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REFERENCES

1. Cheng MY, Sukhov A, Sultani H, et al. Trends in National Institutes of Health funding of principal investigators in dermatology research by academic degree and sex. 2016; 152(8):883-888.
2. Boris C, Cotsarelis G, Fairley JA, et al. A cross-sectional survey and analysis of Dermatology Foundation Career Development Award recipients. *J Am Acad Dermatol*. 2019;81(5):1093-1098.
3. Roskoski R, Parslow TG. Ranking tables of NIH funding to US medical schools in 2019 as compiled by Robert Roskoski Jr. and Tristram G. Parslow. Blue Ridge Institute for Medical Research. Available from: http://www.brimr.org/NIH_Awards/2019/NIH_Awards_2019.htm. Accessed February 25, 2020.

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Risk factors for recurrent and metastatic cutaneous squamous cell carcinoma in immunocompromised patients

To the Editor: Immunosuppressed states, such as solid organ transplant, are associated with a greater cutaneous squamous cell carcinoma (cSCC) disease burden.[1-3] Immunosuppressed patients with high-risk cSCC have inferior outcomes compared with immunocompetent patients with similar tumors, even when the same multimodality treatment is used.[4] There is a critical need to expand classification of clinical and pathologic factors to prognosticate recurrence and metastasis across different categories of immunocompromising diseases.

We present a single-institution retrospective cohort study to characterize and compare disease-related risk factors for recurrence or metastasis of primary cSCC in patients with a history of solid organ transplant, HIV/AIDS, chronic kidney disease (CKD), and immunoproliferative disorders (IPD).

After Mount Sinai Hospital institutional review board approval (16-00822), we retrospectively identified patients with histologically confirmed cSCC that recurred or metastasized after treatment of the primary tumor and a diagnosis of 1 of the following at least 6 months previously: (1) organ transplant recipients (OTRs) receiving immunosuppressants; (2) HIV/AIDS; (3) IPDs including leukemia, lymphoma, multiple myeloma, and other myelodysplastic disorders; or (4) CKD.

There were 29 patients (90% men; 76% white; median age, 69 years; range, 33-87 years) identified as having organ transplant only (24%), CKD only (21%), HIV/AIDS only (24%), IPD only (4%), or multiple immunocompromising diseases (28%). Of the primary tumors, 14% were in situ, 21% were Brigham and Women's Hospital stage (BWH) T1, 41% were BWH T2a, 10% were BWH T2b, 4% were BWH T3, and 10% were unstageable because of fragmentation or ulcer. Primary tumors were

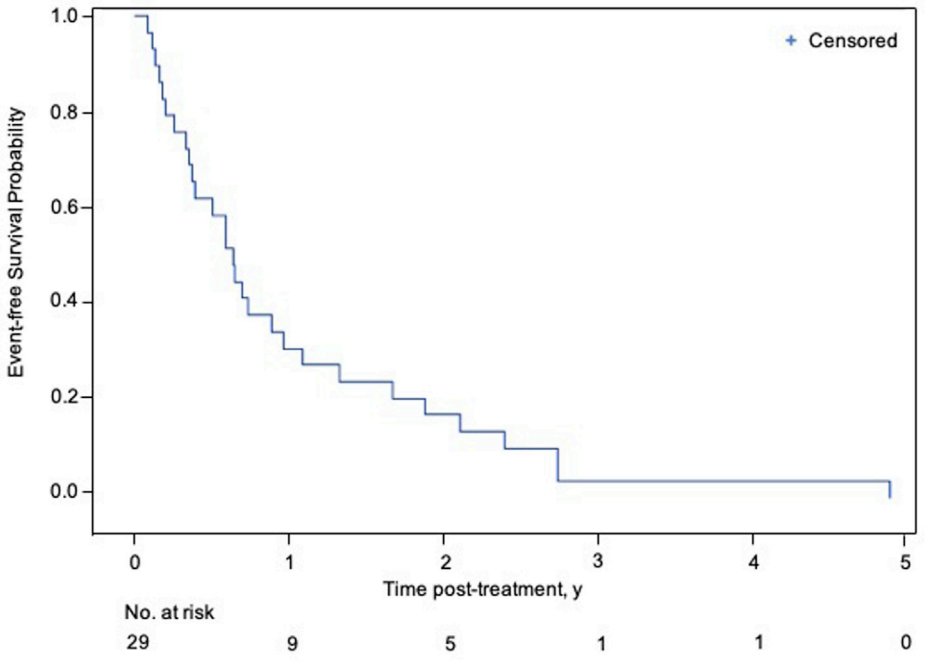

Fig 1. Recurrence or metastasis-free survival after treatment of primary tumor.

Table I. Multivariable predictors of long-term cancer recurrence or metastasis as determined by multivariable Cox model*

Patient or operative detail	HR	HR 95% CI, lower limit	HR 95% CI, upper limit	*P* value
Age, ≥65 y or <65 y	0.90	0.24	3.41	.881
Sex, male vs female	3.85	1.11	12.5	.033
Race, white vs nonwhite	4.29	1.43	12.88	.009
Immunocompromising disease				
CKD vs OTR	2.93	0.67	12.80	.152
HIV/AIDS vs OTR	0.20	0.05	0.81	.024
IPD vs OTR	2.23	1.01	4.96	.049
Multiple vs OTR	0.45	0.14	1.49	.191
Nonsurgical vs surgical treatment	3.33	1.16	9.09	.026
BWH, T0/T1 vs T2/T3/TX	1.30	0.36	4.73	.695

BWH, Brigham and Women's Hospital staging system; *CI,* confidence interval; *CKD,* indicates chronic kidney disease; *IPD,* immunoproliferative disorder; *HR,* hazard ratio; *OTR,* organ transplant recipient.
*Calculated using multivariable Cox modeling fit for the outcome of long-term recurrence or metastasis with the competing risk of death, controlling the listed 6 covariates.

predominantly treated with excision (45%) or Mohs micrographic surgery (38%), and the rest were treated with electrodesiccation and curettage or chemotherapy. Seventeen (59%) patients had recurrence only, 6 (21%) had metastasis only, and 6 (21%) had recurrence and metastasis. Disease-specific death occurred in 3 (10.3%) participants, and death of unknown cause occurred in 2 (7%) participants.

Kaplan-Meier analysis showed 77% (95% confidence interval, 48%-91%) survival at 5 years and 51% (95% confidence interval, 9%-83%) survival at 8 years. Recurrence or metastasis occurred in 50% of the cohort by 8.5 months after definitive treatment of the primary tumor (Fig 1).

Risk factors significantly associated with recurrence or metastasis were male sex ($P > .033$), white race ($P < .009$), and use of electrodesiccation and curettage or chemotherapy as the primary treatment ($P < .026$). Compared with patients with OTR only, patients with IPD only had a significantly greater risk ($P < .049$), and patients with HIV/AIDS only had a significantly smaller risk ($P < .024$) of long-term recurrence or metastasis. Patients with CKD only and those with multiple diseases, the majority of whom included OTR as 1 of their immunosuppressive conditions, showed no difference in risk of recurrence or metastasis compared with those with OTR only (Table I).

Although this cohort's small size limits the generalizability of these findings, these results provide novel insight into an existing differential risk of long-term recurrence or metastasis based on the source of immunosuppression. These findings lay the foundation for future investigations with greater sample sizes to clarify how immunosuppressive diseases of different types can contribute to the risk of recurrence and metastasis in clinically or histologically aggressive cSCC.

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REFERENCES

1. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med.* 2003;348(17):1681-1691.
2. Hock BD, McIntosh ND, McKenzie JL, Pearson JF, Simcock JW, MacPherson SA. Incidence of cutaneous squamous cell carcinoma in a New Zealand population of chronic lymphocytic leukaemia patients. *Intern Med J.* 2016;46(12):1414-1421.
3. Asgari MM, Ray GT, Quesenberry CP Jr, Katz KA, Silverberg MJ. Association of multiple primary skin cancers with human immunodeficiency virus infection, CD4 count, and viral load. *JAMA Dermatol.* 2017;153(9):892-896.

4. Manyam BV, Garsa AA, Chin RI, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. *Cancer*. 2017;123(11):2054-2060.

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Generalized bullous mucocutaneous eruption mimicking Stevens-Johnson syndrome in the setting of immune checkpoint inhibition: A multicenter case series

To the Editor: Although dermatologic immune-related adverse events from immune checkpoint inhibitors (ICIs) are usually mild, severe reactions can occur.[1] Sparse case reports document unusual, late-onset Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) from ICI use,[2,3] labeling it "TEN-like reaction."[3] We report 7 cases representing a distinct entity of a generalized bullous eruption mimicking ICI-related SJS/TEN, which we name progressive immunotherapy-related mucocutaneous eruption (PIRME). Calling for an alternative framework for this toxicity, we propose this more decisive terminology.

A medical record query identified patients seen in the Partners HealthCare system for suspected ICI-induced SJS/TEN from January 2011 through May 2019. Medical record review extracted clinical data and histopathologic analyses. "Concomitant medications" refer to drugs started within 2 months of rash onset.

From January 2011 through May 2019, there were 7 patients (5 men; mean age, 66.6 years) with ICI-induced skin toxicities mimicking SJS/TEN (Table I). All patients presented initially with benign drug eruptions after a median of 4 cycles (range, 1-7 cycles) and 63 days (range, 13-253 days) from ICI initiation. Without documented drug allergies, all patients had received newly initiated concomitant medications, including trimethoprim-sulfamethoxazole and allopurinol.

Initial rash morphologies included lichenoid (n = 3), urticarial (n = 2), and morbilliform (n = 1). Three patients visited outpatient dermatology before hospitalization and were diagnosed with mild dermatologic immune-related adverse events without a skin biopsy specimen. The benign-appearing eruptions in all 7 patients progressed to generalized Nikolsky-positive bullous dermatoses (Fig 1, *A* and *B*), and mucosal involvement, including oral (n = 5), ocular (n = 2), and urogenital (n = 3), developed in all but 1 patient (Table I).

Histopathologic evaluation revealed findings consistent with SJS/TEN, including full-thickness epidermal necrosis and subepidermal clefting, but frequently (4 [57%]) demonstrated a distinct interface dermatitis (Fig 1, *C* and *D*). Once suspected for SJS/TEN, high-risk concomitant medications were discontinued in all patients, and systemic therapy was initiated, comprising intravenous corticosteroids in 5, oral corticosteroids in 1, or cyclosporine in 1. All patients experienced rapid symptomatic resolution without progressive skin detachment (Table I). Median length of stay was 11 days (range, 5-17 days). No patients died of skin toxicity.

Our multicenter case series outlines and defines PIRME, a generalized bullous eruption that mimics SJS/TEN in patients receiving ICIs. Although PIRME shares some clinical and histopathologic features with SJS/TEN, it is notably distinct in its delayed onset, mild initial morphologic presentation, rare ocular involvement, benign clinical course, and favorable treatment response. These key differences call for a renewed exploration and sharpened understanding of this severe mucocutaneous blistering toxicity that accommodate its divergence from classic SJS/TEN.

The observed association with recently initiated concomitant medications suggests a 2-hit mechanism whereby ICIs reduce immune tolerance and induce heightened sensitivity to subsequent drug exposures, leading to a florid exacerbation of an otherwise benign drug reaction. Alongside PIRME's mild course and favorable treatment response, this observation suggests that discontinuation of other potential culprit drugs and a short-course immunosuppressive regimen may allow patients to safely restart their ICIs[4] and avoid the long-term detrimental consequences of high-dose corticosteroids in this patient population.[5]

The study's conclusions are limited by the small sample size and retrospective design. Given its rarity, multi-institutional studies are needed to further investigate PIRME and distinguish it from classic SJS/TEN.

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