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Clinicopathological analysis of patients diagnosed with DRESS

DRESS tanılı hastaların klinikopatolojik analizi

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Abstract

Background and Design: Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon, but potentially fatal, adverse drug reaction. Despite the alarming statistics regarding morbidity, mortality, and hospitalizations, epidemiological data on DRESS are insufficient. In this investigation, we sought to determine the etiology, clinicopathological characteristics, and prognosis of DRESS cases at our institution.
Materials and Methods: In this retrospective, single-center study, 23 patients with DRESS examined between January 2014 and September 2020 were included according to the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system. Patients were examined between January 2014 and September 2020. Descriptive statistics, Shapiro-Wilk test, Kolmogorov-Smirnov test, Mann-Whitney U test, Pearson chi-square test, and Fisher's exact test were performed.
Results: The most frequently detected culprit drug category was anticonvulsants. Maculopapular eruption (100%) and elevated liver function tests (82%) were the most prevalent cutaneous and laboratory findings, respectively. Patients with elevated liver enzymes were more likely to exhibit facial erythema/edema and lymph node enlargement than those without (p=0.021 and p=0.103, respectively). The predominant pathological features were sparse vacuolization of the dermal-epidermal junction and superficial perivascular lymphohistiocytic inflammation with eosinophils. Two patients died during the period of follow-up, three patients were lost to follow-up, and eighteen patients recovered completely.
Conclusion: Our research demonstrated that facial erythema/edema and lymph node enlargement are more prevalent in patients with elevated liver enzymes. Cyclosporine may be a treatment option in the fragile age group to prevent systemic corticosteroid complications. Early diagnosis and treatment that balances benefits and risks remain the most important determinants of prognosis
Keywords: Drug reactions, drug reaction with eosinophilia and systemic symptoms, drug hyper-sensitivity syndrome, antiepileptics

Öz

Amaç: Eozinofili ve sistemik semptomlarla birlikte görülen ilaç reaksiyonu (DRESS), nadir görülen ancak yaşamı tehdit eden bir advers ilaç reaksiyonudur. Morbidite, mortalite ve hastaneye yatışlarla ilgili endişe verici istatistiklere rağmen, DRESS ile ilgili epidemiyolojik veriler hala yetersizdir. Bu çalışmada merkezimizde DRESS'li olguların etiyolojisi, klinikopatolojik özellikleri ve sonuçlarını değerlendirmeyi amaçladık.
Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya, Ocak 2014 ile Eylül 2020 arasında muayene edilen, olası ve/veya kesin DRESS tanılı 23 hasta, Avrupa Şiddetli Kutanöz Yan Etkiler Kayıt Sistemi (RegiSCAR) skorlama sistemine göre dahil edildi. İstatistiksel yöntem olarak tanımlayıcı istatistikler, Shapiro-Wilk testi, Kolmogorov-Smirnov testi, Mann-Whitney U testi, Pearson ki-kare testi ve Fisher'in kesin testi kullanıldı.
Bulgular: Etiyolojide en sık saptanan ilaç kategorisi antikonvülzanlardı. En sık görülen kutanöz ve laboratuvar bulguları sırasıyla makülopapüler döküntü (%100) ve karaciğer fonksiyon testlerinde yükselme (%82) idi. Yüzde eritem/ödem ve lenfadenopati, karaciğer enzimleri yüksek olan

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hastalarda olmayanlara göre daha sık saptandı (sırasıyla; p=0,021 ve p=0,103). Dermal-epidermal bileşkede seyrek vakuolizasyon ve eozinofillerle yüzeyel perivasküler lenfohistiyositik enflamasyon ana patolojik özelliklerdi. Takip süresi boyunca 18 hasta tamamen iyileşirken, iki hastada ölüm görüldü ve üç hasta takipten çıktı.
Sonuç: Çalışmamız fasiyal eritem/ödem ve lenfadenopatinin karaciğer enzimleri yüksek olan hastalarda daha sık görüldüğünü göstermiştir. Siklosporin, kırılgan yaş grubunda sistemik kortikosteroid komplikasyonlarını önlemek için bir tedavi seçeneği olabilir. Erken teşhis ve fayda-zarar dengesi gözetilerek uygulanan tedavi hala sonucu etkileyen en önemli faktörlerdir.
Anahtar Kelimeler: İlaç reaksiyonları, eozinofili ve sistemik semptomlarla birlikte ilaç reaksiyonu, ilaç aşırı duyarlılık sendromu, antiepileptikler

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction characterized by a maculopapular skin rash with fever, lymphadenopathy, hematologic abnormalities (leukocytosis, eosinophilia, and/or atypical lymphocytosis), and multiorgan involvement[1]. Because DRESS can cause long-term complications and is potentially life-threatening[1], a definitive diagnosis, effective treatment, and frequent patient follow-up are crucial.

Geographic and racial variation is a significant factor that can lead to variations in drug metabolism[2,3]. These differences may cause DRESS to manifest in clinically distinct individuals. Despite the high prevalence of morbidity, mortality, and hospitalizations, epidemiological data on DRESS remain scarce in several nations.

This study aims to describe the clinicopathological characteristics, etiology, and laboratory findings of our patients and to compare the outcome of the disease after treatment using various outcome measures, including skin rash severity, European Registry of Severe Cutaneous Adverse Re-action (RegiSCAR) score, full recovery time, and improvement in organ function tests.

Materials and Methods

Study Design and Setting

This study was a single-center retrospective cross-sectional study of patients diagnosed with DRESS in our clinic between January 2014 and September 2020. We followed the ethical principles of the Helsinki Declaration throughout the study. Approval was obtained from the Akdeniz University Faculty of Medicine Local Ethics Committee (approval number: KAEK-499/08.07.2020).

Patients and Data

The RegiSCAR scoring system was administered to all patients. Patients with DRESS diagnosis were included in the study according to the RegiSCAR scoring system. Patients without adequate information in electronic files were excluded.

Variables and Outcomes

Patients' demographics, medical history, clinical features, type of causative drugs, laboratory findings, treatment choices, and the outcome of the disease after treatment were retrospectively collected from electronic patient files. There were four primary focuses of the evaluation:

The skin rash severity RegiSCAR score,

The full recovery time,

The improvement in organ function tests.

We have itemized skin rash severity as the percentage of affected body surface area (BSA), the full recovery time as the time to a complete improvement in symptoms, laboratory findings, organ functions, and resolution of lymphadenopathy following treatment, and the return of hepatic and renal function tests to normal.

Statistical Analysis

Statistical analyses were performed using SPSS version 20 (IBM Corp. in Armonk, NY). Descriptive statistics for categorical data are displayed as the frequency and percentage and the median with interquartile range or minimum and maximum values for non-normally distributed numeric data. Shapiro-Wilk test and Kolmogorov-Smirnov test were used to evaluate the normality of the distribution of numeric data. The Independent-Samples Mann-Whitney U test was used to compare non-normally distributed numeric data between two groups. Pearson chi-square test and Fisher's exact test were used for comparing categorical variables. P<0.05 was considered statistically significant.

Results

Twenty-three patients were enrolled in the study. The median age was 41 years, 52.2% of the population was female, and 47.8% was male. In every patient, erythema and maculopapular eruption were observed. Other frequent cutaneous manifestations included pruritus (n=22, 95.6%), facial edema/erythema (n=18, 78.2%), and oral mucosal involvement (n=4, 17.3%). Eighteen patients suffered from fatigue, 15 from enlarged lymph nodes (ELNs), and 4 from headaches. Twenty-one of the twenty-three patients (91.3%) had a rash covering over 50% of the BSA, and clinical and histopathological concordance was observed in 16 of the 17 patients who underwent a biopsy. The median RegiSCAR score was 5, and the median time between symptom onset and admission and biopsy was 6 days. The median duration of patient follow-up was 22 weeks (Table 1).

Laboratory results for the patients are shown in Table 2. While the majority of patients (82.6%) had elevated hepatic transaminases, only one patient had an aberrant renal function test. Other prevalent hematological findings included eosinophilia in 14 patients (60.8%), leukocytosis in 14 (60.8%), anemia in 12 (52.1%), and lymphocytopenia in 8 (34.7%). In eight patients (34.8%), aberrant thyroid tests were detected. These patients exhibited euthyroid sick syndrome as a manifestation of thyroid dysfunction. One patient was seropositive for viral hepatitis (Table 2). Comparing the clinical and laboratory findings between patients with elevated hepatic transaminases (n=19, 82.6%) and those without (n=4, 17.3%), virtually all characteristics were comparable. Facial edema/erythema was considerably more common in patients with elevated hepatic transaminases than in those without (89.5% vs. 25%, p=0.021). Patients with elevated hepatic transaminases were more likely to have ELNs than those without (73.7% versus 25%, respectively), but this difference was not statistically significant (p=0.103; data not shown).

The most frequently detected culprit drug category was anticonvulsants (n=11), including lamotrigine, carbamazepine, and phenytoin, followed by antirheumatic drugs (n=4) and antibiotics (n=3). Besides these, the causative drug was allopurinol in two patients, amlodipine in one patient, and diosmin/ hesperidin in one patient, and the culprit drug could not be determined in one patient (Table 3).

Skin biopsies were performed on 17 (73.9%) patients. Sparse vacuolization of the dermal-epidermal junction and superficial perivascular lymphohistiocytic inflammation with eosinophils were the most prevalent histopathologic findings.

Topical corticosteroids were used in 18 patients, moisturizers in 8, and antiseptics in 2 patients. Besides bed rest, 13 patients received intravenous (IV) fluid therapy, two patients received nutritional care, and two patients received oxygen support. The most frequently used systemic treatment was systemic corticosteroid (SC) (n=17), followed by antihistamines (n=6) and cyclosporine A (CyA) (n=3). The starting dose of methylprednisolone was 0.5 mg/kg/day, and the dose was gradually reduced and discontinued within 3 to 6 months. Due to superior oral absorption, SC was administered orally or via nasogastric tube to 15 patients (88.2%) and intravenously to two patients for whom neither option was feasible. For one month, a dosage of 3-5 mg/kg/day of CyA was administered.

Table 1. Demographics and clinical features of the patients

Characteristics (n=23)	
Age (years), median (IQR)	41.0 (27.0-64.0)
Sex, n (%)	
Female	12 (52.2)
Male	11 (47.8)
Previous thyroid disease, n (%)	8 (34.8)
Skin symptoms/signs, n (%)	
Generalized erythema	23 (100.0)
Maculopapular eruption	23 (100.0)
Pruritus	22 (95.7)
Fascial edema/erythema	18 (78.3)
Oral mucosal involvement	4 (17.4)
Targetoid eruption	2 (8.7)
Skin tenderness	1 (4.3)
Bullous eruption	1 (4.3)
Systemic symptoms/signs, n (%)	
Fatigue	18 (78.3)
Enlarged lymph nodes	15 (65.2)
Headache	4 (17.4)
Diarrhea	2 (8.7)
Abdominal pain	1 (4.3)
Pneumonia	1 (4.3)
Skin rash severity, n (%)	
≤50% of BSA	2 (8.7)
>50% of BSA	21 (91.3)
Clinical and histopathological concordance[a], n (%)	19 (95.0)
RegiSCAR score, median (min-max)	5.0 (4.0-7.0)
Time-to-admission (day)[b], median (IQR)	6.0 (3.0-11.0)
Time-to-biopsy (day)[c], median (IQR)	6.0 (4.0-11.0)
Follow-up time, (week), median (min-max)	22.0 (3.0-261.0)

IQR: Interquartile range, BSA: Body surface area, min: Minimum, max: Maximum.
[a]Concordance between clinical features and histopathological findings. Biopsy was not performed in six patients.
[b]Time from the beginning of the complaints to the admission.
[c]Time from the beginning of the complaints to the biopsy

Twenty-one patients (91.3%) had complete cutaneous recovery, and eighteen patients' renal and hepatic functions improved. During the period of follow-up, two patients died, three patients were lost to follow-up, and eighteen patients recovered. Table 4 displays that 8 of the 18 patients recovered within one month, 9 within two to three months, and one within six months. The thyroid functions of all patients with euthyroid sick syndrome improved within 6 months. Abdominal pain and pneumonia were associated with a reduced likelihood of recovery (p=0.003).

Except for ELN, other clinical characteristics were comparable between age groups ≤40 and >40 (p>0.05). 90.9% of patients ≤40 years old and 41.7% of patients >40 years old were found to have ELN, which was statistically significant (p=0.027). We also compared age categories younger than 60 (n=16) and older than 60 (n=7); except for SC use, all other characteristics were comparable. Patients ≤60 years old received substantially more SC than patients >60 years old (87.5% vs. 42.9%, p=0.045) (data not shown). Comparing the same characteristics according to sex and skin rash severity, according to BSA, revealed no statistically significant differences between the groups. Facial edema/erythema was more common in women than in men (p=0.048) when we analyzed the relationship between clinical findings and gender.

Table 2. Laboratory findings of the patients

Laboratory findings (n=23)	
Hepatic transaminase elevation, n (%)	19 (82.6)
Abnormal renal function tests, n (%)	1 (4.3)
Anemia, n (%)	12 (52.2)
Lymphocytopenia, n (%)	8 (34.8)
Eosinophilia, n (%)	14 (60.9)
Leukocytosis, n (%)	14 (60.9)
Leukopenia, n (%)	2 (8.7)
Thrombocytopenia, n (%)	4 (17.4)
Thrombocytosis, n (%)	3 (13.0)
Viral hepatitis seropositivity, n (%)	1 (4.3)
Thyroid function test abnormalities, n (%)	8 (34.8)

Table 3. Categories and names of causative drugs

Drug category (n=22)[a]	**n (%)**	**Drug name**	**n (%)**
Anticonvulsants	11 (50.0)	Lamotrigine	4 (22.7)
		Carbamazepine	4 (22.7)
		Phenytoin	2 (9.0)
		Lamotrigine and carbamazepine	1 (4.5)
Antirheumatics	4 (17.4)	Sulfasalazine	3 (13.6)
		Hydroxychloroquine	1 (4.5)
Antimicrobials	3 (13.6)	Vancomycin	2 (9.1)
		Ciprofloxacin	1 (4.5)
Antihypertensives	1 (4.5)	Amlodipine	1 (4.5)
Other	3 (13.6)	Allopurinol	2 (9.1)
		Diosmin/Hesperidin	1 (4.5)

[a]In one patient, the causative drug could not be identified

Table 4. Therapeutic management and prognosis of the patients	
Characteristics	
Withdrawal of the causative drug, n (%)	22 (100.0)[a]
Topical treatment, n (%)	
Corticosteroid	18 (78.3)
Topical moisturizer	8 (34.8)
Topical antiseptic	2 (8.7)
Supportive treatment, n (%)	
IV hydration	13 (56.5)
Bedrest	23 (100.0)
Mucosa care	4 (17.4)
Nutritional care	2 (8.7)
Oxygen support	2 (8.7)
Systemic treatment, n (%)	
Corticosteroid	17 (73.9)[b]
Antihistamines	6 (26.1)
Cyclosporine A	3 (13.0)
Complete recovery of the skin, n (%)	21 (91.3)
Improvement in hepatic/renal function test results, n (%)	18 (90.0)[c]
Overall prognosis during the follow-up, n (%)	
Full recovery[d]	18 (78.3)
Ex	2 (8.7)
Lost to follow-up	3 (13.0)
Full recovery time, n (%)	
Up to 1 month	8 (44.4)
2-3 months	9 (50.0)
4-6 months	1 (5.6)

[a]In one patient, the causative drug could not be identified.
[b]Topical and systemic corticosteroid therapy was given to 17 patients at the same time.
[c]Twenty patients have had hepatic and/or renal function test abnormality.
[d]That means a complete improvement in symptoms, laboratory findings, and organ functions

Facial edema/erythema, ENLs, headache, and eosinophilia were statistically more prevalent in the group with high RegiSCAR scores (p=0.037, p=0.027, p=0.037, and p=0.049, respectively; Table 5).

Discussion

Insufficient data exist regarding the epidemiology of DRESS. The reported incidence is approximately 1 in 100,000 per year, and the prevalence ranges from 2 to 10 patients per 100,000 inpatients[3-7]. DRESS is observed in adults as opposed to children and does not differ by gender, as observed in our patient cohort[6].

DRESS is characterized by both symptomatic and asymptomatic clinical features, which usually develop in two weeks to two months following treatment with a culprit drug. The most common signs and symptoms are dermatologic manifestations, such as maculopapular eruption, pruritus, and a diffuse and confluent rash, which can be edematous, pustular or vesiculobullous, and clinical and laboratory features, such as fever, organ involvement, eosinophilia[1]. The facial edema/erythema is often localized in the periorbital and midfacial region, often symmetric and persistent. In addition, half of the patients developed mucosal involvement (cheilitis, erosions, erythematous pharynx, and enlarged tonsils)[1,8,9]. Besides that, systemic symptoms are associated with the involved organs, such as the liver, kidney, lung, heart, brain, and endocrine glands[1,10].

Although diverse scoring systems are used for diagnosing and assessing the severity of the disease and the prognosis of patients[8,10-12], the most widely accepted system for DRESS is the RegiSCAR scoring system[13]. Our findings of a strong correlation between the RegiSCAR score and the clinical and laboratory characteristics of the patients demonstrate the utility of this scoring system.

Several pharmacologic agents may play a role in developing DRESS[14-28]. In our study, carbamazepine and lamotrigine were seen together in the first place as causative agents, which were also shown in previous reports[29,30]. Finally, looking for just "one" drug can lead us astray, as sometimes the same patient may have multiple medications[31]. It is essential to identify the causative drug(s) because a crucial step in the treatment is the withdrawal of the culprit drug[10,12].

The initial step in the treatment of DRESS is the discontinuation of the offending medication followed by a wide range of topical and systemic therapies and supportive therapy[8]. Hospitalization is recommended for all patients, except for mild cases with close clinical monitoring[32]. Guidelines and numerous recent studies suggest very high or high potency topical corticosteroids and other topical agents, such as antiseptics and moisturizers, may be used as first-line treatment if there is minimal or no involvement of the liver and kidneys[33,34]. If patients have moderate or severe organ involvement, consultation and cooperation with the appropriate clinical departments should be incorporated into the treatment plan, and intensive care unit care should be considered if necessary[8,35]. In the presence of such a severe disease, SC should be initiated first in younger patients, as in our study. Considering the side effects of SC, clinicians can utilize relatively safer therapeutic alternatives, such as topical corticosteroids, especially in elderly patients, patients with comorbid diseases, and/or patients with mild organ involvement. In addition, CyA could be administered if SC fails to control the eruption, if a relapse occurs after the initial treatment, or if SC is contraindicated[36]. Where the eruption could not be controlled with these two treatments, IV immunoglobulin can be the following choice, and plasmapheresis and cyclophosphamide should be kept in mind as the last resort[8,12,37,38]. Our clinical practice's treatment options are analogous to those recommendations. Predicting the outcome for patients with DRESS is difficult. Early diagnosis and withdrawal of causative agents typically result in a full recovery, whereas the severity of affected BSA is an indicator of a poor prognosis[6,8,12,13]. In our study, our patients have excellent recovery times, although BSA involvement is not at all low. This can be attributed to the relatively young age of the patients in the study, the relatively brief admission time after the onset of symptoms, and the early discontinuation of the culprit drug.

As a dermatological emergency, fatality may increase up to 10% in patients with DRESS[10-12]. Although the two fatalities in our study appear comparable at this rate, in one of the fatal cases, the skin recovered, while in the other, it did not. Because both patients were being monitored in the intensive care unit, sepsis developed, and one patient perished from meningoencephalitis and the other from respiratory complications (Supplement Table 1).

Table 5. Comparison of some clinical features according to the RegiSCAR score

Characteristics	RegiSCAR		p
	≤5 (n=12)	≥6 (n=11)	
Fascial edema/erythema, n (%)	7 (58.3)	11 (100.0)	**0.037[a]**
Oral mucosal involvement, n (%)	2 (16.7)	2 (18.2)	>0.999[a]
Fatigue, n (%)	10 (83.3)	8 (72.7)	0.640[a]
Enlarged lymph nodes, n (%)	5 (41.7)	10 (90.9)	**0.027[a]**
Headache, n (%)	0 (0.0)	4 (36.4)	**0.037[a]**
Hepatic involvement, n (%)	2 (16.7)	0 (0.0)	0.478[a]
Hepatic transaminase elevation, n (%)	8 (66.7)	11 (100.0)	0.093[a]
Abnormal renal function tests, n (%)	0 (0.0)	1 (9.1)	0.478[a]
Anemia, n (%)	8 (66.7)	4 (36.4)	0.146[b]
Lymphocytopenia, n (%)	6 (50.0)	2 (18.2)	0.193[a]
Eosinophilia, n (%)	5 (41.7)	9 (81.8)	**0.049[b]**
Leukocytosis, n (%)	6 (50.0)	8 (72.7)	0.400[a]
Leukopenia, n (%)	2 (16.7)	0 (0.0)	0.478[a]
Thrombocytopenia, n (%)	1 (8.3)	3 (27.3)	0.317[a]
Thrombocytosis, n (%)	3 (25.0)	0 (0.0)	0.217[a]
Systemic corticosteroid treatment, n (%)	8 (66.7)	9 (81.8)	0.640[a]
Complete recovery of the skin, n (%)	11 (91.7)	10 (90.9)	>0.999[a]
Improvement in the organ function tests, cn (%)	8 (88.9)	9 (81.8)	>0.999[a]
Fatality, n (%)	0 (0.0)	2 (18.2)	0.217[a]
Full recovery time, dn (%)			
Up to 1 month	4 (40.0)	4 (50.0)	0.478[c]
2-3 months	6 (60.0)	3 (37.5)	
4-6 months	0 (0.0)	1 (12.5)	

[a]Fisher's Exact test was used.
[b]Pearson chi-square test was used.
[c]Twenty patients have had hepatic and/or renal function test abnormality.
[d]Eighteen patients had reached full recovery.
RegiSCAR: European Registry of Severe Cutaneous Adverse Reactions

Although antiepileptic drugs and allopurinol[13] were the most commonly observed causal agents in fatal cases, vancomycin and sulfasalazine were the two culprit drugs in our fatal cases. Since some studies have demonstrated that fatal cases of DRESS were associated with the reactivation of viruses, such as human herpesvirus 6 or cytomegalovirus[39,40], it may also be due to multi-organ failure resulting from a variety of causes, including liver, pulmonary, and/or myocardial involvements, and nosocomial infections in intensive care[1,35,41,42]. Close monitoring, consideration, and treatment of potential causes may be lifesaving for these patients. There are no standardized recommendations for the frequency and duration of patient follow-up. Autoimmune diseases, such as autoimmune thyroiditis, may have long-term sequelae in young and middle-aged individuals, and this sequela may begin 2 years after acute illness; therefore, routine follow-up is generally advised at least during this time frame[1].

Study Limitations

This study has several limitations. First, the study was conducted in a single center with a relatively small sample size, limiting the generalizability of the results to the entire population of patients with DRESS. The others included the fact that we could not structure and compare the treatment methods and the lack of randomization of the patients related to the study's retrospective design.

Conclusion

A wide variety of drugs could be detected in DRESS patients. Patients can manifest with a variety of skin and systemic symptoms and laboratory findings. Intensive monitoring and treatment of concomitant conditions may save the lives of patients with severe diseases. It is essential to individualize treatment based on the severity of the disease and the patient's characteristics and to implement the benefit-risk ratio, particularly in the fragile age group.

Ethics

Ethics Committee Approval: Approval was obtained from the Akdeniz University Faculty of Medicine Local Ethics Committee (approval number: KAEK-499/08.07.2020).

Informed Consent: Since the study is in the retrospective pattern, the ethics committee did not consider it necessary to take the informed patient consent form.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.C.B., A.A., A.B., Concept: B.C.B., A.B., E.A., Design: B.C.B., A.A., A.B., Data Collection or Processing: B.C.B., A.A., C.I.B., B.Ü., Analysis or Interpretation: B.C.B., A.A., A.B., E.A., Literature Search: B.C.B., A.A., A.B., Writing: B.C.B., A.A., A.B.

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Supplement Table 1. Summarized patient data of 23 cases

Patient	Age	Sex	Facial edema/ erythema	ELN	Oral mucosal lesion	Time-to-admission (day)	RegiSCAR score	Laboratory findings			Leukocytes ($x10^9$/L)	Thrombocytes ($x10^9$/L)	AST (U/L)	ALT (U/L)	Therapy	Prognosis, FRT (months)
								Anemia	Lymphocytes ($x10^9$/L)	Eosinophils ($x10^9$/L)						
1	74	M	Yes	Yes	No	2	6	0	2,620	760	22,550	252,000	45	50	T	FR (3rd month)
2	22	F	Yes	Yes	No	7	6	0	1,240	40	7,200	190,000	204	307	T, S	FR (1st month)
3	20	M	Yes	Yes	No	14	5	1	2,420	870	7,590	210,000	120	426	T, S	LFU
4	70	M	No	No	No	4	5	0	570	50	9,600	130,000	24	23	T	LFU
5	28	F	Yes	Yes	No	3	5	1	1,310	20	5,210	638,000	56	82	S	FR (3rd month)
6	28	F	Yes	Yes	Yes	5	5	0	1,330	110	9,630	286,000	55	118	T, S	FR (3rd month)
7	34	M	Yes	No	No	4	4	0	970	570	6,440	265,000	21	26	S	FR (3rd month)
8	60	F	Yes	No	No	3	5	1	460	460	4,090	191,000	300	589	T, S	FR (3rd month)
9	28	F	Yes	Yes	No	21	6	0	3,210	570	9,200	251,000	44	55	T, S	FR (1stmonth)
10	50	M	No	No	No	10	5	0	1,910	3,760	13,360	317,000	16	33	T, S	FR (1st month)
11	72	F	No	No	No	4	5	1	930	110	5,130	241,000	40	48	T	FR (1st month)
12	27	M	Yes	Yes	Yes	16	6	0	9,050	560	20,840	248,000	81	288	S	FR (6th month)
13	66	M	Yes	No	No	20	6	0	3,800	1,060	18,330	344,000	27	71	T, S	FR (3rd month)
14	25	F	Yes	Yes	No	U	6	1	2,780	20	11,090	129,000	25	108	T, S	FR (3rd month)
15	41	F	Yes	Yes	No	7	6	1	730	2,990	30,200	68,000	912	345	S	Ex
16	37	F	Yes	Yes	No	3	7	0	2,690	1,290	17,540	236,000	83	95	T,S	FR (1st month)
17	64	M	Yes	Yes	No	7	7	1	2,890	1,550	11,140	342,000	58	91	T, S	FR (1st month)
18	43	F	Yes	Yes	No	8	6	1	9,580	3,810	23,940	304,000	1840	1419	T, S	Ex
19	72	M	No	No	Yes	20	4	1	550	200	7,950	271,000	183	231	T, S	LFU
20	56	F	Yes	Yes	No	7	5	1	1,680	770	15,270	436,000	62	43	T, S	FR (3rd month)
21	25	M	No	Yes	No	3	5	1	2,490	2,170	19,310	608,000	23	12	T, S	FR (3rd month)
22	9	M	Yes	Yes	Yes	4	6	0	3,540	500	7,790	143,000	77	75	T, S	FR (1st month)
23	42	F	Yes	No	No	1	4	1	3,760	320	24,190	298,000	58	71	T, S	FR (1st month)

M: Male, F: Female, RegiSCAR: European Registry of Severe Cutaneous Adverse Reactions, AST: Aspartate transaminase, ALT: Alanine transaminase, FRT: Fractionated radiotherapy, ELN: Enlarged lymph node, T: Topical treatment, S: Systemic treatment, U: Unknown, LFU: Lost to follow-up