Markers of systemic involvement and death in hospitalized cancer patients with severe cutaneous adverse reactions

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Background: Severe cutaneous adverse reactions (SCARs) are frequent in inpatient oncology. Early intervention might reduce morbidity, mortality, and hospitalization costs; however, current clinical and histologic features are unreliable SCAR predictors. There is a need to identify rational markers of SCARs that could lead to effective therapeutic interventions.

Objective: To characterize the clinical and serologic features of hospitalized patients with cancer who developed SCARs.

Methods: Retrospective review of 49 hospitalized cancer patients with a morbilliform rash, recorded testing for serum cytokines (interleukin [IL] 6, IL-10, and tumor necrosis factor [TNF] α) or elafin, and a prior dermatology consultation. Patients were categorized as having a simple morbilliform rash without systemic involvement or complex morbilliform rash with systemic involvement.

Results: Fifteen out of 49 patients (30.6%) were deceased at 6 months from time of dermatologic consultation. Elafin, IL-6, and TNF-α were significantly higher in patients who died compared with patients who were still alive at 6 months. IL-6 and IL-10 were significantly higher in patients with a drug-related complex rash.

Limitations: Retrospective design, limited sample size, and high-risk patient population.

Conclusion: In cancer patients with SCARs, elafin, IL-6, and TNF-α levels might predict a poor outcome. Agents directed against these targets might represent rational treatments for the prevention of fatal SCARs. (J Am Acad Dermatol 2019;80:608-16.)

Key words: cytokine; drug-induced hypersensitivity syndrome; drug rash; drug reaction; drug reaction with eosinophilia and systemic symptoms; graft versus host disease; severe cutaneous adverse reaction.

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Severe cutaneous adverse reactions (SCARs) to drugs, which encompass a spectrum of entities, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) are associated with significant morbidity, mortality, and hospitalization costs.[1,2] Incidence of these entities ranges from 2-7 cases/1 million persons/year for SJS and TEN to 1 case/1,000 drug exposures to 1 case/10,000 drug exposures for DRESS.[3-5] Prompt recognition and treatment of SCARs is critical, as these patients can rapidly develop multiorgan dysfunction or failure without treatment.[6]

Several studies have demonstrated an increased risk for SJS/TEN in active cancer patients, which might be attributed to the role of the immune system in the development of SCARs as well as exposure to multiple medications.[7-9] Furthermore, cancer patients have a significantly higher risk for mortality with SJS/TEN compared with noncancer patients.[10] Several factors have been proposed to explain this elevated risk, including an immunocompromised status, malnutrition, toxicity from chemotherapeutic or immunotherapy agents, and organ dysfunction from malignancy, although the exact mechanisms remain to be elucidated. In addition to having an elevated risk for SCARs, patients with hematologic malignancy and history of hematopoietic stem cell transplant are also at risk for graft-versus-host disease (GVHD). GVHD and SCARs can be difficult to distinguish given their similar clinical presentations.

Diagnosis of SCARs largely relies on clinical assessment. Furthermore, prediction of progression of a simple drug rash into a systemic reaction can be difficult, as clinical morphology of the rash, histopathology, and standard laboratory values are often insufficient to predict outcome.[11-13] There is a need to identify reliable markers that can help identify the patients with SCARs who are at increased risk for progression and possible death. The identification of cancer patients at high-risk has important implications, including earlier treatment and ability to resume cancer treatment. The objective of this study was to identify clinical and serologic features of hospitalized patients with cancer who developed SCARs.

CAPSULE SUMMARY

- Cancer patients have increased risk of severe cutaneous adverse reactions, without reliable biomarkers to identify predisposition for associated morbidity and mortality.
- In hospitalized cancer patients with morbilliform rash, elafin, interleukin [IL] 6, and tumor necrosis factor α were associated with mortality. IL-6 and IL-10 were associated with drug-related systemic involvement. These biomarkers might guide future therapeutic research.

METHODS

This was a retrospective cohort study approved by the institutional review board of Memorial Sloan Kettering Cancer Center. A database query of adult patients with cancer who were hospitalized during August 1, 2016-July 31, 2017, and had International Classification of Diseases 9 or 10 codes for rash (R23, R21, 693, 692, 695, 690-698, L20-L30, L51, L43.2, T88.7, L55-59), recorded testing for serum cytokines (interleukin [IL] 6, IL-10, tumor necrosis factor alpha [TNF-α]) or serum elafin, and prior dermatology consultation revealed 191 eligible patients (Fig 1). Given the limited impact of skin biopsy and serum studies on diagnosis and management of morbilliform rash[14,15] and the recent Food and Drug Administration approval of IL-6 receptor antibody tocilizumab for cytokine release syndrome, with utility in pro-inflammatory disorders,[16-20] select biomarker levels are obtained at our institution as standard of care for patients presenting with possible drug eruption to better understand the disease course and as a potential therapeutic target for intervention. All data was retrospectively collected.

In total, 142 patients were excluded: 70 because cytokines were checked for a reason other than a morbilliform rash (ie, cytokine release syndrome, study protocol, sepsis, or cellulitis/panniculitis) and 72 because they were not admitted to the hospital (ie, the patient was seen as an outpatient). Forty-nine patients were admitted as inpatients or seen at the urgent care center at Memorial Sloan Kettering Cancer Center with a diagnosis of morbilliform rash and tested for cytokines or elafin. Chart review was performed for all patients, so they could be assigned to the simple or complex morbilliform rash groups. Simple morbilliform rash was defined as a rash with no systemic involvement, rash with spontaneous resolution and remote systemic involvement (ie, transient elevation in liver transaminases or bilirubin that returned to baseline), or rash with limited course that did not require systemic therapy. Complex morbilliform rash was defined as a SCAR with

Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
DIHS:	drug-induced hypersensitivity syndrome
DRESS:	drug reaction with eosinophilia and systemic syndrome
GVHD:	graft versus host disease
IL:	interleukin
NLR:	neutrophil-to-lymphocyte ratio
SCAR:	severe cutaneous adverse reaction
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis
TNF-α:	tumor necrosis factor alpha

systemic organ involvement requiring systemic therapy with prolonged rash duration.

For each patient, a modified RegiSCAR score[21] was calculated on the basis of the following items: fever ≥38.5°C; peripheral eosinophilia (≥700/mm^3 or ≥10%, or ≥1500/mm^3 or ≥20%); atypical lymphocytes; rash ≥50% of body surface area with facial edema, purpura, infiltration, or desquamation; organ involvement; disease duration >15 days; and performance of ≥3 biologic investigations (eg, blood cultures, viral serology, biopsy) to rule out alternative diagnoses that had negative results. A comprehensive metabolic panel, including glomerular filtration rate, blood urea nitrogen, creatinine, transaminases, total bilirubin, and urine eosinophils, were also reviewed. For all laboratory values, only results within 7 days of cytokine testing were used in the analysis for consistency and to minimize the impact of events unrelated to the rash. Our reference values for cytokines (IL-10 ≤18 pg/mL, IL-6 ≤5 pg/mL, TNF-α ≤22 pg/mL) are determined by our institution's laboratory. Elafin is an elastase inhibitor overexpressed in epithelial tissues upon inflammation or injury[22] and has been found to be a diagnostic and prognostic plasma biomarker in cutaneous GVHD.[23] Elafin has not been formally validated in this patient population; therefore, there is no diagnostic threshold.

Descriptive statistics and graphical methods were used to assess distributions of patient and medical test characteristics. Chi-squared tests and Fisher's exact test were used to assess the association between rash type and nominally scaled patient and medical test characteristics. Wilcoxon rank-sum tests were used to assess differences in continuously scaled variables by rash type. All analyses were performed with STATA 12 (StataCorp LP, College Station, TX).

RESULTS

Patient characteristics and laboratory values

Of the 49 patients with cancer and morbilliform rash who were admitted to the inpatient or urgent care center units and received dermatology consultation, 27 patients had a simple morbilliform rash without systemic involvement, and 22 had a complex morbilliform rash with systemic involvement (Fig 1). Of the 22 complex morbilliform rash patients, 9 were cutaneous manifestations of GVHD (of which 7 were acute GVHD, 1 late-onset acute GVHD, and 1 on the clinical spectrum of GVHD with engraftment syndrome). The remaining 13 complex rashes were secondary to drug exposure. Demographics and other characteristics of simple and complex morbilliform rash patients are shown in Table I. Most patients were admitted as an inpatient to the hospital (N = 41) than to the urgent care center (N = 8). For both simple and complex rash patients, there were more patients with hematologic malignancy (18 simple, 16 complex) than solid organ malignancy (9 simple, 6 complex). Fifteen of the 49 patients (30.6%) were deceased at 6 months from the time of dermatologic consultation. Causes of death included organ failure, sepsis, and other multifactorial cancer—related causes.

Median modified RegiSCAR score was 3 in complex rash patients and 1.5 in simple rash patients ($P < .001$, score range −1 to 5). Complex rash patients were significantly more likely to have a rash covering >50% of their body surface area with purpura, edema, or scale ($P = .006$), peripheral eosinophilia ($P = .001$), internal organ involvement ($P = .001$), and resolution of rash after >15 days ($P < .001$). Relative to baseline levels, complex rash patients had significant elevations in transaminases ($P < .001$). Median white blood cell count was 8550 cells/μL in complex morbilliform rash patients compared with 3420 cells/μL in simple rash patients ($P = .05$). The median values for all cytokines (IL-6, IL-10, and TNF-α) and elafin were higher in the complex rash group than the simple rash group, although only TNF-α reached statistical significance ($P = .03$). The median neutrophil-to-lymphocyte ratio (NLR) was higher in the simple rash patient group (8.5) than in the complex rash patient group (6.6).

Among the variables included in the modified RegiSCAR score in Table I, only elevated bilirubin relative to baseline was significantly associated with death at 6 months from time of dermatologic consultation. Furthermore, this was an inverse association, with 55.3% of patients having elevated bilirubin relative to baseline alive at 6 months, compared with 17.7% in those who died ($P = .01$).

Cytokines and organ involvement

The median IL-6 level was significantly higher in patients with elevated bilirubin than in patients with bilirubin within the standard range (63.5 pg/mL vs 22

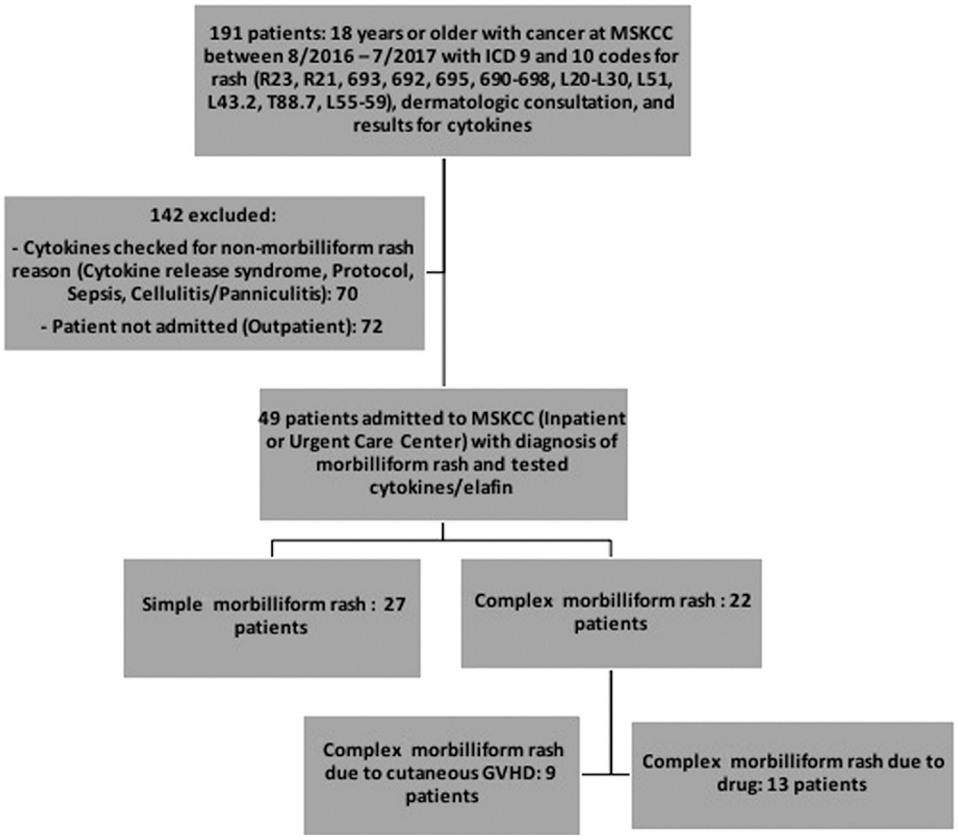

Fig 1. Flowchart of patient selection. *GVHD*, Graft-versus-host disease; *ICD*, International Classification of Diseases; *MSKCC*, Memorial Sloan Kettering Cancer Center.

pg/mL, $P < .05$). Median IL-10 was higher in patients with than without elevated transaminases, although it did not reach statistical significance (31 pg/mL vs 19.5 pg/mL, $P < .10$). IL-6, IL-10, TNF-α, and elafin were not associated with peripheral eosinophilia or renal dysfunction, as measured by decreased glomerular filtration rate relative to baseline.

Cytokines and all-cause mortality

Median values for elafin, IL-6, IL-10, and TNF-α for patients who were alive (N = 34) versus deceased (N = 15) at 6 months from time of dermatologic consultation are shown in Fig 2. Elafin, IL-6, and TNF-α were significantly higher in patients who were deceased at 6 months ($P = .029$, $P = .002$, $P = .04$, respectively) compared with patients who were alive.

Cytokines and progression to complex morbilliform rash

The group of complex rash patients (due to drug or GVHD) had a higher median IL-6 value than the group of simple rash patients (Fig 3), although the difference did not reach statistical significance ($P = .06$). Patients with complex morbilliform rash due to drug (Fig 4) had a significantly higher median IL-10 ($P = .03$) and IL-6 ($P = .05$) value than all other patients (those with a simple or complex rash due to GVHD; or simple rash due to drug).

DISCUSSION

In this study, elafin, TNF-α, and IL-6 were significantly associated with all-cause mortality in hospitalized cancer patients who developed SCARs. This is the first study to report elafin levels in a cohort of patients with SCARs. Elafin is undetectable in normal skin but overexpressed in wound healing; inflammatory disorders, such as psoriasis, Sweet syndrome, Behcet syndrome, and neutrophil-mediated vasculitis; in skin with actinic damage; and in alveolar injury.[24-29] Elafin might be released in response to tissue degradation by neutrophil infiltration and in response to IL-1 and TNF-α.[28,30] In patients with acute GVHD, significantly decreased 2-year overall survival was associated with high cutaneous elafin expression.[31] In a recent case report, elevated elafin expression was found after hematopoietic stem cell transplantation in a patient initially thought to have bullous GVHD but later

Table I. Characteristics of hospitalized cancer patients with simple morbilliform rash and complex systemic morbilliform rash

Category	Simple morbilliform rash, n = 27, n (%)*	Complex morbilliform rash, n = 22, n (%)*	*P* value
Patient sex			
Female	15 (55.6)	12 (54.6)	.94
Male	12 (44.4)	10 (45.4)	
Location			
Inpatient	22 (81.5)	19 (86.4)	.65
Urgent care center	5 (18.5)	3 (13.6)	
Cancer diagnosis			
Hematologic malignancy	18 (66.7)	15 (68.2)	.54
Solid organ malignancy	9 (33.3)	6 (27.3)	
Both solid and hematologic	0 (0)	1 (4.6)	
Hematologic malignancy	18	16	
Acute myeloid leukemia	8 (29.6)	6 (27.3)	—
Acute lymphoblastic leukemia	2 (7.4)	0	—
Multiple myeloma	3 (11.0)	2 (9.1)	—
Chronic myeloid leukemia	0	2 (9.1)	—
Chronic myelomonocytic leukemia	1 (3.7)	0	—
Myelofibrosis	1 (3.7)	0	—
Myelodysplastic syndrome	0	2 (9.1)	—
Diffuse large B-cell lymphoma	1 (3.7)	2 (9.1)	—
Mantle cell lymphoma	1 (3.7)	0	—
Gray zone lymphoma	1 (3.7)	0	—
Indolent B-cell lymphoma	0	1 (4.5)	—
Adult T-cell leukemia/lymphoma	0	1 (4.5)	—
Solid organ malignancy	9	6	
Melanoma	2 (7.4)	1 (4.5)	—
Colon	2 (7.4)	1 (4.5)	—
Ovarian	2 (7.4)	1 (4.5)	—
Breast	1 (3.7)	0	—
Urothelial	1 (3.7)	0	—
Prostate	1 (3.7)	0	—
Renal	0	1 (4.5)	—
Cutaneous T-cell lymphoma	0	1 (4.5)	—
Sarcoma	0	1 (4.5)	—
Status			
Alive	19	10	
Deceased	8	12	
Modified RegiSCAR score, median	1.5	3.0	<.001†
Atypical lymphocytes	5 (18.5)	4 (18.2)	.98
Fever, >38°C	7 (25.9)	4 (18.2)	.52
Rash, (>50% BSA + purpura, edema, scale), median	1	2	.006†
Eos score 0-2, median	0	1	.001†
Internal organs involved			
0	16 (59.3)	2 (9.1)	.001
1	10 (37.0)	16 (72.7)	
2	1 (3.7)	4 (18.2)	
Decreased GFR relative to baseline	4 (14.8)	4 (18.2)	.75
Presence of urine eosinophils	0	3 (13.6)	.05
Elevated transaminases relative to baseline	3 (11.1)	16 (72.7)	<.001
Elevated total bilirubin relative to baseline	6 (22.2)	8 (36.4)	.28
Skin biopsy supportive of drug reaction	10 (37.0)	13 (59.1)	.12
Resolution >15 days	10 (37.0)	19 (86.4)	<.001
≥3 negative biologic investigations excluding alternate diagnosis	27 (100)	22 (100)	1.0

Continued

Table I. Cont'd

Category	Simple morbilliform rash, n = 27, n (%)*	Complex morbilliform rash, n = 22, n (%)*	*P* value
White blood cells, cells/μL, median	3420	8550	.05†
Median CTCAE v4.03 grade	3	3	.26†
Cytokines and biomarkers			
Elafin, ng/mL, median	17.9	25.5	.22
Interleukin 6, pg/mL, median	16	26	.11
Interleukin 10, pg/mL, median	19.5	31	.07
Tumor necrosis factor α, pg/mL, median	12	18	.03

BSA, Body surface area; *CTCAE*, Common Terminology Criteria for Adverse Events; *Eos*, peripheral eosinophilia (Score of 0: <700/mm^3, or <10%; Score of 1: 700-1500/mm^3; Score of 2: ≥1500/mm^3 or ≥20%); *GFR*, glomerular filtration rate; *SCAR*, severe cutaneous adverse reaction.

*Values are n (%) except where indicated.

†Based on the 2-sample Wilcoxon rank-sum test.

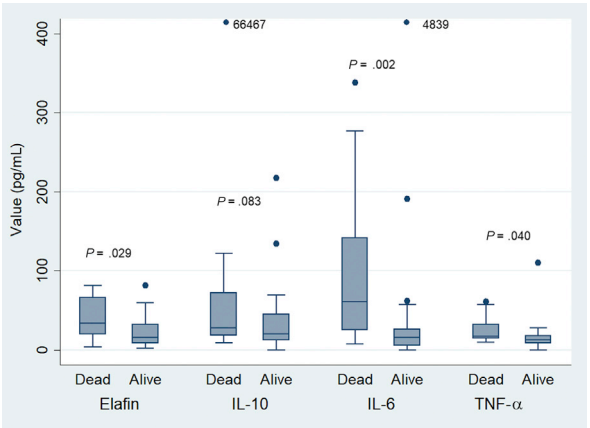

Fig 2. Cytokines and all-cause mortality. Mortality defined as status at 6 months from time of dermatologic consultation. Numbers 66,467 and 4839 refer to cytokine values that were much higher than the *y*-axis of the graph. *IL*, Interleukin; *TNF-α*, tumor necrosis factor *α*.

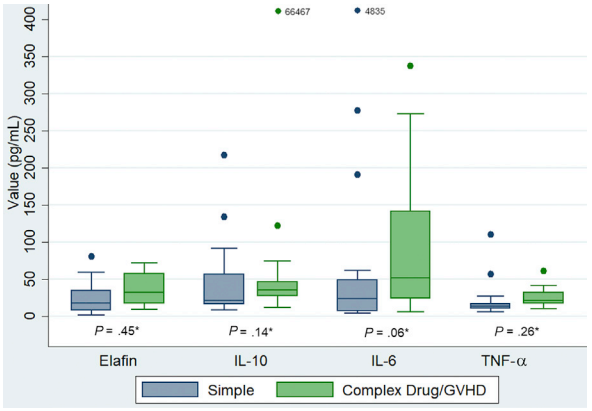

Fig 3. Comparison of cytokine levels in patients with simple morbilliform rashes and complex morbilliform rashes due to drug exposure or GVHD. Numbers 66,467 and 4839 refer to cytokine values that were much higher than the *y*-axis of the graph. *2-sample Wilcoxon rank-sum (Mann-Whitney) test. *GVHD*, Graft-versus-host disease; *IL*, interleukin; *TNF-α*, tumor necrosis factor *α*.

favored to have TEN, given the overall clinical picture.[32] Although GVHD and drug-related SCARs are difficult to distinguish clinically, our results suggest that elafin might be a useful biomarker to identify patients with a suspected diagnosis of SCAR or GVHD who are at increased risk for death within 6 months. In addition, recombinant human elafin has shown efficacy in mitigating or preventing epithelial lung injury.[33,34] Given its broad anti-inflammatory activity, elafin's potential as a therapeutic agent for SCARs should be further explored.

TNF-*α* was also significantly associated with all-cause mortality. Elevated TNF-*α* has been found in SCARs, such as acute generalized exanthematous pustulosis (AGEP), SJS, TEN, and GVHD.[35-37] Furthermore, the successful use of TNF-*α* inhibitors, such as infliximab and etanercept, has been reported for the treatment of AGEP, SJS, TEN, and DRESS.[37-41] Of note, infliximab is already used to treat ipilimumab-induced severe colitis in cancer patients[42]; TNF-*α* might serve as a similar potential therapeutic target in SCARs in the cancer population.

We found IL-6 to be significantly associated with higher all-cause mortality and significantly elevated in patients with drug exposure—related complex rashes compared with patients with simple drug-related or GVHD-related rashes or complex GVHD-related rashes. IL-6 promotes an inflammatory state by stimulating the acute phase responses and inhibiting the production of regulatory T cells that are induced by tumor growth factor *β*.[43,44] In a study of patients who presented with clinical symptoms suggestive of an adverse drug reaction or viral infection, IL-6 levels were found to be significantly elevated in

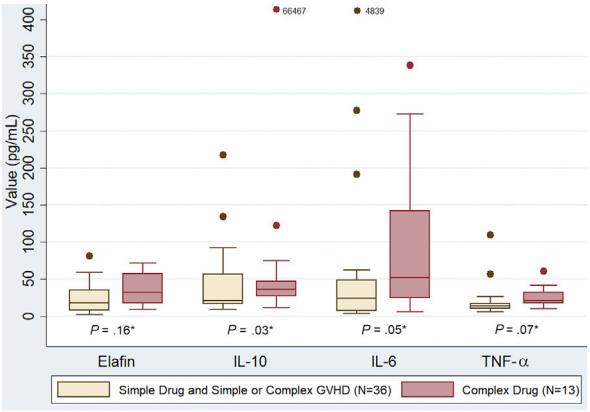

Fig 4. Cytokines in patients with simple morbilliform rashes due to drug exposure or GVHD and patients with complex morbilliform rashes due to GVHD versus patients with complex morbilliform rashes due to drug exposure only. Numbers 66,467 and 4839 refer to cytokine values that were much higher than the *y*-axis of the graph. *2-sample Wilcoxon rank-sum (Mann-Whitney) test. *GVHD*, Graft-versus-host disease; *IL*, interleukin; *TNF-α*, tumor necrosis factor *α*.

SJS, TEN, and DRESS patients compared with healthy controls.[45] Elevated IL-6 production is also associated with increased incidence and severity of GVHD.[16] Blockade of the IL-6 receptor with tocilizumab or siltuximab has been shown to attenuate the pathologic damage caused by IL-6 mediated processes such as GVHD, cytokine release syndrome, and psoriasis.[16-18] Targeted therapy with tocilizumab has shown efficacy and is Food and Drug Administration approved for the treatment of cytokine release syndrome after chimeric antigen receptor T-cell therapy.[17,19] Tocilizumab has also been successfully used for anti—PD-1 inhibitor—associated cytokine release syndrome and for skin GVHD with a cytokine pattern resembling cytokine release syndrome.[20,46] Furthermore, IL-6 receptor antibodies suppress T-cell activation through inhibition of IL-2 production and induction of regulatory T cells and effectively treat other IL-6 mediated syndromes, suggesting a potentially novel therapeutic role in drug eruptions associated with IL-6 elevations.[47]

We also found significantly elevated IL-10 levels in patients who ultimately developed a complex drug-related SCAR compared with patients with a simple rash due to drug exposure or GVHD and complex GVHD rash patients. IL-10 is important for maintaining the integrity of tissue epithelia[48] and has an anti-inflammatory role in the immune response. IL-10 is chemotactic for peripheral $CD8^+$ T cells and inhibits the production of inflammatory cytokines, such as IL-6 and TNF-*α*.[49] Elevated IL-10 has been found in patients with acute GVHD, SJS, and TEN.[36,49] Thought to originate from activated keratinocytes in TEN, elevated IL-10 might reflect a defense mechanism against drug-specific cytotoxic T cells that are activated during the disease process.[50] In GVHD, whether IL-10 is protective or reflects a compensatory response is less clear. Further research is needed to explore the significance and utility of IL-10 as a therapeutic agent in these disease entities.

An additionally notable study finding is the higher median NLR in simple rash patients versus complex rash patients. Although NLR has garnered recent interest for its prognostic role, particularly in solid organ malignancies,[51] our findings show that NLR might have limited utility in a patient population with a higher proportion of hematologic malignancies. Moreover, we did not find significant associations of established clinical markers, such as rash body surface area or internal organ involvement, with all-cause mortality in this patient cohort. These findings support the need for alternative biomarkers, such as the cytokines we evaluated. In a recent analysis of inpatient dermatologic consultations performed at a cancer hospital, nearly half of consultations were for patients with underlying hematologic malignancies, and these patients had significantly longer hospital stays than those not consulted by dermatology.[52]

Limitations of this study include its retrospective design and limited sample size. All cases were recruited from a tertiary referral cancer center. As mentioned previously, cancer patients have a higher risk for mortality with SJS/TEN than noncancer patients. A larger, prospective study examining the association of cytokines with SCARs is needed, as well as longitudinal assessment of cytokine levels to assess their prognostic significance. This exploratory analysis presents potential therapeutic targets in a high-risk patient population, for whom a complex rash can disrupt and delay treatment of underlying disease.

CONCLUSION

In hospitalized cancer patients presenting with morbilliform rash, elafin, IL-6, and TNF-*α* might have an important role in identifying patients at higher risk for mortality. IL-10 might be a useful diagnostic marker for drug-related morbilliform rash with systemic organ involvement. Further research is needed to elucidate the potential utility of these cytokines as therapeutic targets and of elafin as a therapeutic agent.

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