

## Alopecia in Lymphomas

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### Abstract

Abnormal hair development and regeneration occurs in some skin diseases, including lymphomas when hair follicles are eliminated. Otherwise, neoplastic cells, both malignant and benign, local occurring and metastatic, can cause alopecia of the scalp. In lymphomas alopecia can develop due to direct infiltration by the disease, or it may be a secondary or paraneoplastic manifestation. Total -body hair loss can be diagnosed only in those with generalized erythroderma in mycosis fungoides and Sézary syndrome. Patchy alopecia clinically identical to alopecia areata is revealed in 34% patients suffering from mycosis fungoides or Sézary syndrome. Discreet patch/plaque or follicular lesions is observed within mycosis fungoides lesions in 66%. The involvement of hair follicles usually presents in folliculotropic mycosis fungoides. 65% of patients have alopecia. Follicular mucinosis is frequent in folliculotropic mycosis fungoides. Alopecia is also observed in ichthyosiform mycosis fungoides, syringotropic cutaneous T-cell lymphoma panniculitis-like T-cell lymphoma, primary cutaneous follicle center lymphoma Occipital alopecia areata, occipital and parietal alopecia were observed in B- cell lymphoma. Alopecia is a rare manifestation of Hodgkin's disease. Alopecia may develop due to therapy and can be even a sign of therapeutical efficacy.

**Keywords:** Alopecia areata; Lymphomas; Hair follicles; Mycosis fungoides

### Introduction

Neoplastic cells, both malignant and benign, local occurring and metastatic, can cause alopecia of the scalp. The infiltration of neoplastic cells is sometimes not florid; a condition known as "Scalp Alopecia due to a Clinically Unapparent or Minimally Apparent Neoplasm" (SACUMAN). Neoplastic cells can destroy hair follicles by inducing inflammatory mediators, attracting inflammatory cells and/or replacing normal cellular populations. The infiltrative nature of such alopecia can be unapparent or only minimally apparent. The most common neoplasm in which an uncomplicated, minimally or unapparent scalp alopecia occurs and no infiltrate of cancer is suspected is metastatic breast carcinoma. Other causes include squamous and basal cell carcinomas, angiosarcoma, gastric carcinoma, placental site trophoblastic tumor, and mycosis fungoides. In lymphomas alopecia can develop due to direct infiltration by the disease, or it may be a secondary or paraneoplastic manifestation [1].

### Alopecia in Mycosis Fungoides and Sézary Syndrome

The most frequent cutaneous lymphomas may be accompanied by different types of alopecia. Total -body hair loss can be diagnosed only in those with generalized erythroderma in mycosis fungoides and Sézary syndrome. Patchy alopecia clinically identical to alopecia areata is revealed in 34% patients suffering from mycosis fungoides or Sézary syndrome. Discreet patch/plaque or follicular lesions are observed within mycosis fungoides lesions in 66% [2,3]. Extremely rare ocular structures may be involved a 33-year-old woman who had received therapy for mycosis fungoides on the trunk for 11 years, presented to the clinic with new plaques and tumors on her eyebrows and eyelid margin, and alopecia of her eyelashes and eyebrow. The histopathological examinations supported the diagnosis of mycosis fungoides. There was no intraocular involvement with tumor [4].

On the other hand, no less than 21% patients with Sézary syndrome suffer from alopecia. Generalized alopecia is an additional symptom associated with Sézary syndrome [5,6].

So, alopecia areata & generalized alopecia are described in mycosis fungoides and Sézary syndrome.

### Hair Loss in Folliculotropic Mycosis Fungoides

The involvement of hair follicles usually presents in folliculotropic mycosis fungoides. The morphologic spectrum of lesions is broad and includes erythematous papules and plaques with follicular prominence with or without alopecia; comedonal, acneiform, and cystic lesions; alopecic patches with or without scarring; and nodular and prurigo like lesions. 65% of patients had alopecia, which in 71% of cases involved the face. Severe pruritus was seen in 68% of patients [7]. 2 adult patients who presented with alopecia and disseminated follicular erythematous papules, comedones and cysts were described. In both patients, histology showed a folliculotropic infiltrate of atypical lymphocytes that spared the epidermis, in the absence of follicular mucinosis. Molecular genetic analysis confirmed the oligo/monoclonal nature of the T-cell infiltrate [8].

Folliculotropic mycosis fungoides is associated with a worse prognosis than classical mycosis fungoides. There was reported a case of a patient with folliculotropic (stage IIA) who progressed to develop Sézary syndrome, stage IVB, over 6 years. A 40-year-old man presented with pruritic plaques affecting his head and trunk, characterized by follicular plugging. The histology was consistent with folliculotropic mycosis fungoides and T-cell gene analysis studies revealed a T-cell clone in the skin only. His condition gradually deteriorated and 5 years after presentation, T-cell gene analysis studies revealed the presence of a clone in the blood identical with that seen in the skin. His condition progressed with the development of erythrodermic disease and a leukaemic blood picture and he subsequently died of systemic nodal and visceral involvement [9].

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Juvenile folliculotropic and Ichthyosiform mycosis fungoides was described in a 15-year-old boy. The patient presented with a 5-year history of enlarging pruritic plaques on the forehead and back, patchy alopecia and generalized ichthyosis. Histology of the forehead and back showed a dense, lymphocytic, folliculocentric and perivascular infiltrate of predominantly CD4+ positive T cells consistent with folliculotropic mycosis fungoides. Histological examination of biopsies from ichthyotic skin found similar features [10].

In another case ichthyosiform mycosis fungoides with alopecia and atypical membranous nephropathy was described. The diagnosis was made based on the following findings: generalized ichthyosis-like eruption, alopecia, enlarged superficial lymph nodes, proteinuria, and hematuria, the histological features of the skin biopsy from both ichthyotic and alopecic lesions with immunohistochemical staining, and the renal biopsy examination with immunofluorescence. The histological examination of ichthyotic and alopecic lesions displayed a predominant infiltration of atypical lymphocytes in the upper dermis with the characteristics of epidermotropism and folliculotropism. Immunohistochemical studies demonstrated that most infiltrated atypical lymphocytes were CD3, CD4, and CD45RO positive, whereas negative for CD5, CD7, CD20, CD30, and CD56. A renal biopsy examination revealed atypical membranous nephropathy with deposition of immunoglobulin G (IgG), IgM, IgA, C1q, and C3 [11].

Granulomatous mycosis fungoides presenting as an acquired ichthyosis was described in 69-year-old man. The patient presented with a 3-month history of unexplained fevers and malaise that developed generalized pruritus, alopecia and an ichthyosiform erythematous eruption on his forearms, legs, chest and back. Skin histology, immunophenotyping and molecular features were consistent with granulomatous mycosis fungoides [12].

Histologically, the quintessential finding in follicular mycosis fungoides is small to medium atypical CD3+ CD4+ CD8- T lymphocytes around and within the epithelium of the hair follicles. Immunohistochemistry of all cases uniformly show a CD4+ T cell infiltrate [13].

The cases presented multivariant clinical features of folliculotropic mycosis fungoides. Both generalized hair loss and alopecia areata with or without scarring are observed in this form. The involvement of hair follicles may be combined with different clinical signs, such as disseminated follicular erythematous papules, and comedones and cysts, systemic nodal and visceral involvement, generalized ichthyosis, atypical membranous nephropathy, unexplained fevers, malaise and pruritus.

### **Alopecia Mucinosa as a Morphologic Manifestation of Mycosis Fungoides**

Follicular mucinosis is frequent in folliculotropic mycosis fungoides. It was found that the folliculotropic variant of mycosis fungoides appeared more commonly to have an aggressive course than classic mycosis fungoides [14].

A patient with an aggressive folliculotropic variant of mycosis fungoides was described. Clinical manifestation initially presented as follicular mucinosis with alopecia. One month after the diagnosis of follicular mucinosis, a diagnosis of mycosis fungoides was made, and 3 months later inguinal lymph node involvement with mycosis fungoides developed. A skin biopsy specimen demonstrated prominent follicular mucinosis with folliculotropism of atypical cells and intrafollicular Pautrier's micro abscesses. The case is another confirmation of the

point of view that follicular mucinosis can be a presenting sign of rapidly progressive mycosis fungoides [15].

Mycosis fungoides associated with follicular mucinosis commonly pursues an aggressive course, often undergoing large-cell transformation, which is associated with resistance to therapy and poor prognosis [16-18]. The findings in sections of tissue cut from 54 biopsy specimens taken from 45 patients, clinico-pathologic correlation of lesions were behind the affirmation that so-called alopecia mucinosa is but one of many morphologic manifestations of mycosis fungoides [19].

In examining 40 children with a clinical diagnosis of alopecia mucinosa/follicular mucinosis was diagnosed 6 months after diagnosis of alopecia mucinosa/follicular Mucinosis in one patient.) In patients with mycosis fungoides the sign seems to be more frequent. Histopathologic examination showed folliculotropism in 28 patients (90%) and epidermotropism in 15 (48%). Twelve cases fulfilled the International Society of Cutaneous Lymphomas (ISCL) diagnostic criteria for early mycosis fungoides. The histopathologic findings were typical of mycosis fungoides in only in two of these cases. T-cell receptor gene rearrangement was positive in 3 of 6 (50%) of tested samples, one in a patient who fulfilled the ISCL criteria for early mycosis fungoides [20].

In another case, 12-years old patient was described. The boy presented an 8-month history of erythematous mucinous plaques on the scalp. Three months later, he developed erythematous patches and plaques on his whole body, accompanied by cervical lymphadenopathy. A biopsy showed follicular mucinosis and epidermotropism of the lymphocytic infiltrate. Immunophenotyping and a PCR clonality test were consistent with CTCL [21].

In 2 cases mycosis fungoides developed 4 and 8 years after the diagnosis of alopecia mucinosa had been made [22]. It was found out that no single, indisputable feature can reliably differentiate primary (idiopathic) follicular mucinosis from lymphoma-associated follicular mucinosis and a considerable overlapping among the two groups exists, the use of multiple clinical, histological and immunopathological criteria associated with gene rearrangement analysis can be useful in evaluation of these patients [23].

So, alopecia mucinosa as a morphologic manifestation of mycosis fungoides and any patient suspicious for the diagnosis needs thorough examination.

### **Alopecia in Other Types of T-Cell Lymphomas**

The development of alopecia may be observed not only in most frequent types of T- cell cutaneous lymphoma. Syringoma-like proliferations can underlie alopecia in neoplasms [1]. The association of syringolymphoid hyperplasia with alopecia and mycosis fungoides was described. Follicular mucinosis is not a common sign in these cases. Although syringolymphoid hyperplasia can be idiopathic, it can also reflect a syringotropic cutaneous T-cell lymphoma. Careful follow-up with a biopsy of persistent lesions is recommended to evaluate for the presence of lymphoma [24].

Syringotropic cutaneous T-cell lymphoma mainly occurs in men, but a woman who suffered from with erythroderma, cutaneous nodules, poikilodermatous patches, widespread alopecia and lymphadenopathy was described [25].

Panniculitis-like T-cell lymphoma clinically manifested as alopecia was reported. A 45-year-old woman presented with multifocal scalp

lesions with the clinical impression of alopecia areata. Histological findings first suggested cytophagic histiocytic panniculitis; although a 'burned-out' panniculitis-like T-cell lymphoma could not be excluded. After a 20-month follow-up period, assessment of the T-cell receptor gamma-chain gene rearrangement verified the diagnosis of subcutaneous panniculitis-like T-cell lymphoma [26].

A patient who presented simultaneously with primary cutaneous follicle center lymphoma of the face and scalp and alopecia areata of the scalp and beard bearing a clonal T-cell receptor gene rearrangement was reported [27]. Later primary cutaneous follicle centre cell lymphoma of the scalp presenting with scarring alopecia was described [28].

So, alopecia areata can develop in ichthyosiform mycosis fungoides, panniculitis-like T-cell lymphoma, and primary cutaneous follicle center lymphoma. In syringotropic cutaneous T-cell lymphoma widespread alopecia is possible.

### Alopecia in B-Cell Lymphoma

The hair loss in B- cell lymphoma is known as well. Alopecia areata was observed in a patient with diffuse large B-cell lymphoma. The involvement was presented with rectangular-patterned occipital alopecia areata [29]. The case of a 44-year-old man with a primary cutaneous large B-cell non-Hodgkin's lymphoma of the scalp was reported. His mother died of gastric lymphoma and his sib brother was in a 20-year remission of T-cell lymphoma. The patient presented with a 16-year history of occipital and parietal alopecia and a recently worsening scalp rash. The histopathology and immunohistochemistry indicated a bcl-6+, MUM- and bcl-2-, primary cutaneous follicle center B-cell non-Hodgkin's lymphoma, with an aggressive transformation to a diffuse large B-cell lymphoma. Bone marrow biopsy and CT chest, abdomen, and pelvis were negative for systemic lymphoma [30].

So, occipital alopecia areata, occipital and parietal alopecia were observed in B-cell lymphoma.

### Alopecia in Hodgkin's Disease

Alopecia is a rare manifestation of Hodgkin's disease. A case of Hodgkin's lymphoma, based on clinical and histopathological features was described. The pattern of hair loss was diffuse and generalized in nature involving scalp, eyebrows, axilla, and groin. Hair loss, diffuse hyperpigmentation, and generalized itching preceded other manifestations of the disease. This case highlighted the importance of keeping a high suspicion of an underlying malignancy in patients presenting with such cutaneous manifestations [31].

A case of initial alopecia areata preceded Hodgkin's disease was described. Besides hair loss, a 17-years old girl suffered from a generalized scaling skin, enlargement of the inguinal lymph nodes and severe back pain. Staging procedures revealed multifocal bone disease and generalized lymphadenopathy. The diagnosis of nodular sclerosing Hodgkin's disease was established by biopsies of the os ileum and a left inguinal lymph node. The case illustrates that alopecia areata may occur as a paraneoplastic phenomenon or an autoimmune process related to the deranged cellular immune system in children and adolescents with Hodgkin's disease [32].

The cases demonstrated the possibility of the development of both generalized alopecia and alopecia areata in Hodgkin's disease.

### Alopecia Developed due Top Treatment

On the other hand, it is well known that alopecia can develop due to the treatment. For example, there is an association between alopecia

and response to chemotherapy in patients with lymphomas. It was noted that in intensively treated patients with Hodgkin's disease, the absence of alopecia may predict a poor response to treatment [33]. In patients treated with doxorubicin-containing chemotherapy, the absence of alopecia may predict poor response to treatment along with fewer episodes of bone marrow suppression. The absence of alopecia in such patients should alert clinicians to the possibility of treatment failure [34].

Another case of a 33-year-old man in remission from Hodgkin lymphoma was described. The patient suffered from hair loss. Initial endocrine tests revealed autoimmune hypothyroidism. Hyperplasia of his pituitary gland was revealed. He tolerated replacement endocrine therapy with good response, but with no improvement in his alopecia universalis [35].

Alopecia developed in 100% patients with Burkitt's lymphoma treated by three cycles of Endoxan in association with 3 injections of methotrexate and hydrocortisone [36].

In fact the secondary alopecia due to treatment may develop in any type of lymphoma.

### Conclusion

So, alopecia can be observed in different types and stages of lymphomas. It is described in patients of different age & sex. Total-body hair loss can be diagnosed only in those with generalized erythroderma and Sézary syndrome. Patchy alopecia, discreet patch/plaque or follicular lesions may be revealed in different forms of mycosis fungoides. The hair loss usually presents in folliculotropic mycosis fungoides. 65% of patients have alopecia. Follicular mucinosis is frequent in folliculotropic mycosis fungoides. Alopecia is also observed in ichthyosiform mycosis fungoides, syringotropic cutaneous T-cell lymphoma panniculitis-like T-cell lymphoma, and primary cutaneous follicle center lymphoma. Occipital alopecia areata, occipital and parietal alopecia were observed in B- cell lymphoma.

Alopecia is a rare manifestation of Hodgkin's disease; still the cases of generalized alopecia & alopecia areata are described. Alopecia areata was reported in association with malignancy as a paraneoplastic symptom.

Secondary alopecia may develop due to therapy and can be even a sign of therapeutical efficacy.

Any type of alopecia developing in lymphoma patients is troublesome, even when it was the first clinical sign allowed to make a correct diagnosis or when it is a beneficial sign of therapy. Today, a wig is the most frequent solution. We hope that the future improvement of lymphoma treatment will be accompanied by the solution of this problem as well.

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