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Comment on “Association of bullous pemphigoid with malignancy: A systematic review and meta-analysis”

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3 **Title:** Comment on “Association of bullous pemphigoid with malignancy: A systematic review and meta-
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44 **To the Editor.** We read with interest the manuscript published by Atzmony et al, concerning the
45 association between bullous pemphigoid (BP) and malignancies.¹ As known, numerous studies have
46 tried to investigate the link between BP and cancer. Besides the temporal association, some clinical
47 evidences such as skin lesions improvement while on cancer-targeting procedures and the lack of
48 recurrence after tumour excision are thought to support this relationship. Conversely, experimental
49 studies providing plausible explanations about cancer-induced production of anti-basement membrane
50 zone autoantibodies are still lacking. Moreover, revision studies have yielded contrasting results,
51 because devoid of systematic approach.¹ Thus, the issue remains open to speculation as yet.

52 Interestingly, analysing the data of one cohort and four cross-sectional studies, Atzmony et al found a
53 possible association between BP and hematoproliferative diseases, but not with overall malignancies.¹

54 It is our opinion that the results by Atzmony et al might be influenced by an overestimated incidence of
55 BP in hematologic patients, due to its clinico-pathologic, and sometimes immunopathologic, overlap
56 with eosinophilic dermatoses of haematologic malignancies (EDHM). The latter refer to a heterogeneous
57 spectrum of cutaneous manifestations occurring in patients with underlying hematologic cancer, mostly
58 B-cells chronic lymphocytic leukaemia (B-CLL). Clinically, EDHM may present with urticarial papules,
59 plaques, or nodules mimicking the pre-bullous phase of BP. Even blistering eruptions have been often
60 reported.^{2,3,4} Histopathologically, dermo-epidermal detachment and eosinophil-rich dermal
61 inflammatory infiltrates are classically detected in both diseases.⁴ Finally, EDHM may show confounding
62 immunopathologic features, as reported in a study by Bottoni et al, in which six B-CLL patients with
63 insect bite-like reactions had positive anti-BP180 antibodies on immunoblotting test,⁵ and in a case by
64 our group, in which a B-CLL patient with EDHM had linear deposition of Immunoglobulin M and C3 at
65 direct immunofluorescence test.⁴ Indeed, EDHM and BP appear challenging to distinguish, leading to
66 potential diagnostic pitfalls. However, their distinction is crucial for many reasons: i) patients with
67 idiopathic eosinophilic dermatoses has to be closely monitored because of the further risk of developing

68 hematologic malignancies, compared to idiopathic BP; ii) EDHM follow a waxing and waning behaviour
69 despite both dermatologic and hematologic treatments; iii) the treatment of the two conditions is
70 different.

71 To conclude, although BP may occur as a paraneoplastic event in patients with hematoproliferative
72 diseases, clinicians should keep in mind EDHM in the diagnostic work-up of hematologic patients
73 experiencing BP-like blistering eruptions.

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92 **References**

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116 **ABBREVIATIONS**

117 Bullous pemphigoid: BP.

118 Eosinophilic dermatoses of hematologic malignancies: EDHM.

119 B-cells chronic lymphocytic leukemia: B-CLL.

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