

Peer Review File

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**Reviewer A**

**Comment 1:**

In this manuscript, Kang et al. describe a case report of a patient presenting with a combined syndrome of juvenile polyposis and hereditary hemorrhagic telangiectasia (JP/HHT), associated with a de novo SMAD4 mutation. This is a well-structured and straightforward paper that contains an interesting and detailed analysis of the patient's clinical phenotype and genotype. The manuscript describes for the first time a patient with JP/HHT in Korea who carries a novel SMAD4 variant. One specific point should be clarified before publication.

Specific point

Currently, HHT diagnosis is based on the Curaçao criteria which are: i) spontaneous and recurrent epistaxis; ii) multiple telangiectases at characteristic sites (lips, oropharynx, fingers and nose; ii) visceral involvement, including GI telangiectases, pulmonary, hepatic, brain and spinal AVMs; and iv) family history with one first degree relative with a definite HHT clinical or genetic diagnosis. The HHT diagnosis is considered definite if three criteria are present, possible or suspected with two criteria, and unlikely if only one is present.

The authors should briefly explain in the manuscript the consensus criteria used to reach a definite HHT diagnosis in this patient. This information should also be visualized in Figure 6 (right panel). Please note that the locations of telangiectases and AVMs are specific in HHT and it is unclear whether the patient meets criteria of item ii. Were telangiectases observed in lips, oropharynx, fingers or nose? In case the patient does not meet three HHT Curaçao criteria, this limitation must be stated and explained.

**Reply 1:**

Thank you for your great comment. Yes, there were telangiectases on the lip and tongue. We have added the photographs (telangiectases on the lip and tongue) of the patient in Figure 1. The patient fulfilled the first 3 criteria for the diagnosis of HHT, i)

spontaneous and recurrent epistaxis; ii) multiple telangiectases at characteristic sites (lips, oropharynx); iii) visceral involvement, including GI telangiectases, pulmonary AVMs, and met the Curaçao criteria for HHT. We have revised the manuscript according to your comments.

**Changes in the text:** We have modified our text as advised (see “Track changes” version Page 6, line 110; Revised Figure 1; Page 8, line 156-162; Revised Figure 6).

## Reviewer B

Overall, it is well written manuscript. These two separate syndrome are very rare, therefore it is important to describe them as in this case report

Few Major and minor comments:

In general, I recommend to describe these two syndromes as individual entities as not all JPS patients have HHT features and vice-versa and to write as JUVENILE POLYPOSIS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA .

**Comment 1:** Abstract is too long with repeating sentences. The abstract in case reports should be short.

**Reply 1:** Thank you for your comment. We agree and have shortened the abstract.

**Changes in the text:** We have modified our text as advised (see “Track changes” version Page 3, line 46-50, 56-61).

**Comment 2:** Introduction – I rather start with description of JPS and then describe the association with HHT in those who have SMAD4 mutation.

**Reply 2:** Thank you for your comment. We agree and have revised according to your comment.

**Changes in the text:** We have modified our text as advised (see “Track changes” version Page 5, line 74-92).

**Comment 3:** Case presentation – before current hospitalizing - did the boy had upper endoscopy? Evaluation of small intestine? How many of polyps in the colon? Size and distribution? Histology?

**Reply 3:** Thank you for your comment. Before the current hospitalization 30 to 50 colonic polyps were observed at each exam, and histologic exams of the

polypectomized specimens were compatible for juvenile polyps.

Esophagogastroduodenoscopy and small bowel series conducted along with polypectomies were unremarkable.

**Changes in the text:** We have added this in our text as advised (see “Track changes” version Page 6, line 103-106).

**Comment 4:** Discussion – line 182 "Patients with JPHT are at a high risk of developing early-onset GI cancers" I rather write that JPS ( and not JPHT) to describe that all JPS patients are at risk, no matter if HHT was diagnosed also.

**Reply 4:** Thank you for your comment. We agree and have revised according to your comment.

**Changes in the text:** We have modified our text as advised (see “Track changes” version Page 10, line 194).

**Comment 5:** Figure 6 – no legend. Please add.

**Reply 5:** Thank you for your comment.

**Changes in the text:** We have added the legend for Figure 6 as advised (see “Track changes” version Page 15 line 306-308).