Transformation of primary cutaneous follicle centre lymphoma into primary cutaneous diffuse large B-cell lymphoma of other type

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Non-Hodgkin lymphomas (NHL) arising from the skin with no evidence of extracutaneous involvement, at the time of diagnosis, are recognized as primary cutaneous lymphomas (PCL). Primary cutaneous lymphomas have to be distinguished from other nodal NHL affecting skin secondarily. Therefore, the European Society for Medical Oncology (ESMO) observed PCL as separate entities from their nodal/systemic counterparts defining distinct diagnostic, treatment and follow-up guidelines.

Skin is the second most affected organ by extranodal NHL with an estimated annual incidence of 1/100 000 in Western countries [1]. Within the group of PCL, cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL) can be distinguished [2]. Geographically, their distribution varies among different world regions. Regarding data from the Western world, CTCL are the most common with an estimated incidence of 75–80%, while CBCL are found to be rare with an incidence of 20–25% [2, 3]. Specifically, the region of southeast Asian countries have a presumable high incidence of CTCL, in particular Epstein-Baar virus associated natural killer/T-cell lymphomas, while CBCL are very uncommon [4, 5].

According to the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC), it has been proposed that CBCL should be divided into the following types: primary cutaneous follicle center lymphomas (PCFCL), cutaneous marginal zone lymphomas (PCMZL), and cutaneous large B-cell lymphomas (CLBCL). Furthermore, CLBCL can be divided to leg skin, the other, and exceedingly rare type CLBCL. A summarized review is presented in Table 1.

We report a rare case of CBCL with a long-term clinical course of an indolent PCFCL transforming to a more aggressive, rare variant, of other type (PC-DLBCL-O), stressing a natural biological event in lymphoma biology.

A 60-year-old Serbian male diagnosed with PC-DLBCL-O was admitted to our Institution for staging and decision on the treatment strategy.

The disease primarily appeared in 2001, 13 years prior to actual dissemination. It presented as a solitary erythematous macular-papular lesion of the middle chest skin, which was surgically removed. The pathohistology revealed low-grade LCA+, CD20+, MPO- CBCL composed of small to medium-sized lymphoid cells (centrocytes) some tissue specimens of which had a nodular growth pattern. According to the WHO 2008 classification, this lesion highly resembles PCFCL. The disease-free interval (DFI) was 2 years. The relapse occurred at the same location of the body. However, the new lesion was quite slow in progress and the patient underwent the "watch and wait" strategy, which lasted for almost 10 years. During 2014, the tumor began to grow slightly and disseminate. It clinically appeared as disseminated erythematous macules and patches on the patient's trunk skin (Figure 1). The biopsy was performed from the middle chest skin, and it revealed massive lymphoid infiltrate composed of large B-cells (centroblasts) infiltrating the dermis and hypodermis. It resembled PC-DLBCL. The immunophenotype confirmed PC-DLBCL-O with germinal center origin (GCB) (Figures 2 A–D): LCA+, CD20+, CD79α+, BSAP+, MUM1–, CD10+, bcl6–, bcl2–, CD5–, cyclin D1–, CD23–, CD30–, CD3–, CD34–, EMA–, EBV–, ALK–, CD38–, CD68–, NSE–, actin–, desmin–, EMA–, HMB45–, S100–, MelanA–; Ki 67 index was 70%. The patient was HIV, HCV, HBsAg, IgM/IgG *Borrelia burgdorferi* negative. The blood cell count and biochemistry analysis (LDH, β_2-microglobuline) were remarkable. Multislice computed tomography (MSCT) of the neck, chest, abdomen and pelvis did not confirm the disease spreading outside the skin. Bone marrow biopsy revealed regular hematopoiesis. According to Ann Arbor

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Table 1. WHO/EORTC 2005 classification of CBCL

1	Primary cutaneous follicle center lymphoma (PCFCL)	
2	Primary cutaneous marginal zone lymphoma (PCMZL)	
3	Primary cutaneous large B-cell lymphoma (PCLBCL)	
3A	Primary cutaneous diffuse large B-cell lymphoma, leg type (PC-DLBCL-LT)	
3B	Primary cutaneous diffuse large B-cell lymphoma, the other (PC-DLBCL-O)	
3C	Exceedingly rare PC-LBCL*	Intravascular PC-LBCL
		T cell/histiocyte rich PC-LBCL
		Anaplastic PC-LBCL
		Plasmablastic PC-LBCL

**Provisional entities, not included in the official classification.*

criteria, the patient was staged as CS I E, A (asymptomatic disease). A low International Prognostic Index (IPI)-0 was calculated.

The treatment approach included 8 cycles of R-CHOP$_{21}$ (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) induction chemo-immunotherapy. Post-treatment positron emission tomography/CT (PET/CT) evaluation showed no metabolically active sites of the disease. Complete remission (CR) was obtained. The patient is attending his regular follow-up visits, being in excellent condition.

Primary cutaneous follicle center lymphomas is a distinct type of follicular lymphoma (FL) compared with its nodal/systemic counterpart, and is not associated with typical FL features: translocation (14;18) or bcl2 overexpression, although the presence of those characteristics does not exclude its diagnosis. Its incidence is around 55–60% of all CBCL, having an excellent prognosis with 5-year overall survival (OS) over 95% [6]. However, relapses occur in more than 30% of cases [7]. Recently, the cutaneous lymphoma IPI (CLIPI) has been identified, which is based on 3 parameters: elevated lactate dehydrogenase (LDH), > 2 skin lesions, and nodular lesions. This index is prognostic for DFI [7]. Retroactively observed, our patient had a low CLIPI index, even so he relapsed soon. However, the disease has had no progression for a long period of time.

PC-DLBCL is a rare entity which accounts for approximately 6% of all PCL, and in 15% of cases it can be found outside the legs [8]. More information is available about PC-DLBCL-LT, which tends to be very aggressive. It is characterized by strong bcl2, MUM1/IRF4 and FOXP1 expression and post-germinal center origin (non-GCB) has been postulated [9]. However, our patient lacked typical PC-DLBCL-LT immunophenotype features (bcl2, and MUM1/IRF4 negativity), and had a high Ki67 proliferative index (low index is typical for FL with the cut-off level < 40%), therefore it could reasonably be considered as PC-DLBCL-O. The diagnosis of PC-DLBCL-O is set up for CBCL with composition of large B-cells that lack the typical features of PC-DLBCL-LT, and do not conform to the definition of PCFCL [8]. There are clinical data which support the lack of bcl2 expression in CBCL arising outside the leg skin region [10]. Our patient fits the above description since he had trunk skin lesions.

Transformation of PCFCL to an aggressive PC-DLBCL has not been clarified in the literature. The data reported so far are mostly related to a cumulative incidence of nodal/systemic FL transformation to DLBCL to an annual level of 3% [11]. We found an article which explored the transformational status for CBCL. Eighty-two patients with PC-DLBCL were included, exploring CD21/CD35 expression which could be found on remnant follicular dendritic cells (FDC) that exist in FL. Based on the expression of these 2 biomarkers, the study concluded that it could be assumed that there were 15 cases of transformed lymphoma [12]. In our case CD21/CD35 were not used, but

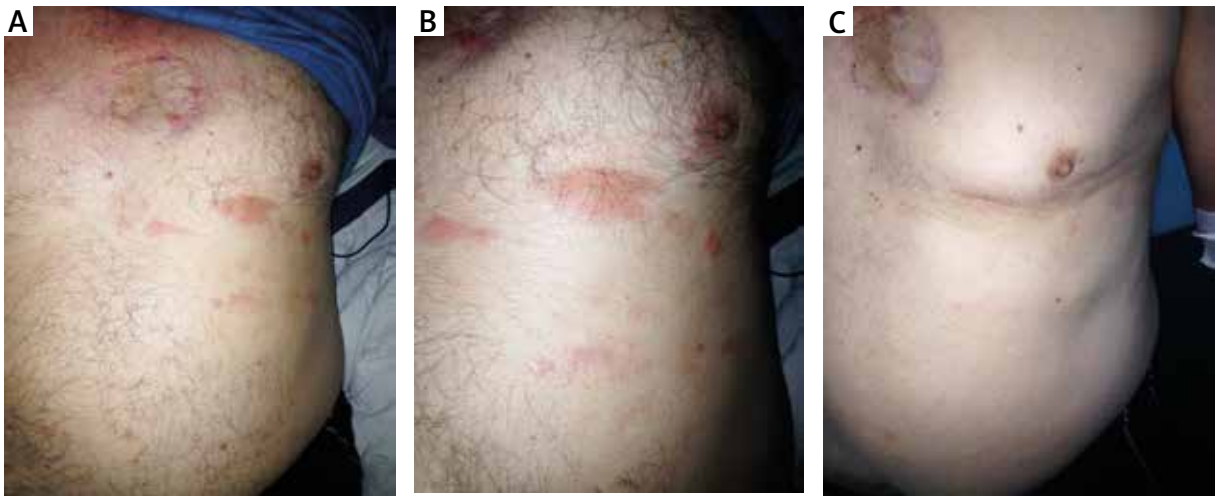

Figure 1. Disseminated erythematous macules and patches on the patient's trunk skin

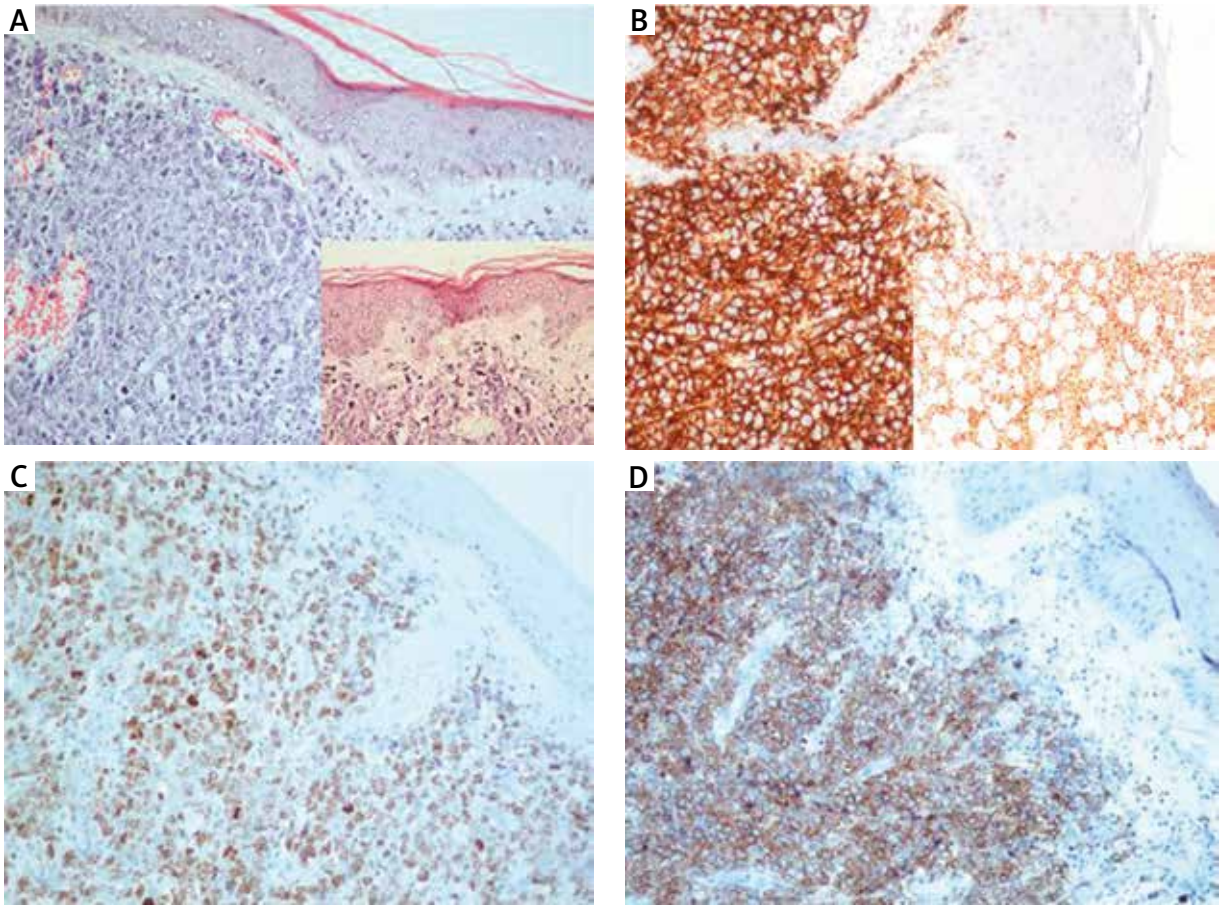

Figure 2. Diffuse large B-cell lymphoma of the skin. **A** – Dense and diffuse dermal infiltrate of large lymphoid cells sparing a subepidermal grenz zone (H + E, 200×); Inset: Large neoplastic lymphoid cells of centroblast morphology (H + E, 400×). **B** – Neoplastic dermal infiltrate displays a strong membranous and cytoplasmic expression of CD20; Inset: Diffuse infiltration of subcutaneous fat tissue (200×). **C** – Ki67 nuclear staining in up to 70% of tumor cells (200×). **D** – CD10 membranous staining of neoplastic lymphoid cells (200×)

CD10 positivity, and MUM1/IRF4 negativity indicates GCB origin which is typical of FL, and it is highly unlikely that it comes from pre-existing PCFCL.

Based on the ESMO and the National Comprehensive Cancer Network (NCCN) recommendations, PCFCL, if solitary, may be treated by surgery or local radiotherapy. Regarding scarce data and lack of randomized prospective trials, treatment options for PC-DLBCL-O, virtually have not been defined at all. Based on the aforementioned recommendations, the use of R+chemotherapy (i.e. CHOP) or R solely may be proposed [7]. However, contradictory literature data regarding the clinical behavior of these peculiar cases were obtained. Some clinical studies suggested that such cases have an indolent clinical course and may be treated in a conservative manner [8]. It appears that recommended treatment strategies are mostly based on data obtained from nodal/systemic DLBCL or PC-DLBCL-LT. Even we decided to treat our patient with a standard R-CHOP regimen, we had doubts whether this option was too aggressive. Our main dilemma was whether R monotherapy would have the ability to eradicate the disease. Finally, existing data regarding the clinical course of transformed nodal/systemic FL to DLBCL indicating a high risk of aggressive behavior, redirected us to apply anthracycline-based chemo-immunotherapy. The R-CHOP regimen has documented benefit in OS for patients with low IPI [13]. The second reason was reflected in our Health Fund restriction (R application accompanied only by chemotherapy).

In conclusion, we presented a case of an immunocompetent patient with a long-term history of pre-existing PCFCL which is highly suspected of transformation to more aggressive PC-DLBCL-O. A very limited number of cases considering this phenomenon has been published in the literature. It is a well-known biological event in FL natural course. However, data are exclusively collected for nodal/systemic disease forms. By this article we wanted to draw attention of the scientific community to a possible distinct entity which may be provisionally named as a transformed PC-DLBCL-O. For clarification of

the exact nature of the disease, clinical data accompanying gene expressing profile (GEP) analysis are needed.

Conflict of interest

The authors declare no conflict of interest.

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