Cutaneous Pseudolymphoma

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KEYWORDS

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

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

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]