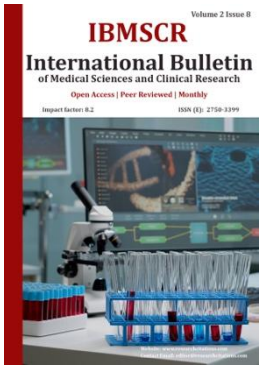

MODERN APPROACHES TO THE DIAGNOSIS OF CUTANEOUS PSEUDOLYMPHOMAS

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Cutaneous pseudolymphomas represent a heterogeneous group of reactive lymphoproliferative disorders characterized by benign lymphoid hyperplasia of the skin resulting from prolonged antigenic stimulation. Despite their benign nature, pseudolymphomas demonstrate significant clinical and histopathological similarities with primary cutaneous lymphomas, which complicates the diagnostic process. In recent years, interest in this problem has increased due to the growing incidence of lymphoproliferative skin diseases and the need for accurate differential diagnosis between reactive and neoplastic processes. This article reviews modern diagnostic approaches to cutaneous pseudolymphomas, including clinical, histopathological, immunohistochemical, and molecular-genetic methods.

Keywords: cutaneous pseudolymphoma, cutaneous lymphoma, immunohistochemistry, molecular diagnostics, lymphoproliferative disorders.

Modern Approaches to the Diagnosis of Cutaneous Pseudolymphomas

Introduction

Cutaneous pseudolymphomas represent a heterogeneous group of benign reactive lymphoproliferative disorders characterized by lymphoid hyperplasia occurring in response to persistent antigenic stimulation. Despite their benign biological behavior, pseudolymphomas demonstrate substantial clinical, histopathological, and immunophenotypic similarities to primary cutaneous lymphomas, making accurate diagnosis particularly challenging. The need to distinguish between reactive and neoplastic lymphoid infiltrates is essential because misdiagnosis may lead to inappropriate therapeutic strategies, including unnecessary aggressive treatment or insufficient monitoring.

Interest in cutaneous pseudolymphomas has significantly increased in recent decades due to advances in dermatopathology, immunohistochemistry, and molecular biology, as well as the rising incidence of lymphoproliferative skin disorders. Contemporary diagnostic approaches rely on an integrated clinicopathological correlation involving detailed clinical evaluation, histopathological examination, immunophenotyping, and molecular genetic techniques. A comprehensive understanding of the etiology, classification, pathogenesis, and diagnostic criteria of cutaneous pseudolymphomas is therefore essential for dermatologists, dermatopathologists, and oncologists.

Historical Background and Concept Evolution

The concept of pseudolymphoma was first introduced in 1891 by Moriz Kaposi, who described reactive lymphoid hyperplasia of the skin resembling malignant lymphoma. Early reports often described conditions such as lymphocytoma cutis and sarcomatosis of the skin, which were initially suspected to represent malignant neoplasms. However, subsequent clinicopathological observations demonstrated the benign reactive nature of these infiltrates.

In 1980, Caro and Helwig analyzed biopsy specimens and confirmed that many lesions previously interpreted as cutaneous lymphoma actually represented reactive lymphoid proliferations. Later, Smolle and colleagues introduced immunohistochemical methods that significantly improved the differentiation between benign and malignant lymphoid infiltrates. These developments marked an important step toward the modern understanding of pseudolymphomas as a spectrum of reactive lymphoid proliferations rather than true neoplastic processes.

Currently, pseudolymphomas are recognized as reactive conditions triggered by chronic antigen exposure. The improved understanding of immunologic mechanisms and lymphocyte biology has contributed to the refinement of classification systems and diagnostic criteria.

Etiology and Pathogenesis

Cutaneous pseudolymphomas develop as a result of persistent antigenic stimulation leading to localized immune responses in the skin. A wide range of exogenous and endogenous triggers has been implicated in the development of pseudolymphomas.

Common etiological factors include:

- Infectious agents, including Borrelia burgdorferi and viral pathogens
- Arthropod bites and parasitic infestations
- Drug-induced reactions
- Tattoos and cosmetic fillers
- Vaccinations
- Trauma
- Contact allergens
- Chronic inflammatory dermatoses

Drug-induced pseudolymphomas represent an important subgroup and may occur following administration of anticonvulsants, antibiotics, antihypertensive agents, or biologic therapies. In such cases, the pathogenesis is thought to involve delayed hypersensitivity reactions leading to lymphocyte activation and proliferation.

Borrelia-associated lymphocytoma cutis represents another well-recognized form of B-cell pseudolymphoma, particularly in endemic regions. Persistent antigenic stimulation results in polyclonal proliferation of lymphocytes within the dermis.

Immunologically, pseudolymphomas are characterized by reactive proliferation of T- or B-lymphocytes, often accompanied by dendritic cells, macrophages, and plasma cells. Cytokine release and activation of antigen-presenting cells contribute to the maintenance of the inflammatory infiltrate.

Unlike malignant lymphomas, pseudolymphomas typically demonstrate polyclonal lymphocyte populations and preserved immune regulation.

Classification of Cutaneous Pseudolymphomas

Several classification systems have been proposed to categorize cutaneous pseudolymphomas based on clinical presentation, histopathological features, and immunophenotype.

Traditionally, pseudolymphomas are divided into three main groups:

1. T-cell pseudolymphomas
2. B-cell pseudolymphomas
3. Mixed T- and B-cell pseudolymphomas

T-cell pseudolymphomas include:

- Idiopathic cutaneous T-cell pseudolymphoma
- Lymphomatoid drug reactions
- Lymphomatoid contact dermatitis
- Lymphomatoid papulosis-like reactions
- Post-scabietic lymphoplasia

B-cell pseudolymphomas include:

- Cutaneous lymphocytoma
- Borrelia-associated lymphocytoma
- Post-infectious lymphoid hyperplasia
- Nodular lymphoid hyperplasia

Mixed-cell pseudolymphomas demonstrate combined T- and B-cell infiltrates and may show variable histological patterns.

A more recent classification proposed in 2020 incorporates histopathological characteristics of the lymphoid infiltrate and distinguishes several major subtypes:

- Nodular pseudolymphomas
- Pseudolymphomas mimicking mycosis fungoides
- Other variants of reactive lymphoid hyperplasia
- Intravascular lymphoid infiltrates

This classification emphasizes the importance of morphological patterns in guiding differential diagnosis.

Clinical Features

Clinically, pseudolymphomas usually present as solitary or multiple papules, plaques, or nodules with red, violaceous, or brownish coloration. Lesions most frequently occur on the face, trunk, and extremities.

Typical characteristics include:

- slow growth
- asymptomatic or mildly pruritic lesions
- absence of systemic symptoms
- absence of significant lymphadenopathy
- stable or regressing clinical course

In contrast to malignant lymphomas, systemic manifestations such as fever, night sweats, or weight loss are generally absent.

Lesions may appear weeks or months after exposure to triggering factors such as insect bites, tattoos, or medications. In some cases, spontaneous regression may occur after removal of the causative factor.

Because clinical presentation alone is insufficient for diagnosis, histological confirmation is mandatory.

Histopathological Features

Histopathological examination remains the cornerstone of diagnosis. Skin biopsy typically demonstrates dense lymphoid infiltrates located in the dermis, sometimes extending into the subcutaneous tissue.

Key histological features include: polymorphous cellular infiltrate presence of small mature lymphocyte ,plasma cells, histiocytes, eosinophils, preserved dermal architecture,

absence of significant cytological atypia, presence of reactive germinal centers in some cases. Patterns of infiltration may include: perivascular distribution, nodular infiltrates, diffuse dermal infiltration, follicular structures resembling lymph nodes

Reactive germinal centers with tingible body macrophages are more commonly observed in B-cell pseudolymphomas.

However, histological differentiation between pseudolymphomas and early-stage cutaneous lymphomas may be difficult due to overlapping features.

Immunohistochemical Diagnosis

Immunohistochemistry plays a crucial role in determining the cellular composition of lymphoid infiltrates and assessing clonality patterns. Commonly used immunohistochemical markers include: T-cell markers: CD3,CD4,CD5,CD7, CD.8B-cell markers: CD20,CD79a, PAX5.Additional markers: Ki-67 proliferation index, BCL2, BCL6, CD30,CD68.

Pseudolymphomas usually demonstrate polyclonal lymphocyte populations with balanced expression of T- and B-cell markers.

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