Review

Etiopathogenesis of Mycosis Fungoides

Vefa Aslı Erdemir, Ozan Erdem
Department of Dermatology and Venereology, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye

Abstract

Mycosis fungoides (MF), first described by Jean Louis Alibert in 1806, is the most common subtype of primary cutaneous T-cell lymphomas. MF is a subtype of non-Hodgkin lymphoma and is characterized by malignant clonal T-lymphocytes infiltrating the skin. Although MF primarily affects the skin in the early stages, it can also involve the lymph nodes, blood, and internal organs in more advanced stages. Although the exact cause of MF remains unknown, research suggests that genetic, immunological, environmental factors, and microbial agents may play a role in its pathogenesis. The most widely accepted theory assumes that clonal T-cells arise as a result of antigenic stimulation in genetically predisposed individuals, suggesting that chronic inflammation is crucial to disease development. In this review, we discuss the current knowledge of the factors contributing to the pathogenesis of MF. We collected data from PubMed searches using the combined terms "cutaneous T-cell lymphoma, mycosis fungoides, pathogenesis, etiology, etiopathogenesis" and applying the filters "Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review" without any date restriction.

Keywords: Cutaneous T-cell lymphoma, mycosis fungoides, pathogenesis, etiology, etiopathogenesis

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), primarily affecting the skin but capable of advancing to involve lymph nodes, blood, and other internal organs in later stages. MF is characterized by a clonal expansion of epidermal T-lymphocytes, resulting in distinctive cutaneous manifestations that vary from patches and plaques to tumoral growths. This pathological progression highlights the disease's complexity and indicates that genetic, environmental, immunological, and infectious factors may play a role in its development.[1]

Recent studies indicate that continuous antigenic stimulation in genetically predisposed individuals may initiate the clonal proliferation of T-cells, suggesting a potential connection between persistent inflammation and the pathogenesis of MF. Genetic research has identified numerous mutations and chromosomal anomalies, especially in genes that regulate the cell cycle, provide resistance to apoptosis, and modulate immunological checkpoints, all of which are essential to the course of MF.[2,3] Moreover, the impact of environmental and lifestyle factors, including occupational exposure and chronic antigenic stimulation, is under examination, with possible associations to particular industries and lifestyle practices, such as smoking and obesity.[4-7] Infectious agents, such as specific bacteria and viruses, have been investigated as potential catalysts for MF. While precise links to specific infections remain unclear, recent studies indicate that the skin-resident microbiota may affect disease progression and symptom severity.[8,9] Immunological variables significantly influence MF, with current research emphasizing the involvement of cytokine and chemokine signaling pathways in guiding the migration and behavior of malignant T-cells in the skin.[10-12]

This review aims to elucidate the present understanding of MF pathogenesis, highlighting the contributions of genetic, environmental, immunological, and microbiological components to disease initiation and progression.

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Adress for correspondence: Vefa Aslı Erdemir, MD, Department of Dermatology and Venereology, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye
Email: vefaasli@hotmail.com
ORCID ID: 0000-0002-0433-7669

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Genetic Factors

Understanding the genetic risk factors of MF is essential for early diagnosis, development of targeted therapies, and improvement of disease prognosis. Numerous genetic alterations and mechanisms potentially involved in the onset and progression of MF have been identified. Various genes involved in cell proliferation, immune checkpoint regulation, apoptosis resistance, and immune response are implicated in MF progression. Specific pathways, including those involved in cell cycle regulation, chromosomal instability, and DNA repair, are activated in MF.[2,3]

Familial clustering of MF suggests a genetic predisposition, with certain HLA class II alleles (e.g., *DRB111* and *DQB1*03) being more common in patients with both sporadic and familial MF. Additionally, it has been documented in multiple families, often involving first-degree relatives such as siblings or parent-child pairs. The clinical features and response to therapy are generally similar between familial and sporadic cases. However, some unique variants like hypopigmented MF, have been observed in familial cases.[13,14]

Conventional karyotypic studies have primarily focused on the blood of patients with Sézary syndrome because of the challenges of culturing tumor cells from MF skin lesions. However, these studies revealed multiple structural and numerical chromosomal abnormalities. The most frequently observed abnormalities include the loss of chromosomes 1, 10, and 17 and the gain of chromosome 7.[3,15] In addition, deletions in the 9p21 region, encompassing the *P15* and *P16* genes, are prevalent in both early and advanced phases of MF.[16,17]

Mutations in the *P53* gene are among the most frequent genetic anomalies in human malignancies. Mutations in the tumor suppressor gene *TP53* have been identified in approximately 40% of patients with tumor-stage MF.[18] Interestingly, the mutation spectrum aligns with ultraviyole B-induced mutations, suggesting that ultraviolet radiation may play a role in advanced cutaneous lymphomas.[15,18]

Frequent deletions of tumor suppressor genes, including *BCL7A*, *SMAC/DIABLO*, and *RHOF*, have been observed in early-stage MF, indicating their role in the initial pathogenesis of MF.[19] The loss of other tumor suppressor genes, such as *RB1* and *DLEU1*, has been associated with poor prognosis.[16] Additionally, the deletion of tumor suppressor genes including *CDKN2A* and *CDKN2B*, elevated expression of *NAV3*, *JUNB*, and *c-MYC*, and hypermethylation of mismatch repair genes have been documented.[20]

Some patients with MF harbor Fas mutations, which result in defective apoptosis and lead to the accumulation of malignant T-cells in the skin.[21]

Studies have also indicated the involvement of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway in MF pathogenesis and progression. Mutations in JAK3 have been identified in approximately 8.3% of patients with tumor-stage MF, and recurrent deletions of JAK-STAT pathway inhibitors, such as HNRNPK and SOCS1, have been observed. In the early stages of CTCL, STAT5 activation is prevalent, whereas STAT3 activation becomes predominant in the later stages.[3,22]

In the initial phases, interleukin-2 (IL-2), IL-7, and IL-15 induce STAT5 activation through JAK1 and JAK3 kinases, whereas in subsequent phases, autocrine stimulation by IL-21 is considered essential for STAT3 activation. Recent studies have provided molecular evidence indicating that overexpression of STAT5 during the initial stages of the disease results in elevation of oncogenic miR-155, which subsequently targets STAT4 mRNA. The absence of STAT4 signaling results in a transition from the Th1 phenotype to the Th2 phenotype in malignant T-cells. In advanced phases, STAT3 and STAT5 activation may become independent of cytokines and solely mediated by constitutively active JAK1 and JAK3 kinases.[23]

STAT3 activation plays a particularly important role in advanced-stage disease and large-cell transformation. Given these functions of the JAK-STAT pathway, JAK inhibitors have emerged as promising therapeutic targets for the treatment of MF.[24]

Studies have also demonstrated the activation of the nuclear factor-kappa B (NF-κB) pathway, which is critical for tumor resistance to apoptosis in CTCL. Genetic alterations in the NF-κB pathway genes *PLCG1*, *CARD11*, *TNFRSF1B*, and *KIT* have been reported. These alterations influence the regulation of T-cell survival, proliferation, and transcriptional programs following T-cell receptor signaling.[25]

PIM2, an oncogene regulated by pathways such as JAK-STAT and NF-B, has been implicated in CTCL pathogenesis. A previous study identified increased PIM2 expression in patients with MF, suggesting that it could serve as a marker to distinguish MF from benign inflammatory diseases.[26]

In recent years, there has been a growing interest in studying non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long ncRNAs, in the epigenetic regulation of CTCLs. These ncRNAs are crucial for modulating gene expression and are important for diagnosis, prognosis, and therapeutic decision-making. They play roles in tumor progression and modulating the tumor microenvironment, making ncRNA-based therapies a promising area of research for CTCL patients.[27]

Environmental Factors

The increasing incidence of MF in recent years has prompted investigations into various environmental and lifestyle factors that may contribute to disease development. Persistent exogenous antigenic stimulation of Th-cells in the skin is a key factor in the clonal evolution of these cells.[28]

Although initial studies did not find a significant association between occupational exposure and the disease, later studies have yielded some notable findings.[29] In a study that collected data from Europe, North America, and Australia, an increased risk was identified among workers involved in vegetable and crop farming, as well as those involved in painting, carpet-making, and woodworking. However, this study did not examine the specific substances to which these workers were exposed in their occupations.[4] In a case-control study conducted in Europe, aromatic and/or halogenated hydrocarbons used as solvents and pesticides were identified as potential risk factors for MF.[5] Other industries found associated with an increased risk of MF include textile, petrochemical, and metalworking industries.[6]

Although studies on lifestyle factors have reported varying results regarding smoking, an increased likelihood of developing MF has been noted in individuals who have smoked for 40 years or more.[29] Obesity is one of the factors that stimulate inflammation.[7] One study found that a high body mass index [(BMI) $\geq$ 30 kg/m^2] increases the risk of developing MF, whereas increased physical activity was associated with a decreased risk.[29] Another lifestyle factor, heavy alcohol consumption ($\geq$ 24 g/day), is also linked to an increased risk of developing MF.[30]

There is no definitive evidence that drugs cause MF; however, certain medications, such as mogamulizumab, quinine, phenytoin, and carbamazepine, can induce reactions that mimic MF both clinically and histopathologically.[31,32]

Additionally, a family history of multiple myeloma and personal eczema for more than 10 years are considered risk factors for MF.[29]

Infectious Factors

It is well established that certain bacteria and viruses are associated with human cancers, but the mechanisms by which cancers develop through these infections remain incompletely understood.

Studies on human T-lymphotropic viruses I and II and Epstein-Barr virus, which are linked to certain types of lymphomas, have found that these viruses do not play a role in the etiology of MF.[33,34] However, cytomegalovirus infection seropositivity has been detected in patients with late-stage MF patients.[35]

Studies on human herpesvirus 8 infection have also not found an association with MF, but a significant relationship has been identified with large plaque parapsoriasis.[36]

There are only a few studies regarding the role of the newly identified parvovirus cutavirus (CuV) in the etiology of MF. One of these studies specifically compared patients with large plaque parapsoriasis (BPP), which is considered a premalignant stage of MF, with those with inflammatory skin diseases.[37] Another study found that viral DNA was detected in the lesional skin of patients with BPP at a significantly higher rate (38%) than in those with inflammatory diseases.[38] Further research is needed to fully understand the impact of CuV infection on MF progression.

In a genetic study in which PCR was performed on skin biopsies, CuV DNA was not detected in patients with normal skin or skin carcinoma, but was found in 4 out of 17 patients with CTCL.

In a study conducted with the hypothesis that bacterial superantigen may lead to clonality by causing inflammation, *Staphylococcus aureus* was found in the blood and skin cultures of 75% of patients with advanced-stage disease and Sézary syndrome. In 50% of these cases, the bacteria produced enterotoxins, which act as superantigen, potentially leading to lymphoproliferative infiltrations.[39]

Additionally, a case-control study conducted in a region where Lyme disease is endemic detected *Borrelia burgdorferi*-specific sequences in 18% of patients with MF; however, this finding is not sufficient to conclude a definitive role for *Borrelia* in the etiology of MF.[40]

Recent research has also investigated the role of the skin microbiome in the pathogenesis and symptomatology of MF, aiming to understand how microbial communities influence the disease course and patient outcomes. Changes in the skin microbiota are associated with the severity of MF symptoms. Greater erythema has been associated with higher *Staphylococcus* levels, while discomfort and thicker skin have been linked to reduced levels of *Propionibacterium*.[8,9] *Staphylococcus aureus,* in particular, may contribute to the morbidity and development of MF. Furthermore, the integrity of the skin barrier and interactions between the host and microbiota are also linked to the disease advancement.[41]

Immunological Factors

The immune milieu is essential for the progression of MF. In typical circumstances, T-cells that have not yet encountered their specific antigens continuously traverse from the bloodstream to lymph nodes to examine antigen-presenting cells that deliver peptides compatible with their

T-cell receptors. This process is predominantly mediated by cell surface markers, including L-selectin (CD62L) and CC chemokine receptor 7 (CCR7), present on naïve T-cells. Upon T-cell activation, alterations in the cell surface profile occur. The production of molecules including cutaneous lymphocyte antigen (CLA) and CCR4, which significantly enhance T cell migration to the skin, is induced in skin-draining lymph nodes.[10,11]

One of the primary responses of keratinocytes to cell damage and stress is the secretion of cytokines, which initiate and sustain cutaneous inflammation and promote leukocyte recruitment. This cytokine response stimulates the upregulation of adhesion molecules in dermal endothelial cells and the release of chemokines from basal keratinocytes. The movement of T cells along the sticky endothelium, utilizing a "tethering and rolling" technique, occurs through the interaction of CLA on T-cells with E-selectin on the endothelium. The lymphocytes then tightly adhere to the endothelium and extravasate into the dermis.[10]

In addition to the crucial role of CLA in the migration into the dermis, chemokines are considered to be responsible for epidermotropism.[42] The sources of chemokines are keratinocytes, Langerhans cells, and dermal fibroblasts.[43] In the early stages of MF, interactions between CXCL9, CXCL10, and CXCR3 appear to play key roles in the aggregation of tumor cells, whereas in the tumor stage of the disease, increased expression of CCR4 and decreased expression of CXCL9 and CXCL10 have been observed.[44] In the later stages, chemokine receptors like CCR7, which facilitate homing to the lymphatics, become dominant. Consistent with this, a previous study found a correlation between CCR7 expression and the subcutaneous spread of MF cells.[12]

Dendritic cells not only contribute to chemokine production during pathogenesis and should also be discussed within the context of the antigen hypothesis. Although their exact function is not fully understood, their presence in Pautrier microabscesses and a study showing that Sézary cells can survive long-term in cell cultures through stimulation by immature dendritic cells seem significant. Despite these findings, it should not be forgotten that dendritic cells are also crucial for immunity.[45,46]

Cytokines also play an important role in the pathogenesis of MF. Both Th1 (interferon-gamma, IL-2) and Th2 cytokines (IL-4, IL-5, IL-10) are important cytokines for MF. Different cytokines are associated with different disease stages. For instance, although Th1 and Th2 cytokine mRNAs are detected in the plaque stage, it has been reported that only Th2 cytokine mRNAs are detected as the disease progresses to the tumor stage.[47] The Th1 response is responsible for the eczema-like appearance in the early stages, whereas the Th2 response has been found to be associated with tumoral lesions and weakened immunity.[48,49]

Conclusion

The pathogenesis of MF is a complex, multifactorial process influenced by genetic, immunological, microbiological, and environmental factors. Although significant progress has been made in understanding the roles of cytokines, chemokines, and immune cells such as T-cells and dendritic cells, the precise mechanisms that drive the initiation and progression of the disease remain incompletely understood. Continued research on these molecular and cellular interactions is crucial for improving diagnostic strategies and developing targeted therapies for MF, ultimately aiming to enhance patient outcomes.

Footnotes

Authorship Contributions

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