

Incidence of adverse cutaneous drug reactions in 22,866 Chinese inpatients: a prospective study

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Abstract Cutaneous adverse drug reactions (ADRs) are common. However, no prospective study assessing cutaneous ADRs is available for Chinese populations. This study aimed to assess the incidence, manifestations, causative drugs, and other factors related to cutaneous ADRs. A total of 22,866 inpatients were surveyed prospectively from January to April 2012 at the Peking Union Medical College Hospital. Only cutaneous ADRs induced by systemic drugs were considered. Fifty cases were confirmed as cutaneous ADRs, for an estimated incidence of 2.2 per 1000 during this period (95 % confidence interval 1.6–2.8). Cases of cutaneous ADRs comprised 69 % females, while 63 % of all inpatients were female ($\chi^2 = 0.641$, $P = 0.427$). The department of infectious diseases was the most frequently involved department. Morbilliform exanthema (40 %) was the most frequent cutaneous ADR, followed by urticaria (23.1 %). Anti-infection drugs (36.9 %) caused most cases of cutaneous ADRs, followed by iodinated contrast media (ICM, 18.5 %) and non-steroidal anti-inflammatory drugs (NSAIDs, 18.5 %). The most

frequently associated disorders were cancer (24 %), infection (22 %), cardiovascular and cerebrovascular diseases (20 %), and autoimmune diseases (18 %). In this first prospective study assessing the incidence of cutaneous ADRs in China, anti-infection drugs were the most commonly involved drugs, followed by ICM and NSAIDs. No evidence of increased cutaneous ADR incidence in AIDS or SLE patients was observed. Our findings indicate that cancer and its treatments were often related to cutaneous ADRs in China.

Keywords Cutaneous adverse drug reaction · Adverse effects · Drugs · Hospital · Incidence

Introduction

The World Health Organization defines adverse drug reactions (ADRs) as undesired effects of a drug occurring at doses normally used in patients [11]. Cutaneous ADRs are the most common ADRs, representing 10–15 % of all reported ADRs [19]. Dermatologists are often consulted for cutaneous ADRs, but it is often difficult to clearly distinguish these lesions from other skin diseases. Indeed, cutaneous ADRs' severity vary from transient maculopapular rashes to fatal toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) [6, 22]. The offending drugs also vary every year as more products are approved for clinical use.

The incidence of cutaneous ADRs ranges from 0.15 to 30 % according to a number of prospective and retrospective studies [7]. Only three prospective studies have assessed cutaneous ADRs in the last decade and incidence rates 3.6–10 per 1000 patients were reported in France and Mexico [4, 8, 10]. Moreover, a network-based electronic

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notification system for drug allergy in Singapore identified 210 cases of ADRs among 90,910 admissions from December 1, 1997 to December 31, 1999, for an overall incidence of 4.2/1000, including cutaneous and non-cutaneous cases, and including patients admitted due to ADRs and those who developed ADRs during hospitalization [18].

To the best of our knowledge, no prospective study describing cutaneous ADRs has been reported in a Chinese population. Therefore, the present epidemiologic study was performed to estimate the actual incidence of cutaneous ADRs in hospitalized patients and determine the drugs responsible for cutaneous ADRs. In addition, we analyzed the patients' demographic profiles and clinical manifestations.

Materials and methods

Setting

The present study was a 4-month prospective observational study conducted from January to April 2012 at the Peking Union Medical College Hospital, a public 2000-bed acute care general hospital with an average of 200 daily admissions. The study was approved by the Medical Ethics Committee of the hospital.

Survey plan

All wards' clerks, nurses, and physicians were informed of the study, and some were recruited as volunteers. A resident in each involved ward was designated for checking the patients on a daily basis. When patients were found to develop cutaneous ADRs during their hospital stay, they were asked to report to two dermatologists. The two dermatologists made a final diagnosis based on physical examination (including a full skin check), detailed medical history, consideration of the particular dermatosis, and the latency between drug ingestion and skin lesion appearance, except for some local reactions (such as folliculitis, alopecia areata, striae distensae, or local contact dermatitis). If cutaneous ADR was diagnosed by both dermatologists separately, they confirmed the case together. Acute generalized exanthematous pustulosis (AGEP), TEN or Stevens-Johnson syndrome (SJS), erythroderma (ED), anaphylaxis and drug-induced hypersensitivity syndrome (DIHS) or DRESS were defined as severe cutaneous ADRs. These diseases are potentially life-threatening, and were responsible for hospitalization or prolonged hospital stay.

For the incidence calculation, patients with cutaneous ADRs that developed before admission or after discharge were excluded. Cutaneous ADRs caused by blood or blood

products and chemotherapy drugs were excluded as well, either due to their high allergy rates or short patient stay in the hospital. Fifteen patients from the dermatology department admitted due to cutaneous ADRs that developed in other hospitals were included because complete clinical records were available. These 15 patients were diagnosed with cutaneous ADRs in other hospitals and were referred to our dermatology department for second opinions and treatments. However, since they were diagnosed elsewhere, they were not included for incidence calculation, but we considered them in the characterization of cutaneous ADRs in order to increase our sample size.

Standard questionnaire

A standard questionnaire was used to collect data including gender, age, nationality, department of admission, underlying diseases, and history of drug reactions. The morphological description of the lesions included rash type, clinical manifestations, and severity of damage. Drug information included the causative medicine and the period between intake and eruption (the latency period). The identification of causative drugs was based on medicinal products used during hospitalization, drug reaction history of the patient, and clinical remission after discontinuation of the suspected drugs.

Data analysis

The Fisher's exact test was used to compare the incidence of cutaneous ADRs in different groups of patients. Where appropriate, *t* tests and χ^2 tests were used. All analyses were carried out using SAS 9.2 (SAS Institute, Cary, NY, USA). *P* < 0.05 was considered statistically significant.

Ethical disclosure

This research was carried out in accordance with the Helsinki Declaration and ethical standards of the committee on human experimentation at the Peking Union Medical College Hospital. The need for informed consent was waived as this study included only data without information about the identity of the patients.

Results

Incidence of cutaneous ADRs

Fifty cases (32 females and 18 males) were confirmed with cutaneous ADRs from 22,866 admissions during the 4-month study period. There were eight patients who were diagnosed as cutaneous ADR by one dermatologist but not

by the other. These cases were not included in the final calculation. The overall incidence was 2.2/1000 during this period [95 % confidence interval (CI) 1.6–2.8]. During the same period, 15 patients (13 females and 2 males) admitted to the department of dermatology were diagnosed with cutaneous ADR due to a previous treatment in other hospitals. These patients were included in the analysis of cutaneous ADR characteristics. Patients with cutaneous ADR ($n = 65$) were 51.1 ± 20.2 (range 11–85) years old, which was similar to the patient population (47.3 ± 18.3). Females made up 69 % of the cases, while 63 % of all patients hospitalized during the study period were female ($\chi^2 = 0.641$, $P = 0.427$).

Of the 65 patients with cutaneous ADRs, 19 (29 %) had previously been exposed to the suspected drug(s) or another medicine of the same category before admission to our hospital. Patients with positive drug reaction history had a higher cutaneous ADR incidence compared with those without (5.8/1000 vs. 1.7/1000, $P < 0.001$).

Incidence in different departments

The average hospitalization periods were 10 days for the surgical department, 17 days for the internal medicine department, 8 days for the pediatrics department, 4 days for the gynecology department, 4 days for the obstetrics department, 9 days for the stomatology department, 7 days for the ear-nose-throat department, 16 days for the dermatology department, and 16 days for the traditional Chinese medicine department. The department of infectious disease was the most frequently involved unit of the hospital. Higher incidence of cutaneous ADRs was observed in the department of internal medicine (5.6/1000 of 7490 patients in total) compared with surgical departments ($<0.1/1000$ of 15,376 patients in total) (Table 1).

Most cutaneous ADRs were found in patients with cancer ($n = 20$), infection ($n = 11$), cardiovascular and cerebrovascular disease ($n = 10$), and autoimmune diseases ($n = 9$), followed by disease of the digestive tract ($n = 7$), epilepsy ($n = 4$), endocrine disease ($n = 2$), and others (aplastic anemia, $n = 1$; infertility, $n = 1$). Of the 20 patients with cutaneous ADRs and cancer, seven had non-Hodgkin lymphoma, six had leukemia, four had oophoroma or cervical cancer, and one each suffered from lung cancer, thymoma, and pheochromocytoma. Of the nine cases of cutaneous ADR suffering from autoimmune diseases, three had polymyositis (PM), two suffered from SLE, and one each had Takayasu arteritis, primary biliary cirrhosis, acute myelitis, and immunopancytopenia. During the study period, 32 and nine cases of PM and acute myelitis, respectively, were hospitalized. Therefore, cutaneous ADR incidence rates of 93.8/1000 and 111/1000 were obtained for hospitalized PM and acute myelitis

Table 1 Cutaneous ADR cases in various departments

Department	<i>N</i>	%	Incidence (/1000)
Infectious disease	9	18.0	61.6
MICU	1	2.0	18.2
Neurology	7	14.0	14.3
Respiratory disease	3	6.0	12.6
Cardiology	8	16.0	10.1
Gastroenterology	3	6.0	8.8
Endocrinology	3	6.0	7.6
Nephrology	2	4.0	6.7
Internal medicine	1	2.0	6.7
Rheumatology	2	4.0	6.6
Hematology	3	6.0	4.5
General surgery	4	8.0	2.0
Urology	1	2.0	2.0
Obstetrics and gynecology	3	6.0	0.6

patients, respectively. The incidence of cutaneous ADR in SLE patients was similar to that found for individuals hospitalized with other autoimmune diseases.

Cutaneous ADR types and causative drugs

Among the 65 cases, nine cutaneous ADR types were observed. Morbilliform exanthema ($n = 26$) was the most frequent type observed, followed by urticaria ($n = 15$), purpura ($n = 6$), TEN ($n = 5$), SJS ($n = 3$), angioedema ($n = 4$), erythema multiforme ($n = 2$), anaphylaxis ($n = 2$), and DRESS ($n = 2$).

The drugs most commonly involved in cutaneous ADR were anti-infection drugs ($n = 24$ patients), followed by iodinated contrast media ($n = 12$) and non-steroidal anti-inflammatory drugs (NSAIDs, $n = 12$). Among the anti-infection drugs, cephalosporins were the most frequent cause of cutaneous ADRs (20 %, Table 2). The drugs and their corresponding cutaneous reactions are listed in Table 3.

Identification and withdrawal of the culprit drug(s) are the most important steps in the treatment of cutaneous ADR. Most patients recovered from drug-induced eruptions after treatment with anti-histamine drugs and discontinuation of suspected medicines. One patient died from complications related to anaphylaxis and two patients died from underlying diseases (cardiovascular disease and infection).

Discussion

An overall incidence of 2.2 per 1000 was estimated in the present study, including cutaneous ADR cases that developed during hospitalization and patients hospitalized for

Table 2 Types of drugs implicated in cutaneous ADRs

Drugs	N	%
Anti-infection		
<i>Cephalosporins</i>	13	20
<i>Quinolones</i>	5	7.7
<i>Penicillin</i>	3	4.6
<i>Sulfonamides</i>	1	1.5
<i>Carbapenems</i>	1	1.5
<i>Anti-virus</i>	1	1.5
Iodinated contrast	12	18.5
NSAIDS	12	18.5
Immunosuppressive	6	9.3
Anticonvulsive	5	7.7
Anti-tumor	2	3.1
Parenteral nutrition medicine	1	1.5
TCM	2	3.1
Unconfirmed	3	4.6

TCM traditional Chinese medicine, NSAIDS non-steroidal anti-inflammatory drugs

cutaneous ADRs. This incidence rate was lower than those previously reported [4, 7, 8, 10, 18]. Three reasons might explain this discrepancy. Firstly, previous prospective studies confirmed that cutaneous ADR incidence is dependent upon the medical department, with the department of infectious diseases being the most commonly affected [7]. Our data also support this conclusion. In our hospital, there are about 10 beds in the surgery department for each one in the infectious disease unit. Therefore, the

small number of infectious disease patients and high hospitalization rate in surgery departments in this study might have led to a lower incidence of cutaneous ADRs being recorded. Secondly, we excluded cases of cutaneous ADRs induced by blood or blood products, as in a previous study in Mexico [10], as well as those induced by chemotherapy agents because some patients receiving chemotherapy agents often stay in the hospital for only 1 day, which could affect the reliability of the results. Finally, there is often a latency period between beginning a new drug and the appearance of ADRs. Therefore, there is a possibility that some cases have been missed because ADR developed after hospitalization, leading to a lower incidence.

A number of studies have clearly suggested that ADRs are 50–75 % more likely to occur in women than in men [9, 15]. In contrast, a study in Taiwan has suggested that males seemed to be at higher risk of drug reaction [5]. However, the present study found that female and male patients have a similar risk of developing cutaneous ADRs. The reasons for these contradictory results are unclear and multi-center studies with larger sample size should be carried out to confirm these findings.

Several underlying diseases and the reasons for hospitalization were analyzed. This survey indicated that cancer is a risk factor of cutaneous ADR among hospitalized patients. Non-Hodgkin's lymphoma patients were the most frequently affected, in agreement with reported data [10]. Putative involved medications were similar to those reported in the literature, namely, antibiotics [10]. Acquired immune deficiency syndrome (AIDS) is generally considered to be an identifiable risk factor for

Table 3 Cutaneous ADR inducing drugs and corresponding cutaneous reactions

Drugs	Exanthema	Urticaria	Angioedema	Purpura	Anaphylaxis	Erythema multiforme	DRESS	TEN	SJS
Anti-infection									
<i>Cephalosporins</i>	6	5				1			1
<i>Quinolones</i>	1	1	1	1		1			
<i>Penicillin</i>	1				1			1	
<i>Sulfonamides</i>	1								
<i>Carbapenems</i>	1								
<i>Anti-viral</i>	1								
Iodinated contrast	3	7		1	1				
NSAIDS	5	1	2					2	2
Immunosuppressive		1		3					
Anticonvulsive	1			1			1	2	
Biological agent	1	1							
Parenteral nutrition medicine	1								
TCM	1	1							
Unconfirmed	3								
Total	26	17	3	6	2	2	1	5	3

cutaneous ADRs [10]. In this survey, no cutaneous ADRs were observed in AIDS patients. The low number of AIDS patients in our hospital might explain these findings. Previous studies have shown that the risk of allergic reactions in SLE patients is higher than in rheumatoid arthritis patients and healthy controls [1, 14]. However, SLE was not identified as risk factor for cutaneous ADR in the present study. Though cutaneous ADR incidence rates in PM and acute myelitis patients were higher than in individuals with SLE and other autoimmune diseases, we could not confirm that PM and acute myelitis were risk factors for cutaneous ADRs, as only a few cases were observed in the present study. The dissimilar frequencies of drug exposure between patients with DM/PM and other patients might partially account for the different incidence rates observed.

Antimicrobial drugs are widely used in both medical and surgical departments of our hospital and were identified as the most common cutaneous ADR inducers in this study. Cephalosporin was the leading drug causing cutaneous ADR among all anti-infection agents. In other studies, anti-infection drugs were also found to be the main drugs causing cutaneous ADRs, with penicillin yielding the highest incidence of cutaneous ADRs [2, 7, 10, 12, 16]. The use of larger amounts of cephalosporin in our hospital in particular and in China in general may explain this difference.

Iodinated contrast media (ICM), used to facilitate radiographic imaging modalities since the 1950s [13], were the second most frequent medicines found to cause cutaneous ADRs in the present study. These findings are supported by Korean studies but not by those conducted in other countries [19]. One of the common points between our study and the Korean ones is that all data were collected from hospitalized patients. Hypersensitivity reactions to ICM can be divided into two types according to the time elapsed between drug administration and symptom appearance: immediate reactions occur within 1 h after drug administration, while non-immediate reactions appear later than 1 h after ICM exposure [20]. Immediate reactions involve ICM-reactive IgE, while delayed skin eruptions appear to be T cell mediated [3]. In our study, immediate ICM-induced reactions were very common, with the most frequent clinical manifestation being urticaria (7/12, 58.33 %), in agreement with previous data [3].

Of the 65 recorded reactions, morbilliform exanthema was the most common cutaneous manifestation (40 %), followed by urticaria (23.1 %), consistent with previous studies in other countries [13].

Aromatic anticonvulsive drugs, such as carbamazepine, lamotrigine, and phenobarbital, are the most common medicines known to induce DRESS and TEN [17, 21]. In the present study, five cases of TEN and one patient with DRESS were diagnosed. Among them, three cases were

induced by carbamazepine, which are consistent with previous studies.

Limitations

Several limitations of this study need to be acknowledged. Blood products and chemotherapy drugs were excluded in our study because of the reasons mentioned above. A few cases were not fully documented, as mild cases were often considered not to be cutaneous ADR by patients and doctors, which might introduce a bias. Meanwhile, frequent staff turnover and high patient loads could result in inaccuracy and incompleteness of medical records, potentially leading to underestimated cutaneous ADR incidence. The most difficult task in obtaining accurate cutaneous ADR incidence is to foster a culture of reporting among the clinicians, especially among the junior doctors who have the most contact with the patients [7]. The diagnosis was purely clinical, and the use of tools such as the Naranjo scale could help to better assess cutaneous ADRs. In addition, this study was conducted in a single center for only 4 months, although the total number of patients was very high. Finally, only cutaneous ADRs induced by systemic drugs were recorded.

Overall, this is the first study assessing cutaneous ADR incidence in China. Using a prospective survey, we found a lower incidence of cutaneous ADRs compared with that reported in previous studies involving hospitalized patients. The drugs most commonly inducing cutaneous ADRs were anti-infective medicines; ICM and NSAID were the second most frequent causes of cutaneous ADRs in China. No difference was found between cutaneous ADR frequencies in different genders. We found no evidence that cutaneous ADRs are more frequent in AIDS or SLE patients. However, the incidence rates of cutaneous ADRs in PM and acute myelitis patients were higher than those observed in individuals with other autoimmune diseases, but larger samples and multi-center surveys need to be performed to confirm this finding. The results of this study identified cancer as a risk factor for cutaneous ADRs in China.

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Compliance with ethical standards

Ethical standards This research was carried out in accordance with the Helsinki Declaration and ethical standards of the committee on human experimentation at Peking Union Medical College Hospital. The requirement for informed consent was waived as this study included only data without information about the identity of the patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Aceves-Avila FJ, Benites-Godinez V (2008) Drug allergies may be more frequent in systemic lupus erythematosus than in rheumatoid arthritis. *J Clin Rheumatol* 14(5):261–263. doi:[10.1097/RHU.0b013e31817a241a](https://doi.org/10.1097/RHU.0b013e31817a241a)
2. Bigby M, Jick S, Jick H, Arndt K (1986) Drug-induced cutaneous reactions. A report from the Boston Collaborative drug surveillance program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA* 256(24):3358–3363
3. Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, Dewachter P, Gueant JL, Rodriguez Gueant RM, Mouton-Faivre C, Ring J, Romano A, Sainte-Laudy J, Demoly P, Pichler WJ, Enda, hypersensitivity Eigod, (2005) Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 60(2):150–158. doi:[10.1111/j.1398-9995.2005.00745.x](https://doi.org/10.1111/j.1398-9995.2005.00745.x)
4. Chaabane H, Masmoudi A, Amouri M, Ghorbel S, Boudaya S, Hammami S, Zghal K, Turki H (2013) Cutaneous adverse drug reaction: prospective study of 118 cases. *Tunis Med* 91(8–9):514–520
5. Chen CJ, Cheng CF, Lin HY, Hung SP, Chen WC, Lin MS (2012) A comprehensive 4-year survey of adverse drug reactions using a network-based hospital system. *J Clin Pharm Ther* 37(6):647–651. doi:[10.1111/j.1365-2710.2012.01359.x](https://doi.org/10.1111/j.1365-2710.2012.01359.x)
6. Chen YC, Chiu HC, Chu CY (2010) Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol* 146(12):1373–1379. doi:[10.1001/archdermatol.2010.198](https://doi.org/10.1001/archdermatol.2010.198)
7. Dang A, Bhandare PN (2012) The profile of voluntary reported adverse drug reactions at a tertiary care hospital: a fifteen month prospective study. *J Clin Diagn Res* 6(9):1504–1509. doi:[10.7860/JCDR/2012/4340.2544](https://doi.org/10.7860/JCDR/2012/4340.2544)
8. Fiszenson-Albala F, Auzeur V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, Descamps V (2003) A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 149(5):1018–1022
9. Halevy S, Cohen AD, Grossman N (2005) Clinical implications of in vitro drug-induced interferon gamma release from peripheral blood lymphocytes in cutaneous adverse drug reactions. *J Am Acad Dermatol* 52(2):254–261. doi:[10.1016/j.jaad.2004.05.006](https://doi.org/10.1016/j.jaad.2004.05.006)
10. Hernández-Salazar A, Rosales SP, Rangel-Frausto S, Criollo E, Archer-Dubon C, Orozco-Topete R (2006) Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. *Arch Med Res* 37(7):899–902. doi:[10.1016/j.arcmed.2006.03.010](https://doi.org/10.1016/j.arcmed.2006.03.010)
11. International drug monitoring: the role of national centres. Report of a WHO meeting (1972) World Health Organ Tech Rep Ser 498:1–25
12. Park CS, Kim TB, Kim SL, Kim JY, Yang KA, Bae YJ, Cho YS, Moon HB (2008) The use of an electronic medical record system for mandatory reporting of drug hypersensitivity reactions has been shown to improve the management of patients in the university hospital in Korea. *Pharmacoepidemiol Drug Saf* 17(9):919–925. doi:[10.1002/pds.1612](https://doi.org/10.1002/pds.1612)
13. Pasternak JJ, Williamson EE (2012) Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist. *Mayo Clin Proc* 87(4):390–402. doi:[10.1016/j.mayocp.2012.01.012](https://doi.org/10.1016/j.mayocp.2012.01.012)
14. Pope J, Jerome D, Fenlon D, Krizova A, Ouimet J (2003) Frequency of adverse drug reactions in patients with systemic lupus erythematosus. *J Rheumatol* 30(3):480–484
15. Rademaker M (2001) Do women have more adverse drug reactions? *Am J Clin Dermatol* 2(6):349–351
16. Sharma VK, Sethuraman G, Kumar B (2001) Cutaneous adverse drug reactions: clinical pattern and causative agents—a 6 year series from Chandigarh, India. *J Postgrad Med* 47(2):95–99
17. Ständer S, Metze D, Luger T, Schwarz T (2013) Drug reaction with eosinophilia and systemic symptoms (DRESS): a review. *Hautarzt* 64(8):611–622. doi:[10.1007/s00105-013-2615-0](https://doi.org/10.1007/s00105-013-2615-0) (quiz 623–614)
18. Thong BY, Leong KP, Tang CY, Chng HH (2003) Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 90(3):342–347. doi:[10.1016/S1081-1206\(10\)61804-2](https://doi.org/10.1016/S1081-1206(10)61804-2)
19. Thong BY, Tan TC (2011) Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 71(5):684–700. doi:[10.1111/j.1365-2125.2010.03774.x](https://doi.org/10.1111/j.1365-2125.2010.03774.x)
20. Torres MJ, Gomez F, Dona I, Rosado A, Mayorga C, Garcia I, Blanca-Lopez N, Canto G, Blanca M (2012) Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. *Allergy* 67(7):929–935. doi:[10.1111/j.1398-9995.2012.02840.x](https://doi.org/10.1111/j.1398-9995.2012.02840.x)
21. Viera MH, Perez OA, Patel JK, Jones I, Berman B (2010) Phenytoin-associated hypersensitivity syndrome with features of DRESS and TEN/SJS. *Cutis* 85(6):312–317
22. Walsh S, Diaz-Cano S, Higgins E, Morris-Jones R, Bashir S, Bernal W, Creamer D (2013) Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. *Br J Dermatol* 168(2):391–401. doi:[10.1111/bjd.12081](https://doi.org/10.1111/bjd.12081)