Letter in Response to Previous Publication

Secondary skin infection as trigger for post-rituximab paradoxical pemphigus flare?

Dear Editor,

We thank the authors for their interest in our study of clinical and immunological predictors of post-rituximab paradoxical pemphigus flare[1] and are happy to respond to their queries.

Out of the 57 patients screened, we included 50 in our study. The treatment plan was changed in three patients: corticosteroid pulses due to financial constraints in two patients and intravenous immunoglobulin due to concurrent sepsis followed by steroid pulses in one patient. The remaining four patients received only the first dose of rituximab: two patients declined the second dose due to financial reasons, one developed a urinary tract infection and the second dose was withheld, while another patient did not return after the first dose. We agree with the authors that these patients could have been followed up to look for flare; however, at the time, we chose to exclude them as the plan to administer the second rituximab dose was abandoned.

The included patients were evaluated at two and four weeks for a post-rituximab pemphigus flare. As stated in our results, ten patients experienced a flare: eight after the first rituximab dose within two weeks and two patients within four weeks.

It is interesting to learn that the authors have also observed this unusual phenomenon of post-rituximab pemphigus flare in their practice and hypothesise that secondary skin infection caused by rituximab-induced hypogammaglobulinemia could be a triggering event. Though an attractive hypothesis, we feel the evidence provided in their study is insufficient to support it. The authors reported paradoxical flare in 4 (9%) out of 44 patients. However, what defines a 'flare' in terms of Pemphigus Disease Area Index (PDAI) or treatment change was not specified, which could potentially lead to an inaccurate estimation of the flare incidence. Further, the authors should have compared the infection rates in the 'flare' group with that of the 'non-flare' group to detect an association between secondary skin infection and pemphigus flare, but no information is provided on the 40 patients who did not experience pemphigus flare. The timeline of flare vis-à-vis secondary skin infection is also not clear, and thus establishing a cause-effect relationship is challenging. Secondary skin infection developing as a complication of pemphigus flare is equally plausible, as was the case with one of our patients who succumbed to sepsis.

The authors propose that rituximab-induced hypogammaglobulinemia could predispose to infections, which, in turn, can trigger an epitope-spreading phenomenon leading to the pemphigus flare.[2] There is conflicting evidence on the link between rituximab-associated hypogammaglobulinemia and infection risk in the published literature.[3,4] Even so, paradoxical pemphigus flares have not been noted with other immunosuppressive treatments that also predispose to infections. Rituximab has been shown to alter the balance between B-effector and regulatory B-cell populations in favour of effector cells, depending on the timing of B-cell depletion in a murine model, which may explain why this phenomenon is unique to rituximab among all pemphigus treatments.[5]

In our study, we did not report the baseline skin microbial studies as skin infection was not selected as *a priori* baseline predictor of flare. Similarly, skin microbial studies at the time of flare were also not reported, as the objective of our study was to evaluate the baseline predictors of flare and not to characterise changes at the time of or after a flare.

We appreciate the authors for bringing forth some interesting points through their work, providing us with a chance to further discuss a few nuanced aspects of this unusual phenomenon of post-rituximab paradoxical pemphigus flare.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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