Author’s response to reviews

Title: DRESS syndrome in a patient taking phenytoin and levetiracetam: a case report

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Author's response to reviews: see over
To the Journal of Medical Case Reports Editorial Team:

Thank you for your consideration of our manuscript, “Phenytoin-induced DRESS syndrome: a case report,” (MS: 1216111037893134) for publication in the Journal of Medical Case Reports. We greatly appreciate the referees’ comments and constructive suggestions to help strengthen the work. We continue to feel that the report of this case is important and will benefit the broader medical community by increasing practitioners’ awareness of DRESS syndrome as an under-recognized and under-diagnosed adverse medication reaction. Publication of this report will also allow for others in the field to perform relevant reviews of the literature and meta-analyses with regard to DRESS in the future. After careful assessment of the comments from the editor and referees, we have prepared the following responses to the reviewers and have revised our manuscript accordingly for reconsideration by the Editorial Team.

RESPONSE TO REVIEWERS

Editor:

Comment 1: Manuscript would benefit from adding a picture or two of the skin rash if available. Answer 1: We agree that pictures of the rash would certainly strengthen the manuscript, but regrettably we do not have any pictures of this patient available, as we were not able to gain consent for photograph. Fortunately, the DRESS skin rash is well-described and photographed in the literature, including in several references that we have cited.

Comment 2: Please include the study design in your title, i.e. Case report. For example: A presenting with B in C: a case report. Answer 2: The study design, “a case report,” is included in the title as it currently exists. Please note that the title of the manuscript has been revised per the suggestion of Referee #2 to be “DRESS syndrome in a patient taking phenytoin and levetiracetam: a case report.”

Comment 3: Please use the term male in describing the patient’s gender both in abstract and case presentation sections. Answer 3: Thank you for the suggestion, changes have been made to the abstract and manuscript accordingly.

Comment 4: Please remove word count sections, as these are not needed for publication. Answer 4: Changes have been made to the abstract and manuscript accordingly.
Reviewer 1:

Comment 1: In the abstract, authors say that DRESS occurs after initiation of antiepileptic medications. It is true, of course, since Chaiken’s first description in 1950 of an anticonvulsant-induced DRESS (reference below)……In table 1, it would be more useful to present drugs families rather than isolated drugs, (such as aromatic anticonvulsants, sulfonamides, lactams etc) since biologically reactive products derived from drug metabolism, (arene oxides for aromatic antiepileptics, hydroxylamines for sulfamethoxazole etc.) are believed to play an important role in triggering DRESS.
Answer 1: Thank you for your very informative explanation and related suggestions. We have made several changes throughout the abstract and manuscript clarifying this and other related points. Additionally, we have altered Table 1 to instead list drug groups commonly associated with DRESS syndrome.

Comment 2: In the introduction, the usual terminology in literature is drug-induced hypersensitivity syndrome (DIHS) rather than drug-induced hypersensitivity reaction (DIHR).
Answer 2: Thank you for this suggestion/correction. After a more careful look at the literature, we agree and have made the relevant changes to the manuscript.

Comment 3: “the defining characteristic of DRESS syndrome is organ dysfunction, typically of the liver, kidneys, or lungs”. I would add heart dysfunction also, since hypersensitivity myocarditis is believed to be an important feature of DRESS, unfortunately underrecognized, although life-threatening (Bourgeois, Ben m’rad, Sabatine).
Answer 3: Thank you for the suggestion. Later in the paper we reference the heart as being a commonly involved organ but unintentionally left it out of the quoted list in the introduction and it certainly belongs there. Changes to the manuscript have been made accordingly.

Comment 4: “Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome… is rare”; “DRESS syndrome is estimated to occur in approximately 1 out of 1500 new users of phenytoin or carbamzepine”. Unfortunately epidemiologic estimations are provided by a rather old literature, essentially in pediatric patients exposed to antiepileptics. Thus, Carroll gave the incidence of 1/1000–1/10000 DRESS in 2001, for children treated with anticonvulsants. Precise epidemiologic data are scarce: the real incidence of DRESS is unknown probably because this condition is underdiagnosed and because data are retrieved mainly from retrospective series and literature review of case-reports.
Answer 4: Thank you for those suggestions and for the interesting reference. We have made several changes to the manuscript in this regard, placing emphasis on the fact that the true incidence is unknown and that it is an often under-recognized and under-diagnosed condition. Further, we have added reference to Carroll’s work and revised our reported incidence to be more consistent with those findings.
Comment 5: “DRESS syndrome often includes hepatitis, pericarditis, interstitial nephritis or interstitial pneumonitis”. Hepatitis is probably the most common feature during the course of DRESS: Cacoub and colleagues extracted 172 cases of DRESS in literature through a Pubmed search over a 12 years-period and found that liver involvement occurred in 94% of cases, eosinophilia in 66%, lymphadenopathy in 56%, myocarditis in 2%, kidney in 8%, lung in 5%, central nervous system in 2%. In a cohort of 24 consecutive patients over a four year-period, clinical involvement was as follows: liver 54%, kidney 17%, heart 21%, lung 17%, brain 17%. Other authors suggest that hypersensitivity myocarditis might be largely underecognized (Bourgeois).

Answer 5: Thank you for those interesting data, we have added reference to Cacoub’s work

Comment 6: “First described as a distinct syndrome by Bocquet et al”. Chaiken has first described drug-induced hypersensitivity syndrome in 1950 as a triad of fever, rash and multiorgan failure occurring 1–8 weeks after an aromatic anticonvulsant drug had been started. Bocquet et al have later designated the acronym DRESS.

Answer 6: Thank you for this important point of clarification, we have made the relevant changes to the manuscript and added reference to Chaiken’s initial report.

Comment 7: Since increase of liver enzymes may also be due to myocarditis, did the authors searched for heart involvement by eventually using biologic tools such as N-terminal-probrain natriuretic peptide (NT-proBNP), Creatin PhosphoKinase (CPK), troponin, electrocardiogram, echocardiography?

Answer 7: This is a very valid suggestion. Indeed we were also concerned for myocarditis in this patient. After we began to suspect DRESS in this patient, we performed an EKG and echocardiogram which were both negative for abnormalities. Further, cardiac markers (CK-MB, CK Total, and Troponin T) were within normal limits. We have added mention of this to the manuscript as it is certainly important to rule out myocarditis in patients suspected of DRESS syndrome as the diagnosis.

Comment 8: How long has been the patient followed-up? Do the authors know if patient experienced later any flare on glucorticoids tapering or withdrawal? Is there any hepatic sequela?

Answer 8: Follow-up 5 months after discharge revealed that the patient was doing well with no recurrence of his rash or other symptoms, no seizures, and normalization of his serum transaminases. He experienced no later flare after corticosteroid tapering or withdrawal and to date has not had any hepatic sequelae. We have added mention of this to the manuscript.

Comment 9: Will it be possible to precise if other causes of transaminitis have been eliminated, such as viral infection with the following viruses: hepatitis A, B, C, Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV)? Will it be also possible to precise if the following data are available: antinuclear antibodies?
Answer 9: Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) testing were all negative, as were anti-nuclear antibodies (ANA). Evaluation for acute and chronic hepatitis with serologies was negative. These important tests were double-checked in the medical record and have been added to the manuscript, as it is certainly important to show that we evaluated for other causes of transaminitis. Several of these were also important to exclude with regard to the RegiSCAR scoring criteria, and we have added our results to that discussion as well.

Comment 10: As mentioned above, “rare” could be changed for under-diagnosed or under-recognized or for another adjective or sentence explaining that its real incidence is unknown.
Answer 10: We have altered this sentence to more accurately describe rare as “under-diagnosed and under-recognized.”

Comment 11: “in response to antiepileptic medications”. It would be better to say that DRESS might occur with any drug although the majority of DRESS are due to a small list of drug families such as aromatic anticonvulsants, sulfonamides, fluindione, etc. (Cacoub, Ben m’rad)
Answer 11: We have altered this sentence to more accurately reflect that DRESS can occur with any medication. “DRESS Syndrome is an often under-diagnosed and under-recognized severe type IV (delayed type) hypersensitivity reaction that can occur with any medication but most commonly in response to aromatic anticonvulsants.”

Comment 12: “recently” is usually used for a period <2 years.
Answer 12: Thank you, we have corrected this and other references and replaced them with the year they were published for better accuracy.

Comment 13: Apart Shiohara, Kardaun et al. have also designed a very pertinent scoring system for classifying DRESS cases as definite, probable, possible or no case. This tool has been used for the european registry of severe cutaneous adverse reactions (SCAR) including Stevens-Johnson Syndrome, Toxic epidermal necrolysis, Acute generelazied exathematous pustulosis and DRESS.
Answer 13: Thank you for this very valid and important suggestion. Although we originally chose to present only the Shiohara DRESS criteria, we agree that this manuscript is more complete with mention of the RegiSCAR scoring system for DRESS. Please note that we have added a discussion of the system and its application to DRESS in particular our patient from the case report who scored six points, a “definite case.”

Reviewer 2:

Comment 1: The title must be changed to "Phenytoin and Levetiracetam-induced DRESS syndrome: a case report." Recently was reported DRESS syndrome related to levetiracetam:

Answer 1: Thank you for this very interesting reference. We were previously unaware that levetiracetam had the potential to cause DRESS (indeed, this is apparently only the second case ever reported). In light of the report by Gómez-Zorrilla et al, we can no longer assume that our patient’s reaction was to phenytoin and not levetiracetam or a combination thereof. As such, we have adjusted the title of our manuscript accordingly for syntax to be “DRESS syndrome in a patient taking phenytoin and levetiracetam: a case report” and added a discussion of the potential contribution of levetiracetam to the patient’s symptoms.

Comment 2: "A fine eczematous rash..." Is it correct? I suggest "A fine exanthematous rash..."

Answer 2: Thank you for the suggestion, change has been made to the manuscript accordingly. On closer review “exanthematous” is indeed the term most often used in the literature to describe the rash in DRESS and accurately reflects the skin involvement in our patient.

Comment 3: "The patient was admitted with a presumptive diagnosis of phenytoin hypersensitivity" change to "The patient was admitted with a presumptive diagnosis of drug-induced hypersensitivity"

Answer 3: Thank you for the suggestion, this wording is more accurate giving the changing nature of the report based on the inclusion of levetiracetam as a potential cause. Changes have been made to the manuscript accordingly.

Comment 4: Add mention to position paper of French Dermatology Society about the use of ganciclovir in cases with herpesvirus 6 infection reactivation:


Answer 4: Thank you for the interesting references. We have added a further discussion of treatment and the potential use of ganciclovir in cases with HHV-6 reactivation to the Discussion section of the manuscript.

Reviewer 3:

Comment 1: Beware of overuse and redundancy of words, for example the word "typically" is used in 3 consecutive sentences in the beginning of the introduction.
Answer 1: Thank you for this important suggestion, we have reviewed the manuscript again in its entirety and made these and several other syntax adjustments.

Comment 2: What was your clinical differential diagnosis in this case? There is no discussion of what other diseases or reactions would have similar findings.
Answer 2: We agree it is important to discuss the differential in this case and thus have added a discussion of the differential diagnosis following the physical exam findings section in the manuscript: “At this point the differential included drug-induced hypersensitivity, Erythema Multiforme, Toxic Epidermal Necrolysis, vasculitis, an exanthem due to viral infection such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV), and auto-immune conditions such as systemic lupus erythematosus (SLE).” Further we have added discussion of several further laboratory tests and imaging studies that were performed to evaluate for these and other diagnoses. Because evaluation of other potential causes of the patient’s reaction is a RegiSCAR criteria (ANA, HepA/B/C, blood culture, etc), we have also made mention of our differential during our discussion of the scoring systems.

Comment 3: DRESS was actually first described in association with phenytoin, and additionally there are approximately 50 drugs that have been reported to cause DRESS. Although antiepileptics have an increased tendency to cause DRESS, it should be stated in the discussion that there are numerous other culprit medications and DRESS should not be ruled-out if the medication is not an anti-epileptic.
Answer 3: Per your suggestion and those of the other reviewers, we have made several changes throughout the manuscript emphasizing that indeed any medication has the potential to cause DRESS syndrome and that anti-epileptics are just one of many classes of medications that have been associated with DRESS (albeit the most common). DRESS is an often under-recognized and under-diagnosed complication from many different types of medications and indeed a hypersensitivity reaction should be included in the differential anytime a patient presents for medical evaluation of a rash or other systemic symptoms with a recent change in medication regimen. As such, we have also revised Table 1 to reflect the drug groups that have most commonly been associated with DRESS syndrome in the literature and also made several changes throughout the manuscript.

Comment 4: Along the same lines as #3 above, the table seems incomplete. Eleven medications are listed, not all anti-epileptics, that are presumably more commonly associated with DRESS. However, the case report focuses on anti-epileptic therapy and DRESS. In my mind, the table should either include only anti-epileptics, or should be omitted. If the latter, then the common anti-epileptic medications can be listed in the discussion, with the clarification that there are up to 50 other associated drugs, and you can mention some of those.
Answer 4: Agreed, please see above response to Comment 3 and relevant changes to the manuscript and Table 1.
Comment 5: Several typographical errors noted: “medication” should be “medications” on p3, line 3; "lymphadenopathy" is misspelled on p6, 2nd line from the bottom; "dysfunction" is misspelled on p5, 6 lines from the bottom.

Answer 5: Thank you for these suggestions, we have made the relevant adjustments to the manuscript as well as several other typographical and syntax errors.

Comment 6: There are 2 diagnostic criteria in the literature, with only one being mentioned in the discussion. The Japanese consensus group is mentioned; however, the RegiSCAR scoring system (2007) has also been used and grades a diagnosis of DRESS syndrome as “no, possible, probable, or definite.” This should be mentioned for completeness.

Answer 6: Thank you for this very valid and important suggestion. Although we originally chose to present only the Shiohara DRESS criteria, we agree that this manuscript is more complete with mention of the RegiSCAR scoring system for DRESS. Please note that we have added a lengthy discussion of the system and its application to DRESS – in particular our patient from the case report.

Thank you again for the opportunity for revision and further consideration for publication in The Journal of Medical Case Reports. Please feel free to contact us with any further questions or concerns.

Sincerely,

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