Hypopigmented mycosis fungoides

Subjects: Oncology

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Hypopigmented mycosis fungoides (HMF) is a variant of **cutaneous T-cell lymphoma** (CTCL), a heterogeneous group of extranodal non-Hodgkin's lymphomas. HMF and classic (erythematous patch/plaque) Mycosis Fungoides (MF) display contrasting clinical characteristics: (i) HMF presents with light colored to achromic patches, as opposed to classic MF, which presents with erythematous scaly patches, plaques, tumors or erythroderma, (ii) HMF primarily affects individuals with darker skin types (Fitzpatrick phototypes IV-VI), while classic MF affects mostly Caucasians, (iii) HMF is commonly seen in pediatric/adolescents and young adults, whereas classic MF is more prevalent in elderly individuals, and (iv) the predominant malignant cells in HMF are CD8+T-cells, as opposed to CD4+T-cells in classic MF. Our recent review paper highlights that active antitumor immune response, specifically a Th1/cytotoxic antitumor immune response seen robustly in HMF, is likely responsible for the differential behavior between these two MF variants. Furthermore, we propose that the hypopigmentation (clinical sign) may serve as a surrogate marker for the presence of antitumor immune response and may portend better prognosis.

mycosis fungoides | cutaneous T-cell lymphomas | hypopigmentation | hypopigmented mycosis fungoides | Th1 | antitumor immune response | cytotoxic cells | immunosurveillance | immunoediting

1. Hypopigmented Mycosis Fungoides

Mycosis fungoides(MF) is a form of **cutaneous T-cell lymphoma** (CTCL), a heterogeneous group of extranodal non-Hodgkin's lymphomas characterized by the expansion of monoclonal T-cells involving the skin [1][2][3]. MF can present with several variants including the classic MF (also known as the conventional Alibert-Bazin), poikilodermatous/poikiloderma vasculare atrophicans, granulomatous slack skin, hypopigmented MF (HMF) [4][5] among others. Each variant has its own set of clinical and pathologic characteristics. In the current summary we focus on **Hypopigmented Mycosis Fungoides (HMF)**.

1.1 Clinical presentation of Hypopigmented Mycosis Fungoides

The main clinical defining feature of HMF are the light colored to achromic patches seen in patients (Figure 1) [6][7], however a few tumors cases have been reported [8][9]. Current evidence suggests that the hypopigmentation is

caused by a damaged and reduced number of melanocytes in addition to an abnormal melanogenesis [6][10].

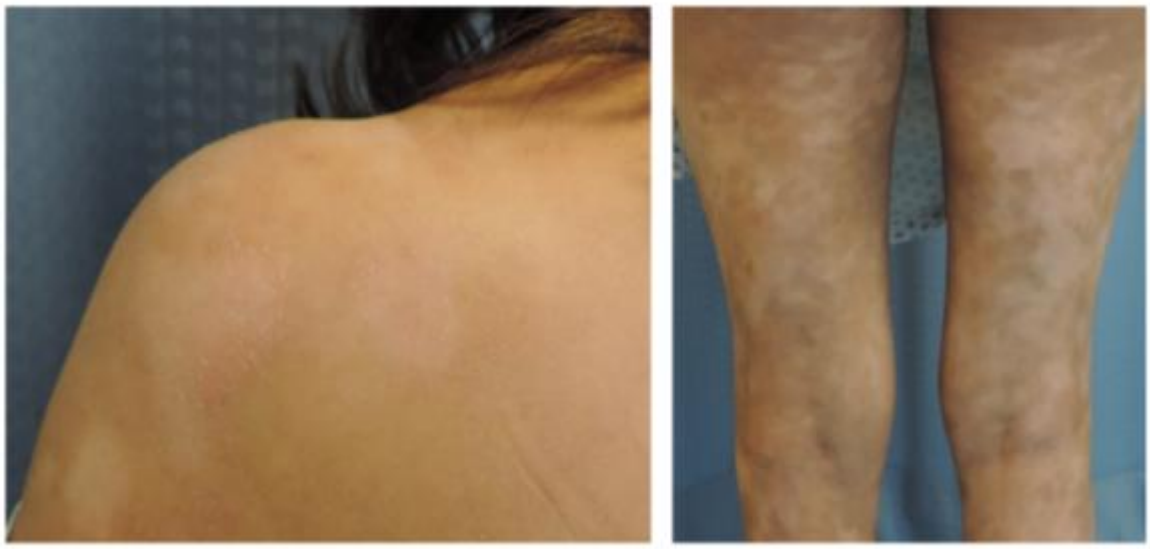

Figure 1. Clinical images of hypopigmented mycosis fungoides (HMF) patient, where the light colored patches can be observed. Figure adapted from [11].

Patients commonly present with lesions on the trunk, buttocks, and extremities in, what is called, a “bathing-suit” distribution pattern [5] [12]. Although not common, facial involvement has been reported [7]. Lesions range from a single patch [13] to generalized lesions covering a large body surface area (BSA). Patients may experience pruritus. However, systemic symptoms such as weight loss, fever or night sweats are uncommon [6][7][14].

1.2 Demographic characteristics of Hypopigmented Mycosis Fungoides

HMF has an earlier mean age of onset than classic MF. While classic MF commonly appears in patients > 55 years of age, HMF is typically reported at younger age, with patients in pediatric, adolescent and early adulthood populations [6]. The female to male ratio most commonly reported is approximately 1:1 [15]. HMF has a higher prevalence in Fitzpatrick IV-VI skin phototypes (i.e., populations with darker skin, including but not limited to African-American, South Asian, Middle Eastern, and Hispanic individuals) [7][16]. However, cases in fair skin patients, particularly Caucasian populations, are not uncommon [17].

1.3 Prognosis and Treatment of Hypopigmented Mycosis Fungoides

Given that HMF is a variant of MF, stratification and staging is the same for both and prognosis is closely associated with clinical disease stage. Stratification and staging are determined according to BSA involved and extracutaneous involvement [1]. MF cases diagnosed at early stages (IA-IIA) have an indolent course and slow progression [16], and cases diagnosed at advanced stages (≥IIB) often have reduced life expectancy of 3.2 to 9.9 years [2]. HMF is typically recognized as a variant with an excellent prognosis. Most individuals present at IA stage (i.e., <10% BSA involvement) to IB (≥10% BSA) stages and progression beyond IB clinical stage is rare. However, HMF recurrence is often reported and may occur months or even years after a complete remission [6].

The majority of HMF cases are treated with skin-directed therapies. In general, the first line of treatment for this variant is phototherapy (e.g., narrowband ultraviolet B or in select cases, ultraviolet A1), photochemotherapy (e.g., psoralen and ultraviolet A (PUVA)), and topical products (e.g., topical steroids, retinoids, imiquimod, or nitrogen mustard). Use of narrowband ultraviolet B light, usually in a cabinet, (NUVB; 311 nm) suppresses malignant cell proliferation by increasing keratinocytes cytokine production and by inhibiting antigen-presenting cells. PUVA involves exposure to ultraviolet A (UVA) radiation (320–400 nm) after ingestion of 8-methoxypsoralen and induces DNA damage, reduction of Langerhan cell population, apoptosis of malignant cells and suppression of keratinocyte cytokine production [5][6].

The most common topical treatment products include steroids, nitrogen mustard, retinoids and imiquimod. Steroids decrease cytokine production and induce apoptosis. Topical nitrogen mustard induces DNA damage due to its alkylating properties. Retinoids, specifically bexarotene, bind to retinoid receptors (Retinoid X Receptor or RXR in the case of bexarotene) that regulate cellular differentiation and apoptosis. Imiquimod augments antitumor immune response by activating Toll-Like Receptor-7 (TLR7), which in turn induces local interferon-α (IFN-α) and interferon-β (IFN-β) production[6].

2. Immunopathogenesis of Alibert-Bazin and Hypopigmented Mycosis Fungoides

Currently, the pathogenesis of MF and HMF is incompletely understood, however external triggers have been identified. *Staphylococcus aureus* toxins have been proposed as an external trigger. Cell autonomous factors promoting carcinogenesis and cancer progression include but are not limited to activation/deregulation of JAK-STAT, NOTCH, MAPK, and other signaling pathways [3][18][19][20][21][22].It is believed that this malignancy arises in T-cells with a mature resident $CD45RO^+$ phenotype [23].

Environmental or pathogen-driven damage to the skin, cellular injury, or stress triggers a pro-inflammatory response initiated by keratinocytes. Keratinocytes release cytokines that activate both, innate and adaptive immune system. The innate immune response is executed by immune cells, such as dendritic cells (DCs), mast cells, and macrophages, which have direct effects on pathogens and the activation of Antigen Presenting Cells (APCs) [23][24].

The specialized APCs in the epidermis are the Langerhans cells and their dermal counterparts are the dermal DCs, and once activated by the innate immune response cells, will migrate to the skin-draining lymph nodes. In the lymph nodes, APCs will encounter naive T-cells that can be activated [24]. Active T-cells are antigen-specific, express cutaneous lymphocyte antigen (CLA) as well as CC chemokine receptor 4 (CCR4), which induces a skin-targeted migration [25]. The skin-targeted migration is facilitated by the dermal vessels keratinocyte-induced expression of the adhesion molecules complementary to the CLA and CCR4 receptors, E-selectin and CC chemokine ligand 17 (CCL17), respectively. Specific receptor-ligand recognition allows active T-cells to tether and roll along the endothelium and extravasate into the dermis. Once in the dermis, active T-cells mediate the inflammatory response [24][25]. Under normal conditions, activated T-cells should be eventually eliminated; however,

MF cancer T-cells continue to proliferate driven by activation/deregulation of JAK-STAT, NOTCH, MAPK, and other signaling pathways, stimulated by exposure to *S. aureus* enterotoxins, upregulation of oncogenic miRNAs, among others [3][18][19][20][21][22][26].

3. Hypopigmented Mycosis Fungoides presents an active antitumor immune response

3.1 Antitumor immune response in Mycosis Fungoides

The three phases of cancer immunoediting have been proposed in MF in part explaining its progression while detailing varying predominant cytokine profiles [11]. Briefly, during the elimination phase malignant T-cells remain occult/incognito and under the control of the immune system [27][28]. However, no specific antigens have been discovered in early stage MF patients [29]. The next phase, the equilibrium phase, is a period of latency characterized by a balance between surviving and dying cancer cells. This phase corresponds to stage IA-IB in HMF, and has been characterized by the presence of tumor infiltrating CD8+ T-cells and a Th1 cytokine profile in lesional skin [27][28]. Finally, the escape phase is enabled by the genomic instability of the cells and a Darwinian pressure by the immune system, enabling the malignant cells to resist/evade immunosurveillance [28]. This phase is characterized by a shift to a Th2 cytokine profile with the concomitant expression of pro-eosinophilic/immunosuppressive molecules and additional molecules such as Fas ligand. As a result, malignant cells proliferate in the skin and beyond, in lymph nodes, blood and visceral organs [27].

3.2 Hypopigmented Mycosis Fungoides remains in the equilibrium phase of cancer immunoediting

In the recently published review paper [11], we proposed that HMF remains in the equilibrium phase of cancer immunoediting. This is supported by research regarding cytokines and cytotoxic molecules secreted by both neoplastic and infiltrating cells and by a low infiltration number of regulatory T-cells (Tregs). As highlighted previously, the equilibrium phase in MF is characterized by a Th1 cytokine profile and among these cytokines, high levels of TNF-α expression have been reported at mRNA [30] and protein [31] level in HMF. Furthermore, blocking this cytokine promotes CTCL progression in patients [32].

Tumor Infiltrating Lymphocytes (TILs), particularly CD8+ cytotoxic T-cells, have a major role in cancer prognosis in general, and specifically in classic MF [33]. CD8+ cytotoxic T-cells produce a set of molecules that have an effect on tumor cells, and several of these molecules have been assessed in HMF. Specifically, it has been reported that TILs in HMF samples express: T-cell intracytoplasmic antigen 1 (TIA1) [34], a cytotoxic molecule constitutively expressed by CD8+ cytotoxic cells; granzyme B [31], a serine protease which induces apoptosis on its target cells; and granulysin [34], which is expressed by activated cytotoxic lymphocytes and NK cells. The expression of these cytotoxic molecules in HMF suggests an active antitumor immune response and indicates that this variant remains in the equilibrium phase of cancer immunoediting.

Another key player in antitumor immune response are the Tregs. Tregs inhibit natural or therapeutic immune response against tumors and can be identified by their immunophenotype CD4+ CD25+ FOXP3+ [27]. Lower number of infiltrating Tregs have been found in HMF, when compared to classic MF [34], suggesting an active antitumor response. The question remains how HMF patients maintain a controlled antitumor immune response.

3.3 Hypopigmented Mycosis Fungoides characteristics as a result of an active antitumor immune response

HMF has its own set of clinical characteristics. Current evidence suggests several of them can be partially understood within the scope of an active antitumor immune response. In the current publication, we have addressed three characteristics: 1. Hypopigmentation, 2. Earlier age of onset and 3. Overall favorable prognosis.

We have hypothesized that reactive CD8+ cytotoxic T-lymphocytes are causing damage and alteration of melanocyte function and differentiation, impacting two melanocyte pathways: the pathway activated by basic fibroblast growth factor (bFGF) and the pathway activated by the stem cell factor (SCF) (i.e., c-kit ligand). Under normal circumstances, both pathways result in melanocyte growth and survival [6]. When compared to MF, a decreased expression of molecules within these pathways have been reported in HMF. HMF has lower levels of expression of bFGF mRNA [30] and CD117, tyrosinase, MART-1/melan-A [6][35], gp100 [35], and MiTF [6] proteins, leading to hypopigmentation. Furthermore, an association between low levels of bFGF mRNA and increased TNF-α in stage I HMF patients has been stablished [30] indicating a likely impact of this Th1 cytokine on hypopigmentation. Indeed, skin hypopigmentation or in other cases, depigmentation, can be associated with inflammatory/autoimmune diseases such as Darier disease, vitiligo [36] and with immune-related adverse events in cancer patients receiving immunotherapy [37][38]. Notably, re-pigmentation in HMF patients after treatment is commonly reported [6], suggesting that the depletion of malignant T-cells allows the re-establishment of functional melanocyte activity.

Childhood/juvenile MF is not common and it ranges from 2.7% to 16.6% of all MF cases and HMF is commonly overrepresented in pediatric case series [39][40][41]. In general, elderly patients' immune system is declining due to immunosenescence. Among the signs of immunosenescence, a declining adaptive immune response and a decreased number of CD8+ cells make the elderly individuals susceptible to deleterious changes that may enable carcinogenesis [42].

It has been consistently reported that HMF has a better prognosis than classic MF [6]. Among all HMF cases reported, we have identified that the majority with an immunophenotype other than CD8+ presenting with early (≤IB) disease still demonstrated a favorable prognosis, where disease remained in early stages. This indolent nature of HMF is seen regardless of the cell immunophenotype of the infiltrating malignant T-cells. Thus, we conclude that the differential behavior of HMF is not associated with the cell immunophenotype of the malignant T-cells. Furthermore, mixed MF (hypopigmented lesions in addition to other types of lesions) also has a better prognosis when compared to classic MF. African-American and dark-skinned patients with hypopigmented lesions

in general have a longer overall survival rate [43]. Therefore, hypopigmentation alone may be viewed as a favorable prognostic marker [44].

4. Conclusions

Different clinical features of conventional Alibert-Bazin MF *vs.* HMF can be explained by the presence of active antitumor immune response in younger individuals, who have not experienced immunosenescence. In particular, HMF in juvenile/adolescents and young adults remains in the equilibrium phase of cancer immunoediting. Several lines of evidence support this hypothesis: the immunopathogenesis of MF implies the activation of the cytotoxic immune response; the three phases of cancer immunoediting have been identified with specific cellular and cytokine profiles, where HMF was shown to have a higher expression of TNF-α the Th1 cytokines associated with the equilibirum phase. Moreover, HMF TILs express cytotoxic molecules such as TIA1, granzyme B, and granulysin and a lower Treg infiltration that together support the notion of an active antitumor immune response. Furthermore, we propose that hypopigmentation in HMF is a marker for an active antitumor immune response, and therefore a favorable prognostic indicator.

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