Primary Cutaneous Lymphoma

Malek, Yotam

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

YOTAM MALEK

Primary Cutaneous Lymphoma

GRADUATE THESIS

Zagreb, 2024

This graduate thesis was made at the Department of Dermatovenerology, University Hospital Centre Zagreb, and School of Medicine at University of Zagreb, Croatia, mentored by Professor Romana Čeović, MD. PhD., and was submitted for evaluation in the academic year of 2023/2024.

Abbreviations

BCL – B-cell Lymphoma Anti-apoptotic Gene

C-ALCL – Cutaneous Anaplastic Large Cell Lymphoma

CBCL – Cutaneous B-cell Lymphoma

CD – Cluster of Differentiation

CDNK2A – Cyclin-Dependent Kinase Inhibitor 2A

CHOP – Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

CMV – Cytomegalovirus

CTCL – Cutaneous T-cell Lymphoma

DLBCLLT – Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

EBV – Epstein-Barr virus

FOXP1 – Forkhead Box P1

HLA – Human Leukocyte Antigen

HLTV – Human T-Lymphotropic Virus 1

HSV-1 – Herpes Simplex Virus 1

IGH – Immunoglobulin Heavy Chain

IRF4 – Interferon Regulatory Factor 4

LyP – Lymphomatoid Papulosis

MF – Mycosis Fungoides

MUM1 – Multiple Myeloma Oncogene 1

MYC – MYC Proto-oncogene

PD-L – Programmed Death-ligand

PCFCL – Primary Cutaneous Follicle Center Lymphoma

PCL – Primary Cutaneous Lymphoma

PCLBCL – Primary Cutaneous Diffuse Large B-cell Lymphoma

PCMZL – Primary Cutaneous Marginal Zone Lymphoma

PCR – Polymerase Chain Reaction

PUVA – Psoralen Plus Ultraviolet A

SS – Sézary Syndrome

TCR – T-cell Receptor

UVA/B – Ultraviolet A/B

VZV – Varicella-Zoster Virus

Table of Contents

1. Summary

Title: Primary Cutaneous Lymphoma
Author: Yotam Malek

Primary cutaneous lymphoma is a rare heterogenous group of extranodal non-Hodgkin's lymphomas of which primary manifestation involve the skin. Primary cutaneous lymphoma consists of two major entities: cutaneous T-cell lymphoma and cutaneous B-cell lymphoma, each further divided into common subgroups. Cutaneous T-cell lymphomas account for the majority of diagnosed cases, with mycosis fungoides and Sézary syndrome being its most important entities. The etiopathogenesis of primary cutaneous lymphoma is relatively unknown and poorly understood. However, recent breakthroughs in research have established an involvement of abnormal inflammatory stimulation and expression of various cytokine cascades, driving tumorigenesis. Given the significant overlaps and resemblances of primary cutaneous lymphoma subtypes in clinical features and immunohistopathological findings, a thorough and comprehensive assessment process is required to correctly diagnose the nature of the tumor, determine the prognosis of the disease, and initiate accurate treatment. Primary cutaneous lymphomas, as rare diseases, require a multidisciplinary approach in diagnosis and treatment. The main goal of treatment in these patients is to improve the quality of live while avoiding diverse toxicities.

Keywords: primary cutaneous lymphoma, cutaneous T-cell lymphomas, cutaneous B-cell lymphomas, mycosis fungoides, Sézary syndrome, primary cutaneous follicle center lymphoma.

2. Sažetak

Naslov: Primarni limfomi kože

Autor: Yotam Malek

Primarni kožni limfomi su rijetka heterogena skupina ekstranodalnih ne-Hodgkinovih limfoma čija primarna manifestacija uključuje kožu. Primarni kožni limfomi sastoje se od dva glavna entiteta: kožnih T-staničnih limfoma i kožnih B-staničnih limfoma, od kojih je svaki dalje podijeljen u zajedničke podskupine. Kožni T-stanični limfomi čine većinu dijagnosticiranih slučajeva, pri čemu su mycosis fungoides i Sézaryjev sindrom najvažniji entiteti. Etiopatogeneza primarnih kožnih limfoma još uvijek je relativno nepoznata i nedovoljno istražena. Novija istraživanja utvrdila su uključenost abnormalne upalne stimulacije i ekspresije različitih kaskada citokina u tumorogenezi. S obzirom na značajna preklapanja i sličnosti primarnih podtipova kožnih limfoma u kliničkim značajkama i imunohistopatološkim nalazima, potreban je temeljit i sveobuhvatan pristup bolesnicima kako bi se ispravno dijagnosticirala priroda tumora, odredila prognoza bolesti i započelo ciljano liječenje. Primarni kožni limfomi kao rijetke bolesti zahtijevaju multidisciplinarni pristup u dijagnostici i liječenju. Glavni cilj liječenja ovih pacijenata je poboljšati kvalitetu života uz izbjegavanje toksičnosti različitih modaliteta liječenja.

Ključne riječi: Primarni kožni limfom, kožni T-ćelijski limfomi, kožni B-ćelijski limfomi, mikozis fungoides, Sézaryjev sindrom, primarni kožni folikularni centarski limfom.

3. Introduction

Primary cutaneous lymphoma (PCL) is a rare heterogenous group of extranodal non-Hodgkin's lymphomas of which primary presentations manifest in the skin. Such lymphomas originate from a malignant alterations of T cells or B lymphocytes that either reside in the layers of skin or migrate to it. PCL can arise from lymphocytic precursors of such cells as well. Primary cutaneous lymphomas are confined to the skin at time of presentation following careful staging procedures. Different subtypes of PCL exhibit their own properties, e.g., clinical symptoms and behavior, histological findings, immunophenotype and prognosis, which necessitating a specific approach in diagnostics and assessment that differ from the classical nodal non-Hodgkin's lymphomas.

PCL consists of two major entities: cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL). CTCLs are more common and account for the majority of diagnosed cases. CTCL and CBCL are additionally further divided into their frequent subtypes. CTCL is mostly comprised of (1) mycosis fungoides (MF), the most common form in this group; (2) Sézary syndrome (SS), an aggressive leukemic subtype; and (3) a subgroup of $CD30^+$ lymphoproliferative disorders. CBCL is often divided into (1) primary cutaneous follicle center lymphoma (PCFCL), (2) primary cutaneous marginal zone lymphoma (PCMZL), and (3) primary cutaneous diffuse large B-cell lymphoma (PCLBCL). Other subtypes in these major segments are exceedingly rare, and therefore, do not necessitate mentioning or further discussion due to limited available data.

4. Epidemiology of Primary Cutaneous Lymphoma

Although PCL is rare, it represents the second most common group of extranodal lymphomas, following gastrointestinal ones. PCL is attributed for 20% of all extranodal lymphomas. [1] CTCL comprises approximately 75-80% of all PCL neoplasms, while CBCL accounts for the remaining ones. [2] The incidence rate of new CTCL cases has appeared to remain stable in recent years; this is despite having been increased in the distant past. While a higher incidence rate is observed in the elderly — peaking in the eighth decade — some types of CTCL lymphomas can still manifest in children. CTCL neoplasms are generally predominant in males with a 1.6-2:1 male-to-female ratio. [2, 3] It has been evaluated that the incidence of CTCL is approximately 5-7 cases per million. The median age of diagnosis typically occurs in the fifth decade of life. [2]

The total number of CTCL cases was approximated at 6230 cases worldwide as of last decade, highlighting the rareness and infrequency of CTCL neoplasms across the world. [4] Mycosis fungoides was reported in more than 50% of all documented cases of CTCL, making it the most frequent form of this group, and thus, most important for diagnostics and treatment. The incidence of Sézary Syndrome was estimated to be at a steady incidence rate of 3% worldwide; with both MF and SS occurrences combined responsible for more than 70% of all CTCL cases. [3] Modest variations in reported incidences of various subtypes were described worldwide; especially in parts of Europe, America and Asia. The rest of CTCL cases are attributed to other $CD30^+$ and $CD30^-$ lymphoma subtypes; with the latter — being scarce.

CBCL accounts for 20-25% of all reported PCL cases; and similarly with CTCL, is also considered to remain at a stable incidence rate in recent years. [5] The most frequent subtype in this group is PCFCL, which represents 55-60% of all CBCL cases. It is slightly more prevalent in males. The

PCMZL subtype, accounting for 2-7% of all CBCL cases, follows as the second most common entity in this group. Finally, PCLBCL subtype, a much more rare and aggressive entity, is observed twice as commonly in elderly females. The leg-type is the predominant form of this entity, responsible for approximately 20% of all such sparse cases. [6]

All the aforementioned subtypes constitute more than 90% of all PCL neoplasms, while the rest is distributed amongst numerous scarce subtypes. [7]

5. Etiopathogenesis of Primary Cutaneous Lymphoma

The etiopathogenesis of PCL is unknown. Despite constant ongoing research, no precise causing agents have been identified, nor definitive pathogenic cascades were established. Conversely, owing to moderate available data, certain inflammatory pathways and factors regarding the etiopathogenesis have been suggested.

5.1 Etiopathogenesis of Cutaneous T-cell lymphoma

Despite uncertainty surrounding the etiology of CTCL, it has been led to believe that the pathogenesis stems from a prolonged antigen stimulation, which induces an inflammatory response. This extended inflammation is presumed to induce an abnormal T-cell proliferation and malignant transformation.

5.1.1 Endogenous Factors

Limited data has shown a correlation between specific HLA-II molecules with MF and Sézary syndrome. HLA-II subtypes DRB1∗11 and DQB1∗03 were described. [5]

5.1.2 Exogenous Factors

HTLV-1 has been identified in a limited subtype of CTCL worldwide, particularly in endemic regions such as Japan and Asia. Since HTLV-1 infections were not widely reported in other documented cases in Europe or USA, the role of this virus as an etiologic factor remains questionable. Plausible explanations may involve the predisposition of oncologic patients to acquire HTLV in endemic areas, or in their inability of clearing infections. [8, 9]

A theory regarding the etiological role of HSV and VZV has also been suggested. Lesions induced by these viruses commonly appear in CTCL patients. However, no strong association has been established as of their role in CTCL etiology. It is more convincing to assume that these infections are more likely to suggest an immunosuppressive state of CTCL patients, rather than an etiological factor. [8]

Epstein-Barr virus (EBV) is another virus of the *Herpesviridae* family that was also speculated to be an etiological agent of CTCL. EBV is a worldwide infective microorganism found in 90% of the US population. EBV has already been associated with a variety of lymphocytic neoplasms and other types of tumors. It has been observed that CTCL patients were found to have higher seroreactive titer of EBV antibody. Positive biopsies were also reported. Unfortunately, multiple contrary researches have led to a failure in establishing a definitive connection with etiological factors. Cytomegalovirus (CMV), yet another global infective agent of the *Herpesviridae* family, has followed a similar path regarding its role in the etiology of CTCL. Both CMV and EBV contribution to the issue remains a mystery. It is unknown whether they are truly related to the etiopathogenesis of CTCL or are merely an incidental finding appertaining to their immersive global prevalence. [8]

The involvement of *Staphylococcus aureus* in the pathogenesis of CTCL has caught a significant attention in recent years. [9] Some pathogenic strands of *S. aureus* are major agents of colonization, able to induce infection, bacteremia and sepsis due to their high virulence factors. It has been observed that antibiotic treatment showed a favorable course in some cases. [7, 8] The explanation for this association might stem from the impaired skin barrier and immunosuppressed state of CTCL patients rather than etiopathogenetic roles. Alternatively, carcinogenic effect was theorized

to progress from oligoclonal proliferation induced by staphylococcal superantigens due to their relationship with the T-cell receptor β variable. [8, 9]

Additional bacterial agents may include *Chlamydophila pneumoniae* and *Borrelia burgdorferi*; the latter is believed to be associated with CBCL rather than in CTCL. [8] Other exogenous factors, besides infections, include environmental and occupational aspects. Due to limited data, these elements will not be discussed any further. [7]

5.1.3 Inflammatory Cascades and Cytokine Stimulation

CTCL is a malignancy involving T-cell homing lymphocytes. Unlike the common types of skin cancer — basal cell carcinoma (BCC), squamous cell carcinoma (SSC) and melanoma — CTCL presents with patches and plaques that predominantly manifest on sun-protected areas. In advanced stages, malignant lymphocytes can disseminate to the blood, viscera and adjected location (e.g., surrounding skin and lymph nodes). In leukemic form, malignant T-cells constitute the vast majority of circulating T-lymphocytes, leading to an immunocompromised state. This is due to reduction in functioning lymphocytes paired with predominance of defective malignant T-cells which lack their receptor (TCR), thereby hampering immunologic function. [7]

It has been observed that there is an involvement of tissue-resident memory T-lymphocytes (T_{RM}) in MF and central memory T-cells (T_{CM}) in Sézary syndrome; the latter retain the ability to migrate peripherally. This might explain the persistent inflammatory skin lesions and transitory erythroderma seen in these forms of CTCL, respectively. Another $CCR7^{+}$ L-$selectin^{-}$ T-cells (T_{MM}) have also been found. Modern molecular technologies have now helped support the idea that MF and SS arise from genetically distinct subsets of T-lymphocytes. Furthermore, it is believed that

Th2 lymphocytes play an integral role in MF and SS, since these entities were associated with expression and production of Th2-associated genes and cytokines, respectively.[7, 9-11]

In early stages of CTCL, cytokines involved in the activation of STAT3 and STAT5 pathways were identified. [10] Once activated, a shift from Th1 differentiation toward Th2 differentiation ensues. Additionally, several transcription factors (e.g., NF-kB2, ZEB1) and other signaling pathways and enzymes associated with Th2 differentiation were discovered to be mutated. The activation of JAK3 and STAT5 induces the expression of IL-4, which allows progression of Th2 response. This generates the expression of other interleukins (e.g., IL-10) which play a role in tumor induced immunosuppression. This activation also prompts the repression of miRNA-22, a known tumor suppressor, allowing for the progression of the malignant state. Therefore, inhibition of JAK/STAT cascade may be in theory targeted therapeutically with the aim of impeding tumor growth and proliferation. STAT3 is also responsible for the expression of IL-17 and IL-2, which promote additional expression of other proinflammatory cytokines, chemokines, and angiogenic and antiapoptotic factors. [9]

It has now become widely palatable that due to recent evidence, cytokine signaling portray a crucial role in the pathogenesis of CTCL.

5.2 Etiopathogenesis of Cutaneous B-cell lymphoma

Comparably with CTCL, the etiopathogenesis of cutaneous B-cell lymphoma is unknown and poorly understood. Due to similar association of gastric extranodal marginal zone lymphoma with *Helicobacter pylori*, infectious agents were presumed to have a role in the etiopathogenesis of CBCL. *Borrelia burgdorferi* has been observed in limited PCMZL cases. Hepatitis C was also

suspected of being a causative agent, but inconsistent and opposing evidence makes such claims questionable. [12]

Because CBCL tumors are exceedingly rare, data regarding their development is markedly insufficient. Conversely, an innovative concept of aberrant somatic hypermutation was introduced, and is now believed to play a significant role in CBCL development. Somatic hypermutation is a unique process occurring in functional B-lymphocytes, accounting for affinity maturation and immunoglobulin production. Abnormal function of this process in loci that contain oncogenic genes may lead to the disruption of DNA repairing genes and introduction of tumorigenic mutations. [12]

6. Main Subtypes of Cutaneous T-cell Lymphoma

CTCL encompasses a variety of different entities. It accounts for 75-80% of all PCL cases. [2] Although each subset includes its own set of characteristics, some of these aspects may overlap. Thus, a distinction between different features is crucial for definitive diagnosis. This section will discuss and provide a brief review of the manifestations and findings of the most common type of CTCL.

6.1 Mycosis Fungoides

MF is the most common form of CTCL. It has a male predominance with a 2:1 male-to-female ratio. It is commonly diagnosed in the fifth decade of life. [13, 14]

6.1.1 Clinical Features of Mycosis Fungoides

MF presents as a maculopapular rash that is commonly observed in sun-protected areas, predominantly in the pelvic region. In its early stages, singular or multiple erythematous lesions that vary in size can be observed. Macules and patches may gradually evolve into scaly plaques or a tumor-like growths, normally in a course of over months to years. Conversely, some patients may present with various types of skin lesions simultaneously without a progressive course. The lesions are usually well-demarcated and can vary in colors, ranging from orange to violet-red. These lesions can be intensely pruritic, asymptomatic, or alternate between the two. This stage of MF is extremely challenging to diagnose and is often mistaken for a chronic, treatment-resistant eczema, psoriasis or other types of dermatitis.

Lesions in the disease may also exhibit various behaviors. They may spontaneously regress, coalesce, clear centrally, or evolve into another form. They may be hyper- or hypopigmented, with the latter especially common in blacks. In such cases, it is known as a hypopigmented MF subtype. Tumors-like lesions, which represent a more aggressive form of the disease, are typically seen on the face or in body folds, and notably in inframammary regions in females. Nodules may ulcerate and become infected. Erythroderma may be seen as a primary manifestation in MF, or progress from earlier stages. Other features include nonspecific symptom as malaise, fever, and weight loss, as well as skin-related magnifications such as hyperkeratosis on the palms and soles, nail dystrophy, alopecia, and insomnia secondary to sever pruritus. [14]

6.1.2 Immunohistopathology of Mycosis Fungoides

In all stages, a band-like infiltrate can be observed in the epidermis. This infiltrate is primarily composed of reactive and neoplastic T-cells. These neoplastic T-lymphocytes have a characteristic lobulated or convoluted cerebriform nuclei, and they tend to form microepidermal microabscesses. In the tumor form of the disease, there is a nodular infiltrate that protrudes into the epidermis. In such cases, the underlying epidermal infiltrate is often less pronounced.

As mature T-cells, T-lymphocytes in MF typically present with the $CD4^{+}CD8^{-}$ phenotype. They are also positive for the CD3. In some cases, $CD3^{+}CD4^{-}CD8^{+}$ T-lymphocytes can be seen, but such a phenotype is not as common. The CD7 antigen is observed in a third of all documented cases. In the more progressive stage of the disease, partial T-cell antigens, like CD2, CD3, and CD5 may be lost. Therefore, immunotyping may play a limited role in early-stage diagnosis. [14, 15] TOX, which is usually suppressed in healthy mature T-lymphocytes, may be abnormally expressed

in MF neoplastic T-cells, and therefore, may contribute to diagnosis. However, abnormal TOX expression is not limited to MF and cannot be solely relied upon. [16]

6.1.3 Prognosis of Mycosis Fungoides

As with other malignant diseases, the prognosis of MF in heavily influenced by the stage of the disease at presentation and other contributory manifestations. The survival rate of MF is excellent. The 5-year survival is estimated to be above 90% for stage I and still favorable for stage II, but significantly reduced to around 20% for stage IV. [17] The 10-year survival rate for early stage disease is still estimated to be above 90%, but for advanced stages, it is reduced by almost half. [18] Involvement of lymph nodes or further dissemination correlates with a worse prognosis.

6.1.4 Common Variants of Mycosis Fungoides

In addition to the classical mycosis fungoides, further variants have been observed. Each variant presents with a unique clinicopathologic characteristics.

6.1.4.1 Folliculotropic Mycosis Fungoides

The follicular subtype of MF occasionally manifests with follicular papules, acneiform lesions or comedo-like plugs, in which hair loss frequently occurs. Pruritus is reported to be more severe than in classical MF. It commonly affects the trunk and head and neck regions. Histopathologically, a folliculotropic infiltrate is observed, which may be accompanied by mucinous hair follicles degeneration. [14] Alopecia involving the eyebrows is typical for the disease [7]. Follicular MF is almost exclusively observed in adults and is associated with a worse prognosis than classical MF.

6.1.4.2 Pagetoid Reticulosis

The main manifestation of this rare MF subtype is described by a psoriasiform or hyperkeratotic patches or plaques involving the extremities. Histopathologically, an intraepidermal proliferation of neoplastic $CD4^+$ or $CD8^+$ T-cells is observed. It has a favorable prognosis. [19]

6.1.4.3 Granulomatous Slack Skin

This subtype of MF is exceedingly rare and is characterized by lax areas of folding skin. It mainly affects the axillae and groin. Histopathologically, a dense granulomatous dermal infiltrate comprised of various cell types is observed. Recognized cell types include macrophages, multinucleated giant cells, and atypical cerebriform T-cells of a $CD3^+CD4^+CD8^-$ phenotype. [19]

6.2 Sézary Syndrome

Sézary syndrome is a type of CTCL that is characterized by a triad of (1) diffuse erythroderma, (2) generalized lymphadenopathy, and (3) circulating malignant cerebriform T-lymphocytes. These malignant lymphocytes are also known as Sézary cells, and they can also be observed in the skin and lymph nodes. [20] Latest evidence suggests that, contrary to previous beliefs, SS arises from different subsets of T-lymphocytes, rather than a continuation of mycosis fungoides. Nevertheless, no final conclusion has been established between the two hypotheses.

6.2.1 Clinical Features of Sézary Syndrome

The main clinical manifestation of Sézary syndrome is a diffuse erythroderma, which is required to involve more than 80% of the superficial skin at presentation. It may be accompanied by pruritus, scaling, and exfoliation. Lichenification, keratoderma with fissuring in the palms and

soles, alopecia, and nail hypertrophy are also common manifestations. Sézary syndrome has a leukemic component. Although rare, visceral involvement can occur. [7, 21]

6.2.2 Immunohistopathology of Sézary Syndrome

T-lymphocytes in SS resemble those in MF, as they are of the $CD3^+CD4^+CD8^-$ phenotype. Additionally, PD-1 is frequently expressed, and the loss of T-cell antigens, such as CD7 and CD26, is a common finding in SS. In contrast to MF, the infiltrate in SS is more monotonous with Sézary cells exhibiting less epidermotropism. By definition, SS requires a Sézary cell count of at least 1000 cells/mL, and either CD4:CD8 ratio greater than 10, or abnormal loss of CD26 or CD7 of 30% and 40%, respectively [5, 21]

6.2.3 Prognosis of Sézary Syndrome

As a leukemic disease, the prognosis of SS is unfavorable, and the 5-year survival is estimated to be less than 25%. This is believed to stem from the tumor-induced immunosuppressive state. Consequently, patients with SS usually die due to infectious complications. [21]

6.3 Primary Cutaneous $CD30^+$ Lymphoproliferative Disorder

Primary cutaneous $CD30^+$ lymphoproliferative disorders mainly consist of two subsets of CTCLs: (1) primary cutaneous anaplastic large cell lymphoma (C-ALCL) and (2) lymphomatoid papulosis (LyP). Both C-ALCL and LyP comprise a spectrum of a singular disease with overlapping clinical, histological and immunophenotypic aspects. Diagnosis heavily relies upon the clinical course. However, it may be rather challenging to establish a definitive distinction between C-ALCL and LyP. In such cases, the term ‘borderline’ can be used to describe the diagnosis.

6.3.1 Lymphomatoid Papulosis

This form of CTCL is characterized by chronic, recurrent, self-healing papulonecrotic or papulonodular skin lesions. The characteristic lesions are typically observed on the trunk and the extremities in various stages of healing. The lesions are red-brown in color and may present a central hemorrhage or necrosis. The course of the disease is benign, and it correlates with an excellent prognosis.

The histologic appearance of LyP exhibits a substantial variability, with five different subtypes described based on cellular type. Multiple subtypes can manifest simultaneously in a patient at different locations. Type A, which is associated with an early relapse of the disease, is the most common subtype. In this type, $CD3^+CD4^+CD25^+$ T-cell are commonly observed. In type B, $CD30^-$ T-lymphocytes are typical, although a variable $CD30^+$ expression is still observed. Types D and E are associated with $CD8^+$ T-lymphocytes. [22]

6.3.2 Primary Cutaneous Anaplastic Large Cell Lymphoma

Cutaneous ALCL is typically an adult-exclusive condition and it has a slight male predominance. It is characterized by a singular or localized cluster of nodules or tumors that usually ulcerate. Spontaneous resolution may occur, but relapses are also frequent. While regional lymph nodes or further involvement is observed in about 10% of all cases, it does not negatively impact the prognosis. Although not as remarkable as in LyP, the prognosis is still favorable, with a 10-year survival rate of 90%. [23]

C-ALCL is composed of large cells, the majority of which express the CD3 marker. Such cells can be anaplastic, pleomorphic, or immunoblastic. However, regardless of the underlying morphology,

the presentation and course of the disease remain the same. In addition, no evidence of MF should be present. [7]

Histopathologically, a diffuse infiltrate consisting mainly of non-epidermotropic $CD30^+$ large cells can be observed. Although a pleomorphic or immunoblastic cells can be seen, it is the anaplastic type that is most commonly associated with C-ALCL. These cells are characterized by their abundant cytoplasm, irregular borders, and prominent nucleoli. The atypical mitotic rate is commonly high. [5, 24]

Neoplastic T-cells frequently bear the $CD4^+$ phenotype, although $CD8^+$ T-cells have also been observed. The CD2, CD5, and CD3 phenotypes may sometimes be lost. Cytotoxic proteins, MUMI1/IRF4, and CLA are commonly observed as well. In contrast to systemic ALCL, cutaneous ALCL typically lacks the t(2;5) translocation and is normally negative for anaplastic lymphoma kinase (ALK). [23, 25]

7. Main Subtypes of Cutaneous B-cell Lymphoma

CBCL is observed in 20-25% of all PCL cases. It constitutes a group of rare malignant B-cell lesions. The main types in this group are: (1) PCFCL, (2) PCMZL, and (3) PCLBC. [6] As in the previous section, this part will briefly describe the basic aspects of each of the aforesaid entities.

7.1 Primary Cutaneous Follicle Center Lymphoma

PCFCL is the most common form of CBCL. It is defined by a malignant germinal center proliferation, which presents with a cellular composition of cleaved follicular center cells and large follicular center cells with prominent nuclei. These cells are known as centrocytes and centroblasts, respectively.

7.1.1 Clinical Features of PCFCL

PCFCL present with a singular or a grouped cluster of papules, plaques and tumors, mainly appearing on the trunk, back, head, and neck. These lesions are firm and erythematous; annular redness around lesions can be observed. Pain is not a common manifestation of PCFCL lesions. PCFCL exhibits a male predominance with a 1.5:1 male-to-female ratio, and it is commonly diagnosed around the fifth to sixth decade of life. B symptoms are uncommon. [26]

7.1.2 Immunohistopathology PCFCL

A diffuse or follicular infiltrate consisting of centrocytes and centroblasts is observed involving the dermis. Other cell types, such as macrophages and immunoblasts, are commonly seen. While subcutaneous fat involvement can be seen, the epidermis remains unaffected. [26]

As a B-lymphocytic neoplasm, B-cell phenotypes such as CD19, CD20, and CD79a are naturally expressed. Bc16, a germinal center marker, is present as well. Bcl2 and t(14;18) chromosomal translocation are not typical, which distinguishes PCFCL from the classic nodal follicular center lymphomas. The CD10 marker is often observed in cases with a follicular growth pattern. Anti-Ki-67, which symbolizes proliferation activity, is peculiarly low. [26, 27]

7.1.3 Prognosis of PCFCL

The course of the disease is indolent, and prognosis is excellent despite its common recurrences. The 5-year survival is assumed to be above 95%, with the 10-year survival rate still stands roughly at 90%. Further dissemination beyond the involving skin is rare. [26, 27]

7.2 Primary Cutaneous Marginal Zone B-cell Lymphoma

In this type of CBCL, a variety of cells are observed in the marginal zone. These cells may include B-cells, plasma cells, and lymphplasmatic cells. *Borrelia burgdorferi* is believed to play a role in the etiology of PCMZL development, although no final conclusion has been established. [8, 28]

7.2.1 Clinical Features of PCMZL

Unlike PCFCL, lesions can be found in various locations in the body, commonly appearing on the trunk and the extremities. When the extremities are involved, lesions are mostly observed on the upper limbs. The lesions present as macules, papules, and tumors in shades of violent to red with annular erythema. The diagnosis commonly occurs after the fifth decade of life. B symptoms are absent. [26, 28]

7.2.2 Immunohistopathology of PCMZL

In PCMZL, the infiltrate is observed in the marginal zone rather than in the follicle. The infiltrate commonly consists of plasma cells, plasmacytoid cells, small lymphocytes and eosinophils. Plasma cells are frequently observed as the predominant cell type. Expression of CD20, CD79a and Bcl2 are common, while the expression of CD5, CD10 and Bcl6 is not detected. [28]

7.2.3 Prognosis of PCMZL

Like PCFCL, the course of PCMZL is indolent and correlates to an excellent prognosis. The 5-year survival rate is nearly 97%. Responses to therapy is excellent. While extracutaneous spread is uncommon, relapses are often observed. [26]

7.3 Primary Cutaneous Diffuse Large B-cell Lymphoma

PCLBCL is a rare and aggressive subtype of CBCL. Approximately 20% of the cases of PCLBCL are attributed to the leg type (DLBCLLT), which, as the name suggests, mainly manifests on the legs. Other diffuse large B-cell lymphomas are scarce and will not be discussed further in this section [6].

7.3.1 Clinical Features of DLBCLLT

DLBCLLT manifests as a singular or clustered plaques and tumors located on either one or both legs, commonly on the distal part. The lesions are erythematous to bluish in color. Contrary to the aforementioned CBCL types, PCDLBCL often present with ulceration, which might be mistaken as venous insufficiency. The leg type is typically observed in elderly women, and the incidence and diagnosis occur at an advanced age in the seventh decade of life. [29]

7.3.2 Immunohistopathology of DLBCLLT

The infiltrate of DLBCLLT comprises immunoblast and centroblast, with the former being the predominant cell type. The infiltrate involves the papillary dermis, with extensions to the dermal-epidermal junction often observed. The CD20 and CD79a markers are positive. Bcl2, IRF4-MUM1, FOXP1 and MYC are commonly positive, while their absence makes the diagnosis of PCFCL more probable. Monoclonal rearrangement of *IGH* is also present. [29]

7.3.3 Prognosis of DLBCLLT

The prognosis of DLBCLLT is less favorable, with a 5-year survival rate lower than 50%. Loss of CDNK2A, presumably secondary to 9p21 chromosomal deletion or methylation, is associated with a worse prognosis. [26, 27]

8. Diagnosis and Assessment of Primary Cutaneous Lymphoma

Primary cutaneous lymphoma, as has been emphasized in previous sections, encompasses a variety of cutaneous neoplasms of T-cells and B-lymphocytes in origin. While entities in CTCL and CBCL have their own unique features and characteristics, significant overlaps and resemblances in various aspects exist, such as in clinical features and immunohistopathological findings. Therefore, a careful and thorough examination of the observed findings must be conducted with high accuracy.

Furthermore, as is the case with virtually all neoplastic diseases, further systemic assessments and imaging are required to accurately determine their stage. Staging is a crucial and fundamental aspect in the evaluation of neoplastic diseases. It is essential in selecting a proper treatment, and it provides vital information for assessing the prognosis of the disease.

8.1 Clinical Picture

The clinical presentation of various PCL types may overlap, making it rather challenging to distinguish between each one of them based solely on their clinical presentation. Conversely, the clinical presentation can sometime be the most crucial aspect in establishing the diagnosis, especially when the immunohistopathological findings are similar. Many PCL tumors can present as typical nodular or plaque-like lesion in similar locations, but the predominant area involved can raise the suspicion of specific tumor subtypes.

In CBCL, the difference between PCMZL and PCFCL can often be suspected based on the predominant location of the typical lesions. PCMZL lesions commonly occur more frequently on the extremities, while PCFCL is commonly observed on the face and scalp. PCLBCL, unlike

PCFCL and PCMZL, predominantly affects the distal leg, with ulceration being a typical manifestation that raises a high suspicion towards its diagnosis. The predominant sex and age of diagnosis of CBCL subtypes also vary. Other symptoms, such as unintentional weight loss, night sweats and fever, which are known as B-symptoms, may increase suspicion into classical nodal B-cell lymphoma rather than early stages of CBCL. [26-29]

In CTCL, the difference in erythroderma involvement may help to differentiate between SS and MF. While diffuse erythroderma might be observed in advanced MF cases, more than 80% body surface erythroderma should raise suspicion regarding the diagnosis of SS, which can be confirmed by further different assessment methods. Alopecia, hypopigmentation, and skin laxity are distinct features of specific MF variants. Clinical history is also crucial for distinguishing between cutaneous ALCL and LyP due to overlappings in the immunohistopathological findings and clinical presentation. [14, 19, 21-23]

The assessment of the clinical presentation, lesions morphology, clinical history in the course of disease presentation, sex and age of diagnosis is crucial for early assessments of PCL.

8.2 Immunohistopathological Findings

As with clinical features, immunohistopathological findings overlap amongst different cellular types and markers. As of previous example, the differentiation between cutaneous ALCL and LyP heavily relies on the patient's clinical history, due to the similarity in immunohistopathological findings between the two conditions. In another instance, the predominance of an immunoblastic cellular infiltrate may indicate a typical finding in PCLBCL, while a predominance of a centroblastic cellular infiltrate may suggest a diagnosis of PCFCL instead. PCFCL by itself can be distinguished from classical nodal B-cell lymphoma, as it lacks Bcl2 and t(14;18) expression. The

presence of such markers raises the suspicion of classical B-lymphoma extension in the differential diagnosis, rather than of CBCL. [21-23, 25, 28]

The immunohistopathological profile of SS and MF are almost identical, involving similar subsets of T-lymphocytes with overlapping markers. The expression of PD-1, and the lack of CD5 and CD26 markers, along with increased ratio of CD4:CD8 greater than 10, are crucial immunohistopathological findings for diagnosis of SS. [5, 20, 21]

It is clearly evident that a biopsy of suspicious lesions is an integral part in assessing and classifying subtypes of primary cutaneous lymphoma. Once a specimen is obtained, various immunohistopathological techniques can be used to assess the nature of the tumor. [30, 31]

8.3 Staging

Staging is a fundamental process in tumor assessment. It helps establish proper treatment and evaluate the prognosis. Imaging is the recommended modality in establishing the final extent of a neoplastic disease. Computed tomography (CT), with or without positron emission tomography (PET), for the chest, abdomen and pelvis, is recommended in most cases to detect visceral and lymph node involvement. Magnetic resonance imaging (MRI) may substitute for CT, but it is mainly reserved for cases in which CT is contraindicated (e.g., contrast allergy). Biopsies may also be used in various cases to establish organs and lymph nodes involvement. Ultrasound (US) is yet another imaging technique that can sometimes be used to assess lymph nodes. [31]

The staging of PCL commonly follows the TNMB system, which evaluates the degree of tumor skin extension (T_1-T_4), lymph node involvement (N_0-N_3), the presence of metastasis (M_0-M_1), and the existence of atypical malignant cells in the blood (B_0-B_2).

MF is the most prevalent form of PCL, and its clinical relationship to SS makes the TNMB classification of these conditions both important and closely related (Tables 1 & 2). [5, 30]

Table 1

TNMB Classification of Primary Cutaneous Lymphoma. Adapted from Olsen EA. [29]

	MF/SS	Non-MF/SS CTCL + CBCL
T_1	Patches/plaques; < 10% of total skin area	Solitary lesion
T_2	Patches/plaques; ≥ 10% of total skin area	Multiple lesions limited to 1 region
T_3	Tumor(s); any skin involvement	Generalized involvement
T_4	Erythroderma; ≥80% of total skin area	
N_0	No lymph node involvement	No lymph node involvement
N_1	Lymph node element; normal histology	1 peripheral lymph node draining the area
N_2	Lymph node element; abnormal histology; nodal architecture is spared	≥ 2 darning lymph nodes draining the area or 1 lymph node that does not
N_3	Nodal architecture is affected	Central lymph node involvement
M_0	No presence of further involvement	No presence of further involvement
M_1	Visceral involvement present	Visceral involvement present
B_0	Blood atypical cells < 250 μL (or none)	
B_1	Blood atypical cells ≥ 250 μL & < 1000 μL	
B_2	Blood atypical cells ≥ 1000 μL	

Table 2

Clinical Staging of Mycosis Fungoides and Sézary Syndrome. Adapted from Bolognia JL. [5]

IA	T_1	N_0	M_0	B_{0-1}
IB	T_2	N_0	M_0	B_{0-1}
IIA	T_{1-2}	N_{1-2}	M_0	B_{0-1}
IIB	T_3	N_{0-1}	M_0	B_{0-1}
III	T_4	N_{0-2}	M_0	B_{0-1}
IV	Any T with either N_3, M_1 or B_2			

8.4 Other Methods of Assessments

Other methods of evaluation may include PCR and blood work. PCR can be used in some cases of CBCL, due to a possible association with *Borrelia burgdorferi*. [5, 28] Blood work is needed to assess the evidence of Sézary cells in order to establish a diagnosis of SS. [20] A complete blood count, blood chemistry (e.g., liver enzymes and metabolic panel) and other prognostic factors (e.g., LDH levels, Ki-67), might also be required for a conclusive evaluation. [30-32]

To conclude this section, it has become evident that the assessment of primary cutaneous lymphoma requires a comprehensive and diverse evaluation of varied aspects.

9. Treatment of Primary Cutaneous Lymphoma

The treatment of PCL requires a multidisciplinary approach to assess the correct nature of the disease, as it mainly follows a stage-based strategy. The treatment is often divided into either topical or systemic interventions. This section will largely discuss the diverse treatment modalities for CTCL, particularly MF and SS, due to their major significance and the rareness of CBCL. Most patients with CTCL present with early stages of the disease that correlates to an excellent prognosis. The main goal of treatment in these patients is to improve the quality of live while avoiding diverse toxicities.

9.1 Corticosteroids

Corticosteroids have a potent inhibitory effect on inflammation by inducing T-lymphocytes lysis and blocking cytokine secretion. Topical corticosteroids are the first-line of treatment in the early stages of MF. Efficacy is reported exceedingly high with minimal side effects. When side effects do occur, either contact or irritant dermatitis are typically reported. Clobetasol propionate is widely used as a drug of choice. In more severe cases, systemic corticosteroids can be used, but they have significant metabolic effects that may lead to an array of symptoms. [33, 34]

9.2 Radiotherapy

Radiotherapy can be utilized in some early stages of CTCL, especially in MF or SS, as they are radiosensitive. In cases of advanced disease, low-dose radiotherapy may have a role in palliative care, by either as a low-dose local intervention or as a full-body irradiation. [33] Radiotherapy is readily feasible and cost effective. [34]

9.3 Phototherapy

Phototherapy is one of the most common modalities in use, owing to its exceptional availability and efficacy. It is mainly used for treating early stages of MF, particularly in people of color. It can be either used alone or in combination with topical therapy. The modalities in use include either UVA (PUVA) or UVB (Narrowband UVB). [33]

A particular treatment utilizing UVA irradiation can take the form of extracorporeal photopheresis, in which pooled leukocytes are irradiated via plasmapheresis procedure. UVA exposure induces cross-linkage of DNA, resulting in the apoptosis of abnormal cells. This modality is mainly used in treating SS or advanced MF. Despite extracorporeal photopheresis being a safe procedure, it may cause iron deficiency anemia secondary to blood loss. It can also be used in combination with interferon treatment. [33, 34]

9.4 Retinoids

Retinoids can affect the cell cycle (e.g., division, reproduction and differentiation) and are used either topically or systemically. They work through the retinoic X or retinoic acid receptors. [34] Bexarotene is a common drug of this family used in treating CTCL, owing to its ability to induce apoptosis in malignant T-lymphocytes. Adverse effects include hypertriglyceridemia, central hypothyroidism and myelosuppression, although the latter is uncommon. In scares cases, hypertriglyceridemia can be followed by pancreatitis. Due to the reversibility of such toxicities, lipid panel and thyroid function tests should be closely monitored. Fenofibrate may be recommended as a prophylactic therapy for hypertriglyceridemia. [33]

9.5 Histone Deacetylases Inhibitors

This class of drugs helps to sustain chromatin in its relaxed form. Chromatin relaxation occurs via the introduction of acetyl groups to histones. Inhibiting deacetylases, which operate to remove acetyl groups, allows chromatin to stay in its relaxed state. This relaxation promotes gene transcription, enabling the expression of DNA repair proteins, apoptotic factors and other cell-cycle-related mediators that are believed to be silenced. Vorinostat and romidepsin are commonly used in advanced diseases (e.g. SS) for a symptomatic relief (e.g., pruritus). Gastrointestinal disturbances, including nausea, diarrhea and vomiting, are common and seen in half of all cases. Anemia and thrombocytopenia are also often observed. A rare but potentially lethal toxicity may involve a QT interval prolongation. [33]

9.6 Chemotherapy

Systemic chemotherapy has shown overall poor efficacy in treating CTCL, with patients requiring additional sessions within the first year after therapy. Moreover, chemotherapy is associated with increased mortality. Therefore, it is infrequently utilized in treatment of CTCL. However, and individualized decision to use chemotherapy may still be considered, such as in cases of systemic tumor involvement. [34] Pralatrexate and methotrexate may be used together to reduce drug resistance. The CHOP regimen, which includes cyclophosphamide, doxorubicin, vincristine and prednisolone, can also be used. Folic acid and cobalamin supplementations are advised in systemic chemotherapy treatment to reduce mucositis. Even though high responses may still be observed with systemic chemotherapy, they are short-lived and correspond to significant toxicities. [33]

9.7 Biological and Immunomodulating Drugs

These drugs can present with a powerful efficacy in treating and controlling CTCL. Therapeutic decisions should be tailored individually according to age, health status, extent and progression of the disease.

9.7.1 TRL7 Agonists

Topical imiquimod, which activates T-cells via TRL7, has shown some efficacy in treating early stages of MF. Its adverse side effects include localized pain, redness, pruritus, and ulceration. However, toxicities are relativity limited. Further side effects include flu-like symptoms and fatigue, but they are rarer than localized toxicities. Side effects commonly resolve spontaneously after a few weeks. Resiquimod, another analog in this drug family, while still under research, shows acceptable efficacy. [33]

9.7.2 Interferons

Interferons may present pleiotropic and immunomodulatory effects on CTCL. Interferon-α and interferon-γ are often used as a second-line treatment for early stages of CTCL. However, interferon-α can be considered first-line in advanced disease. Interferon-α is often combined with PUVA or retinoid therapy. High doses of interferons correlate with an increased incidence of myelosuppression and flu-like symptoms. [33]

9.7.3 Monoclonal Antibodies

CD53 is widely present on T-lymphocytes. Therefore, the utilization of alemtuzumab (a monoclonal antibody against CD52) may impose a logical intervention in dealing with CTCL.

However, it shows significant dose-related toxicity, presented by an increased incidence of infectious complications. Cytomegalovirus reactivation was reported to be the most common complication. HSV and VZV reactivation, as well as *Pneumocystis jirovecii* pneumonia, are commonly observed. Therefore, it is recommended that patients treated with alemtuzumab be given a prophylactic dose of acyclovir and trimethoprim-sulfamethoxazole, along with weekly CMV surveillance. [33]

Mogalizumab is another monoclonal antibody targeted towards chemokine receptor CCR4 that is present on T-cells. It is associated with increased antibody-dependent cell-mediated cytotoxicity. It is more effective on circulating cells rather than those that reside in the skin. Therefore, it should be engaged in treating SS. Though well-tolerated, rashes are commonly observed. Its use is indicated after a prior failed systemic therapy. [33]

CTCL that presents with high CD30 expression may be treated with brentuximab vedotin (a CD30 monoclonal anybody), which shows effectiveness in cases of diseases confined to the skin. [33] A combination with PUVA can be considered in cases of CTCL that are treatment-resistant to other modalities. [34]

9.7.4 Checkpoint Blockade

In some cases, CTCL neoplasms develop the ability to evade the immune system, either by downregulating MHC-1 or by over-expressing PD-L. Therefore, pembrolizumab, a PD-L blocker, may have the ability to counter such mechanism of immune evasion and help to eradicate the disease. [33]

9.8 Stem Cells Transplantation

Stem cell transplantation may be attempted in younger patients, especially those who are refractory to MF treatment. While efficacy is not exceedingly high, complete remission can be observed even in advanced stages. [34]

9.9 Antibiotics

Due to the plausible relation between CTCL and *Staphylococcus aureus*, the usage of antibiotics has been proposed and has shown a favorable disease progression in a few cases. It may also be used in cases in which sepsis is suspected. [8, 34]

9.10 Specific Treatment Methods for Cutaneous B-cell Lymphoma

CBCL cases are scarce, and thus, due to limited research, the best definitive approach for CBCL treatment has not been established. Radiation therapy may be used for treatment of various types of CBLC with excellent rates of resolution. Conversely, surgical excision may be associated with higher recurrences, despite being an acceptable modality for the treatment of localized lesions. The CD20 monoclonal antibody rituximab is widely used for treatment of both systemic and cutaneous B-cells neoplasms of various subtypes, owing to their expression of the native B-lymphocytic cellular line CD20 phenotype. Chemotherapy (e.g., CHOP) may be used in aggressive diseases, particularly in DLBCLLT. Unfortunately, in such cases, aggressive chemotherapy may be contraindicated due to the advanced age and status of the patients. [26, 35]

10. Conclusion

PCL is a rare group of extranodal non-Hodgkin's lymphomas that many present as either a CTCL or CBCL subtype. While manifestations primarily affect the skin, systemic or visceral involvement can be observed in advanced cases. Generally, the factors contributing to the occurrence of PCL are unknown. Both CTCL and CBLC subtypes comprise overlapping clinical and immunohistopathological features. Therefore, a thorough assessment must be conducted to differentiate between the various forms, as the prognosis and treatment depend on the stage and nature of the tumor. Although most cases are diagnosed and present in the early stage of the disease, which is associated with topical treatment and an excellent prognosis, some rarer cases may present with an advanced stage or aggressive course that prompts systemic treatment and correlate with a poor prognosis. Much is still not known regarding the nature of PCL, and further research on its tumorigenesis and treatment is needed. Alas, due to its rarity, many questions are still left unanswered.

11. Acknowledgement

I would like to thank my mentor, Professor Romana Čeović, MD. PhD., for the opportunity to allow me to carry out this thesis work in the Department of Dermatovenerology at University Hospital Centre Zagreb under her guidance. Additionally, and most importantly, I want to express my deepest gratitude towards my parents and family for supporting me thus far.

12. References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood. 2009;113(21):5064–73. ht

2. Willemze R. Cutaneous T-cell lymphoma: Epidemiology, etiology, and classification. Leuk Lymphoma. 2003;44(sup3):S49–54.

3. Dobos G, Pohrt A, Ram-Wolff C, Lebbé C, Bouaziz J-D, Battistella M, et al. Epidemiology of cutaneous T-cell lymphomas: A systematic review and meta-analysis of 16,953 patients. Cancers (Basel). 2020;12(10):2921.

4. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. JAMA Dermatol. 2013;149(11):1295.

5. Bolognia JL, Schaffer JV, Cerroni L. Dermatology: 2-Volume Set. 4th ed. London, England: Elsevier Health Sciences; 2017.p. 2113-2147.

6. Vitiello P, Sica A, Ronchi A, Caccavale S, Franco R, Argenziano G. Primary cutaneous B-cell lymphomas: An update. Front Oncol. 2020;10.

7. Kang S. Fitzpatrick's dermatology, ninth edition, 2-volume set. 9th ed. McGraw-Hill Education/Medical; 2018. p. 2072-2107.

8. Mirvish JJ, Pomerantz RG, Falo LD Jr, Geskin LJ. Role of infectious agents in cutaneous T-cell lymphoma: Facts and controversies. Clin Dermatol. 2013;31(4):423–31.

9. Bobrowicz M, Fassnacht C, Ignatova D, Chang Y-T, Dimitriou F, Guenova E. Pathogenesis and therapy of primary cutaneous T-cell lymphoma: Collegium Internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol. 2020;181(10):733–45.

10. Abraham RM, Zhang Q, Odum N, Wasik MA. The role of cytokine signaling in the pathogenesis of cutaneous T-cell lymphoma. Cancer Biol Ther. 2011;12(12):1019–22.

11. Chung CG, Poligone B. Cutaneous T cell lymphoma: An update on pathogenesis and systemic therapy. Curr Hematol Malig Rep. 2015;10(4):468–76.

12. Nicolay JP, Wobser M. Cutaneous B-cell lymphomas – pathogenesis, diagnostic workup, and therapy. J Dtsch Dermatol Ges. 2016;14(12):1207–24.

13. Boulos S, Vaid R, Aladily TN, Ivan DS, Talpur R, Duvic M. Clinical presentation, immunopathology, and treatment of juvenile-onset mycosis fungoides: A case series of 34 patients. J Am Acad Dermatol. 2014;71(6):1117–26.

14. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. J Eur Acad Dermatol Venereol. 2004;18(4):397–415.

15. Cerroni L. Mycosis fungoides—clinical and histopathologic features, differential diagnosis, and treatment. Semin Cutan Med Surg. 2018;37(1):2–10.

16. Pileri A, Cavicchi M, Bertuzzi C, Righi S, Zengarini C, Sabattini E, et al. TOX expression in mycosis fungoides and Sezary syndrome. Diagnostics (Basel). 2022;12(7):1582.

17. Chen Z, Lin Y, Qin Y, Qu H, Zhang Q, Li Y, et al. Prognostic factors and survival outcomes among patients with mycosis fungoides in China: A 12-year review. JAMA Dermatol. 2023;159(10):1059–67.

18. Farabi B, Seminario-Vidal L, Jamgochian M, Akay BN, Atak MF, Rao BK, et al. Updated review on prognostic factors in mycosis fungoides and new skin lymphoma trials. J Cosmet Dermatol. 2022;21(7):2742–8.

19. Muñoz-González H, Molina-Ruiz AM, Requena L. Clinicopathologic variants of mycosis fungoides. Actas Dermosifiliogr. 2017;108(3):192–208.

20. Hwang ST, Janik JE, Jaffe ES, Wilson WH. Mycosis fungoides and Sézary syndrome. Lancet. 2008;371(9616):945–57.

21. Vakiti A, Padala SA, Singh. D. Sezary Syndrome. StatPearls Publishing. September 24, 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK499874/. Accessed November 18, 2023.

22. Martinez-Cabriales SA, Walsh S, Sade S, Shear NH. Lymphomatoid papulosis: an update and review. J Eur Acad Dermatol Venereol. 2020;34(1):59–73.

23. Melchers RC, Willemze R, van de Loo M, van Doorn R, Jansen PM, Cleven AHG, et al. Clinical, histologic, and molecular characteristics of anaplastic lymphoma kinase-positive primary cutaneous anaplastic large cell lymphoma. Am J Surg Pathol. 2020;44(6):776–81.

24. Kadin ME, Carpenter C. Systemic and primary cutaneous anaplastic large cell lymphomas. Semin Hematol. 2003;40(3):244–56.

25. Brown RA, Fernandez-Pol S, Kim J. Primary cutaneous anaplastic large cell lymphoma. J Cutan Pathol. 2017;44(6):570–7.

26. Goyal A, LeBlanc RE, Carter JB. Cutaneous B-cell lymphoma. Hematol Oncol Clin North Am. 2019;33(1):149–61.

27. Cretella P, Peluso AL, Picariello C, Cozzolino I, Triggiani M, Puzziello A, et al. Immunohistochemical algorithms and gene expression profiling in primary cutaneous B-cell lymphoma. Pathol Res Pract. 2022;231(153804):153804.

28. Cho-Vega JH, Vega F, Rassidakis G, Medeiros LJ. Primary cutaneous marginal zone B-cell lymphoma. Pathol Patterns Rev. 2006;125(1):S38–49.

29. Hope CB, Pincus LB. Primary cutaneous B-cell lymphomas with large cell predominance–primary cutaneous follicle center lymphoma, diffuse large B-cell lymphoma, leg type and intravascular large B-cell lymphoma. Semin Diagn Pathol. 2017;34(1):85–98.

30. Olsen EA, Whittaker S, Willemze R, Pinter-Brown L, Foss F, Geskin L, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood. 2022;140(5):419–37.

31. Olsen EA. Evaluation, diagnosis, and staging of cutaneous lymphoma. Dermatol Clin. 2015;33(4):643–54.

32. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous lymphoma international consortium study of outcome in advanced stages of mycosis fungoides and Sézary syndrome: Effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol. 2015;33(32):3766–73.

33. Hristov AC, Tejasvi T, Wilcox RA. Cutaneous T-cell lymphomas: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(1):193–209.

34. Lauren C Pinter-Brown RAS. Cutaneous T-Cell Lymphoma. MedScape. October 16, 2023. Available at: https://emedicine.medscape.com/article/2139720-overview. Accessed November 18, 2023.

35. Wilcox RA. Cutaneous B-cell lymphomas: 2019 update on diagnosis, risk stratification, and management. Am J Hematol. 2018;93(11):1427–30.

13. Biography

Yotam Malek was born on September 1994 in Israel. His formal education was acquired at various schools around the country. In 2012, he enlisted in the army, where he served until the end of 2016. While in military service, he completed his bachelor's degree in Computer Science and Mathematics Education. Subsequently, in 2018, he decided to pursue his medical studies in the University of Zagreb in Croatia.