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EOSINOPHILIC DERMATOSIS OF HEMATOLOGIC MALIGNANCY: A CLINICOPATHOLOGIC STUDY WITH A CRITICAL REAPPRAISAL OF THE ROLE OF INSECT BITES

PhD Tutor: Prof. Carlo Francesco Tomasini

PhD dissertation of
Dr. Andrea Michelerio

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Index

CHAPTER 1:

INTRODUCTION

1.1 Historical overview and pathogenesis of Eosinophilic Dermatosis of Hematologic Malignancy

The skin and mucous membrane are highly vascular and susceptible to abnormalities in the blood, both malignant and non-malignant.

Hematological malignancies constitute a diverse group of neoplastic disorders, exhibiting significant heterogeneity in clinical presentations, behavioral characteristics, and prognosis. These malignancies can originate from either myeloid or lymphoid cell lineages, encompassing neoplasms exhibiting aggressive or indolent biological behavior, which, in turn, results in an acute or chronic clinical course.[1–3]

Patients with these malignancies often present a broad spectrum of cutaneous manifestations at the time of diagnosis or later in the disease course, which may impact their quality of life and, in certain cases, potentially complicate prognosis.[4] These dermatological manifestations are traditionally categorized into two classifications: specific skin lesions, characterized by direct infiltration of tissue by malignant hematopoietic cells, referred to as leukemia cutis, and non-specific manifestations.

Non-specific manifestations classically involve immune-mediated diseases and paraneoplastic disorders, but they also encompass reactions to specific treatments and other underlying conditions. Chemotherapeutic agents, such as cytarabine, and targeted drugs, including sorafenib and other tyrosine kinase inhibitors, frequently cause skin eruptions that may visually resemble disease-related skin changes, presenting diagnostic challenges.[4–6]

Additionally, patients may experience skin signs resulting from hematologic dysfunction or abnormal hematopoiesis, including pallor, petechiae, and ecchymoses. These skin findings could be easily misconstrued for benign dermatologic diseases, especially in patients without a prior diagnosis of cancer. The differential diagnosis of skin lesions in patients with hematologic malignancies must also consider infectious etiologies.

Notably, these cutaneous manifestations can serve as the first sign of underlying hematologic disease or an indicator of disease progression, affecting disease stage, prognosis, and treatment (Table 1).

Among the diverse and complex cutaneous manifestations associated with hematological malignancies, eosinophilic dermatosis of hematologic malignancy (EDHM) stands out as a particularly intriguing condition. EDHM encompasses a heterogeneous group of cutaneous eruptions

that predominantly occur in patients with indolent lymphoproliferative disorders, mostly B-cell chronic lymphocytic leukemia (CLL). These eruptions are clinically characterized by pruriginous papules, vesicles, bullae, or nodules, dispersed throughout the skin, and bear a striking resemblance to reactions to insect bites. In fact, historically, these manifestations were considered to be directly caused by insect bites. However, current understanding considers insect bites as one of the possible triggers, rather than the sole cause. This disorder was first described by Weed in 1965 and has since become a subject of particular interest in the field of dermatology and hematology. The following section delves into the discovery, clinical and pathological characteristics, and historical evolution of this condition, shedding light on this intriguing condition.

Specific skin lesions, characterized by direct infiltration of tissue by malignant hematopoietic cells
Leukemia cutis
Plasmocytoma cutis
Non-specific skin lesions
Pruritus and chronic prurigo
Immune-mediated diseases and paraneoplastic disorders
Neutrophilic dermatoses
Sweet syndrome
Pyoderma gangrenosum
Neutrophilic eccrine hidradenitis
Erythema Elevatum Diutinum
Subcorneal Pustular Dermatosis
Paraneoplastic vasculitides
Paraneoplastic pemphigus
Eosinophilic dermatosis of hematologic malignancy
Connective Tissue Diseases
Granulomatous Dermatoses
Adverse reactions to anti-neoplastic drugs
Skin signs resulting from hematologic dysfunction
Skin infections

Table 1. Skin manifestations in oncohematologic patients.

The clinical entity now recognized as Eosinophilic Dermatosis of Hematologic Malignancy (EDHM) - a term subsequently coined by Chassine[7] and Farber[8]- was initially delineated by Weed in a study

conducted in 1965.[9] In an examination of 97 patients diagnosed with chronic lymphocytic leukemia (CLL), Weed identified that 8 of these individuals (8.3% of the sample) manifested exaggerated cutaneous responses to insect bites. This phenomenon was observed notwithstanding the patients' normal skin reactivity to antigens known to elicit delayed hypersensitivity reactions. The atypical responses were characterized by skin lesions exceeding 20 mm in diameter, exhibiting infiltration, erythema, edema, and intense pruritus. These lesions typically reached their peak within 12-24 hours, with the development, in the most severe instances, of extensive blistering lesions, measuring up to 10 cm in diameter.[9] Histologically, the lesions were characterized by preservation of the epidermidis, subepidermal edema, dense dermal infiltration with lymphocytes and eosinophils, and disruption of collagen bundles.

Despite the definition introduced by Weed, which underscored a definitive causal relationship with insect bites, such bites were not uniformly observed across all patients. In certain instances, the role of insect bites was inferred rather than directly observed, as the cutaneous manifestations were consistently marked by a pinpoint depression at their center, occasionally exhibiting a crusty or vesicular appearance, identified as the site of the bite. When the insect was visually identified, it was invariably recognized as a mosquito. Weed's observations were further supported by the localization of the lesions to exposed areas of the body and their seasonal occurrence, predominantly manifesting during the spring-summer period, coinciding with the mosquito season in Rochester, where the study was undertaken.[9] Within the context of Weed's research, the distinct association of such manifestations with CLL was emphasized. In contrast, none of the 54 patients with chronic myeloid leukemia, who were evaluated as part of a control group, exhibited analogous lesions.[9] This work was the forerunner of numerous small case series describing the finding of this condition. In 1970, Huston et al. made a contribution to the literature by reporting a case with lymphocytic lymphoma bearing resemblance to those previously described by Weed.[10] Despite extending the case series related to hypersensitivity to insect bites, this work did not advance any specific pathogenetic hypothesis.

In 1986, Rosen et al. described vesiculobullous eruptions in 10 patients with CLL and hypothesized that the lesions might either be indicative of insect bite reactions or constitute an atypical presentation of bullous pemphigoid.[11] The histopathological examination revealed similar findings across patients, particularly a superficial and deep, perivascular, periadnexal, and interstitial infiltrate composed of small lymphocytes and eosinophils. Severe edema and bullae formation occurred in the papillary dermis in 50% of subjects. Epidermal changes included spongiosis, vesicle formation, and focal necrosis. In 60% of patients, the inflammatory infiltrate extended into the subcutaneous fat. Notably, Rosen and his team were the first to report the presence of flame figures on histopathological

examination. Additional observations included remnants of the basement membrane along the blister roof, as evidenced by periodic acid-Schiff staining. These findings, in conjunction with immunofluorescence results, argued against a diagnosis of bullous pemphigoid. Consequently, the authors concluded that the cases likely represented insect bite reactions that histopathologically resembled bullous pemphigoid.[11] A further step forward in understanding insect bite hypersensitivity was made in 1990 by Pederson and collaborators who delineated the histopathological characteristics of the clinical presentations.[12]

In the years following these initial studies, the literature has been enriched with various anecdotal reports and small case series. These reports have described EDHM patients suffering from a wide range of lymphoproliferative diseases, extending beyond CLL to include acute monocytic leukemia,[13] acute lymphoblastic leukemia,[13] myelofibrosis,[13] chronic myeloid leukemia,[14] large cell lymphoma, mantle cell lymphoma,[8,13,15–17] MALT lymphoma,[16] diffuse large B-cell lymphoma,[16] follicular lymphoma,[16] small lymphocytic lymphoma,[16] lymphoplasmacytic lymphoma,[16] marginal zone lymphoma,[18,19] aggressive T-cell lymphoma,[20] multiple myeloma/monoclonal gammopathy of undermined significance.[20] These reports have also highlighted a wide variety of clinical presentations, ranging from erythematous papules or nodules[9,11–13,15,16,21,22] to blisters and vesicles,[8,11,12,21,23–27] urticarial[26–28] or cellulitis-like plaques,[29] or cutaneous ulcerations.[24] However, the once-assumed association with insect bites has been increasingly challenged, as a significant number of patients could not recall being bitten by insects.[13,16,21,22,30–33]

The first systematic study of this condition was conducted by Davis et al. in 1998.[21] Their research involved a retrospective clinical, histopathological, and immunopathological investigation of 8 patients with CLL who developed severe, debilitating papular and vesiculobullous skin lesions, apparently in response to arthropod bites. The authors proposed a pathogenetic hypothesis, attributing the clinical manifestations to an intense infiltration of eosinophils within the skin lesions. These eosinophils, locally recruited by pro-inflammatory cytokines, particularly IL-5, were released in response to the insect bite and subsequently degranulated, creating a cytokine *milieu*. This environment amplified the local inflammatory response, culminating in visible histological alterations such as blisters and vasculitis. Notably, while the term "exaggerated reactions to insect bites" was retained in the study, 6 of the 8 patients could not recall an insect bite. This observation suggested that that insect bites might have served as triggers for these skin reactions, whilst other factors could have also contributed to their onset. Remarkably, a patient was diagnosed with CLL

following a decade-long history of exaggerated responses to arthropod bites, underscoring for the first time the potential of these skin reactions as an early harbinger of hematologic malignancies.

Building on the work of Davis et al, Barzilai et al. conducted an equally seminal study in 1999, examining 8 patients, 3 with CLL and 5 with other B-group lymphoproliferative diseases, including myelofibrosis, acute lymphoblastic leukemia, mantle cell lymphoma, acute monocytic leukemia and large-cell lymphoma.[13] This investigation marked the first report of an association between these skin lesions and B-group lymphoproliferative diseases other than CLL. The Authors conducted a meticulous examination of the clinical, histological, and immunopathological aspects of the skin lesions, presenting a perspective distinct from that of Davis et al. They posited that there might not be a direct causal link between the skin manifestations and actual insect bites. In their case series, the lesions appeared ubiquitously over the body, unconfined to exposed or uncovered areas, and exhibited no seasonality. Moreover, patients did not consistently report witnessing the insects. Based on these observations, Barzilai et al. suggested that the skin manifestations should more aptly be defined as "insect bite-like reaction" or "eosinophilic eruption of hematoproliferative diseases". Their definition encapsulates the clinical resemblance to insect bite lesions while also recognizing their potentially distinct etiology. The authors theorized that these lesions might be symptomatic of a dysregulation of the immune system, responding excessively to various skin stimuli, which could encompass insect bites. They further speculated that a shared mechanism, possibly involving a cytokine imbalance with an excess of interleukin 4 and interleukin 5, might precipitate both the proliferation of malignant B cells and the altered immune response characterized by eosinophilic infiltration. Barzilai et al. also drew analogies between these reactions and the papular rash observed in patients with human immunodeficiency virus (HIV) infection, proposing a broader context for these skin manifestations. They concluded that this reaction should be cataloged among the various nonspecific rashes accompanying hematoproliferative disorders and posited that Wells syndrome is likely a variant of these insect bite-like reactions.

In 2001, Byrd et al. introduced the term "eosinophilic dermatosis of myeloproliferative disease" to characterize a dermatologic condition observed in 4 patients.[30] A total of 15 histological specimens were analyzed. Each of these specimens exhibited both superficial and deep lymphohistiocytic infiltrates. Specifically, perivascular involvement was observed in 100% of the specimens, while periadnexal and perifollicular infiltrates were detected in 67% and 93% of the samples, respectively. Furthermore, diffuse dermal eosinophilia was present in all specimens. The study found no evidence of a seasonal pattern associated with the manifestation of this condition and all the subject denied an

history of insect bites. Based on their findings, Byrd et al. proposed the existence of two types of abnormal cutaneous responses in patients with hematologic disorders. The first type manifests in patients with a history of antecedent insect bites, characterized by an exaggerated response to insect antigen and an acute course with rapid resolution (2-14 days) requiring minimal therapy. The second type, mirroring the cases in their study, follows a chronic course that is resistant to conservative treatment. In these patients, a history of insect bites is seldom elicited. Byrd et al. also delineated diagnostic criteria for this condition:

1) Pruritic papules, nodules, and/or vesiculobullous eruption resistant to conservative treatment;
2) Eosinophil-rich dermal lymphohistiocytic infiltrate (superficial and deep) on histopathologic examination;
3) Exclusion of other causes of tissue eosinophilia, including immunobullous diseases, parasitic infections, known insect bite, or drug reactions;
4) Preexisting diagnosis of a hematologic malignancy or dyscrasia or its subsequent development.

The aforementioned bullous nature of some of these skin manifestations prompted inquiries into their relationship with autoimmune bullous diseases.[11] In 2006, Bottoni et al. embarked on a study to investigate the occurrence of bullous eruptions in patients with B-cell chronic lymphocytic leukemia (B-CLL) and to elucidate the pathogenetic mechanism underlying this reaction.[26] Conducted on a cohort of 11 patients, representing 1% of all B-CLL patients followed a the Department of Hematology at the University of Rome ‘‘La Sapienza’’ (n=1010 patients), the study provided a valuable incidence rate. The researchers concluded that the bullous eruptions could represent a pemphigoid-like eruption in patients with B-CLL, possibly caused by a serum antibody detectable only by immunoblotting tests. Direct immunofluorescence revealed deposits of IgG and complement (C3) along the dermo-epidermal junction in only one patient. The researchers hypothesized that this bullous pemphigoid-like eruption might manifest in patients with B-CLL as an aberrant immune response following insect bites, though they could not substantiate this with significant experimental or clinical data.

Further insights into the nature of EDHM were provided by a comprehensive study conducted by Bairey and the Israeli Chronic Lymphocytic Leukemia Study Group in 2012.[32] This investigation, the most extensive to date, retrospectively examined 48 CLL patients with a diagnosis of insect-bite-like reaction. The affected patients constituted 6–7% of all patients with CLL, with no gender predilection. The clinical expression of these eruptions was polymorphic, and histopathology and

immunohistochemistry could easily exclude specific lesions of CLL. Bullous lesions were also observed, necessitating immunofluorescence staining for anti-basement membrane antibodies to exclude autoimmune blistering disorders. The researchers considered these reactions to be relatively common non-specific eosinophilic eruptions in patients with CLL, likely correlated with the immune suppression associated with the disease. In this series, the cutaneous eruption was not linked to disease activity or the course of the hematological disease, a finding that resonated with the observations of Barzilai et al. Notably, the cohort included a relatively high proportion of patients with poor prognostic features of CLL, such as high serum levels of β2 microglobulin, deletion of 17p or 11q, increased expression of ZAP-70, and CD38 positivity. The study further noted that in many cases the eruption appeared only at or after the start of different chemo/chemoimmunotherapy regimens, hinting at a potential connection between these treatments and the development of skin reactions, and had no seasonality.

In 2010, Chassine et al. were the first to use the term "Dermatose éosinophilique associée aux hémopathies" (eosinophilic dermatosis of hematologic diseases).[7] Their study, conducted between 2004 and 2009, focused on 6 patients with this disorder in association with blood dyscrasias. The patients, with a mean age of 75.6 years at the onset of dermatosis, presented with a variety of skin manifestations, including erythematous papules, wheals, and plaques. The initial skin lesions appeared concurrently with or after the diagnosis of the hematological neoplasm, and notably, the reappearance of these skin lesions preceded a relapse of the blood disease in 3 cases, with an average lead time of 2-3 months. This observation led the authors to propose that the dermatosis might indicate a certain degree of activity of the hematological disease and could potentially have a prognostic value. In all skin biopsies histological examination revealed a dense dermal infiltrate of predominantly CD4+ T-cells and numerous eosinophils in all lesions. In 3 patients, there was marked folliculotropism, resembling folliculotropic T-cell lymphoma. The most effective treatment for the dermatosis was identified as a 15-day regimen of prednisone at an approximate dose of 40 mg/day. However, in most cases, the eruption disappeared following appropriate chemotherapy for the underlying blood disorder. Chassine et al. also concluded that the appearance of EDHM may precede the hematologic malignancy or herald a relapse.[21]

Farber was the first to introduce the term 'Eosinophilic dermatosis of hematologic malignancy' into English literature in his 2012 case report published in the Journal of Cutaneous Pathology.[8]

In 2012, Mitteldorf et al. first demonstrated the presence of leukemic cells within EDHM skin lesions utilizing the Fluorescence In Situ Hybridization (FISH) technique.[34] In this single-patient study, neoplastic cells comprised about 20% of the infiltrate. This was a novel finding, as prior to their study, cutaneous infiltrates had not been compared with the clonal immunoglobulin gene rearrangement of the underlying hematological disease, and FISH analysis had not been performed. Earlier studies used different methods (Southern blot analysis or IgH-polymerase chain reaction) to detect neoplastic cells in the infiltrate and found monoclonal B-cell populations indicating malignant infiltrates in variable amount.[13,17,21] Based on their findings, Mitteldorf et al. proposed that the malignant leukemic cells themselves could be the cause of the skin lesions. However, it remained unclear whether even a minimal number of neoplastic cells are sufficient to maintain these cutaneous eruptions. Alternatively, B-CLL cells could be acting as bystander cells in the dermis, drawn there by a process of tropism caused by dysregulation of adhesion molecules, and not directly causing the skin lesions.

In 2018, Visseaux et al.[16] proposed a new term, "T-cell papulosis associated with B-cell malignancy" (TCP-BCM) to describe what they believed to be a distinctive skin eruption associated with hematologic malignancies. This proposal was based on their multicenter retrospective study, which aimed to characterize the eruption and investigate its pathogenesis and relationship with the underlying B-cell malignancy. The study included 37 patients with a B-cell malignancy who presented with a cutaneous eruption consisting of chronic and/or recurrent papules, papulo-vesicles, and/or nodules. These eruptions predominantly occurred on the head and neck, and the authors found no significant insect bite history or seasonal predominance among the patients. The most commonly associated B-cell malignancy was CLL (73%).

In all cases histological and immunohistochemical review revealed a dense dermal lymphocytic infiltrate predominantly composed of T lymphocytes. A perivascular and periadnexal pattern was observed in 77.6% of the cases, sometimes suggestive of a folliculotropic mycosis fungoides. Using morphological features and immunohistochemical stainings (including CD20, CD23, CD5, IgD, CD79a, and PAX5), clusters of tumor B cells of various sizes were found in 41% of biopsy samples and 47% of patients.[16]

A monoclonal IgH gene rearrangement (identical to that found in the peripheral blood in almost all available cases) was identified in 71.4% of evaluated cases. In contrast, no significant monoclonal TCR gene rearrangement was observed in the skin lesions.[16] Notably, eosinophils were observed in 77.6% of cases and, hence, absent in around one-fifth of the cases.

The term TCP-BCM was proposed by the authors to reflect the involvement of both T and B cells in the pathogenesis of the skin eruption, eliminating the reference to eosinophilic infiltration as a

hallmark of the diagnostic criteria established by Byrd et al.[30] They hypothesized that an extravasation of tumor B cells with skin-homing properties, associated with a secondary, predominant, T-cell immune reaction, could explain the clinicopathologic aspect and the prolonged and recurrent course of the disease.

In their 2019 study, Meiss et al. provided compelling evidence supporting the hypothesis that tumor B-cells play a direct pathogenic role in EDHM.[35] They conducted a comprehensive analysis of monoclonal IgH gene arrangements in EDHM cases, which included both their own research and a review of some previous cases. They discovered that monoclonal IgH gene arrangements were identifiable in 54.1% (20 out of 37) of EDHM cases. However, when they narrowed their focus to recent studies that utilized the standardized BIOMED2 protocol, the proportion of confirmed monoclonal IgH gene arrangements rose to 80% (16 out of 20 cases). Moreover, in 86.6% (13 out of 15 cases) of these instances, the IgH rearrangement mirrored the one found in extracutaneous manifestations of CLL. While these tumor B-cells are typically present in low numbers and evade detection by conventional histology, they can be identified in approximately 50% of cases through the use of appropriate immunohistochemical staining techniques, such as CD20, CD79a, CD5, and CD23. Meiss et al. further observed that the precision of the diagnostic work-up was directly proportional to the number of cases with confirmed CLL-infiltrates. This was demonstrated by the fact that conventional histology detected 0%, immunohistochemistry detected 47%, IgH-PCR detected 80%, and FISH analysis detected 100% (in cases with cytogenetic aberrations).

In 2020, Cohen put forth a proposal for an alternative nomenclature for EDHM.[36] He suggested the term "Hematologic-related Malignancy-Induced Eosinophilic Dermatosis," abbreviated as "He Remained." The term is not only a reflection of the condition characteristics but also an acronym that encapsulates its association with hematologic malignancies, its pathogenesis, and its histopathological features. The first word "He" and the initial two letters of the second word "Re" represent the first two letters of the words “Hematologic-Related”. This emphasizes the condition relationship with hematologic cancers such as chronic lymphocytic leukemia. The third, fourth, fifth, and sixth letters of the second word "main" refer to the first two letters of the words “Malignancy-Induced”. This highlights the proposed mechanism of pathogenesis for the condition, suggesting that it is induced by the associated malignancy. Finally, the last two letters of the second word "ed" represent the first letter of the words “Eosinophilic Dermatosis”. This underscores the associated pathology for the pleomorphic cutaneous lesions, which is characterized by eosinophilic infiltration. Cohen's proposed name, "He Remained," is intended to underscore the persistent nature of the

condition in patients with hematologic malignancies, reflecting its chronic course and resistance to treatment.[37] While Cohen's proposed name, "He Remained," may provide a more accurate description of the condition association with hematologic malignancies and its pathogenesis, it is currently a suggestion and has not replaced the widely used term EDHM (Table 2).

Author (year of publication)	Nomenclature	Reference
Weed (1965)	Exaggerated delayed hypersensitivity to mosquito bite in chronic lymphocytic leukemia	[9]
Barzilai et al. (1999)	Insect bite-like reactions or eosinophilic eruption of hematoproliferative diseases	[13]
Byrd et al. (2001)	Eosinophilic dermatosis of myeloproliferative disease	[30]
Farber et al. (2012)	Eosinophilic dermatosis of hematologic malignancy (EDHM)	[8]
Visseaux et al. (2018)	T-cell papulosis associated with B-cell malignancy (TCPBCM)	[16]
Cohen (2020)	Hematologic-related malignancy-induced eosinophilic dermatosis: (He Remained)	[36]

Table 2. Proposed nomenclature of EDHM. Reproduced by Cohen PR. What's in a name? a new nomenclature has been proposed for eosinophilic dermatosis of hematologic malignancy (EDHM): hematologic-related malignancy-induced eosinophilic dermatosis (He Remained). Dermatol Online J. 2020 Jun 15;26(6):13030/qt1zd6p6z2. PMID: 32815699.

In a study by Maglie et al.[38] the expression of T and B cell as well as the expression of Th2-related molecules, including interleukin (IL) 4, IL-31, and eotaxin-1 were investigated in EDHM patients and bullous pemphigoid (BP) patients and compared to healthy controls. The study revealed an overexpression of Th2 associated molecules in EDHM patients and BP patients when compared to healthy controls, confirming an immunologic skewing toward Th2 immunity in EDHM.

IL-4 and IL-31 were significantly overexpressed in the dermis of EDHM and BP patients compared to healthy controls and colocalized with the Th2-associated marker GATA3.

IL-4 serum concentration was significantly increased in EDHM and BP compared to healthy controls. IL-4 is the main Th2-cell–derived cytokine contributing to eosinophil recruitment and direct stimulation of pruritogenic sensory fibers.[39]

Eotaxin-1, a potent attractant for eosinophils and mainly produced by keratinocytes, was significantly overexpressed in EDHM epidermidis compared to BP and healthy controls.
Interestingly, a low expression of B cell markers was seen in EDHM skin similarly to previous reports. Once again, this finding would support the hypothesis that leukemic cells interfere with the local immune mediators, promoting a Th2-type inflammatory response.

1.2 Insect Bite Reactions: physiological and pathological perspectives

Following the exploration of the historical evolution of EDHM, it is essential to delve into the closely related subject of insect bite reactions. Initially, EDHM was thought to be an exaggerated reaction to insect bites, especially from mosquitoes.
This connection necessitates a thorough examination of insect bite reactions from clinical, histopathological and immunopathological point of view, both in immunocompetent and immunodeficient subjects.

Skin manifestations, histopathologic changes, and immunopathologic mechanisms of mosquito bites in immunocompetent, healthy subjects

Immunocompetent, healthy individuals are routinely exposed to insect bites. Apart from specific species or unique circumstances (such as indoor infestations), bites predominantly occur during hot and humid seasons and are generally mild, seldom necessitating medical intervention. Mosquitos are usually the most common culprits.
Mosquito-induced skin reactions are ubiquitous, occurring across various latitudes, with an increased incidence during summer and spring in temperate and humid climates.[40] However, mosquito bites may manifest during autumn and winter as well, since their survival vary among different species. Moreover, factors such as climatic variability and widespread use of indoor heating systems may contribute to their survival.[40,41]
Mosquitoes belong to the order *Diptera* and the *Culicidae* Family and comprise approximately 3500 species divided into various genera, including *Anopheles*, *Culex*, and *Aedes*, which are of significant relevance in many regions. These genera are known vectors for diseases such as malaria (transmitted by female *Anopheles*), filariasis (*Culex*), and yellow fever and dengue (*Aedes*).[42] *Culex* and *Anopheles* represent our "common mosquito", being the most widespread genera in Italy. *Aedes*, which originated in Southeast Asia, have spread to Europe, the Americas, Africa and Australia in recent

decades, demonstrating their ability to travel great distances. *Aedes albopticus*, the "tiger mosquito" first appeared in Albania in the 70s.[43]

Generally, mosquitoes are nocturnal, although some are diurnal. The females feed on the blood of vertebrates, including humans.[41] An intensely itchy pomphoid lesion usually appears almost immediately at the site of the bite and reaches its peak within about 20 minutes, and then gradually resolves. Small, itchy, papular lesions may appear later, reaching their maximum cutaneous representation within 24 to 36 hours, then slowly diminishing over the next few days.

An extreme reaction to a mosquito bite, known as Skeeter syndrome, is characterized by extensive local inflammatory reactions, intense edema, erythema, and sometimes low-grade fever.[44] This syndrome, often mistaken for cellulitis,[44] can occur in patients with altered or compromised immunity as well as in healthy, immunocompetent patients who have had intensive exposure to a high number of mosquito bites, children, and subjects from other geographical areas who come into contact for the first time with species of insects (specifically mosquitoes) not indigenous to their regions.[45]

The skin reaction to a mosquito bite is largely related to the allergens in its saliva, containing components capable of temporarily inhibiting the innate immune system and the coagulation and platelet aggregation process, favoring vasodilation instead. [41,46] In addition, at the time of the bite, the mosquito introduces allergens into the human body from both its mouthparts and its saliva.[44]. Salivary allergens are numerous, some shared, some species-specific.[47–49]

Studies have demonstrated that skin reactions to mosquito bites are based on immunological mechanisms, including both humoral and cell-mediated immunity.[50] In 1946, Mellamby was the first to describe the characteristic sequence of events following exposure to mosquito bites, studying what happened by exposing a group of 25 English volunteers to *Aedes aegypti*, a mosquito species that was not present in the United Kingdom at that time.[51]

Based on extensive studies and clinical observations, the immunological response to a mosquito bite has been systematically classified into five distinct stages:

- **Phase 1:** Initial Exposure - A subject bitten for the first time typically exhibits no response beyond minor irritative reactions.
- **Phase 2:** Delayed Response - Upon repeated bites, a delayed skin response manifests, characterized by itchy papules that appear approximately 4-6 hours post-bite and persist for several days.
- **Phase 3:** Immediate and Delayed Response - With continued exposure over several weeks, an intensely itchy pomphoid lesion may appear within 10-15 minutes of the bite, regressing

within one or two hours. This immediate response is followed by the typical delayed response, marked by itchy papules.

- **Phase 4:** Immediate Response Only - After several months of exposure, the immediate response persists, but the delayed response ceases to occur.
- **Phase 5:** Desensitization - Following thousands of bites, an acquired type of desensitization may develop, resulting in only modest pomphoid reactions or no reaction at all.[42,45,50,52]

Peng and Simons conducted a study in which 100 mosquito bites were administered once every two weeks, for a total of 48 weeks, to subjects who had never been exposed to this species of mosquito. Immediate and delayed immune reactions began to develop around the third week, peaking between the fifth and nineteenth weeks, and subsequently diminishing significantly by about the twenty-sixth week (Figure 1).[45]

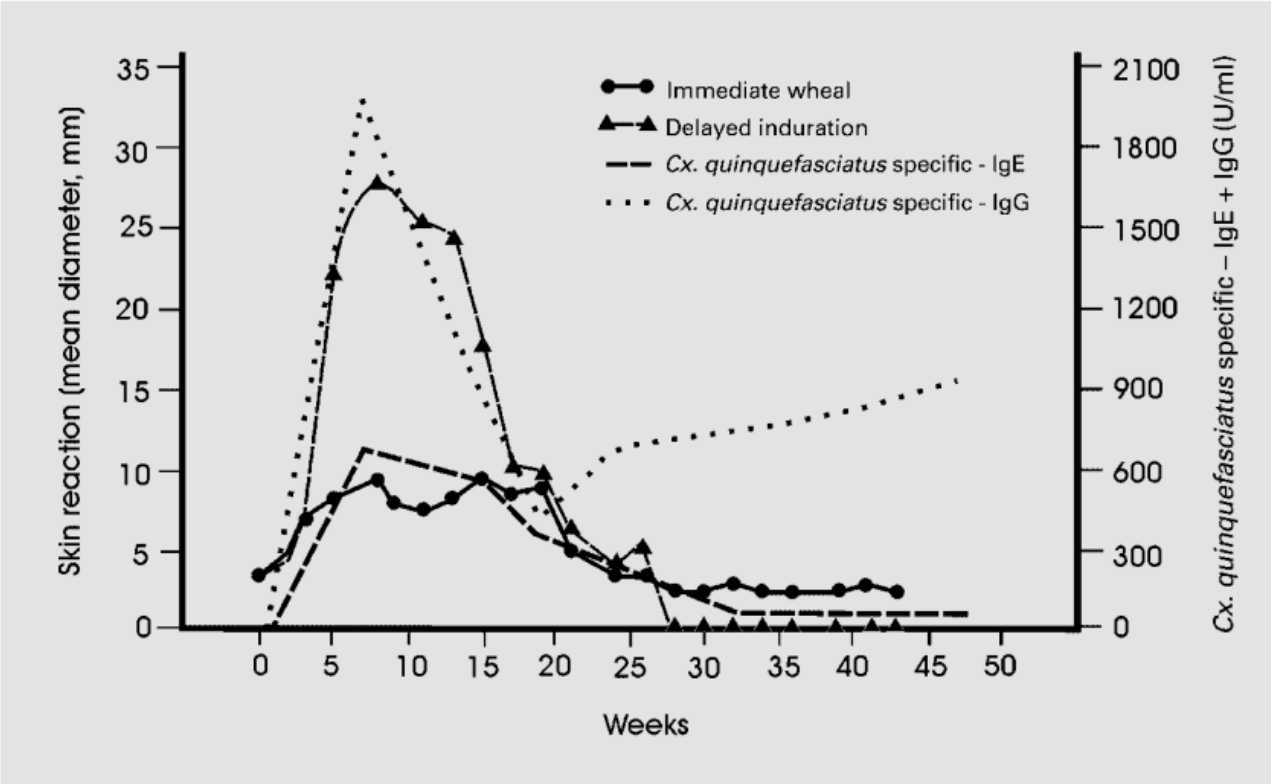

Figure 1. Naturally acquired sensitization and subsequent desensitization to mosquito bites. A man received 100 mosquito (*Cx. quinquefasciatus*) bites, to which he had never been previously exposed, every 2 weeks for 48 weeks. Skin immediate wheals (mean diameter recorded 20 min after a bite test) and delayed indurations (mean diameter recorded 24 h later) were monitored and serum *Cx. quinquefasciatus* saliva-specific IgE and IgG were measured using an indirect ELISA.
Reproduced with permission from Zhikang Peng, F. Estelle R. Simons; Mosquito Allergy: Immune Mechanisms and Recombinant Salivary Allergens. Int Arch Allergy Immunol 1 February 2004; 133 (2): 198–209. https://doi.org/10.1159/000076787.[45]

The entire process of sensitization and desensitization in the study took place in about 26 weeks, whereas, in real life, natural desensitization can take several years or even never be completed if mosquito bites are avoided.[45].

The immunological responses to mosquito bites can be understood within the framework of Gell and Coombs classification. Immediate skin reactions are triggered by IgE-mediated immunological mechanisms against mosquito allergens, leading to the activation of mast cells. This activation results histamine release and the characteristic pomphoid lesion.[53,54] In contrast, the mechanisms underlying delayed responses are more intricate and appear to involve both humoral immunity, primarily mediated by IgG, and cell-mediated immunity, chiefly involving T lymphocytes.[45] The presence of IgG specific to certain mosquito allergens may lead to the formation of immune complexes, thereby activating the complement system and initiating an inflammatory response 3-8 hours post-bite. This marks the onset of delayed hypersensitivity, associated with type III immunity as per Gell and Coombs classification. Several studies have shown the role of T lymphocytes in both instigating and sustaining delayed hypersensitivity reactions. This has been further corroborated by experiments demonstrating the transfer of delayed skin reactions to mosquito bites through the transplantation of splenic cells (rather than serum) in guinea pigs.[45]

The late phase of skin reactions also implicates eosinophil granulocytes and mast cells. A study by Depinay et al. in 2006 posited that mast cells play a role in tempering the delayed immune response following a mosquito bite. After initial attraction to the bite site and activation by mosquito salivary antigens, mast cells release a substantial amount of IL-10, an anti-inflammatory cytokine, thus modulating the overall local response.[55]

In a manner analogous to pollen allergies, antibody responses mediated by IgE, IgG4, and IgG1 specific for salivary antigens have been observed to increase following seasonal exposure to mosquito bites.[56] A 1995 Japanese study further demonstrated that the presence of specific IgG4 in serum confers a protective effect, with subjects with high titers of specific IgG and IgE and no IgG4 having more severe reactions.[57]

While mosquito bites typically manifest as pomphoid and delayed papular reactions, more severe symptoms may occasionally arise. These can include blisters, eczematous reactions, cellulitis, or lymphangitis. Anaphylactic shock and systemic reactions, although extremely rare, have also been documented.[42,58]

Histopathology of insect bite reactions

Insect bite reactions manifest a complex array of histopathologic features, the nature of which depends on both the species of insect involved and the individual immunologic response.[59–61] In the

early stages of the reaction, the histological examination typically reveals an inflammatory infiltrate predominantly composed of lymphocytes. This infiltrate is often located in the superficial, mid, and occasionally deep perivascular regions of the dermis. Eosinophilic granulocytes may be sporadically present in the reticular dermis, usually in the interstitium between collagen bundles. A notable feature of the inflammatory infiltrate is its "wedge-shaped" or "V-shaped" distribution, with the apex directed towards the deep reticular dermis and sometimes extending to the subcutaneous fat whilst the base is oriented towards the papillary dermis. Epidermal spongiosis, in particular spongiosis of the infundibular epithelium and acrosyringia as well as eosinophilic spongiosis, are often characteristic findings.[59]

As the reaction progressed, the lymphocytic and eosinophilic infiltrate becomes more densely concentrated and penetrates deeper layers of the skin. The edema within the papillary dermis may be severe, leading at times to the formation of a subepidermal blister. Vesiculation and epidermal necrosis may also occur.

The frequent acroinfundibular and/or acrosyringeal inflammatory reaction seen on histopathology reflects what appears to be an ideal environment for the insect meal due to the presence of bacteria, yeasts, mites, and lipids in these sites. Indeed, folliculocentricity is a characteristic feature of infiltrates associated with arthropod puncture.[60,61] The vesicles are spongiotic and commonly accompanied by keratinocyte necrosis. Initially, these vesicles are intraepidermal, located above the base of the “wedge” of inflammatory infiltrate. Extensive local inflammation may lead to the formation of smaller adjacent vesicles and, if associated with prominent papillary dermis edema, subepidermal detachment may result in eosinophilic blisters.

In some cases, eosinophils may be so abundant in the dermis that their degranulation and subsequent enzymatic release leads to collagen fiber degradation with the formation of "flame figures", a unique reddish metachromatic hue.

A minority of cases may present with features of small vessel vasculitis, primarily localized in the superficial dermis, directly attributable to the insect bite. These vasculitic processes are characterized by thrombi within the lumen of the superficial dermal plexus venules, occasionally extending into the deep plexus, or solely by fibrin deposits within the vessel walls. These phenomena are often accompanied by a perivascular inflammatory infiltrate, sporadic focal necrosis of the epidermis, and erythrocyte extravasation.[59]

Exaggerated insect bite reactions

Insect bites, particularly those inflicted by mosquitoes, can elicit an exaggerated inflammatory response in certain populations. This response may manifest as ecchymotic, vesicular, blistering, or

bullous reactions, or even as Arthus reactions, occurring 2–6 hours after the bite and persisting for several days or weeks.[62] Systemic allergic reactions to mosquitoes have also been documented.[63]
These severe reactions are more common among individuals with high exposure, such as outdoor workers; those with diminished natural immunity, including infants or young children; or those unfamiliar with indigenous insects, such as immigrants or visitors.[64] Acquired immune disorders further predispose individuals to exaggerated reactions.
Children with atopic conditions, such as asthma, allergic rhinitis, or atopic dermatitis, are particularly susceptible to mosquito hypersensitivity.[65] This susceptibility may present as urticaria or Skeeter syndrome, a severe local inflammatory reaction characterized by localized redness, warmth, swelling, and pruritus, sometimes accompanied by fever and lymphadenopathy.[44] This syndrome resembles cellulitis but is of shorter duration.[44] Cross-reactivity with other arthropods has been observed, and exaggerated reactions following exposure to *Aedes aegypti* mosquitoes may also occur in individuals sensitive to wasp venom, bee venom, dust mites, cockroaches, and shrimp.[66,67]

A distinct and rare form of Hypersensitivity to Mosquito Bite associated with Epstein-Barr viral infection and Natural Killer cell lymphocytosis (HMB-EBV-NK or HEN) has been described in East Asian countries, predominantly in children.[68] This condition is associated with natural killer (NK) cell lymphocytosis and elevated Epstein-Barr virus (EBV) DNA levels in the peripheral blood (typically above 1000 copies/μg).[68] It has been hypothesized that EBV infection immortalizes NK cells, which are then activated by mosquito bites, leading to severe local reactions like bullae, ulcers, or necrosis as the primary clinical manifestations in childhood. As affected individuals grow older, several episodes of worsening general symptoms and hydroa vacciniforme-like eruptions occur.[69] Eventually, the condition may evolve into systemic diseases, including hemophagocytic lymphohistiocytosis, chronic active EBV disease, and EBV-associated lymphoproliferative disorders. The different stages may overlap.[64,69,70]

Individuals with HIV infection may experience severe mosquito bite reactions, including pruritic papular eruptions, although the underlying etiology remains elusive.[71,72] Smith et al. postulated that exaggerated skin reactions in HIV patients might stem from the progressive loss of memory CD4+ lymphocytes, responsible for progressive desensitization to insect bites in immunocompetent individuals.[73] This theory has been supported by subsequent studies, such as the work of Farsani et al. (2013), which established a correlation between exaggerated skin lesions from mosquito bites, particularly papular-pruritic eruptions, and a lower CD4+ T count, and the work by Ajithkumar et al. (2001).[74,75]

The increased susceptibility to insect bites in some HIV-infected patients after initiation of antiretroviral therapy (HAART) initiation may be due to lipoatrophy associated with this treatment. Greub et al. suggested that lipoatrophy results in a more superficial vascular network, leading to increased body temperature and cutaneous perspiration, thereby increasing mosquito attraction.[76]

1.3 Clinical and histopathological features of Eosinophilic Dermatosis of Hematologic Malignancy

Patients afflicted with EDHM typically present with a wide variety of clinical presentations, ranging from erythematous papules or nodules[9,11–13,15,16,21,22] to blisters and vesicles,[8,11,12,21,23–27] urticarial[26–28] or cellulitis-like plaques,[29] or cutaneous ulcerations.[24] In these patients, the underlying hematologic malignancies was not limited to CLL, but also included a range of lymphoproliferative diseases, such as acute monocytic leukemia,[13] acute lymphoblastic leukemia,[13] myelofibrosis,[13] chronic myelogenous leukemia,[14] large cell lymphoma, mantle cell lymphoma,[8,13,15–17] MALT lymphoma,[16] diffuse large B-cell lymphoma,[16] follicular lymphoma,[16] small lymphocytic lymphoma,[16] lymphoplasmacytic lymphoma,[16] marginal zone lymphoma,[18,19] aggressive T-cell lymphoma,[20] and multiple myeloma/monoclonal gammopathy of undermined significance.[20]

CLL patients diagnosed with EDHM are most likely to present symptoms in the fifth to seventh decade of life.[8] Cutaneous eruptions typically occur months to years after the diagnosis of CLL, although cases have been reported where the eruptions preceded the diagnosis of the underlying malignancy.[7,13,17,21,34]

Histopathologically, the lesions of EDHM are characterized by a superficial and deep dense perivascular infiltrate of small lymphocytes, accompanied by numerous eosinophils, with periadnexal distribution of the infiltrate often observed.[11,12,16,77,78] In some cases, folliculotropic lymphocytes may also be present.[1633] Neutrophils have been identified within the lesions.[15,24]

Immunophenotypically, the lymphoid infiltrate is composed of either mixed T- and B-cells or predominantly of T-cells that are CD3+, CD43+, CD45RO+ with occasional presence of nodular lymphoid aggregates and germinal centers, reflecting the reactive nature of the process.[13,23,24]

Eosinophils may be found within the epidermis, associated with spongiosis, as well as in the subcutis.[7,11,13,21,23] The infiltrate can exhibit a wedge-shaped pattern,[22,79,80] as it is usually observed in insect bite reactions, with the base towards the epidermis and the apex towards the hypodermis.[59]

Follicular mucinosis, a reaction pattern in the follicular epithelium characterized histologically by the accumulation of dermal-type mucin in the external root sheath of the follicular epithelium and sebaceous glands, may also be observed.[33,34,81] Follicular mucinosis can occur in various secondary

conditions, including inflammatory, hyperplastic, and neoplastic processes including lupus erythematous, hyperplastic lichen planus, leukemia cutis, cutaneous B-cell lymphoma, mycosis fungoides, and Sezary syndrome.[82] The association of follicular mucinosis with lymphoproliferative disease, especially with mycosis fungoides and its variants, is well documented.[82]

Extensive intraepidermal or subepidermal edema may result in vesicles or intraepidermal or subepidermal blisters filled with eosinophils, plasma, and fibrin.[11–13,21,23,24,81] Focal epidermal necrosis has been observed. [11,21,33]

Flame figures can be found in the dermis,[8,21,27,31] representing the coating of degenerating collagen fibers with the major basic protein (MBP) released from the degranulated eosinophils.[83]

Additionally, granulomas (without insect parts)[12,16] and extravasated erythrocytes have been described.[11,12] Vasculitis has been found, albeit rarely.[21,22,84]

Eosinophilic septal panniculitis has been described.[21,22,31,33] However, the subcutaneous layer is not always detectable in biopsies, emphasizing the necessity for sufficiently deep biopsy samples to reveal this feature.

1.4 Differential diagnoses

Entities that may pose problems of clinical and histopathologic differential diagnosis with EDHM are numerous, mainly including leukemia cutis, cutaneous plasmocytoma, Sweet syndrome, bullous pyoderma gangrenosum, neutrophilic eccrine hidradenitis, paraneoplastic vasculitides, bullous pemphigoid, paraneoplastic pemphigus, eosinophilic folliculitis and Wells syndrome, all of which require systematic exclusion.

Leukemia cutis

Leukemia cutis (LC) refers to the infiltration of leukemic cells (myeloid or lymphoid) into the skin, including the epidermis, dermis, or subcutaneous tissue, resulting in clinically identifiable cutaneous lesions.[85] The condition is rare, with a reported frequency of 2.1–30% depending on the underlying form of leukemia.[86] Most of the data are derived from case reports or case series, limiting the availability of accurate and robust information.[87] Confusion is also caused by varied terminology. When composed of neoplastic monocytic precursors (monoblasts and promonocytes), leukemia cutis has been designated as monoblastic sarcoma.[88] When composed of neoplastic granulocytic precursors, leukemia cutis has been designated also as granulocytic sarcoma,[3] myeloid sarcoma or chloroma.[89] The term "chloroma" originates from its greenish appearance caused by myeloperoxidase oxidation, but not all cases of chloroma contain myeloperoxidase granules.[86] Nevertheless, the term

"chloroma" is still used. Similarly to EDHM, LC usually occurs after a diagnosis of the hematological disorder, although it can also occur before or concurrently, as the first sign of the disease.[86,87,90–92] Cases where LC appears before bone marrow or peripheral blood involvement, with systemic symptoms taking months to years to develop, are referred to as aleukemic leukemias.[93]

LC most commonly affects individuals with acute myeloid leukemia (AML), but it has also been observed in chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndromes (MDS), chronic myeloid leukemia (CML), and acute promyelocytic leukemia (APL).[87] The exact mechanisms by which leukemic cells invade the skin are not well understood, but it is believed that interactions between various chemokine receptors and adhesion molecules expressed by the leukemic cells and the skin vessels play an important role. Indeed, these interactions are analogous to the homing of memory T cells and, possibly, certain B cells to the skin.[94,95] For example, the skin homing of memory T cell is regulated by the concomitant expression of cutaneous lymphocyte antigen (CLA) and specific chemokine receptors.[94] In cutaneous T-cell lymphoma, a substantial fraction of malignant lymphocytes express CLA and CCR4, which in part explains their affinity for the skin.[96,97] In the context of leukemia cutis, a small study showed CLA expression in the majority of cases.[98]

An intriguing hypothesis suggests that the skin may serve as a sanctuary for dormant leukemic cells. In essence, the structural characteristics of the skin, including its barrier function, may provide a protective environment for these leukemic cells, shielding them from the full effects of chemotherapy and immunotherapeutic interventions.[99,100] Upon the completion of treatment, surviving leukemic cells could reinitiate their growth and proliferation, leading to cutaneous extramedullary relapse.[100]
In collaboration with the Hematology Unit, our research group investigated the phenomenon of LC following allogeneic stem cells transplantation (allo-SCT) in patients diagnosed with AML.[100] In a cohort of 214 AML patients, 91 were underwent allogeneic bone marrow transplantation, of which 7 (7.7%) manifested cutaneous relapse. The median age of this subgroup was 57.6 years, encompassing various AML subtypes, and the time of cutaneous relapse after allo-SCT ranged between 2 and 36 months, with a mean of 13.3 months. Lesions presented predominantly as large plaques and nodules localized to the abdomen, thorax, and dorsum, characterized by a firm texture to palpation and a reddish-violaceous hue. Donor chimerism analysis showed complete chimerism with 100% donor cells in all patients evaluated. FISH analysis of skin biopsies from 5 patients with XY mismatch, targeting the Yp11.1-q11.1 locus, demonstrated that the blast cells infiltrating the skin were of patient

rather than donor genotype. The findings of this study highlight the skin as a potential sanctuary site for neoplastic leukemic cells.

The role of cytogenetic alterations in the development of LC is also being investigated.[85] Chromosomal abnormalities, particularly involving chromosome 8, have been frequently observed in patients with AML who present with leukemia cutis.[85] These molecular abnormalities often mirror those observed in AML affecting the bone marrow. However, direct examination of leukemia cutis specimens has yielded limited molecular data and the exact genes or epigenetic alterations affected by aneuploidy of chromosome 8 thar predispose AML patients to leukemia cutis have not been identified.[85]

Clinically, the lesions caused by LC are not distinctive and have different morphologies. These lesions may present as single or multiple, usually firm to palpation, violaceous, reddish-brown, or hemorrhagic papules, nodules, and plaques of various sizes and shapes (Figure 2A-B-C).[85,86,90,92,101] Erythematous papules and nodules are the most common clinical manifestations. Lesions occur mainly on the trunk, extremities, and head-neck region, less commonly on the mucosa and groin.[87] However, unusual presentations of LC have been rarely reported, including maculopapular exanthema, exfoliative erythroderma, leonine facies, and single or multiple ulcers affecting atypical sites such as the groin, scrotum, or face.[85,86]

Another notable clinical feature of LC is the leukemic cell infiltration of scars (Figure 2D).[86] The most common change affecting the oral mucosa in LC is gingival hyperplasia, which often appears hemorrhagic and may progress to necrosis.[86,90] The majority of skin lesions associated with LC are asymptomatic, although a minority of patients may experience discomfort or pruritus.[101] There is no correlation between the distribution and location of the lesions and specific cellular types of leukemia cutis. However, generalized lesions are more commonly observed in acute forms of leukemia, whereas solitary, clustered, or scattered lesions may be seen in both chronic and acute forms.[86,87]

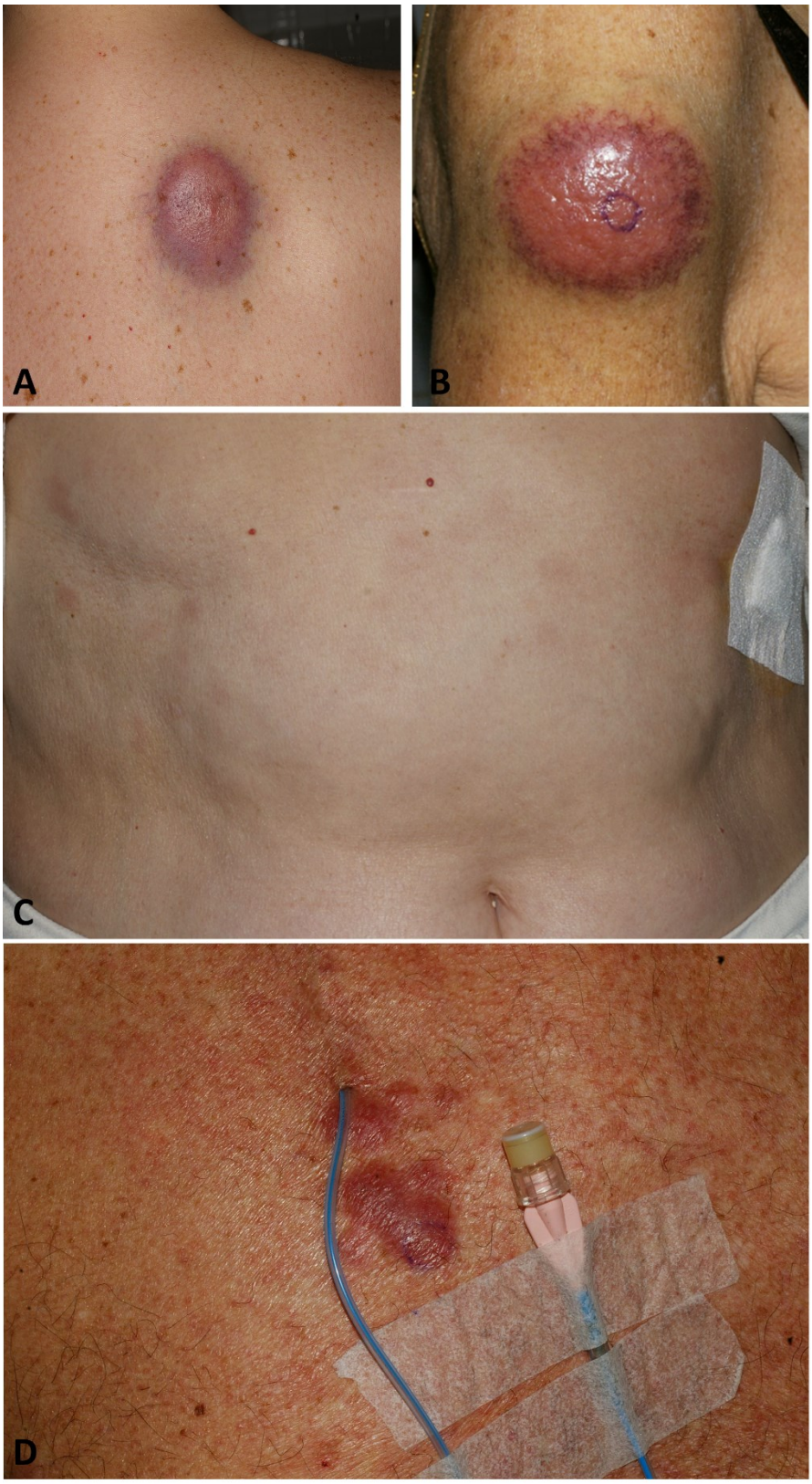

Figure 2. Leukemia cutis presenting as solitary lesions (A-B) and multiple erythematous macules on the trunk (C). LC involving the site of insertion of a catheter (D).
Reproduced with permission from **Michelerio A**, Kirsh A, Croci GA, Colombo AA, Bernasconi P, Paulli M, Brazzelli V, Vassallo C. Cutaneous relapse after allogenic hematopoietic stem cell transplantation for acute myeloid leukemia: a clinical and immunophenotype study of seven patients. *G Ital Dermatol Venereol*. 2020 Apr;155(2):250-252. doi: 10.23736/S0392-0488.18.06010-8. Epub 2018 Jul 17. PMID: 30014683.

Skin biopsy is the gold standard for the diagnosis of LC and involves histopathologic evaluation, taking into account the distribution patterns, cytologic features, and immunohistochemical characteristics.[85,86] Cytologic features vary depending on the underlying leukemia type. The infiltrate is typically perivascular and/or periadnexal, nodular or diffuse, and predominantly involves the deep dermis and subcutaneous tissue, with a "grenz zone" (Figure 3A).[85,86] Necrotic cells, mitotic figures, and nuclear pleomorphism may be observed (Figure 3B). Immunohistochemical analysis is helpful in identifying the specific cell line involved, especially in cases where differentiation from cutaneous lymphoma is challenging. For example, the absence of specific T and B-cell markers and the expression of myelomonocytic markers such as CD68, CD43, CD33, lysozyme, myeloperoxidase, CD117, and CD15 are indicative of myeloid origin (Figure 3C). Instead, LC in CLL is characterized by the coexpression of CD19, CD5, CD20, CD79, and CD23. [85,86] Immunohistochemical findings should always be correlated with bone marrow and peripheral blood results, as well as molecular genetic studies.[85,86] In cases without a history of leukemia, the diagnosis can be challenging, as the cells may be poorly differentiated, leading to potential confusion with non-Hodgkin's lymphoma.

Imaging studies, such as radiography, can assist in assessing the location, number, and differential diagnosis of subcutaneous nodules.[85,86]

There is no consensus on the treatment of LC. Systemic treatment is aimed at treating the underlying leukemia. The choice of treatment protocol depends on factors such as the cell line involved, immunohistochemical characteristics, time of onset in relation to systemic disease, and cytogenetic abnormalities. Traditional anti-leukemic chemotherapy, either as a single treatment or in combination with other interventions such as stem cell transplantation, radiotherapy, or surgery, are among the treatment options.[87]

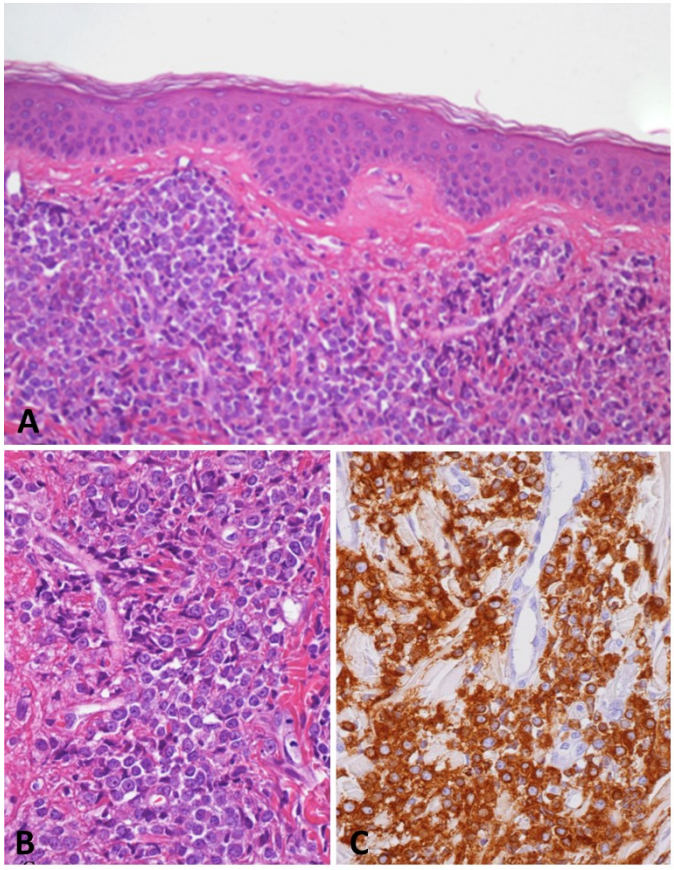

Figure 3. A dermal infiltrate of LC composed of medium-sized blasts with an upper "grenz zone" and a perivascular and periadnexal distribution (A-B). The blasts display a myeloid phenotype and stain positive for myeloperoxidase (C).
Reproduced with permission from **Michelerio A**, Kirsh A, Croci GA, Colombo AA, Bernasconi P, Paulli M, Brazzelli V, Vassallo C. Cutaneous relapse after allogenic hematopoietic stem cell transplantation for acute myeloid leukemia: a clinical and immunophenotype study of seven patients. *G Ital Dermatol Venereol*. 2020 Apr;155(2):250-252. doi: 10.23736/S0392-0488.18.06010-8. Epub 2018 Jul 17. PMID: 30014683.

Cutaneous plasmocytoma

The vast majority of plasma cell myeloma (PCM) cases are confined to the bone marrow (BM), with lytic bone lesions being the most common manifestation of the disease. Secondary cutaneous involvement of PCM is relatively rare, occurring in 1% to 4% of cases.[102] This condition may present as a direct extension of a bony focus of disease, as a metastatic lesion, or even as the initial manifestation of multiple myeloma.[103] It is most commonly associated with all classes of myeloma proteins, with the exception of IgE myeloma.[103] Clinically, cutaneous plasmocytoma often presents as nodules on the extremities, trunk, or head.[102] Lesion color varies from violaceous to skin-colored to erythematous.[102]

The diagnosis of cutaneous plasmocytoma is typically made based on a combination of clinical presentation, histopathologic findings, and immunohistochemical staining showing positivity for CD38 and CD138.

Histopathologically, malignant plasma cells of cutaneous plasmocytoma often form discrete nodules in the dermis, but they may also infiltrate between collagen bundles. This pattern of infiltration can vary and contributes to the wide variety of clinical presentations observed in patients with this condition.[103] The presence of a Grenz zone, a clear area in the superficial dermis that separates the

epidermis from the malignant plasma cells, can be a helpful diagnostic clue, although its absence does not rule out the diagnosis.[102,103]

Immunohistochemical staining is a crucial part of the histopathologic evaluation of suspected cutaneous plasmocytoma. The malignant plasma cells typically stain positive for CD38 and CD138, markers of plasma cells. In addition, light chain restriction is often observed, which is consistent with the clonal nature of the plasma cells in multiple myeloma and its cutaneous manifestations, including cutaneous plasmocytoma.[102,103]

Primary cutaneous plasmocytoma (PCP) is a rare form which occurs in the absence of other medullary or extramedullary plasma cell disorders.[104] The treatment of cutaneous plasmocytoma varies and may include surgery, radiation, chemotherapy, or a combination of radiation and chemotherapy. The choice of treatment depends on several factors, including the patient's overall health status, the number and location of the lesions, and the potential side effects of the treatment.[102,103] Skin involvement in multiple myeloma typically indicates a poorer prognosis, with a median overall survival of 9 months from the time of cutaneous manifestation.[102]

Sweet syndrome

Sweet syndrome (SS) is an acute febrile neutrophilic dermatosis characterized by the abrupt onset of painful, edematous, and erythematous cutaneous papules, plaques, or nodules (Figure 4A-B). Fever and leukocytosis often accompany the cutaneous lesions.[105] Three variants have been described: classic or idiopathic, drug-related and malignancy-associated. Malignancy-associated Sweet syndrome accounts for approximately 20% of all cases.[106]

SS may precede, follow, or occur concurrently with a malignancy. The development of Sweet syndrome may also predict cancer recurrence.[106]

The exact pathogenesis of SS remains to be elucidated. Various factors such as circulating autoantibodies, cytokines, dermal dendrocytes, human leukocyte antigen serotypes, immune complexes, paraneoplastic phenomena, and leukotactic mechanisms may play a role in its development.[107] The most commonly proposed hypothesis for the pathogenesis of SS in malignancy involves the overproduction and misregulation of inflammatory cytokines such as IL-1, IL-3, IL-6, IL-8, G-CSF, and GM-CSF.[107]

The diagnosis of SS is based on the recognition of consistent clinical and laboratory findings and the exclusion of diseases that may present with similar clinical features.

Histopathologic examination reveals an infiltrate primarily composed of mature neutrophils located in the upper dermis without evidence of vasculitis. The epidermis appears normal, and papillary

dermis oedema is common, sometimes leading to subepidermal vesiculation. Infiltrates of neutrophils may extend into the subcutaneous tissue with septal and/or lobular involvement.

A distinct subtype of SS is the histiocytoid variant, first described by Requena et al.[108] and classically associated with hematologic malignancies. [109,110] Clinically, this condition mirrors the classic Sweet syndrome; however, it is distinguished by a dermal infiltrate primarily composed of myelomonocytic cells with histiocytoid features (Figure 4C-D).[108]

Our research group has recently described a unique case of the histiocytoid variant of SS with concomitant neurologic and cutaneous manifestations. This case involved an elderly patient who presented with an abrupt onset of skin rash and mental confusion, spatial and temporal disorientation. The diagnosis was confirmed by clinical examination, laboratory tests, MRI findings, and skin biopsy, which revealed a dermal infiltrate primarily composed of mononuclear cells interpreted as immature myeloid cells. A notable feature of this case is that central nervous system involvement in SS has been previously reported only in the mature neutrophilic variant and not in the histiocytoid variant. Treatment of the patient resulted in complete resolution of both skin lesions and neurological symptoms. This case highlights the importance of recognizing and investigating neuro-Sweet syndrome when neurologic symptoms are referred in the context of antecedent or concomitant Sweet syndrome, to avoid neurologic misdiagnosis. It also emphasized the need to evaluate for the presence of a concomitant hematologic disease, given the potential association with hematologic malignancies and the possibility of disease recurrence or sequelae.[110]

Treatment of SS typically involves the administration of systemic glucocorticoids. If systemic corticosteroids are contraindicated due to comorbidities or other factors, colchicine, dapsone, or potassium iodide may also be effective alternatives.[111]

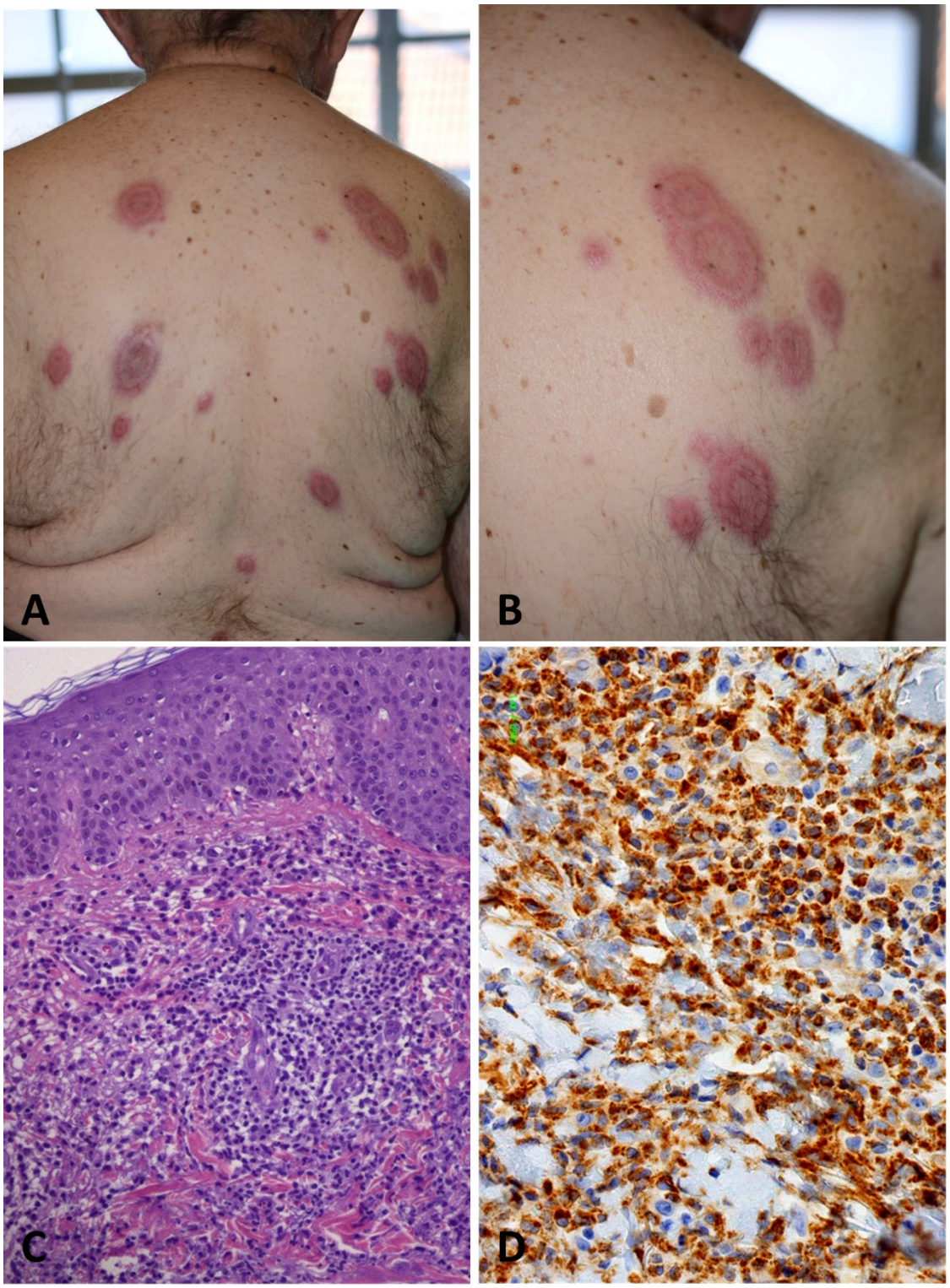

Figure 4. Markedly edematous lesions with targetoid appearance on the upper back of the patient with histiocytoid SS (A), some of which show the characteristic raised erythematous border and a slightly depressed violaceous center (B). Moderate edema in the papillary dermis and a rather dense dermal infiltrate composed mainly of neutrophils and histiocytoid cells, representing immature myeloid cells (C). Immunohistochemistry shows positivity for CD68/KP1 (D).
Reproduced with permission from **Michelerio A**, Novario M, Vassallo C. Concomitant neurologic and cutaneous manifestations of histiocytoid Sweet's Syndrome. Ital J Dermatol Venerol. 2021 Dec;156(Suppl. 1 to No. 6):34-36. doi: 10.23736/S2784-8671.19.06293-X. Epub 2019 May 14. PMID: 31104460.

Bullous pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that presents as an inflammatory, painful and ulcerative disorder of the skin. More than half of patients with PG develop the disorder in association with an underlying systemic disease.[112] Inflammatory bowel disease, hematologic disorders, and arthritis are the most common comorbidities. PG presents with a variety of clinical manifestations, that can be categorized into five primary subtypes: ulcerative (or classic), bullous (or atypical), pustular, vegetative and peristomal.[112] The ulcerative type is the most common and the other four types are relatively rare. Common features across these subtypes include the onset of an inflammatory papule, pustule, vesicle, or nodule, which subsequently enlarges and deteriorates into an erosion or ulcer. Except for vegetative PG, lesion development is typically rapid and associated with severe pain. The presence of fever is variable. The term "pathergy" refers to the induction or exacerbation of PG at sites of accidental or iatrogenic trauma.[113,114]
Myelodysplastic syndrome is the most commonly reported hematologic malignancy associated with PG, followed by monoclonal gammopathy of undetermined significance and acute myeloid leukemia. In most cases, the diagnosis of a hematologic malignancy precedes the development of PG and the disease is “multifocal” or limited to the lower extremity.[115]

The pathogenesis of PG is multifactorial and not yet fully understood. The disease is thought to be caused by dysregulation of the immune system, involving both innate and adaptive immune responses. Research has revealed complex gene expression profiles in the skin of patients with PG, with increased expression of interleukins (IL) such as IL-1-beta, IL-1β, IL-8, IL-17, IL-23 and tumor necrosis factor (TNF)-alpha.[113] This upregulation leads to a proinflammatory state through increased activation of inflammasomes, dysregulation of the innate immune system, and recruitment and activation of neutrophils. PG tissue also has increased expression of pattern recognition receptors (PRRs), JAK2, and STAT1, indicating dysfunction of both adaptive and innate immune response.[113,114] Genetic susceptibility is also likely to contribute to the development of PG. Familial cases of PG have been reported, and certain genetic mutations have been associated with the disease. For example, PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome, an autosomal dominant disorder, has been linked to mutations in the PSTPIP1/CD2BP1 gene. This mutation leads to decreased inhibition of the inflammasome and ultimately to increased production of IL-1-beta and autoinflammation. Mutations in the autoinflammatory genes MEFV, NLRP3, NLRP12, NOD2, and LPIN2 have been demonstrated in PG, PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis) syndrome, and other inflammatory conditions.[113,114] Certain drugs have also been linked to PG.[113]

The bullous (atypical) form is a superficial variant of PG and is the most commonly seen in patients with PG associated with acute myeloid leukemia and myeloma.[115] A review of 38 well-documented cases of bullous PG shows that females are predominantly affected (25/38, 65.8%), with a mean age of 51.6 years, ranging between 18 and 80 years. Associated diseases include acute myeloid leukemia (AML) (17/38, 44.7%), chronic myeloid leukemia (4/38, 10.5%), myelodysplastic syndrome (MDS) (2/38, 5.3%), multiple myeloma (1/38, 2.6%), myeloid metaplasia (1/38, 2.6%), IBD (4/38, 10.5%), rheumatoid arthritis (1/38, 2.6%), and Klinefelter's syndrome (1/38, 2.6%). Only seven cases (7/38, 18.4%) had no associated disease. The prognosis for patients with these hematological disorders and bullous PG is notably poor.[116]

Clinically, bullous PG is characterized by scant ulceration, and little tissue destruction. Ulceration, when present, is always superficial, and an intense neutrophilic infiltrate is highly characteristic. Bullous PG is most common on the upper extremities, and lesions may begin as large, dark red, indurated plaques that are very painful and rapidly progress to hemorrhagic, sero-hemorrhagic blisters.[117] Other lesions may show bullous features at onset, and several types of lesions may occur simultaneously or over time in the same patient. Histologically, lesions usually appear as erosions or superficial ulcerations with partial preservation of the epidermis, intraepidermal or subepidermal vesiculation and neutrophilic and erythrocytic exocytosis. A massive neutrophilic infiltrate fills the dermis and hypodermis, forming large abscesses, without vasculitis or any sign of specific infection. Approximately 70 cases of BPG have been reported in the Literature since it was first described, although clinical and pathologic details are often absent or scant in older cases.[118]

PG is a diagnosis of exclusion, and the histopathology may be nonspecific, especially in partially treated or minimally inflamed disease. Early lesions often show a neutrophilic vascular reaction, which may be folliculocentric. Active, untreated, expanding lesions typically show neutrophilic infiltrates, often with leukocytoclasia.[117] As the disease progresses to fully developed ulcers, there is significant tissue necrosis surrounded by mononuclear cell infiltrates.

Treatment strategies for pyoderma gangrenosum are not definitively established due to limited data, but they typically involve the use of topical or systemic immunomodulatory agents. Wound care is crucial, with a preference for dressings that maintain a moist wound environment to optimize healing.[112] The role of surgery in PG treatment is controversial due to the risk of pathergy. In most cases, surgical procedures should be avoided unless necessary, such as when tissue necrosis presents a risk for infection or when vital tissues like tendons or ligaments are exposed.[119] The severity of PG significantly influences the treatment approach. For mild, localized PG, initial treatment typically includes a high-potency topical corticosteroid or topical tacrolimus. For localized PG not responding to topical treatment and for more extensive or rapidly progressive PG, systemic treatment is indicated,

often starting with systemic glucocorticoids.[112] Cyclosporine, with or without systemic glucocorticoids, may be used as an alternative first-line therapy. Dapsone may be useful in some cases. Infliximab may be particularly useful in patients requiring treatment for both PG and Crohn's disease, although its cost and need for infusion may be limiting factors.[112]

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis (NEH) is a rare, benign neutrophilic dermatosis which may occur in association with malignancy (with or without chemotherapy), infections, and/or certain medications.[120,121]

The etiology of NEH is not completely understood. It has been associated with several medications, including acetaminophen, minocycline, granulocyte colony-stimulating factors, cyclophosphamide, methotrexate, carbamazepine, cetuximab, BRAF inhibitors, bleomycin, 5-fluorouracil, and antiretroviral medications.[120,121] Heat damage to eccrine glands may also cause NEH, particularly in the pediatric population.[121]

The pathogenesis of NEH is thought to involve a direct cytotoxic effect of chemotherapy as the initial trigger, with the release of toxic by-products secondary to cell death promoting neutrophil recruitment to the eccrine glands.[121] Alternatively, NEH may be a reactive process in response to an underlying malignancy (paraneoplastic phenomenon) or an abnormal neutrophil response to an offending agent.[121,122]

Clinically, patients with NEH often present with erythematous papules and plaques most commonly on the face, back, trunk, and extremities. Fever is a common symptom, in addition to solitary or multiple lesions that are best described as dark red, violaceous macules, papules, nodules, or plaques. The disease preferentially affects the trunk and extremities, and half of the patients are asymptomatic, with lesional pain and tenderness being the most common complaints.[120,121]

Definitive diagnosis of NEH requires a skin biopsy. Histopathologically, NEH is characterized by a dense neutrophilic infiltrate surrounding and infiltrating within and around eccrine glands with necrotic eccrine epithelial cells. Intraductal abscess formation may also be observed. The hallmark histologic finding in NEH is necrosis of the eccrine unit.[120,121] A routine complete blood count (CBC) should be ordered to confirm NEH cases and to screen for possible underlying hematologic malignancy.

There is no generally accepted treatment for NEH; supportive care is recommended.[121] In general, NEH is a self-limiting disease and does not require therapy.[121] In most cases, the lesions resolve spontaneously within one month. The use of corticosteroids, both topical and systemic, is controversial.[123] Symptomatic treatment of fever and/or pain is recommended. Many patients

experience recurrent NEH with subsequent courses of chemotherapy; if the patient's NEH is associated with a specific chemotherapeutic agent, one case report recommends the use of dapsone 100 mg daily, for 48 hours, prior to drug rechallenge.[124]

Paraneoplastic vasculitides

Vasculitides comprise a large group of heterogeneous diseases characterized by an inflammatory reaction localized in the vessel wall and perivascular tissues. Systemic vasculitis is divided into two main categories: primary vasculitis syndrome and secondary vasculitis syndrome. The former is caused inflammation of blood vessels of unknown etiology, while the latter one is induced by underlying conditions, including connective tissue diseases, neoplasia, infections, and drug allergies. Hematologic disorders are the most common group of malignancies associated with cutaneous vasculitis.[125,126]

In patients with hematologic malignancies, the most common presentation is a small vessel cutaneous leukocytoclastic vasculitis (CSVV), but polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyangiitis, Wegener's granulomatosis, and Henoch-Schönlein purpura have also been described.[126] The disease has similar clinical features of non-malignancy-related cutaneous vasculitis, including palpable purpura, ulcers and urticarial vasculitis, with a prominent involvement of the lower limbs.[127] Vasculitis may occur before, near or after the diagnosis of a malignancy.[128]

CSVV is frequently associated with hematologic disorders such as myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelofibrosis, polycythemia vera (PV), and essential thrombocythemia.[4] The mechanisms underlying paraneoplastic vasculitis are not fully understood, but a combination of factors including abnormal clearance of immune complexes, binding of nonspecific antibodies to vessel walls, and dysregulated production of immunoglobulins are thought to be responsible.[129]

Polyarteritis nodosa (PAN) affects small and medium-sized vessels in multiple organs, including the skin. Among hematologic malignancies, PAN is most commonly associated with hairy cell leukemia, MDS, and chronic myelomonocytic leukemia (CMML).[130] Cutaneous manifestations are common and include palpable purpura, subcutaneous nodules, livedo reticularis or livedo racemosa, ulcerations, and/or bullae.[126]

Erythema elevatum diutinum is a chronic and rare form of localized leukocytoclastic vasculitis, associated with various hematologic malignancies, particularly IgA monoclonal gammopathies and MDS. Less commonly, it is associated with multiple myeloma (MM), CML, and non-Hodgkin's lymphoma.[131] Clinically, lesions present as firm, tender, brownish-red to purple, papules, plaques, or

nodules. Extensor aspects of the extremities, usually near joints such as the fingers, hands, elbows, ankles, and knees are the preferred sites.[131]

The treatment of vasculitis depends on the treatment of the associated neoplasm, as well as its prognosis. Refractory cases may be treated with systemic corticosteroid, with paraneoplastic cases being more resistant to treatment. Improvement of vasculitis with chemotherapy to treat the hematologic disorder, with subsequent recurrence of skin lesions, is a sign of neoplastic recurrence.[126]

Bullous pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease. It typically presents in older adults as a generalized pruritic bullous eruption and is potentially associated with significant morbidity. The incidence of BP in European populations is reported to be 10.3 per million.[132]

The clinical presentation may be quite polymorphic, especially in the early stages of the disease or in atypical variants, in which bullous lesions may be absent. In these cases, the diagnosis of BP requires a high index of suspicion. BP is an example of an immune-mediated disease associated with a humoral and cellular response directed to two well-characterized self-antigens: BP antigen 180 (BP180, also known as BPAG2 or type XVII collagen) and BP antigen 230 (BP230, also known as the epithelial isoform of BPAG1 [BPAG1e]).[133] These represent two components of hemidesmosomes, the junctional adhesion complexes found in skin and mucosa.

Clinically, a prodromal phase lasting weeks to months may precede the development of cutaneous bullae, manifesting as pruritic, eczematous, papular, or urticaria-like skin lesions (Figure 5A-B); some patients may never progress to the bullous stage.[134,135] The bullous stage of BP is characterized by the development of vesicles and bullae on apparently normal or erythematous skin, along with urticarial and infiltrated papules and plaques, occasionally in an annular or figurate pattern. The blisters are tense, up to 1–4 cm in diameter, contain a clear fluid, and may persist for several days, leaving eroded and crusted areas. Occasionally, the blister fluid becomes sero-hemorrhagic. The lesions often have a symmetrical distribution pattern and predominate on the flexural aspects of the extremities and the lower trunk, including the abdomen. Vegetating plaques may be observed within the intertriginous zones (pemphigoid vegetans). Residual postinflammatory changes include hyper- and hypopigmentation and, occasionally, milia. Oral involvement occurs in 10–30% of patients. Ocular, nasal, pharyngeal, esophageal, and anogenital mucosa are less commonly involved.[135] Peripheral blood eosinophilia is seen in approximately 50% of patients. Common sites of cutaneous

involvement include the trunk, flexures of the extremities, and axillary and inguinal folds. Nail changes may also occur.

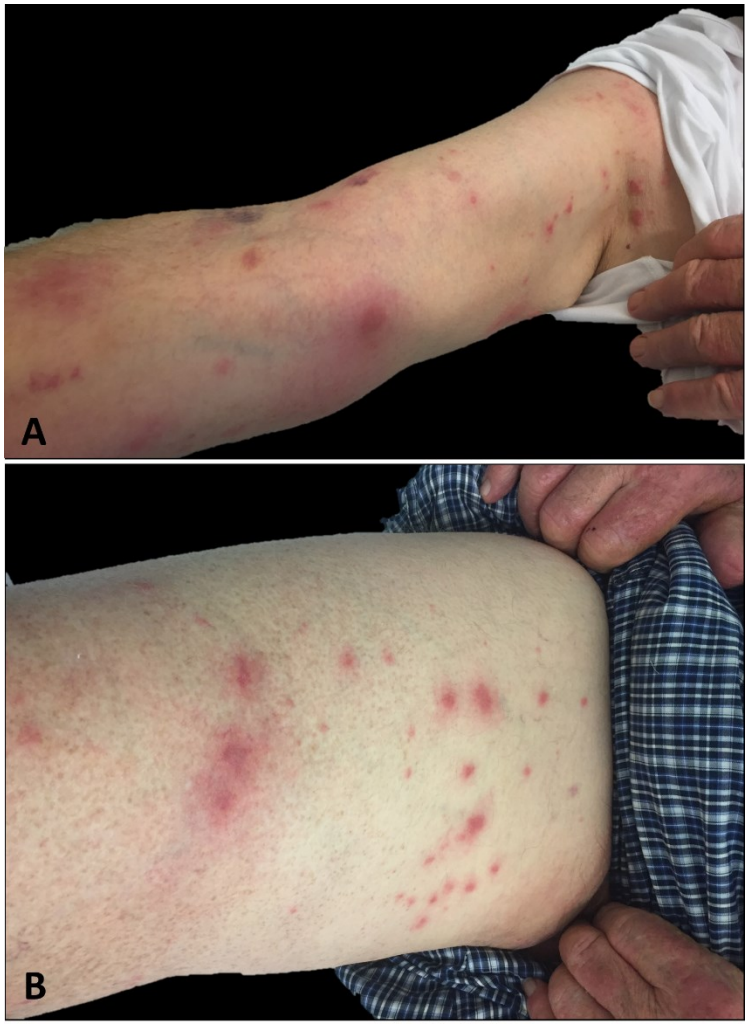

Figure 5. Clinical presentation of pruritic nonbullous pemphigoid with urticarial plaques, eczematous lesions and excoriated nodules. These lesions may resemble EDHM (A-B).

Localized forms of bullous pemphigoid, accounting for up to 30% of cases, have been documented, including disease confined to specific regions such as the soles and palms (Figure 6), lower legs, anogenital area, peristomal skin, or sites affected by incidental or iatrogenic trauma (e.g., radiation therapy). Disease initially presenting in localized areas may either remain confined or progress to generalized involvement.[136–138] Notably, our group has described the second documented case in the Literature of localized BP around the peritoneal dialysis catheter exit site (Figure 7).[139] Given that current estimates suggest that approximately 11% of the global dialysis population receives peritoneal dialysis, with a global annual growth rate of 8%,[140] an increase in the number of such presentations of localized BP can be expected. The clinical manifestation of this localized BP may mimic contact dermatitis, a more common and benign dermatologic condition, or a bacterial infection, which is a

serious and potentially life-threatening event. Such similarities may delay accurate diagnosis and appropriate treatment.

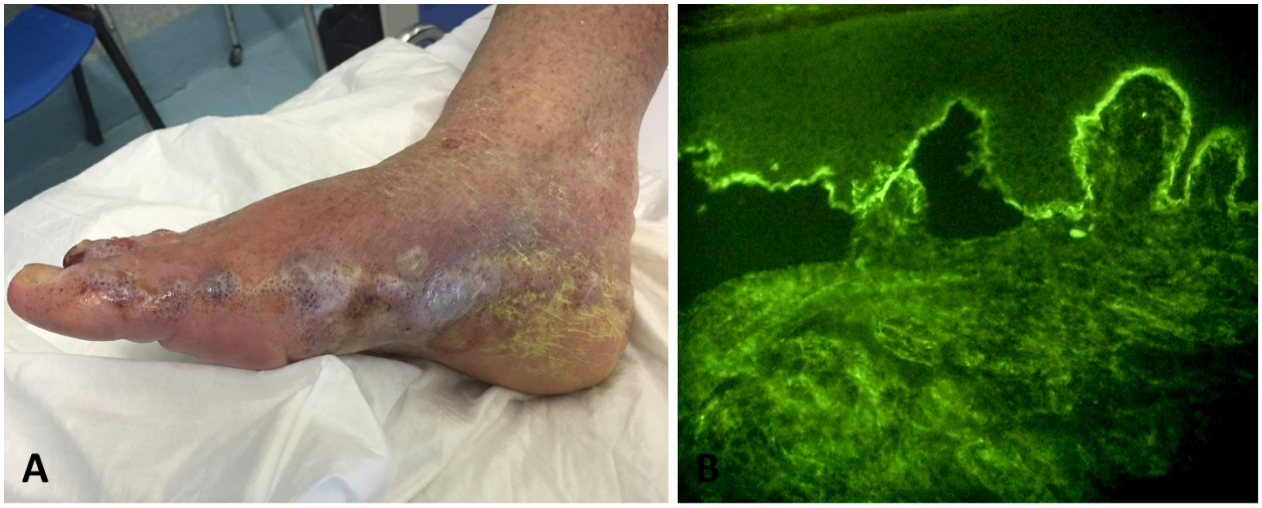

Figure 6. Multiple tense vesiculobullae of dyshidrosiform bullous pemphigoid, some of them hemorrhagic, on nonerythematous skin of the soles and the lateral surfaces of the feet (A). Direct immunofluorescence of the perilesional skin shows continuous linear deposits of IgG along the dermoepidermal junction, consistent with BP. Note the roof staining pattern in the salt split technique, which further supports BP diagnosis (B).
Reproduced with permission from **Michelerio A**, Croci GA, Vassallo C, Brazzelli V. Hemorrhagic vesiculobullous eruption on the palms and the soles as presentation of dyshidrosiform bullous pemphigoid. JAAD Case Rep. 2017 Dec 19;4(1):61-63. doi: 10.1016/j.jdcr.2017.09.002. PMID: 29387751; PMCID: PMC5771739.

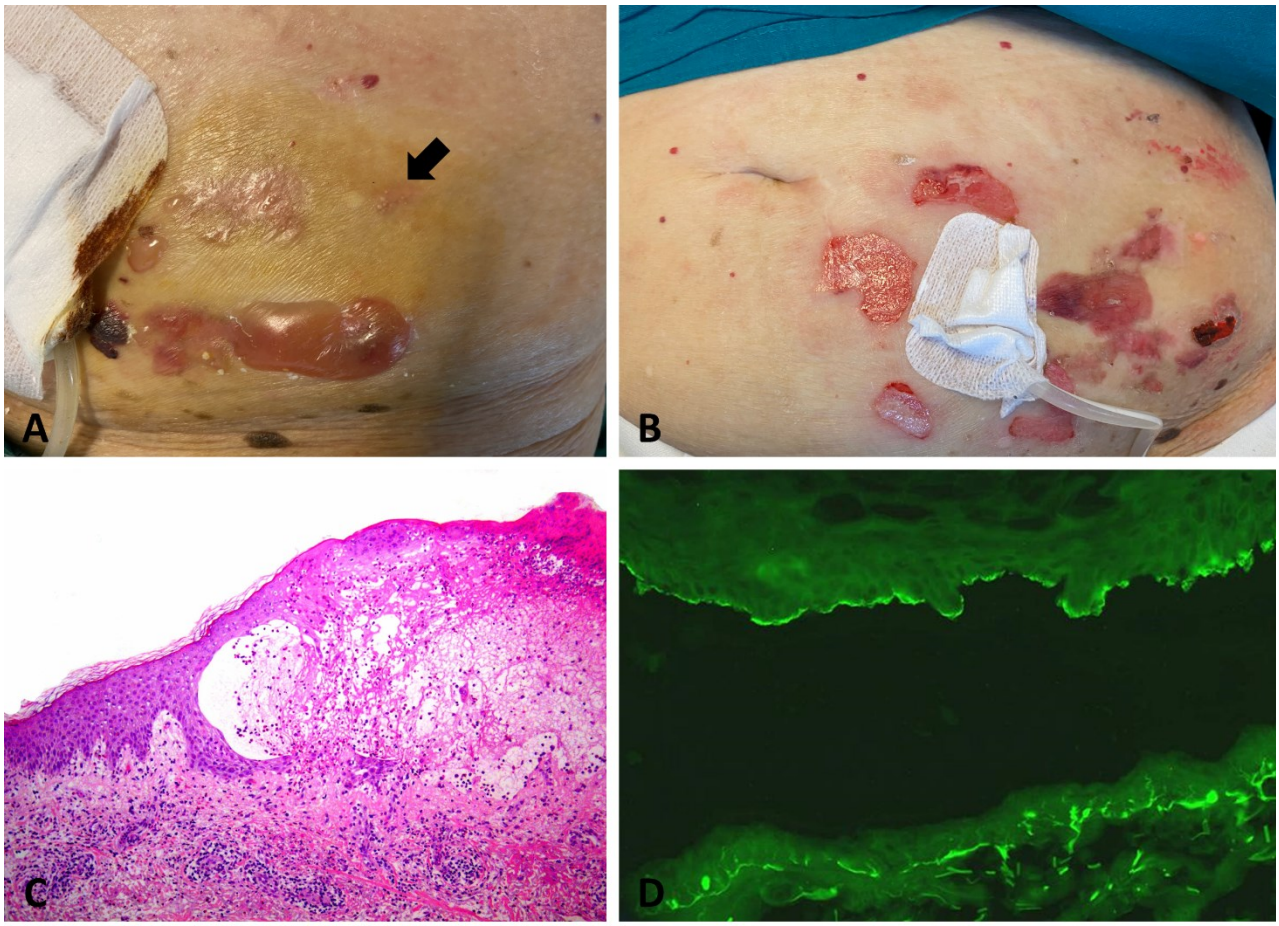

Figure 7. Localized bullous pemphigoid. Tense vesicles, blisters and crusts surrounding around the peritoneal dialysis catheter exit site (A). Milia can be seen (arrow). Healing erosions without new blisters around the peritoneal dialysis catheter exit site after two weeks of therapy (B).
Punch biopsy of the BP lesion showing a subepidermal blister containing fibrin, eosinophils and mononuclear cells (C). Direct immunofluorescence on salt-split skin shows IgG on the epidermal side of split skin (blister roof) (D).
Reproduced with permission from **Michelerio A**, Tomasini C. Blisters and Milia around the Peritoneal Dialysis Catheter: A Case of Localized Bullous Pemphigoid. Dermatopathology (Basel). 2022 Aug 4;9(3):282-286. doi: 10.3390/dermatopathology9030033. PMID: 35997350; PMCID: PMC9397036.

In some individuals, the onset of BP can be triggered by various systemic medications. The list of associated drugs is extensive and includes categories such as diuretics (e.g., furosemide and spironolactone), NSAIDs (e.g., ibuprofen and topical diclofenac), antibiotics (including amoxicillin and ciprofloxacin), ACE inhibitors, TNF inhibitors, potassium iodide, vaccines, and recently identified dipeptidyl peptidase-4 inhibitors (such as vildagliptin) and checkpoint inhibitors (such as pembrolizumab).[141,142] The previously observed association of internal malignancies with BP is probably primarily related to the older age of the patients. In recent case-control studies, the trend toward an increased risk of malignancy was marginal, and a recent English national record linkage study found no increased risk of concurrent or subsequent malignancies in patients with BP.[143]

EDHM closely resembles BP (Figure 5A-B). Therefore, differential diagnosis is essential for the accurate treatment selection. In the non-bullous phase or in atypical variants of BP, routine histology may provide less specific information, as only eosinophilic spongiosis and/or dermal infiltrates of eosinophils may be seen. Biopsy specimens of early bulla typically show a subepidermal blister accompanied by a dermal inflammatory infiltrate composed of eosinophils and mononuclear cells is typically observed. The infiltrate favors the upper dermis, and the cavity of the bulla contains fibrin with a variable inflammatory infiltrate. Electron microscopy studies have shown that subepidermal blistering occurs at the level of the lamina lucida.

In almost all patients with BP, DIF microscopy of perilesional, uninvolved skin will characteristically show the presence of fine, linear, continuous deposits of IgG and/or C3 (and less commonly other Ig classes) along the epidermal basement membrane. Enzyme-linked immunosorbent assay (ELISA) is used to detect an increasing number of autoantibodies targeting specific antigens such as the NC16A domain of BP180 and the C-terminus of BP230. These tests are quite specific (≥90%), with occasional false positives in healthy or elderly subjects. The overall sensitivity of the BP180-NC16A ELISA is comparable to indirect immunofluorescence (IIF) and combining ELISA tests can increase sensitivity by approximately 10%. IIF microscopy, using salt-split normal human skin as a substrate, detects circulating anti-basement membrane autoantibodies in 60–80% of patients. These autoantibodies usually bind to the epidermal side of the skin.[144]

In EDHM patients, both immunofluorescence and serum tests are negative for autoantibodies to BP180. Thus, immunological testing can help clinicians differentiate malignancy-related BP from EDHM.

Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome (PAMS), is a rare and often fatal autoimmune blistering disease.[145] It was first described in 1990 by Anhalt et al., who differentiated this entity from pemphigus vulgaris by demonstrating an association with malignant neoplasms and the presence of antibodies to desmoplakin I and BP 230 antigen.[146] The disease predominantly affects adults between 45 and 70 years of age, but it can occur in any age group, including children.[147]

The association with neoplasms or hematologic disorders is found in more than 84% of cases.[148,149] Lymphoproliferative disorders are most commonly associated, with non-Hodgkin's lymphomas being the most common (38.6% of all cases of PNP), followed by CLL (18.4%), Castleman's disease (18.4%), thymomas (5.5%), Waldenström’s macroglobulinemia (1.2%), Hodgkin's lymphomas (0.6%), and monoclonal gammopathy (0.6%).[148] The neoplasm is usually diagnosed before the PNP

manifests.[150] However, in 30% of cases, the cutaneous manifestation precedes the diagnosis of the occult neoplasm.

The pathogenesis of PNP is complex and involves both humoral and cell-mediated immune responses. The neoplastic process appears to induce an autoimmune disorder, leading to the production of antibodies against multiple epithelial antigens.[147,151] Among these, desmoplakins, which are intracellular proteins involved in anchoring of intermediate filaments to desmosomal plaques and in epidermal cell adhesion, are primary antigenic targets.[147,151]

Central to its development is the impairment of immune tolerance at both the central and peripheral levels.[151] In the thymus, the process of eliminating autoreactive T cells may be compromised, leading to the escape of these cells into the peripheral circulation. This problem is often related to abnormalities in key regulatory proteins such as the autoimmune regulator (Aire). In the periphery, several tolerance mechanisms that normally keep self-reactive T cells in check are also disrupted. These include the failure of mechanisms such as T cell anergy and deletion, as well as dysregulation in the function of regulatory T cells (Tregs). Tregs, which are crucial for maintaining immune self-tolerance, may lose their effectiveness, allowing the activation of self-reactive T cells. Another significant aspect in the pathogenesis of PNP is the role of cytokines, especially interleukin (IL)-6. This pro-inflammatory cytokine can inhibit the differentiation and suppressive function of Tregs, contributing to an autoimmune milieu. Elevated levels of IL-6 are often found in PNP, highlighting its potential role in promoting autoimmunity. Additionally, molecular mimicry might play a role in PNP. The immune system's response to tumor-specific neoantigens might inadvertently trigger reactions against similar self-antigens, especially those found in desmosomal and hemidesmosomal proteins. This cross-reactivity can initiate autoimmune responses, further exacerbated by the phenomenon of epitope spreading.[151]

Clinically, PNP is characterized by severe erosive stomatitis, polymorphous skin lesions, and association with lymphoreticular or other malignancies.[152] Pulmonary involvement with features of bronchiolitis obliterans may also be present, adding to the complexity and severity of the disease.[152] Mucosal lesions are typically chronic, erosive, progressive, and painful, with oral involvement being the most common.[152] Cutaneous lesions usually develop after the onset of mucosal lesions and may present in a variety of forms, including bullae resembling those of pemphigus vulgaris or bullous pemphigoid, inflammatory violaceous papules or plaques resembling lichen planus or graft-versus-host disease, targetoid lesions similar to those of erythema multiforme or Stevens-Johnson syndrome, or extensive cutaneous desquamation resembling toxic epidermal necrolysis.[147,152]

The diagnosis of PNP requires a comprehensive evaluation of clinical, histopathologic and laboratory findings. The histologic features are variable, depending on the different clinical presentations. Hance, lesions show a combination of erythema multiforme-like, lichen planus-like, pemphigus vulgaris-like, and pemphigoid-like features.[153,154] The main findings are suprabasal acantholysis with basal apoptosis, associated with interface dermatitis (erythema multiforme-like) with or without (lichen planus-like) band-like infiltrate. PNP may present exclusively with lichenoid interface dermatitis in the absence of acantholysis. A subepidermal vesicle is present in pemphigoid-like lesions.[153,154]

Direct immunofluorescence (DIF) of perilesional skin or mucosal tissue often shows intercellular IgG and C3 within the epidermis, a finding that is characteristic of pemphigus. However, PNP can also show linear or granular deposition of IgG and/or C3 at the basement membrane zone, which is not seen in classic pemphigus.[155] Indirect immunofluorescence (IIF) is also used to detect circulating autoantibodies in the patient's serum. In PNP, IIF can detect antibodies against a variety of antigens, including plakins, cadherins, and desmogleins. However, the sensitivity of IIF can be increased by using rat bladder epithelium as a substrate, which is rich in plakins, the primary target antigens in PNP.[155]

Treatment of PNP is multifaceted and includes the suppression of disease manifestations, management of patient symptoms, and treatment of the underlying malignancy when possible. Systemic glucocorticoids are often the initial treatment, with other immunosuppressive agents often combined to achieve further clinical improvement or to take advantage of their glucocorticoid-sparing effects.[156] Rituximab, a chimeric antibody targeting CD20 on B lymphocytes, has been used in patients with PNP, but the response to rituximab therapy is highly variable. Alemtuzumab, a monoclonal antibody against CD52 expressed on T and B lymphocytes, has shown promise in the treatment of some cases associated with hematologic malignancies, but severe immunosuppression and the inability to reverse bronchiolitis obliterans remain limitations to its use.[147]

The prognosis of PNP is generally poor, with most patients succumbing within two years to sepsis, respiratory failure, or the underlying malignancy.[151]

Eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF) is a chronic, culture-negative folliculitis of unknown etiology characterized histologically by eosinophilic follicular inflammation, first described by Ise and Ofuji in 1965 as a variant of superficial pustular dermatosis.[157] Four major forms of eosinophilic folliculitis have been described: eosinophilic pustular folliculitis (Ofuji disease), eosinophilic pustular folliculitis

of infancy, immunosuppression (or HIV)-associated eosinophilic pustular folliculitis, and hematologic malignancy-associated EPF.

The classic form of EPF, commonly referred to as Ofuji's disease, is characterized by chronic and recurrent annular clusters of pruritic sterile follicular papules and pustules, superimposed on plaques with central clearing and peripheral extension. These individual clusters persist for a duration of 7 to 10 days and are prone to relapse every 3 to 4 weeks. The anatomical distribution of classic EPF predominantly involves the face (in 85% of cases), back, and trunk (59%), but can also extend to the extremities, palms, and soles. This is an intriguing observation, considering the absence of follicles in the palms and soles. Approximately 20% of patients present with palmoplantar lesions. The lesions typically resolve without scarring, although postinflammatory hyperpigmentation is common. These cutaneous manifestations are accompanied by mild to moderate leukocytosis with eosinophilia in up to 35% of patients. Systemic involvement is generally absent.

Histopathologically, EPF lesions exhibit folliculotropic infiltration of eosinophils, which is a diagnostic hallmark. In a study of 20 patients, eosinophils were located around hair follicles, with the outer root sheaths showing both intracellular and intercellular edema.[158] Eosinophilic inflammation was present also in sebaceous glands (65%), around vessels, collagen fibers, and sweat glands (80%). Abscess formation in the follicles, sebaceous glands, or both was observed in 40% of the patients. Additionally, the accumulation of acid mucopolysaccharides in spongiotic lesions of follicles or sebaceous glands was present in 35% of the patients. In 10% of the patients, Grocott staining revealed positive reactions for *Pityrosporum* yeast, either in the stratum corneum or in keratotic plugs of the follicle. In addition, a moderate increase in mast cells around follicles and sebaceous glands was found in all patients. A relationship between EPF and intrafollicular mucin deposits has been proposed, with the mucin production possibly resulting from the degeneration of epithelial cells in the outer root sheath.[158] Flame figures can rarely be observed.[159]

In addition to the classic variant, three clinical subtypes of EPF have been identified:

- **Infantile EPF**: A benign and self-limiting condition that manifests in early infancy. The condition was much more common in males than in females.[159] It is characterized by recurrent crops of pruritic follicular or nonfollicular papulopustules lacking the typical annular distribution seen in the classic variant. The scalp is the typical site of involvement. Approximately 70% of patients with I-EPF present with the first eruption by 6 months of age, and the lesions resolve by 3 years of age in over 80% of cases.[160]

- **Human immunodeficiency virus (HIV)-associated EPF**: This subtype differs from classic EPF in that it is exquisitely pruritic and presents with discrete, erythematous, raised, follicular papules that are often largely excoriated and edematous, rather than clusters of large, annular pustules..[161] The disease most commonly affects the head and neck in patients with a CD4 cell count below 250 cells/mL.[159,162]
- **Hematologic Malignancy-associated EPF**: This intensely pruritic condition may occur in patients who have undergone bone marrow or peripheral blood stem cell transplantation, as well as in patients with hematologic malignancies who have not undergone transplantation.[163]

Peripheral eosinophilia and elevated serum immunoglobulin E levels may be a concomitant feature in any of the subtypes of EPF.

Of note, EDHM has striking clinicopathologic overlap with EPF in terms of morphology, distribution, context of underlying lymphoproliferative disorder (including CLL), perifollicular and intrafollicular eosinophilia, and natural history. Thus, it is likely that EDHM and hematologic malignancy-associated EPF represent the same entity.[164,165]

Wells syndrome

Wells syndrome, also known as eosinophilic cellulitis, is a dermatologic disorder of unknown etiology firstly described by Wells in 1971 as "recurrent granulomatous dermatitis with eosinophilia".[166] It is clinically characterized by a progression from erythematous-edematous plaques resembling cellulitis (early stage) to indurated plaques (late stage). The condition was subsequently renamed "eosinophilic cellulitis." Spigel and Winkelmann proposed the eponym Wells syndrome in 1979.[167]

The condition has no ethnic or gender predilection and primarily affects adults. A limited number of pediatric cases have been reported, some showing an association with atopy.

The pathogenesis of Wells syndrome remains unclear. The involvement of abnormal Th2 cells, IL-5, and activated eosinophilic granulocytes suggests a nonspecific hypersensitivity response to either exogenous or endogenous stimuli.[168] Local hypersensitivity reactions to so-called "triggers" such as insect bites or stings, drugs, allergic contact dermatitis, underlying myeloproliferative disorders, and infections have been proposed.[168] Interleukin-2 has been found to prime eosinophil degranulation in hypereosinophilia and Wells' syndrome.[169] Notably, peripheral lymphocytes isolated from patients with Wells syndrome have shown exaggerated responses to mosquito salivary gland extracts, leading to a contentious debate regarding the distinctiveness of Wells syndrome as a clinical entity or merely a histologic reaction pattern.[170]

Diagnostic criteria have been proposed, although they have not been validated in large cohorts of patients (Table 5).[171]

Major (2 of 4 required)
• Diverse clinical picture to include any of the previously reported variants: - Plaque-type - Annular-granuloma-like - Urticaria-like - Papulovesicular - Bullous - Papulonodular - Fixed-Drug Eruption-like • Relapsing, remitting course • No evidence systemic disease • Histology: eosinophilic infiltrates, no vasculitis
Minor (at least 1 required)
• Flame figures • Histology: Granulomatous change • Peripheral eosinophilia not persistent and not greater than >1500/µl • Triggering factor (e.g., drug)

Table 5. Proposed diagnostic criteria for Wells syndrome by Heelan K et al.[171]

Clinical manifestations of Wells syndrome include recurrent episodes of prodromal itch or burning, followed by markedly edematous nodules and plaques, which may have annular or arcuate configurations and occasionally violaceous borders. Vesicles and bullae may also be present. The lesions vary in color from bright red to shades of pinkish-brown, green, brown, or slate-gray. The plaques may become indurated, and the lesions typically resolve over a period of 4 to 8 weeks. Less common presentations include papules and hemorrhagic bullae. Different skin lesions may occur simultaneously present in the same patient. Thus, there is no typical clinical presentation.[172] The extremities are most commonly affected, with occasional trunk involvement. Systemic complaints may include malaise and fever in a minority of cases. Peripheral blood eosinophilia is common, and the erythrocyte sedimentation rate may be significantly elevated in cases of particularly severe cases.[172] Patients have often been misdiagnosed as having erysipelas or acute cellulitis.

Histologic findings may vary depending on the time of biopsy, which may explain the clinical variability of this disorder. The infiltrate is most prominent in the mid to deep dermis, with occasional involvement of subcutaneous fat, fascia, and skeletal muscle. The acute stage (2–3 days) may be characterized by tissue eosinophilia accompanied by massive papillary dermal edema with subepidermal bulla formation. Intraepidermal vesiculation with eosinophilic spongiosis may also be

present. The characteristic bright 'flame figures' appear only later, following eosinophil degranulation (subacute stage, weeks 1–3). Finally, macrophages migrate into the tissue, forming granulomatous infiltrates and leading to the resolution of tissue eosinophilia (regression phase, 2–8 weeks).[172,173] Vasculitis is rare.

Initial therapy with daily prednisone (usually up to 0.5 mg/kg, in individual cases up to 2 mg/kg of prednisolone equivalent) often results in substantial improvement within a few days in most patients. Gradual tapering over a month is generally well tolerated. Flares may be managed with additional courses of prednisone. Alternative therapeutic options include minocycline, colchicine, antimalarials, dapsone, griseofulvin, interferon-α, and antihistamines. Cyclosporine (1.25–2.5 mg/kg/day) administered for 3–4 weeks has resulted in clinical resolution in two patients, with no recurrence observed over the subsequent 10 months. For milder cases, potent topical corticosteroids may be sufficient.[168] Table 6 resume the main differential diagnoses of EDHM.

	Clinical features	Histopathology
Leukemia cutis	More common in acute myeloid leukemia. Single or multiple violaceous, reddish-brown, or hemorrhagic papules, nodules, plaques. Unusual: maculopapular exanthema, exfoliative erythroderma, leonine facies, ulcers in atypical sites (groin, scrotum, face), oral mucosa involvement (gingival hyperplasia). Mostly asymptomatic.	Perivascular and/or periadnexal infiltrate, nodular or diffuse, involving deep dermis and subcutaneous tissue. Grenz zone may be present. Presence of necrotic cells, mitotic figures, nuclear pleomorphism. Immunohistochemical analysis identifies specific cell line, aiding in differentiation from cutaneous lymphoma.
Cutaneous Plasmocytoma	Associated with myeloma. Violaceous to skin-colored to erythematous nodules on extremities, trunk, head.	Varied infiltration pattern. Grenz zone may be present. Immunohistochemical staining positive for CD38, CD138; light chain restriction is common.
Sweet syndrome	Abrupt onset of painful, edematous, erythematous papules, plaques, nodules on the skin; often associated with fever and leukocytosis.	Infiltrate of mature (or histiocytoid) neutrophils in upper dermis, no vasculitis; normal epidermis; common papillary dermal edema, may cause subepidermal vesiculation; neutrophilic infiltrates may extend into subcutaneous tissue with septal/lobular involvement.

Bullous pyoderma gangrenosum	Superficial, scant ulceration, little tissue destruction; mostly in upper extremities. It begins as large, dark red, indurated, painful plaques, which develop into hemorrhagic bullae.	Erosions or superficial ulcerations with partial epidermis preservation; intraepidermal or subepidermal vesiculation; neutrophilic and erythrocytic exocytosis; massive neutrophilic infiltrate in dermis and hypodermis, forming large abscesses; no vasculitis or specific signs of infection.
Neutrophilic eccrine hidradenitis	Erythematous-violaceous papules and plaques on face, back, trunk, extremities; fever may occur.	Dense neutrophilic infiltrate around and within eccrine glands; necrotic eccrine epithelial cells; intraductal abscess formation possible.
Bullous pemphigoid	Classically an elderly patient with multiple tense bullae over an urticarial base.	Subepidermal cleft with neutrophilic and eosinophilic fluid content. DIF is diagnostic in equivocal cases.
Paraneoplastic pemphigus / Paraneoplastic autoimmune multiorgan syndrome (PAMS)	Chronic, erosive, progressive, and painful stomatitis and polymorphous skin lesions that usually develop after the onset of mucosal lesions.	Variable histologic features: erythema multiforme-like, lichen planus-like, pemphigus vulgaris-like, pemphigoid-like. DIF: intercellular IgG, C3 in the epidermis; linear/granular IgG, C3 at basement membrane zone. IIF: antibodies to plakins, cadherins, desmogleins; sensitivity increased with rat bladder epithelium substrate.
Eosinophilic folliculitis	Pruritic folliculocentric papules, vesicles, pustules, and urticarial plaques may all be observed, usually distributed over the head, neck and upper trunk.	Folliculotropic infiltration of eosinophils.
Wells syndrome	Prodrome of itch or stinging sensation with subsequent development of annular or circinate erythematous-edematous plaques. Groove sign is classic. Polymorphous eruption resembling EDHM is also reported. Association with underlying hematologic malignancy has been described, but not always.	Tissue eosinophilia is present. Flame figures are not pathognomonic and are seen only in later stages of the disease.

Table 6. Differential diagnoses of EDHM.

1.5 Treatment

EDHM is a recalcitrant, pruritic skin condition that can be challenging to treat. The disease is generally refractory to oral antihistamines and topical corticosteroids, while systemic corticosteroids (prednisone 40-80 mg/day) with or without concomitant topical steroid have shown to be effective in the active phase of treatment.[77,20] However, alternatives for maintenance therapy are still lacking. In a retrospective cohort study by Grandi and colleagues, 63% of patients relapsed at a mean interval of 5 months.[20]

In addition to systemic corticosteroids, doxycycline, nicotinamide, and UVB light phototherapy, IntraVenous ImmunoGlobulin (IVIG) may be effective therapeutic alternatives considering their lower long-term toxicity.[84,174] Dapsone is known to be beneficial in disorders with abnormal neutrophil and eosinophil accumulation and has been shown to be effective at a dose of 50-150 mg, but side effects may limit its use.[23,32] In some reported cases, improvement was noted with chemotherapy, but the disease often recurred.[78]

Lor et al. describe the case of a patient with EDHM who remained well controlled on omalizumab after a one-month taper of prednisone and a brief trial of narrow-band ultraviolet B phototherapy. Omalizumab, a monoclonal antibody, works by binding to IgE, thereby reducing the release of inflammatory mediators from mast cells and basophils. It is prescribed for the treatment of asthma and chronic idiopathic urticaria, although it has been used off-label for several dermatologic conditions, including atopic dermatitis and bullous pemphigoid. This observation suggests that omalizumab may inhibit flares in patients diagnosed with EDHM. However, it remains an open question whether these results are applicable to patients without elevated IgE levels, as the preponderance of documented cases does not include this specific laboratory data.[175]

Recent case reports have documented an excellent response to dupilumab in the treatment of EDHM, further supporting the theory that Th2 cell activation is involved in the pathogenesis of the disease.[176,177] Dupilumab is an anti-IL-4Rα monoclonal antibody targeting IL-4 and IL-13. Sibaud et al. conducted a study in six patients to evaluate the effects of dupilumab in the treatment of EDHM. Patients received an initial loading dose of 600 mg, followed by 300 mg every two weeks. Their progress was systematically evaluated at 1 and 2 months, including assessments of pruritus, impact on quality of life, and the observation of skin lesions. After two months of treatment, the results were mixed. One patient showed significant improvement, with a 40% reduction in all measured parameters after only two injections. Another patient showed partial improvement, one patient remained clinically stable, while three others experienced worsening conditions, two of whom required systemic corticosteroids. Skin lesions were similar to baseline at months 1 and 2 for all

patients, except one who improved significantly and one who worsened. Three patients also had hematic eosinophilia at the baseline, but this did not correlate with treatment efficacy. These results, although not as striking as those seen in other studies, provide valuable insights into the potential use of dupilumab in the treatment of this disease. It is worth noting that this study did not evaluate certain factors, such as the serum concentration of IL-4 or the expression of IL-4 and IL-31 within the lesions, which could provide a further understanding of the effects of therapy.[177]

1.6 Aim of the thesis

Our research project was designed to systematically investigate EDHM.

The primary objective was to elucidate the potential triggers and underlying pathophysiologic mechanisms associated with EDHM in patients diagnosed with chronic lymphocytic leukemia and non-Hodgkin's B lymphoma.

Central to this study was the hypothesis that external factors, particularly insect bites, could serve as triggers for EDHM. This hypothesis was based not only on the compromised adaptive immune response often seen in patients with hematologic malignancies -either intrinsically related to the malignancy or as a consequence of chemotherapy- but was also on a number of observations, including clinical findings, epidemiologic data, seasonal patterns, patient reports, and histologic evidence.

Additionally, the study aimed to:

- Describe and define the **clinical manifestations** in patients diagnosed with EDHM, particularly in relation to the histopathological patterns of this disease.
- study the **immunopathological features** of patients diagnosed with EDHM.
- investigate the **virological status** of these patients, focusing on viruses of primary hematologic/ transplantology interest, to highlight a potential triggering role of viruses with a high circulating load.
- Define a **panel of laboratory tests** for patients diagnosed with EDHM to investigate any repeatable alterations that may have a pathogenetic role.
- Collect data on this cohort and **compare them with existing literature**, aiming to elucidate the relationship between EDHM and its manifestations in patients with chronic lymphocytic leukemia and other B-cell lymphoproliferative disorders. This includes tracing the underlying pathogenetic mechanisms leading to the appearance of such manifestations.
- Understand the **inflammatory cascade** that may lead to lesions in EDHM and the relationship between the onset of these manifestations and the hematologic disease. This includes outlining

potential predisposing factors (related to the disease itself or iatrogenic) and prognostic indicators, while also assessing the challenges in managing and treating a patient with this condition.

- Provide a clear definition of all these aspects to support **differential diagnosis** against other pathological conditions with similar manifestations that may occur in this group of patients.

Additionally, the study aimed to determine whether EDHM could serve as **a prognostic indicator** of the progression of the underlying hematologic disease. Such an understanding is critical for refining patient management strategies and therapeutic decision making.

Furthermore, potential pathogenetic links between EDHM and other eosinophilic dermatoses were explored, with a particular focus on Wells' syndrome. The goal was to determine if there are common etiologic or pathophysiologic pathways between these conditions.

In summary, through these investigations, the research aimed to provide a comprehensive understanding of EDHM, focusing on clinical, pathologic, and immunologic findings, potential triggers, and its prognostic implications.

CHAPTER 2:
MATERIALS AND METHODS

2.1 A single center prospective clinicopathological study

The research project was conducted in collaboration with the Hematology Clinic of the Fondazione IRCCS Policlinico San Matteo, Pavia.
Patients followed up at the Hematology Clinic undergo a structured schedule of visits. The frequency of these visits is determined by the patient's current state of health. In particular, patients in remission are scheduled for six-monthly visits. On the other hand, who are experiencing a relapse or are on therapy are monitored more closely, with visits scheduled either monthly or bi-monthly.
A thorough physical examination is conducted as a standard procedure during these visits. This examination focuses primarily on the evaluation of superficial lymphadenopathies and possible organomegalies. In addition to the physical examination, hematochemical analyses are performed. These analyses are essential for monitoring various parameters, including the blood count and indirect indices of the disease, such as β2 microglobulin and lactate dehydrogenase (LDH). In addition, patients undergo a complete abdominal ultrasound annually to further evaluate organomegaly.

Patients undergoing follow-up for hematologic lymphoid B-cell malignancies at the Hematology Clinic of our hospital between April 2017 and December 2018 were eligible.
Patients with skin lesions such as papular, urticarial, plaque-like, or even bullous were referred directly to the Dermatology Clinic for clinical evaluation and initial therapeutic approach.

Patients were then examined, and with their consent, photographs were taken. If EDHM was suspected, dermatologic clinical data, including seasonality and duration of lesions, awareness of insect bites, and history of allergies were collected. Data on hematological disease type and prognostic factors such as genetics (immunoglobulin heavy chain gene mutation status, CLL FISH Panel, TP53), therapy, and outcome were also collected.
Skin lesions were classified according to their number as rare (≤ 2), intermediate (3-20), and numerous ≥ 21. The clinical picture was classified as monomorphic or polymorphic based on the type and number of primary lesions present at the same time.

An Analogue Visual Scale (VAS) was used to measure itch intensity, ranging from 1 ("no itch") to 10 ("worst imaginable itch").[178,179] Blood samples were collected for allergologic, immunologic and laboratory studies. In addition to total IgE levels, specific IgE levels were determined for venom/salivary antigens of insects and allergens commonly found in our latitudes. In particular we have screened for specific IgE antibodies to *Dermatophagoides pteronissimus, Dermatophagoides farinae, Acarus siro, Lepidoglyphus destructor, Birch, Hazel, Gluten, Cat dander, Dog dander, Ambrosia artemisiifolia, Artemisia vulgaris, Parietaria judaica, Holcus lanatus, Candida albicans, Alternaria alternata, Ascaris lumbricoides, Anisakis*, latex and venoms/salivary antigens of insects commonly found in our latitudes: Cockroach, Ant, Common Mosquito, Chironomidae Diptera, Red Mosquito Larvae, Flour Moth.

Immunologic testing included determination of autoantibodies to BP180 and BP230 and indirect immunofluorescence (IFI) with salt split. The determination of circulating autoantibodies to dermo-epidermal junction antigens is performed by ELISA (enzyme-linked immunosorbent assay). The latter assessment is motivated by the need to differentiate the cutaneous manifestations of bullous pemphigoid, which, as mentioned above, may be characterized by the appearance of intensely pruritic urticarial lesions in addition to the presence of blisters.
The indirect immunofluorescence (IFI) test was performed on the patient's serum using a substrate expressing potential target antigens, consisting of sections of monkey esophagus incubated with fluorescent antibodies to human immunoglobulins. Antigen-antibody complexes formed by these antibodies were identified.
Salt split skin (SSS) is performed using indirect immunofluorescence techniques with modifications to the normal primate skin preparation. Incubation of the skin with a 1 molar concentrated sodium chloride (NaCl) solution for three days allows separation of the epidermis from the dermis at the level of the lamina lucida. This method allows for a better evaluation of the antibody-antigen binding by making the antigens of the dermo-epidermal junction more exposed and accessible and by identifying antibodies that react with antigens located on the epidermal side from those located on the dermal side, below the lamina lucida.

Circulating specific IgG and IgM antibodies to Epstein Barr virus (EBV), cytomegalovirus (CMV), and varicella zoster virus (VZV), as well as circulating DNA copy numbers, were assessed.
In addition to routine laboratory tests, our study included quantitative assays for eosinophil cationic protein, mast cell-derived tryptase, and interleukin-4 (IL-4) and interleukin-5 (IL-5). Regarding the procedures for IL-4 and IL-5, serum titers were assessed in the peripheral blood of all patients enrolled

in the study. To detect and quantify IL-4 and IL-5, we used a commercially available enzyme-linked immunosorbent assay kit (Immunoassay, R&D Systems, Minneapolis, MN), closely following the manufacturer's instructions. The resulting concentrations of IL-4 and IL-5 were expressed as pg/mL.

For each patient, one 6 mm and one 4 mm punch biopsy were taken from recent non-ulcerated lesions for histologic and direct immunofluorescence (DIF) examination. Skin biopsy specimens were fixed in 10% buffered formalin, paraffin-embedded, and stained with hematoxylin and eosin. PAS-Alcian Blue and Giemsa staining were performed in all cases. Immunophenotypic studies were performed in all cases using streptavidin-biotin-peroxidase staining (Dako OMNIS© system) with monoclonal antibodies against B- and T-cell antigens, including CD20, CD79a, CD3, CD5, CD23, CD10, Bcl6, Bcl1, CD30/BerH2. Histopathologic sections were reviewed by one pathologist (GF) and one dermatologist trained in cutaneous pathology (CT). For each case, the following parameters were evaluated: changes in the epidermis (atrophy, acanthosis, spongiosis, basal vacuolization, exocytosis, necrosis), dermis (edema, fibrosis, mucinosis, necrosis, presence of flame figures, granulomas) and hypodermis (presence of panniculitis); distribution (dermal-hypodermic, perivascular, periadnexal, interstitial) and composition of the inflammatory infiltrate (lymphocytes, eosinophilic and/or neutrophilic granulocytes, histiocytes, mast cells); presence of lymphomatous infiltrate; presence and distribution of CD30-positive lymphoid elements; vascular changes (ectasia, extravasation, vasculitis); presence of hemophagocytosis. In each sample, representative hot spots with the highest density of eosinophils in the dermal inflammatory infiltrate were identified and the number of eosinophils per high-power field (HPF; 40x objective, 400x total magnification) was calculated. The peak eosinophil count (highest number of eosinophils per HPF) was determined for each biopsy.
DIF specimens were collected from a perilesional area of a recent, untreated, non-excoriated lesion and frozen at -80°C. The assay is performed on 4-5 μ-thick cryostat sections of the biopsy material placed on a microscope slide. The specimen is then coated with a fluorescein isothiocyanate (FITC)-labeled antibody specific for different classes of human Ig and complement components. After 30 minutes of reaction, excess labeled antiserum is removed with washes, and the specimen is coverslipped and visualized under a fluorescence microscope.
Patients with a final diagnosis other than EDHM were excluded from the study. Patients underwent periodic evaluations and data collection was completed on September 30, 2022.

2.2 Collaborative Research with the University of Turin and Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Ospedale Molinette)

In the next phase of this research, we started a collaboration with the Dermatology Clinic of the University of Turin and the S.C.D.U. Hematology I, A.O. Azienda Ospedaliera-Universitaria Città della Salute e della Scienza, Ospedale Molinette, Torino.

Through a retrospective approach, patients diagnosed with EDHM were identified from the aforementioned institutions. All available dermatologic and hematologic clinical data were extracted from the medical records. These data included age at diagnosis of hematologic disease, prognostic factors, clinical course of hematologic disease, hematologic treatments, morphology, distribution, and time of onset of dermatologic lesions.

In addition, histopathologic specimens previously analyzed at the Dermatopathology Unit of the University of Turin were re-examined to ensure consistency and accuracy in the pathologic evaluation of EDHM and to verify the histopathologic features. In the retrospective study, due to organizational reasons, the biopsy could be performed with some delay, which provided the opportunity to study the histopathologic features of late lesions.

CHAPTER 3:

RESULTS

3.1 A single-center prospective clinicopathologic study

A total of 217 patients with chronic lymphocytic leukemia (CLL) and 205 patients with non-Hodgkin's lymphoma (NHL) were seen at the hematology clinic between April 2017 and December 2018. Of these, 12 patients with CLL (8 females and 4 males, 5.5%) and 3 patients with B-NHL (2 females and 1 male, 1.4%) were diagnosed with EDHM and included in the study for a total of 15 patients. All patients were adults with a mean age ranging from 53 to 87 years (mean age 70 years, median 68 years) (Table 7).

3.1.1. Relationship between EDHM and hematologic disease progression

Three patients were diagnosed with non-Hodgkin B-cell lymphoma. Specifically, patient 9 and patient 11 had follicular B-cell lymphoma, while patient 10 was diagnosed with marginal zone B-cell lymphoma. All three patients had advanced stage disease: patient 9 had stage III disease, while patients 10 and 11 had stage IV disease. All three had previously received rituximab-bendamustine chemotherapy. Patient 9 was in remission and not receiving any treatment at the time of lesion onset, while patient 11 was receiving maintenance rituximab, albeit in complete remission. Patient 10 had active disease and was on her fourth cycle of chemotherapy. In all three cases, the cutaneous lesions appeared both after hematologic diagnosis and after chemotherapy.

The remaining 12 patients were diagnosed with CLL. In three patients (#7, #8, and #12), dermatologic lesions preceded the hematologic diagnosis. Specifically, the onset of dermatologic symptoms occurred 1.5 years before the hematologic diagnosis in patient #7 and 1 year before in both patients #8 and #12. On average, the dermatologic manifestations occurred approximately 14 months prior to the hematologic diagnoses. These skin lesions were identified as being caused by insect bites in patients #8 and #12.

In the other nine cases, skin lesions occurred after the hematologic diagnosis. Specifically, in one case (#14), the skin lesions coincided with the first cycle of chemotherapy (fludarabine-cyclophosphamide-rituximab). In the other eight cases, the skin lesions occurred several months after the first chemotherapy, ranging from 3 months post-treatment in patient 2 to 16 years in patient 6, with an average of 4.5 years. Of these eight patients, three (#1, #2, #3) were in complete remission

and were not receiving any treatment at the time of lesion onset; two patients (#4, #13) had disease relapse, although only one (#13) was already undergoing a new cycle of chemotherapy; and three (#5, #6, #13) were in partial remission, with only one case (#6) currently receiving chemotherapy.

The mean follow-up for hematologic disease was 7 years. The disease progressed or relapsed in 9 patients. Five patients were lost to follow-up, while 3 patients died (2 due to infectious complications).

Mutation status for the immunoglobulin heavy chain (IgHV) gene was determined in 12 patients, 10 of whom were found to be unmutated.

Using the CLL FISH panel, no alterations were found in 5 patients, 2 patients had trisomy 12, 3 patients had 13q deletions, 1 patient had 13q and 11q deletions, and 1 patient had 13q and 17p deletions.

Wild-type p53 function was lost in 3 patients and could not be assessed in 4 patients.

None of the monitored patients ever had evidence of hematologic manifestations due to autoimmunity. Only two patients (#7 and #14) were found to be ANA positive, at 1:320 and 1:160, respectively, with the latter patient also presenting with polyarthralgia.

Case/Gender	Hematologic disease	STAGE (Binet if CLL, Ann Harbor if other)	IgHV mutation status	FISH panel LLC	TP53	Spleno megaly	Therapy at diagnosis	TTFT (months)	Treatment for hematologic disease	Therapy at the time of skin lesion appearance	Disease status at last follow-up	Relapse/progression – follow-up	Autoimmunity
1/F	SLL/CLL	A	mutated	trisomy 12	wt	no	no	29	rituximab-bendamustine	no	RC	no, LFU	no
2/F	CLL	A	unmutated	del(11q); del(13q)	wt	no	no	41	rituximab-bendamustine	no	SD	no, death	no
3/F	CLL	A	unmutated	del(13q)	wt	no	no	36	rituximab-bendamustine	no	RC	no	no
4/M	CLL	A	unmutated	no alterations	wt	no	no	25	rituximab-bendamustine	no	PD	yes, LFU	no
5/F	CLL	A	unmutated	no alterations	wt	no	no	24	cyclophosphamide	no	PD	yes, death	no
6/f	CLL	A	mutated	del(13q)	mut	yes	yes	0	chlorambucil	chlorambucil	RC after ibrutinib	yes	no
7/F	CLL	B	unmutated	no alterations	mut	yes	no	12	FCR	no	SD, in treatment with ibrutinib	yes, LFU	ANA 1:320
8/F	CLL	A	unmutated	trisomy 12	wt	no	no	/	/	/	RC in treatment with venetoclax	yes	no
9/M	FL	III	NA	NA	NA	no	yes	1	rituximab-bendamustine	no	RC	no	no
10/F	MZL	IV	NA	NA	NA	yes	yes	1	rituximab-bendamustine	RB	PD	yes	no
11/F	FL	IV	NA	NA	NA	no	yes	1	rituximab-bendamustine	RB (maintenance)	RC	no	no
12/M	CLL	A	unmutated	no alterations	wt	no	no	10	rituximab-bendamustine	no	SD	no, death	no
13/M	CLL	A	unmutated	del(13q), del(17p)	mut	no	no	43	FCR	RB	PD	yes, LFU	no
14/F	CLL	A	unmutated	del(13q)	wt	no	no	26	FCR	FCR	SD with chlorambucil	yes	Polyarthralgia ANA 1:160
15/M	SLL/CLL	B	unmutated	no alterations	NA	yes	yes	1	FCR	no	RP	yes, LFU	no

Table 7. Hematologic data of the study patients. LNH, non-Hodgkin's lymphoma; IgHV, immunoglobulin heavy chain variable regions; TTFT, time to first lymphoma treatment; SLL, small lymphocytic lymphoma; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; NA, not assessed; WT, wild-type; FCR, fludarabine-cyclophosphamide-rituximab; RB, rituximab-bendamustine; RC, complete remission; SD, stable disease; RP, partial remission; DP, disease progression; LFU, lost to follow-up; ANA, anti-nuclear antibodies.

3.1.2. Clinical presentation, distribution, and management of cutaneous lesions in patients with EDHM

Of the 15 patients studied, 6 (40%) showed a significant clinical picture with numerous lesions (≥21) (#5, #7, #8, #11, #12, #13). In 3 of these cases (#5, #7, #12), lesions were distributed on the upper limbs, lower limbs, trunk, and face. In one case (#8), the lesions were present on the trunk, upper, and lower limbs, while in 2 cases (#11, #13), they were limited to the limbs. Of these 6 patients, 3 reported severe and persistent pruritus (score 10 on the VAS itch scale) that disturbed sleep (#5, #7, #8). Two patients (#11, #12) reported moderate but persistent pruritus (scores 5 and 6 on the VAS scale, respectively), while one patient (#13) reported moderate pruritus (score 5 on the VAS scale).

Of the 15 patients, 6 (#1, #2, #3, #9, #10, #15) (40%) presented with an intermediate number ((3-20) of lesions. In 2 of these cases (#1 and #2), lesions were found on the legs, upper limbs, and face. In 3 cases (#9, #10, #15), they were present on the upper and lower limbs, and in one case (#3), they were limited to the face and legs. Intense and persistent pruritus was reported in 3 of these cases (#2, #3, and #15) with scores of 9, 10, and 10 on the VAS scale, respectively. The remaining 3 patients (#1, #9, #10) reported milder pruritus with a score of 6 on the VAS scale.
The last 3 patients (#4, #6, #14) (20%) presented with few (≤2) skin lesions. In 2 of these cases, the lesions were located on the legs (#4, #14), and in one case (#6), they were on the arm. All 3 reported moderate to severe persistent pruritus (scores of 8 for #4, 7 for #6, and 6 for #14 on the VAS scale), generally localized to the lesion sites.

Regarding the topography of the lesions, the most affected areas were the lower limbs, especially the legs, with lesions present in 14 out of 15 cases (93.3%). This was followed by the upper limbs in 12 out of 15 cases (80%), the face in 6 out of 15 cases (40%), and the trunk with lesions present in only 3 out of 15 cases (20%).

Regarding the morphology of the lesions, in 8 patients (53.3%) the lesions manifested as persistent, monomorphic, firm, erythematous papules (Figures 8-9). Conversely, 7 patients (46.7%) had polymorphic lesions characterized by erythematous-violaceous or urticarial papules, plaques, nodules, and blisters, sometimes mimicking hypodermitis (Figure 10).

Eight of 15 patients (53.3%) recalled the insect bite as the cause. There was a seasonal variation in the appearance of lesions in 13 patients (86,7%), with eruptions appearing in the summer and resolving in autumn. Two cases (#5, #7), with numerous lesions and a VAS score of 10, continued to

exhibit skin manifestations and pruritus until late autumn, and 1 of them (case #7) developed new skin lesions during the winter; both of these patients experienced relapses only during the summer months.

The use of low-dose systemic prednisone (0.5 mg/kg/day), oral antihistamines, and high-potency topical steroids resulted in a significant improvement in most cases after 4 weeks. Patients were advised to take precautions, including wearing protective clothing, using insect repellent, and avoiding outdoor activities.

The mean duration of the dermatological disease was 62 months. During dermatological follow-up, 8 out of 15 patients experienced relapses during the summer months. An attempt was made to treat patient 8 with omalizumab at a dose of 300 mg every 4 weeks, but it was unsuccessful.[180]

3.1.3. Allergy profile of EDHM patients

Of the 15 patients studied, 4 (26.7%) had a known history of allergy. In 3 of these cases, patients reported allergic symptoms affecting the upper respiratory tract (allergic asthma, seasonal oculo-rhinitis), and in 2 cases, a known allergy to bee/wasp stings was reported. The remaining 11 patients (73.3%) denied any allergies.

In the 15 patients studied, total IgE levels and RAST for selected specific allergens were measured as part of the allergologic evaluation.

Out of the 15 patients, 6 (40%) (but only 2 of those who reported known allergic symptoms) had elevated total IgE levels. Of these 6 patients, 4 also had elevated specific IgE levels on the RAST test (specifically, 2 patients had high specific IgE levels to wasp venom and mosquito, respectively). Among the patients with IgE levels in the normal range, 2 patients with a positive allergologic history had positive specific IgE on the RAST test.

All patients (100%) denied having a history (referring conventionally to youth) of exaggerated reactions to insect bites.

Table 8 summarizes the dermatologic and allergologic data of the patients.

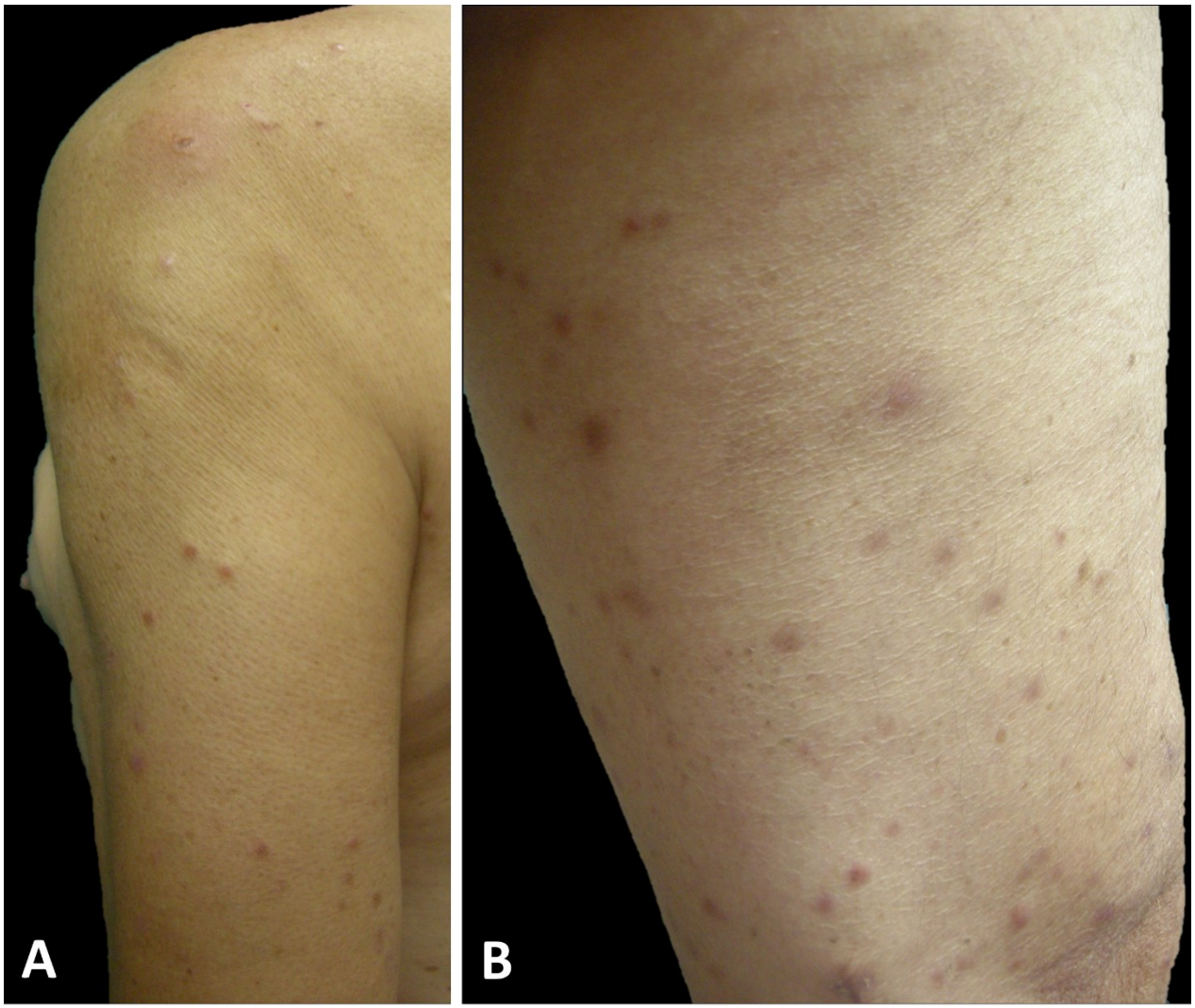

Figure 8. Clinical features of EDHM in patient 9. Monomorphic lesions consisting of erythematous excoriated papules with different stages of evolution on exposed skin (VAS 6) (A-B).
Reproduced from **Michelerio A**, Tomasini C, Fiandrino G, De Amici M, Varettoni M, Defrancesco I, Cavalloni C, Brazzelli V, Derlino F, Paulli M, Arcaini L, Vassallo C. Eosinophilic dermatosis of hematologic malignancy in patients with chronic lymphocytic leukemia/non-Hodgkin's B lymphoma: a single center prospective clinico-pathological study. Front Med (Lausanne). 2023 Aug 8;10:1231003. doi: 10.3389/fmed.2023.1231003. PMID: 37614953; PMCID: PMC10442565.

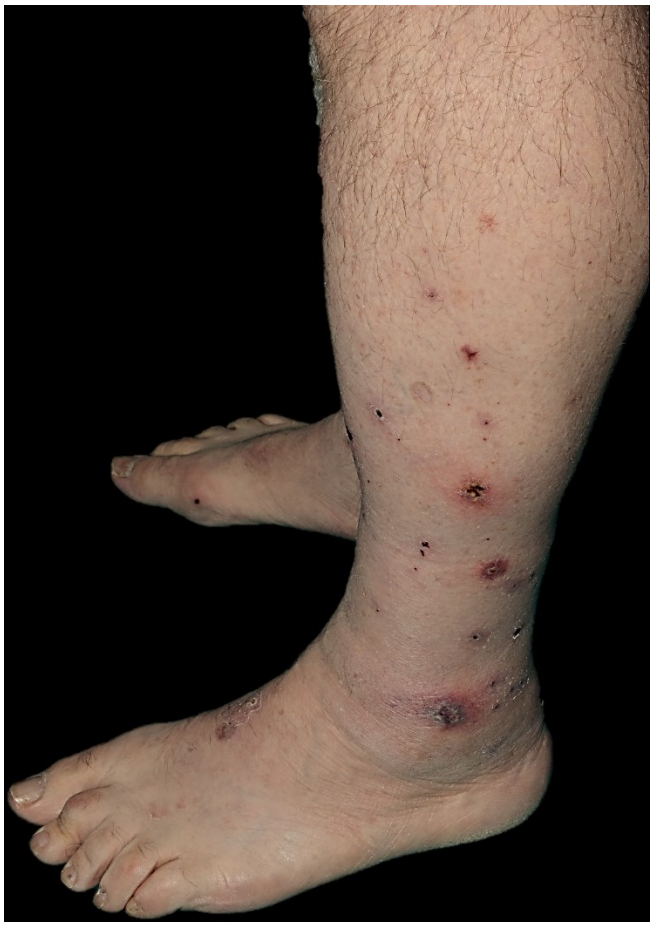

Figure 9. Clinical features of EDHM in patient 13. Monomorphic; centrally excoriated, crusted erythematous papules and nodules on the legs (VAS 5).

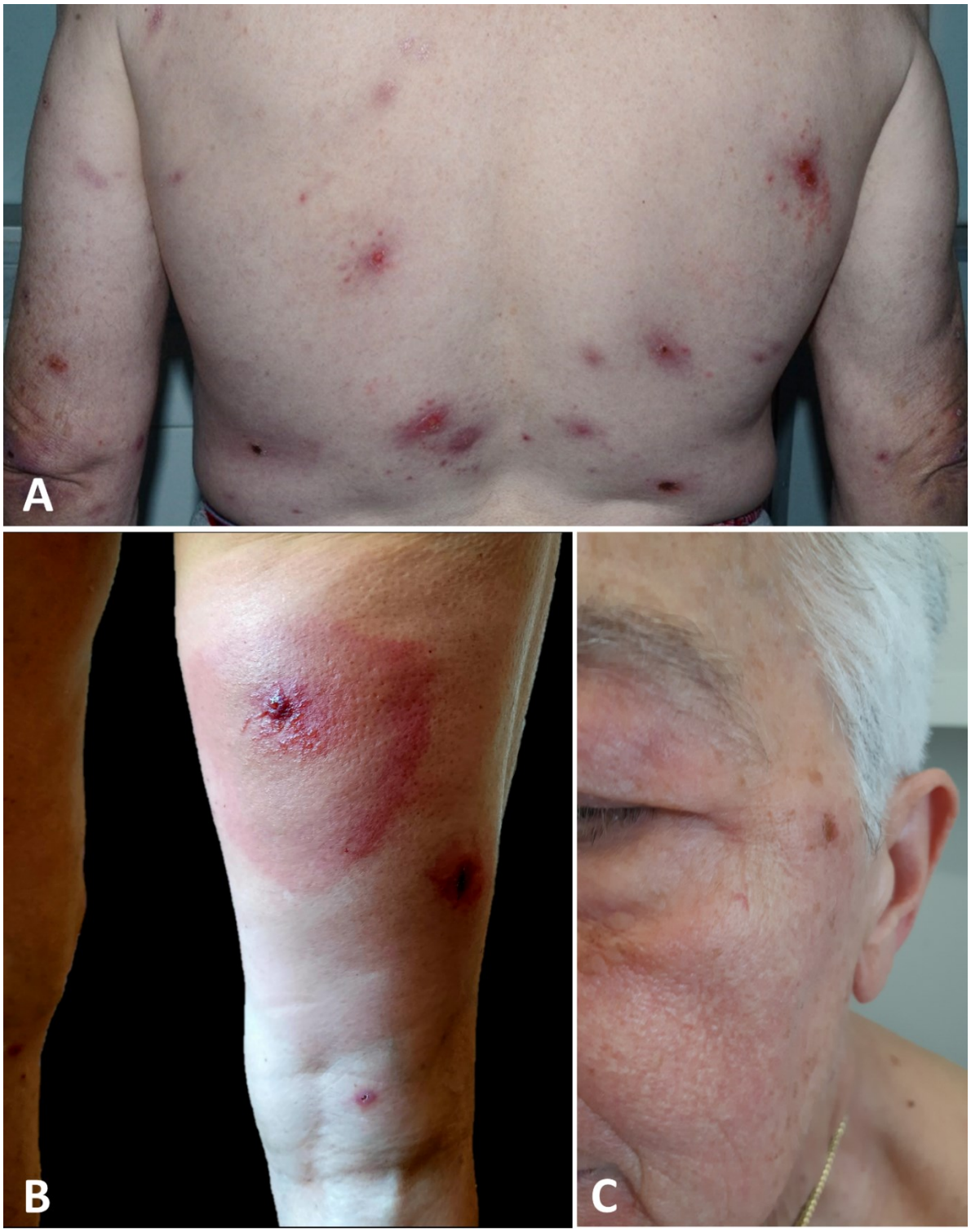

Figure 10. Clinical features of EDHM in patient 12. There are numerous and widespread polymorphic lesions, including erythematous plaques on the trunk (A) and a hypodermitis-like lesion on the right leg (B) and face (C) (VAS 5). Note: many lesions have vesicular and/or crusted and hemorrhagic centers.
(A) and (B) reproduced from **Michelerio A**, Tomasini C, Fiandrino G, De Amici M, Varettoni M, Defrancesco I, Cavalloni C, Brazzelli V, Derlino F, Paulli M, Arcaini L, Vassallo C. Eosinophilic dermatosis of hematologic malignancy in patients with chronic lymphocytic leukemia/non-Hodgkin's B lymphoma: a single center prospective clinico-pathological study. Front Med (Lausanne). 2023 Aug 8;10:1231003. doi: 10.3389/fmed.2023.1231003. PMID: 37614953; PMCID: PMC10442565.

Case/ Gender	Age (y)	Comorbidities	Lesion location	Main clinical presentation	Lesion number	Itch (VAS scale)	Known bites / seasonality	Allergy	Total IgE/Specific IgE (RAST)	Relation to the hematologic disease/ chemotherapy
1/F	77	hypertension, depression, diverticulosis, MRGE	upper and lower extremities, face	polymorphic; purpuric papules and nodules on the limbs, urticarial plaques on the face	intermediate	6	Y/Y	aquagenic urticaria in youth	<2	one year after chemotherapy
2/F	76	previous endometrial carcinoma	upper and lower extremities, face	monomorphic; urticarial plaques centrally excoriated	intermediate	9	Y/Y	/	2,49	3 months after chemotherapy
3/F	87	glucose intolerance, heart failure	lower extremities, face	polymorphic; blisters on the limbs, urticarial plaques on the face	intermediate	10	N/Y	/	<2	3 years after chemotherapy
4/M	57	previous pulmonary embolism, DVT, hypertension, benign prostatic hypertrophy	lower extremities	monomorphic; purpuric urticarial plaques centrally excoriated	rare	8	N/Y	asthma, seasonal rhinitis	191 / parietaria	18 months after chemotherapy
5/F	76	HBV+, diabetes mellitus type II, recurrent cystitis	upper and lower extremities, face, trunk	polymorphic; purpuric papules and nodules on the limbs, urticarial plaques on the face and trunk	numerous	10	N/N	/	11,8	one year after chemotherapy
6/F	77	/	upper extremities	monomorphic; urticarial plaques	rare	7	Y/Y	/	46,4	16 years after the first chemotherapy
7/F	61	hypertension	upper and lower extremities, face	polymorphic; panniculitis-like plaques, excoriated erythematous papules, urticarial plaques	numerous	10	N/N	seasonal rhinitis	1554 H /gluten	18 months before hematological disease diagnosis
8/F	66	hypertension	upper and lower extremities, trunk	monomorphic; centrally excoriated erythematous papules and nodules	numerous	10	Y/Y	/	310 H / penicillin, egg	one year before hematological disease diagnosis

9/M	71	hypertension, arrhythmia	upper and lower extremities	monomorphic; centrally excoriated erythematous papules and nodules	intermediate	6	Y/Y	bee sting allergy	13 / wasp	one year after diagnosis and chemotherapy
10/F	66	anxiety	upper and lower extremities	polymorphic; urticarial plaques on the upper extremities, bullous lesions on the lower extremities	intermediate	6	Y/Y	/	<2	during chemotherapy (third cycle)
11/F	78	schizophrenia, gastropathy associated with H. pylori, thyroidectomy for goiter	upper and lower extremities	polymorphic; erythematous papules, cellulitis-like plaques on the upper extremities	numerous	5	N/Y	/	966 H	after fourth chemotherapy cycle
12/M	68	chronic kidney failure, steroid-induced diabetes, atrial fibrillation	upper and lower extremities, face, trunk	polymorphic; panniculitis-like plaques; urticarial plaques, centrally excoriated erythematous papules	numerous	6	Y/Y	/	5000 H / common mosquito	one year before hematological disease diagnosis
13/M	65	previous choroidal melanoma	upper and lower extremities	monomorphic; centrally excoriated erythematous papules and nodules	numerous	5	N/Y	/	24,5	six years after chemotherapy
14/F	53	autoimmune polyarthralgia	lower extremities	monomorphic; centrally excoriated urticarial plaques	rare	6	N/Y	/	496 H	concomitant with first chemotherapy cycle
15/M	67	HBV+	upper and lower extremities	monomorphic; excoriated vesico-papules	intermediate	10	Y/Y	asthma, bee sting allergy	>5000 H / wasp, dermatophagoides, Ascaris, Anisakis	three years after diagnosis and chemotherapy

Table 8. Dermatologic and allergologic data of the patients. H: values above the normal reference range**.**

3.1.4. Serological and hematochemical profiles of patients with EDHM

None of the patients had detectable VZV DNA, but thirteen (86.7%) had anti-VZV IgG antibodies with negative IgM antibodies, one had negative IgG and IgM antibodies (#6), and one had positive IgG and IgM antibodies (#5).

None of the patients had detectable CMV DNA detectable, but all had anti-CMV IgG antibodies with negative IgM antibodies.

Only two patients (#12 and #15) had detectable EBV DNA (360 copies/ml and 7380 copies/ml, respectively), but this finding was not confirmed in subsequent repeat testing. Fourteen out of fifteen patients had anti-EBV IgG antibodies and negative IgM antibodies while only one patient (#5) had positive IgG and IgM antibodies (Table 9).

In all cases, circulating IL-4, IL-5, complement fractions C3 and C4 were within normal limits.

Only one patient (#14) out of 15 had elevated circulating tryptase levels, while one patient (#5) had borderline levels, but without concomitant elevation of IL-4 and IL-5. Three patients (#5, #9, #12) had elevated eosinophil cationic protein levels, and 2 (#7 and #14) had borderline levels. Peripheral eosinophilia was present in 5/15 patients (#3, #5, #7, #9, #12, 33%). There was a history of eosinophilic facial granuloma in 1 case (#5) (Table 10)

Case	Epstein-Barr serology	Epstein-Barr DNA (normal value <90 copies/ml)	Cytomegalovirus serology	Cytomegalovirus DNA (normal value <90 copies/ml)	Varicella zoster serology	Varicella zoster DNA (normal value <90 copies/ml)
1	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
2	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
3	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
4	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
5	IgG+; IgM+	undetectable	IgG+; IgM-	undetectable	IgG+; IgM+	undetectable
6	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG-; IgM-	undetectable
7	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
8	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
9	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
10	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
11	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
12	IgG+; IgM-	360 copies/ml	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
13	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
14	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable
15	IgG+; IgM-	7380 copies/ml	IgG+; IgM-	undetectable	IgG+; IgM-	undetectable

Table 9. Virological status of the study patients. + positive, - negative.

Case	Eosinophils (0.1-0.5 x 10^3/µl)	IL-4 (pg/ml; 0.00-31,20)	IL-5 (pg/ml; 0.00-7,80)	Tryptase (<11.4 µg/L)	ECP (<15,0 µg/L)	C3 (80-185 mg/dl)	C4 (15-53 mg/dl)	IgG (700-1600 mg/dl)	IgA (70-500 mg/dl)	IgM (40-280 mg/dl)	CRP (0,00-0,59 mg/dl)	ESR (<15 mm/h)	β2 microglobulin (<2530 µg/L)	LDH (125-220 mU/ml)
1	0,3 x 10 3	0,1	0,1	6,83	<2	95	26,8	331 L	79	7 L	5,48 H	21 H	3281	222 L
2	0 L	0,1	0,1	3,42	3,15	86	24,3	430 L	34 L	22 L				177
3	1,2	0,1	0,1	5,7	4,1	89	25,5	390	99	87				
4	0,5	0,1	0,1	6,45	5,8	84	20,3	1060	317	97	0,25	4		
5	0,8 H	0,1	0,1	11 BL	36,1 H	90	14,8	378 L	48 L	11 L				358 H
6	0,2	0,1	0,1	6,39	2,73	107	26,5	997	241	90			3689	
7	1,4 H	0,1	0,1	5,54	23.1 BL	119	22,2	875	76	24 L				
8	0,2	0,1	0,1	3,14	10,7	110	23,8	1167	89	72				254 H
9	0,9 H	0,1	0,1	5,01	34,8 H	106	20	1070	417	33 L				379 H
10	0,3	0,1	6,91	5,83	10,2	114	30,3	498 L	36 L	12L	0,8	22 H		
11	0,1	0,1	0,1	8,54	14,7	112	21,1	948	108	103				300
12	0,8 H	0,1	0,1	8,65	44,3 H	115	16,9	2480 H	12 L	67	3,99 H	6		
13	0,2	0,1	0,1	7,15	3,93	119	21,8	736	43 L	22 L	0,13	1		
14	0,3	0,1	3,42	43,40 H	23.7 BL	109	19,5	817	125	75				
15	0,4	0,1	0,1	4,4	13,3	130	19,9	2280 H	118	90				

Table 10. Hematochemical parameters of the study patients. H: values above the normal reference range. L: values under the normal reference range. ESR: erythrocyte sedimentation rate; CRP: C-reactive Protein; ECP: eosinophil cationic protein, BL: borderline.

3.1.5. Histopathology and immunohistochemistry

Histopathologic examination revealed epidermal acanthosis (11/15) and spongiosis (11/15) with associated exocytosis of isolated CD3+ lymphocytes and/or granulocytic elements (14/15).

Superficial and deep perivascular (15/15) and peri-annexal and interstitial (10/15) eosinophilic infiltrates were seen in the papillary and mid dermis (Figures 10A-B-C). Fourteen out of fifteen patients showed features of periadnexal involvement (either sweat glands or hair follicles). The sweat glands were extensively involved in the inflammatory process, as evidenced by the lymphocytic and eosinophilic infiltration in the acrosyringium, around and within the sweat ducts, and in their deep portion of the dermis/subcutis (Fig. 10D). In eight cases, the infiltrate involved the hair follicles (perifollicular infiltration). Extravasated erythrocytes were observed in 12 patients.

The number of eosinophils per HPF ranged from 25 to 200 (mean 90, median 80). No correlation was found between the number of lesions, pruritus, or IgE levels and the number of eosinophils/HPF. Flame figures (5/15), focal necrobiosis (7/15), and eosinophil-associated microgranulomas (3/15) were observed (Figures. 11E-F). Interstitial edema was common (10/15) and dermal sclerosis with hyaline collagen degeneration was observed in all cases.

A wedge-shaped infiltrate was observed in three cases (Figure 12A).[22,79] The inflammatory reaction in 11/15 also involved the hypodermis, with lobular and septal eosinophilic panniculitis (Figure 12B). Eosinophilic rimming of subcutaneous fat lobules was observed in two cases (Figure 12C). Vasculitis of medium-sized vessels was also observed in eight of fifteen patients (Figure 12D).

In four cases, (#5, #8, #13, #14) the infiltrate was lymphocyte-rich, mostly CD3+, with rare CD30+ and CD20+ lymphocytes.

Two cases (#13, #15) showed a small leukemic B-cell component (CD20-/+, CD79a+, CD23+), not exceeding 10% of the infiltrate.

The presence of Alcian Blue-positive interstitial mucin was observed in six patients, one of whom also had also follicular mucinosis. In high-power microscopic fields (40x), the number of mast cells was normal.

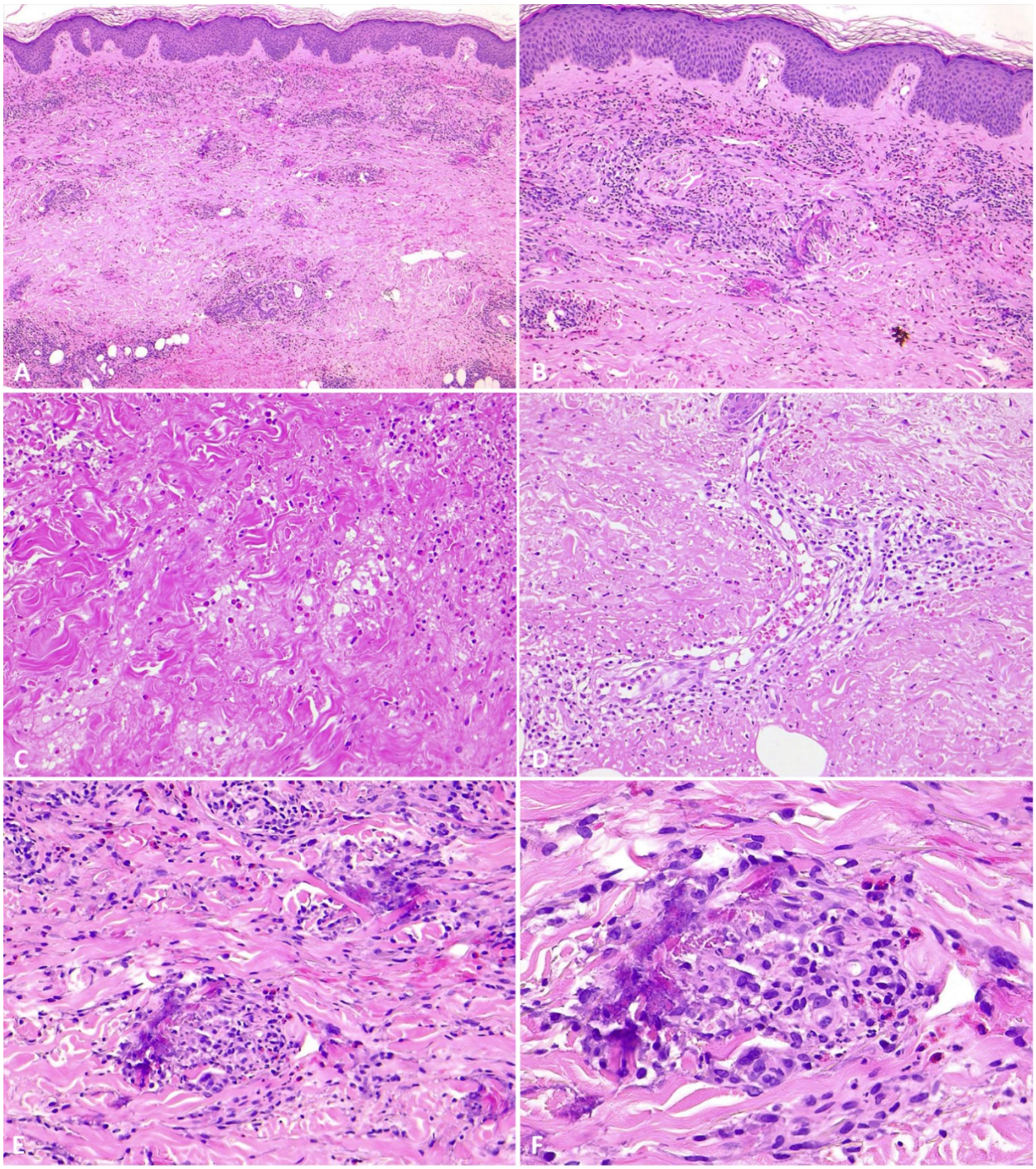

Figure 11. Histopathologic features of EDHM in patient 9. A superficial and deep perivascular, periadnexal, and interstitial infiltrate with numerous eosinophils in the papillary and mid dermis (A-B) In the dermis, sclerosis with hyaline collagen degeneration can be observed (C). The sweat glands are involved from the acrosyringium along the sweat ducts to the coiled glands in the deep dermis. Eosinophils and erythrocytes are seen in and around the sweat glands (D). Flame figures with eosinophilic granular deposits are evident in the mid and deep reticular dermis (E-F).
(B), (C), (D), (E), reproduced from **Michelerio A**, Tomasini C, Fiandrino G, De Amici M, Varettoni M, Defrancesco I, Cavalloni C, Brazzelli V, Derlino F, Paulli M, Arcaini L, Vassallo C. Eosinophilic dermatosis of hematologic malignancy in patients with chronic lymphocytic leukemia/non-Hodgkin's B lymphoma: a single center prospective clinico-pathological study. Front Med (Lausanne). 2023 Aug 8;10:1231003. doi: 10.3389/fmed.2023.1231003. PMID: 37614953; PMCID: PMC10442565.

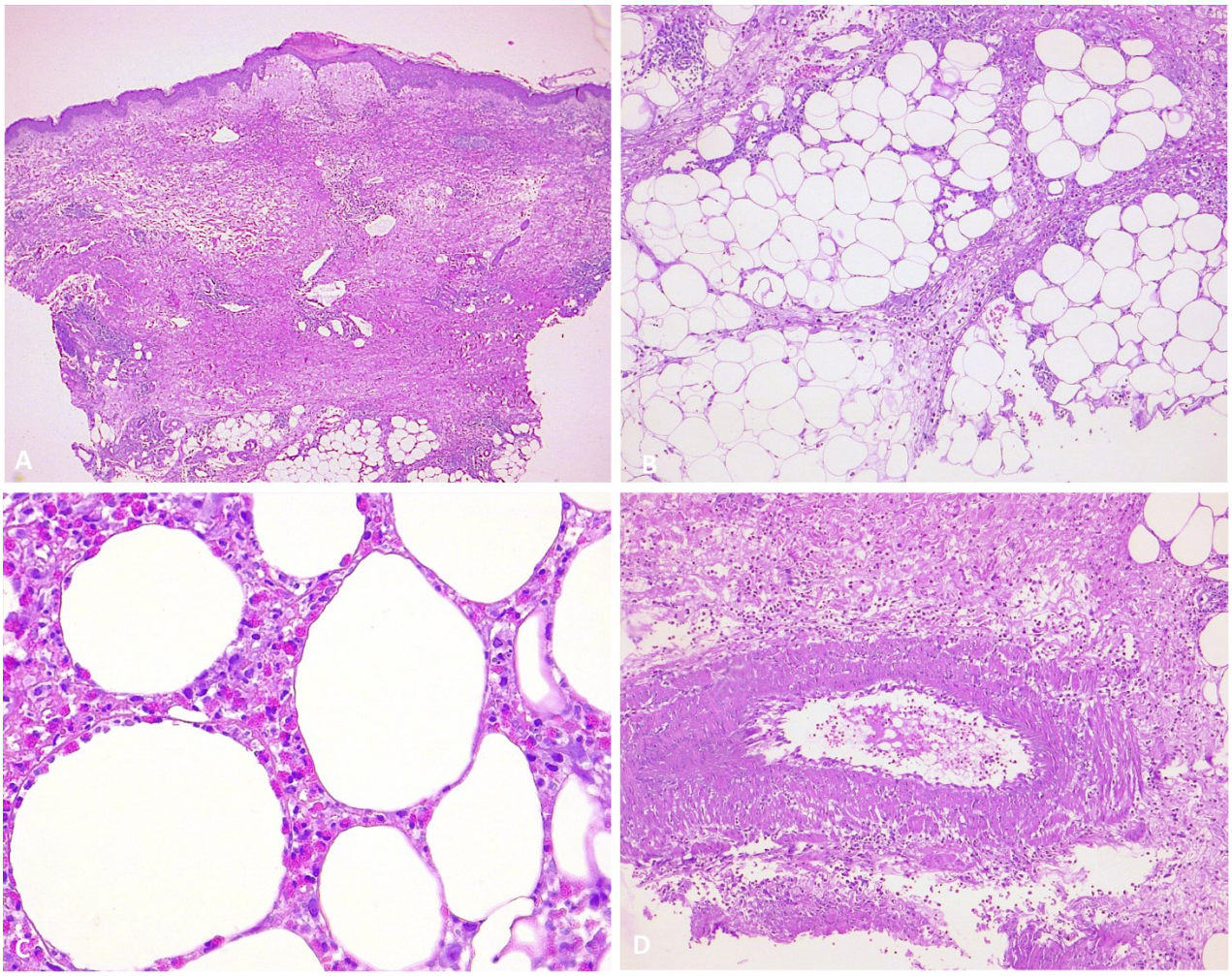

Figure 12. Histopathologic features of EDHM in patient 12. A central crust in the epidermis, flanked by epidermal spongiosis and a markedly edematous papillary dermis, underlying a superficial and deep dermal eosinophilic inflammatory infiltrate (A). In the hypodermis, septal and lobular panniculitis are seen due to the infiltrate (B). High-power view shows diffuse eosinophilic infiltration of fat lobules (C). An area of leukocytoclastic vasculitis with neutrophils, cytoclasis, and focal fibrinoid necrosis in the vessel walls may be seen in the hypodermis (D).
Reproduced from **Michelerio A**, Tomasini C, Fiandrino G, De Amici M, Varettoni M, Defrancesco I, Cavalloni C, Brazzelli V, Derlino F, Paulli M, Arcaini L and Vassallo C (2023) Eosinophilic dermatosis of hematologic malignancy in patients with chronic lymphocytic leukemia/ non-Hodgkin's B lymphoma: a single center prospective clinico-pathological study. Front. Med. 10:1231003. doi: 10.3389/fmed.2023.1231003

3.1.6. Immunopathologic serology findings

Among the 15 patients studied, one had low titer serum anti-BP180 antibodies (#12) and one had low titer serum anti-BP230 antibodies (#3). Direct immunofluorescence results were heterogeneous and nonspecific; however, weak perivascular IgM deposits were detected in 13 out of 15 patients (86.7%). Weak IgG positivity was found in three of 15 cases (20%), while weak IgA positivity was found in five of 15 cases (33.3%). Four patients had perivascular fibrinogen deposition, eight patients had fibrinogen deposition in the dermis, two patients had both dermal and perivascular fibrinogen

deposition, and one patient had fibrinogen deposition at the dermo-epidermal junction. In all cases, salt split and indirect immunofluorescence studies were negative.

3.2 Collaborative Research with the University of Turin, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Ospedale Molinette)

Due to the retrospective nature of this part of the study, data availability was not as comprehensive as in our previous prospective study.

A cohort of 20 patients (9 females, 11 males) from the Dermatology Clinic of the University of Turin were diagnosed with EDHM. The age of the patients ranged from 54 to 86 years, with a mean age of 70 years at the time of diagnosis of the hematologic disease (median age was 72 years). The gender-specific mean age was 65 years for females and 74 years for males.

The cohort included a variety of hematologic malignancies: 15 patients had CLL, 2 had monoclonal B-cell lymphocytosis (cases #18 and #20), 1 had mantle cell lymphoma (case #23), 1 had multiple myeloma (case #20), and 1 had chronic myelomonocytic leukemia (case #29).

The mutation status for the immunoglobulin heavy chain gene (IgHV) was determined in 7 CLL patients (cases #17, #21, #22, #25, #26, #31, #35), of which 5 showed an unmutated status. The CLL FISH panel was performed in 11 patients, revealing trisomy 12 in 5 and 17q deletions in 3.

Follow-up data were available for 13 patients. Disease progression or relapse was observed in seven patients (cases #17, #21, #22, #28, #31, #32, #33), while seven patients had stable disease (cases #19, #24, #25, #26, #30, #34, #35). Eleven patients required therapeutic intervention during the course of their disease. Four patients were receiving therapy at diagnosis (#19, #22, #32, #34). The mean survival was 8 years. Six patients were lost to follow-up (#16, #18, #20, #23, #27, #28). Table 11 summarizes the data of these second cohort of patients.

In 16 patients, the diagnosis of EDHM followed the diagnosis of hematologic disease. In 11 of these patients, the interval between the two diagnoses was recorded, with a median of 14 months (ranging from 3 to 216 months). In cases #20 and #31, EDHM was diagnosed 3 and 17 years, respectively, before the hematologic disease diagnosis. In cases #33 and #34, the diagnoses were concomitant.

Seasonal variations were observed in the manifestation of EDHM lesions: 14 patients developed lesions in summer (cases #17, #18, #19, #21, #25, #26, #27, #28, #30, #31, #32, #33, #34, #35), 3 in spring (cases #16, #20, #23), and 3 in the autumn (cases #22, #24, #29). The lesion morphology was variably described as erythematous papules, nodules, and plaques (Figures 13A, 14A); bullous lesions were reported in 4 patients (Figure 15A) (Table 12).

Dermatologic lesions predominantly involved the limbs in 15 patients and were diffuse in 5 patients (cases #26, #27, #29, #31, #35).

Case/Gender	Age at hematologic disease diagnosis	Hematologic disease	IgHV mutation status	FISH panel LLC	TP53	TTFT (month)	First line treatment	Further treatments	Hematologic disease evolution /follow-up	Survival (years)
16/M	82	CLL	/	/	/	/	/	/	LFU	NA
17/M	71	CLL	unmutated	del17q	/	62	R-CHOP x 6	alemtuzumab, chlorambucil + rituximab, ibrutinib, venetoclax	P, death	17
18/M	79	monoclonal B cell lymphocytosis	/	/	/	/	/	/	LFU	NA
19/F	56	multiple myeloma	/	negative	/	0	PAD x 4 + 2 ASCT + thalidomide as maintenance	/	SD, death	7
20/M	78	monoclonal B cell lymphocytosis	/	/	/	/	/	/	LFU	NA
21/F	58	CLL	mutated	del17q	/	23	chlorambucil	OxDHA, RB, alemtuzumab, chlorambucil	P, death	25
22/M	71	CLL	unmutated	tris12	/	1	FCR	bendamustine + alemtuzumab	P, death	3
23/M	81	mantle cell lymphoma	/	/	/	/	/	/	LFU	NA
24/F	63	CLL	/	/	/	/	/	/	SD, alive	11
25/M	74	CLL	unmutated	negative	wt	27	chlorambucil	/	SD, death	3
26/F	70	CLL	unmutated	tris12	/	29	COP	RB	SD, death	9
27/M	73	CLL	/	/	/	/	/	/	LFU	NA
28/F	72	CLL	/	tris12	/	/	/	/	LFU	NA
29/M	76	LMMC1	/	negative	/	12	hydroxycarbamide	/	P, death	2

30/M	80	CLL	/	/	/	/	/	/	SD, death	11
31/M	54	CLL	unmutated	tris12	/	82	RB	/	P, alive	14
32/F	55	CLL	/	del17q	/	3	R-Ibrutinib	venetoclax	P, alive	7
33/F	86	CLL	/	/	/	27		acalabrutinib	P, alive	3
34/F	61	CLL	/	/	/	3	R-Ibrutinib	/	SD, alive	1
35/F	64	CLL	unmutated	tris12	wt	/	/	/	SD, alive	2

Table 11. Hematologic data from the second cohort of patients. LFU, lost at follow-up; NA, not available; P, progression; SD, stable disease; CLL, chronic lymphocytic leukemia; LMMC1, chronic myelomonocytic leukemia; wt, wild-type; R-CHOP, rituximab-cyclophosphamide-doxorubicin hydrochloride-vincristine sulfate-prednisone; PAD, bortezomib-doxorubicin-dexamethasone; ASCT, autologous stem cell transplantation; FCR, fludarabine-cyclophosphamide-rituximab; RB, rituximab-bendamustine; COP, cyclophosphamide-vincristine-prednisone; OxDHA, oxidized docosahexaenoic acid.

Case/Gender	Age at hematologic disease diagnosis (years)	Lesion location	Main clinical presentation	Season of EDHM onset	EDHM onset in relation to the hematologic disease diagnosis
16/M	82	upper and lower limbs	erythematous papules and nodules	spring	after
17/M	71	lower limbs	erythematous papules and plaques	summer	8 months after
18/M	79	upper and lower limbs	erythematous urticarial plaques and bullous lesions	summer	after
19/F	56	lower limbs	erythematous papules and urticarial plaques	summer	after
20/M	78	lower limbs	Erythematous-violaceous nodules	spring	36 months before
21/F	58	lower limbs	erythematous urticarial plaques and erythematous nodules	summer	18 years after
22/M	71	upper limbs	erythematous nodules	autumn	7 months after
23/M	81	upper limbs	excoriated erythematous papules	spring	after
24/F	63	upper limbs	erythematous papules and urticarial plaques	autumn	after
25/M	74	upper and lower limbs	excoriated erythematous papules	summer	3 months after
26/F	70	diffuse	erythematous urticarial plaques and bullous lesions	summer	3 months after
27/M	73	diffuse	erythematous papules	summer	after
28/F	72	lower limbs	erythematous papules	summer	45 months after
29/M	76	diffuse	excoriated erythematous papules	autumn	14 months after
30/M	80	upper and lower limbs, face	monomorphic erythematous papules and urticarial plaques	summer	36 months after
31/M	54	diffuse	erythematous nodules	summer	17 years before
32/F	55	upper and lower limbs	erythematous nodules and urticarial plaques	summer	after
33/F	86	upper and lower limbs	erythematous nodules and bullous lesions	summer	concomitant
34/F	61	upper and lower extremities	hemorrhagic plaques and nodules, blisters	summer	concomitant
35/F	64	diffuse	erythematous plaques	summer	2 years after

Table 12. Dermatologic data of the second cohort of patients.

Histopathology

Histopathologic examination revealed epidermal acanthosis (10/20) and mild spongiosis (10/20), with rare eosinophilic intraepidermal vesicles (3/20). Papillary dermis edema was observed in 11 cases and subepidermal blistering in 7 cases.

Superficial and deep perivascular (20/20), interstitial (13/20), and periadnexal (17/20) infiltrates with eosinophils and lymphocytic elements were observed in the papillary and mid dermis (Figures 13 B-C). The periadnexal infiltrate involved the hair follicle in 5 patients (Figure 13D), up to eosinophilic folliculitis with sebaceous gland involvement (Figure 14). The infiltrate was wedge-shaped in 3 cases and nodular in one case.

Eosinophils per HPF ranged from 25 to 300 (mean 80, median 60). The infiltrate was eosinophilic-rich in 11 cases and lymphocytic-rich in 9 cases.

The reticular dermis was characterized by variable sclerosis with piecemeal fragmentation of collagen in all cases (Figure 13E). Eosinophils surrounding collagen bundles and forming granulomas (6/20) and flame figures (9/20) were observed (Figure 13E-F).

In 4 cases (#22, #23, #24, #28) the infiltrate was scant with sparse eosinophils (Figure 15 A-B-C). These findings were accompanied by a modest clinical picture.

The inflammatory reaction in 13/20 involved also the hypodermis, with lobular and septal eosinophilic panniculitis (Figure 15 B-D) and eosinophilic rimming of subcutaneous fat lobules (5/20). Vasculitis of medium-sized vessels was also observed in 6/20 patients.

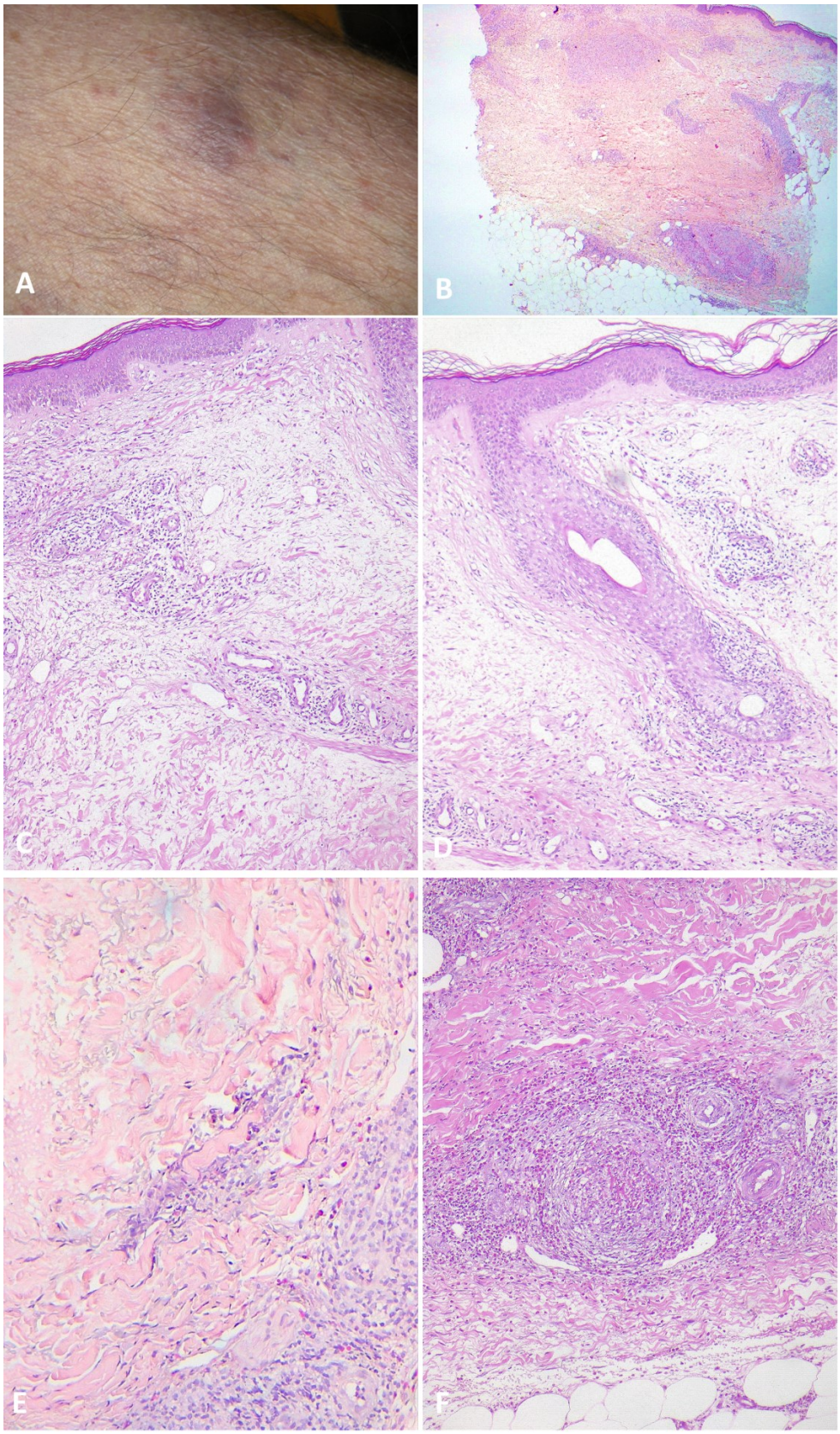

Figure 13. Clinical and histopathologic features of EDHM in patient 20. Erythematous-violaceous nodule on the leg (A). Histopathologic examination shows a superficial and deep perivascular, periadnexal and interstitial eosinophilic infiltrate with eosinophilic panniculitis and collagen sclerosis (B). The eosinophilic infiltrate involves the eccrine (C) and follicular (D) units. In the deep dermis diffuse collagen sclerosis with eosinophils and histocytes around collagen bundles (E) up to eosinophilic granuloma formation (F) can be observed.

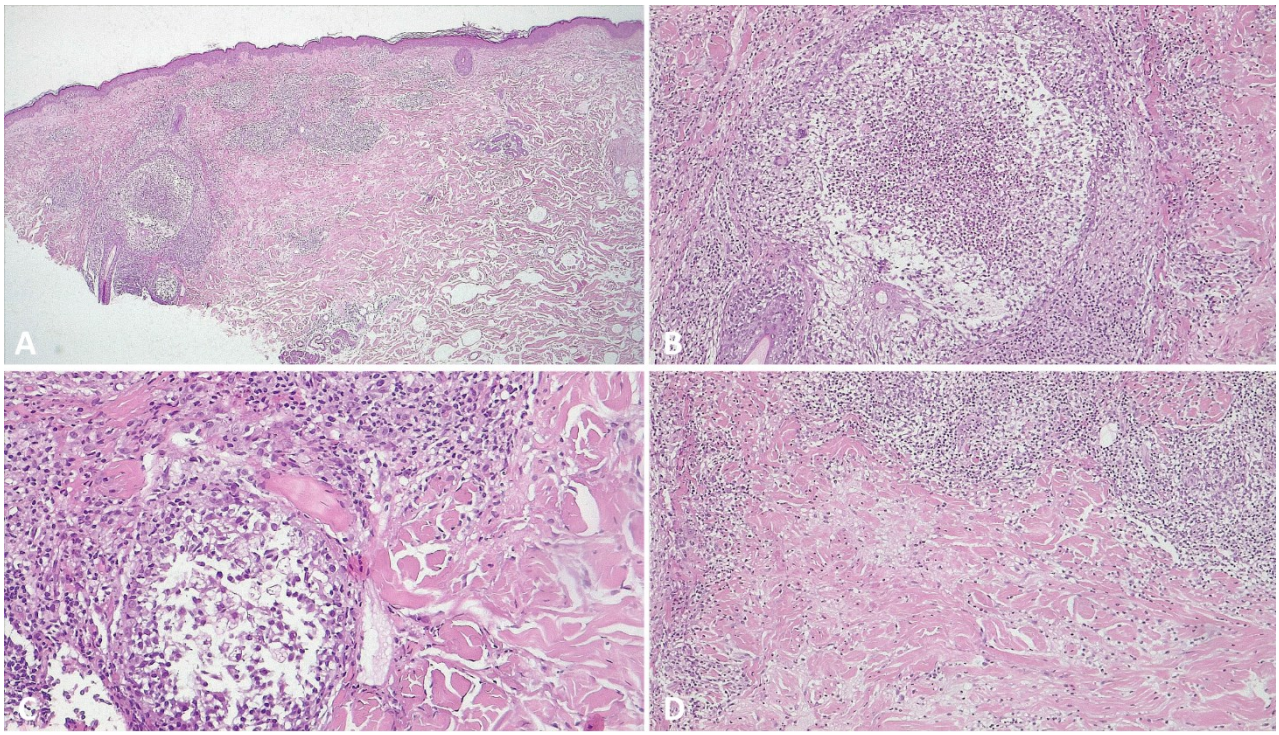

Figure 14. Histopathologic features in patient 29. Superficial eosinophilic folliculitis with involvement and destruction of the sebaceous gland (A-B). The presence of sclerosis in the perifollicular space and surrounding the inflammatory process suggests a chronic etiology (C). Areas of altered collagen with collagen fibers showing an eosinophilic, hyaline or basophilic granular appearance (necrobiosis) are evident (D), further supporting the chronicity of the inflammatory process.

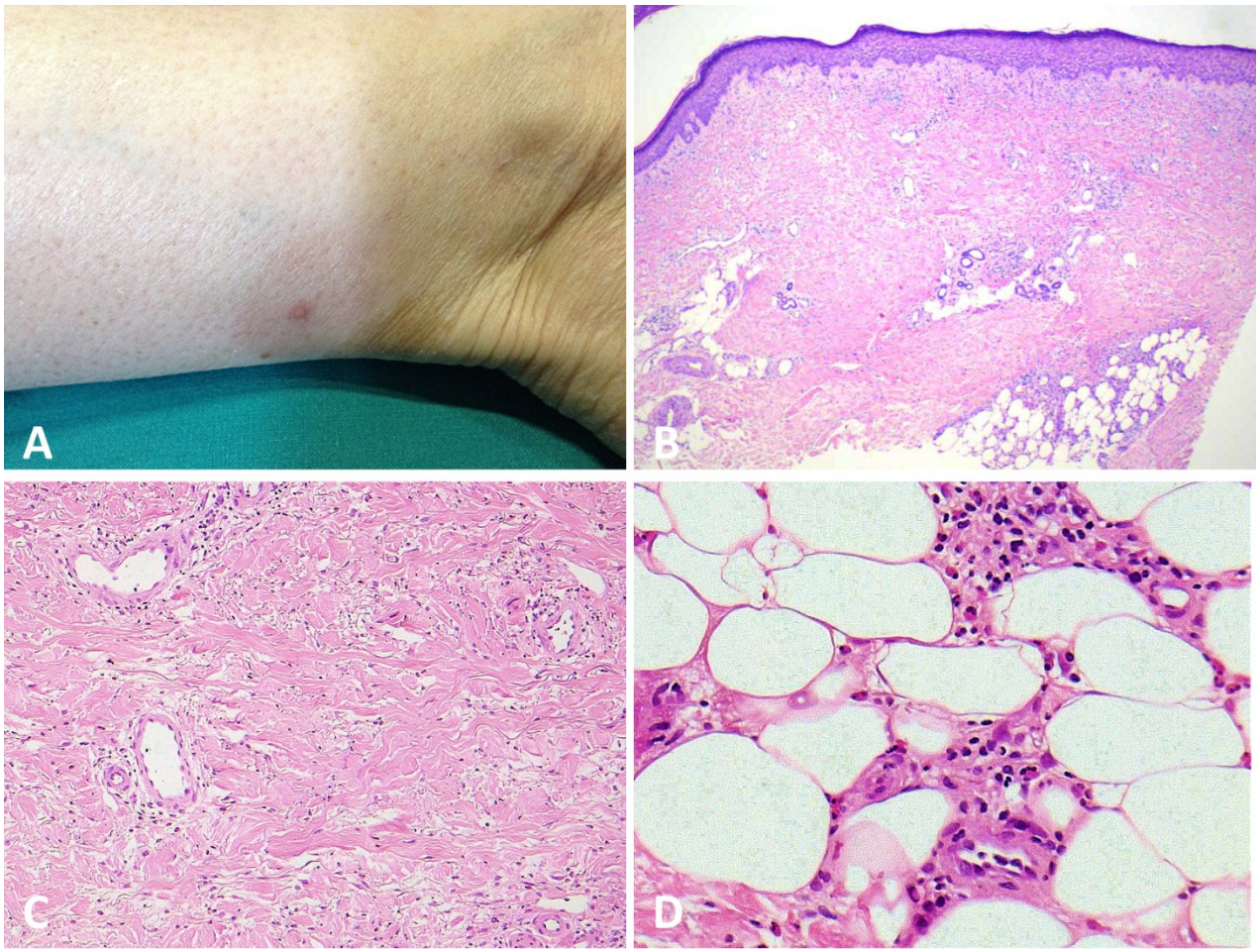

Figure 15. Clinical and histopathologic features of EDHM in patient 28. Regressing lesion: erythematous papule on slightly erythematous skin of the leg (A). Histopathologic examination shows a modest superficial and deep perivascular, periadnexal and interstitial infiltrate with few eosinophilic and prominent sclerosis of the entire dermis extending into the fat with thickened collagen bundles and "trapped" eccrine glands (B-C). The eosinophilic infiltrate involves the hypodermis with panniculitis (D).

CHAPTER 4:
DISCUSSION

To date, the pathogenesis of EDHM and its relationship with hematologic malignancies are poorly understood, and the literature consists mainly of case reports and a few retrospective studies.[13,16,20,21,26,32] Indeed, the second largest retrospective study in the literature included 38 patients from a country where the estimated number of new incident cases of CLL alone in 2018 was 4674[181] and EDHM is likely to be an under-recognized condition. In the first cohort, which was studied prospectively, we observed an overall incidence of EDHM of approximately 3.55% in the combined CLL and NHL patient population.

One of the most controversial aspects of EDHM is the role of insect bites. Typically, insect bite reactions present as clustered or disseminated erythematous, pruritic papules on exposed areas, but may evolve into a more prolonged papular urticaria or a generalized and pleomorphic eruption.[182]

Our results support a key role for insect bites in the pathogenesis of EDHM. In most cases, the lesions were located on exposed areas, whereas the trunk was involved in only eight (22%) cases, in which atopy (two of the patients in the first cohort had elevated IgE levels) or a particular insect (e.g., bed bugs, mites) may have contributed to a wider distribution of lesions.

In our study, a distinct seasonality in the occurrence of EDHM symptoms was observed in both study cohorts. In the first cohort of patients, 86.7% showed a temporal pattern characterized by eruptions appearing in the summer and resolving in the autumn, while only two patients had persistent lesions or pruritus into late fall and early winter. In the second cohort of patients, 14 developed lesions specifically in the summer months, three in the spring, and another three in the autumn. As our geographical area is characterized by hot and humid summers and–cold winters, insects, such as common mosquitos, are expected to be most prevalent in the summer.

The interpretation of data concerning the seasonal occurrence of EDHM is more complex in other geographical contexts. For example, in Israel -where two important studies failed to detect any seasonal patterns[30,32]- the climate is characterized by cool, rainy winters and hot, dry summers, conditions that allow for certain insect populations to be present year-round.[13,32,183]

In our study more than half of the patients recalled insect bites as the cause of the lesions. This contrasts with most EDHM reports, in which no positive history or response to preventive measures supported insect bites.[9,12,14,16,21,25,28,79,184] In this regard, it should be noted that the bites are usually painless and the skin reaction can be delayed for days.[185] Furthermore, patients may be reluctant to

accept insects as responsible for their dermatosis[186] and even Davis reported a patient with linear lesions who denied being bitten.[21] It is also important to broaden the etiological considerations to include agents that may not be immediately visible or recognized, such as mites.[187] For example, *Pyemotes ventricosus* dermatitis is characterized by the rapid development of skin lesions within 24 hours of receiving painless bites.[188] Notably, these lesions manifest in covered areas under occlusive clothing, thereby challenging the conventional expectation that insect bites occur only in exposed areas. This condition also has a seasonal prevalence, occurring primarily between May and November.[188] Adding to the complexity of etiologic factors are conditions such as Cheyletiella dermatitis, often associated with pet infestations, and trombiculosis, caused by the larvae of the *Trombiculidae* family, particularly *Neotrombicula autumnalis* in Europe.[189] The latter is most prevalent in late summer and autumn.[189]

The incorporation of enhanced observational techniques, such as fluorescence-advanced videodermatoscopy, into diagnostic procedures offers the potential for more accurate in vivo identification of difficult-to-see etiological agents, including mites, in dermatological conditions such as EDHM.[189] These advances are not merely diagnostic, but potentially preventive, as they could contribute to a more targeted approach to prevention based on accurate identification of the causative agents.

In light of these considerations, the limited effectiveness of conventional preventive measures warrants further consideration. The failure of these measures may be due to reactivation of older lesions by new bites, a mechanism thought to be triggered by circulating insect antigens that activate cutaneous T cells at previously sensitized sites.[190] Thus, the limitation of preventive measures may be due in part to an interplay between elusive etiologic agents and host factors. Finally, it should be noted that, unlike neutrophils, eosinophils can survive in the tissue for weeks, depending on the cytokines that are released.[191] The persistence of eosinophils in lesional tissue may further contribute to the recurrent course and to the clinical and pathologic findings of the disease.

A pathogenetic role for insect bites is also supported by the histopathology. Indeed, the classic histopathologic hallmark of an arthropod bite is a superficial and deep, perivascular, periadnexal, and interstitial inflammatory dermal infiltrate composed of lymphocytes and eosinophils, often associated with an overlying epidermal spongiosis, sometimes evolving into a vesicle or even progressing to epidermal necrosis, flame figures and vasculitis.[59,60] The histopathologic findings of the current study are consistent with those previously published on the histopathology of arthropod bites.[59,60] Moreover, 31/35 skin biopsies showed features of periadnexal involvement (either sweat glands or hair follicles). Ackerman et al. suggested that insect bite reactions have a periadnexal and, especially, perifollicular distribution of the infiltrate because the insects are attracted by microbes and lipids that

are present in hair follicle ostia and sebaceous glands, resulting in folliculocentric infiltrates.[59] The wedge-shaped infiltrate and involvement of the acrosyringium also suggest arthropod bite reactions due to sweat attractiveness to mosquitoes and other insects, as well as flame figures and vasculitis.[60,61]

The pathogenesis and prognostic significance of EDHM were also investigated. In accordance with the Literature, the majority of our patients (77.1%) were diagnosed with CLL. The higher incidence of CLL compared to other hematologic disorders could be attributed to the dysfunctional T-cell compartment in CLL patients, which shows an imbalance in the T-helper Th2/Th1 ratio with an aberrant shift of a Th2-dominant response.[192,193] The Th2 response polarization may also occur in the skin as a result of a specific cytokine microenvironment that promotes EDHM formation through eosinophil recruitment.

To investigate a possible role of atopy in this polarization to the Th2 response, we evaluated allergy history and the IgE levels in our first cohort of patients. Six of them had elevated levels of IgE, which may be responsible for driving both eosinophil granulocytes and a few neoplastic B cell expressing CD23, a low affinity IgE receptor, to the lesional site.[194] This may be particularly pertinent to patient 12, who had high total IgE level and specific IgE to the common mosquito. Indeed, patient 12 presented with diffuse and pleomorphic cutaneous manifestations, and histopathologically showed a dense eosinophilic infiltrate with panniculitis and vasculitis. Similarly, patient 15 had elevated levels of total IgE and a small leukemic B-cell component at the histopathologic examination, representing no more than 10% of the infiltrate.

Our study found no excess of serum levels of IL-4 and IL-5, which play a role in type 2 immune responses and eosinophil regulation, respectively.[195] However, levels of these two interleukins were not tested in skin lesions, which is a limitation of the study. The few anecdotal reports of the use of monoclonal antibody blocking IL-4 and IL-13 (dupilumab) in the treatment of EDHM show discordant results that neither confirm nor contradict the possible role of IL-4.[176,177,196,197]

In our study, we also investigated the role of chemotherapy in the development of EDHM. In our first cohort, 12/15 patients developed the dermatosis after starting the chemotherapy, and of note, 11 received rituximab. Rituximab has been shown to reduce serum IgG4,[198] which is notable given the protective effect of IgG4 against severe allergic reactions, including those caused by mosquito bites.[57] We speculate that reduced serum IgG4 induced by rituximab therapy may have played a role in EDHM.

In East Asian countries, a distinct and rare form of hypersensitivity to mosquito bites has been described, predominantly affecting children and presenting a unique pathophysiology.[68] This rare condition is marked by natural killer (NK) cell lymphocytosis and elevated levels of Epstein-Barr

virus (EBV) DNA in the peripheral blood, usually exceeding 1000 copies/μg.[68] This condition has the potential to progress to systemic diseases, including hemophagocytic lymphohistiocytosis, chronic active EBV disease, and EBV-associated lymphoproliferative disorders.[64,69,70] Our findings do not support a role for EBV in the development of EDHM and these observations may reflect different genetic and epigenetic factors of EBV infection between East Asian and Western countries.

Another controversial issue is the prognostic value of EDHM in hematologic malignancies. As previously mentioned, in our first cohort, the patients with NHL were in an advanced stage of hematologic disease at the time of diagnosis of EDHM, and in general, all patients in the first study group required chemotherapy during the course of their hematologic disease, including those who had developed EDHM prior to hematologic disease. Follow-up data from the second cohort were available for 13 patients, 11 of whom also received chemotherapy during the course of their disease. Although CLL usually runs an indolent course and is treated in a minority of cases, the need for therapeutic intervention in a significant proportion of patients in both cohorts may suggest that EDHM may represent a worsening clinical sign of the underlying hematologic malignancy. Where data are available, a similar trend has also been observed in the Literature.[13,15,21]

Of note, among CLL patients in whom IgHV mutation status was available (n=19), 15 had unmutated status. Specifically, 10/12 CLL patients in the first cohort and 5/7 in the second cohort had an unmutated IgHV gene, a condition generally associated with a worse prognosis.[199] Unmutated IgHV CLL cells generally produce less IL-10, an immunosuppressive molecule, which may explain the exaggerated responses and higher incidence of EDHM in CLL patients compared to other hematologic malignancies.[200] Finally, the shift to a Th2-dominant response, which may have contributed to the development of EDHM as previously hypothesized, correlates with the progression of CLL, and type 2 cytokines facilitate the escape of cancer cells from the immune system.[192]

Our study includes two cases of patients with monoclonal B-cell lymphocytosis. To the best of our knowledge, this association has not yet been reported in the Literature. Given the limited number of such cases and the lack of follow-up data on these patients, further speculation on a potentially accelerated or aggressive evolution toward CLL cannot be made.

EDHM is named after the eosinophilic infiltrate found in the tissue. The clinical and histopathologic results of our study support the hypothesis that EDHM is part of the reaction pattern associated with what is defined as Wells' syndrome (WS). First described in 1971 by G.C. Wells as “recurrent granulomatous dermatitis with eosinophilia”,[201] WS is a rare dermatosis without ethnic or gender predilection that primarily affects adults, with a minority of pediatric cases associated with atopy.[168] Clinically, WS is characterized by a variety of pruritic cutaneous manifestations that usually recur over several years.[43] t can present in a variety of morphologic forms, such as a plaque-like lesion,

annular granuloma-like, urticaria-like, papulovesicular, bullous, papulonodular, or fixed drug eruption-like,[43] and different lesions may occur simultaneously in the same patient.[172] Lesions predominantly affect the extremities.[172] WS has been associated with various underlying conditions and triggers, including hematologic disorders and arthropod bites.[202–204] Peripheral eosinophilia, leukocytosis, or elevated inflammatory markers may be observed.[203]

The histopathologic findings of WS are not static, but rather evolve with the disease, contributing significantly to its clinical variability.[173] The timing of biopsy plays a critical role in the resulting histologic features.[173] As a result of an as yet unidentified stimulus, eosinophilic granulocytes undergo degranulation. The early histopathologic picture is characterized by a nonspecific dermal infiltrate of lymphocytes and eosinophils, sometimes accompanied by papillary dermis edema. Following eosinophilic degranulation, cytotoxic compounds are released, leading to the denaturation of proteins, mainly collagen. Eosinophilic material and cellular debris then adhere to these altered collagen fibrils. Within 1-3 weeks following the onset of the disease, characteristic "flame figures" appear. These later lead to the formation of perivascular histiocytic granulomatous infiltrates accompanied by multinucleated giant cells and collagen sclerosis, markers of the cellular-mediated tissue repair in the healing phase. [168,173] It should be emphasized that although flame figures are characteristic of Wells' syndrome, they are not pathognomonic and may be observed in a number of other dermatologic conditions, including but not limited to bullous pemphigoid, eczema, prurigo, scabies, herpes gestationis, Churg-Strauss syndrome, and parasitic infections.[168] According to the current definition, vasculitis is not found in WS, but vasculitis features have actually been seen in a few patients.[204] On a pathophysiological level, the aforementioned clinical variability may be explained by the varying degree of eosinophil infiltration and degranulation. Thus, infiltration that results in only mild degranulation will produce a plaque-like appearance. Conversely, if a greater amount of mediators and toxic granules are released, urticarial, vesicular, or lesions will develop due to vasodilation and additional tissue damage.[205]

Our patients also showed this clinical polymorphism, even with blisters and urticarial plaques, which may explain some of the "pemphigoid-like eruptions" reported by some Authors in association with CLL.[26] Furthermore, insect bites and hematologic malignancies are often cited as potential triggers of WS.[168]

In our study the histopathologic features of skin biopsies from patients with EDHM closely parallel the typical evolving stages of WS previously mentioned. The corresponding figures provide insights into these changes and illustrate the dynamic nature of the disease. Figure 12 shows an active lesion with central epidermal crusting, surrounded by epidermal spongiosis and a severely edematous papillary dermis, along with a superficial and deep eosinophilic dermal infiltrate. Figure 13 shows a

subacute lesion with a similar but denser and more diffuse eosinophilic infiltrate. Eosinophilic panniculitis is observed, accompanied by collagen sclerosis, a sign of chronicity. In the deep dermis, diffuse collagen sclerosis is usually observed, and eosinophils and histiocytes are present in the interstitium between collagen bundles, forming small eosinophilic granulomas around degenerated collagen bundles. Figure 14 focuses on a skin biopsy characterized by eosinophilic folliculitis and prominent perifollicular and dermal sclerosis, the latter finding suggesting a subacute/chronic course of the pathologic process. Figure 15 shows a probable late-stage lesion, characterized by scant inflammatory infiltrate and prominent dermal sclerosis reminiscent of morphea. This collagen sclerosis in the late/regressing lesions warrants differential diagnosis, especially with morphea, a dermatologic condition characterized by skin inflammation and sclerosis due to increased collagen deposition. In the late stage of morphea, the inflammatory infiltrate typically diminishes and eventually disappears, although it may persist focally.[206] The epidermis has a normal morphology, but with attenuated rete ridges resulting in a flattened dermal-epidermal junction. Dermal edema is absent. In addition, there is a marked reduction in capillaries and small vessels, which are replaced by densely packed collagen bundles aligned parallel to the dermal-epidermal junction. These collagen bundles show intense eosinophilic staining. Additionally, the eccrine glands are atrophic and encapsulated within the thickened dermis, while the underlying subcutis appears homogenized and hyalinized.[206]

It is noteworthy that the aforementioned interstitial granulomatous dermatitis as seen in Figure 13 may pose a diagnostic problem of differential diagnosis with annular elastolytic giant cell granuloma (AEGCG) and a reactive granulomatous dermatitis (RGD). AEGCG is an idiopathic granulomatous dermatosis, which is characterized histologically by the absence of elastic fibers, due to elastophagocytosis by multinucleated giant cells in the dermis. Clinically, AEGCG presents with plaques with a raised, erythematous border and central atrophy on sun-exposed areas.[207] RGD is a unifying term to describe overlapping entities such as interstitial granulomatous dermatitis (IGD), palisaded neutrophilic and granulomatous dermatitis (PNGD), and interstitial granulomatous drug eruption (IGDR), which share the common thread of granulomatous inflammation.[208] Clinically, PNGD presents as symmetric, smooth, umbilicated, or crusted, skin-colored to erythematous papules, predominantly localized to the elbows and extremities. Histologically, the early phase is characterized by neutrophilic inflammation, karyorrhectic debris, and leukocytoclastic vasculitis with minimal mucin. In the later stages, piecemeal collagen degeneration, small granulomas, and histiocytic palisades may be seen.[208,209]

IGD commonly presents as firm, asymptomatic, linear truncal bands (called the “rope sign”) in patients with a background of inflammatory arthritis.[208,209] Histologically, it is characterized by

interstitial inflammation, with histiocytes often surrounding foci of abnormal collagen with a pattern described as "clefting away". Vasculitis and mucin are absent in IGD, distinguishing it from other forms of granulomatous dermatoses.[208,209] The presentation of IGDR generally consists of erythematous to violaceous, often annular, plaques located on the inner portions of the arms, proximal medial aspects of the thighs, trunk, and intertriginous regions. Histologically, it is characterized by diffuse interstitial histiocytes with granulomas surrounding degenerating collagen. There is little mucin, no vasculitis, and a distinct interface dermatitis with basal vacuolar degeneration, areas of dyskeratotic keratinocytes, and prominent eosinophilia. RGD may be associated with other conditions, including autoimmune disorders, hematologic malignancies, drug eruptions, and infectious diseases.[208,209]

Complementing these observations, the significant collagen sclerosis seen in many of our cases also warrants a histopathologic differential diagnosis also with eosinophilic fasciitis (EF). EF is a rare connective tissue disorder characterized by symmetrical and painful swelling, accompanied by progressive induration and thickening of the skin and soft tissues. First described by Shulman in 1974,[210] the syndrome presents with scleroderma-like skin changes associated with peripheral eosinophilia, hypergammaglobulinemia, and an elevated erythrocyte sedimentation rate (ESR).[211] In the absence of internationally accepted diagnostic criteria, the diagnosis is often based on clinicopathologic correlation. In particular, the upper limbs are involved in approximately 88% of cases of EF, while the lower limbs are involved in up to 70% of instances. Although less common, other localizations such as the neck and trunk may also be involved.[211] Morphea coexists in approximately one third of EF patients. It is interesting to note that all of our patients had sclerosis. Hematologic disorders coexist in less than 10% of EF cases, further highlighting the potential confluence of these distinct conditions within a broader spectrum of eosinophilic dermatoses. [211,212]

It is noteworthy that one of our patients had a history of granuloma faciale, an eosinophilic dermatosis associated with vasculitis, supporting the role of a non-specific eosinophilic hypersensitivity reaction to either endogenous or exogenous stimuli in a continuum spectrum.

In conclusion, the results of our study support the role of insect bites as a trigger for EDHM in the context of a dysfunction of the adaptive immune response, either as a result of the disease itself or as a consequence of chemotherapy. In addition, we hypothesize that EDHM may have a negative prognostic value and in some cases represent a hallmark of disease progression, suggesting the need for closer follow-up, although the size of our sample does not allow for definitive conclusions.

Furthermore, we propose a possible pathogenetic link between EDHM and other eosinophilic dermatoses, especially Wells syndrome. Further studies are needed to clarify the pathogenetic mechanisms underlying this disorder as well as its prognostic value.

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