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A Novel Variaiton in the *ACVRL1* Gene in a patient with Cirrhosis and Hereditary Hemorrhagic Telangiectasia

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To the editor;

Hereditary hemorrhagic telangiectasia (HHT) is a rare bleeding disorder characterized by arteriovenous malformations (AVMs), telangiectasia, and bleeding episodes [1]. Pulmonary, hepatic, and cerebral AVMs could be seen in the course of the disease [2]. Mutations in the *ENG, ACVRL1,* and *SMAD4* genes were associated with HHT [3]. A 65-year-old man was admitted to our hospital with anemia and intermittent nose bleeding. Upon physical examination,

telangiectasias were noticed on his face and nose. Further investigations in his work-up revealed hypochromic microcytic anemia with a hemoglobin level of 8 g/dl. His detailed laboratory analysis revealed iron deficiency anemia. In the upper gastrointestinal endoscopy performed for iron deficiency anemia, grade 1 esophageal varices were detected and intravenous iron carboxymaltose treatment was planned. His epistaxis severity score was 3.22 which can be categorized as mild bleeding [4].

Family history revealed positive findings for nose bleeds, telangiectasia in his first degree relatives and molecular genetic analysis was performed on the next-generation sequence analysis platform (NextSeq550-Illumina) using the Qiaseq-Targeted DNA Panel Kit (CDHS-14647Z-252-Qiagen), which includes *ACVRL1, ADAM17, ENG, GDF2, PTPN14, RASA1, SMAD4* genes. The variant analysis was performed by using Qiagen Clinical Insight software. As a result of the bioinformatics analysis performed considering the ACMG-2015 criteria, the NM_000020.3(*ACVRL1*):c.1415G>A (p.Trp472Ter) variant was evaluated as pathogenic according to the PVS1, PM2, PP3 rules. (In silico analyzes results: DANN score: 0.9944, Gerp score:4.4, MutationTaster: Disease causing). The *ACVRL1*:c.1415G>A variant was reported in the dbSNP database with reference number rs1555154144, but its clinical significance was not reported in ClinVar, HGMD Professional 2020.3 databases. Besides, minor allele frequency was not reported in dbSNP, ExAC, GnomAD_exome databases. [5, 6]. Computed tomography (CT) of the Abdomen showed nodularity of the surface of the liver, a heterogeneous appearance of the liver parenchyma, and atrophy of the left liver lobe (Figure 1). No arteriovenous malformations were found in the liver and evaluation of the portal venous system was normal. Hepatitis virus markers, immunoglobulin levels, and autoimmune markers were normal. As the patient's anamnesis was detailed, the history of regular ethanol use was elucidated and the patient was diagnosed with Child A liver parenchymal disease. A colonoscopic evaluation was also performed on the patient, and multiple small telangiectasies were seen in the rectal mucosa. Local preventive measures and tranexamic acid given for epistaxis and also low-dose propranolol started for grade 1 esophageal varices.

Gastric and hepatic manifestations of HHT are broad, and on rare occasions HHT can be associated with liver cirrhosis [7, 8]. However, as in our case, HHT and ethanol intake have both caused and triggered liver cirrhosis. Our patient has quitted alcohol intake and followed as an

outpatient for both HHT and cirrhosis. Mutations in the *ACVRL1* gene occur more frequently in HHT type 2 patients, according to the University of UTAH mutation database there were 571 variants in the *ACVRL1* gene associated with HHT, and our novel variation was not reported before [9]. Regardless of the age of the patient, HHT should be on the physicians' mind when evaluating a patient with telangiectasias and unexplained iron deficiency.

Keywords: Hereditary hemorrhagic telangiectasia, *AVCRL1* mutation, Cirrhosis, Epistaxis, Anemia

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