COMMENTARY

Frequency, risk factors and prognosis of systemic haematologic malignancies, cutaneous and other neoplasms in lymphomatoid papulosis: where are we now?

Lymphomatoid papulosis (LyP), since its first description in 1968, presented itself as a strange disease characterized by a relapsing and self-healing chronic papulonodular eruption following a relatively benign course, even though it has malignant histopathological features with large atypical CD30 lymphoid cells. In fact, LyP has been classified in the chapter of cutaneous T-cell and NK-cell lymphomas in the 2018 update of the WHO-EORTC classification of primary cutaneous lymphomas.[1] It is well known that patients with LyP have a lifelong increased risk to develop some haematologic malignancies (HM) including mycosis fungoides (the most common one), cutaneous or systemic anaplastic large cell lymphoma (ALCL), or Hodgkin lymphoma.[2] In spite of these data, the disease-specific survival of LyP patients after 5 years reaches almost 100% and the prognosis of the disease is considered excellent.[3] In this number of JEADV, Melchers *et al.*[4] investigate the frequency and prognosis of associated malignancies in a large cohort of 504 LyP patients (i.e. probably the largest LyP study to date) based on the Dutch registry data of cutaneous lymphomas. Although not a new observation, the reported prevalence of associated HM is positioned at 15.5% that is lower than in most previously published studies where the percentage is approximately of 20%.[5] This might be explained by the reported referral efficient system in the Netherlands, where referral bias might have been overcome and this prevalence seems to be closer to the real evolutionary risk of LyP, also considering that a few studies report frequency data of <10% and other studies of more than 50%.[6] Mycosis fungoides and ALCL have been confirmed as the most common HM associated with LyP with a good prognosis for patients with both diseases. While an identical *TCR* gene rearrangement seems to be a sound explanation for the association between LyP and T-cell lymphomas suggesting that both disorders arise from a common lymphoid progenitor, the reason why patients with LyP may develop other types of HM is unknown and the data of this paper lead the authors to conclude that this association could be only a coincidence.[4] The observation that LyP patients have an increased risk of developing cutaneous squamous cell carcinoma, melanoma and other systemic neoplasms has rarely been reported and mostly on anecdotal basis[7]; thus, it is important to stress this finding that may further increase the awareness among dermatologists. The explanation for possible major risk of developing cutaneous squamous cell carcinoma and melanoma could be related to UV therapy exposure, immunosuppressive treatments and/or frequent skin examination of LyP patients. The finding of a relatively high prevalence of 29% of atopic dermatitis in patients with LyP is not even negligible because patients with atopic dermatitis not only have an increased risk of developing T-cell lymphoma and primary cutaneous $CD30^+$ lymphoproliferative disorders[8] but also have an increased risk of SCC development and possibly of other neoplasms,[9,10] although larger studies need to confirm this last finding. It remains an open question how can we predict the development of an HM in LyP patients. Histologically, there are at least seven major histological types of LyP lesions according to the cell type, and the pattern of infiltration or tropism: A, B, C, D, E, (F)ollicular and LyP with 6p25.3 rearrangement but the data from the literature fail to confirm a relationship between the histopathological subtypes and the prognosis.[11] It has been reported but not confirmed that subtypes A and D of LyP have been associated with a lower risk for developing a second malignancy while subtypes B and C present a higher risk.[2] Although the histopathological subtypes have not been included in the article of Melchers *et al.* to rule out or confirm these findings, a manuscript of the same group including a large part of these same patients showed that there are no prognostic differences between the different histological subtypes, considering in particular A and C subtypes.[11] Other prognostic markers that has been suggested as useful to predict the development of a second lymphoid neoplasm such as frequent relapses of LyP lesions, involvement of the face, an older age, the expression of fascin by CD30+ large cells, high blood levels of soluble CD30, CD25, interleukin (IL) 6, and IL-8 and a detectable T–cell clone[3] have not been highlighted by this study, and the risk factors for developing a second HM remains pending. In any case, we all are increasingly aware that patients with LyP require long-term follow-up to monitor the disease course and the response to therapy and need a lifelong surveillance for the development of cutaneous or systemic lymphoma and eventually other types of cutaneous and systemic neoplasms.

F. Rongioletti*
Department of Medical Sciences and Public Health, Unit of Dermatology, University of Cagliari, Cagliari, Italy
*Correspondence: F. Rongioletti. E-mail: rongioletti@unica.it

Linked article: R.C. Melchers et al. J Eur Acad Dermatol Venereol 2020; **34**: 260–266. https://doi.org/10.1111/jdv.16065.

References

1 Willemze R, Cerroni L, Kempf W, *et al.* The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019; **134**: 1112.
2 Martinez-Cabriales SA, Walsh S, Sade S, Shear NH. Lymphomatoid papulosis: an update and review. *J Eur Acad Dermatol Venereol* 2020; **34**: 59–73.
3 Cordel N, Tressières B, D'Incan M, *et al.* Frequency and risk factors for associated lymphomas in patients with lymphomatoid papulosis. *Oncologist* 2016; **21**: 76.
4 Melchers RC, Willemze R, Bekkenk MW, *et al.* Frequency and prognosis of associated malignancies in 504 patients with lymphomatoid papulosis. *J Eur Acad Dermatol Venereol* 2020; **34**: 260–266. https://doi.org/10.1111/jdv.16065.
5 Kunishige JH, McDonald H, Alvarez G, Johnson M, Prieto V, Duvic M. Lymphomatoid papulosis and associated lymphomas: a retrospective case series of 84 patients. *Clin Exp Dermatol* 2009; **34**: 576–581.
6 Kempf W. Cutaneous CD30-positive lymphoproliferative disorders. *Surg Pathol* 2014; **7**: 203–228.
7 Newland KM, McCormack CJ, Prince HM, Lade S. Cutaneous CD30 positive lymphoproliferative disorders with coexistent epithelial neoplasms: report of two cases. *Australas J Dermatol* 2015; **56**: e83–e87.
8 Zychowska M, Woźniak Z, Maj J. Primary cutaneous CD30 + lymphoproliferative disorders in a patient with severe atopic dermatitis: is there a causative link? *Acta Derm Venereol* 2018; **98**: 123–125.
9 Cho JM, Davis DMR, Wetter DA, Bartley AC, Brewer JD. Association between atopic dermatitis and squamous cell carcinoma: a case-control study. *Int J Dermatol* 2018; **57**: 313–316.
10 Arana A, Wentworth CE, Fernández-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol* 2010; **163**: 1036–1043.
11 Bekkenk MW, Geelen FA, van Voorst Vader PC *et al.* Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood* 2000; **95**: 3653–3661.

DOI: 10.1111/jdv.16157