Cutaneous Pseudolymphoma

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KEYWORDS

- Cutaneous pseudolymphoma • T-cell • B-cell • Borreliosis • Tattoo • Histology

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Key Points

- Cutaneous pseudolymphoma (PSLs) are a heterogeneous group of lymphocyte-rich infiltrates, simulating clinically and/or histologically cutaneous lymphoma.
- Numerous causative agents can induce PSLs.
- Clinicopathologic correlation is essential to achieve the correct diagnosis.
- PSLs can be split based on clinical and/or histologic presentation into 4 groups.

ABSTRACT

The term, *cutaneous pseudolymphoma (PSL)*, refers to a group of lymphocyte-rich infiltrates, which either clinically and/or histologically simulate cutaneous lymphomas. Clinicopathologic correlation is essential to achieve the final diagnosis in cutaneous PSL and to differentiate it from cutaneous lymphomas. A wide range of causative agents (eg, *Borrelia*, injections, tattoo, and arthropod bite) has been described. Based on clinical and/or histologic presentation, 4 main groups of cutaneous PSL can be distinguished: (1) nodular PSL, (2) pseudo–mycosis fungoides, (3) other PSLs (representing distinct clinical entities), and (4) intravascular PSL. The article gives an overview of the clinical and histologic characteristics of cutaneous PSLs.

OVERVIEW

DEFINITION

Cutaneous PSL refers to a group of skin diseases, which are defined as benign lymphoproliferative processes that clinically and/or histologically simulate cutaneous lymphomas. A wide range of causative agents (**Box 1**) has been described. Nevertheless a causative factor for PSL can often not be found. Those cases are referred to as idiopathic PSL.

CLASSIFICATION

Various approaches have been proposed to categorize cutaneous PSL, for example, according to the cause, the predominating component in the lymphocytic infiltrate (T-cell, B-cell, or mixed), or distinct clinical features (reviewed by Rijlaarsdam and Willemze,[1] Ploysangam and colleagues,[2] and Gilliam and Wood[3]). In daily work, clinicians or pathologists encountering infiltrates suspicious as a PSL cannot recognize the cause and the phenotype at first glance without further diagnostic work-up. Moreover, the composition of the infiltrate is determined mostly by genetic and immunologic factors of the host rather than the causative agent per se, because the same agents can in many instances induce B-cell PSL (B-PSL) and T-cell PSL (T-PSL) as well.

From a practical point of view, cutaneous PSL can be split into 4 main groups based on clinical and/or histologic presentation:

1. Nodular PSL: solitary or multiple nodule(s), which resemble clinically and histologically lymphoma

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> **Box 1**
> **Causes of pseudolymphoma**
>
> Infectious agents
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> Spirochetal bacteria (*Borrelia* species and *Treponema pallidum*), viruses (eg, herpesvirus species, *Molluscipoxvirus*, and HIV), parasites (eg, *Sarcoptes* mites)
>
> Foreign agents
>
> Tattoo dyes, injected vaccination, or allergen extracts for hyposensitization, piercing)
>
> Other
>
> Insect bites, drugs, and photosensitivity

2. Pseudo–mycosis fungoides (pseudo-MF): mimics mycosis fungoides predominately on histologic grounds
3. Other PSLs: distinct clinical entities, for example, acral papular angiokeratoma of childhood
4. Intravascular PSL

In addition, there are numerous infectious and noninfectious conditions characterized by a lymphocyte-rich infiltrate, which, therefore, are prone to be misinterpreted as cutaneous lymphoma primarily on histologic grounds.

DIAGNOSTIC APPROACH

The clinical presentation of cutaneous PSL ranges from solitary nodule, clustered, or disseminated papules to erythroderma.[2,4] The histologic analysis plays a crucial role in the diagnostic approach to cutaneous PSL. Different infiltrate patterns (nodular vs epidermotropic infiltrates), the size of the lymphocytes (mostly small, occasionally medium-sized and large cells), immunophenotype (T cell vs B cell, CD4 vs CD8, and CD30) can be distinguished. Molecular studies for clonality and infectious agents, especially *Borrelia burgdorferi*, are adjunctive diagnostic tools. It is important to emphasize that the detection of a clonal T-cell or B-cell population per se does not indicate the presence of malignant lymphoma. Moreover, some PSL cases have been reported to harbor clonal T cells or B cells.[5–8] Thus, the histologic as well as the molecular findings always need to be interpreted in synopsis with the clinical context, that is, the clinicopathologic correlation is essential to achieve the final diagnosis.

The diagnostic work-up includes the medical history (in particular, exposure to arthropods, allergens, and exogenic material and drugs) and physical examination, including palpation of lymph nodes. Moreover, examination of peripheral blood (differential blood count and serology for infectious agents, especially *Borrelia burgdorferi*, syphilis, and HIV – depending on the infiltrate type) is recommended. Because PSLs represent benign lymphocytic proliferations without the potential for extracutaneous spread, staging examination generally seems to be not indicated. Nevertheless, a clear allocation to cutaneous PSL and a safe exclusion of lymphoma (primary or secondary cutaneous) is often only possible in knowledge of the clinical behavior. Therefore, staging procedures (CT or PET-CT) should be considered, especially in cases of unusual manifestation (eg, multiple nodular lesions, monotypic expression of immunoglobulin (Ig) light chains, detection of T-cell or B-cell clonality, or other inconsistent or unexpected histologic, phenotypic, or genotypic findings).

CLINICAL COURSE AND TREATMENT

The course of cutaneous PSL is variable. Some lesions show regression after biopsy, but many persist over several months or even years. Recurrences can be observed particularly after re-exposure to the inducing agent in cases induced by drugs or allergens. Progression of PSL has been reported but is a rare event, if it exists at all.[9]

If a causing agent has been identified, it should be removed, if possible. In general, solitary lesions can be treated by complete surgical excision. Alternative treatment options are topical or intralesional corticosteroids and cryotherapy. Especially in tattoo-induced PSL, laser treatment has been reported effective.[10] If those therapeutic approaches are not possible or successful, radiation therapy may be considered. In patients with multiple PSL lesions, in particular those with idiopathic multifocal PSL, systemic corticosteroids or intralesional or systemic interferon alpha[11] or oral hydroxychloroquine can be used.[12] Avoidance of re-exposure to the inducing agent (ie, vaccines, allergen injection, other drugs, *Hirudo medicinalis* treatment, acupuncture, and tattoo) is the most important step to preventing persistence and recurrence of PSL.

NODULAR PSEUDOLYMPHOMA

Nodular PSL represents one of the most common forms of PSL. It is characterized by solitary or multiple nodules, simulating cutaneous T-cell or B-cell lymphomas on clinical and histologic grounds. Based on histology, nodular PSL can be classified according to the predominant lymphocytic subset into B-cell, T-cell, and mixed (T-cell/B-cell) PSL.[2,4]

This classification is somewhat artificial because B-PSL always contains T-cells and vice versa.

CUTANEOUS B-CELL PSEUDOLYMPHOMA

B-PSL is often also referred as lymphocytoma cutis or cutaneous lymphoid hyperplasia.

Clinical Findings

The localized form of B-PSL presents with a solitary nodule, measuring up to 4 cm in most of the cases. One-third of the patients develop multiple lesions (generalized form) either aggregated in clusters (agminated form) or as disseminated papules (miliarial form).

The face, especially the nose and the cheeks; the upper trunk; and the arms are the most commonly involved sites (**Fig. 1**A). A male-to-female ratio of 3:1 has been described.[13] Approximately two-thirds of patients with B-PSL are under the age of 40 years and less than 10% are children and adolescents[14] (**Table 1**).

Histology

Nodular B-PSL is characterized by a dense nodular infiltrate, predominantly located in the reticular dermis and occasionally extending into the superficial parts of the subcutis (see **Fig. 1**B). The infiltrate is mostly composed of small lymphocytes with chromatin dense nuclei and reactive germinal centers (see **Fig. 1**C)

containing tingible body macrophages. The lymphocytes do not show significant nuclear atypia. There is an admixture of diffusely scattered plasma cells. Sometimes admixed eosinophils and a granulomatous component can be observed. In a majority of B-PSL plasmacytoid dendritic cells (CD123$^+$) are found, arranged in clusters with close vicinity to T cells and plasma cells.[15,16] There is an admixture of a variable number of T cells, which usually account for less than 30% of the infiltrate (see **Table 1**).

Immunohistochemistry and Molecular Diagnostics

The majority of the infiltrate is represented by CD19$^+$, CD20$^+$, CD79a$^+$, and PAX-5$^+$ B cells. The cells in the reactive follicles express bcl-6 (see **Fig. 1**D) and are negative for bcl-2 (see **Fig. 1**E). The small B cells in the interfollicular area express bcl-2 but are negative for bcl-6. The networks of CD21$^+$ follicular dendritic cells (FDCs) are sharply demarcated and regularly structured (see **Fig. 1**F). In Ki-67 or MIB-1 stain, the proliferative activity is elevated and mainly confined to the germinal centers. With a few exceptions, the expression of Ig light chains kappa and lambda by plasma cells are polytypic (immunohistochemistry or in situ hybridization) and no monoclonal rearrangement of Ig heavy chain genes by polymerase chain reaction (PCR) or Southern blot (see **Table 1**) is found.
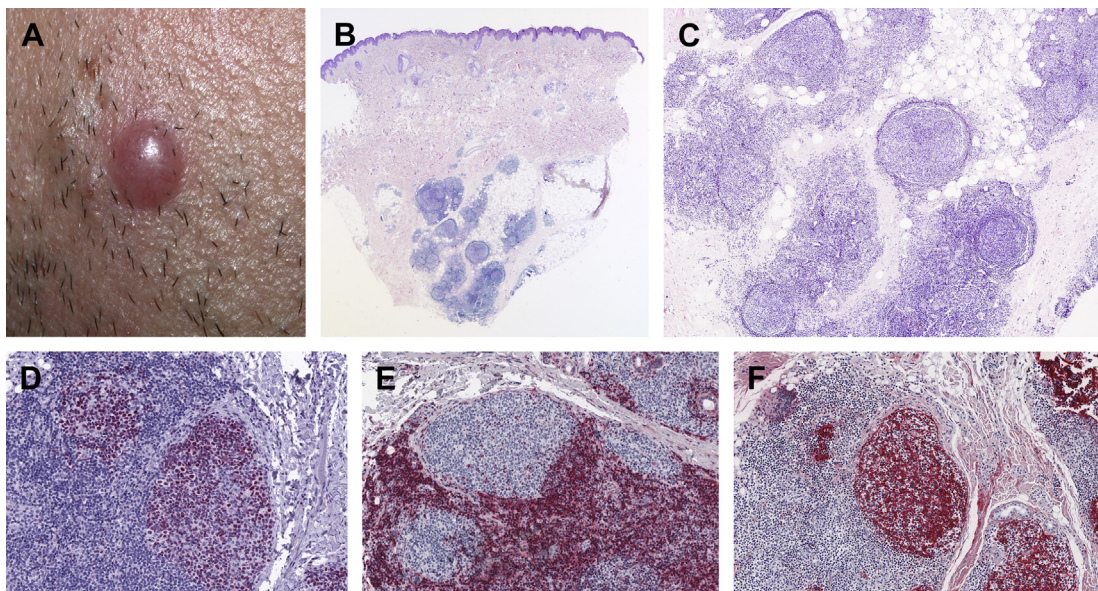
Fig. 1. B-PSL. (*A*) Erythematous nodule on the cheek. (*B*) Dense nodular infiltrate encompassing the deep dermis and superficial parts of the subcutis (hematoxylin-eosin, ×20). (*C*) Reactive germinal centers of different size (hematoxylin-eosin, ×100). The cells in reactive follicles express bcl-6 (*D*) (×200) and are negative for bcl-2 (*E*) (×200). (*F*) The networks of CD21$^+$ FDCs are sharply restricted to the germinal centers (×200).

Table 1
Clinical and histologic characteristics of B-cell pseudolymphoma

Clinical Characteristics	Histologic Characteristics	Immunohistochemistry
Male:female ratio 3:1	Nodular infiltrate in the dermis and superficial parts of subcutis	
75% <40 y	Small B cells, no nuclear atypia	$CD5^-$, $CD20^+$, $CD23^-$, $CD43^-$
Face (especially nose and cheeks), upper trunk, arms	Reactive germinal centers	Follicle centers: $bcl2^-$, $bcl6^+$, well defined and regular structured networks of $CD21^+$ FDCs, elevated Ki-67 rate mostly confined to the germinal centers
	Tingible body macrophages	$CD68^+$
	Scattered plasma cells	$CD79a^+$, $CD138^+$, no light chain restriction (kappa, lambda)
	Sometimes eosinophils	
	Admixed T cells at variable degree (commonly <30%)	$CD3^+$, $CD4^+$, and $CD8^+$
	Small clusters of plasmacytoid dendritic cells	$CD123^+$

Differential Diagnoses

The differential diagnosis of B-PSL primarily includes primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) or their nodal or other extranodal counterparts presenting with secondary cutaneous infiltrates (**Table 2**).

PCMZL presents with nodular infiltrates in the reticular dermis and superficial subcutis.[17] In comparison with B-PSL, the plasma cells in PCMZL are

Table 2
Differential diagnosis of B-cell pseudolymphoma

	B-Cell Pseudolymphoma	Primary Cutaneous Marginal Zone Lymphoma	Primary Cutaneous Follicle Center Lymphoma
Gender (female:male)	3:1	1:2	1:1.5
Age (y)	75% < 40	55	51
Localization	Face > upper trunk > arms	Upper trunk > upper arms > face/head	Head/face > upper trunk
Histology	Dermal/superficial subcutis, reactive germinal centers, tingible body macrophages, scattered plasma cells	Dermal/superficial subcutis, reactive germinal centers can be found, plasma cells in the periphery of the infiltates and near by the epidermis	Dermal/superficial subcutis, neoplastic irregular germinal centers of different size (CAVEAT: not found in diffuse type)
Immuno-histochemistry	$CD20^+$; reactive germinal centers ($bcl-2^-$, $bcl-6^+$); high proliferative activity in geminal centers (Ki-67 $^+$ or MIB-1$^+$), sharply restricted networks of FDCs ($CD21^+$)	Tumor cells: $CD20^+$ $bcl-2^+$; $bcl-6^-$, $CD5^-$, $CD10^-$, $CD43^-$; reactive germinal centers ($bcl-2^-$, $bcl-6^+$)	Tumor cells: $CD20^+$, $bcl-6^+$; $bcl-2^-$ (90%); neoplastic germinal centers ($bcl-2^-$, $bcl-6^+$); proliferating cells (Ki-67$^+$ or MIB-1$^+$) are scattered; irregular networks of FDCs ($CD21^+$)
Molecular diagnostics	Polytypic light chains, polyclonal IgH	Monoclonal IgH (up to 90%)	Monotypic light chain (85%) monoclonal IgH (60%–70%)

usually more prominent and found in sheets, particularly at the periphery of the infiltrates and near by the epidermis.[18] The most important histopathologic diagnostic finding is the monotypic expression of Ig light chains (lambda or kappa) in PCMZL with a ratio of at least 5:1 or 10:1. The presence and number of eosinophils are not useful findings for discrimination between both entities. In 50% to 70% of PCMZL a clonal B-cell population can be detected and used as an additional diagnostic hint.

PCFCL is characterized by the predominance of centrocyte-like differentiated tumor cells arranged in large neoplastic follicles. Tingible body macrophages are only found in small minority of PCFCL.[19] Furthermore, a low proliferative activity in the neoplastic follicles of PCFCL is a characteristic finding, which contrasts with the high proliferative activity in the reactive germinal centers of B-PSL. The networks of CD21^{+} FDCs in PCFCL are irregular and disrupted in contrast to the sharply demarcated and regularly structured networks in B-PSL. A clonal B-cell population is detectable in the majority of PCFCL by PCR or Southern blot. A vast majority of PCFCLs do not show expression of bcl-2 by the neoplastic centrocyte-like differentiated cells. Therefore, the expression of bcl-2 is not of diagnostic value for the discrimination of PCFCL from B-PSL. In cases of expression of bcl-2 by the centrocyte-like tumor cells, secondary cutaneous infiltration by a nodal FCL has to be considered because nodal FCL exhibits expression of bcl-2 by the neoplastic cells due to underlying t(14;18) translocation in a majority of the cases.

Other differential diagnoses include cutaneous infiltrates of B-cell chronic lymphocytic leukemia (CD5^{+}, CD23^{+}, and CD43^{+}) or small cell lymphocytic lymphoma, although the latter one do usually not show reactive germinal centers.[20,21]

Clonality studies in B-PSL are of limited value in the distinction from cutaneous B-cell lymphomas because approximately 10% to 20% of PSL harbor a clonal B-population.[6,22] In some studies, even a higher percentage of cases of clonal B cells was detected in nodular PSL.[23] In lesions with subtle infiltrates, pseudoclonality should always be ruled out because it represents a diagnostic pitfall.[24]

BORRELIA-ASSOCIATED B-CELL PSEUDOLYMPHOMA

Lymphocytoma cutis and lymphadenosis cutis benigna often are synonymously used. The diagnosis is based on histology, the clinical context (history of tick bite and localization at predilection site), serologic findings, and/or detection of Borrelia burgdorferi species DNA in the tissue by PCR.

Clinical Findings

Approximately 1% of clinically apparent Borrelia species infections manifest as B-PSL. A slight female preponderance is observed in some but not all studies.[8] This form of B-PSL has more often been reported in white than in African Americans. Borrelia-associated B-PSL affects typically children and occurs in early adulthood but may be seen in all age groups.[14]

Usually Borrelia-associated B-PSL presents with a solitary red to violaceous nodule. In 10% to 15% of the patients, multifocal skin lesions can be observed. The earlobes (Fig. 2A), nipples, and scrotum are the predilection sites, but the trunk and extremities may also be involved.[8]

Histology

A dense dermal nodular infiltrate of small B cells and reactive germinal centers is found[8] (see Fig. 2B). In Borrelia-associated B-PSL, the germinal centers tend to be larger and confluent with only a small or completely lost mantle zone[8] (see Fig. 2B). A lack of polarization is found in up to 20% of the cases.[8,22] Due to the confluence of the large germinal centers, the lesions resemble the neoplastic follicles in PCFCL (follicular growth pattern).[22] Tingible body macrophages are found in all cases (see Fig. 2C). Plasma cells are almost always present and found particularly at the periphery of the infiltrates. Eosinophils are often admixed. Colli and colleagues[8] provide an overview of histologic findings in Borrelia-associated PSL, summarized in Box 2.

In rare cases of so-called large cell lymphocytoma associated with Borrelia infection, a predominance of large blasts, resembling centroblasts and immunoblasts, are found simulating the findings in large B-cell lymphoma.[25] Therefore, those cases are prone to be misdiagnosed as diffuse large B-cell lymphoma.

Immunohistochemistry and Molecular Diagnostics

Immunohistochemically, the typical findings of B-PSL are found (discussed previously). Molecular studies for the detection of Borrelia burgdorferi species DNA by PCR are a helpful adjunctive diagnostic tool with a sensitivity of approximately 70%.[26] In a vast majority of the cases of Borrelia-associated B-PSL, molecular studies show a polyclonal rearrangement of IgH genes, but detection of monoclonal B cells has been observed and, therefore, does not exclude this diagnosis.[8] The
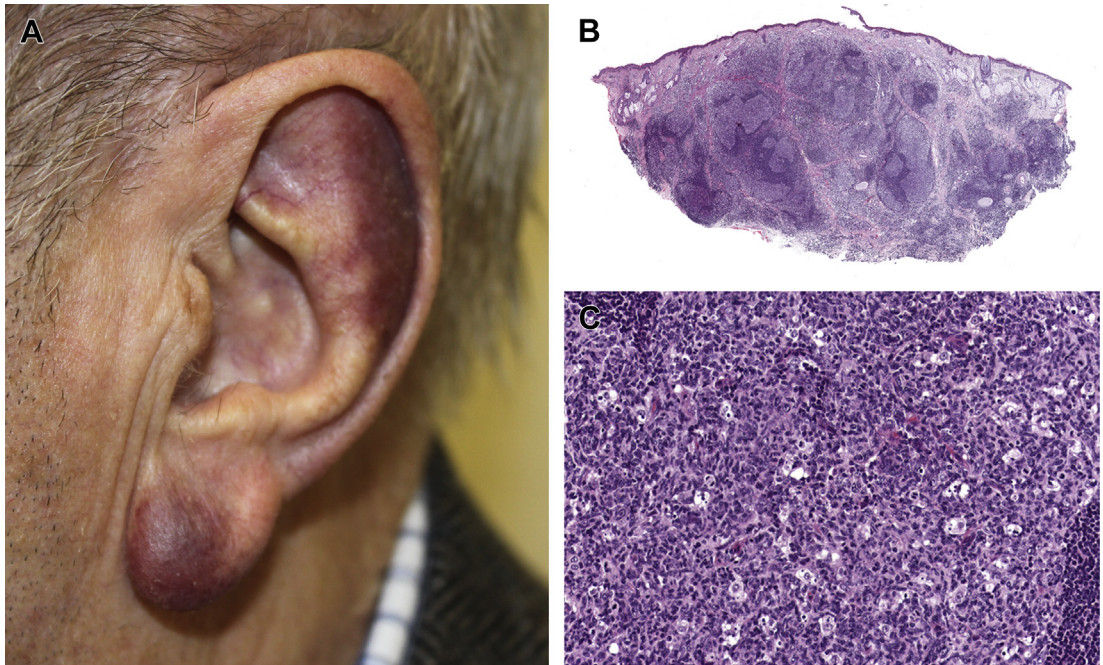
Fig. 2. *Borrelia*-associated B-PSL. (*A*) Blue nodule at the earlobe. (*B*) Dense dermal nodular infiltrate with reactive germinal centers with small or completely lost mantle zones (hematoxylin-eosin, ×20). (*C*) Germinal centers with multiple tingible body macrophages (hematoxylin-eosin, ×200).

light chains are predominately polyclonal, but a few cases of monoclonal Ig light chains have been reported.[27]

Laboratory Tests

Serology shows antibodies against *Borrelia burgdorferi* species with variable pattern, that is, IgG and/or IgM may be elevated. Nevertheless, cases of negative serologic findings can be seen[8] so that negative serology does not exclude *Borrelia*-induced B-PSL.

Box 2
Histologic findings in *Borrelia*-associated B-cell pseudolymphoma

Mostly the entire dermis is involved

Grenz zone, epidermal component in approximately 10%

High number of admixed T cells

Germinal centers (77%), often large and confluent

Absence of mantle zone (88%)

Tingible body macrophages (100%)

Plasma cells (99%)

Eosinophils (84%)

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PSEUDOLYMPHOMA T-CELL AND MIXED PSEUDOLYMPHOMA

Nodular T-PSL is characterized by a dense dermal T-cell–rich nodular infiltrate, which is accompanied by variable number of B cells, which can reach up to 30% of the entire infiltrate.[28] Mixed forms of PSL contain an equal number of T cells and B cells. All causes identified in B-PSL can also be found as underlying stimuli in T-PSL and mixed PSL. Most cases, however, are without known cause and, therefore, are referred to as idiopathic T-PSL or mixed PSL.

Clinical Findings

T-PSL and mixed PSL usually present with a solitary or multiple red to violaceous nodules similar to B-PSL (**Fig. 3**A). There are no detailed epidemiologic data on the prevalence of T-PSL or mixed PSL. They affect patients of both genders and all age and ethnic groups.

Histology

In most cases, a dense nodular infiltrate in the entire dermis and in the superficial parts of the subcutis is found (see **Fig. 3**B). The infiltrate is predominantly composed of small lymphocytes with chromatin dense nuclei. A variable number of slightly enlarged lymphocytes with chromatin
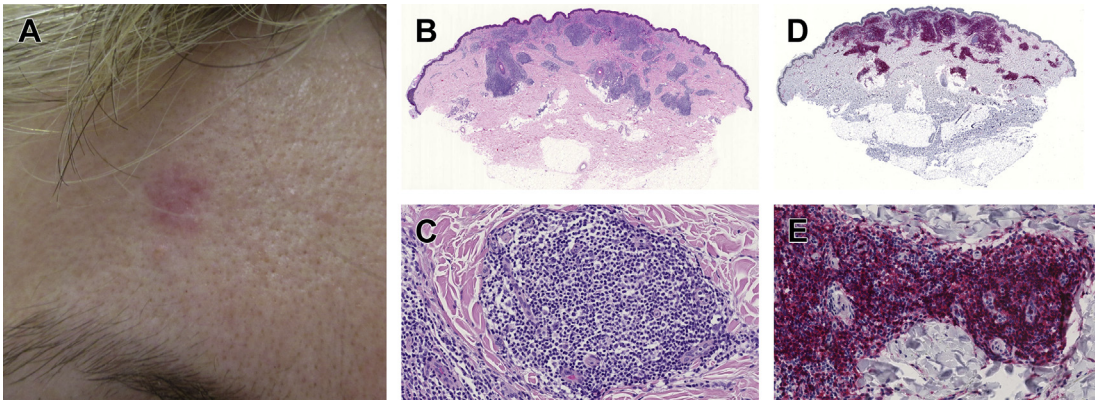
Fig. 3. Nodular T-PSL. (*A*) Solitary red flat nodule on the forehead. (*B*) Dense nodular wedge shaped infiltrate in the entire dermis (hematoxylin-eosin, ×20). (*C*) Variable number of slightly enlarged lymphocytes with chromatin dense nuclei (hematoxylin-eosin, ×200). (*D*) CD4$^+$ expression in a majority of the small lymphocytes (hematoxylin-eosin, ×20); (*E*) detail (hematoxylin-eosin, ×200).

dense nuclei can be seen (see **Fig. 3**C). There is an admixture of a variable number of eosinophils, histiocytes, and plasma cells. The B cells can be arranged in small aggregates, but germinal centers are only rarely found. Granuloma formation can be observed. There may be exocytosis of T-lymphocytes into the epithelia of the hair follicles, but usually there is no significant exocytosis of lymphocytes into the overlying interfollicular epidermis.

Immunohistochemistry and Molecular Diagnostics

A majority of the small lymphocytes belongs to CD4$^+$ CD30$^-$ T cells in most cases (see **Fig. 3**D, E). A few activated CD30$^+$ lymphocytes can be admixed. The number of admixed B-lymphocytes is variable.

Clonality studies reveal a polyclonal infiltrate in a majority of T-PSL, but PSL with clonal T-cells have been reported and referred to as so-called clonal PSL. Some of those cases may progress to overt lymphoma and may present very early stages of lymphoma genesis rather than genuine PSLs.

Differential Diagnosis

Differential diagnosis of nodular T-PSL and mixed PSL includes cutaneous CD4$^+$ small/medium-sized T-cell lymphoma/lymphoproliferative disorder (LPD) (World Health Organization [WHO] classification 2008/2016), which shows overlapping histologic and immunophenotypic features.[29,30] The latter also presents usually with a solitary lesion located mostly on the head and neck area and shows an indolent course. Because nodular T-PSL and cutaneous CD4$^+$ small/medium-sized T-cell lymphoma/LPD cannot be distinguished with certainty either on clinical nor on histopathologic or phenotypic features, some investigators consider them to represent the same process. Therefore, the encompassing term, cutaneous CD4$^+$ small/medium sized T-cell LPD, has been introduced in the updated WHO classification 2016 to emphasize the indolent nature of this process. The expression of PD-1 originally thought to be a discriminative marker is not of diagnostic value in this setting.

Nodular T-PSL should be differentiated from MF in tumor stage. MF in tumor stage presents more often with medium-sized T-cells with atypia. Eosinophils are often admixed and, therefore, are not helpful to differentiate it from T-PSL. A monoclonal T-cell receptor (TCR) rearrangement is a common finding in tumor stage MF. Nevertheless, the most important distinction criterion is the clinical presentation with patches and plaques preceding the tumors in MF. The differential diagnosis further includes secondary cutaneous infiltrates, for example, of angioimmunoblastic T-cell lymphoma (AITL). In AITL, small CD4$^+$ and PD-1$^+$ T cells are accompanied by a significant number of B cells. The clinical context with B symptoms, serologic findings, the nodal involvement shown by radiologic staging examinations, a high proliferation rate in AITL infiltrates, and the association with Epstein-Barr virus in some of the cases of AITL are useful findings for the distinction of AITL from nodular T-PSL. In the authors' experience, sometimes primary cutaneous marginal zone lymphoma with an unusual high number of admixed T cells (>50%) can be observed, which are challenging to differentiate from T-PSL.

Among inflammatory skin disorders, lupus erythematosus (in particular the tumid type) has to be considered, which also can present with dense

- (Lymphomatoid) drug eruption
- Nodular scabies
- Hidradenitis
- Injuries by corals
- Viral infections
  - Orf disease
  - Milker nodule
  - Molluscum contagiosum
  - Herpesvirus infection

dermal lymphocytic infiltrates. Mucin deposits might be helpful in this context. Vacuolization at the interface of the epidermis and the hair follicle epithelium is not found in tumid type of lupus erythematosus.

CD30$^+$ T-CELL PSEUDOLYMPHOMA

CD30$^+$ PSL represent a histologic subtype of T-cell PSL of the skin, which is characterized by the presence of medium-sized to large atypical CD30$^+$ T cells.[31,32] This has been reported in the context various infections and other diseases (**Box 3**).[31,33,34]

In CD30$^+$ PSL, immunohistochemistry shows medium-sized to large CD30$^+$ blastlike cells usually found as single units scattered throughout the infiltrate (**Fig. 4**). The infiltrate is otherwise dominated by small T cells. In some cases, the underlying disease (eg, molluscum contagiosum) could be identified. A significant number of B cells

and plasma cells argue for a reactive process. CD30$^+$ PSL does not harbor a clonal T-cell population in most of the cases.

As differential diagnosis, lymphomatoid papulosis (LYP) (in particular histologic type A) and cutaneous anaplastic large cell lymphoma (ALCL) have to be considered. In contrast to LYP and ALCL, the CD30$^+$ cells in CD30$^+$ PSL are usually not arranged in aggregates as in LYP and ALCL. Helpful histologic criteria to differentiate CD30$^+$ PSL from CD30$^+$ lymphoproliferative disease are given in **Table 3**.

## PSEUDO-MYCOSIS FUNGOIDES—HISTOLOGIC SIMULATORS OF MYCOSIS FUNGOIDES

The term pseudo-MF describes a group of disorders of different etiology, which histologically mimic MF. The clinicopathologic correlation is crucial to avoid misinterpretation.

HISTOLOGY

Pseudo-MF is characterized by a bandlike (**Fig. 5**) or perivascular infiltrate of mostly small lymphocytes, which show exocytosis into the epidermis (see **Fig. 5**) and may exhibit subtle nuclear atypia thereby simulating epidermotropic cutaneous T-cell lymphoma.

IMMUNOHISTOCHEMISTRY

A Predominance of CD4$^+$ or CD8$^+$ cells can be found. In addition, a variable expression of CD30 can be seen in some cases of pseudo-MF. As in other forms of PSL, the lymphocytes are polyclonal in a majority of cases. In some diseases, such as
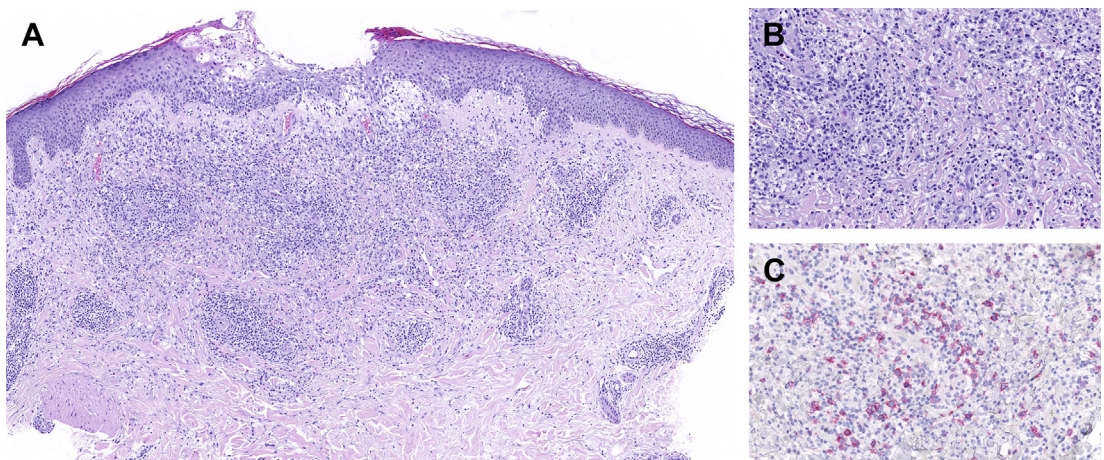
Fig. 4. CD30$^+$ T-PSL. (*A*) Arthropod bite reaction with a wedge shaped mixed infiltrate, spongiotic dermatitis, and papillary edema (hematoxylin-eosin, ×40). (*B*) The infiltrate consists of lymphocytes, histiocytes, and eosinophils. A few (immuno-) blastlike cells are admixed (hematoxylin-eosin, ×200). (*C*) These cells were positive for CD30 (×200).

Table 3
Histologic criteria to differentiate a neoplastic and reactive CD30$^+$ infiltrate

|	Neoplastic	Reactive
Number of CD30$^+$ cells	Often higher number	Lower number
Arrangement	Little clusters or sheets	More scattered distribution as single units
CD30 staining intensity	Often more intensive	Often weak
Composition of the infiltrate	Depending on the type of CD30$^+$ LPD (eg, in LYP type A: mixed infiltrate with many histiocytes, ALCL: predominantly CD30$^+$ cells arranged in sheets)	Higher number of admixed B cells and plasma cells

pityriasis lichenoides et varioliformis acuta, clonal T cells are found in a significant percentage but do not indicate malignancy or a risk for progression to lymphoma.

DIFFERENTIAL DIAGNOSES

Most important differential diagnoses include MF and Sézary syndrome. In cases of predominantly CD8$^+$ infiltrate, CD8$^+$ MF, cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma, and primary cutaneous LYP (types D and E) should be considered. Profound nuclear atypia, predominance of medium-sized to large cells, loss of pan T-cell markers, and monoclonal rearrangement of TCR genes, are findings in favor of cutaneous T-cell lymphoma. The diagnosis of Sézary syndrome can be excluded by blood analysis.

Lymphomatoid Contact Dermatitis

Lymphomatoid contact dermatitis (LCD) is a chronic contact dermatitis, which histologically simulates MF.[35]
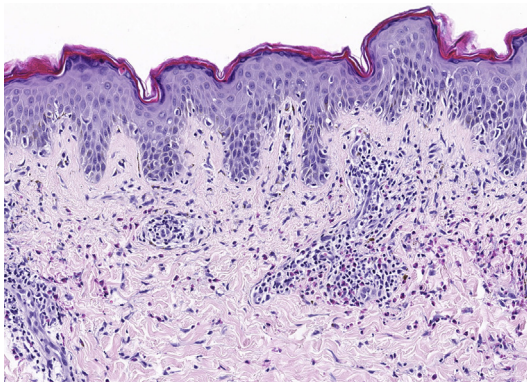
Fig. 5. Pseudo-MF: bandlike infiltrate of mostly small lymphocytes with exocytosis into the epidermis. Many admixed eosinophils in the upper dermis (H&E, original magnification ×100).

Clinically, LCD presents with eczematous and pruritic papules, patches or plaques. In rare cases, erythroderma can be found. LCD occurs mostly in adults and affects both genders.

Histologically, there is a superficial bandlike infiltrate with variable exocytosis of lymphocytes into the spongiotic epidermis. Intra-epidermal accumulations of Langerhans cells (so called pseudo-Pautrier collections) can be found. A mild atypia of the lymphocytes has been described. Eosinophils are generally admixed. The ratio of CD4$^+$ to CD8$^+$ lymphocytes is balanced. An admixture of slightly enlarged activated CD30$^+$ cells may be observed. For differential diagnoses, see **Table 4**.

Lymphomatoid Drug Reaction

Apart from its nodular form, drug-related PSL clinically more commonly presents with macular or papular eruptions.[2,36]

Histologically, in lymphomatoid drug reaction, a bandlike infiltrate in the upper dermis with variable degree of exocytosis of lymphocytes is found.[37] Vacuolar alteration at the dermoepidermal junction and apoptotic keratinocytes may be present. Eosinophils are commonly found but also may be absent. Immunohistochemistry reveals either a predominance of CD4$^+$ or CD8$^+$ lymphocytes and admixture of a variable number of CD30$^+$ lymphocytes.[38] Loss of pan T-cell markers is not observed. The differential diagnoses are given in **Table 4**.

Actinic Reticuloid

Actinic reticuloid is a chronic multifactorial dermatitis with severe photosensitivity, which histologically mimics epidermotropic cutaneous T-cell lymphoma.[39]

Clinically, actinic reticuloid affects mostly middle-aged and older men.[40] It presents with persistent erythematous lichenoid papules and plaques on light-exposed skin areas, particularly

Table 4
Clinical and histologic characteristics of T-cell pseudolymphoma and their differential diagnoses

	Lymphomatoid Contact Dermatitis	Lymphomatoid Drug Reaction	Actinic Reticuloid	CD8^{+} T-cell Pseudolymphoma in Immunodefiency	*Borrelia*-Associated T-cell Pseudolymphoma	Papuloerythroderma of Ofuji	Mycosis Fungoides	Sézary Syndrome
Mean age	Adults	Adults	Middle and older age	NA	60	70	55–60	Adults
Gender	Male = female	NA	Male >> female	NA	Male = female	Male > female	Male > female	Male > female
Prediliction sites	Areas exposed to the allergen(s)	Variable, generalized	Face, neck	Generalized	Lower limb > trunk	Generalized, especially trunk and limbs	Initial skin lesions: buttocks and other sun-protected areas	Generalized
Clinical picture	Eczematous and pruritic papules, patches or plaques	Rush, macular-papular eruptions	In sun exposed areas: persistent erythematous lichenoid papules and plaques, facies leonina	Variable: plaques - > erythroderma, palmoplantar hyperkeratosis, lymphadenopathie	Variable: erythema chronicum migrans, acrodermatitis chronica atrophicans, MF-like, lichenoid aspect	Itchy flat topped red to brownisch papules, erythoderma with (deck chair sign), palmoplantar hyperkeratosis, lymphadenopathy	Patch, plaques and tumors (depending on the stage)	Erythroderma, palmoplantar hyperkeratosis, enlarged lymph nodes
Histology	Superficial bandlike infiltrate, spongiosis, pseudo-Pautrier collections, eosinophils	Superficial, bandlike, eosinohils	Psoriasiform hyperplasia, mild spongiosis, eosinophils, coarsed and vertically arranged collagen bundles in the papillary dermis	Superficial and mid-dermal infiltrate, no atypia	Bandlike or deep, lichenoid aspect, lymphocytes, histiocytes (pseudorosettes), variable number of plasma cells	Pattern of chronic dermatitis with a variable epidermal hyperplasia with mild spongiosis and a mixed inflammatory infiltrate, predominately consist of lymphocytes, histiocytes and eosinophils	Lining up, Pautrier collections, atypia, eosinophils are uncommon in patch MF	Often unspecific, epiderotropism may be absent, often only mild atypia

Immuno-histochemistry	CD4 = CD8, sometimes admixed larger CD30$^+$ cells	CD4 or CD8 predominance, admixed CD30$^+$ cells. Caveat: loss pf pan-T-cell markers is possible	CD8$^+$	CD8$^+$, TIA-1, granzyme B	CD4$^+$	CD4 = CD8	CD4$^+$ or CD8$^+$ or CD4$^-$/CD8$^-$, loss of pan T-cell markers, admixed CD30$^+$ cells possible	CD4$^+$, PD-1$^+$, TOX$^+$
Molecular diagnostics (tissue)	TCR mostly polyclonal	TCR mostly polyclonal	TCR mostly polyclonal	TCR mostly polyclonal	TCR mostly polyclonal	TCR mostly polyclonal	TCR monoclonal up to 90%	Blood involvement
Additional findings	Identification of allergen (patch test)		Increased number of circulating CD8$^+$ cells in the peripheral blood, photosensitivity	HIV with deep immunosuppression, other type of immunosupression, often monoclonal cells in peripheral blood	Detection of *Borrelia burgdorferi* PCR, serology	Blood eosinophilia		Blood involvement (see criteria of International Society for Cutaneous Lymphomas)

Abbreviation: NA, not available.

on the face and neck, in some patients with a facies leonina–like aspect. Progression into erythroderma can be observed. Lichenification and erosions usually occur over time. The skin lesions are accompanied by intense pruritus.

Histologically, actinic reticuloid shows a psoriasiform hyperplasia of the epidermis with slight spongiosis. The cornified layer is compact orthokeratotic with focal parakeratosis. In the dermis, a predominating superficial perivascular infiltrate composed of small lymphocytes, eosinophils, and plasma cells is found. Coarse bundles of collagen arranged in vertical streaks are found in the papillary dermis. Multinucleated fibroblasts may be present. The lymphocytes may show slightly atypical nuclei and exocytosis into the overlying epidermis. Immunohistochemistry reveals a predominance of CD8+ T cells.[41]

In the peripheral blood, an increased number of CD8+ T cells (reversed CD4:CD8 ratio) is characteristic for actinic reticuloid, particularly in erythrodermic patients.[40] The atypical circulating lymphocytes show indented nuclei. For differential diagnosis, see **Table 4**.

CD8+ T-Cell Pseudolymphoma in Immunodeficiency

In patients with immunodeficiency, in particular HIV infections, infiltrates of CD8+ lymphocytes mimicking MF or Sézary syndrome may rarely develop. In HIV, most of the patients are deeply immunosuppressed (CD4+ count <50/mm^3) and have a high HIV-RNA load.[42] This condition seems not to be exclusively limited to patients with HIV infection, because similar features were recently described in a renal transplant recipient.[43]

Clinically, a variety of clinical presentations were described. Often erythematous, infiltrated cutaneous plaques with progression to erythroderma have been observed[44–46]; in addition, palmoplantar hyperkeratosis could be found with generalized lymphadenopathy. These
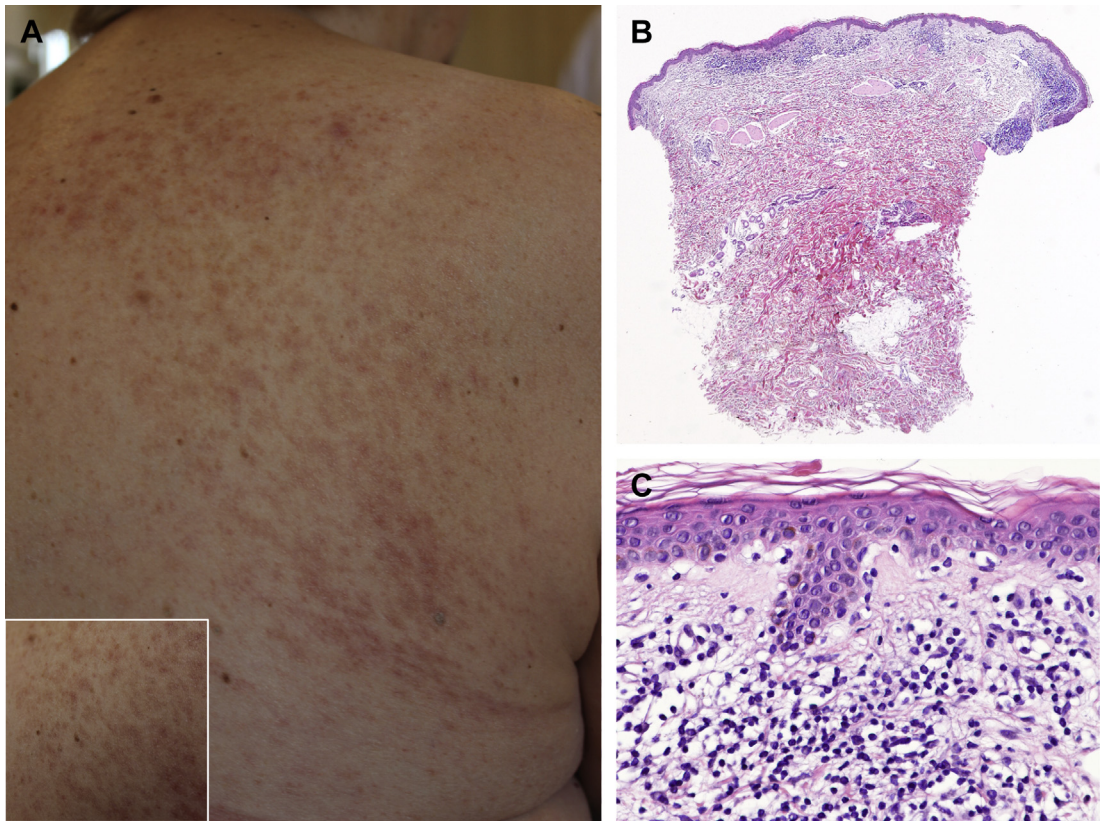
Fig. 6. *Borrelia*-associated T-PSL. (*A*) Multiple lichenoid red-brownish maculae and flat papules on the back, detail *(inset)*. (*B*) Superficial bandlike lymphocytic infiltrate (hematoxylin-eosin, ×20). (*C*) The infiltrate predominately consists about T-lymphocytes with a few admixed plasma cells. Vacular alteration of the junctional zone (hematoxylin-eosin, ×200).

eruptions can, therefore, clinically mimic Sézary syndrome. Some investigators reported a worsening of skin symptoms after ultraviolet light exposure.

Histologically, a superficial and sometimes mid-dermal infiltrate is found, consisting of small lymphocytes without nuclear atypia. Eosinophils are admixed. Immunophenotyping shows a predominance of CD3+ and CD8+ lymphocytes, with expression of cytotoxic markers (granzyme B and T-cell–restricted intracellular antigen [TIA-1]). Molecular studies revealed the polyclonal skin infiltrate but often monoclonal cells in the peripheral blood.[42] The differential diagnosis is given in **Table 4**.

Borrelia-Associated T-Cell Pseudolymphoma

Recently *Borrelia burgdorferi* species infection with T cell–rich pseudolymphomatous infiltrates has been reported.[47]

Clinically, *Borrelia*-associated T-PSL can resemble MF, sometimes a lichenoid aspect is evident (**Fig. 6**A). Other clinical presentations included the typical findings of erythema migrans or acrodermatitis chronica atrophicans. *Borrelia*-serology and detection of *Borrelia* in the skin infiltrate by PCR are necessary to confirm the diagnosis.

Histologically, the dermal T-cell infiltrate is either bandlike (sometimes with vacuolar interface
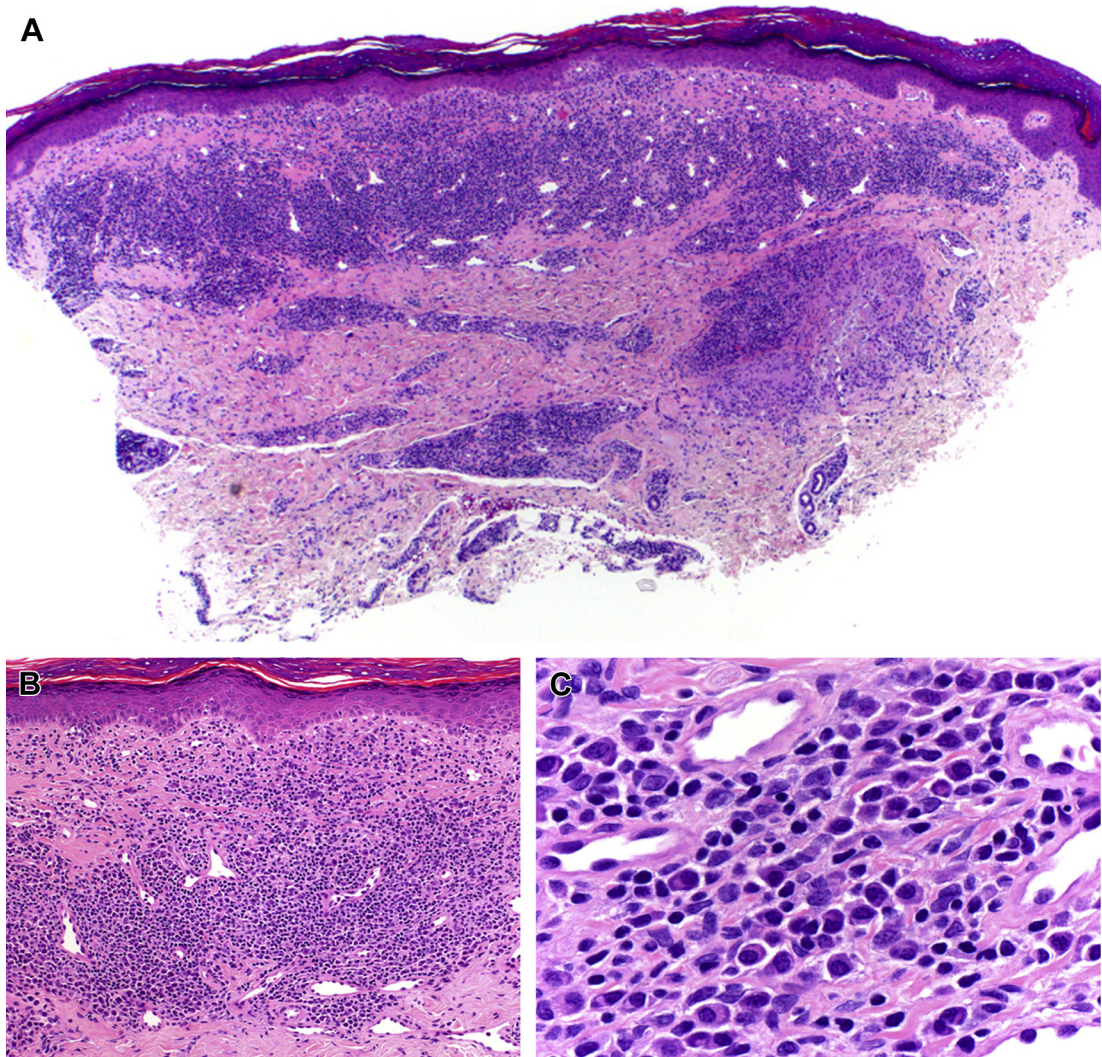
Fig. 7. APA. (*A*) Dense infiltrate of small lymphocytes (polyclonal T cells and B cells), eosinophils, plasma cells, and histiocytes, and sometime histiocytic giant cells is found (hematoxylin-eosin, ×20). (*B*, *C*) Thick-walled vessels lined by plump endothelia, surrounded by plasma cells (hematoxylin-eosin, ×100; detail: hematoxylin-eosin, ×200).

dermatitis) (see **Fig. 6**B) or diffuse. The infiltrate displays focal epidermotropism with lining up of lymphocytes along the junctional zone (see **Fig. 6**C). In addition, a minor interstitial histiocytic component of the infiltrate can be observed. Sometimes histiocytic pseudorosettes are found. The number of admixed plasma cells is variable.[47] For differential diagnosis, see **Table 4**.

Papuloerythroderma Ofuji

Papuloerythroderma of Ofuji (PEO) is a rare pruritic erythrodermic dermatosis, which clinically may simulate cutaneous T-cell lymphoma.[48] Association with drugs, Hodgkin lymphoma, visceral malignancies, and immunodeficiency syndromes have been reported. In some patients,[49,50] PEO was described as a manifestation of MF, in others as a disease accompanying MF.[51]

Clinically, PEO manifests with generalized itchy flat topped red to brownish papules. The axillae, inguinal regions, antecubital and popliteal fossae, and big furrows on the abdomen are typically spared (so-called deck chair sign).[52] The median age is 70 years. It occurs more frequently in men than in women. Blood eosinophilia is detected in most of the patients.

Histologically, PEO resembles chronic dermatitis, with a variable epidermal hyperplasia with mild spongiosis and a mixed inflammatory infiltrate, predominately consisting of lymphocytes, histiocytes and eosinophils.[53] In approximately 10%, plasma cells are admixed.[50] Immunohistochemistry shows numerous dendritic cells and mature CD4^{+} T cells in the dermis. For differential diagnosis, see **Table 4**.

Lymphocytic Infiltration of the Skin and Palpable Arciforme Migratory Erythema

Jessner-Kanof lymphocytic infiltration of the skin (LIS) and palpable arciform migratory erythema (PAME) have been regarded by some investigators as T-PSLs. These eruptions are nowadays primarily assigned to the group of lupus erythematosus.

Clinically, PAME led to its designation with infiltrated annular erythema developing into large migrating lesions.[54] The trunk is the predilection site. LIS is characterized by sharply demarked often symmetric infiltrated plaques, which typically occur on the face.[55]

Histologically, the findings are similar in PAME and LIS. Both shows dense perivascular and periadnexal predominantly lymphocytic infiltrate.[56]
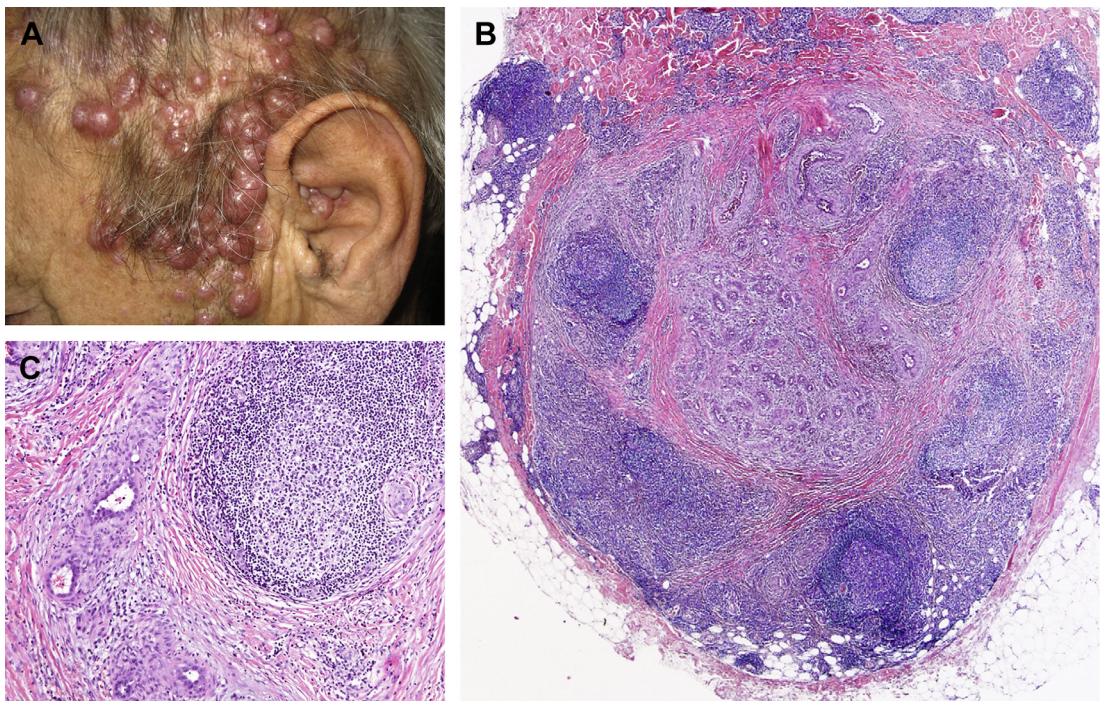
Fig. 8. ALHE. (*A*) Multiple red-brown nodules around the ear. (*B*) Circumscribed proliferates of capillary vessels in the deep dermis and superficial subcutis. These vessels are surrounded by a dense lymphocytic infiltrate with reactive germinal centers (hematoxylin-eosin, ×40). (*C*) The vessels show prominent endothelia with typical vacuolization. The vessels are surrounded by a dense lymphocytic infiltrate, consisting eosinophils and plasma cell. Reactive germinal centers (hematoxylin-eosin, ×200).

Many investigators reported that interstitial mucin deposits are absent. Immunohistochemistry reveals an infiltrate dominated by T cells with admixture of B cells and histiocytes. The lymphocytes are polyclonal. Phenotypically, the infiltrate in LIS is mostly composed of CD8^{+} lymphocytes.[57]

Infections as Simulators of Lymphomas

Various infections, in particular those caused by viruses and parasites, may show dense lymphocyte-rich infiltrates and thereby simulating a lymphoma.

Cutaneous leishmaniasis can histologically simulates lymphoma and, therefore, can be difficult to diagnose, especially in cases of a low number of parasites. The infiltrate is composed of numerous lymphocytes, histiocytes, and plasma cells.[58] The detection of the agents is essential to making a correct diagnosis. Molecular studies demonstrate that a PCR diagnostic is helpful to identify the agent if it cannot be identified by conventional histology or special stains, for example, in Giemsa stain alone.[59]

In infections with herpes simplex virus and varicella zoster virus, occasionally lymphocyte-rich infiltrates without the pathognomonic epithelial changes can be observed and have been referred to as herpes incognito.[60] Lymphocytes with slightly enlarged and atypical-appearing chromatin dense nuclei as well as enlarged CD30^{+} lymphocytes may be found. Those infiltrates are prone to be misinterpreted as lymphoma. Detection of viral antigens by immunohistochemistry and/or detection of viral DNA by PCR allow identifying those infiltrates as herpesvirus-related T-cell reactions.[60]

Parapoxvirus infections may induce cytomorphological changes and expression of CD30 by
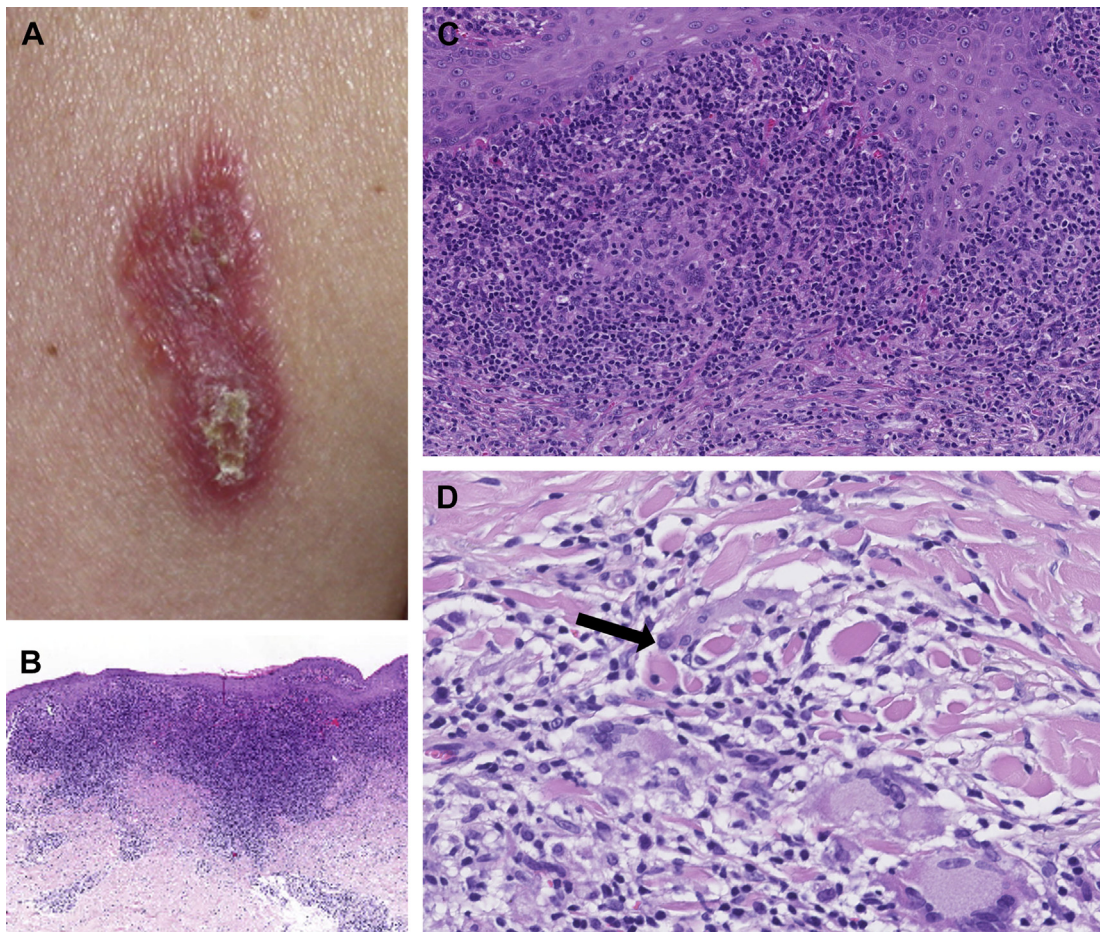
Fig. 9. LPP. (*A*) Longstanding sharply demarcated reddish plaque with scaling. (*B*) Epidermal hyperplasia with a bandlike and superficial perivascular infiltrate (hematoxylin-eosin, ×100). (*C*) The infiltrate consists of lymphocytes, histiocytes, and plasma cells (hematoxylin-eosin, ×200). (*D*) Interstitial histiocytic granulomas around sclerotic collagen bundles (so-called pseudorosettes [*arrow*]) (hematoxylin-eosin, ×400).

the infiltrating T cells, which make distinction from pleomorphic lymphocytes in the context of CD30-LPDs challenging.[31,32] The presence of epithelial changes with inclusion bodies typical for parapox-virus infection, absence of loss of T-cell markers, and lack of monoclonal rearrangement of TCR gamma genes are diagnostic hints to distinguish those infiltrates from cutaneous T-cell lymphoma, in particular CD30^{+} LPDs. The diagnosis is based on the detection of the virus by immunohistochemistry, electron microscopy or PCR.

Inflammatory Disorders as Simulators of T-Cell Lymphoma

Various disorders, especially diseases with interface dermatitis, are prone to be misinterpreted as epidermotropic cutaneous T-cell lymphoma. These disorders include lichen planus, lichen sclerosus et atrophicus, pigmented purpuric dermatitis, and pityriasis lichenoides.[61–64] On the other hand, MF can sometimes present with an interface dermatitis.

Clonal T-cell populations have been found in some cases in the inflammatory skin conditions (discussed previously), for example, in lichen planus and lichen sclerosus et atrophicans, in which clonal T cells were found in 6% and 13% of the cases, respectively. Remarkably, a monoclonal rearrangement of TCR genes is commonly found in pityriasis lichenoides harboring clonal T cells in up to 60% of the cases.[62,65] The significance of these T cell clones is unclear. As a consequence, for the diagnostic work-up of lymphocyte-rich infiltrates, detection of a clonal T-cell population cannot be used as a sufficient finding to diagnose cutaneous T-cell lymphoma.[7] The clinicopathologic correlation is essential.

Furthermore, inflammatory diseases with lymphocyte-rich dermal and/or subcutaneous infiltrates, such as lupus erythematosus, in particular the tumid type and lupus panniculitis, have to be differentiated from cutaneous T-cell lymphoma, in particular subcutaneous panniculitis-like T-cell lymphoma.

OTHER PSEUDOLYMPHOMA (ALPHABETICAL ORDER)

ACRAL PSEUDOLYMPHOMATOUS ANGIOKERATOMA

Acral pseudolymphomatous angiokeratoma (APA) has originally been described as occurring in children (original name, APA of childhood [APACHE]), but it has been shown to also affect adults.[66–68] Some investigators consider the lesions to represent persistent arthropod bite reactions, whereas others categorize APA a benign vascular process with a prominent lymphocytic infiltrate, that is, a form of cutaneous PSL.[66,68]

Clinically, APA manifests as a unilateral eruption of clustered red to violaceous angiomatous papules (diameter 1–5 mm) on acral sites, that is, hands and feet[66] (**Fig. 7**A).

Histologically, a dense infiltrate of small lymphocytes (polyclonal T cells and B cells), eosinophils, plasma cells, histiocytes, and sometime histiocytic giant cells is found (see **Fig. 7**B). Within the infiltrate there are thick-walled vessels lined by plump endothelia (see **Fig. 7**C).

ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA

Nowadays angiolymphoid hyperplasia with eosinophilia (ALHE) is commonly as an angioproliferative process due to the presence of prominent, bizarrely shaped blood vessels and epithelioid endothelia, leading to its alternative synonymous designation as epithelioid hemangioma.[69,70] Some investigators consider ALHE a hyperplastic process in response to tissue damage and formation of vascular shunts.

Clinically, ALHE affect both genders without gender predominance.[70] Most patients are in the third or fourth decade. ALHE presents as angiomatous pink to red-brown papules or nodules most commonly found on the head and neck, especially on the face and ears (**Fig. 8**A)

Box 4
Differential diagnosis of lymphoplasmacytoid plaque

Cutaneous plasmocytosis

Lymphocytoma cutis

Cutaneous marginal zone lymphoma

Primary and secondary cutaneous plasmacytoma

Infections (eg, fungal, mycobacterial, and spirochetal)

but also occurring at the extremities and genital area.

Histologically, there are dermal proliferates of capillary vessels with prominent endothelia (**see Fig. 8**B), which presented typical cytoplasmic vacuoles (see **Fig. 8**C). These vessels are surrounded by a dense lymphocytic infiltrate with reactive germinal centers (see **Fig. 8**B) and eosinophils (see **Fig. 8**C).[71] By immunohistochemistry the endothelial cells were positive for CD31 and ERG but negative for podoplanin/D2-40. A majority of lymphocytes are of T-cell lineage. Admixed B cells may form lymphoid follicles. Clonal T cells have been detected.[72,73]

CUTANEOUS PLASMOCYTOSIS

Cutaneous plasmocytosis is a rare disease, which has been reported in Asian countries, especially Japan. It mostly affects adults.[74,75] It is characterized by multiple brownish small plaques and nodules occurring all over the body. Histology shows dermal infiltrates composed predominantly of mature polyclonal plasma cells.[74,75] In some patients signs of a systemic involvement (eg, lymphadenopathy, hepatospenomegaly, hypergammaglobulinemia, increased levels of interleukin 6 in the serum, and elevated erythrocyte sedimentation rate) can be present.

LYMPHOPLASMACYTIC PLAQUE

Lymphoplasmacytic plaque (LPP) is a recently described rare skin disease, which is considered a form of PSL of unknown etiology. The diagnosis is based on clinicopathologic correlation. Originally, it was reported in children with the pretibial region as predilection site.[76,77] A recent study indicates that LPP can also affect adults and involve the trunk and arms.[78] A female preponderance can be observed.

Clinically, LPP shows a distinct presentation characterized by a longstanding plaque or circumscribed, often linear arranged reddish and brownish papules and plaques (**Fig. 9**A).[78,79]

Histology reveals a superficial, bandlike (see **Fig. 9**B), or deep nodular and interstitial infiltrate, often accentuated around adnexal structures or blood vessels. An epidermal hyperplasia is common (see **Fig. 9**B). The infiltrate consists of lymphocytes and histiocytes with numerous polyclonal plasma cells accounting for up to 25% of the entire infiltrate (see **Fig. 9**C). The interstitial histiocytes may form granulomas around sclerotic collagen bundles (so-called pseudorosettes) (see **Fig. 9**D). Histiocytic giant cells and an increased number of vessels can be seen.[78]

LPPs have been differentiated from other conditions containing plasma cells and histiocytes (**Box 4**). LPP and APA show overlapping clinical and histologic features. Thus it has been postulated
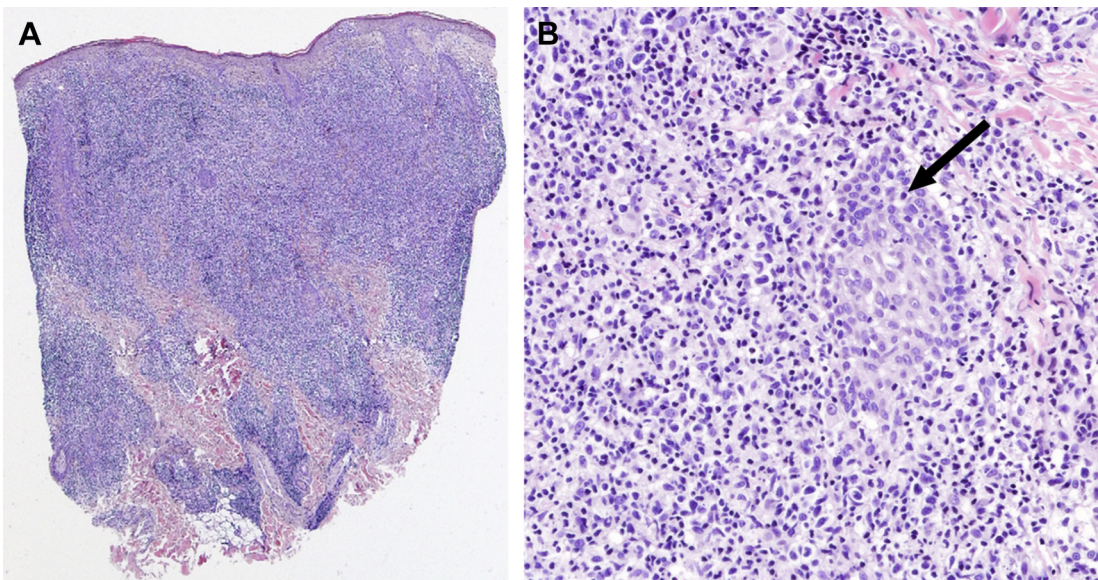
Fig. 10. Pseudolymphomatous folliculitis. (*A*) The lymphocytic infiltrates are located throughout the entire dermis and may extend into the subcutis (hematoxylin-eosin, ×20). (*B*) Exocytosis of lymphocytes (*arrow*) into the hair follicles (hematoxylin-eosin, ×200).

that both entities belong to the same spectrum of diseases and represent a plasma cell–rich PSL with a prominent vascular component.[78]

Pseudolymphomatous Folliculitis

The pseudolymphomatous folliculitis was first described in 1988 by Kibbi and colleagues.[80] It presents with a solitary nodule preferentially located on the face.[81,82] Histologically, T-cell predominance is more often found than predominating B cells; in some cases, these cell types were equally distributed.[82] Admixed epithelioid histiocytes and granulomas are found. The lymphocytic infiltrates are located throughout the entire dermis and may extend into the subcutis (**Fig. 10**A). The epidermis is spared. There is exocytosis of lymphocytes into the hair follicles often showing broadened epithelia[83] (see **Fig. 10**B). A hyperplasia of eccrine and apocrine ducts is often observed. An admixture of numerous dendritic cells with expression of CD1a and S-100 was identified in all cases.[81] Kazakov and colleagues[82] reported an unusual high number (approximately 50% of the cases) of clonal T cells and less often about a monoclonal IgH rearrangement in this entity. These cases have to be carefully differentiated from T-cell or B-cell lymphoma, which can also show follicular involvement.

INTRAVASCULAR PSEUDOLYMPHOMA

Recently, benign intravascular proliferation of blasts with or without expression of CD30
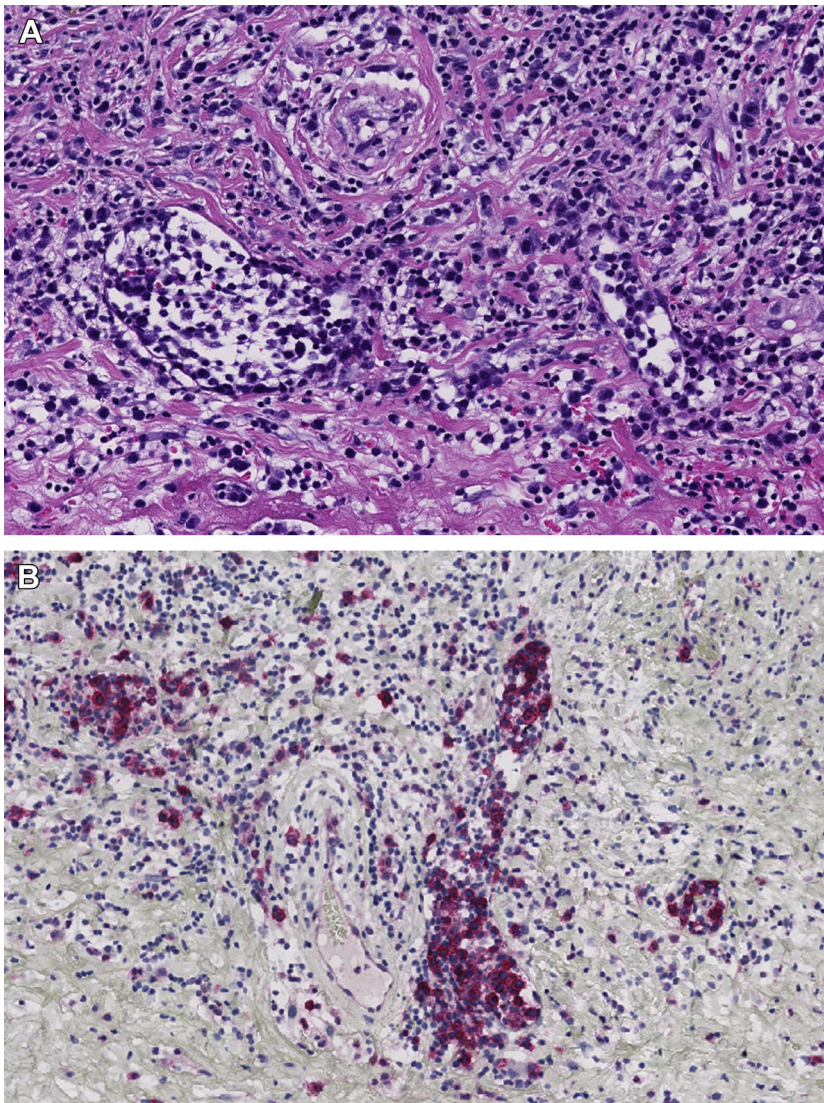
Fig. 11. Benign intravascular CD30+ lymphoproliferation. (*A*) The vessels are filled with activated large lymphocytes (hematoxylin-eosin, ×200). (*B*) The intravascular lymphocytes are positive for CD30 (×200).

have been reported. This condition arises in areas with inflammatory skin diseases or trauma of the skin.[84–86] Pathogenetically, obstruction of lymphatic vessels due to inflammation with disrupted immune cell trafficking may result in the accumulation of activated CD30$^+$ lymphocytes (**Fig. 11**A, B). The lymphocytes are large and have a blastlike morphology. They express T-cell markers (CD3 and CD4) and in some cases CD30. There is no association with Epstein-Barr virus infection. Clonality studies reveal the polyclonal nature of the process. Intravascular lymphoma is the most important differential diagnosis because it is an aggressive lymphoma with various phenotypic forms (B cell, T cell, or natural killer cell/T cell). In addition, benign intravascular proliferation of lymphoid cells needs to be distinguished from intralymphatic histiocytosis representing a reactive proliferation of histiocytes in the lumina of lymphatics in patients with rheumatoid arthritis or orthopedic metal implants.

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