Bendamustine as a Cause of Drug-Associated Bullous Pemphigoid—A Rare Side Effect

Dear Editor,

Bullous pemphigoid (BP) is the most common autoimmune bullous skin disease, first described independently by Lever in 1953. It is a chronic, subepidermal bullous disease caused by antibodies against hemidesmosomes of basal keratinocytes. The disease is more common in old age (>60 years). BP classically manifests with tense blisters over urticarial plaques on the trunk and extremities, accompanied by intense pruritus. Mucosal involvement is rarely reported. Drug-associated bullous pemphigoid (DABP) is a term used to describe instances of BP demonstrating clinical, histological, or immunopathological features identical or similar to those of the idiopathic form of BP, associated with the systemic ingestion, or topical application of particular drugs.[1] DABP is commonly seen after the use of drugs such as certain gliptins, loop diuretics, antibiotics like penicillin and its derivatives, anti-inflammatory, and biologic medications.[2] After the withdrawal of the suspect medication, most patients respond rapidly to treatment and do not experience relapses. Bendamustine is a cell cycle non-specific alkylating agent used in the treatment of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and mantle cell lymphoma. Cytotoxic effects of bendamustine primarily result from alkylation-mediated DNA damage and possibly to a lesser extent from antimetabolite properties of its benzimidazole ring. Bendamustine is a bifunctional alkylating agent containing two reactive groups that can bond to separate DNA sites, a feature characteristic of other nitrogen mustard-related agents such as cyclophosphamide, chlorambucil, and melphalan. Monofunctional alkylating agents, on the other hand, contain a single active chemical moiety that is able to modify only a single DNA site.[3] DABP is a rare side effect of bendamustine, our report will serve to inform physicians about this rare side effect associated with bendamustine use and our approach in managing this condition.

A 67-year-old male patient, a known case of follicular lymphoma, on bendamustine 180 mg intravenously (IV) at the dose of 90 mg/m^2 and rituximab 750 mg IV at the dose of 375 mg/m^2, had completed one cycle. On initiation of the second cycle, the patient presented with multiple raised itchy lesions over bilateral upper limbs and abdomen of two weeks' duration. It was followed by the development of fluid-filled lesions over upper limbs over the preexisting lesions. On dermatological examination, multiple tense bullae over the extensor aspect of bilateral upper limbs along with a few erythematous plaques with central vesiculation over abdomen were seen [Figures 1 and 2]. Nikolsky's sign was negative. Skin biopsy from the extensor aspect of forearm was performed. Histopathological examination revealed intraepidermal clefts with numerous perivascular eosinophils. [Figures 3 and 4] Based on the history and our high clinical suspicion of BP, we performed direct immunofluorescence (DIF) from the normal-appearing perilesional skin which revealed granular staining for antibody against IgG and C3 along dermal-epidermal junction [Figure 5]. We therefore diagnosed the patient with DABP likely due to bendamustine (Naranjo's score 5). The culprit drug was stopped, and systemic prednisolone in tapering doses was administered. His lesions demonstrated improvement with remarkable regression of preexisting bullae, and no fresh lesions appeared subsequently. He has been followed up for six months with no recurrence of lesions.

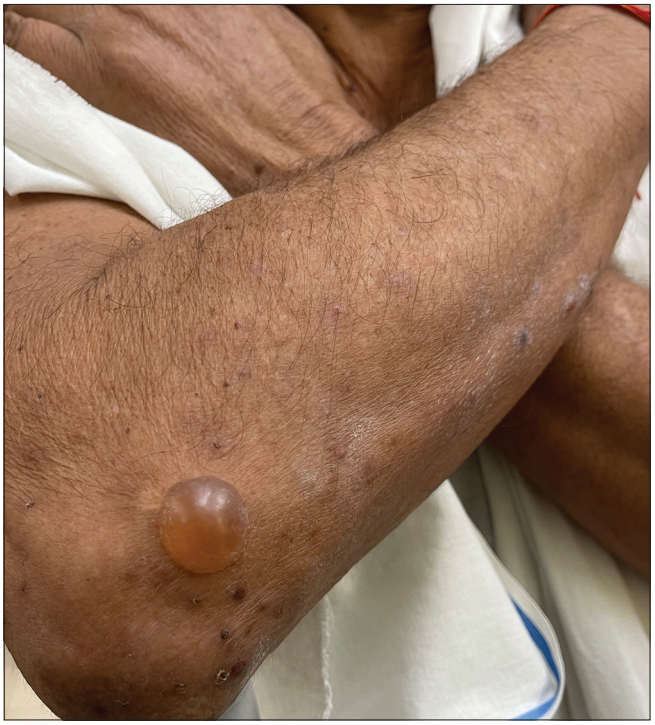

Figure 1: Tense bulla seen over right forearm

BP is the most common autoimmune blistering disease, characterized by subepidermal separation and inflammation with abundant eosinophils leading to tense bullae. Autoantibodies target two main structural proteins of the dermal-epidermal junction, BP antigen 1 (BPAG1 or BP230 antigen) and BPAG2 (or termed BP180 antigen).[4] The annual incidence of BP was estimated to range from 2.4 to 21.7 per million population in different populations worldwide. The classic histopathology in BP reveals a

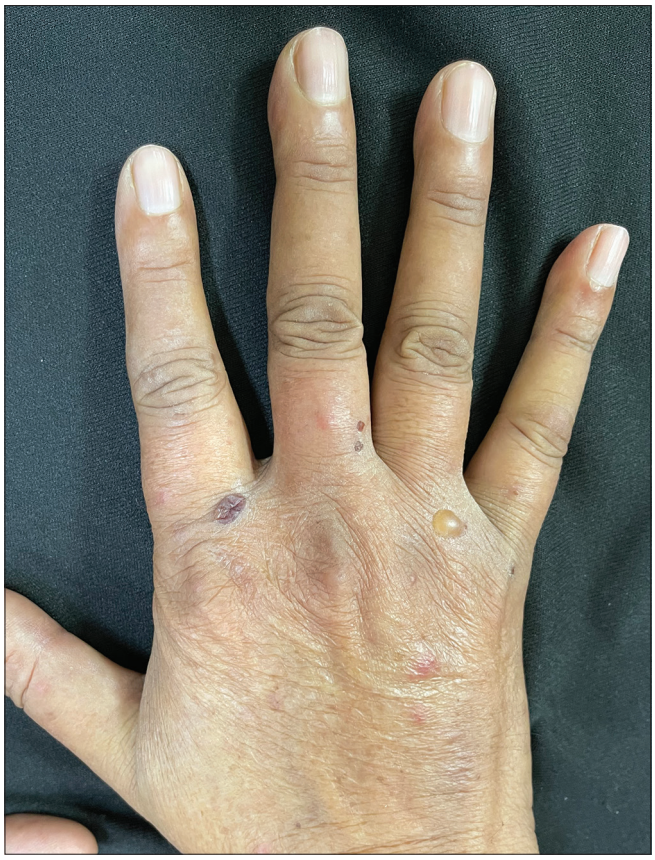

Figure 2: Bullae and urticated plaques seen over right hand

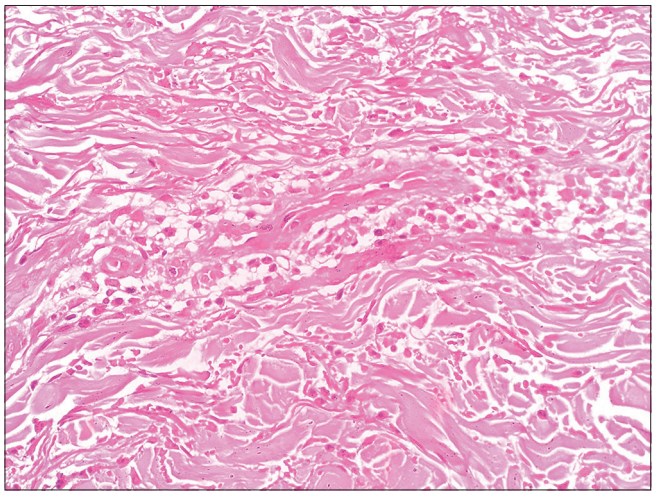

Figure 4: Numerous perivascular eosinophils (H&E, 400x)

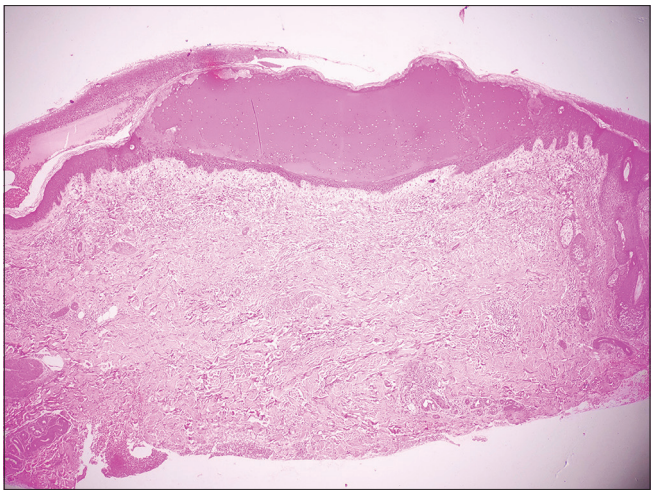

Figure 3: Intraepidermal cleft with proteinaceous material within the cleft (H&E, 100x)

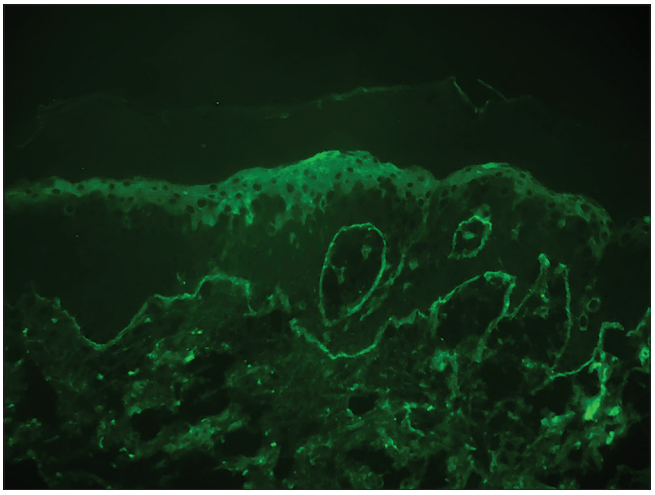

Figure 5: Direct immunofluorescence (DIF) of perilesional skin with FITC (Fluorescein isothiocyanate) tagged anti IgG showed IgG deposited in a granular pattern along basement membrane (100×)

subepidermal blister, though only half of the biopsies in DIF-proven cases of BP were retrospectively found to have a subepidermal blister. Specifically, the presence of an intraepidermal blister and/or epidermal necrosis on routine hematoxylin and eosin-stained specimens does not preclude the diagnosis of BP.[5] Because the tense, durable blisters of BP last a long time, the "end-stage" of epidermal reparative process may produce a pseudo-intraepidermal cleft.[5] The recent surge in the cases of BP has been linked to the increased use of medicines.[6] Medications induce antibody production by acting as haptens to bind to proteins in the lamina lucida, and some may unmask hidden antigens or stimulate an autoimmune response. Autoimmune damage via altered antigenicity of structures within the lamina lucida, negative action on immune suppressor cells, or direct splitting of the skin without the development of antibody are some of the proposed mechanisms of drug-induced BP.[7] Paraneoplastic BP associated with underlying malignancy are rare and often involve mucous membranes.[8]

In our case, the disease may have been triggered by bendamustine or rituximab. The possible explanation of bendamustine as the culprit drug might be its properties similar to purine analogues which are often known to cause vesiculobullous disorders. The lesions too regressed after stopping bendamustine with no recurrence for the next 6 months. A similar case of paraneoplastic pemphigus

has been reported with bendamustine.[9] With the plethora of drugs being used nowadays, similar cases with history of recent drug introduction should raise clinical suspicion and should be investigated with detailed clinical and histopathological investigations. The case is being reported to educate the community of the rare side effect of a commonly used drug bendamustine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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