Dear Editor and Reviewers:

On behalf of all the contributing authors, I would like to thank you for your letter and reviewers' comments on the revision of our manuscript entitled "Idiopathic hypereosinophilic syndrome with hepatic sinusoidal obstruction syndrome: A case report and literature review" (Manuscript NO: 84302). Those comments are valuable for the revision and improvement of our paper, and also have important guiding significance for our research. We have incorporated the comments and made revisions to the manuscript, hoping to be approved for publication in World Journal of Gastrointestinal Surgery. The main corrections in the paper and the responses to the reviewers' comments are as follows:

Responds to the reviewers' comments:

Reviewer #1:

1. Comment: It is inevitable to discuss the mechanism of veno-occlusive disease in a case with the hypereosinophilic syndrome to make this case report valuable.

   Response: The pathogenesis of HSOS involves the injury of endothelial cells and hepatocytes in the hepatic sinusoids caused by HSCT, chemotherapeutic agents, PA, etc., as well as locally released cytokines that also induce the activation of cell adhesion molecules on endothelial cells, leading to local cell damage and shedding, resulting in activation of the coagulation cascade, the formation of blood clots, and the loss of thrombus-fibrinolytic balance. Not only do eosinophils cause tissue damage, they can also be rapidly recruited to the site of injury for platelet adhesion to form thrombus and are activated through direct interaction with platelets. Activated eosinophils contribute to platelet activation, inhibit the function of thrombomodulin, and promote thrombus formation. It is speculated from the pathogenesis that hypereosinophilia may lead to venous thrombosis and hepatic venule occlusion through imbalance of the coagulation fibrinolysis balance caused by endothelial cell injury.

Reviewer #2:

1. Comment: As the meaning of the sentence in conclusion part of the Abstract is obscure it must be refprmulated.

   Response: We have reformulated the conclusion section of the Abstract

(Hypereosinophilia may play a facilitating role in the occurrence and development of HSOS).

2. Comment: The authors should explain why they did not use defibrotide in treatment of HSOS.

   Response: Defibrotide has been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of severe HSOS. However, using the new EBMT criteria for HSOS in adults, we judged that the patient had mild HSOS based on the time since first clinical symptoms, bilirubin levels, transaminases, weight increase and renal function. In addition, the case reported in this paper has shown good efficacy using ursodeoxycholic acid.

3. Comment: As the HSOS is preferred in new nomenclature they should use HSOS instead of HVOD.

   Response: Based on the reviewer's suggestion, we have used the nomenclature for hepatic sinus obstruction syndrome (HSOS) instead of hepatic veno-occlusive disease (HVOD), and the "HVOD" in the manuscript has been changed to "HSOS".

4. Comment: The last status of the patient is not clearly defined.

   Response: To date, under treatment with prednisone and ursodeoxycholic acid, the results of liver function tests, eosinophil count, and CT scanning have all indicated that the patient is in good condition. And we have supplemented the patient's last status in the outcome and follow-up section.

Based on the comments given by the reviewers, we have made the above modifications to the manuscript. Once again, we thank the editors and reviewers for your time and effort in this regard and we look forward to hearing from you.

Yours sincerely,

Round 2

Specific Comments To Authors: Title: Idiopathic hypereosinophilic syndrome with hepatic veno-occlusive disease: A case report and literature review Xu-Tao Xu, Bing-Hong Wang, and Yang-Jie Guo, et al. 1) General Comments In this case report, a 70-year-old male is presented to show the pathological association between hepatic veno-occlusive disease and eosinophilia in the peripheral blood during the course of treatment using corticosteroids, which suggests that eosinophils induce endothelial cell damage of the hepatic sinusoids. This type of rare case is crucial to learn fundamental mechanisms and functions of biology through specific pathophysiology. In this case, the liver biopsy specimen did not reveal the infiltration of eosinophils. Therefore, it is inevitable to discuss the mechanism of veno-occlusive disease in a case with the hypereosinophilic syndrome to make this case report valuable. Response: The pathogenesis of HSOS involves the injury of endothelial cells and hepatocytes in the hepatic sinusoids caused by HSCT, chemotherapeutic agents, PA, etc., as well as locally released cytokines that also induce the activation of cell adhesion molecules on endothelial cells, leading to local cell damage and shedding, resulting in activation of the coagulation cascade, the formation of blood clots, and the loss of thrombus-fibrinolytic balance. Not only do eosinophils cause tissue damage, they can also be rapidly recruited to the site of injury for platelet adhesion to form thrombus and are activated through direct interaction with platelets. Activated eosinophils contribute to platelet activation, inhibit the function of thrombomodulin, and promote thrombus formation. It is speculated from the pathogenesis that hypereosinophilia may lead to venous thrombosis and hepatic venule occlusion through imbalance of the coagulation fibrinolysis balance caused by endothelial cell injury. R1 comment: The discussion made by the authors in the rebuttal pertains to the general mechanisms connecting hypereosinophilia and endothelial cell damage in veins. However, the discussion should focus on the reasons why endothelial cell damage occurs specifically in the hepatic sinusoids, even though the liver biopsy specimen did not reveal eosinophil infiltration.

Response: Eosinophils produce a range of pro-inflammatory mediators and cytokines, including interleukins, chemokines, growth factors and other compounds that may be involved in the regulation of immune responses and tissue damage and repair[1-3]. Cysteinyl leukotrienes, prostaglandins and Charcot-Leyden crystals produced by

eosinophils contribute to tissue inflammation and vascular endothelial damage[4, 5]. In addition, eosinophils can generate and release proteins with direct cytotoxicity, including eosinophil cationic protein (ECP), major basic proteins (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), and other molecules such as eosinophil-derived extracellular DNA traps, which may also lead to hypereosinophilia (HE) related thrombophilia while participating in immune defense[6]. A past case report has suggested that hepatocellular injury caused by the chemotherapeutic drug dacarbazine is associated with an increase in eosinophils in the peripheral blood and liver[7]. Despite the wide range of clinical manifestations of hypereosinophilic syndrome (HES), complication of small hepatic vein occlusion has rarely been reported. In 1995, Kojima *et al* reported a case of HES complicated by acute hepatic sinusoidal obstruction syndrome (HSOS) and speculated that HES might be involved in the development of HSOS[8]. In 2012, it was also reported that a patient diagnosed with HSOS presented with eosinophilia, suspected to be caused by allergic phenomena[9]. In this case, the patient was also diagnosed with a combination of HES, but he had received herbal treatment for pruritus and rash on the extremities before admission. The ingredients of this treatment were frankincense, *Rehmannia glutinosa*, *Akebia quinata*, *Paeonia albiflora* pall, licorice, *Prunella vulgaris*, chrysanthemum, *Divaricate saposhnikovia*, gentian, poria, myrrh, *Angelica sinensis*, *Sophora flavescens*, dandelion and *Angelica dahurica*. The occurrence of HSOS is related to hematopoietic stem cell transplantation (HSCT), chemotherapy, and ingestion of herbs containing pyrrolizidine alkaloid (PA). It cannot be excluded whether the herbal components received were involved in HSOS. Due to the small number of cases of HSOS merging with HES, more cases are needed in the future to explore the impact of HES on the pathogenesis of HSOS.

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8 Kojima K, Sasaki T. Veno-occlusive disease in hypereosinophilic syndrome. *Intern Med* 1995; **34**: 1194-7 [PMID: 8929649 DOI: 10.2169/internalmedicine.34.1194]
9 Yamaga Y, Tsugihashi Y, Nakamura T, Taniguchi T, Honjou G, Kage M. Sinusoidal obstructive syndrome with hypereosinophilia successfully treated with prednisolone. *Clin J Gastroenterol* 2012; **5**: 24-30 [PMID: 26181871 DOI: 10.1007/s12328-011-0264-3]