Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Please edit some of the spelling and grammatical errors.
Answer: Thank you very much for pointing out the language issues. We have sent the manuscript to a professional English language editing company called FILIPODIA to polish the language. The revised manuscript meets the Grade A language requirement.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: I have carefully read the case report. It is about a rare disease with q novel mutation. I have really enjoyed reading the case report however there are some issues to be touched. The case report definitely has novelty and it is appropriately summarized. I will make several article suggestions to enrich the Discussion section. 1.Olivieri C, Pagella F, Semino L, Lanzarini L, Valacca C, Pilotto A, et al. Analysis of ENG and ACVRL1 genes in 137 HHT Italian families identifies 76 different mutations (24 novel). Comparison with other European studies. J Hum Genet. 2007;52:820–9. 2. Karlsson T, Cherif H. Mutations in the ENG, ACVRL1, and SMAD4 genes and clinical manifestations of hereditary haemorrhagic telangiectasia: experience from the Center for Osler's Disease, Uppsala University Hospital. Ups J Med Sci. 2018;123:153–7. 3.Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat. 2006;27:667–75. 4. Letteboer TG, Zewald RA, Kamping EJ, de Haas G, Mager JJ, Snijder RJ, et al. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet. 2005;116:8–16. 5. Lesca G, Burnichon N, Raux G, Tosi M, Pinson S, Marion MJ, et al. Distribution of ENG and ACVRL1 (ALK1) mutations in French HHT patients. Hum Mutat. 2006;27:598. 6.Genetic Diagnosis of Hereditary Hemorrhagic Telangiectasia: Four Novel Pathogenic Variations in Turkish Patients Mehmet Baysal. 7.A Novel Variation in the ACVRL1 Gene in a Patient with Cirrhosis and Hereditary Hemorrhagic Telangiectasia Mehmet Baysal. These are important and pioneer works and ion my opinion should be cited in the case report.

Answer: We sincerely appreciate your valuable suggestions. We reviewed all the references you listed above carefully. Some of the pioneer studies reported different

mutations found in *ENG*, *ALK1*, and *SMAD4* genes, which were covered in the mutation database provided by the University of Utah and ClinVar. We have attached the website link to the database in the second paragraph under the discussion section, with the aim to help readers retrieve the mutations reported in HHT patients so far.

Three of the suggested pioneer references focused on the correlation between genotype and phenotype. Since those independent studies and ours had consistent discoveries that hepatic AVMs and GI bleeding were more common in type II HHT. Therefore, we added this piece of information in the discussion and cited the suggested references, as highlighted below:

The R374Q mutation was also reported in other HHT families[2,7,15-18], further demonstrating its prevalent occurrence and pathological effect in HHT. Intriguingly, most of the HHT patients with the R374Q mutation were reported experiencing hepatic AVMs and GI bleeding, suggesting a possible correlation between genotype to phenotype[2,7,15]. Besides, independent studies in different populations found that hepatic AVMs and GI bleeding were more common in patients with *ALK1* mutations[19,20]. In this family, the proband suffered from GI bleeding and hepatic AVM. Her elder brother experienced GI bleeding, while her son only experienced epistaxis. The diversity of phenotype in the son might be attributed to incomplete penetrance. Given the poor prognosis of the HHT patients carrying the R374Q mutation, this son is most likely to develop hepatic AVMs and GI bleeding when he gets older.

Reference:

18 **Letteboer TG,** Zewald RA, Kamping EJ, de Haas G, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet. 2005;116(1-2):8-16 [doi: 10.1007/s00439-004-1196-5 PMID: 15517393]

19 **Karlsson T**, Cherif H. Mutations in the ENG, ACVRL1, and SMAD4 genes and clinical manifestations of hereditary haemorrhagic telangiectasia: experience from the Center for Osler's Disease, Uppsala University Hospital. Ups J Med Sci. 2018;123(3):153-7. Epub 2018/09/27 [doi: 10.1080/03009734.2018.1483452 PMID: 30251589]

20 **Lux A**, Salway F, Dressman HK, Kroner-Lux G, Hafner M, Day PJ, Marchuk DA, Garland J. ALK1 signalling analysis identifies angiogenesis related genes and reveals disparity between TGF-beta and constitutively active receptor induced gene expression. BMC Cardiovasc Disord. 2006;6:13 [doi: 10.1186/1471-2261-6-13 PMID: 16594992]