Letter in Response to Previous Publications

Hypogammaglobulinemia-induced skin infections as a factor of post rituximab paradoxical flare in pemphigus

Dear Editor,

We read the article 'Clinical and immunological predictors of post-rituximab paradoxical pemphigus flare: A prospective cohort study' with great interest and congratulate the authors for conducting this study, which is highly relevant in clinical practice.[1] Earlier, the data on disease flare after rituximab (RTX) infusion in pemphigus was limited to isolated case reports, case series and retrospective analyses. This was a prospective, observational cohort study where 50 patients with pemphigus vulgaris and foliaceous were included, of which 10 cases (20%) developed disease flare. Eight cases developed a flare after the first dose of rituximab and two cases developed it after the second infusion. Out of the studied clinical and immunological factors, pemphigus disease area index (PDAI) score (>28) and anti-Dsg1 levels (>1137 RU/mL) were found to be statistically significantly associated with post-rituximab disease flare.

Prospective design is an advantage of this study. While going through the manuscript, certain points caught our attention that, in our humble opinion, require further clarification. As the authors have mentioned in the study flow chart, a total of 57 patients were screened but only 50 patients were included in the study. The authors have mentioned that three patients were shifted to corticosteroid pulse therapy, but the reason for this change in the treatment plan was not clarified. Four patients were not administered a second dose of RTX; again, the reason for this is not mentioned by the authors. Also, if these four patients were administered the first dose, they would fulfil the inclusion criteria for the study. The reason for their withdrawal from the study was not mentioned. We observed that although follow-up evaluations at week 2 and week 4 were part of the study design, authors failed to report the clinical characteristics at these time points.

Previously, in a retrospective analysis, Narayanan *et al*. have implicated more frequent secondary bacterial infections of pemphigus lesions as a risk factor for disease flare.[2] Similarly, there was an almost simultaneous publication from our institute where a retrospective analysis of 44 patients with pemphigus vulgaris treated with rituximab was performed.[3] Four cases (9%) developed a paradoxical flare of disease. A rather remarkable finding in our study, which was not reported by the authors of the above study was that all cases with disease flare were associated with secondary bacterial infection of skin lesions, documented with positive culture studies from skin swabs and fall in serum immunoglobulin G levels (≤7 g/L) from baseline. At the time of disease flare, in three out of four cases, gram-positive and gram-negative bacteria, i.e. *Staphylococcus aureus* and *Pseudomonas*, *Klebsiella,* and *Proteus*, respectively, were isolated and in one case, moderate growth of *Staphylococcus aureus* was noted. The identification of gram-negative bacteria is noteworthy as these organisms are typically not isolated from immunocompetent hosts and thus may denote underlying immunosuppression. This aspect has been overlooked by the investigators of the current study. Neither at baseline nor at the time of flare have microbial studies from the lesional skin been reported. The outcome of flares in terms of time taken for resolution, modalities, antimicrobials in particular, used for the management of flare, and the disease course after receiving a second dose of RTX was not discussed by the authors. Though authors have mentioned that one patient died of sepsis, the colonisation status of skin lesions in all other cases remains unreported.

RTX-induced hypogammaglobulinemia is a known adverse event, reported from studies in rheumatology literature as a delayed event.[4] The study from our institute shows hypogammaglobulinemia as an immediate complication of RTX therapy. We propose hypogammaglobulinemia-induced skin infections and resultant epitope spreading as a probable explanation of paradoxical disease flare.

Undoubtedly, the present study along with other recent publications have started a serious conversation about this less explored and potentially fatal phenomenon in patients of pemphigus who are treated with RTX. Further investigations into the role of infections, hypogammaglobulinemia, and other known and unknown underlying factors responsible for this phenomenon are warranted. Translating this understanding into clinical practice, particularly in identifying at-risk populations would be highly relevant in predicting and

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preventing the paradoxical flare of disease activity following RTX treatment.

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

Dear Editor,

We thank the authors[1] for their interest in our study of clinical and immunological predictors of post-rituximab paradoxical pemphigus flare[2] 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

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