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REVIEW

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Cutaneous pseudolymphoma—A review on the spectrum and a proposal for a new classification

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Abstract

Cutaneous pseudolymphomas (PSLs) belong to a group of lymphocytic infiltrates that histopathologically and/or clinically simulate lymphomas. Different causative agents (e.g., *Borrelia* sp., injected substances, tattoo, arthropod bite) have been described, but in many cases no cause can be identified, hence the term idiopathic PSL. Clinicopathological correlation is important to make the diagnosis. Four main groups of cutaneous PSL can be distinguished based on histopathologic and/or clinical presentation: (a) nodular PSL; (b) pseudo-mycosis fungoides (pseudo-MF) and simulators of other CTCLs; (c) other PSL (representing distinct clinical entities); and (d) intravascular PSL. This article gives an overview of the histopathologic and clinical characteristics of cutaneous PSLs and proposes a new classification.

KEYWORDS

B-cell lymphoma, Borreliosis, clonality, cutaneous pseudolymphoma, infection, T-cell lymphoma, tattoo

1 | INTRODUCTION

1.1 | Definition

Cutaneous pseudolymphoma (PSL) is described in the literature as a reactive lymphoproliferation that histopathologically and/or clinically imitates cutaneous lymphomas.[1-3] Based on this wide definition it is clear that many processes fulfill the criteria of PSL. Not surprisingly, the term PSL defined in this way seems to have been overstretched in the literature. Many infectious and non-infectious diseases are characterized by atypical lymphocytic infiltrates, which can be easily misinterpreted as cutaneous lymphoma based on histopathologic features alone. To limit the usage of the term cutaneous PSL, we suggest a narrower definition. In analogy to cutaneous lymphomas, clinical information is essential in arriving at the diagnosis. By histopathology alone, the diagnosis of cutaneous pseudolymphoma can, in many cases, only be suspected. Additional clinical information and further diagnostic work-up are necessary to confirm the suspected diagnosis. Therefore, the term cutaneous PSL should be restricted to cases that histopathologically simulate cutaneous lymphomas and do not fit into any other diagnosis after clinical correlation. Figure 1 illustrates this approach.

1.2 | Etiology

The literature documents a wide range of causes of PSL, broadly divided into infections, drugs, and foreign agents (Table 1). Miguel et al[4] summarized the frequency of different causes of PSL (Figure 2). Despite the wide range of agents, in many PSL cases no trigger can be found; such cases are designated as idiopathic PSL.

1.3 | Classification

The literature describes many approaches to classify cutaneous PSL. These include a separation according to the predominating immunophenotype (T-cell, B-cell, or mixed), the histopathologic growth pattern, the etiology, or distinct clinical features (reviewed in Refs. 1,2,5). None of these approaches allows a consideration of overlapping features. Moreover, the phenotype and etiology are not evident at first glance; further diagnostic work-up is essential. The composition of the infiltrate is variable, being influenced by genetic and immunological factors of the host, as reflected in the observation that identical agents (e.g., *Borrelia sp.*) can induce either B-PSL or T-PSL.

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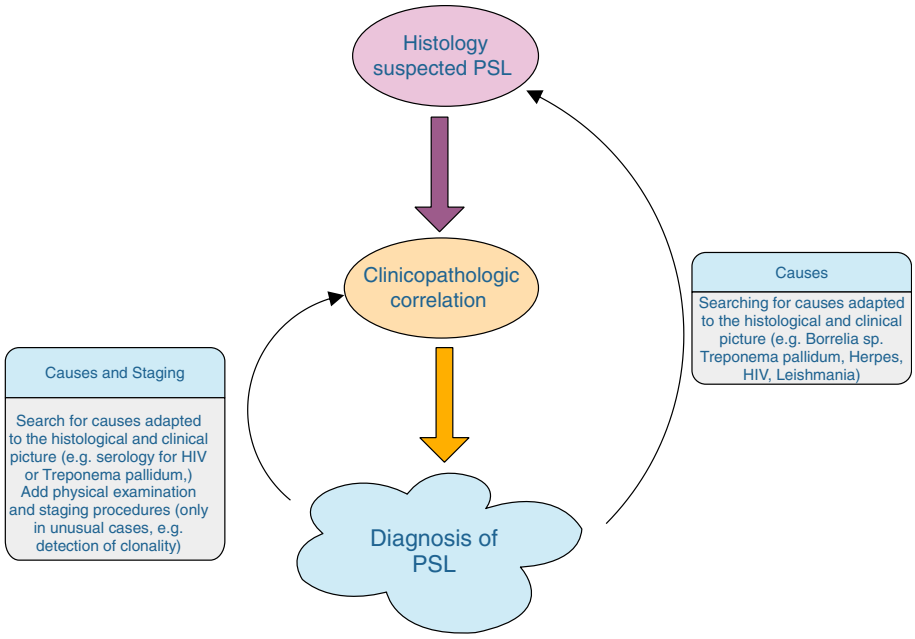

FIGURE 1 Diagnostic approach to cutaneous pseudolymphomas

TABLE 1 Different causes of cutaneous pseudolymphomas

Infections
Bacteria (e.g., *Borrelia* sp., *Treponema pallidum*), viruses (e.g., *Herpes* virus sp., *Molluscipoxvirus*, HIV), parasites (e.g., scabies, leishmaniasis)
Drugs
Anticonvulsans, antipsychotics, antihypertensives, antiarrythmics, antibiotics, antirheumatics, anxiolytics, NSAID
Foreign agents
Tattoo dyes, injected vaccination or allergen extracts for hyposensitization, piercing
Other
Insect bites, Hirudo medicinalis, UV radiation

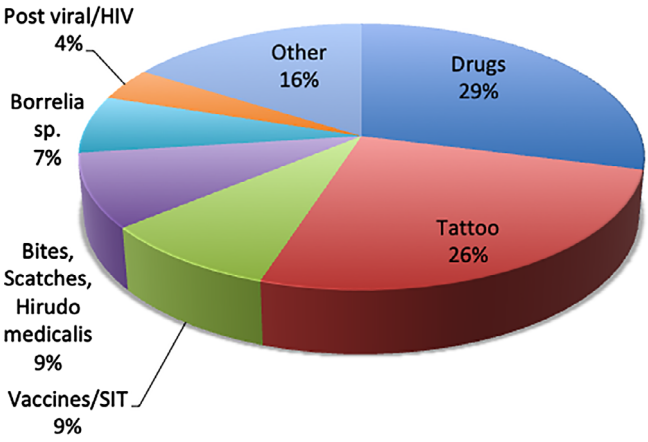

FIGURE 2 Frequency of different causes of cutaneous pseudolymphomas, modified after Miguel et al[4]

In contrast to cutaneous lymphomas,[6] there are only a few proposed classifications of cutaneous PSL, which are not consensus-based and have so far attracted little notice in everyday routine.

We suggest splitting cutaneous PSL into four main groups based on histopathologic features and clinical data. Table 2 provides a suggestion for a detailed classification.

1. **Nodular pseudolymphomas:** This group is well-established and represents the most common PSL ("classical PSL"). They resemble cutaneous lymphomas, histopathologically and clinically, and are characterized by solitary or multiple nodules.
2. **Pseudolymphomas as simulators of mycosis fungoides ("pseudo-MF") and of other CTCLs:** The process here mimics mycosis fungoides or other CTCLs, predominantly on histopathologic grounds. This group shows a broad clinical spectrum.
3. **Other pseudolymphomas:** Distinct clinical entities reported in the literature as PSL.
4. **Intravascular pseudolymphomas:** Reactive accumulations of atypical-appearing lymphocytes within small lymphatic vessels.

1.4 | Diagnostic approach

The diagnostic approach includes a combination of histopathology (including immunohistochemistry and molecular diagnostics), clinical presentation, and a further molecular workup, if necessary.

The **histopathologic presentation** (Figure 3) can be divided according to various patterns (e.g., nodular vs epidermotropic vs dermal diffuse vs subcutaneous vs intravascular); the predominant cellular morphology (e.g., anaplastic vs centoblastic vs centrocytic) and size of the lymphocytes (e.g., small vs medium-sized vs large); the immunophenotype (e.g., T- vs B-cell, CD4+ vs CD8+, CD30+); and the composition of the infiltrate (e.g., admixed plasma cells,

TABLE 2 Classification of cutaneous pseudolymphomas

Nodular pseudolymphomas
Nodular B-cell pseudolymphoma
Borrelia-associated nodular B-cell pseudolymphoma
Nodular T-cell and mixed pseudolymphoma
Nodular CD30+ pseudolymphoma
Pseudolymphomas as simulators of mycosis fungoides or of other CTCLs
Lymphomatoid contact dermatitis
Lymphomatoid drug reaction
Actinic reticuloid
CD8+ T-cell pseudolymphoma in immunodeficiency
Infections as simulators of T-cell lymphomas
Borrelia-associated T-cell pseudolymphoma
Leishmaniasis-associated T-cell pseudolymphoma[a]
Herpesvirus-associated T-cell pseudolymphoma
Syphilis-associated pseudolymphoma
Other Infections als simulators of CTCL
Inflammatory dermatosis as simulators of CTCL
Other pseudolymphomas
T-cell rich angiomatoid pseudolymphoma
Acral pseudolymphomatous angiokeratoma (APA)
T-cell-rich angiomatoid polypoid pseudolymphoma (TRAPP)
Primary cutneous angioplasmocellular hyperplasia
Lymphoplasmacytoid plaque (LPP)
Cutaneous plasmocytosis
Intravascular pseudolymphomas
Benign atypical intravascular (CD30+) lymphoproliferation

[a]Also presents as nodular T-cell pseudolymphoma.

histiocytes, eosinophils, neutrophils). Molecular studies for clonality can be helpful, but should be interpreted only in the clinical context. Clonal T- and B-cells are not specific for lymphoma, and can also occur in inflammatory diseases, infections, and PSL.[7-11]

In the daily routine, in situations with a reasonable suspicion of a PSL caused by infectious agents, an additional diagnostic work-up can be performed before or without clinical correlation.

The **clinical presentation** of cutaneous PSL encompasses a wide spectrum, from solitary or multiple nodule(s), grouped or disseminated papules, patches and plaques, subcutaneous induration, to erythroderma.[2,12]

The **diagnostic work-up** includes medical history (particularly exposure to arthropods, allergens, foreign material, tattoos, UV radiation, and drugs) and physical examination (e.g., full-body inspection, palpation of lymph nodes). A peripheral blood analysis should be adapted to the suspected process or type of infiltration and might include, especially, differential blood count and serology for infectious agents such as *Borrelia burgdorferi sp.*, syphilis, and HIV.

It is debatable to what extent **staging procedures** are necessary in PSL. In clear cases of PSL they are not, but in ambiguous cases a clear allocation to PSL may be possible only in retrospect. In these unclear situations and in cases with unusual manifestations (e.g., multiple nodular lesions, monotypic expression of immunoglobulin light chains, detection of T- or B-cell clonality, or other inconsistent or unexpected histopathologic, phenotypic, or genotypic findings) staging procedures (e.g., computer tomography or PET-CT) can be recommended.

1.5 | Clinical course and treatment modalities

The clinical course of cutaneous PSL can be highly variable. Some cases undergo spontaneous regression, sometimes after a biopsy. Others persist over months or even years. A re-exposure to the particular cause may incite a recurrence.[13] Progression or a so-called "aggressive course" of PSL has been rarely reported.[14,15] From our point of view, a progressive course should lead one to question the original diagnosis.

The most important point of treatment is to remove the causative agent and avoid re-exposure. An infectious cause has to be treated with an appropriate medication, such as antibiotics, anti-(retro)viral, or anti-parasitic drugs. If the causative agent cannot be removed or successfully treated, solitary lesions of PSL can be surgically excised.

In general, treatment options include topical or intralesional substances, physical modalities, or systemic drugs (reviewed in Ref. 4). The most commonly used topical or intralesional substances are corticosteroids, but topical tacrolimus has been also reported.[4] In addition, cryotherapy was described. A laser treatment was reported to be effective in tattoo-induced PSL.[16] Radiotherapy should be considered in refractory cases.

In patients with (idiopathic) multifocal PSL, systemic steroids, intralesional or systemic interferon alpha,[17] or oral hydroxychloroquine can be used.[18] Single-case reports exist of successful treatment with thalidomide.[19]

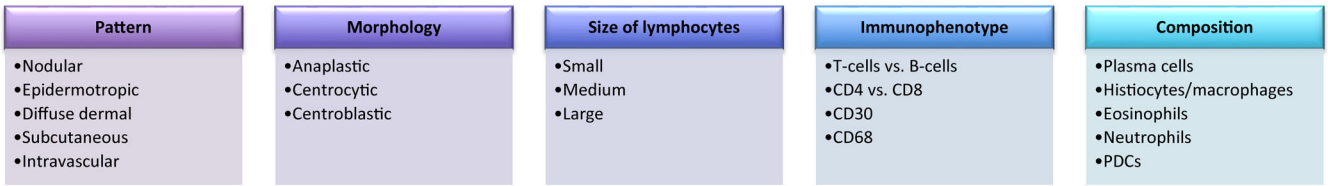

FIGURE 3 Basic histopathologic approach to cutaneous pseudolymphomas. PDCs: plasmacytoid dendritic cells

2 | CLASSIFICATION OF PSEUDOLYMPHOMA

2.1 | Nodular pseudolymphoma

Nodular PSL is the most common and classical form of cutaneous PSL. It presents clinically as solitary nodules in most cases, but sometimes multiple nodules can occur. It simulates cutaneous T- or B-cell lymphoma, both clinically and histologically. According to the predominant lymphocytic infiltrate it can be divided into B-cell, T-cell, or mixed (T-/B-cell) PSL.[2,12]

2.1.1 | Nodular B-cell pseudolymphoma

Clinical findings

Most patients with localized nodular B-cell pseudolymphoma (B-PSL) present a solitary red, bluish, or brownish nodule, measuring up to 4 cm. Sometimes a few nodules are arranged in clusters. About 10% to 15% of the patients develop disseminated papules and nodules (disseminated form).[12] A miliarial form, with multiple papules of a few millimeters in diameter, was also reported.[18]

Men are affected three times more often than women.[20] Approximately two-thirds of the patients are younger than 40 years, and <10% are children and adolescents.[21] The sites of predilection are the face (Figure 4A) (especially nose and cheeks), upper trunk, and upper extremities.

Histopathology

Nodular B-PSL (Table 3) is characterized by predominantly intradermal, dense, lymphocytic infiltrates (nodular or diffuse) (Figure 4B). It extends to the subcutis in some cases. In general, the infiltrate consists of small to medium-sized B-lymphocytes without significant nuclear atypia. Reactive germinal centers (Figure 4C) are commonly found and often contain tingible body macrophages (Figure 4D, arrow). In many cases scattered plasma cells, eosinophils, and/or histiocytes are admixed; in some cases a granulomatous component can also be observed. The number of admixed T-cells is variable, but usually does not exceed 30% of the whole infiltrate. In two-thirds of B-PSLs, plasmacytoid dendritic cells (PDCs) (CD123+) are found, typically arranged in small clusters[22]; they are located in close proximity to plasma cells and T-cells.[22,23]

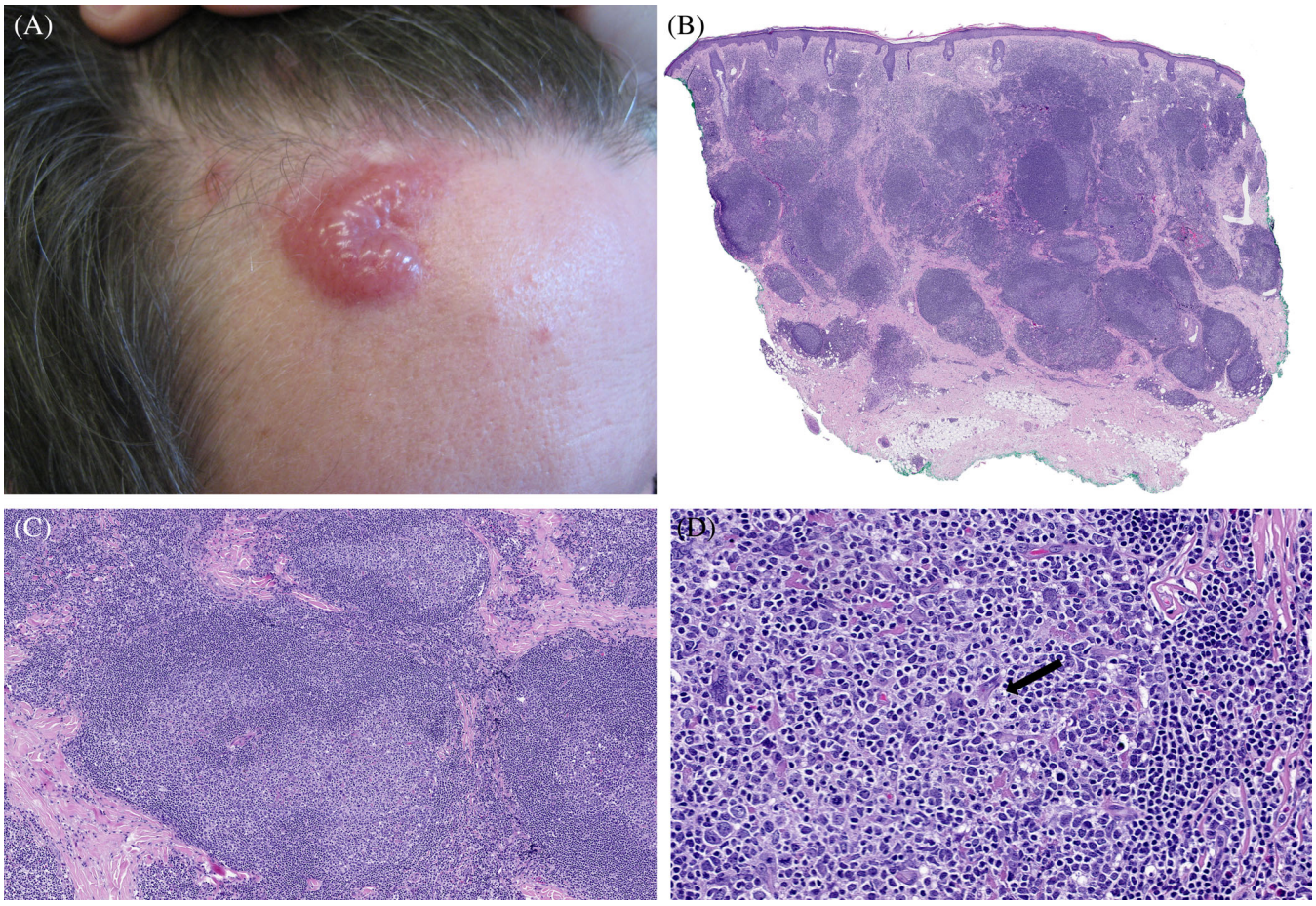

FIGURE 4 Nodular B-cell pseudolymphoma: Clinical image: A, Large red semilunar nodule on the forehead and a small red nodule behind it. Histology: B, Dense nodular infiltrate encompassing the reticular dermis (H&E; ×20). C, Reactive germinal centers of different size (H&E; ×100). D, Tingible body macrophages (H&E; ×200)

TABLE 3 Major histopathologic and immunohistochemical features in nodular B-cell pseudolymphoma

Major histologic features	Immunophenotype
Nodular or diffuse dermal B-cell infiltrate, sometimes extension in the subcutis	CD20+, CD79a, Pax-5+, CD19+, CD5−, CD23−, CD43−
Reactive germinal centers	Bcl6+ and bcl2−, sharply demarcated networks of CD21+/CD23+ follicular dendritic cells, elevated Ki-67 rate mostly confined to the germinal centers
Tingible body macrophages	CD68+
Scattered plasma cells	CD79a+, CD138+, CD38+, normally no light chain restriction (ratio < 1:5) for kappa or lambda
Sometimes eosinophils or neutrophils	
Admixed T-cells at variable degree (mostly less than 30%)	CD3+, CD4+ and/or CD8+ (normally equal distribution of CD4 and CD8) Caveat: macrophages do also express CD4 and T-cells do also express bcl-2
Small clusters of plasmacytoid dendritic cells in close relation to T-cells and plasma cells	CD123+

Immunohistochemistry and molecular diagnostics

The infiltrate predominantly consists of B-cells that express typical B-cell markers, such as CD19, CD20 (Figure 5A), CD79a, and PAX-5 (Table 3). Reactive germinal centers express bcl-6 (Figure 5B) and are negative for bcl-2 (Figure 5C). The networks of follicular dendritic cells (FDCs) can be highlighted by CD21 stain, and are usually regularly structured and sharply demarcated (Figure 5D and 6A). This is an important hint to ascertain the germinal centers as reactive. The proliferative index (Ki-67 or Mib-1) is elevated, especially in the germinal centers (Figure 6B).

The interfollicular B-cells express bcl-2 and are negative for bcl-6. They have to be differentiated from admixed T-cells, which express bcl-2 as well.

With a few exceptions, immunoglobulin (Ig) light chains lambda and kappa are polytypic (at a ratio of <1:5 or 1:10). The variability of the ratio reflects differences in the normal ratios for kappa and lambda; kappa usually predominates by 2 to 4×, while lambda is normally half to a quarter of kappa-positive plasma cells. Clonality studies in B-PSL are of limited value, because 10% to 20% of PSLs harbor a clonal B-population and not all B-cell lymphomas demonstrate a clonal result.[8,24] In some studies, an even higher percentage of cases with clonal B-cells were detectable in nodular PSL,[25] and pseudoclonality should always be ruled out as a diagnostic pitfall.[26] Results of clonality analysis always must be interpreted in the histopathologic and clinical context.

Differential diagnoses

The most important differential diagnoses are indolent primary and secondary cutaneous B-cell lymphomas, especially marginal zone lymphoma and follicle center lymphoma (Table 4).

Primary cutaneous marginal zone lymphoma (PCMZL) presents clinically with solitary or multiple red to bluish papules or nodules (Figure 7A). Based on the clinical picture alone it cannot be

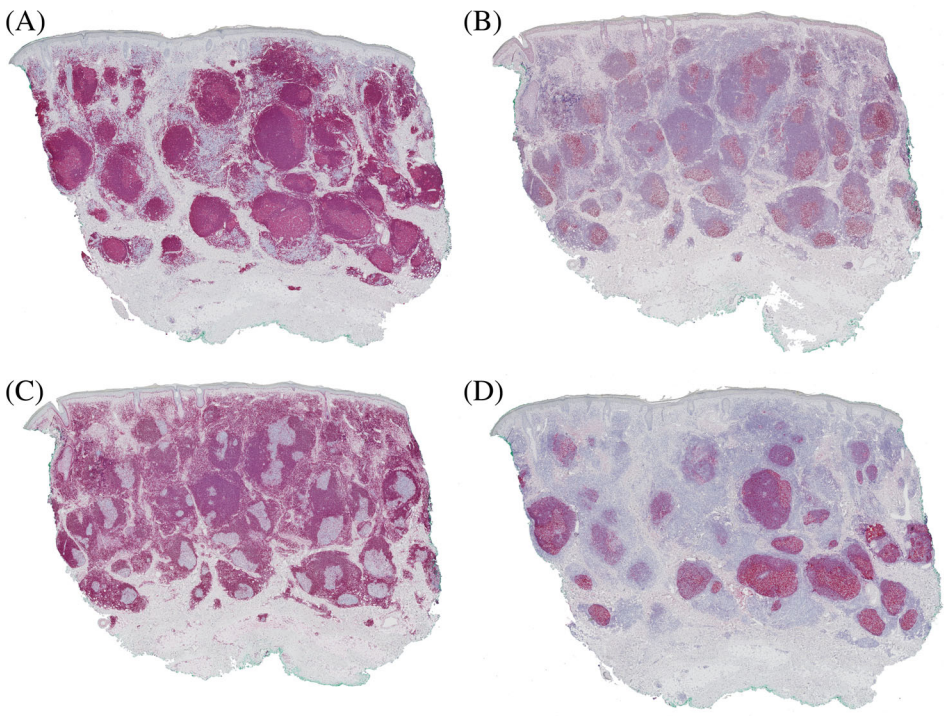

FIGURE 5 Nodular B-cell pseudolymphoma: Immunohistochemistry: A, The infiltrate is predominately positive for CD20 (×20). B, The cells in reactive follicles express bcl-6 (×20) and are C, negative for bcl-2 (×20). D, The networks of CD21-positive follicular dendritic cells (FDC) are sharply restricted to the germinal centers (×20)

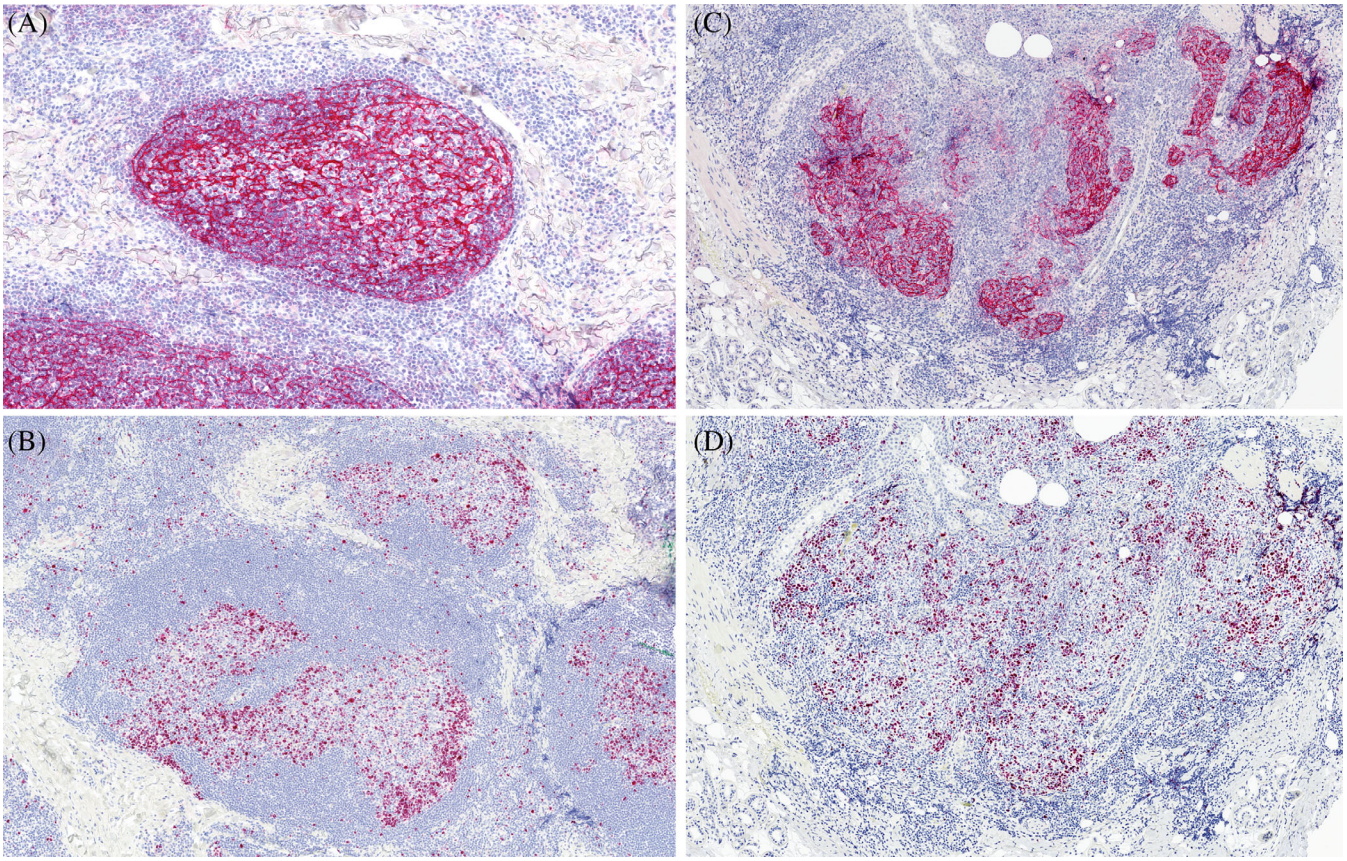

FIGURE 6 Comparison of follicular dendritic cells (FDC) and proliferative rate: Nodular B-cell pseudolymphoma: A, Detail: The networks of CD21-positive follicular dendritic cells (FDC) are sharply restricted to the germinal centers (×200). B, The proliferative rate, highlighted with Ki-67, is elevated and is mainly confined to the germinal centers (×100). Follicle center lymphoma: C, The networks of CD21+ follicular dendritic cells are irregular and disrupted (×100). D, The proliferative rate is elevated and not restricted to the germinal centers (×100)

differentiated from PSL with certainty. Cases are typically located on the upper trunk, upper arms, and less frequently on the head and neck.[27] The female to male ratio is 1:2 and the mean age is 55 years.[27] In some European cases of PCMZL *Borrelia burgdorferi* DNA was detectable. In contrast, this association was not found in cases from Asia and the United States.[14,28-30]

Histopathologically, the dermis contains nodular or diffuse infiltrates,[31] often arranged around vessels or adnexal structures

TABLE 4 Differential diagnoses of nodular B-cell pseudolymphoma

	B-PSL	PCMZL	PCFCL
Major histopathologic features	Dermal lymphocytic infiltrate, subcutis can be involved, reactive germinal centers, tingible body macrophages, often scattered plasma cells, eosinophils.	Dermal infiltrate often around the vessels or adnexal structures, subcutis can be involved, reactive germinal centers (30%), plasma cells in the periphery of the infiltrates and near by the epidermis.	Dermal lymphocytic infiltrates, subcutis can be involved, predom. of centrocyte-like tumor-cells, neoplastic irregular germinal centers of diffent size (CAVEAT: not found in diffuse type).
Immunophenotype	B-cell markers+ (CD20+, CD79a+, Pax-5+); **reactive germinal centers** (bcl-6+, bcl-2–); high proliferative activity in geminal centers (Ki-67+ or MIB-1+), sharply restricted networks of FDCs (CD21+/CD23+).	**Tumor cells:** B-cell markers+ (CD20+, CD79a+, Pax5+), bcl-2+; bcl-6–, CD5–, CD10–, CD43– **Reactive germinal centers** (bcl-6+, bcl-2–).	**Tumor cells:** B-cell markers+ (CD20+, CD79a+, Pax5+), bcl-6+; bcl-2– (90%). **Neoplastic germinal centers** (bcl-6+, bcl-2– CAVEAT: same expression as in reactive germinal centers); proliferating activity (Ki-67+, MIB-1+). Often moderate and not sharply restricted to the germinal centers (if they are even present); irregular networks of FDCs (CD21+/CD23+).
Molecular diagnostics	Polytypic light chains, polyclonal IgH (80%).	Monotypic light chain (85%) monoclonal IgH (60-70%).	Monoclonal IgH (up to 90%).

(Figure 7B); sometimes the subcutis is involved.[31] Plasma cells are admixed and, in contrast to B-cell PSL, they are predominantly found near the epidermis or at the periphery of the infiltrates.[32] Reactive germinal centers occur in about 30% of the biopsies. Leinweber et al[33] reported tingible body macrophages in all their investigated cases (6/6) of PCMZL with reactive germinal centers. Moreover, these entities cannot be discriminated by the presence and number of eosinophils.

The tumor cells in PCMZL are positive for B-cell markers (e.g., CD79a+, CD20+, Pax-5+), positive for bcl-2, and negative for bcl-6. Numerous T-cells are typically admixed. The T-cells are also positive for bcl-2 and have to be carefully differentiated from bcl-2+ B-cells. The presence of CD123+ plasmacytoid dendritic cells (PDCs) does not allow a differentiation between B-cell PSL and MZL, although the majority of MZL presented a higher number and larger clusters.[22]

A helpful finding in MZL is the immunoglobulin light chains restriction for kappa or lambda (Figure 7C,D) (ratio of at least 5:1 or 10:1, see above), which is found in about 85% of the cases. In 60% and 70% of PCMZLs a clonal B-cell is detectable. Nevertheless, some PCMZLs show no monoclonality, while some PSLs can also have a light chain restriction.

Primary cutaneous follicle center lymphoma (PCFCL) presents clinically with solitary and sometimes multiple erythematous to bluish nodules, typically located on the head, face, or neck. A manifestation on the upper trunk with annular erythematous infiltrates and was originally described under the term reticulohistocytoma dorsi (Crosti lymphoma).

Histopathologically, PCFCL is characterized by centrocyte-like differentiated tumor cells arranged in neoplastic follicles of different sizes (Figure 8A, inset, 8B). The tumor cells are positive for bcl-6 (Figure 8C). It should be mentioned that the vast majority of PCFCL do not express bcl-2 (Figure 8D). Therefore, the expression of bcl-2 is mostly not helpful to discriminate PCFCL from B-PSL. Only about 10% to 15% of PCFCLs express bcl-2 in the tumor cells. In contrast, secondary cutaneous infiltrates by nodal FCL express bcl-2, due to underlying t(14;18) translocation in the majority of the cases. Bcl-6 and bcl-2 co-expression in germinal centers excludes a reactive germinal center. Clusters of CD123+ PDCs were found in only 13% of PCFCL; therefore, this finding might be an additional clue to differentiate this entity from B-cell PSL.[22]

In only 20% of primary cutaneous FCL can tingible body macrophages be found.[33] The networks of CD21+ follicular dendritic

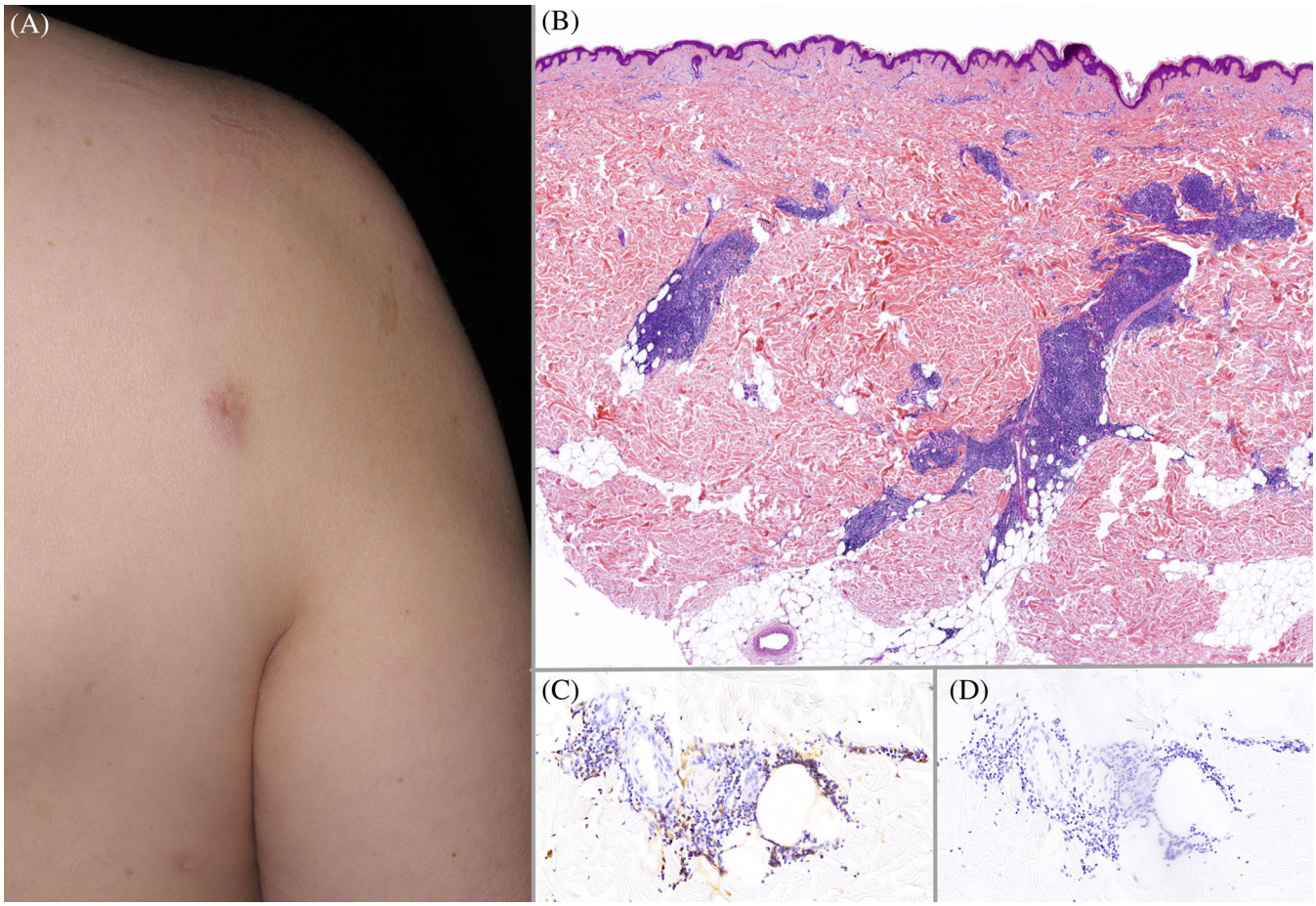

FIGURE 7 Primary cutaneous marginal zone lymphoma: A, Solitary bluish nodules on the trunk. B, Nodular infiltrates in the dermis, predominately arranged around the vessels (H&E, ×200). C, Monotypic expression of immunoglobulin light chain lambda or (D) kappa (×200)

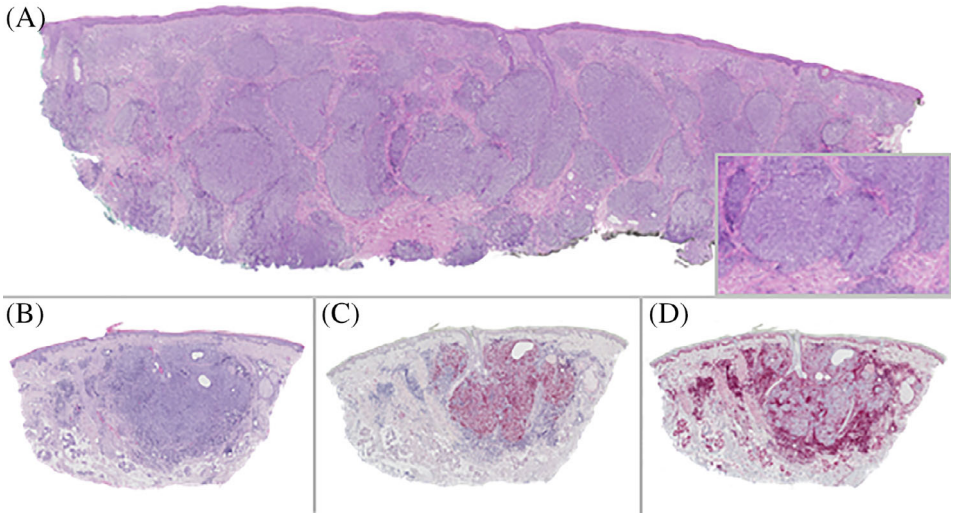

FIGURE 8 Primary cutaneous follicle center lymphoma: A, Large and irregularly structured neoplastic germinal centers throughout the dermis (HE, ×5); inset: Predominance of centrocyte-like differentiated tumor cells arranged in large neoplastic follicles (H&E, ×200). B, Large and irregularly structured neoplastic germinal centers in the dermis, next to a more diffuse infiltrate (H&E, ×5); C, Bcl-6 expression by the tumor cells. D, The vast majority of PCFCLs are bcl-2 negative. The B-cells of the residual mantle zone and the T-cells are also positive for bcl-2

cells (FDCs) in PCFCL are irregular and disrupted (Figure 6C) in contrast to reactive germinal centers (Figure 6A). The proliferative activity in the neoplastic germinal centers is often only moderately elevated and not so sharply restricted to the germinal centers (Figure 6D) as in B-cell PSL (Figure 6B). In comparison to B-cell PSL, a clonal B-cell population is more commonly detectable in PCFCL by PCR; nevertheless, somatic hypermutations can cause false-negative results.[34]

Other differential diagnoses include secondary cutaneous infiltrates of B-cell chronic lymphocytic leukemia (where the neoplastic B-cells express CD5+, CD23+) or small cell lymphocytic lymphoma, although reactive germinal centers are unusual in these entities.[35,36]

2.1.2 | *Borrelia*-associated nodular B-cell pseudolymphoma (synonyms: lymphocytoma cutis, lymphadenosis cutis benigna)

About 1% of clinically apparent *Borrelia sp.* infections manifest as B-PSL. This diagnosis can be rendered through a combination of histopathology and the detection of *Borrelia burgdorferi sp.* DNA in the tissue by PCR. The clinical context (history of tick bite, affection of predilection sites, serology) is also helpful.

Clinical findings

Solitary red to violaceous nodule located on the earlobes (Figure 9A), nipples, and scrotum of Caucasians are characteristic of *Borrelia*-

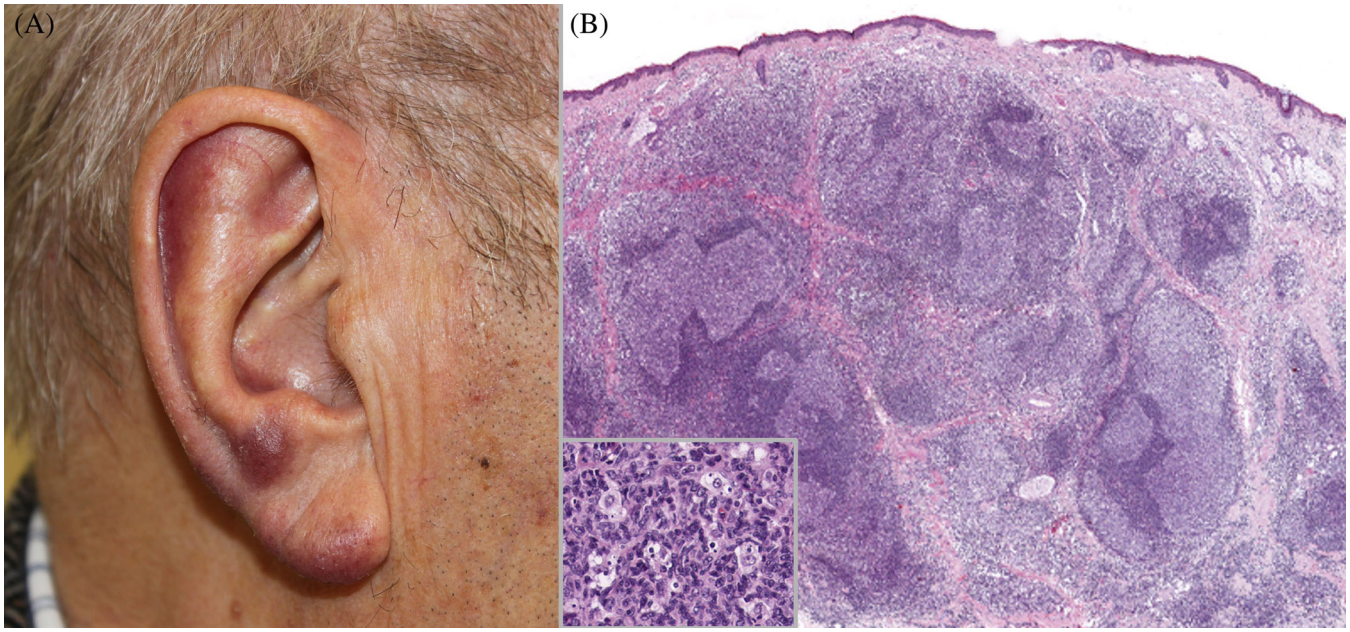

FIGURE 9 *Borrelia*-associated nodular B-cell pseudolymphoma: A, Blue nodule at the earlobe. B, Dense, dermal, nodular infiltrate with reactive germinal centers with small or completely lost mantle zones (H&E, ×20). (B, inset) Multiple tingible body macrophages (H&E; ×400)

TABLE 5 Histopathologic findings in *Borrelia*-associated nodular B-cell pseudolymphoma, modified after Colli et al[10]

Involvement of the entire dermis
Grenz zone, epidermal component in only 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%)

associated nodular PSL;[10] a reason for these predilections might be a lower body temperature in these areas. About 10% to 15% of cases exhibit multifocal skin lesions, and the trunk and extremities may also be involved.[10] Some but not all studies reported a slight female preponderance,[10] the vast majority of cases occur in children or young adults.[21]

Histopathology

A dermal or subcutaneous B-cell infiltrate with large and confluent germinal centers is found (Figure 9B),[10] with lack of polarization in up to 20%.[10,24] The mantle zones are small or even absent in some cases (Figure 9B).[10] Because of the confluence of the large germinal centers *Borrelia*-associated nodular PSL bears many overlapping features with PCFCL, follicular growth pattern.[24] Tingible body macrophages are a helpful clue for *Borrelia*-associated nodular PSL, because they are found in all cases (Figure 9B, inset).[33] Colli et al published an overview of histopathologic findings in *Borrelia*-associated pseudolymphoma, as summarized in Table 5.[10]

Rare cases of so-called *Borrelia*-associated large cell lymphocytoma might imitate diffuse large B-cell lymphoma.[37] They are characterized by centroblast- and immunoblast-like cells.[37]

Immunohistochemistry, molecular diagnostics, and Borrelia *serology*

The immunohistochemical staining profile is identical to that described in nodular B-cell PSL without *Borrelia* association (see 2.1.1.3). Tingible body macrophages can be highlighted by a CD68 stain. *Borrelia burgdorferi sp.* DNA can be detected by PCR. The sensitivity was reported as approximately 70%.[38] In the vast majority of *Borrelia*-associated cases a polyclonal rearrangement of IgH genes has been found; however, in rare cases B-cell clonality (IgH or monotypic light chains) is detected and this finding therefore does not exclude this diagnosis.[10,39]

The results of *Borrelia* serology are variable, for example, IgG and/or IgM might be elevated, but also negative serology can be found.[10]

2.1.3 | Nodular T-cell and mixed pseudolymphoma

Nodular T-cell PSL (T-PSL) is defined by a predominating T-cell infiltrate. It is a matter of debate whether a nodular T-cell lymphoma is identical with CD4-positive small to medium-sized lymphoproliferative disorder (CD4+ SMTLPD) (see also differential diagnoses). In mixed PSLs, more or less equal numbers of T- and B-cells are found. The term pseudolymphomatous folliculitis designates cases with predominantly perifollicular infiltrates.

Clinical findings

The clinical presentation is similar to that of B-cell pseudolymphomas (solitary or multiple red to violaceous nodules [Figure 10A]) and the two entities are therefore clinically indistinguishable. No detailed epidemiological data on the prevalence of T- or mixed PSL exist.

Histopathology

Nodular or diffuse lymphocytic infiltrate encompass the dermis (Figure 10B) and sometimes also the superficial subcutis. The lymphocytes are predominately small and show chromatin-dense nuclei. The

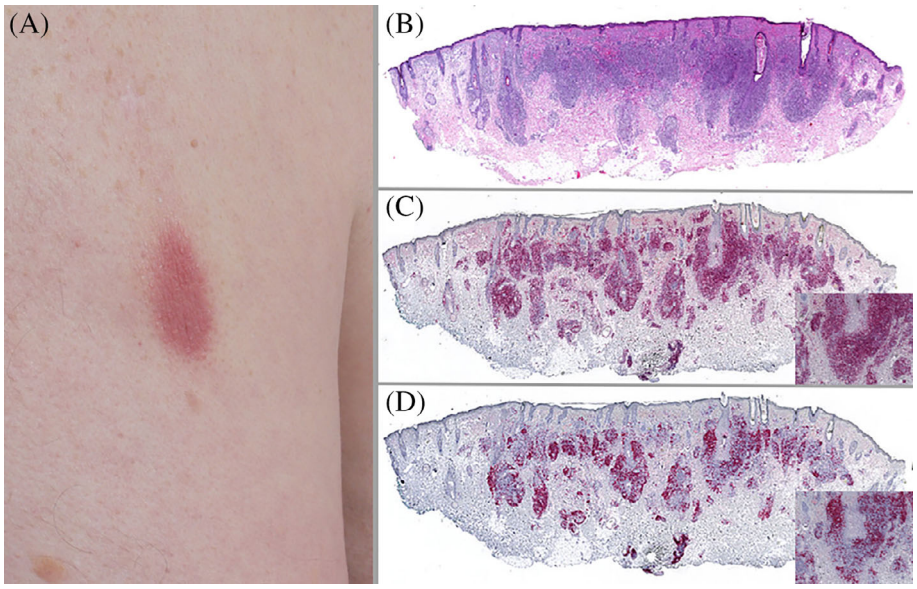

FIGURE 10 Nodular T-cell pseudolymphoma (T-PSL): A, Solitary red flat erythematous plaque on the upper trunk. B, Dense, nodular, wedge-shaped infiltrate in the entire dermis (H&E; ×20). C, CD4+ expression in the majority of the small lymphocytes (×20); D, High number of CD20+ positive B-lymphocytes expression in the majority of the small lymphocytes (×20)

number of admixed eosinophils, plasma cells, histiocytes, and B-cells is variable. In a few cases granuloma formation can be observed, and germinal centers also rarely occur. Some cases show an invasion of T-lymphocytes into the epidermis and the epithelium of the hair follicles.

Immunohistochemistry and molecular diagnostics

Most of the lymphocytes express CD3 (Figure 10C) and CD4 and are negative for CD30. The number of B-lymphocytes (CD20+, CD79a+, Pax-5+) (Figure 10D) is variable and can reach up to 30% in nodular T-cell PSL. The medium- to large-sized atypical T-cells consistently express PD-1, CXCL-13, and bcl-6, and are negative for CD10.[40] Clonality studies are also variable in T-PSL, reinforcing the overlap with CD4+ SMTLPD.[40]

Pseudolymphomatous folliculitis

This is a variant of nodular T-cell PSL, respectively a follicular manifestation of CD4+ SMSLPD. It was first reported in 1988 by Kibbi et al[41] and presents clinically as a solitary nodule with a predilection for the face.[42,43] The T-cell predominant lymphocytic infiltrate is found throughout the dermis and sometimes extends into the subcutis[43]; the epidermis is mostly spared. A hallmark of this PSL is a prominent exocytosis of lymphocytes into the hair follicles (Figure 11A).[44] The infiltrate consists predominantly of CD3+ (Figure 11B) and CD4+ (Figure 11C) T-lymphocytes, but a high number of admixed B-cells (Figure 11D) is often found. Numerous T-cells are also positive for PD-1 (Figure 11E) or other markers of follicular T-helper cells. An admixture of CD1a + and S-100+ dendritic cells (Figure 11F) was found in all cases.[42] Kazakov et al[43] reported an unusually high number (approximately 50%) of cases with T-cell clonality, or less often B-cell clonality. This raises the question if those cases may belong to the group of CD4+ SMTLPD.

Differential diagnoses

The differentiation of nodular T-cell PSL from **CD4+ small- /medium-sized T-cell lymphoproliferative disorder (CD4+ SMTLPD)**[6] is one of the most important and controversial topics. The new term ("lymphoproliferative disorder" instead of "lymphoma") in the current WHO-classification emphasizes the indolent nature of this process. It presents clinically in most cases as a solitary plaque or nodule, predominantly located on the head and neck. CD4+ SMTLPD shows numerous overlapping histological and immunophenotypic features with nodular T-cell PSL;[45,46] the expression of PD-1, bcl6, and CXCL-13 is also identical.[40] The PD-1+ cells are scattered and form pseudorosettes.[40] We and other authors consider nodular T-cell PSL and cutaneous CD4+ SMTLPD to the same process, because they cannot be discriminated by histopathology, immunophenotyping (e.g., PD-1 expression) features, or clinical presentation. Pseudolymphomatous folliculitis can also be regarded as a folliculotropic variant of CD4 + SMTLPD.

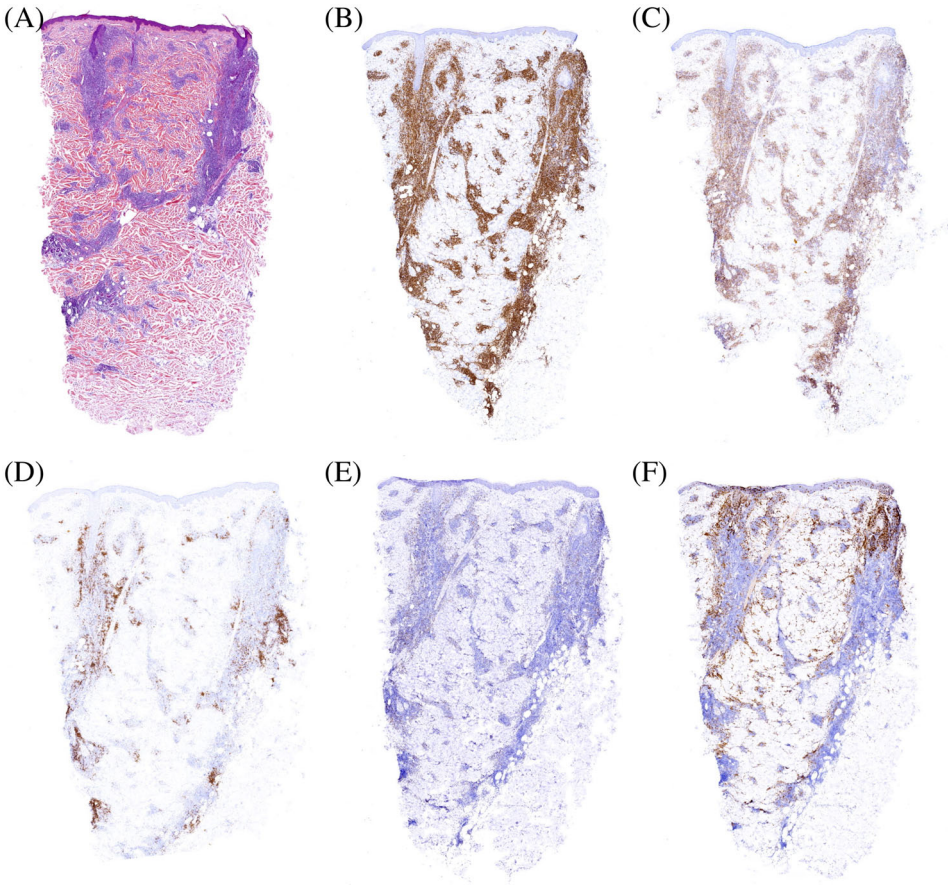

FIGURE 11 Pseudolymphomatous folliculitis: A, Prominent exocytosis of lymphocytes into the hair follicles (H&E, ×1.5); B, The infiltrate consist predominantly of CD3+ (×1.5); and C, CD4+ (×1.5) T-lymphocytes. D, High number of admixed B-cells (×1.5). E, Numerous T-cells are also positive for PD-1 (weak staining, ×1.5). F, Many admixture CD1a-positive dendritic cells

Nodular T-cell and mixed PSL have to be differentiated from **mycosis fungoides (MF), tumor stage**. MF in tumor stage presents with predominantly dermal located infiltrates containing a variable number of medium-sized or large T-cells with atypia. The cytomorphology of the lymphocytes is an important criterion to differentiate these entities. The epidermotropism in tumor stage MF is less prominent than in earlier stages of the disease. Eosinophils are not helpful to discriminate between these entities. Moreover, a significant number of admixed B-cell is often found in T-PSL. A monoclonal T-cell population is commonly found in tumor stage MF. Nevertheless, the most important criterion for discrimination is the clinical presentation, especially the existence of patches and plaques in MF.

The further differential diagnosis encompasses secondary cutaneous infiltrates, for example, of **angioimmunoblastic T-cell lymphoma (AITL)**. The small or slightly enlarged neoplastic T-cells express CD4 and PD-1 and are admixed with a high number of B-cells. The clinical context (B-symptoms, nodal involvement), a high proliferation index and an EBV-association (in some cases) are helpful to make the correct diagnosis.

In our experience, **PCMZL** can have an unexpectedly high number of T-cells (>50%). These cases are prone to be misdiagnosed as T-cell PSL. Clonal plasma cells can be helpful in this context, but they can be also found in CD4+ SMTLPD.

2.1.4 | Nodular CD30-positive T-cell pseudolymphoma

CD30+ PSL represents an immunophenotypic subtype of T-cell PSL of the skin. Because of the heterogeneous clinical and histologic spectrum it is difficult to attribute it to one PSL group only. The literature uses the term "CD30+ PSL" if CD30+ cells are admixed in the infiltrate, even if the pattern is MF-like.

In this article the term CD30+ PSL refers to cases with nodular (or papular) presentation and a histopathologic pattern simulation lymphomatoid papulosis (LyP), especially of type A.[47,48] A CD30+ PSL simulating primary cutaneous (CD30+) anaplastic large cell lymphoma (ALCL) has never been described, because the latter is defined by dense, cohesive-sheets of atypical CD30+ lymphocytes, which reflects a least 75% of the infiltrate, which would be unusual for an reactive process. In contrast, secondary cutaneous infiltrates of ALCL might be less dense and less pleomorphic and could be therefore misinterpreted as reactive.

Clinical findings

The clinical presentation encompasses papules or small nodules. Most of these undergo no spontaneous regression over weeks to months; in contrast, LyP is clinically characterized by waxing and waning. CD30+ PSL has been associated with arthropod-bite reaction, scabies infection (esp. as persistent nodules in scabies), and virus infections (especially molluscum contagiosum, orf or ecthyma contagiosum, milker's nodule, and herpesvirus infection).[49-51] Lesions caused traumatically by coals or lymphomatoid drug reactions can also contain CD30+ cells. The latter is a classical simulator of MF.

Histopathology and Immunohistochemistry

It is characterized by a mixed lymphocytic infiltrate in the dermis, containing medium-sized to large atypical CD30-positive T-cells[50,52] that co-express CD3 and CD4 or, less commonly, CD8. The CD30+ blast-like cells are typically scattered throughout the infiltrate or arranged in little groups (Figure 12A, B). Moreover, numerous small T-cells are admixed. A high number of B-cells and plasma cells can be a clue for a reactive process. In many cases the correct diagnosis can be made only if the underlying disease (e.g., scabies: Figure 12C, molluscum contagiosum) was found.

Differential diagnoses

Lymphomatoid papulosis (LyP) (particularly type A) is the most important differential diagnosis. The number of CD30+ cells in CD30+ PSL is often lower than in LyP and they are more scattered and not arranged in sheets or clusters (Table 6); however, note that some types of LyP contain only few or even no CD30+ lymphocytes. Moreover, in our experience the staining intensity is often weaker in a reactive than in a neoplastic process. If signs of a causative factor (e.g., molluscum contagiosum or herpes infection) are not evident in the biopsy specimen, it can be very difficult or even impossible to differentiate between these entities without clinical-pathologic correlation. Clonality studies for the T-cell receptor do not allow a reliable distinction, because a clonal rearrangement in LyP type A may not be found[53] without microdissection; moreover, monoclonal results can occur in reactive processes containing CD30+ cells.[54]

2.2 | Pseudolymphomas as simulators of mycosis fungoides ("pseudo-MF") and of other cutaneous T-cell lymphomas (CTCLs)

The term pseudo-MF encompasses a collection of different disorders that mimic mycosis fungoides primarily histologically. Based on histopathology alone a cutaneous T-cell lymphoma cannot be assigned to MF with certainty; moreover, other CTCL types than MF can be simulated. Therefore, clinicopathological correlation is essential to avoid misinterpretation. Some general histopathologic and immunochemical features are summarized in 2.1.5.1 and 2.1.5.2. Further details for each entity are discussed in 2.1.5.4.

2.2.1 | Histopathology

In general, pseudo-MF is characterized by a band-like (Figure 13A) or perivascular lymphocytic infiltrate. The lymphocytes are mostly small or medium-sized, sometimes with subtle nuclear atypia. They show exocytosis into the epidermis, sometimes with a band-like arrangement in the junctional zone (lining-up).

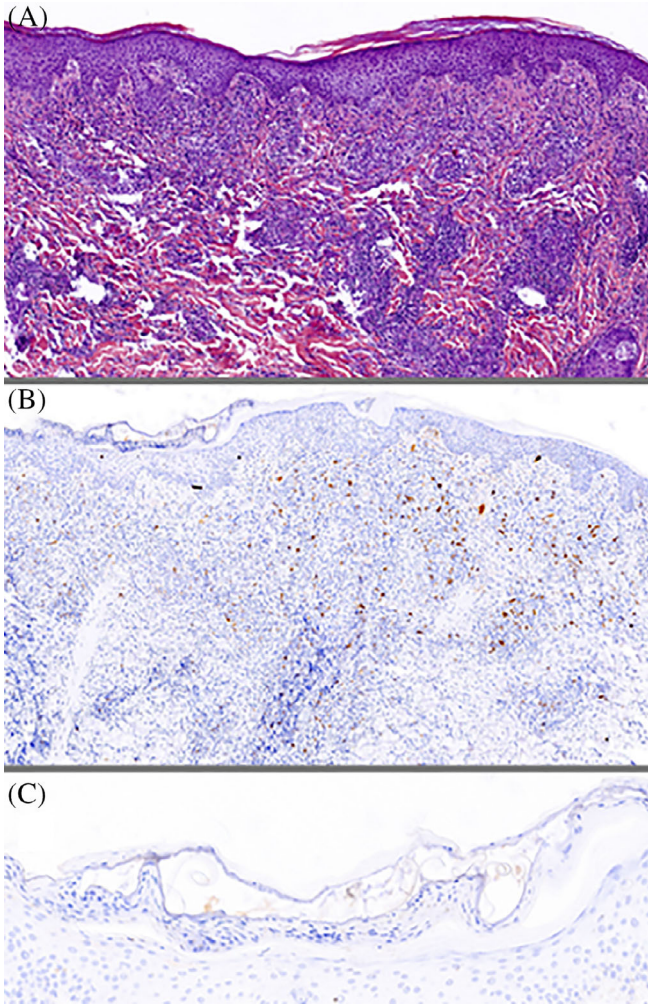

FIGURE 12 CD30-positive T-cell pseudolymphoma in scabies: A, Dense lymphocytic infiltrate with epidermal hyperplasia (H&E; ×100). B, Numerous CD30+ lymphocytes are admixed (×100). C, Detail of B: In the stratum corneum pigtail-like structures can be found. These are pathognomonic for a scabies infection (×400)

2.2.2 | Immunohistochemistry and molecular diagnostics

The T-cells are positive for CD3 and present a predominance of CD4+ or CD8+ cells (Figure 13B), especially in the intraepidermal component. CD30 expression is variably present in some cases. The

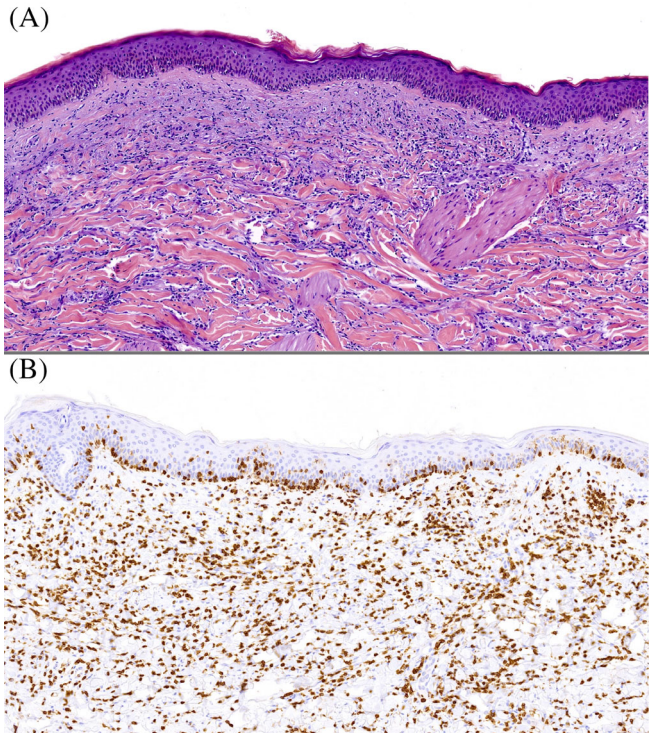

FIGURE 13 Pseudo mycosis fungoides (Pseudo-MF) in recurrent herpes simplex virus infection: A, Band-like infiltrate of mostly small lymphocytes with exocytosis into the epidermis (H&E, ×100). B,: Lining-up of CD8+ lymphocytes at the dermo-epidermal junction (×100)

lymphocytes are polyclonal in the majority of cases, but in a few instances a clonal T-cell population is present. Clinical correlation is important in such cases to avoid misdiagnosis as lymphoma.

2.2.3 | Differential diagnoses

MF and Sézary syndrome are the most important differential diagnoses. In general, a more prominent infiltrate with nuclear atypia, Pautrier collections, and loss of T-cell markers (e.g., CD2, CD7, CD5) favors the diagnosis of MF. Based on the immunohistochemical profile, expression of TOX and PD-1 by at least 50% of the lymphocytes, loss of CD7, low numbers of CD8+ T-cells, and increased proliferative index (Mib-1, Ki-67) are the best indicators o Sézary syndrome.[55,56]

TABLE 6 Histopathologic criteria to differentiate a neoplastic and reactive CD30-positive infiltrate

	Neoplastic	Neoplastic Reactive
Number of CD30+ cells	Often higher number	Lower number
Rangement of CD30+ cel	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 (e.g. in Lyp type A: mixed infiltrate with many histiocytes, ALCL: predom. CD30+ cells arranged in sheets)	Higher number of admixed B-cells and plasma cells

TABLE 7 Clinical and histopathologic characteristics of T-cell pseudolymphomas and their differential diagnoses

	Lymphomas		Pseudolymphomas as simulators of mycosis fungoides (pseudo-MF)				
	Mycosis fungoides (MF)	Sézary syndrome (SS)	Lymphomatoid contact dermatitis (LCD)	Lymphomatoid drug reaction (LDR)	Actinic reticuloid (AR)	CD8+ T-PSL in immunodeficiency (CD8+ PSL)	*Borrelia*-associated T-PSL—mimicker of MF
Sites of predeliction	Buttocks and other sun-protected areas	Generalized	Areas exposed to the allergen(s)	Variable, generalized, often symmetric, sun-exposed areas are affected	Face, neck: sun-exposed areas	Generalized	Lower limbs, trunk
Clinical picture	Patch, plaques, and tumors, sometimes erythroderma (depending on the stage)	Erythroderma, palmoplantar hyperkeratosis, enlarged lymph nodes	Eczematous and pruritic papules, patches or plaques	Rash, macular-papular eruptions	Persistent erythematous lichenoid papules and plaques, facies leonina	Variable: plaques, erythroderma, palmoplantar hyperkeratosis, lymphadenopathies	Variable: erythema chronicum migrans, acrodermatitis chronica atrophicans, MF-like, lichenoid aspect
Major histopathologic features	Lining-up, Pautrier collections, atypia, eosinophils are uncommon in patch MF	Often unspecific, epiderotropism may be absent, often only mild atypia	Superficial band-like infiltrate, spongiosis, pseudo Pautrier collections, eosinophils	Superficial, band-like, eosinophils	Psoriasiform hyperplasia, mild spongiosis, eosinophils, coarsed and vertically arranged collagen bundles in the papillary dermis	Superficial and mid-dermal infiltrate, no significant atypia	Band-like or deep, lichenoid aspect, lymphocytes, histiocytes (pseudorosettes), variable number of plasma cells
Major immunoprofile	CD4+ or CD8+ or CD4−/CD8−, loss of pan T-cell markers possible, admixed CD30+ cells possible	CD4+, PD-1+, TOX+, loss of CD7, elevated proliferative rate (Ki-67)	CD4 = CD8, sometimes admixed larger CD30+ cells	CD4 or CD8 predominance, admixed CD30+ cells. Caveat: loss of CD7 is possible	CD8+	CD8+, TIA-1, granzyme B	CD4+
Additional findings		Blood involvement (see criteria of International Society for Cutaneous Lymphomas [ISCL])	Identification of the allergen (patch test)		Increased number of circulating CD8+ cells in the peripheral blood, photosensitivity	HIV with low CD4 count, other type of immunosupression, often monoclonal cells in the peripheral blood	Detection of *Borrelia burgdorferi* sp. by PCR, serology

Clonality might also argue for MF, but in early MF lesions clonality is detectable in only approximately 50% to 70% of the cases; conversely, monoclonal T-cells have been also reported in reactive processes. Concerning Sézary syndrome, the final diagnosis can be made only in conjunction with blood analysis and the clinical setting.

In cases with an epidermotropic, predominantly CD8+ infiltrate, CD8+ MF, lymphomatoid papulosis (type D), cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, and more rarely primary cutaneous gamma/delta T-cell lymphomas (approximately 10% of which are CD8+) should be considered.

2.2.4 | Different forms of pseudo-MF or simulators of other T-cell lymphomas

Lymphomatoid contact dermatitis (LCD) is a chronic contact dermatitis, occurring mainly in adults and affecting both genders.[57] It presents clinically with eczematous and pruritic papules, patches, plaques, or infrequently with erythroderma.

Histopathology shows a superficial, band-like lymphocytic infiltrate with variable epidermal exocytosis and mild atypia. Eosinophils are usually admixed. Spongiosis is often found and is a helpful clue in the distinction from MF. Pseudo Pautrier collections (intraepidermal accumulations of Langerhans cells) can be observed and sometimes misinterpreted as true Pautrier collections. In contrast to MF, the ratio of CD4+ to CD8+ lymphocytes is balanced. CD30+ lymphocytes may be present. Table 7 shows details and differential diagnoses.

Lymphomatoid drug reaction (LDR) most commonly presents with macules or papules.[2,58] Magro et al[59] mentioned clinical features supportive of a drug-induced reaction: (a) an abrupt onset with a duration less than 6 months, (b) symmetry of the rash, and (c) involvement of the sun-exposed areas.

Histologically, lymphomatoid drug reaction displays a band-like or perivascular infiltrate (Figure 14A) in the upper dermis. Exocytosis of T-cells into the epidermis is variable.[60] Vacuolar alteration at the dermo-epidermal junction (Figure 14A) and apoptotic keratinocytes can be present. The lymphocytes may have moderate atypia (Figure 14B) and eosinophils are usually admixed. Papillary edema and eosinophilic spongiosis favors the diagnosis of LDR.[59] The lymphocytes predominantly express CD4 or CD8. CD30+ lymphocytes can also be found.[61] Important clues for LDR in contradistinction to MF are a predominance of CD8+ intraepidermal lymphocytes with a paradoxical predominance of CD4 in the dermal component. A reduced expression of CD7 may be observed, but a substantial reduction of CD7 (absent in >70% of the lymphocytes) would be unusual for LDR (Table 7).[59]

Actinic reticuloid (AR) is a chronic, multifactorial dermatitis with severe photosensitivity. In the vast majority middle-aged and older men are affected.[62] In photo-exposed sites (particularly on the face and neck), lichenoid red papules and plaques occur, and sometimes progress to erythroderma. Some patients presented a leonine facies. AR is accompanied by intense pruritus and signs of irritation, such as lichenification and erosion.

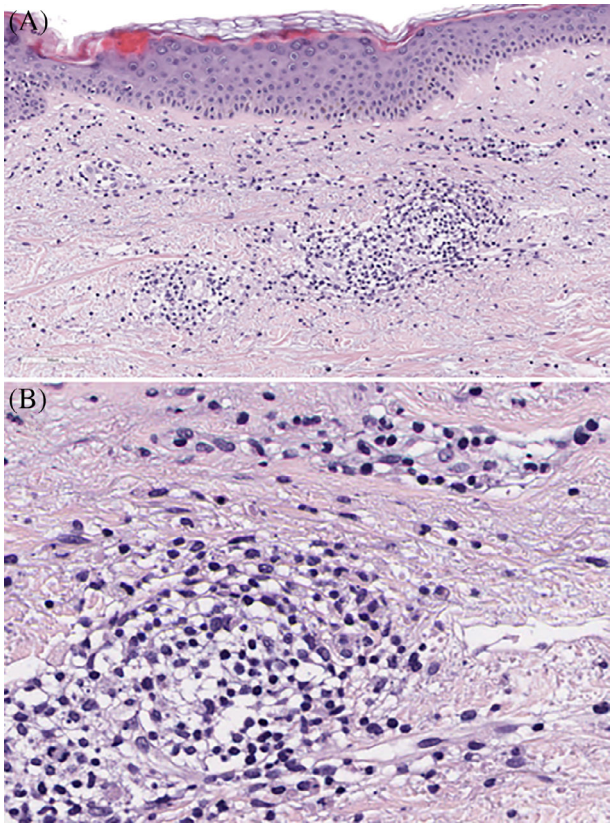

FIGURE 14 Lymphomatoid drug reaction: A, Perivascular infiltrate in the upper dermis and mild vacuolar alteration at the dermo-epidermal junction. B, Moderate, but significant atypia of the lymphocytes

Histopathologically, AR shows epidermal acanthosis with slight spongiosis. As a result of chronic irritation the cornification is compact and focally parakeratotic. The superficial dermis shows fibrosis, sometime with multinucleated fibroblasts. The infiltrate is predominantly located in the superficial dermis and composed of small T-cells (some with slight atypia), plasma cells, and eosinophils. The T-cells are predominantly positive for CD8.[63] Especially in erythrodermic patients, an increased number of circulating CD8+ T-cells (reversed CD4:CD 8 ratio) is characteristic of AR (Table 7).[62]

CD8+ T-cell pseudolymphoma in immunodeficiency occurs particularly in patients with HIV infection, especially in those with profound immunosuppression and a high viral load.[64] Similar features were recently described in renal transplant recipients.[65] A broad clinical spectrum is reported, including infiltrated red plaques, erythroderma, palmoplantar hyperkeratosis, and generalized lymphadenopathy.[66-68] Some authors have reported a worsening of skin symptoms after ultraviolet radiation exposure.

Histopathology discloses a lymphocytic infiltrate in the upper dermis, with epidermotropism. The lymphocytes are predominantly small, without significant atypia. The lymphocytes are CD3+ and show a clear predominance of CD8+. They express cytotoxic markers (granzyme B, TIA-1). Eosinophils are often admixed. Molecular studies revealed the polyclonal nature of the skin infiltrate, but clonal lymphocytes can be found in the peripheral blood (Table 7).[64]

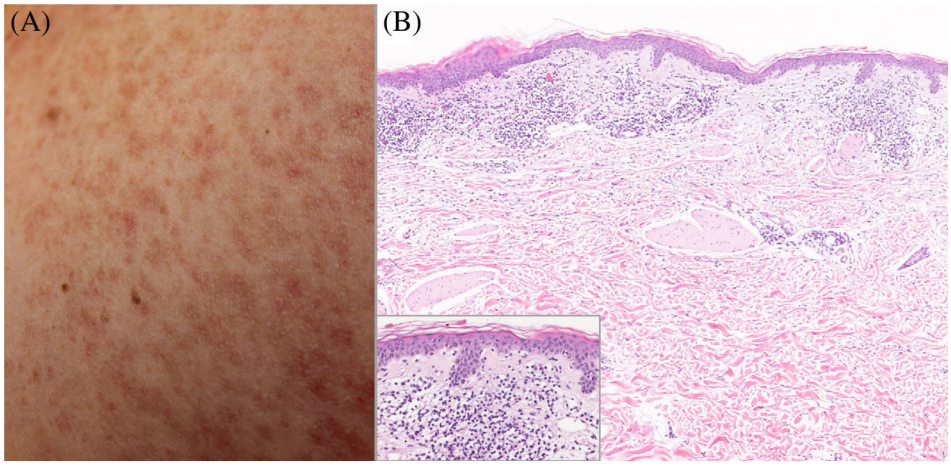

FIGURE 15 *Borrelia*-associated T-pseudolymphoma (BA-T-PSL)—mimicker of mycosis fungoides: A, Multiple, lichenoid, red-brownish macules and flat papules on the back. B, Superficial, band-like, lymphocytic infiltrate (H&E; ×20). Inset: The infiltrate predominately consists of T-lymphocytes, with a few admixed plasma cells. Vacuolar alteration of the junctional zone (H&E; ×200)

2.2.5 | Infections as simulators of T-cell lymphoma

Borrelia-*associated T-pseudolymphoma*

Besides the well-known *Borrelia*-associated B-cell PSL (BA-T-PSL), *Borrelia sp*. can also induce T-cell-rich pseudolymphomatous infiltrates.[69] Two different patterns have been described: (a) an epidermal and dermal infiltrate as a mimicker of MF; and (b) a subcutaneous infiltrate mimicking subcutaneous panniculitis-like T-cell lymphoma.

a) Mimicker of MF: It presents with patches or plaques, sometimes with a lichenoid aspect (Figure 15A) and sometimes also with the classical clinical presentation of acrodermatitis chronica atrophicans.

The histopathology is characterized by a dermal T-lymphocytic infiltrate, which is either band-like (sometimes with vacuolar alteration) (Figure 15B, inset) or diffuse. The infiltrate also contains histiocytes, sometimes forming histiocytic "pseudorosettes." The number of admixed plasma cells is highly variable (Table 7).[69] Detection of *Borrelia* in the skin infiltrate by PCR is necessary to confirm the diagnosis.

b) Mimicker of subcutaneous panniculitis-like T-cell lymphoma: Panniculitis has rarely been reported in borreliosis. One case has been described as a simulator of panniculitis-like T-cell lymphoma.[70] It presented a dense lobular panniculitis (Figure 16A), predominantly consisting of medium-sized lymphocytes with moderate atypia (Figure 16B). The lymphocytes lined up (rimming) around adipocytes (Figure 16B) and expressed T-cell markers with a predominance of CD8 (Figure 16C) and TCR beta.[70] Numerous histiocytes were admixed. The diagnosis was based on positive *Borrelia* PCR and a complete remission after doxycycline treatment. A monoclonal rearrangement of the TCR genes was not detectable in this case.[70]

The amastigote-negative, lymphocytic-rich variant of ***cutaneous leishmaniasis (CL)*** can simulate lymphoma. In usual cases CL is characterized by granulomatous inflammation with plasma cells and lymphocytes in a variable proportion.[71,72] Tomasini et al[72] reported that in five of 27 primarily undiagnosed amastigote-negative cases a pseudolymphomatous reaction occurred. Three cases had a B-cell-predominant infiltrate with reactive germinal centers and two cases had a predominant T-cell pattern with epidermotropism, simulating MF.[72] The detection of the amastigotes is essential to make the correct diagnosis. PCR is helpful to identify the agent if they cannot be identified by conventional histopathology or special stains (Giemsa).[73] Tomasini et al[72] recommend performing PCR for *Leishmania*-specific DNA on all presumptive idiopathic PSL cases, in countries where *Leishmania* is endemic.

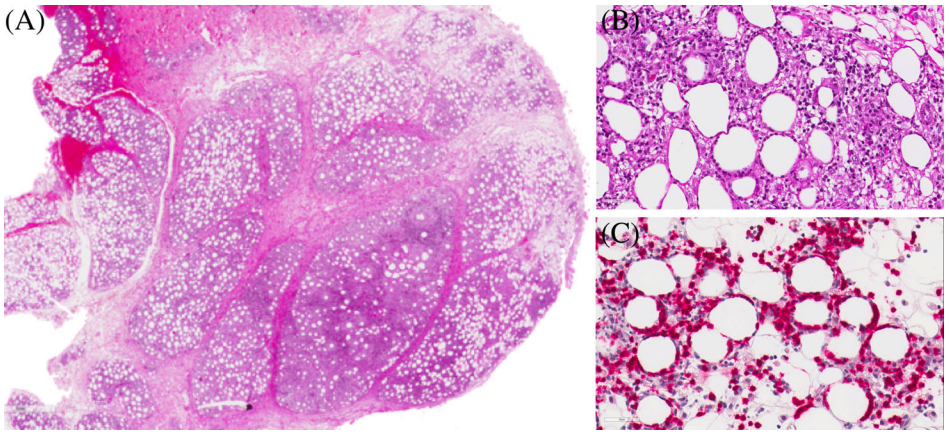

FIGURE 16 *Borrelia*-associated T-pseudolymphoma (BA-T-PSL)—mimicker of subcutaneous panniculitis-like T-cell lymphoma: A, dense lymphocytic infiltrate in the panniculus with admixed histiocytes (H&E; ×5). B, Rimming of atypical lymphocytes around adipocytes (H&E; ×200). C, The lymphocytes are predominantly positive for CD8 (×250)

In infections with **varicella zoster virus (VZV)** and **herpes simplex virus (HSV)**, lymphocyte-rich infiltrates without typical epithelial herpesvirus alterations can occur. Some of these cases were described as herpes incognito,[74] others as simulators of cutaneous T-cell lymphomas.[13,75,76] HSV infections demonstrated a pandermal perivascular and periadnexal T-cell-rich infiltrate with a variable number of admixed histiocytes. The hair follicles were usually affected, with inflammation in the sebaceous glands, in and around the *arrectores pilorum* muscles and around the eccrine/apocrine ducts.[13] Plasma cells were found in all cases, but to a highly variable degree.[13] As already reported as a clue[74] for herpes incognito, papillary edema is a common finding.[13] The lymphocytes were slightly enlarged, with atypical, chromatin-dense nuclei, and presented a lining-up in four of the five investigated cases; the intraepidermal lymphocytes were predominantly CD8+.[13] The number of CD30+ lymphocytes is variable. Immunohistochemical stains for viral antigens and/or detection of viral DNA by PCR allow identifying those reactions as herpesvirus-related T-cell PSL.[74] Moreover, clinical-pathologic correlation is helpful.[13]

Secondary and tertiary syphilis has been described as a mimic of both CTCL and B-cell lymphoma.[77-79] The histopathologic spectrum of syphilis is broad. Most often an interstitial histiocyte-rich ("busy dermis") or even granulomatous dermatitis is described.[80] The epidermis is often acanthotic and lymphocytes infiltrate the epidermis, most commonly accompanied by a vacuolar alteration.[80] The lymphocytes are often enlarged, with ample cytoplasm; moderate nuclear atypia can be observed. Plasma cells are present in only 70% of the cases.[80] A special diagnostic challenge is a co-infection of syphilis (lues maligna) and HIV. In these cases, a predominance of CD8+ lymphocytes[11,81] can occur and monoclonal TCR rearrangement has been documented[11] simulating CD8+ aggressive epidermotropic CTCL.

Poxvirus infections (e.g., parapoxvirus of milker's nodule, or orf [ecthyma contagiosum] and molluscipoxvirus of molluscum contagiosum) can induce atypia of T-lymphocytes and expression of CD30, which can make differentiation from CD30+ lymphoproliferative disorders (CD30+ LPD) challenging (see also 2.1.4).[50,52] The presence of epithelial and virus specific changes (e.g., cytoplasmic inclusion bodies or molluscum bodies) are the best clue to the correct diagnosis. Moreover, a loss of T-cell markers and monoclonal rearrangement of T-cell receptor genes would be unusual in poxvirus infections. Additionally helpful is the detection of the virus by immunohistochemistry or PCR.

2.2.6 | Inflammatory disorders as simulators of T-cell lymphoma

Various inflammatory diseases, especially those with prominent epidermotropism or alteration of the interface zone, can be misinterpreted as MF or other epidermotropic T-cell lymphomas. These diseases include, among others, pityriasis lichenoides, lichen sclerosus et atrophicus, lichen planus, and pigmented purpuric dermatitis.[82-85] In addition, MF is known to have a broad clinical and histological spectrum (e.g., lichenoid) and can therefore also mimic all of these diseases. Remarkably, a monoclonal rearrangement of TCR genes is commonly found in pityriasis lichenoides, harboring clonal T-cells in up to 60% of the cases.[83,86] Clonal T-cell populations have reported in other diseases as well, for example, in approximately 6% and 13% of lichen planus and lichen sclerosus et atrophicans cases, respectively.[54] Clinical-pathologic correlation is critical for the diagnosis.

Inflammatory diseases with lymphocyte-rich dermal and/or subcutaneous infiltrates, for example, lupus erythematosus (esp. tumid type and lupus panniculitis) must be distinguished from CTCL, particularly subcutaneous panniculitis-like T-cell lymphoma and gamma/delta lymphoma.

2.3 | Other pseudolymphomas

This group encompasses distinct clinical entities that do not belong to any of the other groups. We split this group into T-cell rich angiomatoid pseudolymphoma, cutaneous plasmocytoma, and a group of entities formerly assigned as PSL. The last group included cases described in the literature as PSL, but that seem better designated as other (non-pseudolymphomatous), distinct diseases.

2.3.1 | T-cell-rich angiomatoid pseudolymphomas

In recent years it has been suggested that acral pseudolymphomatous angiokeratoma (APA), T-cell-rich angiomatoid polypoid pseudolymphoma (TRAPP), primary cutaneous angioplasmocellular hyperplasia, and lymphoplasmacytic plaque (LPP) belong to the same spectrum of diseases.[87,88] Angiolymphoid hyperplasia (ALHE) is nowadays considered to be a form of hemangioma; with regard to its remarkable lymphocytic infiltrate, however, it would also fit into this group.

Acral pseudolymphomatous angiokeratoma (APA) was originally described in children (synonym: acral pseudolymphomatous angiokeratoma of childhood, or APACHE), but it can also affect adults and its localization is not exclusively acral.[89-91] APA manifests clinically as unilateral eruptions of red to violaceous, angiomatous, grouped papules (diameter 1 to 5 mm). Histopathologically, the infiltrate consists of small, polyclonal T- and B-cells, eosinophils, plasma cells, and histiocytes (Figure 17A). In some cases, histiocytic giant cells are present. Thick-walled vessels lined by plump endothelia are typically found in the infiltrate (Figure 17B).

T-cell-rich angiomatoid polypoid pseudolymphoma (TRAPP) is a polypoid variant that is more common in women than in men (female: male = 16:3).[88] The mean age of manifestation is 39 years (range, 16-71 years).[88] It occurs most commonly on the head, but is also reported in other localizations.[88] It consists of a polypoid lesion and numerous vessels with plump endothelia. Moreover, there is a dense dermal infiltrate of T-cells with admixed histiocytes and plasma cells. In half of the cases eosinophils were also found.

Primary cutaneous angioplasmocellular hyperplasia presents with a solitary nodule (or a few grouped nodules), usually located in the head and neck area.[92] The mean age is 45 years and the gender distribution is equal.[92] It is characterized by dilated capillaries surrounded

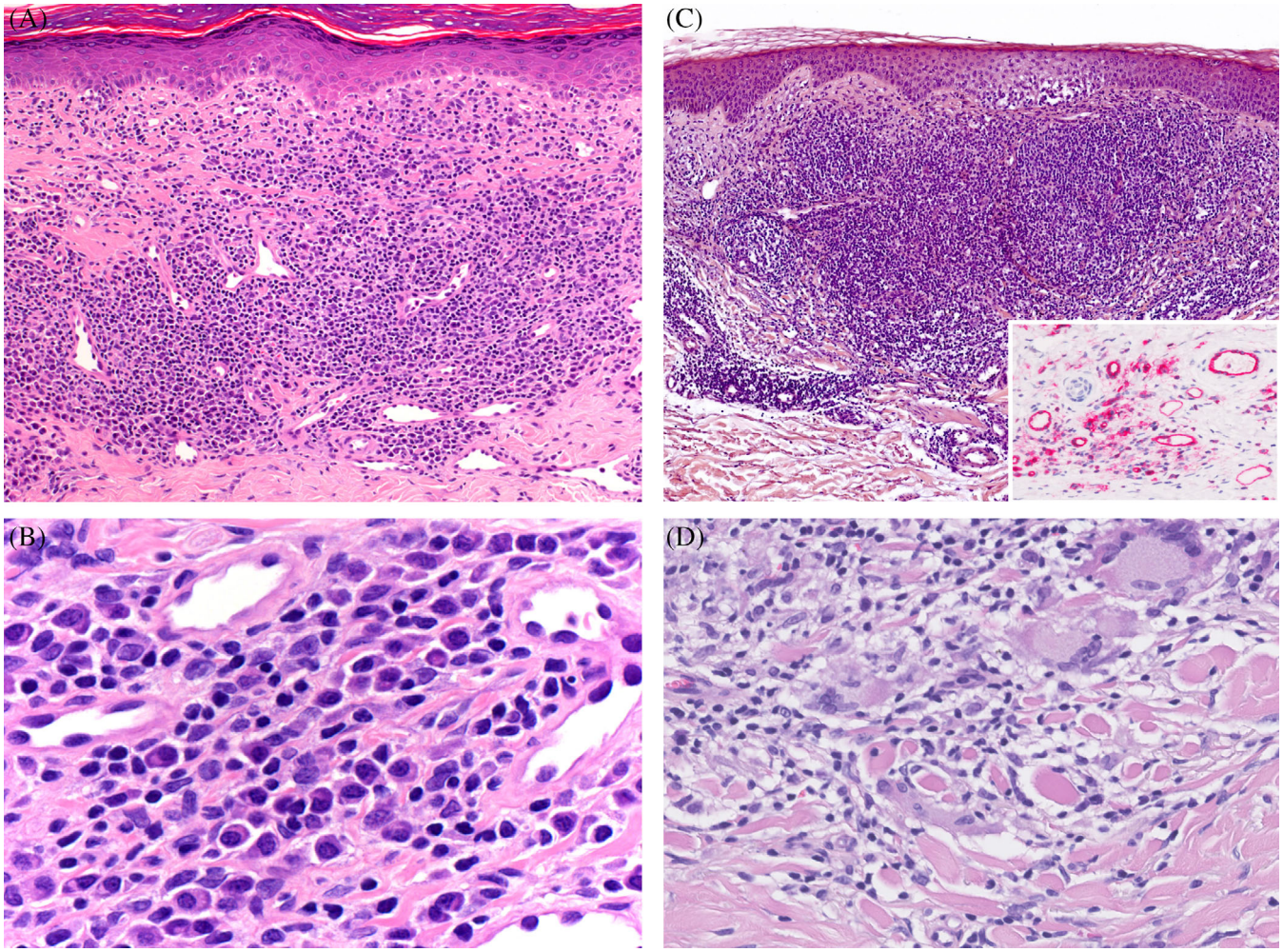

FIGURE 17 Acral pseudolymphomatous angiokeratoma (APA): A, Dense infiltrate of small lymphocytes (polyclonal T- and B-cells), eosinophils, plasma cells, and histiocytes, with scattered histiocytic giant cells (H&E, ×20). B, Thick-walled vessels lined by plump endothelia, surrounded by plasma cells (H&E, ×100; detail: H&E, ×200). Lymphoplasmacytic plaque (LPP): C, Epidermal hyperplasia with a band-like and superficial perivascular infiltrate (H&E; ×100). Inset: numerous vessels highlighted with CD31 stain (×200); D, Interstitial histiocytic granulomas around sclerotic collagen bundles ("pseudorosettes") (H&E; ×400)

by a polytypic plasma-cell rich infiltrate.[92] The proportion of plasma cells ranges from 70% to 90%, admixed with lymphocytes and sometimes also neutrophils.[92]

Lymphoplasmacytic plaque (LPP) was originally reported in children in the pretibial region,[93,94] but it can also affect adults and involve the trunk and arms.[87] Females are more commonly affected. LPP shows a distinct clinical presentation, as a longstanding plaque or as circumscribed, often linearly-arranged reddish and brownish papules and plaques.[87,95] The diagnosis is based on clinicopathologic correlation.

Histopathology reveals a superficial, band-like (Figure 17C), deep nodular, or interstitial mixed infiltrate, often accentuated around vessels or adnexal structures. The epidermis is often hyperplastic. The infiltrate consists of lymphocytes, histiocytes, and polyclonal plasma cells.[87] Histiocytic giant cells and an increased number of vessels are found.[87] The histiocytes may form granulomas around sclerotic collagen bundles (so called "pseudorosettes") (Figure 17D).[87]

2.3.2 | Cutaneous plasmocytosis (CP)

Plasmocytosis is a rare disease that typically affects adults[96,97] in their third to fifth decades, especially in Japan and other Asian countries. CP presents clinically with multiple, brownish, small plaques and nodules, occurring on the face, neck, and trunk.[98] Histopathology shows a superficial and deep dermal infiltrate composed predominately of mature polyclonal plasma cells without atypia.[96,97] A polyclonal hypergammaglobulinemia is the most commonly reported association.[98] In some patients other signs of systemic involvement (e.g., hepatosplenomegaly, lymphadenopathy) are present.

2.3.3 | Entities formerly assigned to the group of pseudolymphomas

In this group we summarize entities that have been described in the literature as PSL, but that seem to fit better into other, distinct (non-pseudolymphomatous) disease categories.

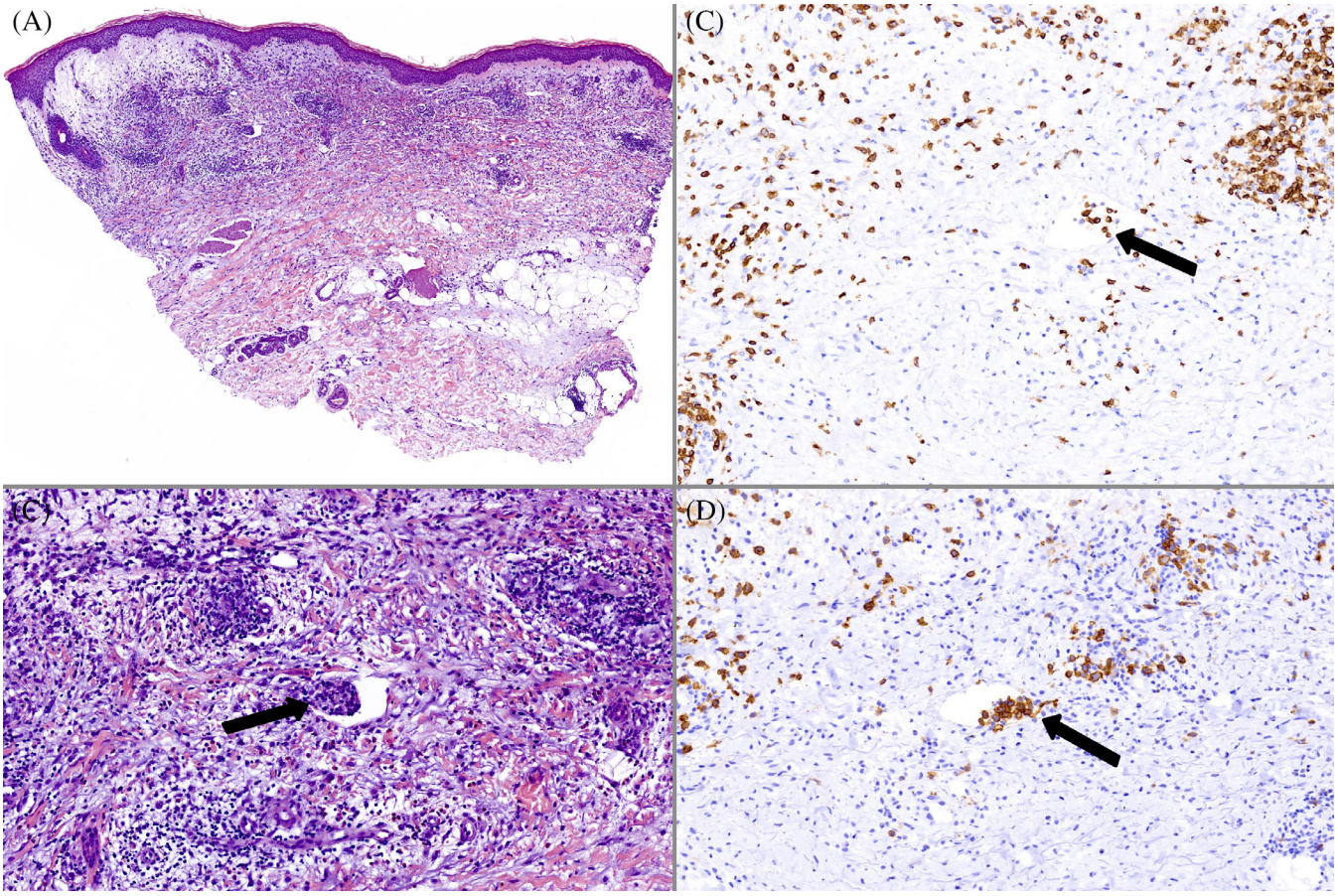

FIGURE 18 Benign atypical intravascular (CD30+) lymphoproliferation: (A) The lymphatic vessels are filled with activated large lymphocytes (H&E; ×5) and (B) detail: activated large lymphocytes both within the lymphatic vessels (arrow) and admixed in the surrounding infiltrate. (C) The intravascular lymphocytes are positive for CD3 (×200, arrow) and (D): for CD30 (×200, arrow)

Angiolymphoid hyperplasia with eosinophilia (ALHE) is commonly regarded as an angioproliferative process (epithelioid hemangioma) rather than a PSL. It affects both genders,[99] mostly in their third or fourth decade of life. ALHE presents clinically with red to brown papules or nodules, especially on the face and ears, but also occurs on the extremities and genitalia. Histopathologically, there are dermal proliferates of capillary vessels with prominent endothelia and cytoplasmic vacuoles. The vessels are surrounded by a predominantly T-lymphocytic infiltrate along with eosinophils; reactive germinal centers can occur.[100] Clonal T-cell populations have been described.[101,102]

Papuloerythroderma of Ofuji (PEO) is a rare, pruritic, erythrodermic dermatosis that may simulate CTCL,[103] especially erythrodermic mycosis fungoides. It occurs more frequently in males and the median age is 70 years. In some patients PEO was described as a manifestation of MF, in others as a disease accompanying MF.[104-106]

Clinically, PEO manifests with generalized itchy 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).[107] Blood eosinophilia is detected in most of the patients.

Histopathologically, PEO resembles chronic dermatitis, with epidermal hyperplasia, mild spongiosis, and a mixed infiltrate consisting predominantly of lymphocytes, histiocytes, and eosinophils (Table 7).[108]

Lymphocytic infiltration of the skin (LIS) and palpable arciform migratory erythema (PAME) have been regarded by some authors as T-cell PSLs. These eruptions are nowadays primarily assigned to the spectrum of lupus erythematosus (LE). PAME presents with infiltrated annular erythema developing into large migrating lesions.[109] The trunk is most commonly affected. LIS is characterized by sharply demarked, often symmetric, infiltrated plaques, typically on the face.[110] Histologically, the findings are similar in PAME and LIS. Both show a dense perivascular and periadnexal infiltrate of T-lymphocytes.[111] Interstitial mucin should not be present. Phenotypically, the infiltrate in LIS is mostly composed of CD8+ lymphocytes.[112]

2.4 | Intravascular pseudolymphoma

Recently, an accumulation of intravascular CD30+ or CD30– lymphoid blasts has been reported[113-115] and named benign **atypical intravascular CD30+ T-cell proliferation** or **intralymphatic**

proliferation of T-cell lymphoid blasts.[115] This finding is associated with inflammatory skin diseases, tumors, or trauma.[113-116] An accumulation of activated large lymphocytes with blast-like morphology within the lymphatics and in the surrounding inflammatory infiltrate is characteristic. An obstruction of lymphatic vessels due to inflammation was discussed as causal (Figure 18A, B). The cells express T-cell markers (CD3, CD4) (Figure 18C) and in most cases CD30 (Figure 18D). Clonality studies are polyclonal. The most important differential diagnosis is an intravascular manifestation of CD30+ LPD.[117]

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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