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

Shoko Mori, BS[1,2], **Alanna Hickey, BA**[3], **Stephen W. Dusza, DrPH**[1], **Mario E. Lacouture, MD**[1,4], and **Alina Markova, MD**[1,4]

[1]Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY

[2]SUNY Downstate College of Medicine, Brooklyn, NY

[3]University of Massachusetts Medical School, Worcester, MA

[4]Department of Dermatology, Weill Cornell Medical College, New York, NY

Abstract

Background: Severe cutaneous adverse reactions (SCARs) are frequent in inpatient oncology. Early intervention may 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 and recorded testing for serum cytokines (IL-6, IL-10, TNF-α) or elafin, and 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 to

Corresponding author: Alina Markova, MD, Dermatology Service, Memorial Sloan Kettering Cancer Center, 16 E 60th St. New York, NY 10022, Telephone: 646-888-6010, markovaa@mskcc.org.

Authorship contributions

(1) Acquisition, analysis and interpretation of data

(2) Drafting and revising the article for important intellectual content

(3) Final approval of the version to be submitted

Shoko Mori, BS: (1), (2), (3)
Alanna Hickey, BA: (1), (2), (3)
Stephen W. Dusza, DrPH: (1), (2), (3)
Mario E. Lacouture, MD: (1), (2), (3)
Alina Markova, MD: (1), (2), (3)

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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, high-risk patient population.

Conclusion: In cancer patients with SCARs, elafin, IL-6, and TNF- α may predict a poor outcome. Agents directed towards these targets may represent rational treatments for the prevention of fatal 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, IL-6, TNF-α were associated with mortality. IL-6, IL-10 were associated with drug-related systemic involvement. These biomarkers may guide future therapeutic research.

Keywords

Severe cutaneous adverse reaction; cytokine; drug reaction; drug reaction with eosinophilia and systemic symptoms; drug induced hypersensitivity syndrome; graft versus host disease; drug rash

Introduction

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 syndrome (DRESS) are associated with significant morbidity, mortality, and hospitalization costs.[1,2] Incidence ranges from 2 to 7 per million cases per year for SJS and TEN to 1 case per 1,000 to 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 of SJS/TEN in active cancer patients, which may 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 of mortality with SJS/TEN compared to non-cancer 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 of SCARs, patients with hematologic malignancy and history of hematopoietic stem cell transplant (HSCT) 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 anticipate those patients with SCARs who are at increased risk of progression and possible death. In cancer patients, identification of high-risk patients 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.

Methods

This was a retrospective cohort study approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (MSKCC). A database query of adult patients with cancer who were hospitalized between August 1, 2016 and July 31, 2017 and had ICD 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-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α)) or serum elafin, and prior dermatology consultation revealed 191 eligible patients (Figure 1). Given the limited impact of skin biopsy and serum studies on diagnosis and management of morbilliform rash[14,15], and recent FDA approval of anti-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 in order to better understand the disease course and as a potential therapeutic target for intervention. All data was retrospectively collected.

One hundred forty-two patients were excluded: 70 patients were excluded because cytokines were checked for a reason other than a morbilliform rash (i.e., cytokine release syndrome, study protocol, sepsis, or cellulitis/panniculitis), and 72 patients were excluded because they were not admitted to the hospital (i.e., the patient was seen as an outpatient).

Forty-nine patients were admitted as an inpatient or seen at the urgent care center at MSKCC with a diagnosis of morbilliform rash and tested for cytokines or elafin. Chart review was performed for all patients to assign to ‘simple’ and ‘complex’ morbilliform rash groups. ‘Simple’ morbilliform rash was defined as a rash with no systemic involvement, or spontaneous resolution of rash with remote systemic involvement (i.e., transient elevation in liver transaminases or bilirubin that returned to baseline), or limited course of rash that did not require systemic therapy. ‘Complex’ morbilliform rash was defined as a SCAR with systemic organ involvement requiring systemic therapy with a prolonged duration of the rash.

For each patient, a modified RegiSCAR score[21] was calculated based on 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; at least 3 biological investigations (e.g., blood cultures, viral serology, biopsy) performed and negative to rule out an alternative diagnosis. Comprehensive metabolic panel, including glomerular filtration rate (GFR), blood urea nitrogen (BUN), creatinine (Cr), transaminases, and 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. Reference values for cytokines are determined by our institution's laboratory and are as follows: IL-10 ≤ 18 pg/mL, IL-6 ≤ 5 pg/mL, TNF-α ≤ 22 pg/mL. 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-square tests and Fisher's Exact test were used to assess the association between rash type ('simple' versus 'complex') 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 software (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 (Figure 1). Of the 22 'complex' morbilliform rash patients, 9 were cutaneous manifestations of GVHD (of which 7 were acute GVHD, 1 was late onset acute GVHD, and 1 was on the clinical spectrum of GVHD with engraftment syndrome). The remaining 13 'complex' rashes were secondary to drug exposure. Demographic and other characteristics of 'simple' and 'complex' morbilliform rash patients are shown in Table 1. Most patients were admitted as an inpatient to the hospital (N=41) vs. Urgent Care Center (N=8). For both 'simple' and 'complex' rash patients, there were more patients with hematologic malignancy (N=18, 16, respectively) compared to solid organ malignancy (N=9, 6, respectively). 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 ($p<0.001$, range −1 to 5). 'Complex' rash patients were significantly more likely to have a rash covering >50% of body surface area with purpura, edema, or scale ($p=0.006$), peripheral eosinophilia ($p=0.001$), internal organ involvement ($p=0.001$), and resolution of rash longer than 15 days ($p<0.001$). Relative to baseline levels, 'complex' rash patients had significant elevations in transaminases ($p<0.001$). Median white blood cell (WBC) count per μL was 8,550 in 'complex' morbilliform rash patients compared to 3,420 in 'simple' rash patients ($p=0.05$). The median values for all cytokines (elafin, IL-6, IL-10, and TNF-α) were higher in the complex rash group compared to simple rash group, although only TNF-α reached statistical significance ($p=0.03$). Median neutrophil-to-lymphocyte ratio (NLR) was higher in 'simple' rash patients (8.5) compared to 'complex' rash patients (6.6).

Among the variables included in the modified RegiSCAR score in Table 1, 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 alive at 6 months having elevated bilirubin relative to baseline, compared to 17.7% in those who died (p=0.01).

Cytokines and Organ Involvement

Median IL-6 level was significantly higher in patients with elevated bilirubin compared to patients with bilirubin in normal limits (63.5 vs. 22, $p< 0.05$). Median IL-10 was higher in patients with elevated transaminases, although it did not reach statistical significance (31 vs. 19.5, $p<0.10$). IL-6, IL-10, TNF-α, and elafin were not associated with peripheral eosinophilia or renal dysfunction, as measured by decreased GFR 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 Figure 2. Elafin, IL-6, and TNF-α were significantly higher in patients deceased at 6 months (p=0.029, p=0.002, p=0.04, respectively) compared to patients who were alive.

Cytokines and Progression to Complex Morbilliform Rash

As shown in Figure 3, ‘complex’ rash patients (due to drug or GVHD) had a higher median IL-6 value compared to ‘simple’ rash patients, although it did not reach statistical significance (p=0.06). Patients with ‘complex’ morbilliform rash due to drug (Figure 4) had a significantly higher median IL-10 and IL-6 value compared to the group of patients with a ‘simple’ rash or with ‘complex’ rash due to GVHD (p=0.03 and p=0.05, respectively).

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] It may 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, high cutaneous elafin expression was associated with significantly decreased two-year overall survival compared to low elafin.[31] A recent case report found elevated elafin expression in a post-HSCT patient initially thought to have bullous GVHD, but later favored to have TEN given the overall clinical picture.[32] While GVHD and drug-related SCARs are difficult to distinguish clinically, our results suggest that elafin may be a useful biomarker to identify patients with a suspected diagnosis of SCAR or GVHD who are at increased risk of death within 6 months. Additionally, 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 AGEP, SJS, TEN as well as 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] Notably, infliximab is already used to treat ipilimumab-induced severe colitis in cancer patients[42]; TNF-α may serve as a similar potential therapeutic target in SCARs in the cancer population.

We found IL-6 to be statistically associated with higher all-cause mortality, and significantly elevated in 'complex' drug-related rash patients compared to 'simple' drug or GVHD rash and 'complex' GVHD rash patients. IL-6 promotes an inflammatory state by stimulating the acute phase responses and inhibiting the production of regulatory T-cells that are induced by TGF-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 SJS, TEN, and DRESS patients compared to 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 FDA-approved for the treatment of cytokine release syndrome following chimeric antigen receptor (CAR) 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, anti-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 to patients with a 'simple' rash due to drug or GVHD and 'complex' GVHD rash patients. IL-10 is important in maintaining the integrity of tissue epithelia[48], and has an anti-inflammatory role in the immune response: it 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 may 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 compared to 'complex' rash patients. While NLR has garnered recent interest for its prognostic role, particularly in solid organ malignancies[51], our findings show that NLR may have limited utility in a patient population with higher proportion of hematologic malignancies. Moreover, we did not find significant associations of established clinical markers, such as rash BSA or internal organ involvement, with all-cause mortality in this patient cohort. These findings support the need for alternative biomarkers such as the cytokines evaluated. A recent analysis of inpatient dermatologic consultations at a cancer

hospital found that nearly half of consultations were for patients with underlying hematologic malignancies, with significantly longer hospital stays for these patients compared to patients not consulted by dermatology.[52]

Limitations of this study include its retrospective design, as well as a limited sample size. All cases were recruited from a tertiary referral cancer center. As mentioned previously, cancer patients have a higher risk of mortality with SJS/TEN compared to non-cancer 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 may have an important role in identifying patients at higher risk of mortality. IL-10 may 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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Abbreviations

SCAR	severe cutaneous adverse reaction
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
DIHS	drug-induced hypersensitivity syndrome
DRESS	drug reaction with eosinophilia and systemic syndrome
GVHD	graft versus host disease
IL-6	interleukin-6
IL-10	interleukin-10
TNF-α	tumor necrosis factor alpha
GFR	glomerular filtration rate
BUN	blood urea nitrogen
Cr	creatinine

WBC	white blood cell
NLR	neutrophil-to-lymphocyte ratio

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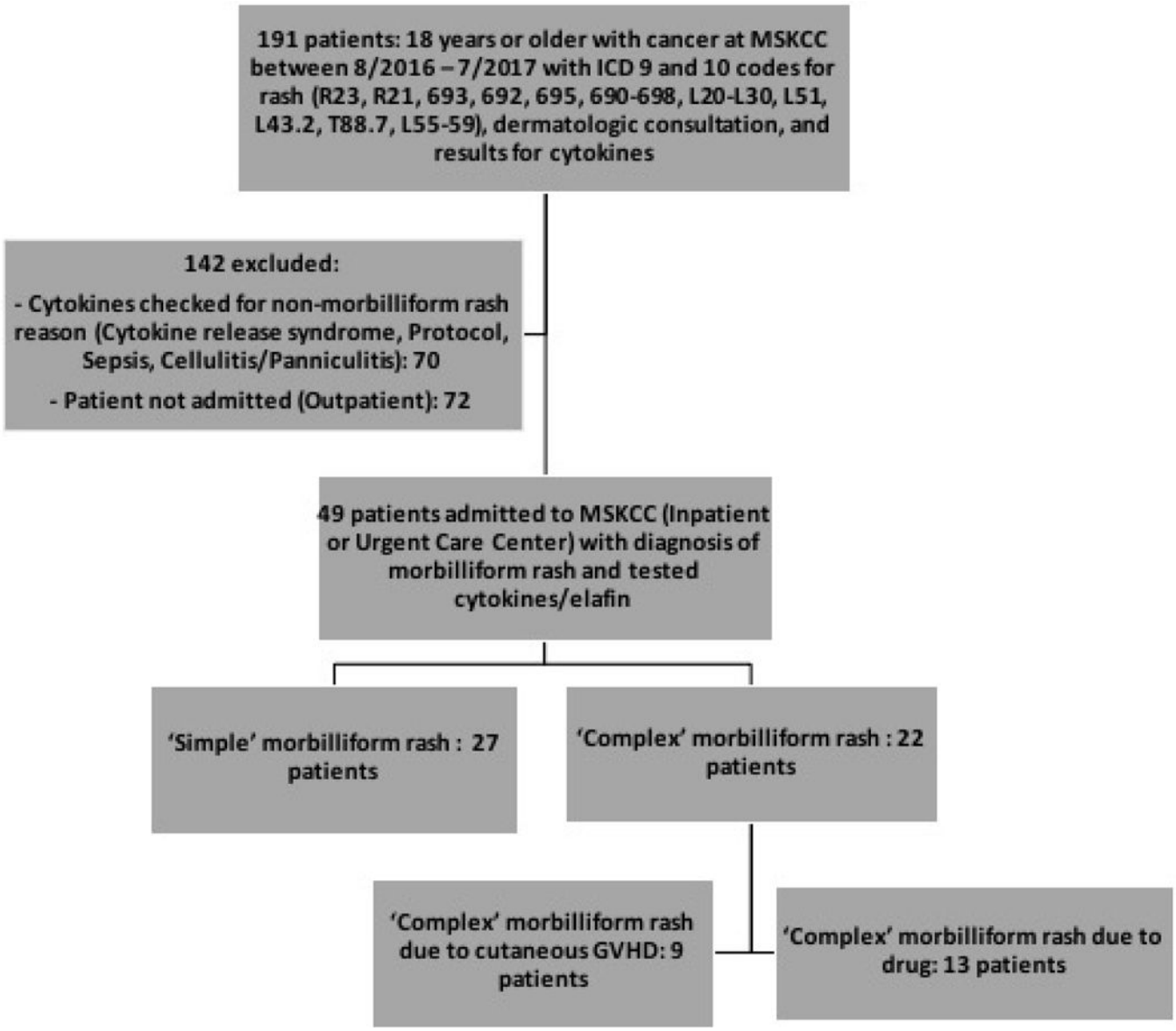

Figure 1.
Flowchart of patient selection.

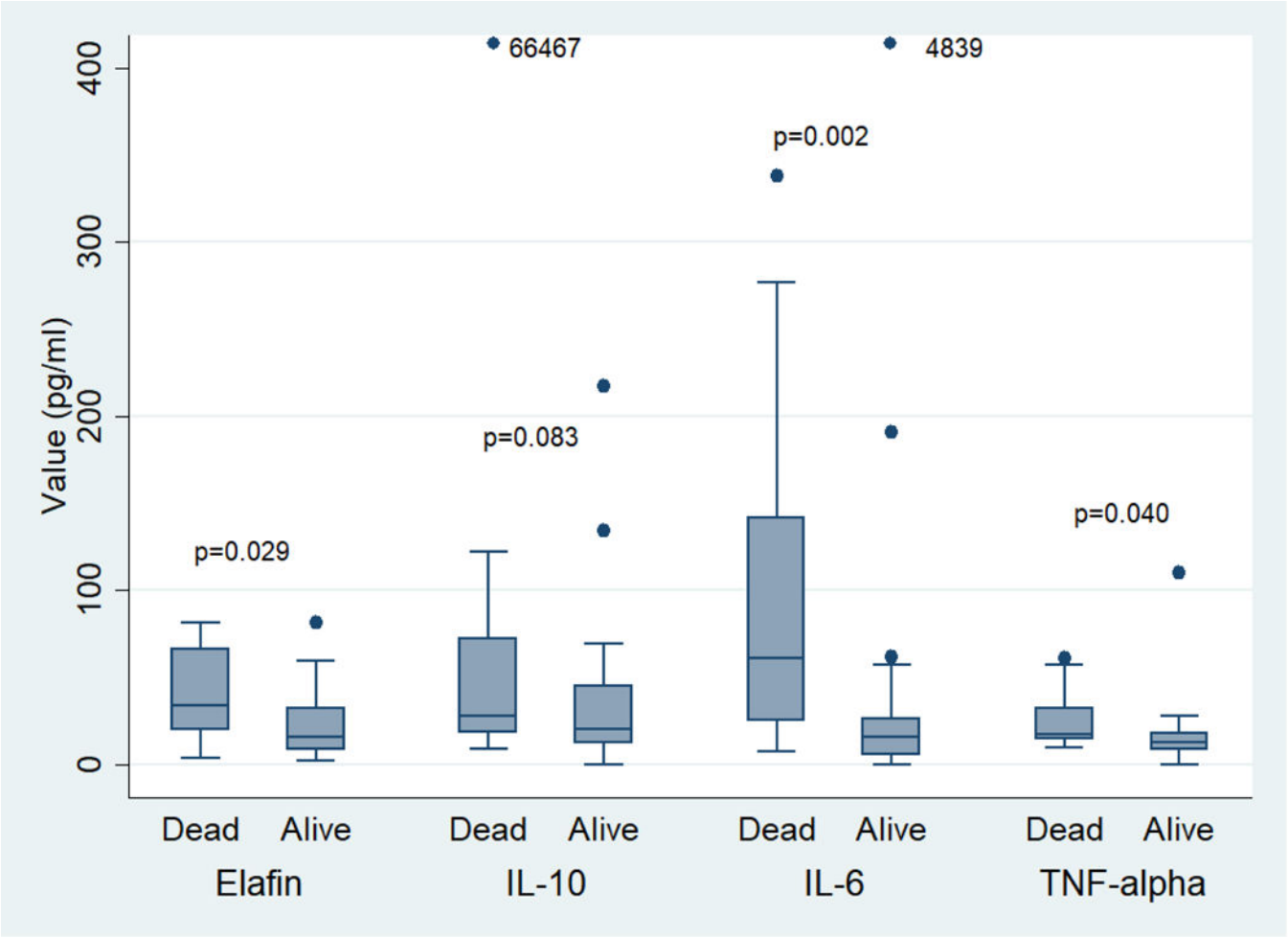

Figure 2.

Cytokines and all-cause mortality. Mortality defined as status at 6 months from time of dermatologic consultation. 66467 and 4839 refer to cytokine values that were much higher than the y-axis of the graph.

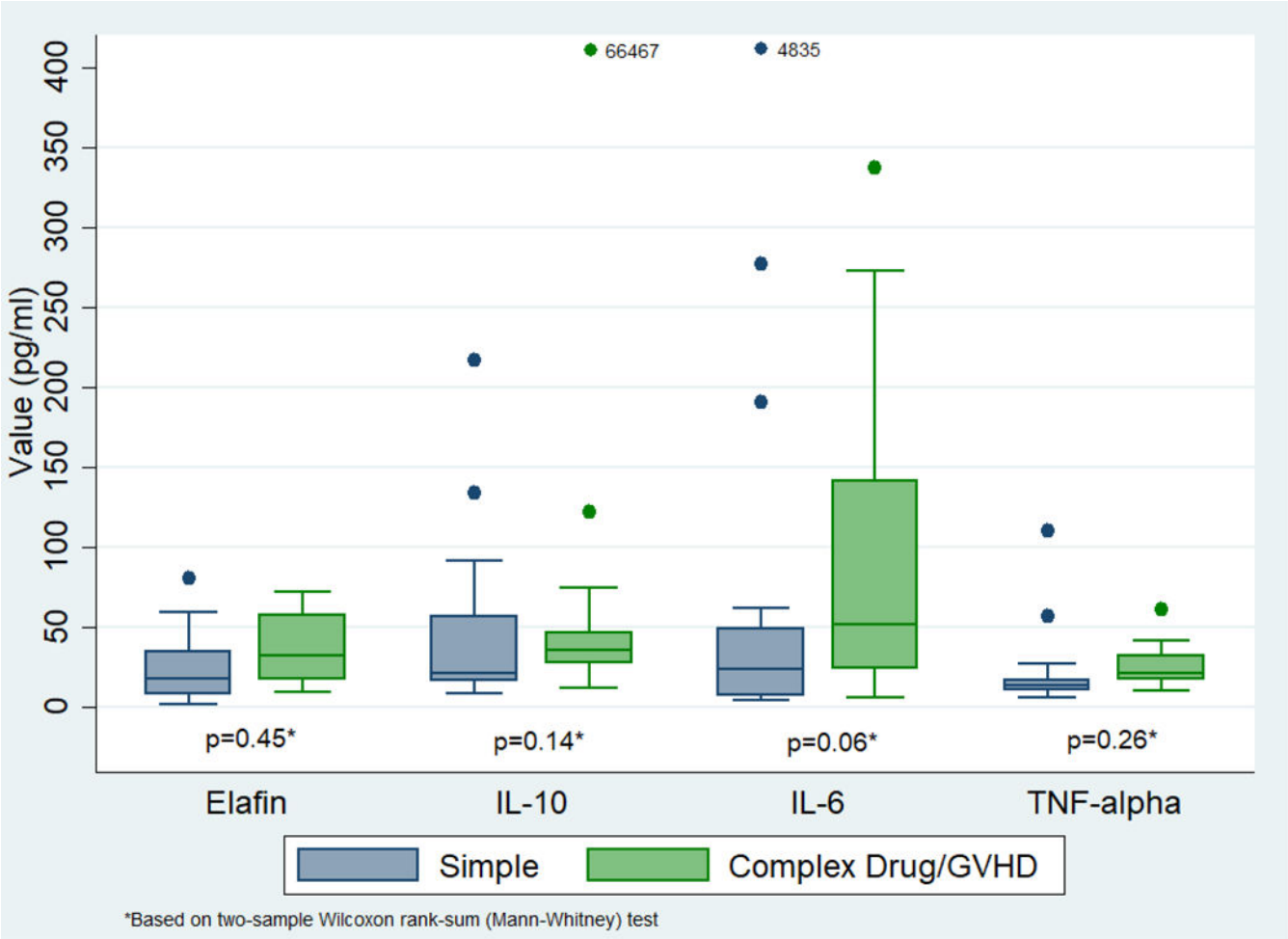

Figure 3.

Cytokines in ‘simple’ rash vs. ‘complex’ morbilliform rash due to drug or GVHD. 66467 and 4839 refer to cytokine values that were much higher than the y-axis of the graph.

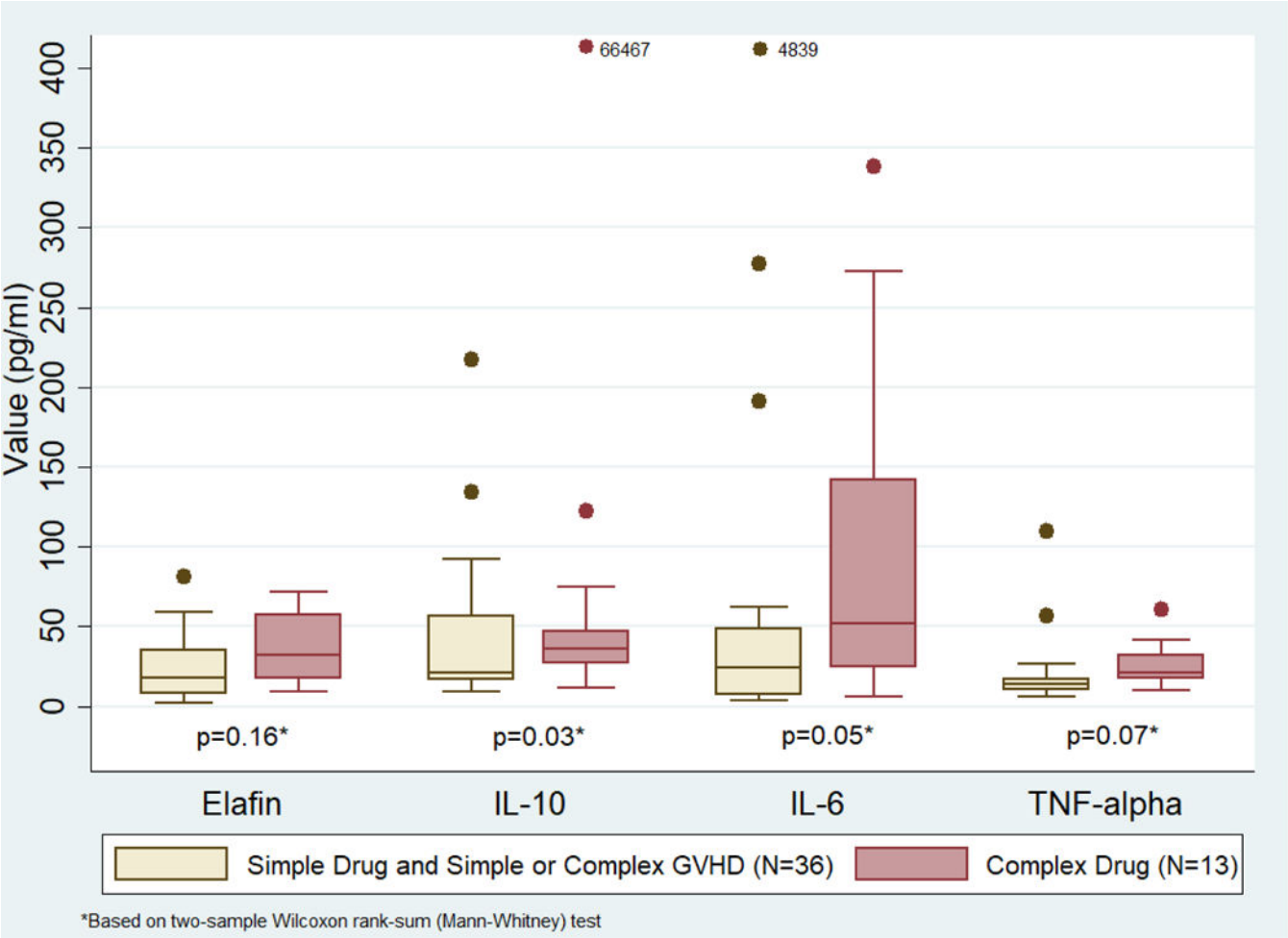

Figure 4.

Cytokines in ‘simple’ rash and ‘complex’ morbilliform rash due to GVHD vs. ‘complex’ morbilliform rash due to drug only. 66467 and 4839 refer to cytokine values that were much higher than the y-axis of the graph.

Table 1.

Characteristics of hospitalized cancer patients and ‘simple’ morbilliform rash vs. ‘complex’ systemic morbilliform rash.

	Simple morbilliform rash (n=27)	Complex morbilliform rash (n=22)	
	n (%)	n (%)	p-value
Patients (N), gender			
Female	15 (55.6)	12 (54.6)	
Male	12 (44.4)	10 (45.4)	0.94
Location			
Inpatient	22 (81.5)	19 (86.4)	
Urgent Care Center (ED)	5 (18.5)	3 (13.6)	0.65
Cancer Diagnosis			
Hematologic malignancy	18 (66.7)	15 (68.2)	
Solid organ malignancy	9 (33.3)	6 (27.3)	
Both Solid and Hematologic	0 (0)	1 (4.6)	0.54
Hematologic malignancy	18	16	
AML	8 (29.6)	6 (27.3)	--
ALL	2 (7.4)	0	--
Multiple myeloma	3 (11.0)	2 (9.1)	--
CML	0	2 (9.1)	--
CMML	1 (3.7)	0	--
Myelofibrosis	1 (3.7)	0	--
Myelodysplastic syndrome	0	2 (9.1)	--
DLBCL	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)	--
ATLL	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)	--
CTCL	0	1 (4.5)	--
Sarcoma	0	1 (4.5)	--
Status			

	Simple morbilliform rash (n=27)	Complex morbilliform rash (n=22)	
	n (%)	n (%)	p-value
Alive	19	10	
Deceased	8	12	
Modified RegiSCAR (median)	1.5	3.0	<0.001 *
Atypical lymphocytes (N)	5 (18.5)	4 (18.2)	0.98
T>38C (N)	7 (25.9)	4 (18.2)	0.52
Rash (>50%, +purpura/edema/scale), median	1	2	0.006 *
Eos score (0–2), median	0	1	0.001 *
Internal organs involved			
0	16 (59.3)	2 (9.1)	
1	10 (37.0)	16 (72.7)	
2	1 (3.7)	4 (18.2)	0.001
Decreased GFR relative to baseline (N)	4 (14.8)	4 (18.2)	0.75
Presence of urine eosinophils (N)	0	3 (13.6)	0.05
Elevated transaminases relative to baseline (N)	3 (11.1)	16 (72.7)	<0.001
Elevated total bilirubin relative to baseline (N)	6 (22.2)	8 (36.4)	0.28
Skin biopsy supportive of drug reaction (N)	10 (37.0)	13 (59.1)	0.12
Resolution > 15 days (N)	10 (37.0)	19 (86.4)	<0.001
At least 3 negative biological investigations to exclude alternate dx (N)	27(100)	22 (100)	1.0
WBC/μL (median)	3,420	8,550	0.05 *
CTCAE v4.03 Grade (median)	3	3	0.26 *
Cytokines/Biomarkers			
Elafin ng/mL median	17.9	25.5	0.22
IL-6 pg/mL median	16	26	0.11
IL-10 pg/mL median	19.5	31	0.07
TNF-α pg/mL median	12	18	0.03

* Based on the two-sample Wilcoxon rank-sum test