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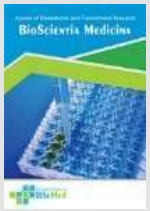

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Case of Hypopigmented Mycosis Fungoides: Clinical and Pathological Discrimination from Mimicking Conditions

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A B S T R A C T

Background: Hypopigmented mycosis fungoides (HMF) is an uncommon variant of mycosis fungoides (MF), a cutaneous T-cell lymphoma. It presents a diagnostic challenge due to its clinical resemblance to various benign dermatological conditions. This case report highlights the importance of a comprehensive approach to diagnosis, incorporating clinical, histopathological, and immunohistochemical findings. **Case presentation:** A 48-year-old Indonesian woman presented with a one-year history of progressive, asymptomatic hypopigmented patches on her extremities. Initially misdiagnosed as progressive macular hypomelanosis, the patient's condition did not improve with topical treatments. Clinical examination revealed multiple hypopigmented patches and macules on both extremities, with some lesions exhibiting fine scales. Histopathological examination demonstrated atypical lymphocytes with epidermotropism and Pautrier's microabscesses. Immunohistochemical staining confirmed the presence of CD3+ T-cells, leading to the diagnosis of HMF. **Conclusion:** HMF can mimic various dermatological conditions, making diagnosis challenging. A thorough clinical assessment, coupled with histopathological and immunohistochemical evaluation, is crucial for accurate diagnosis and appropriate management. This case underscores the importance of considering HMF in the differential diagnosis of hypopigmented skin lesions, particularly in individuals with persistent or atypical presentations. Early recognition and intervention are essential for optimizing patient outcomes.

1. Introduction

Mycosis fungoides (MF) stands as the most prevalent form of cutaneous T-cell lymphoma (CTCL), a heterogeneous group of non-Hodgkin lymphomas characterized by the malignant transformation and infiltration of T lymphocytes into the skin. MF typically manifests with a diverse array of clinical presentations, ranging from erythematous patches and plaques to tumors, often accompanied by pruritus. The disease course is indolent, with slow progression over several years. However, in some cases, MF can transform into aggressive variants, leading to extracutaneous involvement and a poorer prognosis. Hypopigmented mycosis fungoides (HMF) is a distinct and relatively rare variant of MF, primarily affecting individuals with darker skin types, particularly those with Fitzpatrick skin types IV-VI. This variant is characterized by the development of hypopigmented or achromic patches and macules, which can be easily mistaken for benign dermatological conditions such as pityriasis versicolor, post-inflammatory hypopigmentation, vitiligo, and progressive macular hypomelanosis. The clinical resemblance to these benign conditions often leads to misdiagnosis and delayed treatment, highlighting the importance of a comprehensive diagnostic approach for HMF. The pathogenesis of HMF remains incompletely understood, but it is

believed to involve a complex interplay of genetic, environmental, and immunological factors. Studies have suggested a potential genetic predisposition to HMF, with certain human leukocyte antigen (HLA) alleles being associated with an increased risk of developing this variant. Environmental factors such as ultraviolet (UV) radiation exposure and certain infections have also been implicated in the pathogenesis of HMF. Immunologically, HMF is characterized by the infiltration of malignant CD4+ T-cells into the skin, often with a loss of pan-T-cell markers such as CD7. These malignant T-cells are thought to induce a cascade of inflammatory responses, leading to the destruction of melanocytes and subsequent hypopigmentation.[1,2]

The diagnosis of HMF can be challenging due to its nonspecific clinical presentation and the need for histopathological and immunohistochemical confirmation. Clinically, HMF lesions may appear as well-demarcated, hypopigmented patches or macules with varying degrees of scaling. Dermoscopy, a non-invasive technique that allows for the visualization of subsurface skin structures, can aid in the diagnosis of HMF by revealing characteristic features such as perifollicular white halos, telangiectasias, and a patchy vascular pattern. However, histopathological examination remains the gold standard for diagnosing HMF. The histopathological hallmark of HMF is the presence of atypical lymphocytes with epidermotropism, Pautrier's microabscesses, and a band-like lymphocytic infiltrate in the dermis. Immunohistochemical staining is essential for confirming the diagnosis, with CD3, CD4, and CD8 being the most commonly used markers. The management of HMF depends on the stage and extent of the disease. Early-stage HMF, confined to the skin, may be treated with topical corticosteroids, phototherapy, or localized radiation therapy. Topical corticosteroids, such as betamethasone valerate or clobetasol propionate, can be effective in reducing inflammation and pruritus associated with HMF lesions. Phototherapy, particularly narrowband ultraviolet B (NB-UVB) therapy, has been shown to induce remission in a significant proportion of patients with early-stage HMF. Localized radiation therapy, such as electron beam therapy or superficial X-ray therapy, may be used for localized lesions that are resistant to other treatment modalities.[3,4]

For more advanced cases of HMF with extracutaneous involvement or those that are refractory to topical therapies, systemic treatments may be necessary. Systemic therapies for HMF include retinoids, interferon-alpha, and chemotherapy. Retinoids, such as acitretin or bexarotene, can modulate T-cell function and induce apoptosis of malignant cells. Interferon-alpha, a cytokine with immunomodulatory and antiproliferative effects, has also been used with some success in the treatment of HMF. In cases of aggressive or refractory HMF, chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or gemcitabine may be considered. The prognosis of HMF is generally favorable, with most patients experiencing long-term remission with appropriate treatment. However, close monitoring is essential for early detection of any signs of recurrence or progression. Regular follow-up visits with a dermatologist, including skin examinations and laboratory tests, are crucial for ensuring optimal patient outcomes. HMF is a rare but important variant of MF that can pose a diagnostic challenge due to its clinical resemblance to various benign dermatological conditions. A thorough clinical assessment, coupled with histopathological and immunohistochemical evaluation, is crucial for accurate diagnosis and appropriate management. Early recognition and intervention are essential for optimizing patient outcomes and ensuring long-term remission.[5,6]

2. Case Presentation

A 48-year-old Indonesian woman, with Fitzpatrick skin type IV, presented to our dermatology clinic with a chief complaint of progressive, asymptomatic hypopigmented patches on her extremities. The patient reported a one-year history of these lesions, which initially appeared on her right arm and

gradually spread to involve both arms and legs, causing significant cosmetic concern. She denied any associated symptoms such as pruritus, pain, or altered sensation within the affected areas. The patient's medical history was unremarkable, with no known allergies or chronic illnesses. She denied any recent exposure to occupational chemicals, drugs, radiation, or infections that could potentially trigger or exacerbate skin conditions. Notably, she had previously sought medical attention for the hypopigmented patches and had been misdiagnosed with progressive macular hypomelanosis. Despite receiving topical treatments for this initial diagnosis, the patient's condition did not improve, prompting her to seek further evaluation at our clinic. Dermatological examination revealed multiple, well-demarcated, hypopigmented patches and macules scattered across the patient's extremities. These lesions varied in size and shape, ranging from small, circular macules to larger, irregularly shaped patches. The patches were predominantly located on the extensor surfaces of the arms and legs, with some involvement of the flexural areas. The lesions exhibited a smooth surface with fine scaling in some areas, but there was no evidence of erythema, induration, or ulceration. Wood's lamp examination did not reveal any fluorescence, ruling out certain fungal infections.

A comprehensive physical examination was performed, which was unremarkable except for the aforementioned skin findings. The patient's vital signs were within normal limits, and a systemic review revealed no abnormalities. Specifically, there was no lymphadenopathy or hepatosplenomegaly, suggesting that the condition was localized to the skin. Given the patient's clinical presentation and the lack of response to previous treatments, a differential diagnosis was formulated. This included progressive macular hypomelanosis, vitiligo, post-inflammatory hypopigmentation, and hypopigmented mycosis fungoides (HMF). To establish a definitive diagnosis, a skin biopsy was performed on a representative lesion on the patient's right arm. Histopathological examination of the biopsy specimen revealed several key findings that were consistent with HMF. The epidermis showed atypical lymphocytes with epidermotropism, a hallmark feature of MF characterized by the migration of malignant T-cells into the epidermis. Additionally, Pautrier's microabscesses, which are collections of atypical lymphocytes within the epidermis, were observed. The dermis exhibited a band-like lymphocytic infiltrate, further supporting the diagnosis of HMF (Figure 1).

To confirm the diagnosis and characterize the immunophenotype of the infiltrating lymphocytes, immunohistochemical staining was performed. The results showed positive staining for CD3, a pan-T-cell marker, indicating the presence of T-cells in the infiltrate (Figure 2). This finding, in conjunction with the histopathological features, confirmed the diagnosis of HMF. Following the diagnosis of HMF, the patient was initiated on a treatment regimen consisting of topical corticosteroids and narrowband ultraviolet B (NB-UVB) phototherapy. The topical corticosteroids were prescribed to reduce inflammation and pruritus associated with the lesions, while NB-UVB phototherapy was chosen for its immunomodulatory and antiproliferative effects on malignant T-cells. The patient was instructed to apply the topical corticosteroids twice daily to the affected areas and to undergo NB-UVB phototherapy sessions three times per week. After six months of consistent treatment, the patient's condition showed significant improvement. The hypopigmented patches and macules on her extremities decreased in size and number, with some lesions resolving completely. The patient reported a reduction in the associated pruritus, and her overall quality of life improved. The patient continues to be monitored regularly for any signs of recurrence or progression, with ongoing NB-UVB phototherapy sessions and intermittent use of topical corticosteroids as needed.

Table 1. Clinical finding, diagnosis, and treatment.

Finding category	Details
Patient demographics	48-year-old Indonesian woman, Fitzpatrick skin type IV
Chief complaint	Progressive, asymptomatic hypopigmented patches on extremities
History of present illness	1-year history, initially on right arm, gradual spread, misdiagnosed as progressive macular hypomelanosis, no improvement with topical treatments
Past medical history	Unremarkable, no allergies or chronic illnesses
Dermatological examination	Multiple, well-demarcated, hypopigmented patches and macules on extremities, varying in size and shape, smooth surface with fine scaling in some areas, no erythema, induration, or ulceration, Wood's lamp examination negative
Physical examination	Unremarkable except for skin findings
Differential diagnosis	Progressive macular hypomelanosis, vitiligo, post-inflammatory hypopigmentation, hypopigmented mycosis fungoides (HMF)
Skin biopsy	Taken from representative lesion on right arm
Histopathological examination	Atypical lymphocytes with epidermotropism, Pautrier's microabscesses, band-like lymphocytic infiltrate
Immunohistochemical staining	Positive for CD3 (pan-T-cell marker)
Diagnosis	Hypopigmented mycosis fungoides (HMF)
Treatment	Topical corticosteroids, narrowband ultraviolet B (NB-UVB) phototherapy
Follow-up	Significant improvement after 6 months, ongoing NB-UVB phototherapy and intermittent topical corticosteroids

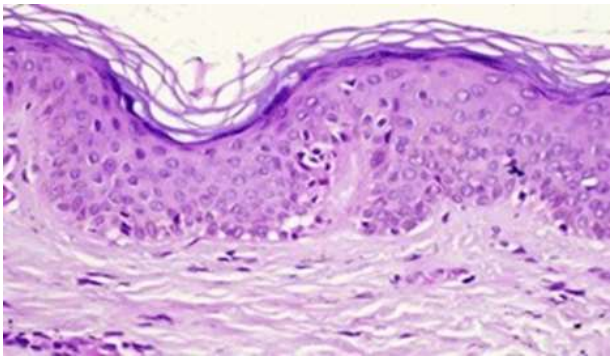

Figure 1. Basal cell degeneration with melanin pigment incontinence. Band-like lymphocytic infiltrate, papillary dermal fibrosis, lymphocytic exocytosis resembling Pautrier abscess and dermal lymphoid cell infiltrate (hematoxylin and eosin ×40).

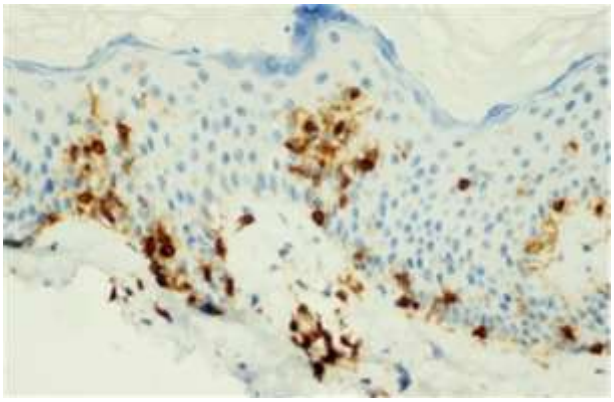

Figure 2. Immunohistochemical staining showing CD3+ T cells.

3. Discussion

Hypopigmented mycosis fungoides (HMF) is an uncommon variant of mycosis fungoides (MF), a type of cutaneous T-cell lymphoma (CTCL). It presents a unique diagnostic challenge due to its clinical resemblance to various benign dermatological conditions, particularly in individuals with darker skin types. This case report highlights the importance of a comprehensive approach to diagnosis, incorporating clinical, histopathological, and immunohistochemical findings, to ensure accurate diagnosis and timely initiation of appropriate treatment. The patient in this case, a 48-year-old Indonesian woman with Fitzpatrick skin type IV, presented with a one-year history of progressive, asymptomatic hypopigmented patches on her extremities. The initial misdiagnosis of progressive macular hypomelanosis (PMH) underscores the challenges in differentiating HMF from other hypopigmented disorders. PMH is a common differential diagnosis for HMF, as both conditions can present with similar clinical features, such as hypopigmented macules and patches. However, PMH typically affects younger individuals and is often associated with sun exposure, whereas HMF can occur at any age and is not necessarily related to sun exposure. The histopathological findings in this case were pivotal in establishing the diagnosis of hypopigmented mycosis fungoides (HMF). The presence of atypical lymphocytes exhibiting epidermotropism, Pautrier's microabscesses, and a band-like lymphocytic infiltrate within the dermis are hallmark features of mycosis fungoides (MF), the broader category of cutaneous T-cell lymphoma to which HMF belongs. These findings, while not exclusive to HMF, are highly suggestive of this variant, especially when considered in conjunction with the clinical presentation and immunohistochemical profile. The hallmark of MF is the infiltration of malignant T-cells into the epidermis, a phenomenon known as epidermotropism. In HMF, this epidermotropism is often less pronounced than in other MF variants, but it remains a crucial diagnostic feature. The atypical lymphocytes in HMF tend to be smaller and less cerebriform than those seen in classic MF, but they still exhibit characteristic nuclear irregularities and hyperchromasia. The presence of these atypical lymphocytes within the epidermis, often forming small clusters or nests, is a strong indicator of HMF.[7,8]

Pautrier's microabscesses are another pathognomonic feature of MF, representing aggregates of atypical lymphocytes within the epidermis. While these microabscesses are more commonly observed in classic MF, they can also be present in HMF, albeit less frequently. The presence of Pautrier's microabscesses in this case further supports the diagnosis of HMF, as they are rarely seen in other inflammatory dermatoses. The band-like lymphocytic infiltrate in the dermis is a common finding in MF and can be helpful in differentiating it from other inflammatory skin conditions. This infiltrate is characterized by a dense accumulation of lymphocytes arranged in a band-like pattern along the dermoepidermal junction. In HMF, the infiltrate may be less dense and less organized than in classic MF, but it still exhibits a predominantly lymphocytic composition with varying degrees of atypia. Immunohistochemical staining plays a crucial role in confirming the diagnosis of HMF and differentiating it from other subtypes of MF. The positive staining for CD3, a pan-T-cell marker, in this case confirmed the presence of T-cells in the infiltrate. While CD3 is not specific for MF, it is a useful marker for identifying T-cell lymphomas. The absence of CD7 expression, a pan-T-cell marker that is often lost in MF, further supports the diagnosis. Additional immunohistochemical markers, such as CD4 and CD8, can be used to further characterize the immunophenotype of the infiltrating lymphocytes. In HMF, the malignant T-cells are predominantly CD4+, although a subset of CD8+ T-cells may also be present. The CD4/CD8 ratio can vary among different cases of HMF, and its prognostic significance is still under investigation. The histopathological and immunohistochemical findings in this case were instrumental in establishing the diagnosis of HMF.

The presence of atypical lymphocytes with epidermotropism, Pautrier's microabscesses, and a band-like lymphocytic infiltrate in the dermis, along with positive staining for CD3 and the absence of CD7 expression, are all consistent with the diagnosis of HMF. These findings, combined with the clinical presentation and the patient's history, provide a comprehensive picture of this rare and challenging variant of MF.[9,10]

The pathogenesis of hypopigmented mycosis fungoides (HMF) is a multifaceted process that involves a complex interplay of genetic, environmental, and immunological factors. While the exact mechanisms underlying the development of HMF remain to be fully elucidated, research has shed light on several key aspects that contribute to its pathogenesis. Genetic studies have identified certain human leukocyte antigen (HLA) alleles that are associated with an increased risk of developing HMF. HLA molecules are cell surface proteins responsible for presenting antigens to T cells, thereby initiating an immune response. Specific HLA alleles, such as HLA-DRB104 and HLA-DQB103, have been found to be more prevalent in individuals with HMF compared to the general population. These alleles are thought to play a role in the immune response to certain antigens, potentially triggering the development of HMF in susceptible individuals. The association between HLA alleles and HMF suggests a genetic predisposition to the disease. It is hypothesized that individuals carrying these specific HLA alleles may have an altered immune response to certain antigens, leading to the activation and proliferation of malignant T-cells. However, the exact antigens involved in this process remain unknown. Further research is needed to identify the specific antigens that trigger the immune response in HMF and to elucidate the mechanisms by which HLA alleles contribute to the development of this disease. Environmental factors, particularly ultraviolet (UV) radiation exposure, have also been implicated in the pathogenesis of HMF. UV radiation is a known carcinogen that can induce DNA damage and mutations in skin cells. These mutations can lead to the activation of oncogenes and the inactivation of tumor suppressor genes, contributing to the development of malignant T-cells. Additionally, UV radiation can suppress the immune system, impairing its ability to recognize and eliminate malignant cells. Studies have shown that individuals with HMF often have a history of chronic sun exposure, suggesting a potential role for UV radiation in the pathogenesis of this disease. However, not all individuals with chronic sun exposure develop HMF, indicating that other factors, such as genetic predisposition, may also play a role. Further research is needed to determine the precise mechanisms by which UV radiation contributes to the development of HMF and to identify other environmental factors that may be involved.[11-13]

Immunological factors play a crucial role in the pathogenesis of HMF. The disease is characterized by the infiltration of malignant CD4+ T-cells into the skin. These T-cells often exhibit a loss of pan-T-cell markers such as CD7, which is a characteristic feature of MF. The malignant T-cells in HMF are thought to induce a cascade of inflammatory responses, leading to the destruction of melanocytes and subsequent hypopigmentation. The mechanisms underlying the hypopigmentation in HMF are not fully elucidated, but it is believed to involve the release of cytokines and other inflammatory mediators by the malignant T-cells. These mediators can directly or indirectly inhibit melanocyte function and survival, leading to a reduction in melanin production and subsequent hypopigmentation. Additionally, the inflammatory response can also damage the surrounding skin tissue, further contributing to the hypopigmentation. The immune system plays a dual role in the pathogenesis of HMF. On one hand, it is responsible for recognizing and eliminating malignant T-cells. However, in HMF, the immune system is dysregulated, allowing the malignant T-cells to evade immune surveillance and proliferate. This dysregulation may be due to several factors, including the loss of pan-T-cell markers, the production of immunosuppressive cytokines by the malignant T-cells, and the impairment of immune function by UV radiation.[13,14]

Cytokines and chemokines are signaling molecules that play a crucial role in the immune response. In HMF, the malignant T-cells produce a variety of cytokines and chemokines that contribute to the pathogenesis of the disease. These molecules can promote the proliferation and survival of malignant T-cells, recruit additional inflammatory cells to the skin, and inhibit melanocyte function and survival. One of the key cytokines involved in HMF is interleukin-17 (IL-17). IL-17 is a pro-inflammatory cytokine that is produced by a subset of T-cells known as Th17 cells. In HMF, the malignant T-cells often exhibit a Th17 phenotype, characterized by the production of IL-17. IL-17 can induce the production of other pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1), which can further amplify the inflammatory response and contribute to the destruction of melanocytes. Chemokines are another important class of signaling molecules involved in HMF. Chemokines are responsible for the recruitment of immune cells to sites of inflammation. In HMF, the malignant T-cells produce chemokines that attract additional inflammatory cells to the skin, further exacerbating the inflammatory response. These inflammatory cells can release additional cytokines and other mediators that contribute to the destruction of melanocytes and the development of hypopigmentation.[15,16]

The microenvironment of the skin plays a crucial role in the pathogenesis of HMF. The skin is a complex organ with a diverse array of cell types, including keratinocytes, fibroblasts, melanocytes, and immune cells. These cells interact with each other and with the extracellular matrix to maintain skin homeostasis. In HMF, the microenvironment is disrupted by the infiltration of malignant T-cells, leading to a cascade of events that contribute to the development of the disease. Keratinocytes, the predominant cell type in the epidermis, play a key role in the pathogenesis of HMF. Keratinocytes can produce a variety of cytokines and chemokines that promote the proliferation and survival of malignant T-cells. Additionally, keratinocytes can express adhesion molecules that facilitate the migration of malignant T-cells into the epidermis. Fibroblasts, the main cell type in the dermis, also contribute to the pathogenesis of HMF. Fibroblasts can produce growth factors and cytokines that promote the proliferation and survival of malignant T-cells. Additionally, fibroblasts can synthesize extracellular matrix components that provide a scaffold for the malignant T-cells to adhere to and migrate through. Melanocytes, the cells responsible for melanin production, are the primary target of the inflammatory response in HMF. The cytokines and other mediators released by the malignant T-cells can directly or indirectly inhibit melanocyte function and survival, leading to a reduction in melanin production and subsequent hypopigmentation. The mechanisms underlying the destruction of melanocytes in HMF are not fully understood, but it is believed to involve a combination of direct cytotoxicity, apoptosis, and inhibition of melanogenesis.[14-16]

The role of ultraviolet (UV) radiation in the pathogenesis of hypopigmented mycosis fungoides (HMF) is a complex and multifaceted issue. While UV radiation is a well-established risk factor for various skin cancers, including cutaneous T-cell lymphomas (CTCLs), its specific contribution to the development of HMF remains an area of ongoing research and debate. UV radiation, particularly UVB radiation, is known to induce DNA damage in skin cells. This damage can lead to mutations in genes that regulate cell growth and differentiation, potentially contributing to the malignant transformation of T-cells. In the context of HMF, UV radiation may play a role in initiating or promoting the development of malignant T-cells, particularly in individuals with a genetic predisposition to the disease. Several studies have investigated the association between UV radiation exposure and the risk of developing MF, including HMF. A retrospective study of 193 MF patients in Kuwait found that a history of sun exposure was significantly associated with the development of hypopigmented lesions, suggesting a potential role for UV radiation in the pathogenesis of HMF. Another

study found that patients with HMF had a higher prevalence of sunburn history compared to patients with other subtypes of MF, further supporting the link between UV radiation and HMF. The mechanisms by which UV radiation may contribute to the development of HMF are not fully understood. One hypothesis is that UV radiation induces the production of reactive oxygen species (ROS) in skin cells, which can damage DNA and other cellular components. This damage can lead to mutations in genes that regulate cell growth and differentiation, potentially contributing to the malignant transformation of T-cells. Additionally, UV radiation can suppress the immune system, impairing the body's ability to recognize and eliminate malignant cells. This immunosuppressive effect may create a favorable environment for the growth and proliferation of malignant T-cells in HMF.[17,18]

Another potential mechanism by which UV radiation may contribute to the development of HMF is through its effect on melanocytes. UV radiation is known to damage melanocytes, the cells responsible for producing melanin, the pigment that gives skin its color. This damage can lead to a reduction in melanin production, resulting in hypopigmentation. In HMF, the malignant T-cells are thought to induce a cascade of inflammatory responses that further damage melanocytes, leading to the characteristic hypopigmented lesions. UV radiation may exacerbate this process by directly damaging melanocytes and impairing their ability to recover from the inflammatory insult. While the evidence for a link between UV radiation and HMF is compelling, it is important to note that not all individuals with HMF have a history of significant sun exposure. This suggests that other factors, such as genetic predisposition and environmental exposures, may also play a role in the development of this disease. Further research is needed to elucidate the precise mechanisms by which UV radiation contributes to the pathogenesis of HMF and to identify other potential risk factors.[17,18]

The potential role of infectious agents in the pathogenesis of HMF is an intriguing area of research. Several studies have investigated the association between certain infections and the risk of developing MF, including HMF. One of the most studied infectious agents in this context is the human T-lymphotropic virus type 1 (HTLV-1). HTLV-1 is a retrovirus that infects T-cells and is associated with a variety of diseases, including adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Several studies have reported an increased prevalence of HTLV-1 infection in patients with MF, suggesting a potential link between this virus and the development of CTCLs. However, the exact role of HTLV-1 in the pathogenesis of HMF remains unclear. One hypothesis is that HTLV-1 infection may directly contribute to the malignant transformation of T-cells. The virus can integrate its genetic material into the host cell's DNA, potentially disrupting the normal regulation of cell growth and differentiation. Additionally, HTLV-1 can produce viral proteins that interfere with cellular signaling pathways, leading to the activation of oncogenes and the inactivation of tumor suppressor genes. These effects may create a favorable environment for the development of malignant T-cells in HMF. Another potential mechanism by which HTLV-1 may contribute to the development of HMF is through its effect on the immune system. HTLV-1 infection can dysregulate the immune response, leading to chronic inflammation and immune suppression. This dysregulation may impair the body's ability to recognize and eliminate malignant cells, allowing them to proliferate and invade the skin. Additionally, HTLV-1 infection can induce the production of cytokines and other inflammatory mediators, which may further contribute to the development of HMF lesions. While the association between HTLV-1 infection and MF is well-established, the evidence for a specific link between HTLV-1 and HMF is less clear. Some studies have reported an increased prevalence of HTLV-1 infection in patients with HMF, while others have not found a significant association. This discrepancy may be due to differences in study design, patient populations, and diagnostic criteria. Further research

is needed to clarify the role of HTLV-1 in the pathogenesis of HMF and to identify other potential infectious agents that may contribute to the development of this disease.[18,19]

In addition to HTLV-1, other infectious agents have been investigated for their potential role in the pathogenesis of HMF. These include Epstein-Barr virus (EBV), human herpesvirus 8 (HHV-8), and Staphylococcus aureus. However, the evidence for a causal relationship between these infections and HMF is limited and inconclusive. Further research is needed to determine whether these or other infectious agents play a role in the development of HMF. Immunologically, HMF is characterized by the infiltration of malignant CD4+ T-cells into the skin. These T-cells often exhibit a loss of pan-T-cell markers such as CD7, which is a characteristic feature of MF. The malignant T-cells in HMF are thought to induce a cascade of inflammatory responses, leading to the destruction of melanocytes and subsequent hypopigmentation. The mechanisms underlying the hypopigmentation in HMF are not fully elucidated, but it is believed to involve the release of cytokines and other inflammatory mediators by the malignant T-cells, which can directly or indirectly inhibit melanocyte function and survival. The clinical presentation of HMF can vary widely, making diagnosis challenging. The lesions can range from small, well-demarcated macules to larger, confluent patches. The hypopigmentation can be subtle or pronounced, and the lesions may be accompanied by varying degrees of scaling, pruritus, and erythema. The distribution of lesions is also variable, with some patients presenting with localized involvement, while others have widespread disease.[17,19]

The differential diagnosis for HMF includes a wide range of hypopigmented skin disorders, such as PMH, vitiligo, post-inflammatory hypopigmentation, pityriasis versicolor, and leprosy. PMH is a common differential diagnosis for HMF, as both conditions can present with similar clinical features. However, PMH typically affects younger individuals and is often associated with sun exposure, whereas HMF can occur at any age and is not necessarily related to sun exposure. Vitiligo is another important differential diagnosis for HMF, as both conditions can present with depigmented patches. However, vitiligo is characterized by the complete absence of melanocytes in the affected skin, whereas HMF typically shows a reduction in melanocyte density rather than complete absence. Post-inflammatory hypopigmentation can also mimic HMF, as both conditions can present with hypopigmented patches following inflammation. However, post-inflammatory hypopigmentation typically resolves over time, whereas HMF lesions tend to persist and progress. Pityriasis versicolor, a fungal infection caused by Malassezia species, can also present with hypopigmented patches, particularly in individuals with darker skin types. However, pityriasis versicolor lesions typically exhibit fine scaling and may fluoresce under Wood's lamp examination, whereas HMF lesions do not. Leprosy, a chronic infectious disease caused by Mycobacterium leprae, can also present with hypopigmented patches, but these lesions are typically associated with sensory loss and nerve thickening. The diagnosis of HMF requires a high index of suspicion and a comprehensive approach, incorporating clinical, histopathological, and immunohistochemical findings. A thorough clinical history and physical examination are essential for identifying any risk factors for HMF, such as a personal or family history of lymphoma or autoimmune diseases. Dermoscopy can be helpful in identifying characteristic features of HMF, such as perifollicular white halos, telangiectasias, and a patchy vascular pattern. However, histopathological examination remains the gold standard for diagnosing HMF.[15,18]

The histopathological hallmark of HMF is the presence of atypical lymphocytes with epidermotropism, Pautrier's microabscesses, and a band-like lymphocytic infiltrate in the dermis. Atypical lymphocytes are characterized by their enlarged nuclei, irregular nuclear contours, and hyperchromatic chromatin. Epidermotropism, the migration of malignant T-cells into the epidermis, is a

hallmark of MF and is often observed in HMF. Pautrier's microabscesses, which are collections of atypical lymphocytes within the epidermis, are another pathognomonic feature of MF, although they may not always be present in HMF. The band-like lymphocytic infiltrate in the dermis is a common finding in MF and can be helpful in differentiating it from other inflammatory dermatoses. Immunohistochemical staining is essential for confirming the diagnosis of HMF and differentiating it from other subtypes of MF. The most commonly used markers for HMF are CD3, CD4, and CD8. CD3 is a pan-T-cell marker that is expressed by all T-cells, including malignant T-cells in HMF. CD4 is a marker for helper T-cells, which are the predominant type of T-cell in HMF. CD8 is a marker for cytotoxic T-cells, which are less common in HMF but may be present in some cases. The loss of pan-T-cell markers such as CD7 is also a characteristic feature of MF and can be helpful in confirming the diagnosis.[17,19]

The management of hypopigmented mycosis fungoides (HMF) is multifaceted and depends on the stage and extent of the disease. Early-stage HMF, which is confined to the skin, can often be effectively managed with topical therapies, phototherapy, or localized radiation therapy. These treatment modalities aim to reduce inflammation, alleviate symptoms, and induce remission of the lesions. Topical corticosteroids, such as betamethasone valerate or clobetasol propionate, are frequently used as first-line therapy for early-stage HMF. These medications exert their therapeutic effects through potent anti-inflammatory and immunosuppressive actions. By binding to glucocorticoid receptors in the skin, topical corticosteroids inhibit the production of inflammatory cytokines and chemokines, thereby reducing the infiltration of inflammatory cells into the skin. This, in turn, leads to a decrease in erythema, edema, and pruritus associated with HMF lesions. Additionally, topical corticosteroids can suppress the proliferation of malignant T-cells, contributing to the resolution of the lesions. The choice of topical corticosteroid depends on the severity and extent of the lesions. For mild to moderate cases, low- to mid-potency corticosteroids, such as hydrocortisone or triamcinolone acetonide, may be sufficient. However, for more extensive or recalcitrant lesions, high-potency corticosteroids, such as betamethasone valerate or clobetasol propionate, may be necessary. The frequency of application also varies depending on the potency of the corticosteroid and the severity of the lesions. In general, topical corticosteroids are applied once or twice daily to the affected areas. While topical corticosteroids are generally safe and well-tolerated, long-term use can lead to adverse effects such as skin atrophy, telangiectasias, and striae. Therefore, it is important to use the lowest effective potency and to monitor patients closely for any signs of side effects.[16,19]

Phototherapy, particularly narrowband ultraviolet B (NB-UVB) therapy, is another effective treatment option for early-stage HMF. NB-UVB therapy involves exposing the skin to a specific wavelength of ultraviolet light, which has been shown to have immunomodulatory and antiproliferative effects on malignant T-cells. The exact mechanisms by which NB-UVB therapy exerts its therapeutic effects are not fully understood, but it is believed to involve the induction of apoptosis in malignant T-cells, the suppression of inflammatory cytokines, and the stimulation of regulatory T-cells. NB-UVB therapy is typically administered two to three times per week, with the dosage and duration of treatment tailored to the individual patient's response and tolerance. The treatment is generally well-tolerated, with the most common side effects being mild erythema and pruritus. However, long-term use of NB-UVB therapy can increase the risk of skin cancer, so patients should be monitored closely for any suspicious skin lesions.[18,19]

Localized radiation therapy, such as electron beam therapy or superficial X-ray therapy, may be considered for patients with localized HMF lesions that are resistant to topical corticosteroids or phototherapy. Radiation therapy works by damaging the DNA of malignant T-cells, leading to their death

and the resolution of the lesions. The dosage and duration of radiation therapy are determined by the size and location of the lesions, as well as the patient's overall health status. Radiation therapy is generally safe and effective, but it can cause side effects such as skin erythema, dryness, and pigmentation changes. In rare cases, radiation therapy can also increase the risk of developing secondary malignancies. Therefore, it is important to carefully weigh the risks and benefits of radiation therapy before recommending it to patients.[16,17]

For more advanced cases of HMF with extracutaneous involvement or those that are refractory to topical therapies, systemic treatments may be necessary. Systemic therapies for HMF include retinoids, interferon-alpha, and chemotherapy. Retinoids, such as acitretin or bexarotene, are vitamin A derivatives that have been shown to have immunomodulatory and antiproliferative effects on malignant T-cells. They work by binding to retinoid receptors in the skin, which regulate gene expression and cell differentiation. Retinoids can induce apoptosis in malignant T-cells, suppress the production of inflammatory cytokines, and promote the differentiation of T-cells into less aggressive phenotypes. Interferon-alpha is a cytokine with immunomodulatory and antiproliferative effects. It works by activating natural killer cells and cytotoxic T-cells, which can directly kill malignant T-cells. Interferon-alpha can also inhibit the production of inflammatory cytokines and promote the differentiation of T-cells into less aggressive phenotypes. Chemotherapy is typically reserved for patients with aggressive or refractory HMF. Chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or gemcitabine have been used with some success in the treatment of HMF. However, chemotherapy can cause significant side effects, such as nausea, vomiting, hair loss, and immunosuppression. Therefore, it is important to carefully consider the risks and benefits of chemotherapy before recommending it to patients.[17,18]

The prognosis of HMF is generally favorable, with most patients experiencing long-term remission with appropriate treatment. However, close monitoring is essential for early detection of any signs of recurrence or progression. Regular follow-up visits with a dermatologist, including skin examinations and laboratory tests, are crucial for ensuring optimal patient outcomes. The management of HMF requires a personalized approach based on the stage and extent of the disease. Early-stage HMF can often be effectively managed with topical therapies, phototherapy, or localized radiation therapy. For more advanced cases, systemic therapies such as retinoids, interferon-alpha, or chemotherapy may be necessary. Close monitoring is essential for early detection of any signs of recurrence or progression, and regular follow-up visits with a dermatologist are crucial for ensuring optimal patient outcomes.[19,20]

4. Conclusion

HMF is a rare but important variant of MF that can mimic various benign dermatological conditions. A thorough clinical assessment, coupled with histopathological and immunohistochemical evaluation, is crucial for accurate diagnosis and appropriate management. This case underscores the importance of considering HMF in the differential diagnosis of hypopigmented skin lesions, particularly in individuals with persistent or atypical presentations. Early recognition and intervention are essential for optimizing patient outcomes.

5. References

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