Skin Involvement of Mantle Cell Lymphoma May Mimic Primary Cutaneous Diffuse Large B-cell Lymphoma, Leg Type

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Abstract: Mantle cell lymphoma (MCL) is a B-cell neoplasm with a variable and generally aggressive clinical course. So far our knowledge of skin involvement of MCL is limited. To understand the clinical and histopathologic features of MCL with skin involvement, the files of the Lymph Node Registry Kiel were screened for MCL diagnosed in the skin. Over a period of 13 years, 1321 biopsy specimens were diagnosed as MCL; among them, 14 patients (1%) showed skin involvement. Of these, skin was the initial site of manifestation in 6/11 (55%) cases. One patient presented with a skin-limited lymphoma. Furthermore, 7/12 (58%) patients presented with lesions on the leg. The lymphomas were highly proliferative with blastoid cytology in 12/14 (86%) cases. Moreover, the immunophenotype with expression of BCL2 (100%), MUM-1/IRF4 (83%), and IgM (82%) and lack of CD10 (25%) and BCL6 (0%) closely resembled the features of primary cutaneous diffuse large B-cell lymphoma, leg type. Solely the expression of cyclin D1 (100%) and the presence of t(11;14) (100%) allowed a distinction from cases of primary cutaneous diffuse large B-cell lymphoma, leg type. Only 2 MCL cases with skin involvement presented with classical cytology. Interestingly, in these 2 cases skin involvement occurred simultaneously in a lesion of coexisting primary cutaneous marginal zone lymphoma. Our data suggest that clinical presentation on the leg and blastoid cytology along with high proliferation and expression of Bcl2, Mum-1/IRF4, and IgM are typical for MCL involving the skin. Lymphomas with these features might be erroneously diagnosed as diffuse large B-cell lymphoma, leg type, if cyclin D1 staining is not performed.

Classical mantle cell lymphoma (MCL) is a mature B-cell neoplasm, which is characterized in the majority of cases by monomorphic small to medium-sized centrocyte-like cells (classical cytology), a typical immunophenotype with expression of CD5 and cyclin D1, and the hallmark translocation t(11;14)(q13;q32) as the underlying cause of constitutive cyclin D1 expression. In addition to classical MCL, rarer cytomorphologic variants of MCL have been described. The pleomorphic and blastic variants are usually associated with a higher proliferation rate and an aggressive clinical course.[1] These large cell variants (pleomorphic and blastic, lumped under the term blastoid) account for about 8% to 9% of all MCLs.[2] The disease is rare, accounting for approximately 8% of non-Hodgkin lymphomas, and manifests in elderly adults with a median age of 60 and a male predominance.[1] This lymphoma has an aggressive clinical course with a median overall survival of 4 to 5 years. With few exceptions like the so-called "in situ" lymphomas, MCL is regarded as a genuine systemic lymphoma presenting in most cases with stage III or stage IV disease and leukemic dissemination.[3,4] Typical clinical sites of involvement are lymph nodes, spleen, gastrointestinal tract, and bone marrow. Nevertheless, infiltration of almost all organs has been described in the literature.[1] However, skin infiltration of MCL seems to be a rare finding. To the best of our knowledge, published series of MCL infiltrating the skin include no more than 5 cases.[5,6]

In the current study, we evaluated the clinical and histopathologic features of MCL involving the skin, with a special focus on the differential diagnosis versus primary cutaneous diffuse large B-cell lymphoma, leg type (pcDLBCL-lt).

MATERIALS AND METHODS

Patients and Specimens

All cases of MCL diagnosed between 2001 and 2014 were identified in the files of the Lymph Node Registry in

the Department of Pathology, University of Kiel. Among 1321 patients with the diagnosis MCL, 14 patients were diagnosed with MCL with skin infiltration. All cases were rereviewed by 2 expert hematopathologists (I.O. and W.K.) to confirm the diagnosis with respect to the currently accepted histopathologic and/or molecular criteria of the World Health Organization classification.[1] Diagnostic slides and formalin-fixed and paraffin-embedded (FFPE) tissue specimens were used for further immunohistochemical analysis. Clinical information including age, sites of involvement, and stage at first diagnosis, primary treatment, and follow-up was provided by the treating oncologists. Three patients were treated within the framework of the European MCL Network, which provided clinical data. The study was performed in accordance with the guidelines of the institutional review board.

Immunohistochemistry

The analyses were performed on FFPE skin biopsy specimens. All cases were investigated for expression of CD20, CD10, Bcl6, Bcl2, CD23, CD5, IgM, Mum-1/IRF4, p53, Sox11, light chains, Ki67, and cyclin D1 using standard protocols (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A286). Expression levels were scored by visual inspection as no expression (< 25% positive lymphoma cells), weak expression (26% to 50%), medium expression (51% to 75%), and strong expression (> 75%). To evaluate the Ki67 proliferation index, 200 lymphoma cells were counted according to the guidelines of the European MCL Network.[7]

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization analysis was performed on paraffin slides with available material and analyzed for breaks in cyclin D1 using a break-apart probe and/or the presence of t(11;14)(q13;q32) by a dual-color fusion probe (all Vysis/Abbott, Green Oak, IL).

RESULTS

Clinical Features

Of 1321 biopsy specimens identified as MCL in the examined period of time, 14 were diagnosed in the skin (1%). Table 1 summarizes the clinical features of these patients. Because of the retrospective nature of the study, the clinical information was incomplete and not available for all patients. Median age at first diagnosis was 72 years (50 to 85 y). Thirteen of 14 patients were male. In 6/12 (50%) patients the skin was the primary clinical site of involvement by MCL. Nevertheless, on staging, 5 of the 6 (83%) patients with primary skin involvement were shown to suffer from systemic MCL with additional extracutaneous manifestation. In 1 patient the disease seemed to be limited to the skin. However, the follow-up of this patient is only 6 months so far. In 6/12 (50%) patients skin manifestation occurred at relapse but was not present at primary diagnosis. In 2 patients lack of clinical information prevented a correlation of the analyzed specimen with the stage of the disease.

Four patients presented with unifocal and 10 with multifocal skin involvement. Lesions on the leg occurred in 7/12 (58%) patients and were the site of the diagnostic biopsy for pathologic assessment. Interestingly, in 3

**TABLE 1.** Overview of Clinical Data of Patient Collective

No.	Sex	Age at ID	Stage at ID	Isolated/ Multiple Skin Lesions	Affected Skin Areas	MCL Diagnosed Because of Skin Lesions	Relapse of MCL in Skin	Primary Therapy	Survival (mo)	Dead/ Alive	Follow-up (mo)
1	Male	NK	NK	NK	Shoulder left	NK		NK	NK	NK	
2	Male	85	1e	M	Thigh left	N	X	Vincristin, cyclophosphamide, R-Benda	6	Dead	
3	Male	45	4	M	NK	NK		R-CHOP/R-DHAP	42	Dead	
4	Male	68	4 ae	M	Both legs	Y		R-CHOP	62	Dead	
5	Male	NK	NK	NK	Back	N	X	STX	NK	NK	
6	Male	74	1e	I	Lower leg right	Y		Surgery		Alive	5
7	Male	76	NK	NK	Skin NK	N	X	NK	NK	NK	
8	Male	82	4a	M	Lower leg right + several SC lesions	Y		Surgery	26	Dead	
9	Male	50	3	I at ID; M at relapse	Scalp	Y		R-CHOP	107	Dead	
10	Male	84	4e	I	Forearm	Y		R-Benda		Alive	11
11	Male	55	4	M	Lower leg left	N	X	R-CHOP/R-DHAP	133	Dead	
12	Female	77	4	M	Both lower legs	N	X	R-FC	85	Dead	
13	Male	70	4	M	Back	Y		No therapy		Alive	9
14	Male	69	4b	I	Lower leg	N	X	R-Benda		Alive	60

I indicates isolated; ID, initial diagnosis; M, multiple; N, no; NK, not known; R-Benda, rituximab-bendamustin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-FC, rituximab, fludarabine, cyclophosphamide; SC, subcutaneous; STX, stem cell transplantation; Y, yes.

patients the leg lesions were the site of primary manifestation of the MCL before any other lymphoma manifestation was clinically evident. Other sites of skin manifestation were the trunk (3/12, 25%), the scalp (1/12, 8%), and the upper extremity (1/12, 8%). The clinical presentation of the skin manifestations varied; they were described as small nodules, erythematous patches/plaques or largely infiltrated areas (Figs. 1, 2). Most patients received chemotherapy as primary therapy (8/12 patients, Table 1). For 7/11 (63%) patients follow-up data were available (6 to 133 mo). In this subgroup of patients the median survival was 62 months.

Histopathologic Features

Table 2 summarizes the histopathologic, molecular, and immunophenotypic characteristics of MCL with skin involvement. The cytology was blastoid in 12/14 (86%) cases and classical in 2/14 (17%). All cases were positive for CD20, except for 1, which showed skin involvement at relapse after prior anti-CD20 therapy. Nuclear staining for cyclin D1 was detected in every case (14/14, 100%). All evaluable cases reacted strongly positive for Bcl2 (11/11, 100%). Expression of IgM and Mum-1 was observed in 10/12 (83%) and 9/11 (81%) cases, respectively. Expression of CD10 was found in
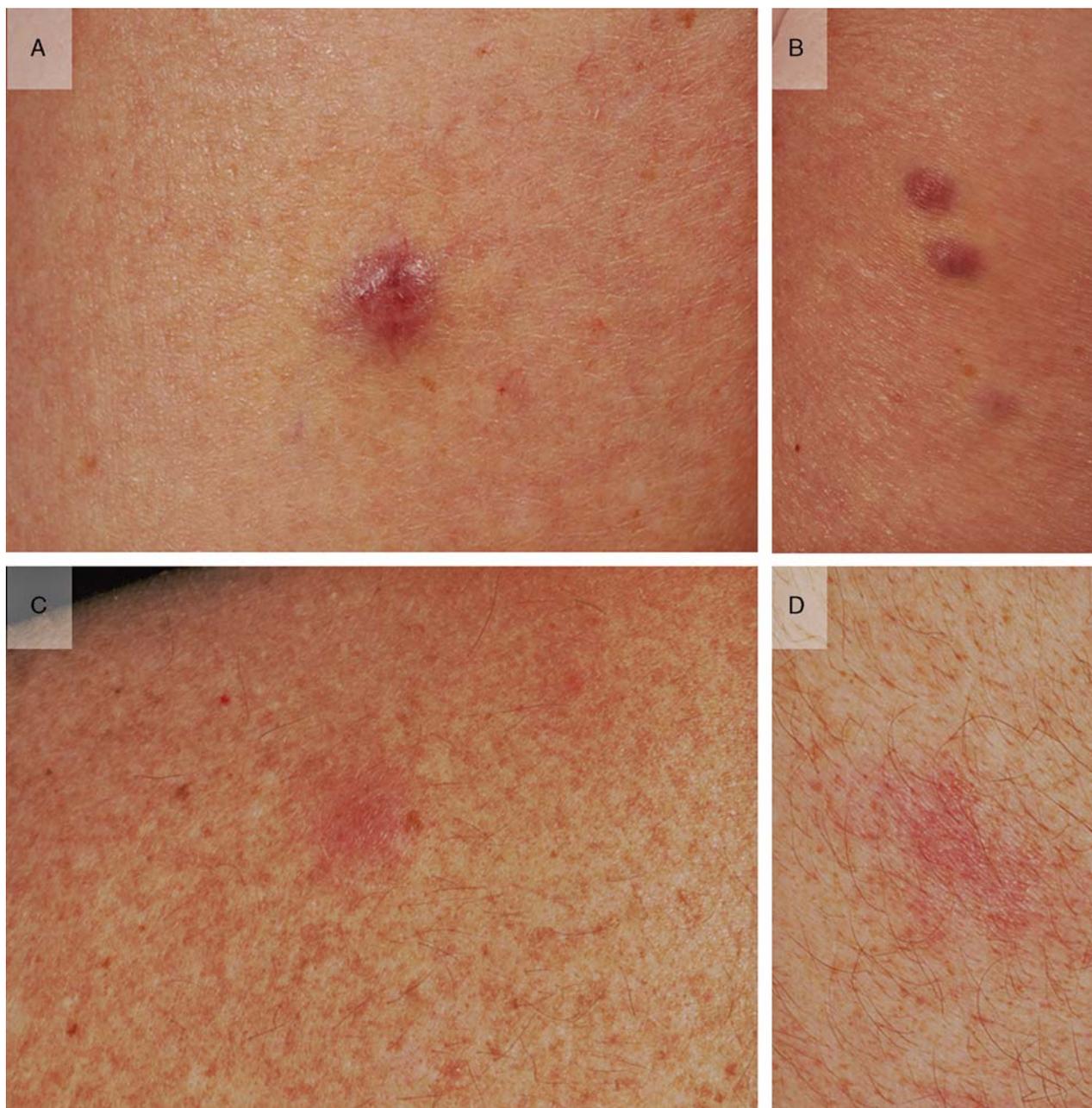
FIGURE 1. Clinical presentation of MCL in the skin can be polymorphous: Presenting as small nodules (A and B) on the trunk and leg in 1 patient or slightly infiltrated patches on the chest and back (C and D) in 1 of the patients with composite lymphoma.

FIGURE 2. Clinically similar presentation of MCL (A and C) and pcDLBCL (B and D) on the leg with tumorous infiltration and heavily infiltrated areas with ulceration.

3/13 (23%) cases. BCL6 expression was not detected (0/11, 0%). P53 was expressed in 9/11 (81%) cases. Sox11 was positive in 11/11 (100%) MCL cases. Most lymphomas showed λ light chain restriction (7/11, 64%), whereas κ was less frequently positive (2/11, 18%). No plasmacytic differ-

entiation of the MCL or strong expression of cytoplasmic light chains was observed. The proliferation rate was high (mean 60%, median 80%) and >40% in all cases. Figure 3 exemplifies the immunophenotype of a patient with MCL in the skin with blastoid cytology.

TABLE 2. Histopathologic Characteristics of MCL With Skin Involvement

No.	Cytology	Cyclin D1	CD20	CD10	CD5	CD23 (Dendr)	bcl2	bcl6	Mum-1	Ki67 (%)	IgM	κ	λ	p53	Sox11	FISH (Cyclin D1-BA)
1*	Small	+	+	−	+	− (+)	+	−	+/−	50	+	−	+	−/+	+	+
2	Blastoid	+	+/−	−	+/−	−	+	−	+/−	93.5	+	−	−	+	+†	+
3	Blastoid	+	+	NM	+	−	NM	NM	NM	80	NM	NM	NM	NM	NM	NM
4	Blastoid	+	+	−	−/+	−	+	−	−	42	+	−	+	+/−	+/−	NM
5	Blastoid	+	+	−	+	− (−)	+	−	+	70	+	−	+	+/−	+/−	+
6	Blastoid	+	+	−/+	+	− (−)	+	−	+/−	90	+	−/+	−	+/−	+/−	+
7	Blastoid	+	+	−	+	− (−)	+	−	+/−	50-90	−/+	−	−/+	−	+/−	+
8	Blastoid	+/−	+	+	+	− (−)	+	−	−	60	+	−	−/+	+/−	+	+
9	Blastoid	+	+	−	+	− (−)	+	−	+/−	90	−	−	−	+/−	+/−	+
10	Blastoid	+	+	−	+/−	− (−)	+	−	+/−	80	+	−	+	+/−	+	+
11	Blastoid	+	−‡	+	+	− (−)	+	−	+	80	+	−	−/+	−	+	+
12	Blastoid	+	+	−	NM	NM	NM	NM	NM	50	NM	NM	NM	NM	NM	+
13*	Small	−/+	+	−	+	− (+)	§	§	§	§	§	§	§	§	−/+	+
14	Blastoid	+	+	−	+	−	+	−	+	43	+	−/+	−	−/+	+	+

+ indicates >75% of cells stained positive; eg. +/− >50%; −/+ >25%; − <25%.
*Patients with MCL+MZL.
†Evaluation for MCL only in the primary tumor.
‡Postchemotherapy with rituximab.
§Main component was MZL, therefore no clear statement for immunohistochemistry in MCL is possible.
BA indicates break-apart; dendr, dendritic network; NM, no material.

The 2 cases of MCL with classical cytology that were identified in our study were detected within a skin lesion that resembled primary cutaneous marginal zone lymphoma (MZL). A distinction between the MCL and the MZL as separate entities is histopathologically feasible, as the MZL showed a λ light chain–restricted plasma cell component that was cyclin D1 negative. Cyclin D1 expression was detectable in the centrocyte-like cells of the MCL, which were positive for κ light chain (Fig. 4). It is worthy of mention that the MCL, but not the MZL, was Sox11 positive (Fig. 4). The intimate mixture of MCL and MZL in the lesion and the quality of the tissue (FFPE) prevented further molecular analysis. However, the restricted expression of Sox11 and cyclin D1 in the centrocyte-like cells and the different light chains in the plasma cells and centrocyte-like cells strongly argue against a plasma cell differentiation in the MCL and suggests 2 clonally unrelated diseases. Figure 4 illustrates the histopathology in one of the patients with a composite lymphoma. The MCL component in this case accounts for 50% of the infiltrate. In the second case the MCL component was limited to approximately 5% of infiltrate. The number of cyclin D1-positive cells correlated with the Sox11 expression level.

Molecular Features

All cases (12/12) with available material for fluorescence in situ hybridization analyses displayed a cyclin D1 break (n = 5) and/or the presence of t(11;14)(q13;q32) (n = 7).

DISCUSSION

This report represents the largest series of MCL infiltrating the skin published so far and describes the histomorphologic and clinical features of these cases. On the one hand, our data confirm findings of previously published smaller cohorts and case reports on MCL in the skin. On the other hand, our data have diagnostic implications for cuta-

neous B-cell lymphomas and additionally provide new insight into the biology of MCL.

The frequency of approximately 1% of MCL showing skin involvement found in our single-center analysis closely matches the incidence described by the German Low-Grade Lymphoma Study group in a previous report.[8] Previously published cohorts of MCL infiltrating the skin contain no more than 5 cases.[6] Only recently, a review of the literature was published comprising a total of 22 cases.[9] However, the diagnostic evaluation of the published cases was not performed according to current diagnostic criteria and frequently lacked staining for cyclin D1 or detection of t(11;14). When we focused our literature review on the lymphomas clearly proven to be cyclin D1 positive, we identified 16 cases of MCL with skin involvement, most of which were described as single-case reports.[10–13] Thus, despite the fact that the disease is leukemic in almost all cases (87% of cases pretreatment) and frequently shows extranodal involvement, dermotropism is not a typical feature of MCL[8,14]

Most of the cases in our analysis as well as in the published literature showed systemic MCL at the time when skin manifestation occurred. However, of 16 published cases with MCL in the skin confirmed by cyclin D1 expression, 5 had involvement limited to the skin and lacked other manifestations (Table 3).[6,9–13] Similarly, we identified 1 patient with an MCL confined to the skin at initial presentation. However, subsequent dissemination of the lymphoma cannot be excluded in our patient, as the follow-up period is short. Disseminated disease is present in most patients at the time of diagnosis. Nevertheless, the skin lesions can occur as the first manifestation of MCL, because in almost half of the patients in our cohort the skin was biopsied to establish the diagnosis. Our data strongly suggest that careful staging is mandated in any MCL within the skin to exclude disseminated disease. The
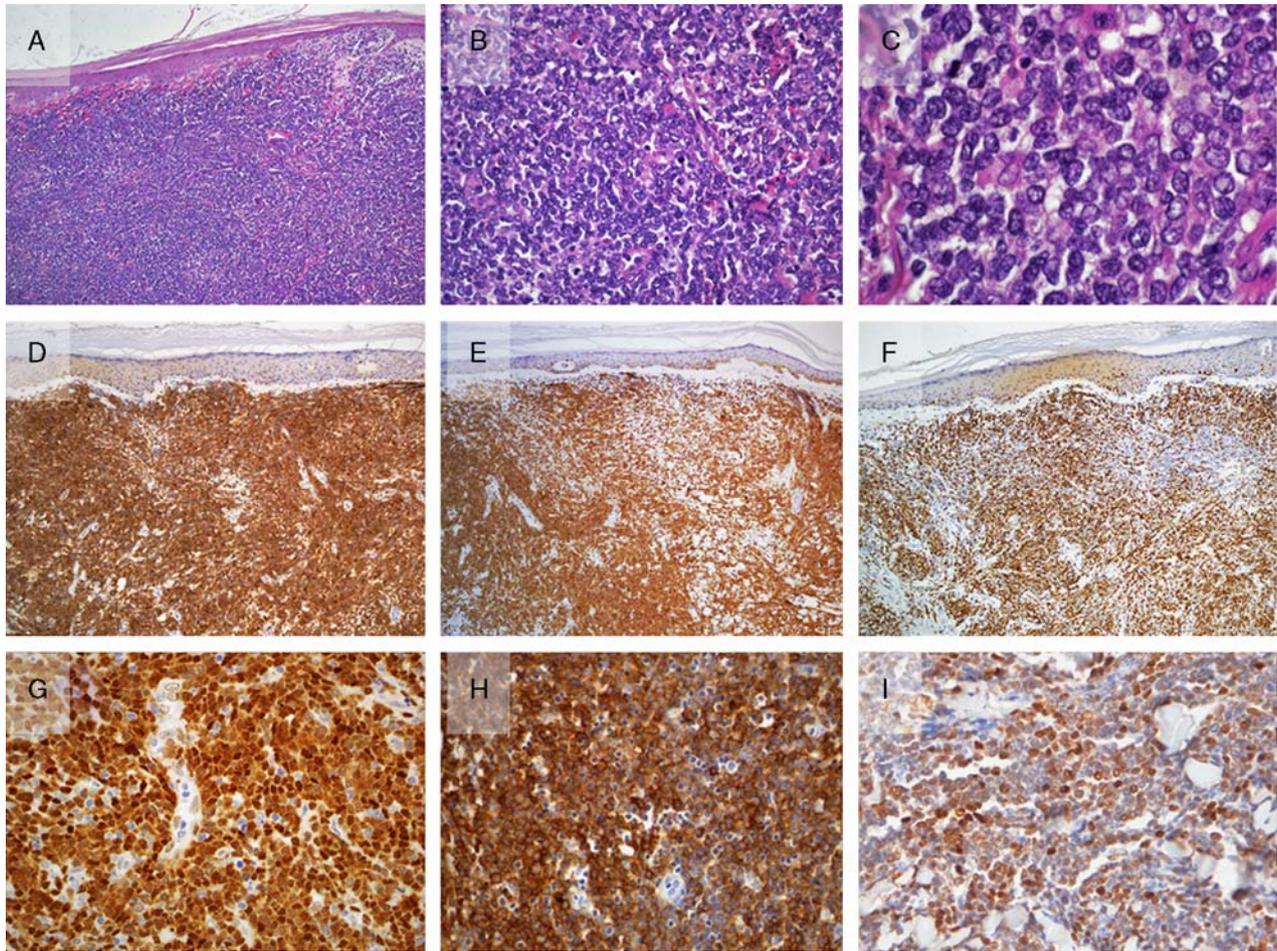
FIGURE 3. Histopathology of a blastoid MCL in the skin (patient no. 11; Table 3). Dense infiltrate in the upper dermis by large blastoid cells without alteration of the epidermis (A–C, hematoxylin and eosin in increasing magnifications). The malignant lymphoid cells express CD5 (D), Bcl2 (E), cyclin D1 (G), Mum-1 (H), and IgM (I). F, The proliferation rate as measured by Ki67 is high.

latter should be suspected in any patient warranting systemic treatment.[15,16]

The majority of MCLs involving the skin in our cohort showed blastoid morphology, which is in line with the published literature (Table 3). Cases of blastoid MCL differ from classical MCL by their higher proliferation and poorer clinical outcome but also genetically by a higher level of genetic aberrations—for example, a high level of p53 inactivation.[17,18] The dermotropism described in our study points to another biological feature of blastoid MCL that differs from classical MCL. The biological principles underlying the tissue manifestation of MCL are poorly understood so far. However, recent studies on a rare subtype of MCL presenting with little lymphadenopathy but high levels of leukemic spread and spleen involvement suggest that the expression of the transcription factor Sox11 is involved in the regulation of tissue manifestation—for example, by inducing blood vessel formation.[19] Interestingly, all of the cutaneous MCLs in our cohort were Sox11 positive. Sox11 positivity is correlated with spread of the lymphoma in tissue. It is doubtful that Sox11 expression is the only factor influencing manifestation in the skin as this site of involvement is so rare. Presumably, there are other important features of these lymphomas leading to growth at this immune-privileged site. Another observation from our cohort points to a specific biological mechanism leading to skin manifestation in MCL. The only 2 cases with classical morphology in the skin were detected within a primary cutaneous MZL, the latter obviously being a clonally unrelated disease on the basis of the light chain expression. Unfortunately, the low level of MCL infiltration and the fact that only FFPE tissue was available prevented further molecular analysis in these cases. However, the skin involvement in these cases of classical MCL might be triggered by a disturbance of the cutaneous microenvironment. The physiological microenvironment of the skin seems to prevent MCL growth in the dermal compartment in the majority of cases. Our literature review did not identify any case report on the coexistence
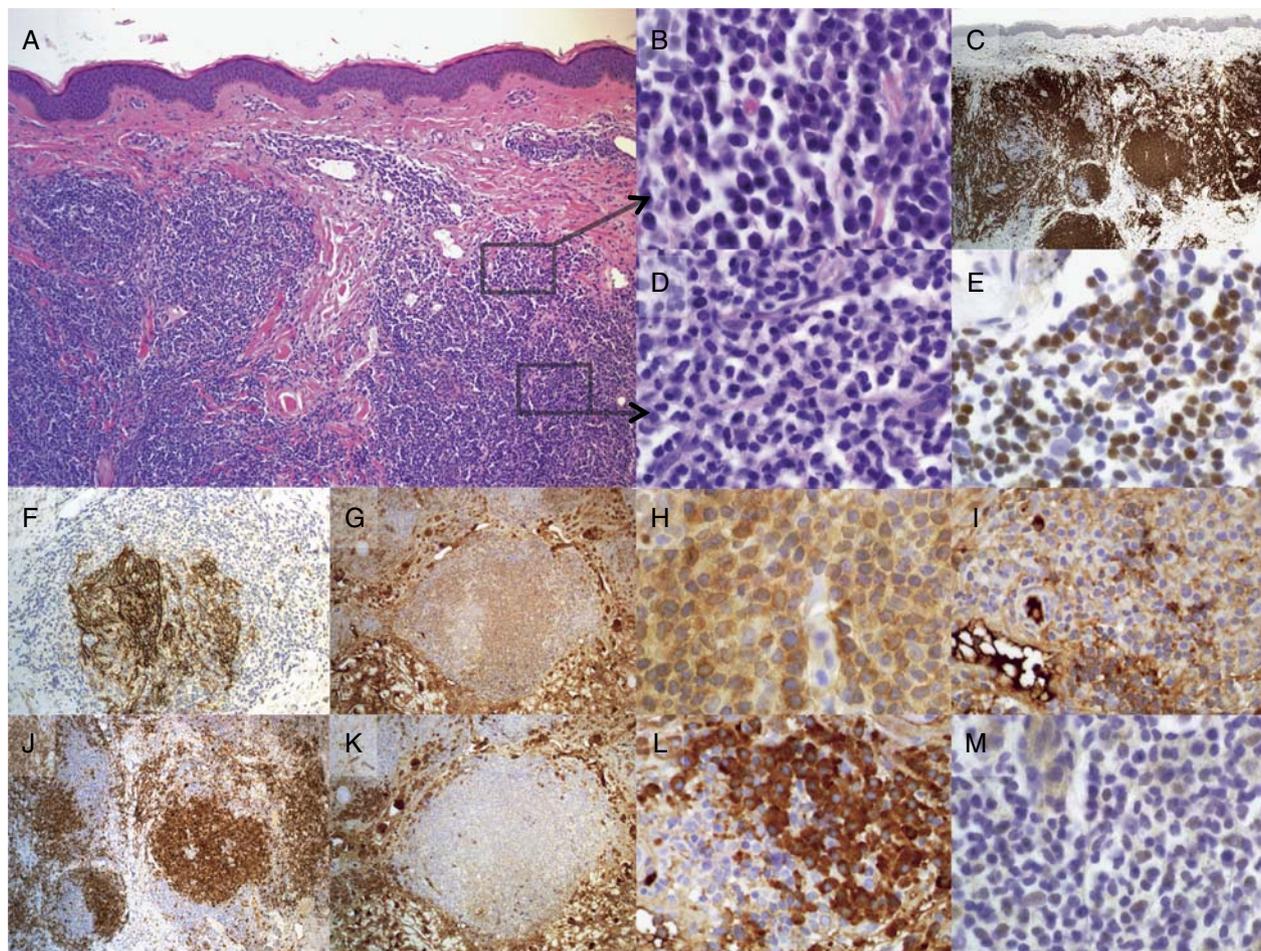
FIGURE 4. Histopathology of a cutaneous composite lymphoma consisting of a marginal zone LYMPHOMA and MCL. Alternatively marginal zone and mantle cell lymphoma. Dense nodular infiltrates in the upper dermis (A, H&E). MCL component with small to medium-sized lymphoid cells (B, H&E) and MZL with plasmacytic differentiation (D, H&E). Both components are positive for CD20 (C). MCL is positive for Sox11 (E) and cyclin D1 (J) and shows λ light chain restriction (G and H). MZL shows κ light chain restriction including a monotypic plasma cell component (K and L). No expression of κ light chain in MCL (M) and λ light chain in MZL (I), respectively. CD23 highlights networks of follicular dendritic cells within the MCL component (F). H&E indicates hematoxylin and eosin.

of MCL with other lymphomas or other neoplasms in the skin. Nevertheless, our findings suggest that in the diagnostic evaluation of indolent/small cell cutaneous B-cell lymphomas like MZL, cyclin D1 testing might be useful.

The most frequent primary cutaneous aggressive B-cell lymphoma, pcDLBCL-lt, is located predominantly on the leg. However, 58% of the MCL cases in our cohort were found on the leg as well, and the macroscopic picture was frequently indistinguishable from pcDLBCL-lt. Given the predominant blastoid morphology of MCL and the similarities in clinical presentation, we attempted to determine how likely it is that pcDLBCL-lt and skin manifestation of MCL might be confused if the immunophenotype is assessed. In fact, in addition to the morphology and clinical presentation, MCL and pcDLBCL-lt share many immunohistochemical features, such as the frequent expression of IgM, Bcl2, and Mum-1 as well as the absence

of Bcl6. Interestingly, CD10 expression was found in a similar percentage of blastoid MCL in the skin to that in pcDLBCL-lt (literature review in Table 4).[20–26] Therefore, we conclude that skin involvement of MCL might erroneously be diagnosed as pcDLBCL-lt if no cyclin D1 staining is performed in a mature aggressive B-cell lymphoma presenting with skin lesions.

In summary, skin involvement is a rare presentation of MCL usually occurring as a secondary involvement by a systemic lymphoma. Skin tropism seems to be restricted to the more aggressive blastoid variant of MCL and consequently to be associated with an aggressive clinical course. Finally, skin involvement by MCL shares many clinical and histomorphologic features with pcDLBCL-lt: localization on the leg of elderly adults, blastoid cytology, and expression of Bcl2, Mum-1, and IgM. Thus cyclin D1 expression should be analyzed in any mature aggressive B-cell lymphoma in the skin.

TABLE 3. Overview of Reported Case of Cyclin D1+MCL With Skin Involvement

References	n	Cytology	Cyclin D1—IH	Cytogenetics*	Skin Only†	Clinical Follow-up (in Months After Presentation Skin Lesions)	Proliferation Rate
Sen et al[6]	5	4 blastoid 1 small/medium	5/5	2/5 positive 3 ND	1/5	3/5 dead (4-30) patient with skin only: alive (21)	4/5 (15.1%-99%)
Cao et al[9] Literature review	7‡	4 blastoid 2 classical 1 mixed	7/7‡	ND	1/7	4/7 dead (1-36)	ND
Mazzuoccolo et al[12]	1	Intermed/large	1/1	ND	1/1	Alive (24)	ND
Phelps et al[13]	1	Blastoid	1/1	1/1 positive	0/1	Not reported	> 90%
Cesinaro et al[10]	1	Blastoid	1/1	1/1 positive	1/1	Dead (40)	> 90%
Hamad et al[11]	1	Intermed/large	1/1	1/1 positive	1/1	Alive (31)	90%-95%

*Cytogenetic analysis either with FISH t(11; 14) or conventional cytogenetic analysis from bone marrow.
†Evaluation after complete staging examinations.
‡Only Cyclin D1$^+$ cases were taken from this literature review, and the cases from Sen and colleagues were not counted again.
IH indicates immunohistochemistry; intermed, intermediate; ND, not done.

TABLE 4. Immunohistochemical Characterization of pcDLBCL-lt (n > 10) in Comparison With MCL in Skin in Our Series

Group	Diagnosis	n	IgM (n [%])	Bcl6 (n [%])	Bcl2 (n [%])	CD10 (n [%])	Mum-1 (n [%])	κ-λ (n [%])
Demirkesen et al[20]	pcDLBCL	10	10/10 (100)	2/10 (20)	9/10 (90)	0/10 (0)	10/10 (100)	ND
Koens et al[21]	pcDLBCL-lt	40	40/40 (100)	18/40 (45)	36/40 (90)	ND	35/40 (88)	26/40 (65)-13/40 (33)
Grange et al[22]	pcDLBCL-lt	60	ND	ND	51/60 (85)	ND	23/41 (56)	ND
Hallermann et al[23]	pcDLBCL-lt	21	ND	12/21 (57)	21/21 (100)	ND	19/21 (90)	ND
Kodama et al[24]	pcDLBCL-lt	40	ND	30/40 (75)	40/40 (100)	2/33 (6)	22/29 (75)	ND
Hoefnagel et al[25]	pcDLBCL-lt	19	ND	17/19 (89)	17/19 (89)	0/19 (0)	ND	ND
Fernandez-Vazquez et al[26]	pcLargeBCL	32	ND	7/17 (41)	8/28 (28)	9/24 (38)	ND	ND
Our series	MCL-skin	14	10/12 (83)	0/11 (0)	11/11 (100)	3/13 (23)	9/11 (82)	2/11 (18), 7/11 (64)

BCL indicates B-cell lymphoma; ND, not done.

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