

Dear Editors and Reviewers,

Thank you for your consideration in publishing our work in the *World Journal of Gastrointestinal Endoscopy*. We welcome the insightful feedback by the reviewers and have revised the manuscript with regards to reviewer and editorial office comments.

Reviewer 1 This is a reported case of juvenile polyposis (JPS) without the commonly known pathological variant of the *BMPR1A* gene. On the other hand, about 70% of JPS without pathological variants of the *BMPR1A* gene have been reported. This can be interpreted as many cases do not have a pathological variant. It is inconsistent to assume that the presence of the *BMPR1A* c.1409T>C (p.Met470Thr) mutation, which has been associated with JPS in only two cases so far, including the present report, is associated with JPS. Without evidence that the c.1409T>C (p.Met470Thr) mutation is present in a certain percentage of JPS cases, we consider this reported case to be of little significance.

Answer: The authors acknowledge that there are a number of patients with juvenile polyposis syndrome without pathological variants of the *BMPR1A* gene. As there is only one previously reported case of JPS with the same *BMPR1A* c.1409T>C (p.Met470Thr) variant it is difficult to entirely conclude its pathogenic role. We have revised the wording in the 'Discussion' section paragraph 2 to acknowledge the limitations discussed and highlight the factors that suggest this may be a pathologic genetic variant. We also highlight in paragraph 4 of 'Discussion' and 'Conclusion' the importance of reporting the phenotypic features of *BMPR1A* variants in JPS to build upon current understanding of possible pathogenic variants.

Reviewer 2 In the current study, the authors aimed to report a case of extensive polyposis found on index screening endoscopy in an asymptomatic female with no prior related family or medical history. The main title accurately reflects the major topic and content of the study. The abstract summarizes and reflects the work described in the manuscript. Also, the abstract presents the significant points related to the background, objectives, materials and methods, results and conclusions. The section of the discussion is well organized. The conclusions are drawn appropriately supported by the literature. The manuscript adequately describes the background, present status and significance of the study. The manuscript interprets the findings adequately and appropriately, highlighting the key points clearly. I think that it will contribute to the literature.

Answer: We thank the reviewer for their kind comments on the quality of the manuscript.

Reviewer 3

1. I would not recommend to the words such as "extensive polyposis" and "ultra-rare" in the title and the entire manuscript. Please remove "extensive" and "ultra".

Answer: Edits have been made throughout the manuscript to remove "Extensive" and "Ultra".

2. In the abstract, please do not give very basic information in the background, such as the incidence rate of JPS. This information should be present in the introduction or discussion. Please try to keep the abstract more concise.

Answer: The incidence rate of Juvenile Polyposis Syndrome has been removed from the abstract and left in paragraph 1 of the discussion section.

3. I would suggest to list "Cronkhite-Canada syndrome " as a differential diagnosis, since the morphology and clinical presentation do not fit Cronkhite-Canada syndrome.

Answer: We have added to the 'Further Diagnostic Work-up' section that Cronkhite-Canada syndrome was considered a differential diagnosis based on histological features. We have also highlighted in the 'Physical Exam' section that there were no clinical features to support a diagnosis of Cronkhite-Canada syndrome.

Reviewer 4 This manuscript provides a comprehensive description of the diagnosis and management of an asymptomatic JPS patient. Through this case, the authors reviewed the management suggestions for such patients in the guidelines of the US and Europe, and provided appropriate measures according to the patient's actual condition. The authors emphasizes several important issues. 1. The differential diagnosis of polyposis subtypes is very difficult, and it is not mandatory for clinical doctors. But at the same time, for gastroenterologists, the key is to identify it, that is, to have a clear understanding of the intestinal and extraintestinal manifestations of polyposis, so that the subsequent treatments can be provided. 3. Benefiting from the development of NGS, the differential diagnosis of polyposis can be accomplished with the help of gene test and genetic counseling. Through this fortunate case of early diagnosis and treatment, we will understand more about JPS. The authors can also further provide readers with information on the phenotypic complexity of BMPR1A associated JPS based on this case. Please refer to this article (PMID 36632626), which showed the phenotype of BMPR1A associated diseases can range from colorectal cancer without polyps to polyposis with more than 100 polyps like in this case. The phenotypic complexity was discovered with the help of the widespread use of NGS. More important, the readers should also recognize that the discovery of genetic variations maybe earlier than the emergence of classic phenotypes in these patients, and these new insights will help readers provide more accurate guidance for patients. The 'ultra rare' in the title should be replaced by 'reported'. For rare diseases, it is strange to emphasize the rarity of pathogenic variants, and it is customary to express them in the binary form of 'novel' and 'reported'. There can be high-frequency mutations in expression to correspond to mutation hotspots, but the opposite situation has not been reported in the literature.

Answer: An edit to the title has been made.

Editorial Office – Reference Citation Analysis was used to supplement the references used within the manuscript.

I look forward to hearing back from you.

Yours Sincerely,

Michael Yulong Wu

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