Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Drug reaction with eosinophilia and systemic symptoms syndrome secondary to isoniazid and ethambutol: a case report and literature review

Yagya Raj Adhikari, MBBS[a], Madhur Bhattarai, MBBS[a,*], Bikash Baral, MBBS[a], Supriya Jha, MBBS[a], Prativa Subedi, MBBS[b], Ruchi Karki, MBBS[b], Amrita Baral, MBBS[c], Prakash Sharma, MBBS[a], Arun Kharel, MBBS[a], Basanta Sharma Paudel, MBBS[a]

Introduction: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, potentially life-threatening condition precipitated by reaction of therapeutic drugs. The prevalence of potential antitubercular therapy (ATT)-induced DRESS is 1.2%.

Case presentation: A 71-year-old female patient after 5 weeks of starting ATT complaints of fever, vomiting, dizziness, and generalized itchy maculopapular rash over the body. It was associated with marked eosinophilia (absolute eosinophil count 3094 cell/mm^3, 36% in peripheral blood smear).

Discussion: Fever, rash, lymphadenopathy, and internal organ involvement with marked eosinophilia constitute the major clinical manifestations of DRESS. RegiSCAR scoring system is usually used to diagnose DRESS. Identification of the culprit drug is based on the temporal correlation of symptoms with drug exposure and rechallenge test, patch test and lymphocytic transformation tests may be valuable adjunctive tools. Treatment includes withdrawal of offending agent and use of topical or systemic corticosteroids, antihistamines, cyclosporin or JAK inhibitor with clinical judgement.

Conclusion: Clinicians from the tuberculosis burden region must be aware of DRESS associated with ATT and they must counsel the patient properly before prescription and manage them without delay if DRESS ensues.

Keywords: antitubercular therapy, DRESS syndrome, isoniazid, ethambutol

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, potentially life-threatening condition precipitated by reaction of therapeutic drugs. It presents with wide array of clinical features like fever with skin involvement-/cutaneous eruptions with internal organ involvement (hepatitis, nephritis, pneumonitis, and or carditis) along with haematological alterations (leukocytosis with predominant eosinophilia and or presence of atypical lymphocytes with lymphadenopathy)[1,2]. The case fatality rate associated with DRESS syndrome is around 10–20%, usually seen in patients with liver involvement[3], thus requires prompt diagnosis and management. DRESS syndrome is caused by many drugs like phenobarbital, phenytoin, carbamazepine, allopurinol, vancomycin etc. usually appear after a latency of 2–8 weeks to months following drug exposure[4].

HIGHLIGHTS

- Drug reaction with eosinophilia and systemic symptoms syndrome is a severe, potentially life-threatening condition precipitated by reaction of therapeutic drugs.
- Clinicians from the tuberculosis burden region must be aware of drug reaction with eosinophilia and systemic symptoms associated with antitubercular therapy.
- Treatment includes withdrawal of offending agent and use of topical or systemic corticosteroids and antihistamines.

WHO estimated 10.6 million people fell ill with tuberculosis worldwide in 2021, where 98% of reported case accounts from low-income and middle-income countries[5]. The annual incidence of tuberculosis in Nepal is 245 per 100 000 population[6]. The standard treatment of tuberculosis is administering antitubercular drug for 6 months. The first-line drug include Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide[7–9]. All antituberculosis drugs are suspected to pose a risk of DRESS[10]. The prevalence of potential ATT induced DRESS is 1.2%[11]. In a literature review on antibacterial antibiotic induced DRESS by Sharifzadeh *et al.*[12], 107 out of 254 cases were due to antituberculosis s. Rifampicin was the most suspected drug, followed by isoniazid, ethambutol, and pyrazinamide among the

[a]Tribhuvan University, Institute of Medicine, Maharajgunj, [b]Kist Medical College and Teaching Hospital, Lalitpur and [c]Patan Academy of Health Sciences, Patan, Nepal

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

*Corresponding author. Address: Tribhuvan University, Institute of Medicine, Maharajgunj, 44600, Nepal.Tel.: +9779861678146 E-mail address: madhurbhattarai180@gmail.com (M. Bhattarai).

Annals of Medicine & Surgery (2023) 85:2180–2185

Received 26 January 2023; Accepted 2 April 2023

Published online 18 April 2023

http://dx.doi.org/10.1097/MS9.0000000000000683

antitubercular drug as per the literature[10]. This will increase the probability of treatment failure, morbidity, and mortality. We report a case of 71-year-old women with extrapulmonary tuberculosis who developed DRESS syndrome after introducing first-line antitubercular drug. We present the following article in accordance with CARE guidelines for case reports[13].

Case presentation

A 71-year-old female presented to us with complaints of shortness of breath and cough for 10 days. She did not have fever and chest pain. She is hypertensive and under medication amlodipine for 15 years. She did not have other significant family history. She did not give history of contact to tuberculosis patient. Her vitals were within normal limits. Plain Chest X-ray showed massive right sided pleural effusion. Pleural fluid analysis was sent which showed sugar 149 mg/dl, protein 5.4 mg/dl, albumin 1.4 gm/dl, Adenosine deaminase 92 IU/l, and Lactate dehydrogenase 983 U/l. Total cell count was 1900 (lymphocyte 94%, neutrophil 6%). Acid Fast Bacilli was Negative and also negative for malignant cells. Contrast enhanced computed tomography showed right upper lobe pneumonia and moderate right pleural effusion with loculations and fissural insinuation. On complete blood count , total count was 11 740 (Neutrophil 80%, lymphocyte 11%, eosinophil 0%, monocyte 8%, and basophil 1%), Haemoglobin 12.8 g/dl, platelets 64500 and red blood cell 4.2 million. Erythrocyte sedimentation rate was elevated to 98. Patient was clinically diagnosed as new primary extrapulmonary tuberculosis (pleural) and started on first-line antitubercular regimen according to national guideline. Isoniazid (300 mg), rifampicin(450 mg), pyrazinamide(1000 mg), and ethambutol (800 mg) for 2 month intensive phase continued with 4 months of isoniazid and rifampicin was advised.

Patient visited us five weeks after starting antitubercular therapy (ATT) for the complaints of fever, vomiting, dizziness, and generalized itchy rash over the body that was disturbing her day-to-day activities including sleep. She did not have history of allergy to any food or drugs. Fever was 101.5 °F without rigour and chills. It was relieved on taking paracetamol. All other vital parameters were within normal limits. On examination, multiple erythematous elevated maculopapular rashes which ranged from 4 mm upto 2 cm in diameter were present in bilateral thighs, legs, arms, and abdomen. Palms and soles were spared, along with the dorsal aspect of hands including webbed spaces. Scratch marks were easily visible over the skin surface. There was no associated regional lymphadenopathy. On haematology report, haemoglobin was 12.1 gm/dl, platelet count was 408 000 per mm^3. Total leucocyte count was elevated to 15 550/mm^3 and eosinophil was 21%. Peripheral blood smear (PBS) revealed increase number of eosinophils of normal morphology (eosinophil 36%, lymphocyte 17%, neutrophil 44%, and monocyte 3%). Atypical lymphocytes were not present. Absolute eosinophil count came out to be 3094 cells/mm^3. Parameters of liver function test were normal (Total bilirubin 0.3 mg/dl, alanine transferase 39.4 U/l, alkaline phosphatase 75.9 U/l). Parameters of renal function test were normal (Blood urea 33.6 mg/dl, serum creatinine 0.8 mg/dl). Routine urine examination showed no abnormality.

The patient experienced a drug hypersensitivity syndrome, which is probable DRESS syndrome, as a result of taking ATT (antituberculosis therapy). The suspected culprit drug was discontinued, and the patient was admitted to the hospital and treated with topical betamethasone 0.01% and oral fexofenadine hydrochloride 180 mg OD for 15 days when her symptoms subsided. After 15 days a rechallenge test was planned to find the culprit drug under monitoring. Isoniazid alone was given on low dose alone as the first drug, but it restarted the allergic symptoms in fourth day, and thus it was discontinued. ATT was restarted with rifampicin, ethambutol pyrazinamide, and levofloxacin. However, the patient again developed fever, itchy rash, and vomiting. Hyperkeratotic scaly lesions were also observed over the trunk and limbs. The ATT was discontinued and the patient was treated with topical steroid and antihistamines.

Another drug was suspected to be culprit, so ethambutol was rechallenged, and rashes reappeared with single dose of ethambutol, so it was discontinued. The patient was given oral prednisolone 10 mg once daily for 1 week. The patient was introduced to the drugs stepwise, starting with rifampicin for three days then pyrazinamide was added to it for three days, and finally levofloxacin was added to them for three days, all of which were all well tolerated by patient. The patient was advised to take a revised ATT regimen of rifampicin, pyrazinamide and levofloxacin for 6 months.

Patient improved well and she developed no issues upon regular follow-up within 6 months.

Timeline of events

Timeline	Event/action
Before ATT	Patient diagnosed with extrapulmonary TB, ATT started
Week 5	Patient presents with symptoms of drug hypersensitivity syndrome (fever, vomiting, dizziness, and rash)
	ATT discontinued, topical betamethasone and oral fexofenadine prescribed
After 15 days	Symptoms subside, rechallenge test planned
Week 7	Rechallenge with Isoniazid: symptoms reappear on day 4, Isoniazid discontinued
Week 8	Rechallenge with Ethambutol: rashes reappear, ethambutol discontinued
Week 8	Oral prednisolone prescribed for one week to manage symptoms
Week 9	Revised ATT regimen (rifampicin, pyrazinamide, and levofloxacin) prescribed for 6 mo
Follow-up within 6 months	Patient improves and develops no further issues

Discussion

A drug hypersensitivity reaction, a subset of adverse drug reaction, is defined as "objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons" by the WHO[11]. A drug reaction with demonstrated immunological mechanisms, either antibody or cell mediated, is referred to as drug allergy[14]. The degree of clinical presentations of drug hypersensitivity reactions varies from urticaria, drug fever, maculopapular exanthema, acute generalized exanthematous pustulosis, DRESS syndrome, or Stevens–Johnson syndrome/toxic epidermal necrolysis. Our patient presents with maculopapular rash 5 weeks after her start of ATT. There is a significant temporal correlation with drug intake and occurrence of rash. Furthermore, reappearance of the rash on rechallenge with both the isoniazid and ethambutol confirmed the

diagnosis of drug hypersensitivity reaction in this case with a score of 9 (definite) according to Naranjo's algorithm[15] and probable/likely association as per the WHO—The Uppsala Monitoring Centre casualty category[16]. Accounting the temporal relation with drug intake, character of rash, presence of fever, and high value of eosinophil count, DRESS syndrome was considered as a diagnosis.

DRESS syndrome is a rare but severe, potentially life-threatening condition following use of therapeutic drugs. It is a delayed hypersensitivity reaction and seen to have a long latency period (2–8 weeks) between drug exposure and disease onset[4]. Jung *et al.*[11] in their retrospective cohort study, the median latency after administration of ATT was 42 days. Our case presented with DRESS after 5 weeks of starting treatment consistent with the literature[4]. It can have a prolonged course with frequent relapses even though the provoking drug is discontinued. It has also been frequently associated with the reactivation of a latent human herpes virus (HHV) infection[4]. Symptoms may develop within 24 h in the case of re-exposure to the culprit drug[17]. DRESS is considered a severe drug reaction with a case fatality rate of 10–20%[3]. Major clinical manifestations consists of fever, rash, lymphadenopathy, and internal organ involvement with marked eosinophilia. Cutaneous presentation that are usually encountered are urticarial and maculopapular rashes and, occasionally vesicles, bullae, pustules, purpura, erythroderma, cheilitis and so on[18]. Liver is the most frequently involved organ followed by the kidney and lungs.

The most predominant cause of DRESS syndrome are anticonvulsants, sulphonamides, and allopurinol. However it is associated with long list of drugs like anticonvulsant (carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin), antibiotics (amoxicillin, ampicillin, dapsone, ethambutol, isoniazid, levofloxacin, minocycline, piperacillin/tazobactam, pyrazinamide, rifampicin, streptomycin, sulfamethoxazole-trimethoprim, vancomycin), anti-inflammatory (celecoxib, diclofenac, ibuprofen, sulfasalazine), anti-viral (abacavir, boceprevir, nevirapine, telaprevir), allopurinol, mexiletine, amitriptyline etc[19]. In a retrospective cohort study by Jung *et al.*[11] on 1253 adult patients of tuberculosis under ATT, the prevalence of potential DRESS syndrome was 1.2%. Alloucherry *et al.*[10]. performed a case series ($n=76$) on antitubercular drug-associated DRESS where they found all antituberculosis drugs to pose a risk of DRESS. According to them rifampicin was the most suspected, followed by isoniazid, ethambutol, and finally by pyrazinamide. Rifampicin has its larger therapeutic indication which could be a reason for its higher number of suspicion however through the allergy investigation isoniazid is more associated to DRESS syndrome[10]. The case fatality rate of DRESS syndrome by ATT in their study was ~3.0%, which is slightly higher than the rate found in a larger prospective study (1.7%)[10]. Simultaneous multiple drug hypersensitivity syndrome with more than one first-line antituberculosis drugs may occur frequently in patients showing drug fever or maculopapular exanthem features[20]. In our case, isoniazid and ethambutol were the suspected drugs which provoked the reaction.

DRESS is a T-cell-mediated delayed-type drug hypersensitivity reaction. The pathogenesis of DRESS syndrome is not yet completely understood. Different mechanisms have been put forward including detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, and reactivation of human herpes, including Epstein-Barr virus and HHV-6 and 7. The detection of HHV-6 reactivation as a diagnostic marker for DRESS has also been proposed. Other types of viral infection were reported, such as cytomegalovirus reactivation and paramyxovirus infection. Genetic predisposition to adverse drug reactions is also increasingly apparent[21,22]. In a case-control study, a genetic predisposition of antituberculosis drug-associated DRESS is suggested to HLA Cw401[23]. Findings from the translational case study by Kim *et al.*(2020) revealed activated Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway as its immunopathogenesis[24].

The diagnosis sometimes poses dilemma since the clinical presentation may be incomplete or nonspecific, and it can also manifests as a purely systemic disease without any cutaneous involvement, the wide group of diseases must be taken into account in the differential diagnosis[25,26]. Bocquet *et al.*[27]. first proposed the diagnostic criteria for DRESS. Nowadays, the usually adapted diagnostic criteria are those of the International Registry of Severe Cutaneous Adverse Reactions group[28] and the Japanese consensus group[29] (Table 1). Sasidharanpillai *et al.*[30]. evaluated that Japanese criterion failed to diagnose a significant proportion of DRESS cases which included severe forms as well. They suggest DRESS/DiHS to be diagnosed on basis of RegiSCAR scoring system[31] (Table 2). This system classifies suspected cases as definite (score 6 and above), probable (score 4 and 5), possible (score 2 and 3), and no DRESS (score <2). In our case, our patient presents with maculopapular rash five weeks after her start of ATT and hyperkeratotic scaly rash in rechallenging drug. It involved more than 50% of the body surface. It was also associated with fever. Resolution occurred after 15 days. There is marked eosinophilia (absolute eosinophil count 3094 cell/mm^3, 36% in peripheral blood smear). RegiSCAR scoring system classifies it as probable case with the score of 4.

The gold standard test would involve re-exposure to the drug for confirming the culprit drug and it also minimizes the interruption to tuberculosis treatment[1]. But due to potential life-threatening reoccurrence of disease, reintroducing drugs are generally contraindicated in patients with DRESS. However, provided there is no effective alternative treatment available, drug could be rechallenged in a hospital setting so that prompt identification of recurrence and intervention with systemic immunosuppression in case of a reaction could be performed[32]. Paucity of affordable, effective antituberculosis drugs and resource constraints, drug challenge is justifiable in low-income and middle-income countries. The usual interval between individual drug rechallenges is 4 days owing to fact that more than 95% of rechallenge reactions (RR) develop within 72 h[32]. In Palmero *et al.*'s[2] study, all tuberculosis medications were discontinued until symptoms subsided. Then the ATT was gradually reintroduced with a quarter of the initial dose and increased proportionally upto full dosage. Levofloxacin was usually given first, followed by ethambutol or streptomycin. Only after these drugs were tolerated, isoniazid, and rifampicin were reintroduced. We identified that isoniazid and ethambutol was a causative drug through the series of drug rechallenge under close monitoring. Although identification of the culprit drug is based on the temporal correlation of symptoms with drug exposure, patch test and lymphocytic transformation tests may be valuable adjunctive tools[33]. In a study by Said *et al.*[34]. in 68 DRESS case, the sensitivity of patch testing was ~57% at 72 h reading and among the positive patient 20% experienced DRESS flare up at 48 h. The

Table 1

Different system of criteria to diagnose DRESS

RegiSCAR study group[28]	Japanese consensus group[29]	Bocquet *et al.*[27]
*Three or more Asterix(*) criteria are required for the diagnosis of DRESS	Typical DRESS (presence of all seven criteria); atypical DRESS (all criteria present except lymphadenopathy and HHV-6 reactivation)	DRESS is confirmed by presence of 1 and 2 and 3
1. Hospitalization	1. Maculopapular rash developing > 3 weeks after starting drug	1. Cutaneous drug eruption
2. Reaction suspected to be drug related	2. Prolonged clinical symptioms 2 weeks after discontinuation of causative drug	2. Adenopathies > 2 cm in diameter or hepatitis(liver transaminases > 2 times the upper limit of normal or interstitial nephritis or intertitial pneumonitis or carditis
3. Acute rash*	3. Fever above 38 °C	
4. Fever above 38 °C*	4. Lymphadenopathy	
5. Enlarged lymph nodes involving at least two sites*	5. ALT > 100 U/l or other organ involvement	
6. Involvement of at least one internal organ*	6. HHV-6 reactivation	
7. Blood count abnormalities*	7. Leucocyte abnormalities (at least one)	3. Haematologic abnormalities
Lymphocytes above laboratory limits	Leukocytosis ($>11\times10^9$ /l)	Eosinophilia $>1.5\times10^9$/l or atypical lymphocytes
Eosinophil above laboratory limits(in percentage or absolute count)	Atypical lymphocytosis (> 5%)	
Platelet count below laboratory limit	Eosinophilia (1.5×10^9 /l)	

ALT, Alanine Aminotransferase; DRESS, drug reaction with eosinophilia and systemic symptoms; HHV, human herpes virus.

epicutaneuous test performed too close to the acute phase and in the context of immunosuppression due to tuberculosis infections, test are difficult to interpret[35]. According to the proposed guidelines for performing patch tests in cutaneous adverse drug reactions, patch tests must be performed 6 months after complete healing of DRESS. The lymphocyte transformation test demonstrate sufficient specificity in some cases, however, sensitivity is typically too low for clinical utility[36].

Discontinuation of the offending drug is the only safe option available along with supportive and symptomatic treatment. Most patients with DRESS syndrome recover completely in weeks to months after the withdrawal of offending drug[4]. Systemic corticosteroids are currently the treatment of choice for DRESS[37]. Topical steroids, antihistamines and emollients are sufficient treatment in milder cases of rashes and itching where signs of severity (transaminase levels >5 times normal, renal involvement, pneumonia, hemophagocytosis, and cardiac severity, etc) are absent however systemic steroids are usually needed for patients with organ involvement and deranged laboratory findings[38,39]. In the presence of signs of severity, systemic corticosteroids equivalent to 1 mg/kg/day of prednisolone is warranted. Once clinical and laboratory stabilization has been achieved, it is recommended that the dosage be gradually reduced over a period of 3–6 months to avoid recurrence of symptoms[40]. Lehloenva *et al.*[32]. in a retrospective study suggests single early infusion of corticosteroids rapidly and sustainably reverses cutaneous and systemic features of Stevens–Johnson syndrome-/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms developing on re-exposure to the offending drug. Their findings support the role of corticosteroids in these reactions and potentially improve the safety of drug rechallenge protocols. A retrospective case-control study showed positive outcomes with cyclosporine in patients who could not receive glucocorticoids[41]. Owning to the JAK-STAT pathways as the pathogenesis, JAK inhibitors are also emerging as potential treatment[24].

Table 2

RegiSCAR scoring system[31]

Features	No	Yes	Unknown
Fever > 38.5 °C	−1	0	−1
Enlarged lymph nodes (> 2 sites, > 1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia			
700–1499 or 10–19%	0	1	
> 1500 or > 20%		2	
Skin rash			
Extent > 50%	0	1	
At least 2; oedema, infiltration, purpura, scaling	−1	1	
Biopsy suggesting DRESS	−1	0	
Internal organ involvement			
One	0	1	0
Two or more		2	
Resolution in > 15 days	−1	0	−1
≥ 3 biological test to exclude alternative diagnosis	0	1	0

DRESS, drug reaction with eosinophilia and systemic symptoms.

Conclusion

Few weeks after the administration of drug, if patient presents with skin rash, internal organ involvement, fever, hyper eosinophilia, and lymphadenopathy, DRESS should be kept as differential diagnosis. Other differential of similar rash could be viral exanthems, bacterial infection such as scarlet fever or staphylococcal scalded skin syndrome, autoimmune diseases like lupus or dermatomyositis, contact dermatitis, idiopathic urticaria. However, by taking a thorough patient history, assessing the temporal relationship with the drug, and conducting additional investigations, it is possible to eliminate these other possibilities. Keeping in mind the high burden of tuberculosis in low-income and middle-income countries, clinicians must be aware of DRESS associated with ATT. Before prescribing ATT, proper counselling should be given about it to the patient though it is a rare event.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Source of funding

None.

Author contribution

Y.R.A., M.B., and B.B. wrote the original manuscript, reviewed, and edited the original manuscript. S.J., P.S., R.K., A.B., P.S., A.K., and B.S.P. reviewed and edited the original manuscript.

Conflicts of interest disclosure

None.

Guarantor

Madhur Bhattarai.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Kim JH, Jang SH, Kim DH, *et al*. A case of DRESS syndrome induced by the antituberculosis drugs, prothionamide, and para-aminosalycilic acid. Ann Allergy Asthma Immunol 2013;110:118–9.
[2] Palmero D, Castagnino J, Musella RM, *et al*. Difficult clinical management of anti-tuberculosis DRESS syndrome [Case study]. Int J Tuberc Lung Dis 2013;17:76–8.
[3] Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. Indian J Dermatol Venereol Leprol 2011;77:7–15.
[4] Cacoub P, Musette P, Descamps V, *et al*. The DRESS syndrome: a literature review. Am J Med 2011;124:588–97.
[5] WHO official website- Tuberculosis fact sheet Tuberculosis [Internet]. [cited 2022 Nov 19]. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
[6] Ministry of Health and Population (Nepal), Research Institute of Tuberculosis/Japan Anti-Tuberculosis Association (RIT/JATA), Save the Children International, World Health Organization (WHO). Nepal National Tuberculosis Prevalence Survey 2018–2019.
[7] Suárez I, Fünger SM, Rademacher J, *et al*. The diagnosis and treatment of tuberculosis. Dtsch Arztebl Int 2019;116:729–35.
[8] Shah S, Adhikari YR, Paudel S, *et al*. Optic neuropathy induced by ethambutol: a rare case from Nepal. Ann Med Surg 2022;77:103637.
[9] Pant P, Joshi A, Adhikari YR, *et al*. Pattern of tuberculosis, trend and outcome of patients registered at DOTS Centre of a tertiary care hospital. J Nepal Health Res Counc 2022;20:54–8.
[10] Allouchery M, Logerot S, Cottin J, *et al*. Antituberculosis drug-associated DRESS: a case series. J allergy Clin Immunol Pract 2018;6:1373–80.
[11] Jung HY, Park S, Shin B, *et al*. Prevalence and clinical features of drug reactions with eosinophilia and systemic symptoms syndrome caused by antituberculosis drugs: a retrospective cohort study. Allergy Asthma Immunol Res 2019;11:90.
[12] Sharifzadeh S, Mohammadpour AH, Tavanaee A, *et al*. Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review. Eur J Clin Pharmacol 2021;77:275.
[13] Riley DS, Barber MS, Kienle GS, *et al*. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol 2017;89:218–35.
[14] Johansson SGO, Bieber T, Dahl R, *et al*. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832–6.
[15] Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.
[16] The use of the WHO-UMC system for standardised case causality assessment [Internet]. [cited 2023 Apr 29]. https://www.who.int/publications/m/item/WHO-causality-assessment.
[17] Míguez-Martín L, Higelmo-Gómez H, Gómez-Farpón Á, *et al*. Delayed aminopenicillin reaction associated to human herpes virus 6 infection mimicking DRESS syndrome. Rev Alerg Mex 2019;66:375–8.
[18] Peyrière H, Dereure O, Breton H, *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2006;155:422–8.
[19] Schunkert EM, Divito SJ. Updates and insights in the diagnosis and management of DRESS syndrome. Curr Dermatol Rep 2021;10:192–204.
[20] Sim DW, You HS, Yu JE, *et al*. High occurrence of simultaneous multiple-drug hypersensitivity syndrome induced by first-line anti-tuberculosis drugs. World Allergy Organ J 2021;14:100562.
[21] Kano Y, Inaoka M, Shiohara T. Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. Arch Dermatol 2004 Feb;140:183–8.
[22] Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? Arch Dermatol 2001;137:357–64.
[23] Kim SH, Lee SK, Kim SH, *et al*. Antituberculosis drug-induced hypersensitivity syndrome and its association with human leukocyte antigen. Tuberculosis 2013;93:270–4.
[24] Kim D, Kobayashi T, Voisin B, *et al*. Targeted therapy guided by single-cell transcriptomic analysis in drug-induced hypersensitivity syndrome: a case report. Nat Med 2020;26:236–43.
[25] Sasidharanpillai S, Riyaz N, Rajan U, *et al*. Drug reaction with eosinophilia and systemic symptoms: Observations from a tertiary care institution. Indian J Dermatol Venereol Leprol 2014;80:221.
[26] Ben M'Rad M, Leclerc-Mercier S, Blanche P, *et al*. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. Medicine (Baltimore) 2009;88:131–40.
[27] Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996;15:250–7.
[28] Kardaun SH, Sidoroff A, Valeyrie-Allanore L, *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609–11.
[29] Shiohara T, Iijima M, Ikezawa Z, *et al*. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 2007;156:1083–4.
[30] Sasidharanpillai S, Ajithkumar K, Jishna P, *et al*. RegiSCAR DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) Validation Scoring System and Japanese Consensus Group Criteria for Atypical Drug-Induced Hypersensitivity Syndrome (DiHS): A Comparative Analysis. Indian Dermatol Online J 2022;13:40–5.
[31] Chen YC, Chang CY, Cho YT, *et al*. Reply to: "Using a diagnostic score when reporting the long-term sequelae of the drug reaction with eosinophilia and systemic symptoms." J Am Acad Dermatol 2013;69:1060–2.
[32] Lehloenya RJ, Isaacs T, Nyika T, *et al*. Early high-dose intravenous corticosteroids rapidly arrest Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms recurrence on drug re-exposure. J allergy Clin Immunol Pract 2021;9:582–84.e1.
[33] Kano Y, Hirahara K, Mitsuyama Y, *et al*. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy 2007;62:1439–44.
[34] Said BB, Berard F, Hacard F, *et al*. Skin tests may induce DRESS relapse. Clin Transl Allergy 2014;4(S3):P136.

[35] Santiago F, Gonçalo M, Vieira R, *et al*. Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Dermatitis 2010;62:47–53.
[36] Suthumchai N, Srinoulprasert Y, Thantiworasit P, *et al*. The measurement of drug-induced interferon γ-releasing cells and lymphocyte proliferation in severe cutaneous adverse reactions. J Eur Acad Dermatol Venereol 2018;32:992–8.
[37] Shiohara T, Kano Y. Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. Expert Opin Drug Saf 2017;16:139–47.
[38] Bayan CAY, Lopez A, Fontecilla NM, *et al*. Successful treatment of drug reaction with eosinophilia and systemic symptoms syndrome relapse with oral pulsed dexamethasone. JAAD Case Rep 2018;4:959.
[39] Mori F, Caffarelli C, Caimmi S, *et al*. Drug reaction with eosinophilia and systemic symptoms (DRESS) in children. Acta Bio Medica Atenei Parm 2019;90(suppl 3):66.
[40] Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. J Am Acad Dermatol 2013;68:709.e1–9.
[41] Nguyen E, Yanes D, Imadojemu S, *et al*. Evaluation of cyclosporine for the treatment of DRESS syndrome. JAMA Dermatol 2020;156:704–6.