

Dear Reviewers and Editor,

Thank you for reviewing our manuscript. We really appreciate your feedback.

In continuation to your previous comments, please find below a detailed summary of the revisions made in the manuscript, based on your suggestions.

Reviewer 1: An interesting case. I recommend the publication in this journal. The authors clearly said that the correlation of HCV and NAE had been known. In the present case report where only a diagnosis of HIV was added in your patient with HCV, the novelty and originality should be further emphasized. As for the figure 1, please specify the locations of necrolytic acral erythema. The authors said the improvement of erythema. Please add the relevant figures. The cases of NAE in HCV patients should be briefly reviewed in a new Table. Spelling errors are readily seen. Please see the highlights in the attachment.

Response to Reviewer 1: To the best of our knowledge, reports of NAE in HIV/HCV co-infected patients are rare, which makes this case unique and novel in an underreported clinical entity. In figure 1, NAE involves the right upper and right and left lower extremities. Unfortunately, no clinical images were obtained after her clinical improvement.

Table 2 is added with literature review of the previously reported cases. Spelling was corrected.

Reviewer 2: Manuscript # 42872 entitled, "Necrolytic Acral Erythema in a HIV/HCV Coinfected Patient : A Case Report and Literature Review" describes a case of NAE in a 66 year-old HIV/HCV coinfecting female patient with well-controlled Human Immunodeficiency Virus (HIV) infection on highly active antiretroviral therapy (HAART) and untreated chronic Hepatitis C (Genotype 1b) with cirrhosis presented with painless, non-pruritic rash for one week at her feet and legs associated with edema. Skin histopathology demonstrated bullous/hemorrhagic cellulitis with thick parakeratosis, impetiginization of the dermis and rare scattered neutrophilic infiltrates with dermal hemorrhage. Patient was started on prednisone and zinc supplementation with resolution of the lesions and improvement of rash. Authors

concluded that clinical recognition of NAE and early skin biopsy to confirm the diagnosis is important specially in HCV/HIV co-infected patients. Comments: NAE has been described since 1996, first in HCV infected patients and later in other non-HCV infected patients. The only novelty of the present report might be the HCV/HIV co-infection of the reported case. Therefore, it is assumed that authors might strongly focus on this aspect. That is:- Is there any different observation for this case and just HCV-infected or even HCV non-infected patients reported to date? - What is the opinion of authors concerning the potential role of HIV coinfection in this reported case? What they can propose? Any additional/different symptoms or response to the therapy compared to the other just HCV-infected or even HCV non-infected patients reported cases to date?- How authors came to this conclusion that clinical recognition of NAE and early skin biopsy to confirm the diagnosis is important specially in HCV/HIV co-infected patients? Is it more important than just HCV-infected patients and Specifically in HCV/HIV infected patients? Therefore, authors are supposed to specifically discuss their results (observatory and clinical examinations) as well as response to the therapy compared to the prior reports one by one to reach to their conclusion. In the present shape of the manuscript the discussion section is just providing background information in a general form.

Response to Reviewer 2: To the best of our knowledge, reports of NAE in HIV/HCV co-infected patients are rare, which makes this case unique and novel in an underreported clinical entity. One of the proposed mechanisms for the pathogenesis of NAE in co-infected patients is the increased zinc loss with urine that can be observed with both HCV and HIV. Additionally, patients with HIV/HCV co-infection have accelerated fibrosis progression due to multiple mechanisms and perhaps this may play a role in NAE. In addition these patients have higher levels of pro-inflammatory cytokines such as TGF-beta and IFN gamma along with higher levels of lipopolysacchrides (LPS) which all can enhance inflammatory response. Perhaps this also plays a role in NAE in HIV/HCV co-infected patients. In terms of appearance of lesions and distribution, there is no significant difference in HCV/HIV co-infected versus mono-infected patients with HCV, or in seronegative patients with isolated zinc deficiency.

Reviewer 3: Dear editor Thanks for inviting me to review this manuscript entitled "Necrolytic Acral Erythema in a HIV/HCV Coinfected Patient: A Case Report and Literature Review". The case report is about Necrolytic acral erythema (NAE) which can be seen in hepatitis C infected patients or subjects without this infection. The manuscript is well-written and the case has been presented well. But I think that the condition of NAE has been reported in both HCV-infected and HCV-non-infected patients in the literature. From this aspect, the case report has no novelty. However, I believe that the case report can be suitable for publication if authors could add a new part to their manuscript as "literature review" in the format a table for review of previously published cases about the aforementioned case. It can provide data regarding the possible existence of HCV infection, the method of diagnosis and treatment and etc. BestReviewer

Response to Reviewer 3: Table 2 describes the already existing cases of NAE, the methods of diagnosis and treatment.

Thank you again for your time and we hope that our manuscript will be given full consideration for publication in this prestigious journals.

Sincerely,

Katerina Oikonomou, MD, PhD