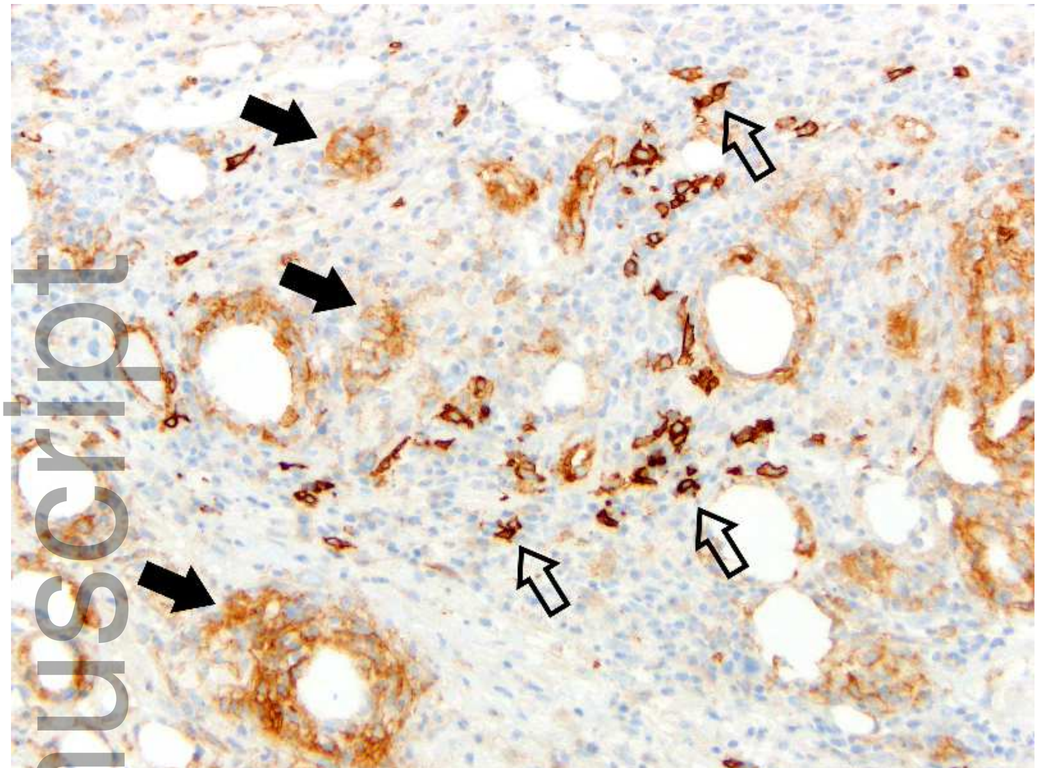

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