Limitations of morphology-based management for immune checkpoint inhibitor-related cutaneous adverse events

To the Editor: We read with interest the Continuing Medication Education (CME) article by Geisler et al[1] on checkpoint inhibitor-related cutaneous adverse events (irCAEs). In their article, the authors thoroughly outline the clinicopathologic features and management of irCAE morphologies, building on prior work in addition to delineating and incorporating best-practice recommendations.

Although organizing skin toxicities by morphology is commonplace,[2] we feel compelled to highlight several constraints of the outlined approach. More specifically, management practices relying on morphologic categorization and fixed timelines may insufficiently address clinically relevant heterogeneity and immunophenotypic details of irCAEs.

With regards to the timelines delineated for different forms of irCAEs, the desire by Geisler et al to provide concrete parameters to inform therapeutic approaches, particularly for dermatologists with limited experience with irCAEs, is laudable. However, the asserted timelines may be too narrow. Although dermatologic toxicities can appear shortly after therapy is initiated, delayed presentations are not uncommon.[3] For example, the large single-centered observational study by Coleman et al[4] assessing irCAEs associated with immune checkpoint inhibitor regimens revealed a mean latency period of 4 to 18 months for bullous pemphigoid and lichenoid dermatitis toxicities, a stark contrast to the authors' proposed chronologies of 2.9 to 3.45 months for bullous pemphigoid and 1.6 to 3 months for lichenoid dermatitis. Considering the demonstrated variability in irCAE chronology alongside patient and institution-related factors that can potentially hinder treatment (ie, delayed referral of a mild reaction), the timelines asserted by Geisler et al may be restrictive.

The pathophysiologic mechanisms of many cutaneous toxicities remain poorly understood,[3] and limited availability of biopsy data suggests significant variability within morphologic categories. In this light, morphology-based irCAE classification may also undermine salient diagnostic details. This is particularly true for nonspecific categories, notably pruritus and maculopapular rash,[2] of the most common irCAEs occurring in approximately 20% of those treated with anti-programmed cell death protein 1/programmed death-ligand 1 agents and 50% of patients receiving anti–cytotoxic T-lymphocyte–associated protein 4.[3,5]

Broad descriptors such as maculopapular rash, for example, are often used to characterize an array of morphologic subtypes, such as lichenoid reactions.[3] Maculopapular rash can also represent prodromal features of more severe cutaneous toxicities, including bullous pemphigoid.[3] As such, use of morphology as a primary guide for irCAE treatment can be flawed.

Although the authors effectively summarize important clinicopathologic features and treatment strategies for irCAEs, additional discussion about the limited reliability of toxicity timelines and broad morphologic categorizations is warranted. Because the use of immune checkpoint inhibitor therapy increases, with up to one-third of patients experiencing dermatologic reactions,[3] greater specificity of morphologic definitions and corresponding treatment ladders will be critical. These changes would help address deficiencies of current management guidelines, including broad recommendations and failure to incorporate other common cutaneous toxicities.[2]

Geisler et al[1] have contributed significantly to the current landscape of knowledge in supportive oncodermatology. As experts in the management of these complex immune events, we should understand limitations of existing evidence and the potential for clinical variability when considering management of patients with irCAE.

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Conflicts of interest

None disclosed.

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