Acute Renal Failure and Its Risk Factors in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Key Words

Acute interstitial nephritis • Acute renal failure • Erythema multiforme • Hypersensitivity

Abstract

Background: Skin lesion is the most frequent manifestation of adverse drug reactions. Drug-induced cutaneous hypersensitivity and drug-induced acute interstitial nephritis might share a similar mechanism involving drug-specific T cells. We thus investigated the renal outcome of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the most severe drug-induced cutaneous hypersensitivity, and hypothesize that skin detachment in SJS/TEN might be associated with acute renal failure (ARF). **Methods:** 234 hospitalized patients were retrospectively classified into an SJS/TEN group (skin detachment) or an erythematous multiforme majus group (target-like exanthema alone). **Results:** Both drugs and chronic kidney disease (CKD) are associated with SJS/TEN. The SJS/TEN group was more likely to develop ARF than the erythematous multiforme majus group (18.8 vs. 4.3%, $p < 0.05$) despite similar initial creatinine clearance. In the ARF patients, RIFLE-F class, dialysis and long-term dialysis were 25, 15 and 5%, respectively. The offending drugs in ARF were also associated with CKD. Hyponatremia and late hypokalemia were more frequently in the SJS/TEN group (15.6 vs. 2.9%, 7.3 vs. 0.7%, respectively, $p <$

0.05). Sepsis, allopurinol, antibiotics, NSAIDs, CKD and hypoalbuminemia (OR: 18.8, 9.8, 10.1, 9.0, 5.3 and 3.3, respectively, $p < 0.05$) were the risk factors of developing ARF. **Conclusion:** ARF, the need for dialysis, and late hypokalemia could be the consequences of SJS/TEN. Skin detachment after certain medication might implicate the associated ARF, especially in CKD patients.

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Introduction

Skin is the most frequent target of adverse drug reactions, probably because of easy detection. Most of them are related to drug hypersensitivity [1]. Still, skin rash is not a frequent feature of drug-induced acute interstitial nephritis (AIN) [2]. The presence of skin lesions might be overlooked as only a skin reaction, rather than a systemic reaction. The relationship between skin and renal lesions in the context of drug hypersensitivity is little known. Hung et al. [3] showed that 50% of allopurinol-induced severe cutaneous adverse reactions were associated with worsening renal function. Then, if a skin lesion is observed in an adverse drug reaction, how much, how severe and what kind of renal lesions will there be? Because drug-induced AIN is fairly unpredictable, will the presentation of adverse skin reactions enable earlier no-

tification of renal injury? Furthermore, Spanou et al. [4] revealed that drug-specific T cells orchestrate a similar local inflammation and allergic reaction in both drug-induced AIN and drug-induced cutaneous hypersensitivity. We would reasonably speculate that the severity of drug-induced AIN might be related to the severity of skin lesions.

Drug-induced cutaneous hypersensitivity presents with a variety of features. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe and are characterized by a rapidly developing target-like exanthema accompanied by mucosal involvement and skin detachment [5]. These presentations differ from erythematous multiforme majus (EMM) which is related to infection and features only target-like exanthemas. SJS/TEN (denotes both SJS and TEN) and EMM are currently considered as cell-mediated reactions aimed at the destruction of keratinocytes expressing drug-related or herpes-related antigens, respectively [6]. Besides, more than 65% of SJS/TEN cases are induced by drugs including antibiotics, nonsteroid anti-inflammatory drugs (NSAIDs) and anticonvulsants [5]. Many of the offending drugs are well-known causes of AIN [2]. Case reports showed the co-existence of biopsy-proven AIN and SJS/TEN [7]. Thus, we hypothesize that the characteristic skin detachment observed in SJS/TEN will predict renal injury in these patients, while the nonspecific target-like exanthema observed in EM will not. Also the renal manifestation in SJS/TEN is largely unknown. Drug, insensible water loss, sepsis and diarrhea might further complicate renal injury [8, 9]. In view of the above, we carried out a retrospective study to investigate renal manifestations and risk factors of acute renal failure (ARF) in SJS/TEN and to determine whether skin detachment in SJS/TEN is associated with ARF.

Methods

Patients

We carried out a retrospective study of all adult cases admitted to Kaohsiung Medical University Hospital who were diagnosed as having EMM, SJS, overlap SJS/TEN, and TEN between January 1998 and June 2005 according to the classification of Bastuji-Garin et al. [10]. EMM patients were classified as the EMM group and all the other patients were classified as the SJS/TEN group [5, 8, 10].

Parameters Investigated

The clinical information of cases and underlying diseases were recorded on a standardized form as listed in table 1. Chronic kidney disease (CKD; with estimated creatinine clearance, Ccr,

Table 1. Clinical and demographic features

Features	SJS/TEN (n = 96)	EMM (n = 138)	p
Age, years	53±2.0	45±1.7	NS
Male gender	55.2%	39.1%	NS
Underlying diseases			
Diabetes mellitus	15.6%	10.1%	NS
Hypertension	27.4%	18.8%	NS
CKD	38.2%	22.3%	0.015
Cardiac disease	7.3%	0.7%	0.009
Chronic liver disease	7.3%	7.2%	NS
Temperature, °C	37.3±0.1	36.8±0.1	0.001
Patterns of EM			
Skin detachment, % of BSA	15.9±1.5	0.6±0.2	<0.001
Oral mucosa involvement	88.5%	18.1%	<0.001
Drug associated (vs. infection)	88.5%	52.9%	<0.001

BSA = Body surface area.

below 60 ml/min), cardiac disease (including arrhythmia, congestive heart failure and ischemic heart disease), and chronic liver disease (including chronic viral hepatitis and liver cirrhosis) were as defined.

ARF was classified according to the RIFLE GFR criteria [11]. Prerenal azotemia or intrinsic ARF was diagnosed based on the ratio of urea to creatinine (BUN:creatinine ratio) and response to hydration. Persistent hypokalemia was defined as serum K⁺ level ≤3.0 mEq/l lasting for more than 2 weeks or requiring potassium supplement to maintain the serum K⁺ level at >3.5 mEq/l.

Statistical Analysis

Data are presented either as actual numbers, percentage or mean ± standard error of the mean. Differences between groups of cases were evaluated by the χ^2 test, Fisher's exact test and Student's t test. A two-sided p value of 0.05 or less was considered as significant. Analyses and calculations were performed using SPSS statistical package, version 12.0 (SPSS Inc., Chicago, Ill., USA).

Multivariate logistic regression models were fitted with a forward stepwise algorithm. Parameter estimation was done by the likelihood ratio method. To test which demographic variables predict SJS/TEN lesion, we fitted into the logistic regression model all the recorded demographic variables. To test which laboratory and demographic variables predict ARF development, we chose the significant factors from univariate analysis for the logistic regression model.

Results

Clinical and Demographic Features

Among the 234 patients enrolled, 96 (41%) and 138 (59%) were classified as SJS/TEN and EMM, respectively (table 1). The SJS/TEN group differed significantly from

Table 2. Distribution of associated drugs in subgroups

Associated drugs	SJS/TEN (n = 85)	EMM (n = 73)	p	CKD (n = 57)	Non-CKD (n = 101)	p
Carbamazepine (n = 41)	65.9	34.1	<0.001	17.1	82.9	0.002
NSAIDs (n = 34)	61.8	38.2	NS	55.9	44.1	0.007
Antibiotics (n = 20)	50	50	NS	25	75	NS
Allopurinol (n = 17)	70.6	29.4	NS	82.4	17.6	<0.001
Herbs (n = 11)	45.5	54.5	NS	18.2	81.8	NS
Phenytoin (n = 10)	40	60	NS	50	50	NS
Other (n = 23)	24	76	0.001	20	80	NS

Figures represent percentages.

the EMM group in the clinical features of older age ($p = 0.005$), higher body temperature ($p = 0.001$), and more associated drugs ($p < 0.001$). These differences were compatible with previous observations [9]. In the SJS/TEN group, patients with CKD and cardiac disease also constituted a higher percentage than those in the EMM group (38.2 vs. 22.3%, $p = 0.015$; 7.3 vs. 0.7%, $p = 0.009$, respectively).

Associated Drugs in Subgroups

Drugs were the cause of SJS/TEN in 88.5% and of EMM in 52.9% of cases. Carbamazepine was the most common offending drug, followed by NSAIDs and antibiotics (table 2). These associated drugs are consistent with other SJS/TEN studies [5, 12]. The allopurinol and NSAID subgroups had a higher percentage of CKD patients. In contrast, the carbamazepine subgroup had a higher percentage of non-CKD patients.

Renal Manifestations and Laboratory Findings

There was no difference in initial renal function between groups as shown by estimated Ccr (table 3). However, abnormal urinalysis, proteinuria and hematuria were higher in the SJS/TEN group (28.3 vs. 8.7%, $p < 0.001$, 32.6 vs. 14.2%, $p = 0.001$, respectively). The C-reactive protein level was also greater in the SJS/TEN group (56.1 vs. 27.0 mg/dl, $p < 0.001$), but no difference in eosinophil count was seen.

The SJS/TEN group had a higher rate of ARF (20.8 vs. 4.3%, $p < 0.001$), but there was no difference in the need for dialysis (table 3). Each group had one case of mortality. Respiratory failure and septic shock were the causes of death for the SJS/TEN group and EMM group, respectively.

Clinical Manifestations of ARF Patients

ARF patients had a higher frequency of CKD (85 vs. 23%, $p < 0.001$), cardiac disease (12 vs. 4%, $p = 0.038$), offending drugs (96 vs. 64%, $p < 0.001$) and sepsis (17 vs. 2%, $p < 0.001$) than non-ARF patients (table 4). The interval between desquamation and admission was 4.55 days. 92% of ARF patients had a higher creatinine level than baseline on admission and 96% of them received corticosteroid treatment. The average peak creatinine level was about 3.44 mg/dl, which took 18.9 days to return to baseline. The ARF patients also showed higher potassium, uric acid, eosinophil count and lower hemoglobin than the non-ARF patients. The types of ARF distributed equally as prerenal azotemia and intrinsic ARF. The factors predisposing to prerenal azotemia were noted as SJS/TEN, sepsis, liver cirrhosis, colitis and bleeding. Three out of the 20 ARF patients (15%) required hemodialysis and one of them (5%) entered long-term dialysis. In one mortality case, dialysis was indicated due to oliguria ARF, but dialysis was not undertaken because of terminal illness. Nearly all of them (95%) had been prescribed offending drugs. Allopurinol (40%) and NSAIDs (35%) were the most commonly used.

Electrolyte Imbalance

Hyponatremia (<130 mEq/l) was found more frequently in the SJS/TEN group (15.6 vs. 2.9%, $p = 0.001$) on admission, and all recovered in the follow-up (table 3). Hypokalemia was observed around 1–2 weeks after admission and more frequently in the SJS/TEN group (7.3 vs. 0.7%, $p = 0.009$). Short-term polyuria was noted in 2 cases. Hyponatremia (18 cases) was associated with anticonvulsants, allopurinol, NSAIDs, herbs and ARF. Hypokalemia (8 cases) was associated with anticonvulsants,

Table 3. Renal manifestations and the laboratory findings

Variable	SJS/TEN (n = 96)	EMM (n = 138)	p
Renal function			
Estimated CCr, ml/min	76.0 ± 9.1	81.5 ± 3.3	NS
BUN, mg/dl	22.3 ± 2.0	16.3 ± 1.1	0.011
Creatinine, mg/dl	1.57 ± 0.21	1.12 ± 0.10	NS
BUN:creatinine ratio	16.0 ± 6.8	16.2 ± 6.7	NS
Urinalysis			
Proteinuria	28.3%	8.7%	<0.001
Microscopic hematuria	32.6%	14.2%	0.001
Electrolytes			
Na, mEq/l	135 ± 0.6	136 ± 1.0	NS
K, mEq/l	4.29 ± 0.07	4.07 ± 0.05	0.01
Hyponatremia (<130 mEq/l)	15.6% (15)	2.9% (4)	0.001
Other initial laboratory findings			
WBC, /μl	8,671 ± 382	8,743 ± 396	NS
Hgb, g/dl	13.1 ± 0.2	12.9 ± 0.2	NS
Eosinophil, %	3.4 ± 0.6	3.4 ± 0.4	NS
C-reactive protein, mg/dl	56.1 ± 6.4	27.0 ± 3.3	<0.001
Albumin, g/dl	3.62 ± 0.06	3.87 ± 0.04	0.002
GPT, IU/l	66.4 ± 10.0	54.4 ± 8.2	NS
Renal consequences			
Acute renal failure	20.8% (20)	4.3% (6)	0.001
Late hypokalemia ¹	7.3% (7)	0.7% (1)	0.009
Polyuria	2.0% (2)	0% (0)	NS
Need of Dialysis	3.1% (3)	1.4% (2)	NS
Corticosteroid treatment	99.0%	94.2%	NS
Mortality	1% (1)	0.7% (1)	NS

To convert BUN in mg/dl to mM, multiply by 0.357; creatinine in mg/dl to mM, multiply by 0.088.

¹ Newly developed hypokalemia during hospitalization as defined in 'Methods'.

NSAIDs, and allopurinol. These hypokalemic cases will be discussed in greater detail in another article. Three cases had transtubular potassium gradient exceeding 4 and 3 cases had ARF. No diuretics use, diarrhea, poor nutrition or active skin detachment were observed in the same period. Hypokalemia persisted from 2 weeks to 5 years and potassium supplement was needed.

Risk Factors of Renal and Skin Outcome

In multivariate analysis, independent risk factors were listed (table 5). Drugs (OR: 7.41), CKD (OR: 2.19) and male gender (OR: 2.19) were the risk factors of SJS/TEN in all patients. Sepsis (OR: 18.82), allopurinol (OR: 9.79), antibiotics (OR: 10.09), NSAIDs (OR: 9.03), CKD (OR: 5.3) and hypoalbuminemia (albumin OR: 0.3) were the risk factors of developing ARF in all patients.

Discussion

We demonstrated for the first time the high frequency of ARF (20.8%), the need for dialysis (3.1%), and hypokalemia (7.3%) in SJS/TEN patients. The incidence of ARF or hypokalemia is significantly higher in SJS/TEN patients than in EMM patients. Most of the patients were hospitalized for 5 days after the onset of desquamation and presented elevated serum creatinine at the time of admission. The use of allopurinol, NSAIDs, and antibiotics are associated with higher risk of ARF. Thus, the presence of characteristic skin detachment in adverse drug reaction should be regarded as a sign of the renal injury. Furthermore, we found that up to 25% of the ARF patients are classified as RIFLE – F class. 15 and 5% of the ARF patients required temporary dialysis and long-term dialysis, respectively. Hypokalemia, partly due to potassium-losing nephropathy, may last for years. Thus, SJS/TEN could result in profound renal injury and should be

Table 4. Characteristics of ARF in SJS/TEN patients

Features	
CKD stage 3–5	85% (17)
Peak creatinine, mg/dl	3.44 ± 0.8
RIFLE classification	
R+I class	75% (15)
F class	25% (5)
Duration of ARF, days	18.9 ± 5.6
Desquamation to admission interval, days	4.55 ± 0.8
Type of ARF	
Prerenal azotemia	40% (8)
Intrinsic ARF	45% (9)
Multifactorial ARF	15% (3)
Need for dialysis	15% (3)
Long-term dialysis	5% (1)
Duration of temporary HD, days	16
Offending drugs	95% (19)
Allopurinol	40% (8)
NSAIDs	35% (7)
Antibiotics	10% (2)
Anticonvulsants	10% (2)
Mortality	5% (1)

Table 5. Risk factors of SJS/TEN and ARF in all patients

Outcome	Risk factors	OR	95% CI	p
SJS/TEN ¹	Drug (vs. infection)	7.41	2.89–19.0	<0.001
	CKD	2.19	1.08–4.45	0.030
	Male sex	1.97	1.01–3.86	0.048
ARF ²	Sepsis	18.82	2.29–155.0	0.006
	Allopurinol	9.79	1.40–68.2	0.021
	Antibiotics	10.09	1.27–80.14	0.029
	NSAIDs	9.03	1.40–58.25	0.021
	CKD	5.30	1.33–21.12	0.018
	Albumin	0.30	0.18–0.48	<0.001

¹ Hosmer-Lemeshow goodness of fit test: $\chi = 8.66$, d.f. = 5, $p = 0.12$.

² Hosmer-Lemeshow goodness of fit test: $\chi = 8.81$, d.f. = 8, $p = 0.36$.

considered as a cause of mixed intrinsic and extrinsic ARF.

We then demonstrated that sepsis, associated drugs, CKD and hypoalbuminemia are the independent risk factors of ARF. To our surprise, skin detachment or mucosal involvement are not independently associated with ARF in total group or subgroup analysis. These results

might be related to the high prevalence of CKD in SJS/TEN patients (38%) and high incidence of ARF among these CKD patients (49%). We found for the first time the association between CKD and the development of SJS/TEN and the association between CKD and allopurinol or NSAIDs in our groups. We suspect the dominant effect of CKD may make SJS/TEN patients prone to develop ARF. These might suggest either the high exposure of allopurinol and NSAIDs in CKD patients or high incidence of SJS/TEN in CKD patients. CKD could increase the risk of adverse drug reactions by changing drug metabolism via altering renal and nonrenal clearance, protein binding and volume of distribution [13]. It is not clear whether CKD patients would have a higher rate of drug hypersensitivity. Further study is needed to clarify the relationship between drug-induced AIN and drug-induced SJS/TEN.

Prerenal azotemia indicated by elevated serum urea and tachycardia was identified as an independent risk factor for death in TEN [3]. ARF in SJS was considered a result of increased insensible water loss from skin and fluid loss from the gastrointestinal tract. However, in our groups, the consequences of skin and mucosal lesions, sepsis and hypoalbumin are independently associated with ARF. In our series, 8 out of 8 sepsis cases had ARF and 2 required dialysis. Liano et al. [14] reported that sepsis caused acute tubular necrosis in 27–35% of hospitalized patients. In addition, hypoalbuminemia, an indicator of malnutrition and possible decreased effective volume, is a strong predictor of ARF in our series and also in other studies with ICU patients [15]. As a consequence, appropriate effective volume should be kept.

Allopurinol, antibiotics and NSAIDs increased the risk for ARF in our multivariate analysis. We found that 50% of allopurinol-induced SJS/TEN patients suffered from ARF, which is in agreement with a previous observation (between 33 and 85%) [3]. Allopurinol is well known for its hypersensitivity syndrome consisting of an erythematous skin rash, fever, hepatitis, eosinophilia, and worsening renal function. Although carbamazepine is the leading cause of SJS/TEN in our series, there is only one ARF case in this group. Carbamazepine and allopurinol are the major causes of SJS/TEN in Asian patients, accounting for 25–33 and 25–37% cases, respectively, which might be related to specific HLA typing in the Chinese population [16–18]. Despite their similarity in frequency and genetic predisposition, they show differences in ARF susceptibility. We suspect this may be related to the high prevalence of CKD in allopurinol but not in the carbamazepine subgroup, as shown in table 2. Allopuri-

nol and oxipurinol are metabolized via the kidneys, whereas the metabolism of carbamazepine depends on the detoxification capacity of hepatocyte [19].

We also demonstrated that initial hyponatremia (15.6%) and late hypokalemia (7.3%) could be manifestations of SJS/TEN patients. Anticonvulsants, NSAIDs and ARF are well known for the induction of syndrome of inappropriate antidiuretic hormone secretion [20]. Hyponatremia resolved quickly without any problem. In contrast, hypokalemia was not detected initially and developed within 1–2 weeks with or without the occurrence of ARF. NSAIDs, anticonvulsants (phenytoin and carbamazepine), and allopurinol, which do not have hypokalemic effects by themselves, might indirectly lead to

hypokalemia in these cases. Here we consider that drug hypersensitivity-related potassium-losing nephropathy might be one of the causes.

In conclusion, we have demonstrated a high frequency of ARF, the need for dialysis, and hypokalemia in the hospitalized SJS/TEN patients. The incidence of ARF or hypokalemia is significantly higher in SJS/TEN patients than in EMM patients. Sepsis, associated drugs (allopurinol, NSAIDs and antibiotics), CKD and hypoalbuminemia are the independent risk factors of ARF in SJS/TEN patients. Thus, skin detachment presented after certain medication may implicate the associated ARF, especially in CKD patients.

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