Original Article

The Expression of CXCR3 and CD30 in Mycosis Fungoides

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Abstract

Background: The clinical progression of mycosis fungoides (MF) often correlates with microscopic large cell transformation (LCT). It is reported that CD30 expression in the LCT of MF is associated with an absence of CXCR3 expression. This study investigates a large number of patients diagnosed with MF to determine the correlation between expression of CXCR3 and CD30 in additional sections.

Methods: The study included archival skin specimens from 101 patients with MF. We analyzed these specimens by immunohistochemistry for expressions of CXCR3 and CD30.

Results: The biopsy specimens showed microscopic features of low grade MF (LG-MF) in 80 cases and transformed MF (T-MF) in 21 cases. Tumor lymphocytes expressed CXCR3 in 61 out of 80 cases (76.3%) of LG-MF and in 10 out of 21 cases (47.6%) of T-MF. CD30 positivity (CD30+) was seen in 16 of 80 cases (20%) of LG-MF and 12 of 21 cases (57.1%) of T-MF. The tumor cells in 8 of the 12 CD30+ T-MF cases showed scattered expression of CXCR3.

Conclusion: CXCR3 expression was associated with epidermotropic T cell tumors but was greatly absent in dermal ones. Scattered or diffuse CD30 expression in T-MF was not associated with an absence of CXCR3 expression.

Keywords: CD30, cytokines, mycosis fungoides

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Introduction

Primary cutaneous lymphomas are the second most common extranodal lymphomas that primarily occur in and remain limited to the skin without detectable extracutaneous manifestation.[1] Mycosis fungoides (MF) is the most common type of cutaneous T cell lymphoma (CTCL), with a gradual clonal expansion of atypical CD3+CD4+CD8–, skin-homing T lymphocytes.[2,3] There are three classical cutaneous phases of MF: patches, infiltrated plaques, and tumors. According to Shapiro and Pinto, four histomorphologic main dominant patterns are described in MF: epidermotropic, perivascular, dermal (nodular or diffuse), and folliculocentric.[4] MF has an indolent course, so it's progression from patches to more infiltrated plaques and tumors may occur over a few years.[3] The clinical progression of MF often correlates with microscopic transformation to larger tumor cells. Transformed MF (T-MF) is a well-defined histopathological condition distinguished by the presence of large cells (four times or more the size of a small lymphocyte) exceeding 25% of the cell population of the infiltrate or forming microscopic nodules.[5]

Chemokine and chemokine receptors

Chemokines are a family of cytokines initially characterized by their ability to induce chemotaxis, or controlled leukocyte migrations. The names of the chemokines and their receptors are generally characterized by the name of their family followed by the letter "L" for ligand or "R" for receptor, and a number.[6–8]

Evidence has accumulated that interactions between chemokines and chemokine receptors are involved in migration and invasion of lymphoma cells.[9–11]

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CXC chemokines are highly expressed in the epidermis and CXCR3 is the high affinity receptor for these chemokines. They are strongly up-regulated in MF and various inflammatory skin diseases. Reactive and MF cells highly express CXCR3 in the patch and plaque stages of MF, but the absence of CXCR3 on MF cells has been reported in the more progressed stage of the disease and in tumor-stage MF, although reactive T cells continuously express CXCR3.[12–14]

It has been shown that several chemokine receptors are expressed preferentially in type 1 T helper (Th1) cells (CXCR3, CCR5) and type 2 T helper (Th2) cells (CCR3, CCR4 and CCR8). Expression of CXCR3 is highly specific for Th1, whereas CCR4 is highly specific for Th2 cells.[15]

Tumor necrosis factor (TNF) receptor super family, member 8: CD30

CD30 is a member of the tumor necrosis factor (TNF) receptor superfamily. Activated, but not resting, T and B cells express this receptor; it is a positive regulator of apoptosis. Some authors assume that CD30 is expressed on T cell clones capable of producing Th2-type cytokines, so they suggest that CD30 is a Th2 – associated antigen.[16]

Up-regulation of CD30 on Th2-type human T cells is a matter of debate. Some authors have revealed that CD30 expression does not discriminate between human Th1- and Th2-type T cells.[17]

The CD30 immunophenotype could be regarded as a useful prognostic marker in T-MF. CD30 expression appears to have a favorable prognostic significance,[18] this could be interpreted by the role of CD30 in up-regulation of Fas, death receptor 3, and TNF-related apoptosis-inducing ligand.[19] In fact, these pro-apoptotic proteins expressed in CD30+ lymphoproliferative disorders of the skin may play an important role in mediating apoptosis-linked regression in these tumors.[20]

There are some evidences of CD30 expression in non-transformed MF.[21] On the other hand, some intraepithelial lymphocytes are seen in certain cases of T-MF. Thus, study plans to investigate a larger number of patients with MF to determine the correlation

Table 1. Frequency of the sites of involvement in various types of mycosis fungoides (MF).

	Head and neck	Trunk	Upper extremity	Lower extremity	Buttocks	Total
LG-MF	2	31	9	26	12	**5**
T-MF	3	7	3	4	5	**21**
Total	**5**	**38**	**12**	**30**	**17**	**101**

LG-MF = Low grade mycosis fungoides;T-MF = Transformed mycosis fungoides.

Table 2. Frequency of microscopic patterns in various types of mycosis fungoides (MF).

	Epidermotropic	Patchy perivascular	Lichenoid	Diffuse dermal -tumoral	Total
LG-MF	33	17	26	4	**80**
T-MF	8	1	4	8	**21**
Total	**41**	**18**	**30**	**12**	**101**

LG-MF = Low grade mycosis fungoides; T-MF = Transformed mycosis fungoides.

Table 3. Comparison of CXCR3 and CD30 expression in LG-MF and T-MF in different studies published in the literature.

	Lu et al. [23]	Jones et al. [21]	Present study
CXCR3 expression in LG-MF	20/25	7/9	61/80
CXCR3 expression in T-MF	5/22	5/8	10/21
CD30 expression in LG-MF	1/19	Ne	16/80
CD30 expression in T-MF	10/18	Ne	12/21

Ne = not evaluated; LG-MF = Low grade mycosis fungoides; T-MF = Transformed mycosis fungoides.

between expression of CXCR3 and CD30 by additional sections.

Materials and Methods

Skin biopsies, patients' characteristics and diagnosis

The study included archived skin specimens from patients with MF at Razi Hospital, Tehran University of Medical Sciences, Tehran, during the period March 2006 to March 2009. The cases included 70 patients with single biopsies, 30 patients with multiple concurrent specimens and 1 patient with 4 follow up biopsy samples over a period of 20 months. Thus, a total 138 MF samples from 101 patients were included in this study. The diagnosis of MF was based on clinical criteria, in addition to microscopic and immunohistochemical analyses of formaldehyde-fixed, paraffin-embedded skin specimens according to the WHO-EORTC classification for cutaneous lymphomas.[3] Patients on systemic therapy in the 6 months preceding study entry were excluded. Large tumor cells were defined as having nuclei that were larger than the size of adjacent histiocyte nuclei, with or without prominent nucleoli. Cases with more than 25% large tumor cells or those which formed microscopic nodules were defined as T-MF. Cases were categorized according to their predominant microscopic patterns as epidermotropic, dermal-epidermal interface, perivascular, or diffuse dermal (i.e., tumor stage) with extension into the deep dermis or subcutis.

Immunohistochemistry

Skin biopsy specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, and 5 µm sections were prepared. Rabbit anti-human antibodies directed against the chemokine receptor CXCR3 (GPR9, Chemicon) and CD30 (BerH2, Dako) were tested for all cases. Before staining, deparaffinized sections were antigen retrieved by immersing the sections in 95°C heated DAKO target retrieval buffer, code S1700, in a water bath for 20 minutes, and the antibodies were detected by EnVision Detection System, Peroxidase/DAB+ (Dako). The specificity of the CXCR3 antibody was tested by sections of normal lymph nodes that were used as positive and negative controls.

Cell membrane staining for CXCR3 was scored as: absent; focal (fewer than 5% positive tumor cells); scattered (5% to 50% positive cells); and diffuse (more than 50% positive cells). Cytoplasmic or cell membrane staining for CD30 was semiquantitatively scored by these criteria: absent; focal (fewer than 5% positive cells), scattered (5% to 20% positive cells), or diffuse (more than 20% positive cells).

Results were analyzed by the chi-square test for calculation of *P* values. For the purpose of statistical analysis, focal and absent were grouped as negative, whereas scattered and diffuse were grouped as positive.

Results

Clinical and microscopic findings in patients with MF

Patients with MF included 47 males and 54 females whose median age at the time of initial biopsy was 45 years (range: 12 – 83 years). The sites of involvement of the tumor have been listed in Table 1.

Biopsy specimens showed the characteristic microscopic features of small cell or low grade MF (LG-MF) in 80 cases and T-MF in 21. The cases of LG-MF had an epidermotropic microscopic pattern in 33 cases, a perivascular pattern in 17, a lichenoid-interface pattern in 26, and a diffuse dermal–tumor stage pattern in 4. Concurrent follicular infiltration was seen in 12 cases. The predominant pattern in the 21 T-MF cases was the diffuse dermal–tumor stage in 8 cases, epidermotropic in 8, perivascular

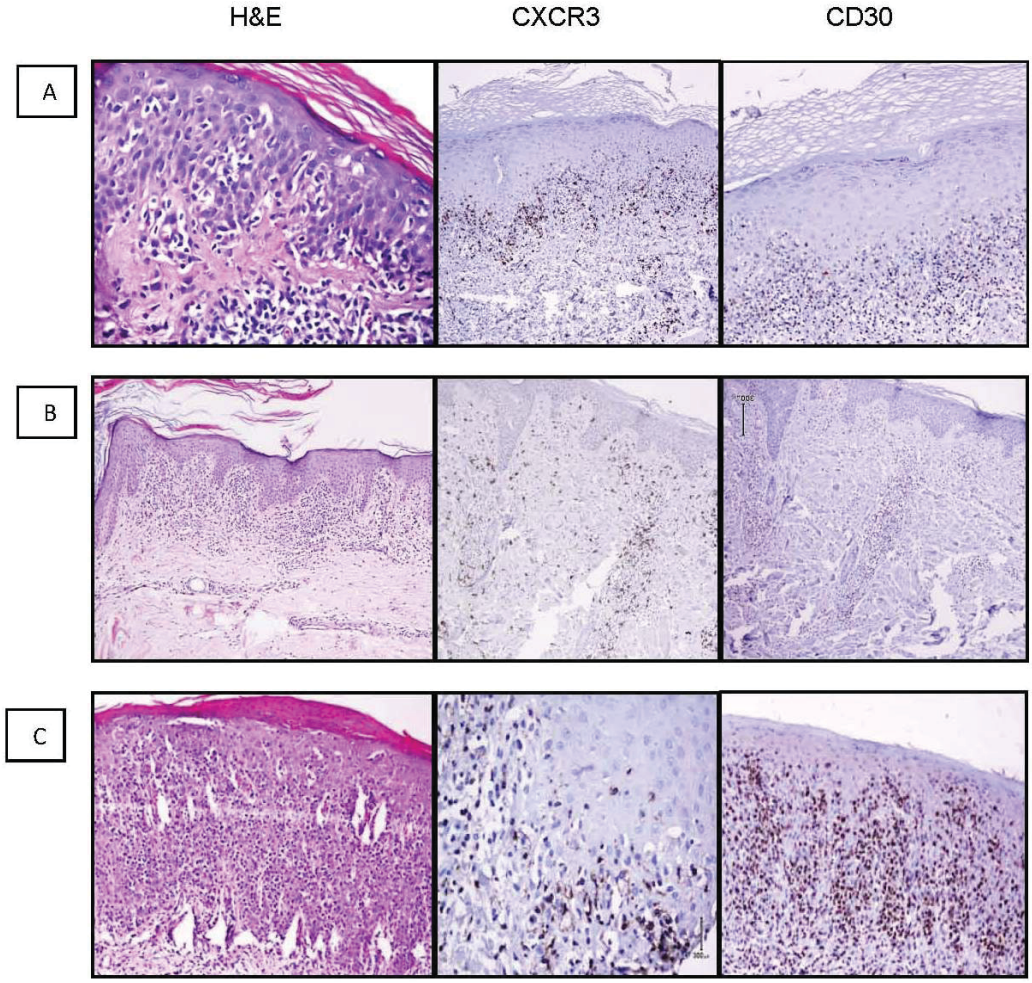

Figure 1. Expression of CXCR3 and CD30 in low-grade and transformed mycosis fungoides (MF). A) Low grade MF with infiltration of the epidermis by small, irregular lymphocytes (H&E, 400x). CXCR3 is expressed in nearly all epidermotropic and superficial dermal T cells (IHC DAB staining, 100x). CD30 is expressed in less than 5% of lymphocytes. (IHC DAB staining, 100x) B) Expression of CXCR3 is seen in perivascular low grade MF; CD30 is negative (IHC DAB staining, 100x). C, Transformed MF with an epidermotropic pattern (H&E, 100x). CD30 is positive in nearly all large, transformed cells (IHC DAB staining, 100x). Scattered CXCR3 expression is seen largely in epidermotropic lymphocytes (IHC DAB staining, 400x).

in 1, and lichenoid-interface in 4 (Table 2). Co-existing follicular infiltration was seen in 6 cases. The diagnosis of 18 cases of MF in the absence of epidermotropism was established based on earlier biopsy specimens that were included in this study.

Expression of CXCR3 in MF

According to immunohistochemical staining of the MF specimens, membrane or cytoplasmic expression of CXCR3 was noted in the lymphocytes. Focal, weak staining was also seen in some adnexal structures.

Some differences were evident in CXCR3 expression between LG-MF and T-MF. A subset of tumor lymphocytes showed CXCR3 expression in 61 cases of LG-MF. 10 out of 21 cases of T-MF showed staining for CXCR3, largely in the small cell population. There were some associations between CXCR3 expression and LG-MF, and between minimal or no expression of CXCR3 and T-MF ($P = 0.01$).

CXCR3 expression in various microscopic patterns of MF

Cases of LG-MF showed diffuse CXCR3 expression in the epitheliotropic lymphocytes in the epidermis and hair follicles (Figure 1–A). In 21 out of 33 LG-MF cases that were predominantly epidermotropic CXCR3 was diffusely expressed. In addition, 5 of 17 predominantly perivascular LG-MF cases also diffusely expressed CXCR3 (Figure 1–B). The lichenoid pattern and diffuse dermal pattern of MF showed variable CXCR3 staining; most of the CXCR3 expression was found in the folliculocentric components.

There were 10 cases of T-MF that retained variable CXCR3 expression in a combination of small and large cells. 6 out of 8 cases of predominantly epidermotropic type of T-MF showed CXCR3 expression largely in the epidermotropic, large tumor cells in epidermis and hair follicles (Figure1–C).

Expression of CD30 in MF and correlation between expression of CXCR3 and CD30

The level of CXCR3 expression was compared with expression of CD30 in T-MF cases. The staining pattern of CD30 was either the membrane or cytoplasmic pattern. A total of 64 out of 80 LG-MF cases were negative and 16 were diffuse or scattered for CD30. In T-MF cases, 12 out of 21 showed diffuse or scattered CD30 expression. The tumor cells in 8 of the 12 CD30+ T-MF

cases showed scattered expression of CXCR3, in 5 cases CXCR3 expression was limited to the epidermotropic large CD30+ tumor cells. Thus, scattered or diffuse CD30 expression in T-MF was not associated with an absence of CXCR3 expression.

Discussion

MF is a type of cutaneous lymphoma characterized by gradual clonal expansion of atypical CD3+CD4+CD8–, skin-homing T lymphocytes that leads to the clinical presentation of 'patches' in the affected skin. Progression of these patches to plaques and dermal-based tumors may occur over years and is correlated with a microscopic transformation to larger tumor cells.[12] The occurrence of large cell transformation (LCT) in MF is pathologically characterized by the morphologic change of small- to medium-sized cerebriform cells to a large cell variant, at least four times greater in size than a small lymphocyte.[5]

In this study, we observed that CXCR3 expression was evident in 76% of LG-MF cases and 47% of T-MF cases. In addition, we found that CD30 expression was positive in 20% of LG-MF cases and 57% of T-MF cases. Also noted was a converse correlation between CXCR3 expression and the transformation to large cell MF. Furthermore, we observed a direct correlation between CD30 expression and the same transformation, which we expected. However, we did not see a significant correlation between the absence of CXCR3 expression and CD30 expression in LCT of the MF cases.

The expression of CXCR3 in CTCL has been reported previously. It was seen in angioimmunoblastic lymphoma, angiocentric lymphoma, peripheral T cell lymphomas, unspecified, and typically in small T cells.[22,23]

We observed a higher proportion of CXCR3 expression in the epidermotropic and the folliculocentric subtypes of MF, which was similar to previous reports.[24] Lu and colleagues showed that CXCR3 expression was absent in the cases of histologic transformation to large cell MF, which agreed with our observations.[24] A plausible explanation could be that the transformed cells have failed to express CXCR3. This would further lead to decreased chemotaxis of the lymphocytes into the epidermis via the ligands Mig, IP-10, and I-TAC, which are highly expressed in the epidermis and are functionally active in a wide subset of T cells.

On the other hand, down-modulation of CXCR3 surface expression and function in CD8+ T cells was shown in a study of advanced CTCL that was associated with selective and efficient inactivation of CXCR3-dependent T cell migration.[25]

It has been reported that LCT is associated with CD30 expression and loss of epidermotropism,[24] which agreed with our study in which a higher proportion of T-MF cases with positive CD30 expression was noted. It could be due to that Th2-type inflammatory states are associated with an increase in CD30-positive cells and circulating soluble CD30 levels.[22] Since the Th2-like T cells have been demonstrated to be similar to CD30-positive anaplastic large cell lymphoma,[22] our observations seem rational.

Although we could not detect any correlation between CXCR3 and CD30 expression, it is reported to be negatively correlated.[22,25] Since the study results seem to be controversial, further studies are necessary to reveal if any true correlation does exist.

Jones et al. also noted that there was a highly significant association between CXCR3 expression in low-grade MF but not in large-cell transformation of MF (Table 3). Tumor cells in large-cell transformation of MF were also positive for both CCR4 and CD30; however, the correlation between expression of CXCR3 and CD30 was not evaluated in this study.[22]

Preferential expression of CXCR3 in epidermotropic tumor cells and of CCR4 in dermis-based CTCL has been demonstrated previously by Yagi et al. They showed that tumor cells in MF constantly expressed CXCR3 at the patch stage, CXCR3 and/or CCR4 at the plaque stage, and CCR4 at the tumor stage and in the folliculotropic variant of MF.[10]

Some authors have proposed that peripheral T cell lymphomas could be subdivided based on the expression of markers of Th1 versus Th2 differentiation, including CXCR3, CD134/OX40 and CCR4, CD30 respectively.[26,27] Others have noted CD30 expression on Th0-, Th2-, and Th1-type clones.[17] By simultaneous measurement of membrane phenotype and cytokine production, they showed that CD30-expressing cells can produce IFN-gamma.

Pellegrini and colleagues have demonstrated that CD30 signals trigger mechanisms that might regulate the physiological balance between Th1 and Th2 functions by integrating Th1 and Th2 specific cytokine production. They have concluded that CD30 antigen is not a physiological marker for Th2 cells, but could be a marker for an immunoregulatory subpopulation.[28]

Modulation of Th1- and Th2-associated markers is an important therapeutic model for controlling MF.[29–32] More studies for markers of Th1 and Th2 differentiation could be helpful for prognostic and therapeutic purposes, particularly for MF.

Our study did have some limitations: a) we did not obtain sequential specimens from all of our patients to study the changes of expressions during disease progression; b) we did not study some of the important chemokines such as CCR4 and CCR5; and c) we did not follow up our patients to determine if the expressions were correlated with the disease prognosis.

In conclusion, although it seems that CXCR3 chemotaxis plays a role in the disease progression of MF cases, its exact role in localization and LCT of the tumor cells is not rigorously evident. Thus, further studies with higher standards that include sequential biopsies and complete chemokine profile analyses seem to be indispensable.

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