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Brief communication

The expression of IgM is helpful in the differentiation of primary cutaneous diffuse large B cell lymphoma and follicle center lymphoma

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ABSTRACT

Diffuse large B-cell infiltration of the skin includes mainly primary cutaneous follicle center lymphoma (PCFCL) with diffuse architecture and diffuse large B cell lymphoma (PCDLBCL), leg type. Differentiation of these lymphomas on morphology may be troublesome. Immunohistochemistry panel, including CD20, CD79a, bcl-6, bcl-2, MUM-1, FOX-P1 is mandatory. However, in minority of cases, these markers would not suffice. In order to search the value of another marker, IgM, 30 cases of PCFCL and 10 cases of PCDLBCL, leg type were included in the study. As suggested in a recent literature, our study denoted that expression of IgM was useful as an additional tool for differentiation.

Diffuse large B-cell infiltration of the skin includes primary cutaneous follicle center lymphoma (PCFCL) with diffuse architecture and primary cutaneous diffuse large B cell lymphoma (PCDLBCL), leg type and PCDLBCL, other type [1]. There have been much controversy among these groups in previous classifications [2]. PCFCCL is an indolent cutaneous lymphoma of B cells of germinal center origin with 5-year survival >90% [3]. On the other hand, PCDLBCL is a more aggressive lymphoma of activated post-germinal center origin, with 5-year survival approximately 50% [4]. The therapeutic approach is radiotherapy in PCFCL, while the combination of anthracyclin-based chemotherapy and rituximab is the treatment of choice in PCDLBLs [5]. Differentiation of these lymphomas merely on morphology may be troublesome. Immunohistochemistry is a highly valuable tool since B cells of germinal center origin are CD20(+), CD79a(+), bcl-6(+) and bcl-2(−), while activated post-germinal B cells are bcl-2(+), MUM-1(+), FOX-P1(+) and bcl-6(±) [6,7]. However, in minority of cases, these markers would not be enough for an accurate diagnosis [5,8]. In a recent literature, it is stated that expression of IgM on paraffin-embedded sections can be used as an additional tool for the differentiation between PCFCL and PCDLBL, leg type in daily pathology routine [7].

The aim of our study was to assess the diagnostic value of IgM expression by immunohistochemistry. Thirty cases of PCFCL and 10 cases of PCDLBCL, leg type were included in the study. Skin punch biopsies were fixed in formalin, processed routinely and embedded in paraffin. Four-micrometer sections from paraffin-embedded blocks were stained with hematoxylin and eosin and immunostained with CD20 (clone L26, dilution: 1:300, Thermo Scientific), CD3 (clone LN10, dilution: 1:200, Novocastra), bcl-6 (clone BL6.02, dilution: 1:100, Labvision-neomarkers), CD10 (clone 56C6, dilution: 1:50, Thermo Scientific), CD21 (clone 2G9, dilution: 1:20, Thermo Scientific), bcl-2 (clone 8C8, dilution: 1:80, Labvision-neomarkers), IRF4/MUM-1 (clone BC5, dilution: 1/200, Biocare), Ki67 (clone SP6, dilution: 1/200, Biocare), IgM (clone 8H6, dilution: 1/800, Novocastra) antibodies using streptavidin–biotin complex method with automated staining instrument (Ventana Benchmark). All cases has been classified according to the criteria of 2008 WHO classification by a hematopathologist (NT) and a dermatopathologist (CD). When the dermal infiltration showed predominance of large cleaved cells, sometimes admixed with variable number of small and medium sized centrocytes, together with the expression of germinal center cell markers such as bcl-6 and less frequently CD10, the diagnosis of PCFCL was established. On the other hand, when dermal infiltration was mainly composed of large, round cells, together with the expression of IRF4/MUM-1, PCDLBCL, leg type was considered. None of the patients had extracutaneous involvement at the time of diagnosis. The clinical data (sex, age, the number of lesions, localization, the mode of therapy, the time of follow-up, current status) were reviewed. The clinical features, the follow-up data and the status of IgM expression are summarized in Table 1. In all 10 cases of PCDLBCL, leg type, there was strong and widespread cytoplasmic staining for IgM (Fig. 1). Three cases

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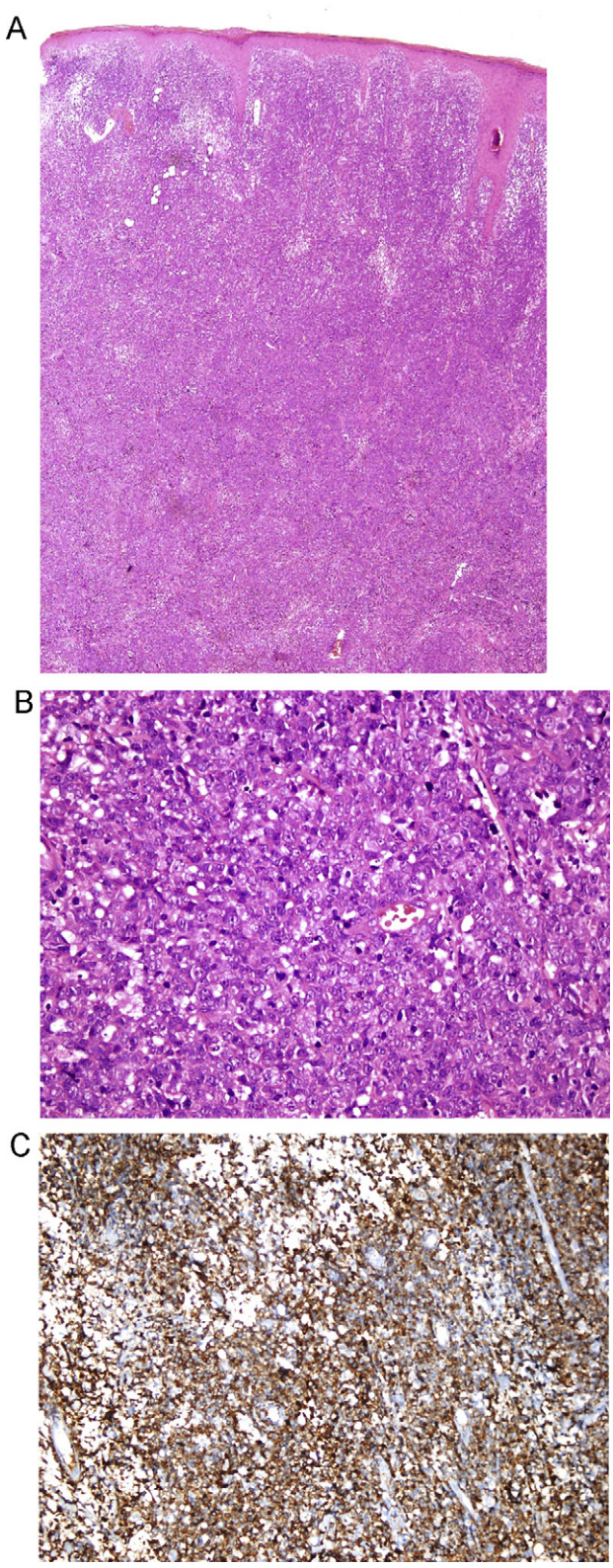

Fig. 1. Primary cutaneous diffuse large B cell lymphoma, leg type. Diffuse dermal infiltration (HE 40×) (A), composed of monotonous population of large noncleaved lymphoid cells (HE 200×) (B), strong and widespread staining for IgM (200×) (C).

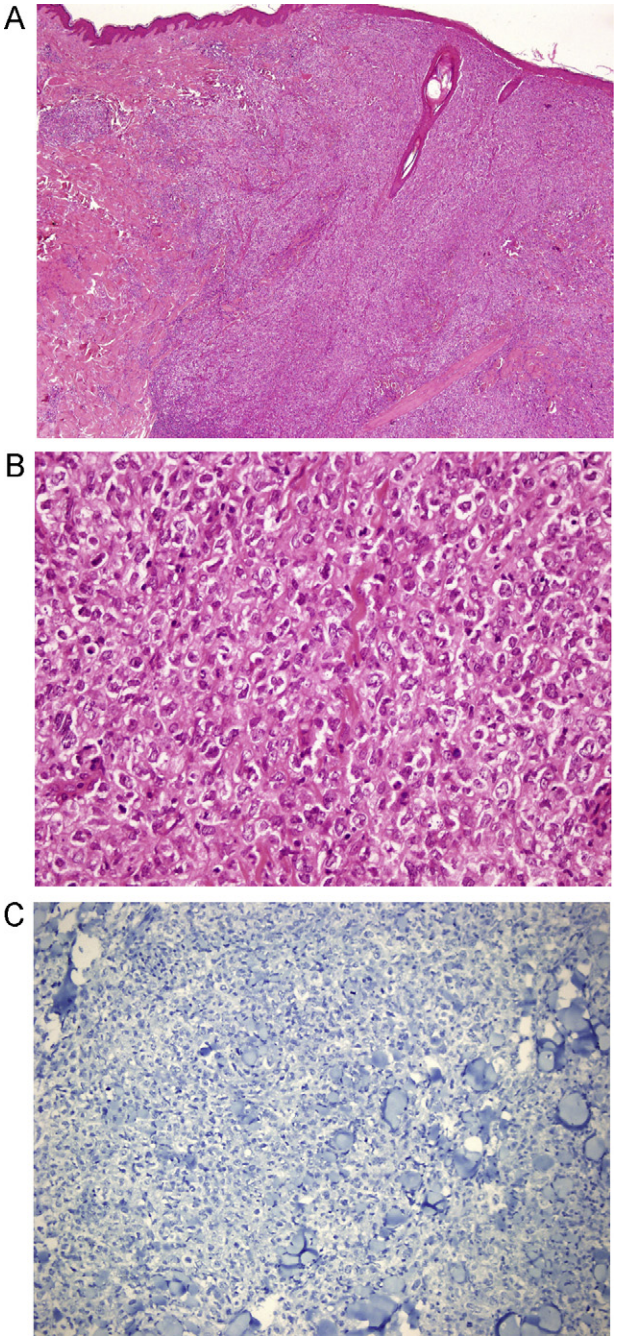

Fig. 2. Primary cutaneous follicle center lymphoma. Diffuse dermal infiltration (HE 40×) (A), composed of large cleaved cells (HE 200×) (B) and negativity for IgM (200×) (C).

(3/10) were seen as a solitary lesion on the leg. Three cases (3/10) were located on the head and 4 cases (4/10) were on the trunk. The nuclear staining of IRF4/MUM-1 were detected in all cases and membranous staining of bcl-2 in 9 cases (9/10) and nuclear staining of bcl-6 in 2 cases (2/10). None of the cases of PCFCL showed staining for IgM (Fig. 2). Out of 30 cases, 8 (8/30) presented as solitary lesion on the head, 9 (9/30) on the trunk, 1 (1/30) on the arm and 2 (2/30) on the legs. The rest were multiple lesions located in different parts of the body. In two of these cases (2/30), leg was one of the sites. All cases showed nuclear staining for bcl-6. In 7 cases (7/30), CD10 expression was seen as well. Membranous expression of bcl-2 were detected in 7 cases (7/30). Nuclear staining of IRF4/MUM-1 was

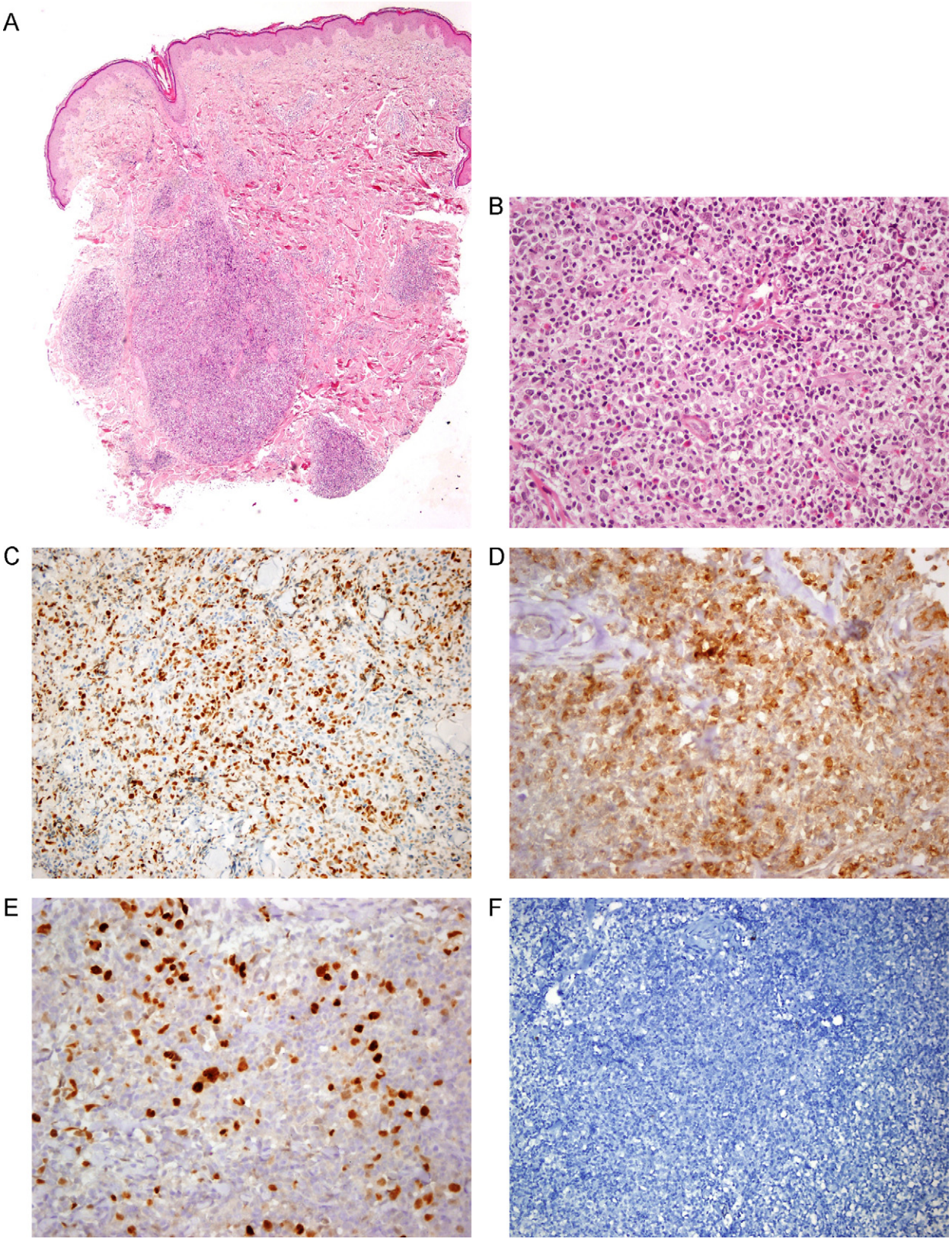

Fig. 3. A case of primary cutaneous follicle center lymphoma presented as a solitary lesion on the leg. Diffuse and nodular dermal infiltration (HE 40×) (A), composed of large cleaved cells, admixed with eosinophils and small lymphocytes (HE 200×) (B), showing immunoreactivity for bcl-6 (200×) (C), for bcl-2 (200×) (D), for MUM-1 (200×) (E) and negative for IgM (200×) (F).

Table 1
Clinical data and the results of IgM expression.

	PCFCL ($n = 30$)	PCDLBCL, leg type ($n = 10$)
Sex		
Male	19	6
Female	11	5
Age		
Median	56.5	76.5
Range	35–79	45–94
Localization		
Head	12	3
Trunk	18	4
Arm	6	–
Leg	4	3
Unknown	1	–
Therapy		
RT	9	6
CT	2	3
RT + CT	1	2
Surgery	6	–
Other	1	–
Follow-up (mo)		
Median	36	12
Range	1–84	3–72
Current status		
AWOD	23	–
AWD	1	7
DWOD	2	–
DWD	–	2
Unknown	4	1
Immunohistochemistry		
Bcl-2(+)	7/30	9/10
Bcl-6(+)	30/30	2/10
MUM-1(+)	3/30[a]	10/10
CD10(+)	7/30	0/10
IgM(+)	0/30	10/10

AWOD, alive without disease; AWD, alive with disease; DWOD, died without disease; DWD, died with disease.
[a] 10–30% of lymphoid cells are positive.

Table 2
Detailed information of PCFCL, showing expression of IRF4/MUM-1.

	1st patient	2nd patient	3rd patient
Sex and age	46 M	36 F	39 M
Number of lesions	5–10	2	1
Site of lesions	Trunk, arm	Head	Leg
Therapy	RT	RT	RT
Follow-up period	24 months	48 months	46 months
Recurrence	None	None	None
Current status	AWOD	AWOD	AWOD
Immunohistochemistry			
CD20	+	+	+
Bcl-2	+	–	+
Bcl-6	+	+	+
MUM-1	+	+	+
CD10	–	+	–
Ki-67	60%	50%	50%

M, male; F, female; AWOD, alive without disease.

seen in 3 cases (3/30). In 2 of these cases, lesions were multiple and located on the head, trunk and arms. In the third case, the tumor was seen a solitary lesion on the leg. The diagnosis of PCFCCL was checked once more due to the possibility of incorrect diagnosis. However, the morphology was clear-cut PCFCCL, showing a dermal infiltration, containing medium to large cleaved cells, intermingled with reactive lymphocytes and eosinophils. Moreover, the proliferative activity with Ki-67 varied from 50-60% in these cases, when compared with a higher proliferative activity of PCDLBCL, leg type. More detailed information, concerning these cases is seen in Table 2. The follow-up period of these 3 cases ranged from 24 months to 48 months. All had radiotherapy and were alive without disease and without any recurrence. None of these cases showed IgM expression (Fig. 3).

Based on our findings, immunohistochemical expression of IgM seems to be a useful tool in the distinction of PCFCL and PCDLBCL, leg type, since all the cases of PCDLBCL, leg type demonstrated strong and widespread cytoplasmic staining of IgM, while all cases of PCFCL were negative. This finding is in parallel with previous reports, pointing out that the expression of IgM is encountered in activated post-germinal B cell type lymphomas as a result of defective class switch recombination and has an adverse prognostic significance [7]. Differing from Koens et al. in our series, none of the cases of PCFCL had the expression of IgM, even those located on the legs [7]. Although there was one case of PCFCL with staining of bcl-6, bcl-2 and IRF4/MUM-1 at the same time, it was also negative for IgM.

In conclusion, the use of immunohistochemical IgM would be of benefit in the differential diagnosis of PCFCL and PCDLBCL, leg type.

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None.

Conflict of interest

All authors have no conflict of interest to declare.

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References

[1] Swerdlow SH, Campo E, Haris NL, et al. WHO Classification of Tumors Haematopoietic and Lymphoid Tissues. Geneva, Switzerland: WHO Press; 2008.
[2] Senff NJ, Hoefnagel JJ, Jansen PM, et al. Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J Clin Oncol 2007;25:1581–7.
[3] Kempf W, Sander CA. Classification of cutaneous lymphomas—an update. Histopathology 2010;56:57–70.
[4] Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. Arch Dermatol 2007;143:1144–50.
[5] Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 2008;112:1600–9.
[6] Robson A. Immunocytochemistry and the diagnosis of cutaneous lymphoma. Histopathology 2010;56:71–90.
[7] Koens L, Vermeer MH, Willemze R, Jansen PM. IgM expression on paraffin sections distinguishes primary cutaneous large B-cell lymphoma, leg type from primary cutaneous follicle center lymphoma. Am J Surg Pathol 2010;34:1043–8.
[8] Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood 2005;106:2491–7.