CXCR3 and CCR4 double positive tumor cells in granulomatous mycosis fungoides

To the Editor: Granulomatous mycosis fungoides (GMF) is a rare histologic variant of cutaneous T-cell lymphoma (CTCL) and demonstrates the histological feature of mycosis fungoides (MF) admixed with giant cells and collections of epithelioid histiocytes within the infiltrates. Although the histopathogenesis or immunopathogenesis of GMF remains unfully elucidated, granulomas can be induced by Th1 or Th2 cells. We present a case of GMF with tumor cells expressed both Th1 and Th2 chemokine receptors.

A 55-year-old Japanese male presented with a 3-year history of a giant tumor on his right thigh. Clinical examination revealed a large reddish tumor on the posterior aspect of the right thigh and grouped nodules on the popliteal region of the right knee (Fig 1, A). Laboratory examination showed normal leukocyte counts (6400/µl) and neither atypical mononuclear cells nor Sézary cells were present on the blood film. The serum value of lactic dehydrogenase was not elevated and soluble interleukin (IL)-2 receptors were within normal limits. Neither lymphadenopathy nor splenomegaly was found on the computed tomodensitometry or whole-body gallium scan.

A biopsy specimen showed a large number of atypical lymphocytes with hyperchromatic, convoluted nuclei infiltrated in the epidermis to the subcutaneous fat, and exhibited epidermotropism, forming occasional Pautrier’s microabscesses (Fig 1, B). In addition, there were prominent collections of histiocytes and Langhans- or Touton-type multinucleated giant cells without central necrosis throughout the dermis, and atypical lymphocytes were also present inside the cytoplasm of these giant cells (Fig 1, C). Double-color immunofluorescence staining showed the tumor cells were positive for both CXC chemokine receptor 3 (CXCR3) and CC chemokine receptor 4 (CCR4; Fig 1, D-F). A flow cytometric analysis of tumor cells isolated from the skin tumor

**Fig 1.** A, Large reddish tumor on the posterior aspect of the right thigh. B, Atypical lymphocytes infiltrating the upper dermis and forming Pautrier’s microabscesses. C, Atypical lymphocytes present inside the cytoplasm of multinucleated giant cells. D and E, Atypical lymphocytes infiltrating the epidermis or upper dermis are positive for both CXCR3 and CCR4. F, Parts D and E are merged into one photograph. G and H, Flow cytometric analysis of tumor-infiltrating lymphocytes, expressing both CCR4 and CXCR3. (B and C, Hematoxylin–eosin stain; original magnifications: B, ×200; C, ×400; D, ×200; E, ×200; F, ×200.)
also demonstrated that CD4⁺ cells highly expressed both CCR4 and CXCR3 (Fig 1, G and H), confirming the dual expression of these chemokine receptors. A standard Southern blot analysis of DNA extracted from the tumoral lesion exhibited monoclonal rearrangement of T-cell receptor Cβ1.

To address Th1 or Th2 polarization, we measured serum Th1 and Th2 chemokine concentrations in a comparison with 5 ordinary MF patients and 3 normal healthy controls. The levels of Th2 chemokines, thymus and activation-regulated chemokine (TARC), and macrophage-derived chemokine (MDC), were slightly higher in our patient than the control group, but lower than ordinary MF (Fig 2, C and D). While the interferon-γ (IFN-γ), inducible protein 10 (IP-10), and monokine induced by IFN-γ (MIG) levels in the ordinary MF patients were higher than those in the controls, our patient had low levels of these Th1 chemokines (Fig 2, A and B). Thus, both Th1 and Th2 chemokines were low in our patient.

A recent study has revealed that MF malignant T cells express CCR4, and the serum level of its ligand TARC fluctuates in parallel with the disease activity, suggesting that CCR4 and its chemokines are key molecules in MF.5 On the other hand, CXCR3 is also substantially expressed on both tumor cells and surrounding reactive T cells in the early patch and plaque stages or low-grade of MF.6-8 It is reported that CXCR3⁺ and CCR4⁺ cells are non-polarized T cells.5 Our case exhibited dual positivity for CXCR3 and CCR4, and neither Th1 nor Th2 chemokines were high in the patient’s sera as compared to the ordinary MF patients, suggesting nonskewed production of Th1 or Th2 chemokine in the skin milieu or other organs. It is possible that the non-Th2 polarization is associated with the extraordinary granuloma-forming nature.

Takatoshi Shimauchi, MD
Kenji Kabashima, MD
Yoshiki Tokura, MD
Department of Dermatology
University of Occupational and
Environmental Health
Kitakyusyu, Japan

The authors have no conflicts of interest to disclose.

Correspondence to:
Shimauchi Takatoshi, MD
Department of Dermatology
University of Occupational and
Environmental Health
1-1, Iseigaoka, Yahatanishi-ku
Kitakyusyu, 807-8555, Japan
E-mail: t-sbima@med.uoeb-u.ac.jp

REFERENCES

doi:10.1016/j.jaad.2006.02.012

Cutaneous involvement by Burkitt lymphoma

To the Editor: Burkitt lymphoma is a poorly differentiated B-cell lymphoma induced by deregulation of the c-myc protooncogene. Endemic, or African, Burkitt lymphoma is most often associated with Epstein–Barr virus (EBV) infection. Sporadic Burkitt lymphoma is less closely associated with EBV and is one of the most common lymphomas arising in patients with AIDS. Rarely, however, does this tumor localize to the skin. We report a case of Burkitt lymphoma that arose in the skin shortly after biopsy and excision of nodal Burkitt lymphoma.

A 50-year-old white male with a medical history significant for AIDS and chronic hepatitis B infection presented with left inguinal adenopathy of 4 months' duration. There were no overlying skin changes. Subsequent medical work-up included needle biopsy, followed by excisional biopsy of the left inguinal nodes. Results of routine histology, immunohistochemistry, cytogenetics, and fluorescent in-situ hybridization (FISH) studies were all consistent with a high-grade lymphoma of the atypical Burkitt type (Fig 1). The patient presented to us 3 weeks after excisional biopsy with an indurated and nodular plaque, roughly 12 cm × 7 cm, extending from the visible healing cicatrix in the left inguinal region (Fig 2, A). In addition, there were also several erythematous nodules 3 cm laterally, as well as an ecchymotic, indurated, erythematous plaque 11 cm distally on the anterior thigh.

Hematoxylin–eosin stained sections revealed an atypical lymphohistiocytic infiltrate in the dermis and subcutaneous fat (Fig 2, B). The epidermis was uninvolved. This dermal infiltrate was primarily nodular, focally interstitial, and surrounded blood vessels and adnexal structures. It was comprised of medium-sized, fairly monotonous lymphoid cells with round nuclei, dispersed chromatin, and occasional prominent basophilic nucleoli. The nuclei were surrounded by a rim of deeply basophilic cytoplasm, and mitoses were common. Similar cells were present in the subcutaneous fat, primarily within lobules, but also in the interlobular septa. The classic “starry sky” pattern, an effect of benign histiocytes engulfing apoptotic tumor cells, could be seen focally in the dermis. CD20 and CD10 immunohistochemical stains marked the tumor cells. Ki67, a proliferation marker, decorated the nuclei of more than 80% of the neoplastic cells.

The biopsy results coupled with the patient’s clinical history strongly support our opinion that these lesions represent cutaneous involvement by Burkitt lymphoma. Cutaneous lesions of Burkitt lymphoma appear only rarely.1-3 A case similar to ours has been reported involving the thigh of a 43-year-old male. In that patient, cutaneous involvement was noted several months after excisional biopsy of a left inguinal lymphoma.4 In our case,