SHORT COMMUNICATION

Association between Primary Cutaneous B-cell Lymphomas and Other Skin Cancers: A Multicentre Cohort Study

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Accepted Feb 23, 2022; Epub ahead of print Feb 23, 2022
Acta Derm Venereol 2022; 102: adv00687. DOI: 10.2340/actadv.v102.319

Primary cutaneous lymphomas (PCLs) are defined as non-Hodgkin lymphomas (NHLs) of the skin without evidence of extracutaneous disease at diagnosis. They are subdivided into primary cutaneous T-cell lymphomas (CTCLs) and primary cutaneous B-cell lymphomas (PCBCLs). The latter account for 25% of all PCLs and have been further categorized into 3 main groups according to the last World Health Organization – European Organization of Research and Treatment of Cancer (WHO-EORTC) classification: primary cutaneous marginal zone lymphomas (PCMZLs), primary cutaneous follicle-centre cell lymphomas (PCFCLs), and diffuse large B-cell lymphomas, leg-type (PCDLBCL, LT) (1). Recently, increasing attention on the increased risk of other primary malignancies in patients with PCL has been focused on CTCL; however, data regarding second malignancies in PCBCL are lacking (2). Rates of 16% and 25% of patients with PCBCL developing other primary cancers have been reported in the only 2 studies conducted to date, suggesting a potential association (3, 4). It is not known whether a dysfunction of cancer surveillance or immunosuppressive drugs is the basis for this association in these patients. It is notable that immunosuppressive therapy is sometimes unnecessary in PCMZL and PCFCL (4). Further clarification of this association might be of considerable importance for the management of PCBCL, as well as for the improvement of cancer screening.

Table I. Patients' demographics and characteristics

Characteristic	Patients ($n = 144$)
Sex, male, *n* (%)	91 (63,0)
Age at diagnosis, years, median (range)	55 (23–84)
Primary cutaneous B-cell lymphoma subtype, *n* (%)	
PCFCL	78 (54.2)
PCMZL	49 (34.0)
PCDLBL	15 (10.4)
Intravascular B-cell lymphoma	1 (0.7)
PCFCL and PCMZL	1 (0.7)
Staging at diagnosis, *n* (%)	
T1N0M0	81 (56.2)
T2N0M0	31 (21.5)
T3N0M0	16 (11.1)
Any N+	6 (4.2)
Any M+	2 (1.4)
Unknown	8 (5.6)
Site of lesions[a], *n* (%)	
Head and neck	42 (29.2)
Trunk	84 (56.3)
Upper limbs	31 (21.5)
Lower limbs	24 (16.7)
Unknown	9 (6.3)
Progression[b], *n* (%)	30 (20.8)
PCFCL	18 (12.5)
PCMZL	7 (4.9)
PCDLBL	5 (3.5)
High-grade transformation[c], *n* (%)	2 (1.4)
PCFCL	1 (0.7)
PCMZL	1 (0.7)

[a]Some patients had more than 1 localization of disease. [b]Progression is defined as increase in tumour node metastasis (TNM) staging system. [c]Trasformation of a low-grade B-cell non-Hodgkin lymphoma (NHL), such as primary cutaneous follicle-centre cell lymphoma (PCFCL) and primary cutaneous marginal zone lymphoma (PCMZL), into a high-grade NHL, such as primary cutaneous diffuse large B-cell lymphoma (PCDLBL).

MATERIALS AND METHODS

In order to shed light on this issue, we conducted a retrospective multicentre cohort study on PCBCLs from 2 tertiary referral centres for cutaneous lymphomas: the Dermatology Clinic of the University of Turin, Italy, and the Dermatology Department of La Fe University Hospital of Valencia, Spain. All histopathological diagnoses were made on the agreement of 2 independent dermatopathologists specialized in PCL. PCBCL staging was performed according to EORTC guidelines (5). Demographics, PCBCL subtype, site of lesions, stage at diagnosis and progression have all been assessed and summarized (**Table I**). A total of 144 patients with PCBCL were collected (78 PCFCLs, 49 PCMZLs, 15 PCDLBCLs, 1 intravascular B-cell lymphoma, 1 PCFCL and 1 PCMZL). Forty patients out of 144 (27.8%) developed at least 1 malignant neoplasm (Table SI), 67.5% were men and 32.5% women. Twenty-seven patients (18.8%) reported at least 1 non-lymphoma skin cancer and 15 (10.4%) patients were diagnosed with other non-skin related malignancy. In 2 patients both neoplastic conditions were observed. As for the non-lymphoma skin cancers, 23 were metachronous, 5 synchronous and 3 previous, whereas in the non-skin-related malignant group, 8 diagnoses were metachronous, 1 synchronous and 8 previous to the diagnosis of PCBCLs. Two patients presented more than 1 type of non-lymphoma skin cancer (i.e. both basal cell carcinoma and squamous cell carcinoma). Mean and median times of second malignancies onset (considering both metachronous and synchronous diagnoses) were, respectively, 71.5 and 48 months (range 1–264), whereas the mean and median times of having previous neoplasia were 130.2 and 138 months (range 4–264). Patients diagnosed with other primary cancers following PCBCL who had undergone radiotherapy (RT), immunosuppressive treatment, or a combination of both, accounted for 37.1% ($n = 13$), 20% ($n = 7$) and

11.4% (n=4), respectively. PCMZL was the most common PCBCL subtype associated with other non-lymphoma skin cancers (28.5% of cases), whereas the more common PCFCL was associated with other non-lymphoma skin cancers in 16.6% of cases. None of the patients with other primary cancers had a family history or other risk factors related to the development of cancer. Ultimately, skin cancers (n=29), followed by prostate malignancies (n=4) and urothelial malignancies (n=3) appear to be the most frequently occurring neoplasms in the current PCBCL patient population.

DISCUSSION

To the best of our knowledge, this first multicentre study on secondary malignancies in PCBCLs collects the largest cohort described, and displays the highest percentage of metachronous skin cancers presented, to date, in the literature. Since more frequent dermatological examinations are performed on patients with PCBCL and given an increased cumulative risk of developing skin cancers in the age range of our cohort (i.e. median age 55 years) compared with the general population, the possibility of selection bias should be taken into account (6). However, the absence of familiar and other risk factors for cancer development, as well as the low number of patients treated with immunosuppressive agents and developing other primary cancers, seems to suggest, in accordance with Chan et al. (3) and Gomez Sanchez et al. (4), a possible increased intrinsic risk for the development of other primary PCBCL-related cancers. Based on the current data, as indicated in CTCL (7), we believe that a careful dermatological examination to screen for skin tumours following the diagnosis of PCBCL is fundmental to promptly identify skin neoplasms in these patients. Moreover, the risk of developing a non-skin-related malignancy should be carefully considered, as most patients with not only primary CTCL (8), but also primary CBCL, do not undergo regular instrumental workups. Further studies are needed to better define the exact risk of tumour incidence in this population.

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