Clinical Letter

Severe bullous drug reaction after COVID-19 mRNA vaccination

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Dear Editors,

mRNA-vaccinations against COVID-19 have been associated with individual cases of bullous autoantibody-mediated skin disorders [1] and bullous non-autoantibody-mediated skin reactions such as Stevens-Johnson syndrome (SJS) [2], toxic epidermal necrosis (TEN) [3], bullous drug reactions (BDR), or fixed bullous drug eruption (FBDE). In most cases the latter conditions are induced by drugs, however, vaccines as causative agents of SJS/TEN have been described in less than 20 cases [4, 5]. Histology presents as subepidermal bulla with overlying full-thickness epidermal necrosis and a sparse perivascular lymphocytic infiltrate, but only few features help differentiate between BDR and SJS/TEN. Cell death of epidermal keratinocytes mediated by peptide-activated $CD8^+$ T cells with involvement of granzyme B, tumor necrosis factor alpha (TNF-alpha) and perforins are considered key pathogenetic factors [6]. In this article, we present a case of a severe BDR after the first administration of the mRNA-vaccine BNT162b2.

A 39-year-old man with no history of skin disorders presented in our outpatient emergency clinic with extensive blistering of the left elbow (Figure 1a) and forearm (Figure 1b). The skin lesions appeared 72 hours after he received the first dose of the BNT162b2 vaccine into his left arm. No further symptoms were reported. The patient's history revealed a well-controlled HIV-infection, with a non-detectable virus-load and arterial hypertension. His regular daily medication with an antiviral combination therapy (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide fumarate 10 mg) and ramipril 5 mg had not been changed during the past nine months. A punch biopsy taken from his left forearm revealed a subepidermal cell-poor blister with full-thickness necrosis of the epidermis and an overlying basket-weave orthokeratosis (Figure 2a). Serologically, we did not detect autoantibodies against BP180/230 or Desmoglein 1/3 after the first vaccination. Standard blood measurements showed no pathological values. Direct immunofluorescence revealed no specific pattern. In line with these findings we diagnosed a severe bullous drug reaction. Immunosuppressive treatment with oral prednisolone 100 mg per day for three days followed by 50 mg daily for two additional days stopped the process and led to almost complete resolution within 14 days (Figure 2b). Although we recommended against a repeated use of the same vaccine, the patient received his second dose of BNT162b2 six weeks after the first one at an authorized vaccination center. After this second dose, he reported the developing of a smaller blister on the right elbow, but no further reactions of the skin on the initially affected left body-side.

Here, we report one of the first cases of severe BDR in the context of BNT162b2 vaccination in a patient with HIV.

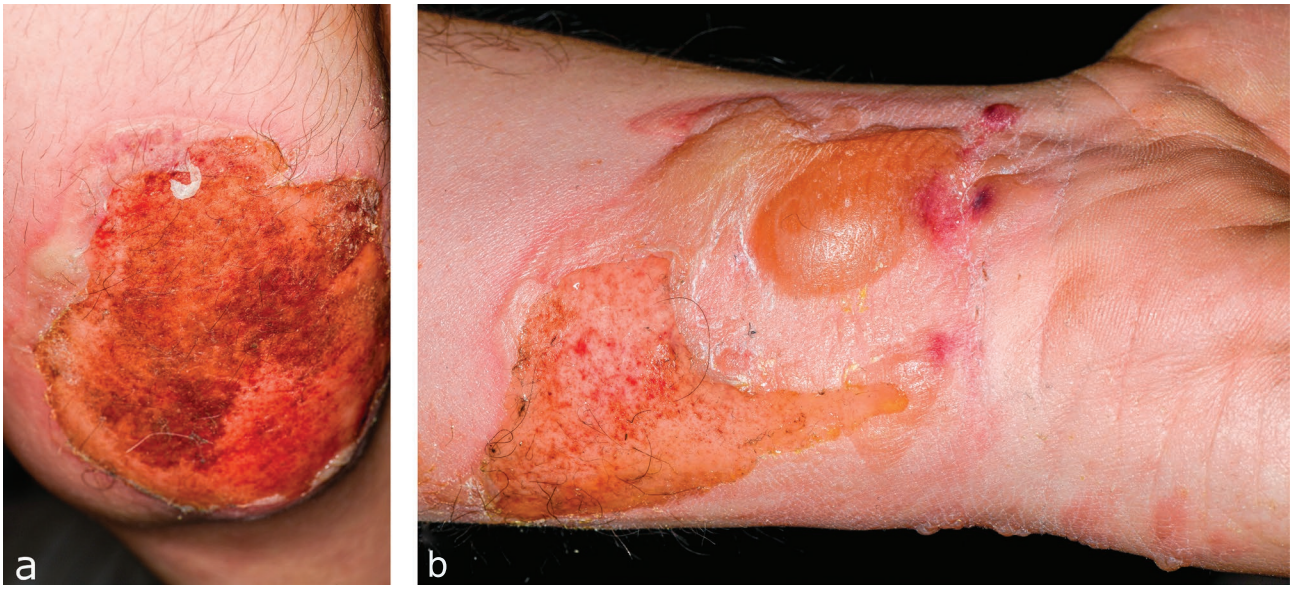

Figure 1 Large erosive blister (10 × 10 cm) with exudation of the left elbow (a) and extensive erosion with central, bulging blister filled with serous, bloody fluid of the left forearm (b) after first injection with BNT162b2 in the left deltoid muscle.

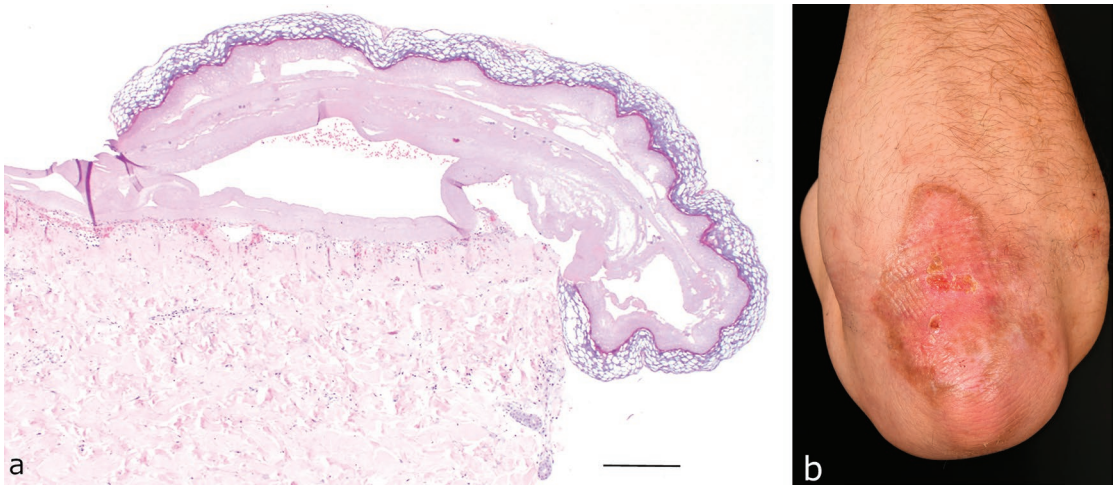

Figure 2 Histology of a skin biopsy from the left forearm shows a subepidermal cell-poor blister with full thickness necrosis of the epidermis and an overlying basket-weave orthokeratosis (a). Left elbow with reepithelialization, six weeks after first dose vaccination with BNT162b2 (b).

To date, only two publications of BDR [7, 8], one case of TEN [3] and two cases of SJS [4, 9] after COVID-19-mRNA vaccinations have been reported. Two reports of generalized bullous fixed drug eruption (GBFDE) after AstraZeneca-vaccination exist. In our case, occurrence of new blisters on the initially unaffected arm does not fit into the diagnosis of a FBDE. Commonly described adverse events after injection of COVID-19-mRNA vaccines, include local redness, swelling, pain, or systemic effects such as fever, headache, joint pain, or diarrhea [10]. In rare cases of severe skin complications such as BDR, SJS or TEN, viral antigens expressed on the surface of keratinocytes may lead to the activation of cytotoxic T lymphocytes and epidermal cell death [11]. The impact of the underlying HIV infection in the herein presented patient remains unclear, given that several extensive bullous eruptions with or without drug intake have been published in this context [12]. Overall, the occurrence of BDR or SJS/TEN is a very rare event after vaccinations. Even for routine vaccines like rubella, measles or mumps only a few case reports exist. Hazir et al. reported SJS in a ten-month-old male baby 36 hours after measles vaccination. Similarly, SJS occurred in a 16-year-old patient four days after receiving measles-mumps-rubella vaccine [13, 14]. With regard to other components of BNT162b2, type I anaphylactic reactions, but no BDR or SJS/TEN have been reported to polyethylene glycol 2000 (PEG-2000) and trometamol [15, 16], rendering involvement unlikely.

Taken altogether, the documentation of such cases in timely association with COVID-19 vaccinations is important. Circumscribed skin reactions as in our case may be tolerated, given that he developed contralateral but significantly milder involvement after his second dose. This observation is in accordance with the overall perception that local and systemic skin reactions to COVID-19 vaccines can usually be tolerated and treated very well. Still, decision making as how to proceed in individual cases requires careful consideration. By sharing this case, we want to create awareness for cases of BDR after mRNA vaccinations. In such individuals we recommend switching to non-mRNA based COVID-19 vaccines.

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Conflict of interest

None.

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