

# Epidermotropic CXCR3 positive marginal zone lymphoma: a distinctive clinical histopathological entity potentially originating in the skin; it does not always indicate splenic marginal zone lymphoma

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## Abstract

Epidermotropic B cell lymphoma represents a rare form of marginal zone lymphoma presenting as a disseminated skin rash resembling pityriasis rosea. To date there are 8 reported cases. In addition to the widespread nature of the skin rash, there is a proclivity for spleen and bone marrow involvement raising consideration regarding its categorization as a systemic lymphoma. We present an 89-year-old man with epidermotropic B cell lymphoma, who presented with a pityriasis rosea-like skin rash. An initial diagnosis of diffuse large cell B cell lymphoma was made based on the extent of dermal-based large cell infiltration. However, after recognizing the epidermotropic component and the distinctive clinical presentation, a diagnosis of epidermotropic B cell lymphoma was rendered. There was minimal bone marrow involvement based only on flow cytometric analysis, but there was no apparent bone marrow or splenic involvement on routine light microscopic assessment. Remission was achieved with single agent rituximab chemotherapy and the patient remained symptom free. The neoplastic CD20 positive epidermotropic B lymphocytes expressed CXCR3. Similar to the prior reported cases by the authors, the neoplastic cells expressed CXCR3, a chemokine whose organ and tissue specific ligands could contribute to its relatively indolent clinical course.

## Introduction

Epidermotropic B-cell lymphoma (EBCL) is a very rare form of cutaneous marginal zone lymphoma (MZL) with a distinctive clinical and histopathologic presentation. This diagnosis is rarely suspected clinically and therefore familiarity with this lymphoma is imperative to allow critical and correct therapeutic interventions. Although there can be extensive clinical disease including bone marrow and spleen involvement, the prognosis appears favorable. As opposed to the other forms of cutaneous B cell lymphoma, which usually present with a solitary or few plaques and nodules, this particular form of MZL characteristically manifests in the skin as widespread papules and plaques with the individual lesions described as salmon-colored, resulting in a presentation that can simulate a reactive papulosquamous eruption [1, 2]. The eruption bears a strong clinical resemblance with pityriasis rosea. In at least one reported case the lymphoma was likely disseminating from the spleen [3], whereas in the other cases the skin involvement presaged any extracutaneous dissemination. However, it was established that there was spleen involvement in four of the cases, and bone marrow involvement in four of the cases at the time that the diagnosis was first made of epidermotropic MZL. In these cases the skin eruption had been present for a period of time ranging from months-to-years prior to a definitive diagnosis of epidermotropic B cell lymphoma. In three of the 8 cases the spleen and

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bone marrow involvement was concurrent [1, 2, 4-9]. A summary of these cases is presented in **Table 1**.

Epidermotropism, the abnormal migration of leukocytes into epithelial structures, is characteristic of cutaneous T-cell lymphoma (CTCL). The spectrum of epidermotropic disorders includes mycosis fungoides (MF), Sezary syndrome, Woringer-Kolopp disease, aggressive CD8+ epidermotropic T-cell lymphoma, gamma/delta T-cell lymphoma, lymphomatoid papulosis types B and D, and Langerhans cell histiocytosis [10]. Epidermotropism is not a feature of B cell lymphoma in general and when one encounters a CD20+ epidermotropic lymphocytic infiltrate, CD20+ mycosis fungoides becomes an important diagnostic consideration [11]. It is likely that certain acquired functional characteristics of neoplastic B cells, mirroring those seen in MF, could account for the epidermotropism. Although our case showed a conspicuous large cell infiltrate in the dermis, the epitheliotropic B cell populace was in the context of small atypical somewhat monocytoid appearing cells tagging along the dermoepidermal junction. A similar

pattern of small cell lymphocytic infiltration of the epidermis as opposed to the larger lymphoid dermal populace was also observed in the prior cases presented by the authors [1, 2]. The parallel would be MF in which the epidermotropic cell populace typically comprises smaller lymphocytes, whereas in disease progression, tumor progression and or large cell transformation, a lack of epidermotropism occurs [12].

It has been previously hypothesized that there is a specific epidermal chemoattractant in neoplastic B cells, namely the chemokine receptor CXCR3. CXCR3 expression by neoplastic T cells in the setting of mycosis fungoides has been postulated as the basis of the epidermotropism [1]. The natural ligands for CXCR3 include interferon gamma-induced protein 10 and P-9/I-TAC (interferon-inducible T-cell alpha chemoattractant) found within the keratinocytes. Interferon  $\gamma$ -induced protein 10 is also expressed by stromal cells of the spleen and bone marrow, potentially accounting for the significant risk of splenic and bone marrow involvement in this rare form of cutaneous B cell lymphoma. Given the

**Table 1.** Cases of generalized Epidermotropic B Cell Lymphoma presenting initially in the skin.

Case Ref.	Age	Sex	Skin Manifestation	Bone Marrow Involvement	Peripheral Blood Involvement	Spleen Involvement	Treatment/ Outcome
Chui et al. [9]	70	M	Abrupt PGSR	+ 7 months	-	-	Chemotherapy/ remission
Pavlović et al. [7]	56	M	1.5 ys W/W PGSR	-	-	-	Phototherapy/ remission
Chiang et al. [6]	57	M	5 year PGSR	+ 5 years	+ 5 years	+ 5 years	Phototherapy/ remission
Gómez-de la Fuente et al. [5]	68	M	1 year GSR	+ 1 year	+ 1 year	+ 1 year	Splenectomy & chemotherapy/ died from hepatitis
Lee et al. [4]	80	M	2 weeks PGSR	N/A	N/A	N/A	N/A
Magro et al. [2]	51	M	7 months GSR	+ 7 months	-	-	Chemotherapy/ remission
Magro et al. [1]	69	M	6 Months GSR	-	-	6 Months	Rituximab/ remission with decrease in spleen size
Hedayat et al. [8]	66	F	12 years w/w GSR	+ 12 years	+ 12 years	+ 12 years	None
Current case	89	M	AGSR	+ BM flowcytometry	-	-	Rituximab /remission

Abbreviations: PGSR: Pruritic generalized skin rash; W/W: waxing and waning; GSR: Generalized skin rash; N/A: Not available; AGSR: Asymptomatic generalized skin rash

frequency of extracutaneous disease, one could argue that epidermotropic MZL is a systemic lymphoma that has unique homing properties largely limiting its anatomic distribution to the skin, bone marrow, and spleen [13], organs in which there is expression of interferon  $\gamma$ -induced protein 10. We describe the ninth case, to our knowledge, of multifocal epidermotropic marginal zone lymphoma.

## Case Presentation

A previously healthy 89-year-old man presented with an abrupt onset of an asymptomatic skin eruption. It started three weeks earlier on the chest and spread to the proximal extremities and face with a daily increase in number and size of lesions. He had no constitutional symptoms.

On physical examination there were multiple non-scaly, oval and dome-shaped red papules and plaques ranging in size from 1-2.5cm on his chest, abdomen, back, face, arms, legs, palms, and soles, manifesting a pityriasis rosea-like distribution (**Figure 1A, B**). A purple plum-like nodule was also present on the left wrist (**Figure 1C**). There were no mucosal lesions or lymphadenopathy. Over the two weeks between the first and second skin biopsies he started to develop leonine facies.

The patient had two sets of biopsies with similar findings. In both, there was an extensive multinodular lymphocytic infiltrate spanning the entire dermis, exhibiting a rather orderly disposition around nerves, blood vessels, and the eccrine coils (**Figure 2A**). The typical syringoepithelial hyperplasia characteristic of syringotropic MF was

not seen. Many of the dermal lymphocytes were in the 15-20 $\mu$ m size range exceeding the size of the intraepidermal lymphocytes (**Figure 2B, C**). The nuclei were round-to-oval and reniform in shape, exhibiting a variable disposition in the cell, including an eccentrically disposed nucleus resulting in a monocytoid quality. The cytoplasm was abundant and lightly eosinophilic. There was a significant degree of histiocytic infiltration resulting in a distinct granulomatous quality to the infiltrate (**Figure 2D**). In all biopsies there was a variable interface dermatitis associated with some degree of vacuolar alteration of the papillary dermis. The lymphocytes infiltrating the epidermis were small-to-intermediate in size revealing some degree of nuclear contour irregularity, although a cerebriform appearance was not observed (**Figure 2E**). Large neoplastic cells permeating the epidermis were also not present. The intraepidermal and intrafollicular epithelial lymphocytic infiltrate, as well as the dermal component including the larger atypical cells were highlighted in part by CD20 and CD79a (**Figure 3A**). Extensive expression of BCL2 and IgG was also noted. A significant degree of T cell hyperplasia was seen as characterized by the extent of immunoreactivity of the infiltrate for CD3. The atypical B cell infiltrate was highlighted by CXCR3 (**Figure 3B**). The neoplastic cells were negative for CD56, CD10, CD30, EBV-encoded RNA (EBER), cyclin-D1, and p16. The Ki-67 proliferation index was higher in the areas of large cell infiltration with an overall 30%-50% proliferation index. MUM1 preparation highlighted the neoplastic large cells.

Fluorescence in situ hybridization on paraffin section slides were negative for c-Myc, IGH-BCL2 gene



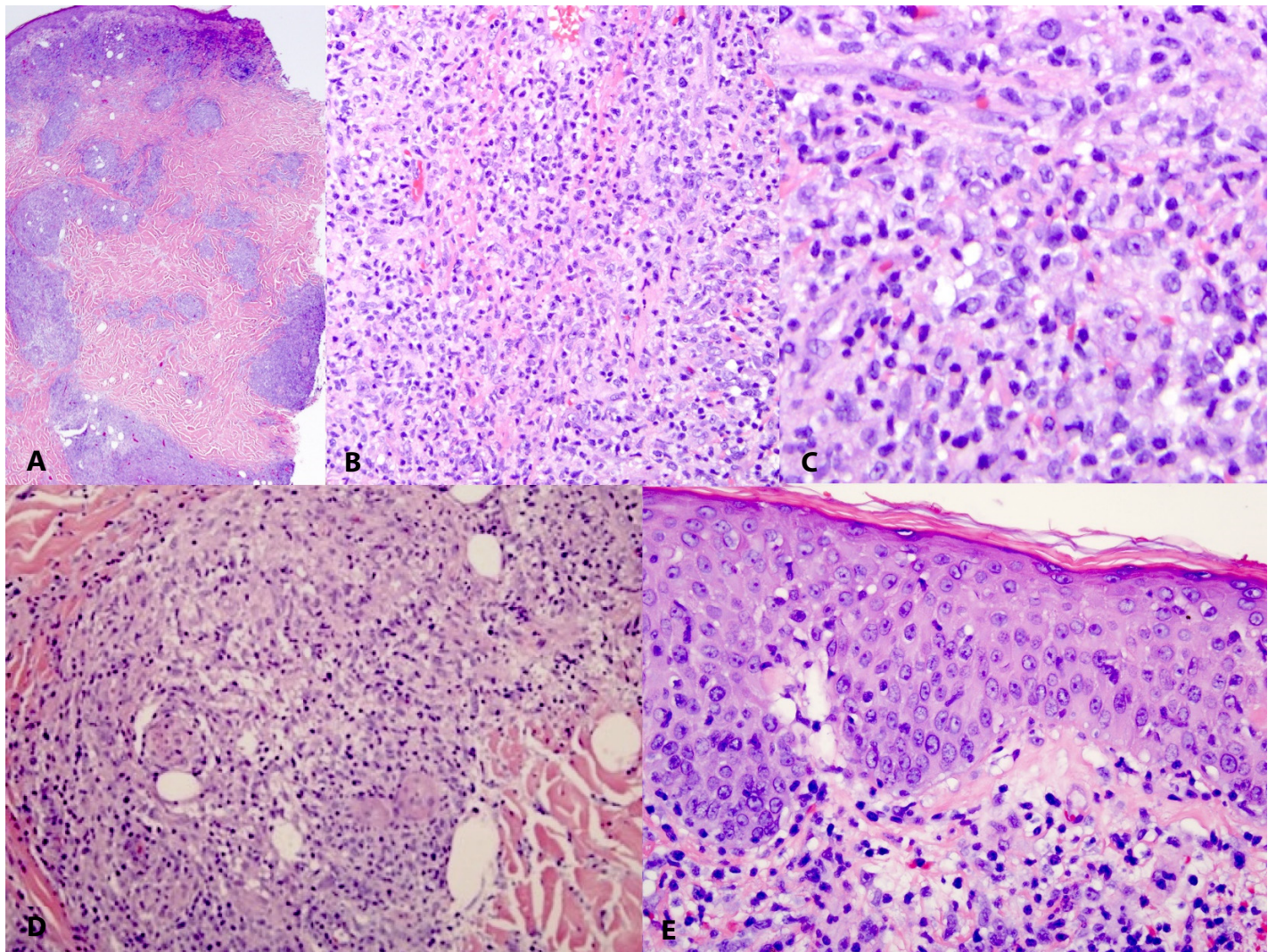
**Figure 1. A)** The patient developed multiple red papules and oval dome-shaped plaques ranging in size from 1-to-2.5cm. **B)** The plaques exhibited a pityriasis rosea-like distribution. **C)** There was a purple plum-like nodule on the left wrist.

rearrangement, and CDKN2A (p16) deletion. Immunoglobulin heavy chain studies revealed B cell clonality.

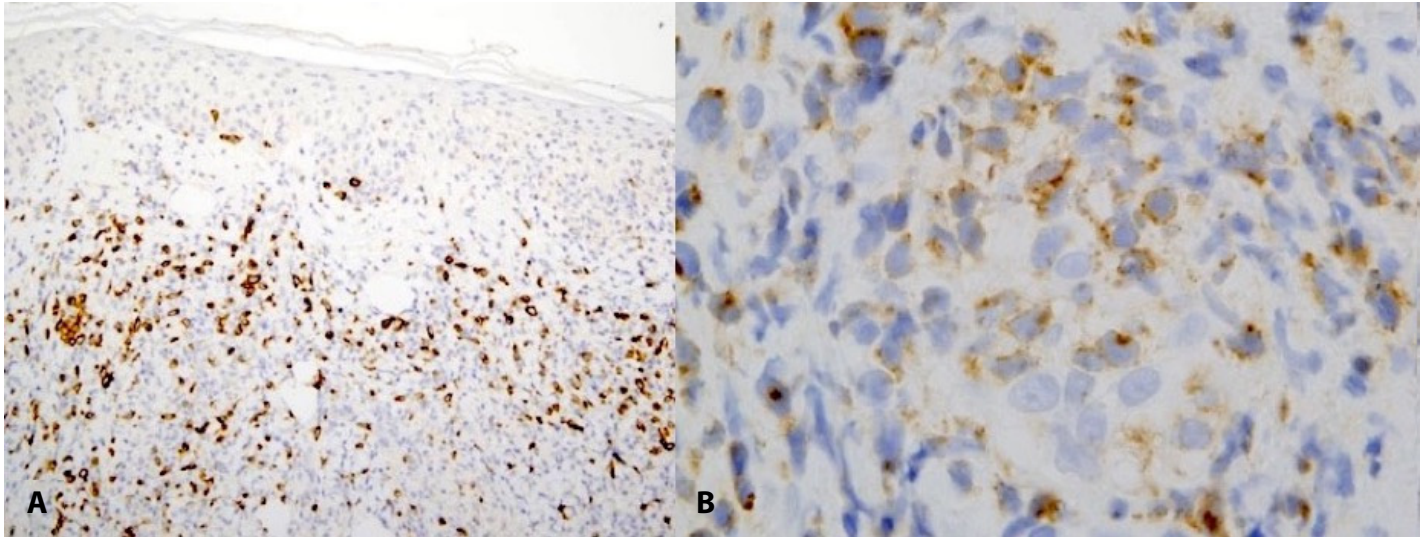
Subsequent analysis that was conducted on a bone marrow sample disclosed a small lambda light chain restricted lymphocytic infiltrate representing less than 0.85% of all cells analyzed by flow cytometry. These cells also expressed dim CD23. In addition, there was a small population of kappa light chain restricted CD38+ CD138+ B cells defining less than 0.01% of all cells present. Although flow cytometry detected this abnormal cell population, routine light microscopic assessment of the bone marrow sample

did not demonstrate any evidence of lymphoma. There was no evidence of spleen involvement either on clinical examination or radiographic studies.

The rapid progression of the skin eruption was associated with facial swelling and prompted a course of prednisone 80mg/day for one week before the first course of chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) was initiated based on the initial diagnosis of a diffuse large cell B cell lymphoma (DLBCL). Subsequent to the revised pathologic diagnosis of EBCL, treatment was changed to rituximab infusions alone, which produced clearing



**Figure 2.** **A)** Low-power magnification shows a multinodular infiltrate that spanned the entire dermis exhibiting an orderly disposition around nerves, blood vessels, and the eccrine coil. H&E, 20 $\times$ . **B)** Many of the dermal lymphocytes were in the 15-20 $\mu$ m size range exceeding the size of the intraepidermal lymphocytes. H&E, 200 $\times$ . **C)** H&E, 400 $\times$ . **D)** There was a significant degree of histiocytic infiltration resulting in a distinct granulomatous quality to the infiltrate. H&E, 200 $\times$ . **E)** The lymphocytes infiltrating the epidermis were small to intermediate in size showing some degree of nuclear contour irregularity, however, cells with a cerebriform appearance were not identified. H&E, 400 $\times$ ; Illustration reveals average density of epidermotropism.



**Figure 3.** The intraepidermal and intrafollicular epithelial lymphocytic infiltrate was highlighted in part by CD20 and CD79a and as well, much of the dermal component including the larger atypical cells were positive for CD20 and CD79a. **A)** CD79a immunohistochemistry, 200 $\times$ . **B)** The atypical B cell infiltrate are also highlighted by CXCR3 immunohistochemical staining, 1000 $\times$ .

of his skin rash. On follow-up, the patient is currently disease free without any symptoms.

## Discussion

The distinctive clinical presentation along with the histomorphology and immunophenotypic profile was diagnostic of a very rare form of B cell lymphoma, namely epidermotropic B-cell lymphoma. It is held to represent an unusual variant of MZL and in this case one might propose the designation of primary cutaneous epidermotropic MZL. In particular the skin involvement occurred initially and subsequent staging did not reveal frank lymphomatous infiltration of other organ sites, although small kappa and lambda light chain restricted B cell populations were identified by flow cytometry despite the lack of any light microscopic evidence of neoplastic B cell infiltration within the bone marrow [1].

The first reported case of epidermotropic B cell lymphoma was in 1999 by Chui and co-workers; they described a 70-year-old man who presented with a mildly pruritic rash involving the trunk and proximal extremities of 7-months duration [9]. The eruption was initially considered a presentation of MF. However, findings of a subsequent work up including a bone marrow biopsy was compatible with an extranodal MZL associated with an

exceptionally uncommon finding of significant B cell epidermotropism neoplasia; the patient underwent chemotherapy.

This case would make the ninth reported case of primary cutaneous epidermotropic B cell lymphoma, to our knowledge. A summary of all known cases with generalized cutaneous epidermotropic B cell lymphoma presenting in the skin is presented in **Table 1**. In general, this unusual variant of B cell lymphoma exhibits a reproducible presentation from a clinical perspective, although the pathological picture is somewhat variable. Clinically, epidermotropic B-cell lymphoma has a characteristic presentation in elderly men (ages range from 51-89 years old, mean age 64, male to female 8:1). Patients are generally healthy without B symptoms (fever, weight loss, night sweats, or malaise) and present with an abrupt onset of unexplained and mostly asymptomatic (5/9 asymptomatic, 4/9 pruritic) disseminated skin rash. The dull red papules and plaques at first examination may appear in a pityriasis rosea-like distribution. On closer inspection, the lesions are dome-shaped and non-scaly. The lesions involve areas that are typically not involved by pityriasis rosea including the palms, soles, face, and distal extremities. Lymphadenopathy, hepatomegaly or mucosal involvement are typically absent. However, bone marrow and splenic involvement are quite common

[1-9]. Bone marrow involvement occurred in 6 of the 9 cases whereas spleen involvement occurred in 4 of the 9 cases, with 3 of the 9 cases having concurrent spleen and bone marrow involvement. In our patient there was evidence of minimal bone marrow involvement, although only based on flow cytometric analysis, which demonstrated small kappa and small lambda light chain restricted infiltrates; there was no evidence of spleen involvement.

Given the initial presentation with skin eruption for a period of at least a few months-to-years that presaged any known extracutaneous involvement, one could make the argument that such cases represent forms of primary cutaneous epidermotropic MZL. However, once the diagnosis was made of epidermotropic MZL, extracutaneous involvement of these other extracutaneous organ sites was established in 4 of the 9 cases. In this regard it is impossible to know if the bone marrow, blood, and spleen involvement had developed first before the skin manifestations became apparent. Hedayat and co-workers indicated that despite an initial presentation in the skin for years, the lymphoma was a splenic MZL secondarily involving the skin [8]. The predilection for involvement of the spleen and bone marrow presumably is reflective of the natural homing tendency of this unique form of lymphoma. It is well established that primary forms of cutaneous lymphoma can exhibit

extracutaneous spread to other organ sites. In a recent letter to the editor by Baykal and co-workers [3], the authors described a case that exactly recapitulates cases of cutaneous epidermotropic MZL, clinically and histologically first presenting in the skin. The patient, however, had an established history of splenic MZL and then developed a relapse in the skin four years subsequent to the initial diagnosis of splenic MZL. Although in this particular case, features that are considered unusual for a diagnosis of a primary splenic MZL include the lack of the distinctive villous cytomorphology and the absence of expression of IgD by the neoplastic cells [3]. It may be impossible to definitively classify cases that have concomitant bone marrow and or spleen involvement at the time of initial diagnosis in the skin

as forms of primary cutaneous marginal zone lymphoma. However, there are clearly cases in which the only affected organ is the skin, although they are indistinguishable from cases with multiorgan involvement. There is at least one case in which the initial systemic evaluation following the skin diagnosis was without bone marrow and spleen involvement. However, several months later the patient developed lymphomatous infiltration of the bone marrow [2].

It is likely that the critical receptor ligand interactions that result in the PR-like disseminated cutaneous form of MZL also lead to bone marrow and spleen involvement. Perhaps one might consider epidermotropic MZL as a unique skin lymphoma with frequent spleen and bone marrow involvement and that may be indeterminate with regard to the initial site of involvement. We have observed cases without documentation of spleen involvement, including the current case, indistinguishable from those cases with spleen involvement.

This case exhibited pathological features that have been encountered in other cases of epidermotropic B cell lymphoma. Although the three cases we encountered in our previously published studies had large cell infiltration [1, 2], the other three published cases that we reviewed showed a neoplastic B cell population that was predominated by small B cells [2].

In this case the striking angiotropism, perieccrine accentuation, and perineural infiltration was similar to that seen in our previously examined cases [1, 2]. This pattern of perineural infiltration and angioinvasion of B cells accompanied by a background reactive T cell infiltrate was highly reminiscent of lymphomatoid granulomatosis. What is not supportive of this diagnosis was the lack of EBER staining amidst the B cells over and above the unusual epidermotropic epidermal changes. In addition, the distinctive pityriasis rosea-like skin rash to date has not been described in the spectrum of lymphomatoid granulomatosis. In this case as well as others, the phenotypic profile did not support a germinal center origin as the cells were BCL6 and CD10 negative [14].

Although this case was initially interpreted as a DLBCL, the distinctive clinical presentation with a disseminated skin rash resembling pityriasis rosea was unusual for DLBCL. In addition, the orderly multinodular non-effacing growth pattern around nerves, blood vessels, and the eccrine coil without diffuse infiltration and the presence of epidermotropism, which has been only rarely reported in DLBCL, were not compatible with DLBCL [15, 16]. Moreover, there were many admixed smaller neoplastic B cells. The overall phenotypic profile along with expression of IgG, that implied an isolated switched neoplastic B cell of post germinal center origin, was not typical for DLBCL. The tendency for the neoplastic cells to gather around pre-existing cutaneous dermal structures produced a picture that architecturally mimicked a reactive inflammatory dermatosis. However, there should be no confusion with a reactive process since the cytologies of the

lymphocytes were clearly in the context of a malignant lymphoma.

The unique homing of the neoplastic cells to epithelial structures, nerves, and blood vessels could also potentially be explained by a ligand receptor interaction. We already demonstrated a prominent pattern of CXCR3 staining amidst the neoplastic B cells in this case and other similar previously reported cases. The ligand is naturally found in keratinocytes but additional ligand sources would also include endothelium and stromal cells found in the spleen and bone marrow, which might account for the angiogenic properties of the infiltrate. A similar pattern of controlled selective migration of neoplastic T cells is best exemplified by MF, in which there is a critical interplay between the T cell and the intraepidermal microenvironment.

## Potential conflicts of interest

The authors declare no conflicts of interests.

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