Acad Med J 2025;5(Suppl 1):S166-S173.
UDC: 616.5-085:616.423-002
https://www.doi.org/10.53582/AMJ2551166p
Case report

DEMODEX-INDUCED CUTANEOUS PSEUDOLYMPHOMA

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Abstract

Cutaneous Pseudolymphoma, also referred to as Lymphoid Infiltrate of the Skin, is defined as a benign, inflammatory, reversible, reactive, and polyclonal proliferation of lymphocytes that spontaneously regresses or resolves following the elimination of the triggering factor. Cutaneous pseudolymphomas represent a heterogeneous group of T-cell or B-cell lymphoproliferative disorders, which may be localized or disseminated, and which clinically and histopathologically mimic cutaneous lymphomas. The literature describes various potential etiological factors, including endogenous (genetic, immunological) and exogenous factors (insect bites, medications, vaccinations, ultrasound exposure, trauma, tattoos, acupuncture, infections, etc.).

We present the case of a 64-year-old patient with pruritic nodular lesions on the face, neck, and back, as well as chronic blepharitis, persisting for over a year despite various therapeutic approaches (topical corticosteroids, antifungals, and antibiotics). Based on clinical examination and detailed anamnesis, our differential diagnoses included follicular mucinosis, cutaneous lymphoma, sarcoidosis, and facial eosinophilic granuloma. A skin biopsy was performed (from a nodular lesion on the frontal region), revealing an increased presence of *Demodex* mites and histopathologically numerous mites and scattered eosinophils. Immunohistochemical analysis demonstrated an immunophenotype of CD4>CD8, CD20(+), CD60(+), Ki67, and CD137, consistent with a benign reactive process. The diagnosis of pseudolymphoma was established based on clinical presentation and histopathological evaluation. Three months of local and systemic antiparasitic therapy led to complete regression of symptoms.

Keywords: cutaneous pseudolymphoma, T-cell lymphoma, immunohistochemistry, *Demodex*

Introduction

Cutaneous pseudolymphoma (C-PSL), also known as a lymphoid infiltrate of the skin, is defined as a benign, inflammatory, reversible, reactive, polyclonal proliferation of lymphocytes, which regresses spontaneously or after the elimination of the causative factor. It refers to a heterogeneous group of T-cell or B-cell lymphoproliferative processes, either localized or disseminated, clinically and histologically simulating cutaneous lymphomas [1]. Chronic persistent antigenic stimulation results in the proliferation of T cells and B cells. Some antigenic stimuli result in the proliferation of only B or T cells, but some stimulate both B and T cells, leading to cutaneous lymphoid hyperplasia [2,3,4].

Cutaneous lymphoid infiltration can be observed in benign and malignant conditions, making the diagnosis particularly challenging. Benign cutaneous lymphocytic infiltration includes classic inflammatory diseases such as psoriasis or lichen planus and another group that does not present the typical features of these classic inflammatory dermatoses. The latter group is called pseudolymphoma (PSL), a benign reactive T-cell or B-cell lymphoproliferative process that can clinically and histologically mimic cutaneous lymphoma [4].
Several factors contribute to C-PSL development, including endogenous factors (such as genetic and immunological factors) and exogenous factors (such as insect bites, medications, vaccination, ultrasound, trauma, tattoos, acupuncture, and infections) [2].

Case report

A 64-year-old male patient was presented to our clinic with a one-year history of red, well-defined, oval nodular lesions on the face and neck, which progressively spread to the back (Figure 1 and Figure 2). The lesions were accompanied by significant pruritus, and the patient also experienced chronic blepharitis, which had been persistent despite previous treatments. The pruritic nature of the lesions caused significant discomfort, leading the patient to seek medical attention. His past medical history included obesity, atrial hypertension, type II diabetes mellitus, and seborrhea localized on the face and scalp for the past ten years. Despite his longstanding history of seborrhea, the patient's skin condition had worsened, prompting further investigation.

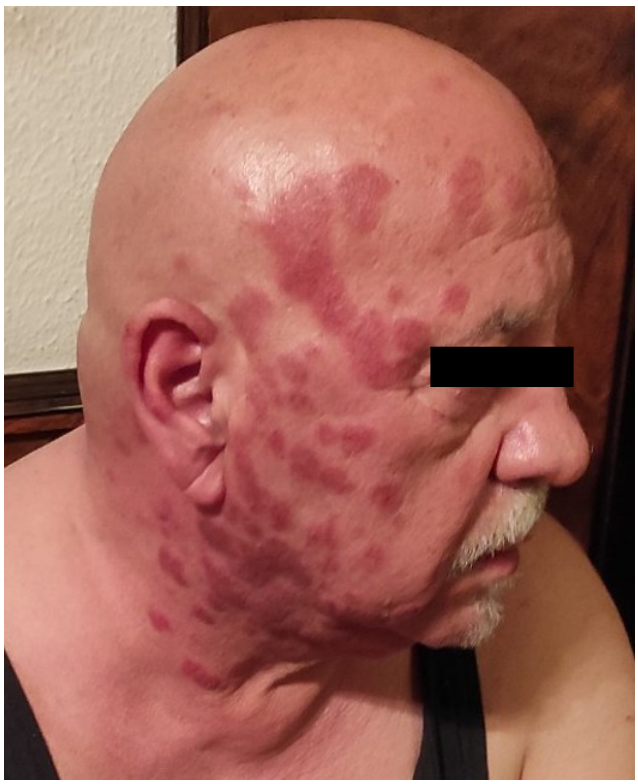

Fig. 1. Face and neck plaques and nodules

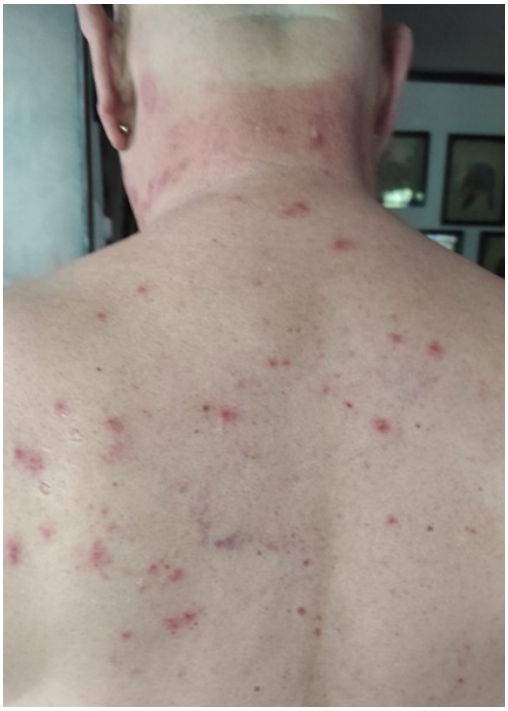

Fig. 2. Upper back nodules, folliculitis

To determine the underlying cause, extensive biochemical, immunological, and virological tests were conducted alongside a chest X-ray, all of which were negative or within reference values. The patient had initially been treated with oral antibiotics, antihistamines, and local therapies, including antifungal, antibiotic, and corticosteroid creams, yet his condition did not improve. The lack of therapeutic response led to reevaluating the patient's diagnosis.

The patient's symptoms were perplexing, and based on clinical examination, detailed medical history, and longstanding skin issues, our differential diagnoses included contact dermatitis, discoid lupus erythematosus, and systemic lupus erythematosus, follicular mucinosis, cutaneous lymphoma, sarcoidosis, and facial eosinophilic granuloma.

To further investigate the cause of the skin lesions, a skin biopsy was performed on a nodular lesion located on the frontal part of the patient's head. Histopathological examination revealed an increased presence of *Demodex* mites, which are typically associated with skin conditions such as rosacea and other inflammatory dermatoses (Figure 3). In addition to the mites, numerous eosinophils were identified scattered within the skin biopsy, suggesting an inflammatory or allergic component. This histopathological finding was crucial in narrowing down the diagnosis.

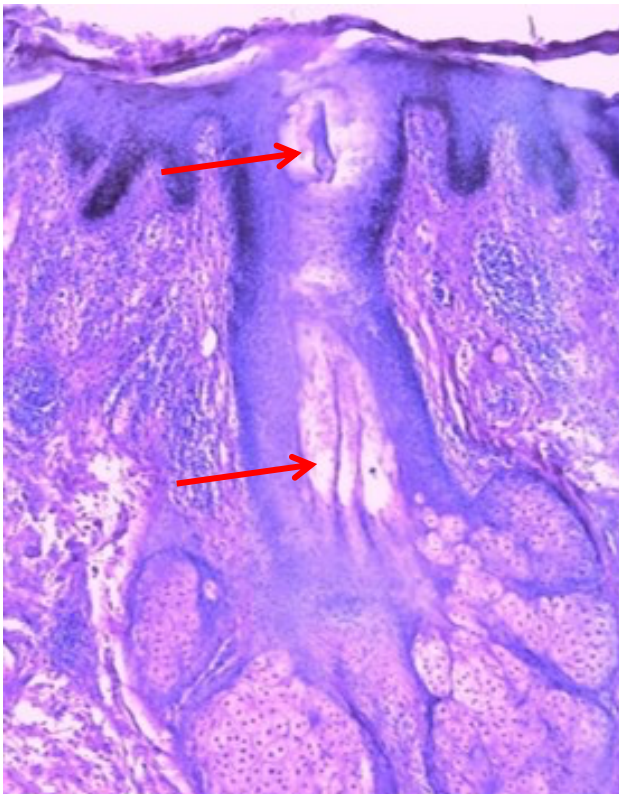

Fig. 3. High numbers of mites

Immunohistochemical analysis was conducted to further characterize the immune response. The immune phenotype revealed a predominance of CD4+ T-cells over CD8+ T-cells, with positive markers for CD20, CD60, Ki67, and CD137. These findings were consistent with a benign, reactive immune process rather than a malignant lymphoproliferative disorder. The pattern of immune cell markers supported a diagnosis of pseudolymphoma, a condition characterized by a reactive lymphoid infiltrate in the skin that mimics cutaneous lymphoma but is benign in nature.

A targeted treatment approach was initiated upon confirming the cutaneous pseudolymphoma diagnosis. The patient began a course of both local and systemic antiparasitic therapy, specifically aimed at addressing the *Demodex* infestation over three months. Remarkably, this treatment regimen led to a complete regression of the skin lesions, with no recurrence of the pruritus or blepharitis. The patient's condition significantly improved, and follow-up evaluations confirmed the absence of further nodular lesions or associated symptoms.

Discussion

Pseudolymphomas can present with a wide array of clinical symptoms, and the timely and accurate identification of these conditions is crucial for establishing a definitive diagnosis. Pseudolymphomas often closely mimic cutaneous lymphomas, leading to potential misdiagnosis if not carefully differentiated.

Pseudolymphomas represent a diverse group of reactive, benign lymphoproliferative disorders that can be triggered by various stimuli. There are several established classifications of pseudolymphomas, including but not limited to drug-induced, actinic reticuloid, CD8+ T-cell, and infectious simulators of T-cell lymphomas. The latter group includes infections caused by pathogens such as Borrelia, Leishmania, herpes viruses, syphilis, and other infectious

agents. Additionally, pseudolymphomas can arise from certain inflammatory dermatoses or other conditions that are not easily categorized into specific subtypes.

Differentiating pseudolymphomas from cutaneous lymphomas is a critical challenge in dermatology, and it hinges on the careful correlation between the patient's clinical presentation and the pathological findings derived from biopsy samples. The diagnostic process typically involves evaluating the lesion morphology and cellular composition within the tissue. Pseudolymphomas can occur in individuals across all age groups. However, certain factors may influence their prevalence within different demographics. For instance, Borrelia burgdorferi-induced pseudolymphoma is more commonly seen in children and young adults, whereas drug-induced T-cell pseudolymphomas are more frequent in older adults. Therefore, age and underlying conditions can help inform the clinical approach to diagnosis.

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. None of these approaches allows a consideration of overlapping features. Moreover, the phenotype and etiology are not evident initially; further diagnostic work-up is essential. The composition of the infiltrate is variable, influenced by the host's genetic and immunological factors, as reflected in the observation that identical agents (e.g., Borrelia sp.) can induce either B-PSL or T-PSL [5].

Table 1. Different causes of cutaneous pseudolymphomas [1,4,6]

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

In contrast to cutaneous lymphomas, only a few proposed classifications of cutaneous PSL exist. These are not consensus-based and have so far attracted little notice in everyday life. 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 well-established group represents the most common PSL ("classical PSL"). Histopathologically and clinically, they resemble cutaneous lymphomas and are characterized by solitary or multiple nodules.
2. Pseudolymphomas as simulators of mycosis fungoides (“pseudoMF") and 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 [5].

Table 2. Classification of cutaneous pseudolymphomas [1,4]

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
Herpesvirus-associated T-cell pseudolymphoma
Syphilis-associated pseudolymphoma
Other Infections as simulators of CTCL
Inflammatory dermatosis as simulators of CTCL
Other pseudolymphomas
T-cell-rich angiomatoid pseudolymphoma
Acral pseudo lymphomatous angiokeratoma (APA)
T-cell-rich angiomatoid polypoid pseudolymphoma (TRAPP)
Primary cutaneous angioplasmocellular hyperplasia
Lymphoplasmacytoid plaque (LPP)
Cutaneous plasmacytosis
Intravascular pseudolymphomas
Benign atypical intravascular (CD30+) lymphoproliferation

Another relevant aspect of pseudolymphomas is demodicosis, a rare skin condition often associated with older individuals with weakened immune systems. An overgrowth of the Demodex mites causes demodicosis, specifically Demodex folliculorum and Demodex brevis, which are naturally present on human skin. The mites primarily reside on the face, including the forehead, cheeks, eyelashes, and external ear canals. While Demodex mites are typically harmless and present in small numbers, certain factors—such as immunosuppression or changes in skin environment—can lead to an overgrowth of these mites, resulting in a condition known as demodicosis [4,7].

Demodex mites were first reported by Jakup Henle in 1871, and detailed descriptions and demonstrations of the pathogen were made in the following years. The Demodex mite belongs to the family *Demodicidae*. Demodex folliculorum and Demodex brevis are the two types of Demodex mites on human skin and follicles. Although the parasite may be found on every area of human skin, the mite has a predilection for the facial area. Demodex mites may be found on normal skin with a <5 mites/cm^2 density. A diagnosis of demodicosis or Demodex infestation is considered when clinical signs/symptoms appear and when more than 5 mites/cm^2 are present or when they penetrate the dermis. Recently, studies evaluating Demodex infestations have increased. The role of demodicosis has been investigated in some facial conditions/dermatoses, and Demodex mites have been reported to be associated with various skin manifestations, including pityriasis folliculorum, papulopustular and granulomatous rosacea, pustular folliculitis, inflammatory papule, folliculitis, Seborrheic Dermatitis (SD, perioral dermatitis, and blepharitis [7]. Demodicosis is often misdiagnosed

because its presentation can overlap with other inflammatory skin conditions, and its association with immune system compromise is sometimes overlooked.

In the case of Demodex-induced pseudolymphoma, the clinical presentation and histopathological results confirm the diagnosis. A biopsy from the affected area typically reveals an increased presence of Demodex mites, alongside inflammation and other changes in the skin immune cell composition. The histopathological findings may show increased eosinophils, a key feature in many inflammatory reactions. Immunohistochemical analysis may also be employed to confirm the presence of specific T-cell or B-cell markers, which are often seen in pseudolymphoma cases. These findings are crucial in distinguishing pseudolymphoma from other conditions that might present similarly, such as cutaneous lymphoma.

Once the diagnosis of Demodex-induced pseudolymphoma is established, appropriate treatment can be initiated. In this case, the patient underwent a therapeutic regimen involving local and systemic antiparasitic therapy, which effectively addressed the underlying Demodex infestation. The therapy typically includes topical treatments, such as metronidazole or ivermectin, which target the Demodex mites. Additionally, systemic treatments may be necessary in more severe cases to reduce the inflammatory response and eradicate the mites from deeper layers of the skin. The success of this treatment is usually evident within a few weeks to months, with complete regression of the clinical symptoms, including the resolution of erythema, nodularity, and pruritus. In the presented case, the therapeutic regimen led to the complete resolution of symptoms, demonstrating the effectiveness of antiparasitic therapy in treating Demodex-induced pseudolymphoma [5].

This case highlights the importance of considering demodicosis as a potential underlying cause in patients presenting with pseudolymphoma-like symptoms. The clinical and histopathological correlation is essential for accurately diagnosing and guiding effective treatment. Given the variability in clinical presentation and the need for precise differentiation from other cutaneous conditions, dermatologists must maintain a high level of suspicion and perform thorough diagnostic work-up to ensure proper management and prevent misdiagnosis. By addressing the root cause of the condition, such as Demodex overgrowth, dermatologists can achieve excellent outcomes and prevent further complications associated with pseudolymphomas [1,3].

Conclusion

In conclusion, this case highlights the importance of a comprehensive clinical and histopathological evaluation in diagnosing cutaneous pseudolymphoma. This rare but benign condition can mimic more serious dermatologic diseases like cutaneous lymphoma. It also underscores the role of *Demodex* infestation in developing certain inflammatory skin conditions and the efficacy of antiparasitic therapy in managing such cases.

Conflict of interest statement. None declared.

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