Epidemiology of cutaneous lymphoma

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Cutaneous lymphomas (CLs) represent a rare and heterogeneous group of lymphomas that present in the skin without extracutaneous manifestations at the time of diagnosis. As the diagnosis and classification of CLs requires integration of clinical, histological, immunophenotypical and molecular characteristics, and is complicated by the rarity of these diseases, clinical care of patients with a CL is often concentrated in national expert centres. Data on the epidemiology of CLs are primarily based on patient cohorts seen in these expert centres and in national pathology registries. However, patient cohorts from expert centres can be influenced by referral bias, while pathology registries are prone to misclassification of patients as central review with the integration of clinical and pathological features is not routinely performed. However, an accurate understanding of the incidence and the prevalence of CLs is important for clinicians, patients, pharma and regulatory policymakers.

In this issue of the BJD, Dobos et al. present a retrospective analysis of epidemiological data from the French Cutaneous Lymphoma Registry (FCLR). Based on 779 patients included in 2018 by the FCLR, the authors report an incidence of CL of 0.96 per 100 000 population. By comparing patients included in the FCLR database from 2005 to 2009 with patients included from 2010 to 2014, and with patients included from 2014 to 2019, several changes in the prevalence of CL subtypes were found.

Previous epidemiological studies on cutaneous T-cell lymphoma (CTCL) performed in Wales and Norway, based on 120 and 337 patients, respectively, reported a much lower prevalence for CTCL of 0.29–0.39/100 000 population. In contrast, studies from the USA based on much larger groups of patients (range 4310–6230) reported a prevalence of 0.64–0.87/100 000 population. Therefore, based on the results of these latter studies and the current paper by Dobos et al., a similar prevalence of CL of around 0.90/100 000 population seems most likely in both Europe and the USA.

In line with previous studies, CTCL represented a much larger proportion (75%) of the included patients than cutaneous B-cell lymphoma (CBCL; 25%). Also, the proportional distribution of CL over different diagnostic entities and the demographic characteristics observed in this study, including age at diagnosis, a female-to-male ratio of 0.6 for mycosis fungoides (MF), diffuse large B-cell lymphoma (leg type) being more frequent in females and the observation that the large majority of patients with MF presented with early-stage disease, are in line with previous studies.

The strong points of the paper by Dobos et al. include the large number of collaborating centres, the large number of included patients, the long duration of data collection and the consistent use of the World Health Organization–European Organisation for Research and Treatment of Cancer’s classification system, allowing for the observation of changes in the epidemiology of CL over time. Whereas for some well-described CL subtypes, such as classical MF and lymphomatoid papulosis, the number of cases remained relatively stable over time, a large (sometimes spectacular) increase was observed in other CL subtypes.

For example, for CTCL, an increased number of included patients was seen for those with folliculotropic MF (10 in 2005–09 and 325 in 2015–19), primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder patients (35 in 2005–09 and 244 in 2015–19) and primary cutaneous anaplastic large-cell lymphoma (one in 2005–09 and 94 in 2015–19). For CBCLs an increase was seen in primary cutaneous marginal zone B-cell lymphoma (113 in 2005–09 and 446 in 2015–19) and primary cutaneous large B-cell lymphoma (leg-type; two in 2005–09 and 111 in 2015–19).

Whether the increase in patients diagnosed with these relatively new and rarer diagnostic entities relates to more accurate diagnosis combined with greater awareness of the FCLR.
Evidence suggests that herpes zoster (HZ) has an increasing incidence and imposes a high economic burden worldwide.\(^1\)\(^2\) The risk of HZ increases in parallel to the decline in varicella zoster virus-specific cell-mediated immunity. The latter may be caused by age-dependent decline in immune responses, immunosuppressive drugs and comorbidities such as haematological malignancies, bone marrow or solid organ transplantation, and HIV.\(^3\) HZ-associated complications, hospitalization and fatality predominantly affect immunocompromised hosts.\(^4\) While immunocompromised individuals are more vulnerable to the sequelae of HZ, immunocompetent individuals may also follow a severe course and develop complications.\(^5\) However, our knowledge about HZ-associated complications in immunocompetent hosts is hampered by the scarcity of population-based studies. Previous studies relied on small-scale study populations and did not include matched reference groups, rendering them underpowered to measure the risk of these complications relative to the general population. A precise estimation of HZ-associated complications bears a substantial significance for the accurate estimation of the disease burden, which is imperative for making decisions on zoster vaccination policy.\(^6\)

In the current issue of the BJD, Forbes et al.\(^7\) performed a well-designed retrospective matched cohort study including 178,964 immunocompetent patients with HZ and 1,799,380 age-, sex- and practice-matched immunocompetent controls. Relative to matched controls, immunocompetent patients with HZ had a significantly increased risk of neurological (3.6-fold), ocular (twofold), cutaneous (1.6-fold) and visceral (1.3-fold) complications in the first 3 months following HZ. In an age-stratified analysis, the relative risk of each of the aforementioned complications was greater among younger patients. This finding reflects the low baseline incidence rates of these complications in young controls.

The current study indicated that HZ contributed a 0.48%, 1.33%, 0.29% and 0.78% increase in the risk of neurological, ocular, cutaneous and visceral complications in the first 3 months following HZ diagnosis, respectively. The absolute risk of HZ-associated hospitalization and mortality was 0.97% and 0.04%, respectively. Considered collectively, HZ-associated complications among immunocompetent hosts are non-negligible and impart a considerable burden on the healthcare system. The current study implies that these substantial outcomes should be taken into consideration in cost-effectiveness and budget impact analyses for zoster vaccination. In most countries, zoster vaccination policy relies on the costs of postherpetic neuralgia and HZ-associated hospitalization, which, in light of the current study findings, underestimates the real burden of HZ.

Of great clinical implication, it was observed that oral antiviral treatment conferred significant protection against neurological complications, Ramsey Hunt syndrome and hospitalization. These observations portray the importance of antiviral prescription, even in immunocompetent hosts.

Taken together, this excellent epidemiological study conveys an insightful lesson about the risk of complications among immunocompetent patients with HZ. The findings of this study should be included in cost-effectiveness models of zoster vaccination to precisely reflect the burden of the disease. As oral antivirals proved beneficial in prevention of neurological complications and decreasing HZ-associated hospitalization,