Letter to the Editor

Dermatologic Therapy

Nivolumab – associated pemphigoid – like blistering dermatosis after sun exposure

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The patient gave his consent for the use of the pictures.

All the authors took part in the manuscript

NK collected the data, interpretation, drafted the manuscript and revised

LL, TM, LV and KL collected the data and revised the final version

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Der Editor,

Bullous pemphigoid (BP) is increasingly reported with immune checkpoint inhibitors (ICI) directed against programmed cell death protein-1 (PD-1) (Lopez, 2018) [1]. Molina *et al* recently report about clinical difference between ICI induced BP and idiopathic BP (Molina, 2020) [2]. We wish to report an atypical case of BP-like eruption after sun exposure under nivolumab.

A 70-year-old man presented an acute exanthema of the upper and lower limbs with blisters on the legs. His medical history was notable for choroidal melanoma of the left eye and right-sided renal clear-cell carcinoma (RCC) both diagnosed and treated in 2015. Two years later, RCC metastases prompted to start tyrosine kinase inhibitor (TKI) sunitinib, that was discontinued after six months due to progression. Nivolumab was initiated (3 mg/kg eow). The patient reported self-limiting oral blisters after each of the first 4 infusions. Before the 12th infusion, he developed an acute itchy rash on the soles that extended rapidly to the lower and upper limbs and the back. Upon examination, the patient displayed a dusky red exanthema mostly on sun-exposed areas (forearms, hands, palms and lower limbs, **Fig. 1**) with tense blisters on the legs and a slight eruption on the trunk. The face was unaffected. The patient was an avid golfer and acknowledged

playing quite much during the summer. The rest of the examination, including mucosae, was unremarkable. Laboratory findings showed hypereosinophilia (800/mm3) and elevated CRP (50 mg/L). Antinuclear antibodies, soluble antigens antibodies, indirect immunofluorescence test and ELISA BP180 were negative. Histology showed a sub- and intra-epidermal blister containing eosinophils and an eosinophil rich infiltration in the dermis without sunburn cells. Direct immunofluorescence on lesional skin revealed junctional C3 deposition without immunoglobulins. Improvement of the skin lesions was rapid under oral prednisolone (starting dose 1 mg/kg/day) and clobetasol propionate ointment. Nivolumab was withdrawn. He presented at follow up visit with only residual pigmentation. After three months of follow-up, the rash had not relapsed. Because of progression of RCC, cabozantinib, a multi-TKI, was initiated as a third line treatment.

We report here a case of PB-like dermatosis, mainly restricted to photoexposed areas during nivolumab therapy. To our knowledge, PD-1 inhibitors have never been associated with increased photosensitivity or phototoxicity. However, BP has been described within 6 to 8 months from initiation [1]. Arguments that favor such hypothesis in our case are: 1) compatible delay of onset after nivolumab initiation (Lopez, 2018), 2) transient hypereosinophilia, histology and DIF features, 3) histology did not support simple severe sunburn, 4) ICI induced BP may exhibit atypical features (Molina, 2020), 5) lack of other BP-inducing drugs, and 6) lack of relapse after nivolumab withdrawal. BP has been reported after UVB or UVA exposure (George, 1996) and sunburn (Lee, 1992). In our patient, BP may be the consequence of intense sun exposure. UV light could have induced the localized exposure of BP antigens through the local production and release of inflammatory mediators and local damage (Lee, 1992). The patient may have had a limited oral BP

induced by nivolumab that went unnoticed until intense sun exposure. Photo-tests with a new DIF would have been of interest. However, we felt untimely to perform such tests now as nivolumab was withdrawn and a new TKI was initiated.

Conflict of interest: none declared

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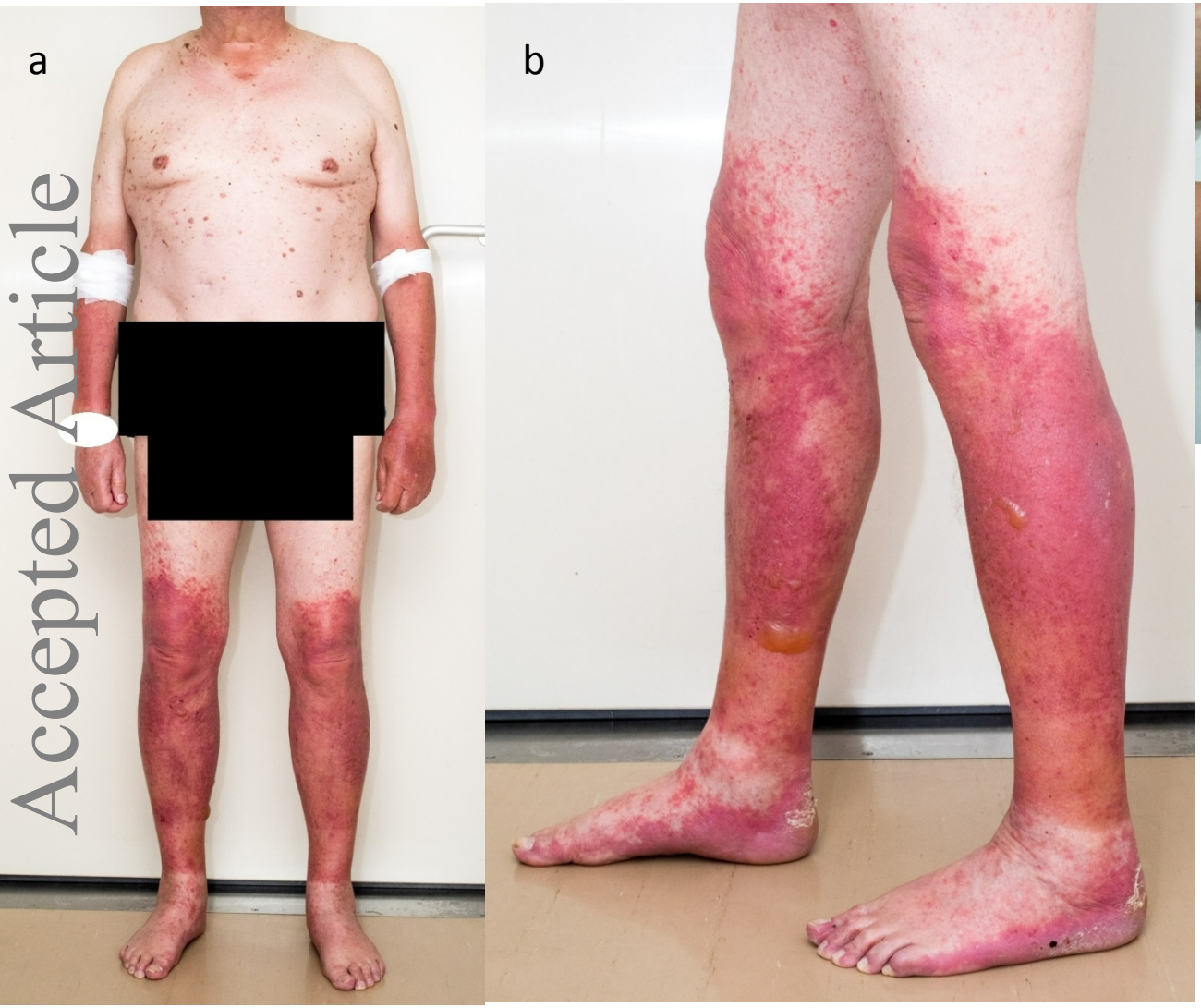
Figure legends

Figure 1. Clinical presentation. (a) Dusky red exanthema of the upper limbs and legs restricted to sun-exposed areas. (b and c) Close-up view of the legs with blisters.



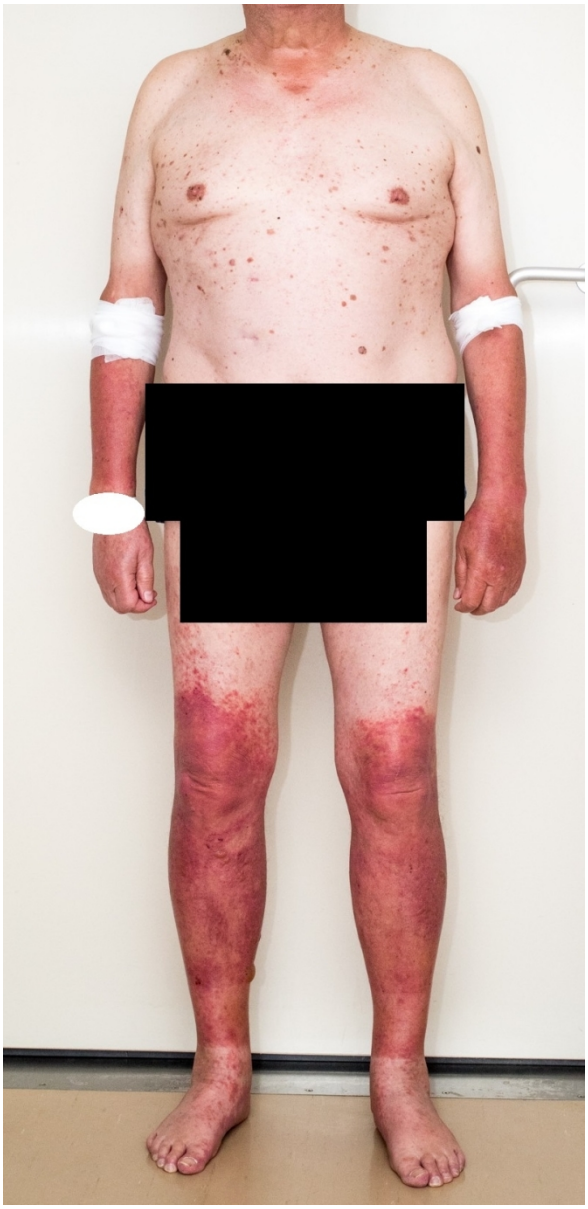


Figure 1A

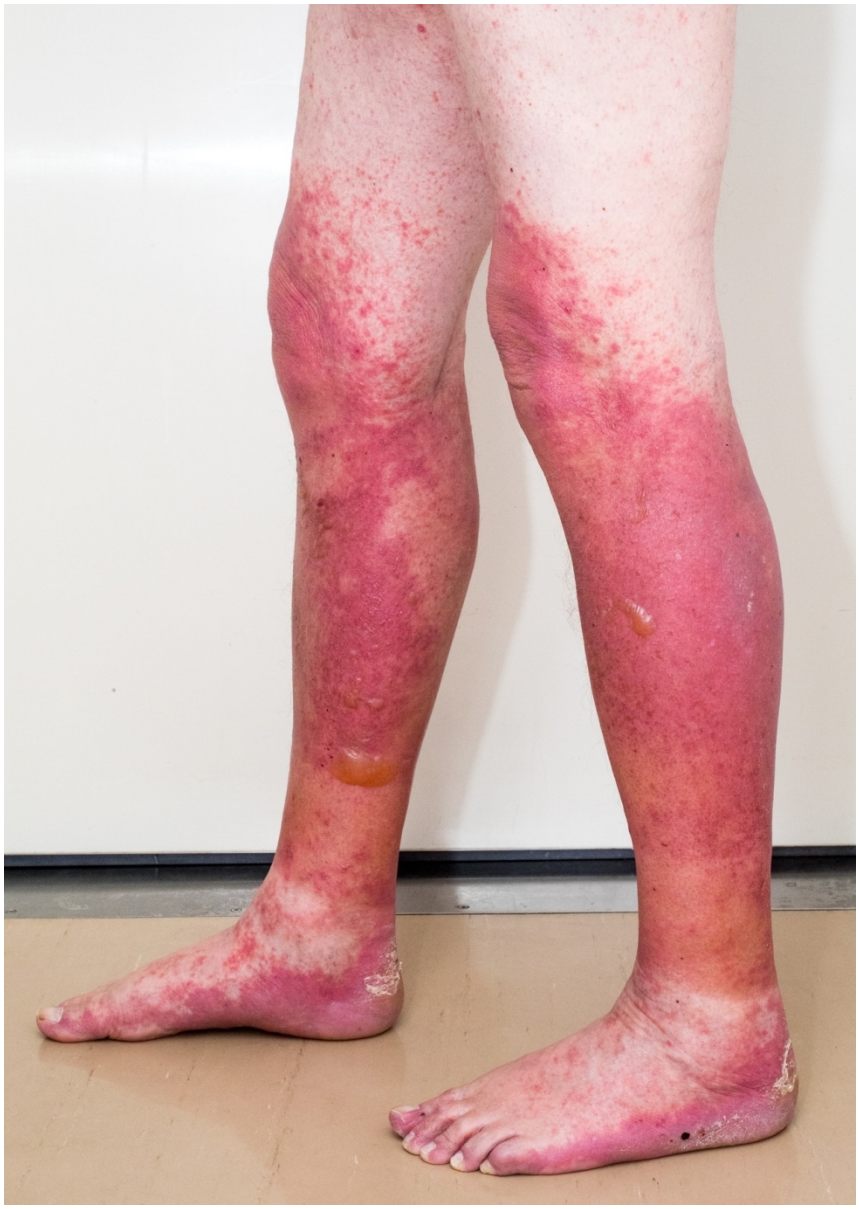


Figure 1B

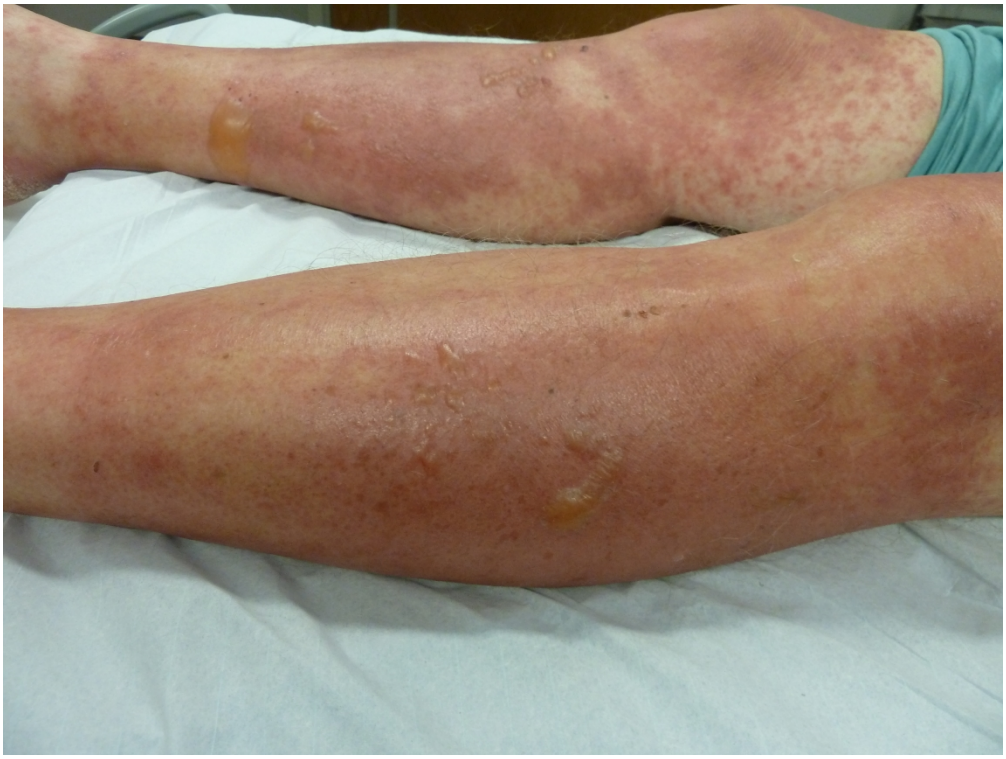


Figure 1C