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Case Report of Osler-Weber-Rendu Syndrome with Incidentally Detected Ipsilateral Renal Adnexal Agenesis

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Abstract

Osler-Weber-Rendu Syndrome, also known as hereditary hemorrhagic telangiectasia, is an autosomal dominant disease characterized by the presence of vascular telangiectasias in the skin and mucosa. Epistaxis can occur due to telangiectasias in the nasal mucosa and oral cavity. Diffuse arteriovenous malformations may occur in the lung, liver, and brain. Histopathology shows superficially located thin-walled vascular structures.

In this case report, we present a multiparous patient in her 50s who was diagnosed with Osler-Weber-Rendu syndrome during examination due to complaints of recurrent nosebleeds and widespread telangiectasia in the skin/mucosa. In addition, ipsilateral renal-adnexal agenesis and a 3 cm intrahepatic mass were incidentally detected on cross-sectional imaging. A biopsy was taken from the mass in the liver and pathological examination revealed follicular nodular hyperplasia. Her kidney function test is within normal limits and she is multiparous. Following all examinations, symptomatic treatment for nosebleeds and iron replacement therapy were started.

Keywords: *Hereditary hemorrhagic telangiectasia, Renal agenesis, Ovarian agenesis,*

Abbreviations:

CT: Computed Tomography, FNH: Follicular Nodular Hyperplasia, HHT: Hereditary Hemorrhagic Telangiectasia, MRI: Magnetic Resonance Imaging, OHRIVA: obstructed hemivagina and ipsilateral renal anomaly, vWF: von-Willebrand Factor

1. INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT) known as Osler-Weber-Rendu disease is an autosomal dominant inherited disorder [1]. HHT is characterized by telangiectases of especially skin, and mucous membranes of the nose, and gastrointestinal tract, and arteriovenous malformations of solid organs like the lungs, liver, and brain. These involvements cause chronic bleeding, acute hemorrhage, and other complications from arteriovenous malformations. The most common symptom of HHT is epistaxis. HHT exhibits age-related penetrance, and the average age of onset varies with manifestation. Approximately 50% of affected individuals have epistaxis by the age of 10 years. Additionally, among the 80 or 90 percent by the age of 21 years. At least 95% eventually develop recurrent epistaxis, and their severity varies with the patient. The percentage of individuals with telangiectasias of the lips, oral cavity, face, and nose approaches 100% by late adulthood but is often not apparent until the second or third decade of life [2].

The mainstay of diagnosis is the Curaçao Criteria, and according to the Curaçao Criteria, there are four clinical diagnostic criteria. The first criterion is epistaxis that is spontaneous, and recurrent. The second criterion is telangiectasias which multiplie at characteristic sites including the lips, oral cavity, fingers, and nose. The third criterion is visceral lesions which include gastrointestinal telangiectasias and solid organs arteriovenous malformation. The last criterion is family history which is related to a first-degree relative with HHT [3]. The patients with three or more criteria are classified as definite HHT. Additionally, they

are classified as possible or suspected hereditary hemorrhagic telangiectasia by two criteria. However, those with fewer than two of the four criteria are classified as unlikely HHT.

Unilateral agenesis of adnexa is the absence of a unilateral ovary and fallopian tube. This finding has rarely been described with only a few cases described in literature. The condition may be asymptomatic and may be incidentally recognized during surgical procedures or medical imaging. The possible pathogenetic mechanisms leading to this malformation are embryological and mechanical hypotheses. The embryological hypothesis includes that the absence may be congenital due to a defect in the development of the entire Müllerian and Mesonephric systems on one side, or it may be a localized defect in the genital dorsal region and the caudal part of the Müllerian duct. On the other hand, the mechanical hypothesis proposes an asymptomatic torsion of one or both adnexa during adult life or childhood or even before birth [4]. In our case, we aimed to highlight this rare condition of ipsilateral renal-adnexal agenesis without uterine anomaly and its possible relationship with HHT.

2. PRESENTATION OF CASE

A multiparous (gravida 2, parity 2 , abortus 0) woman in her 50s has had a recurring complaint of epistaxis since childhood, and has been admitted to the hospital multiple times as her complaint had increased in recent years. The patient had a history of multiple cauterization with electrical and silver nitrate due to epistaxis that could not be controlled with tampons/ pressure and sometimes lasted more than a day.

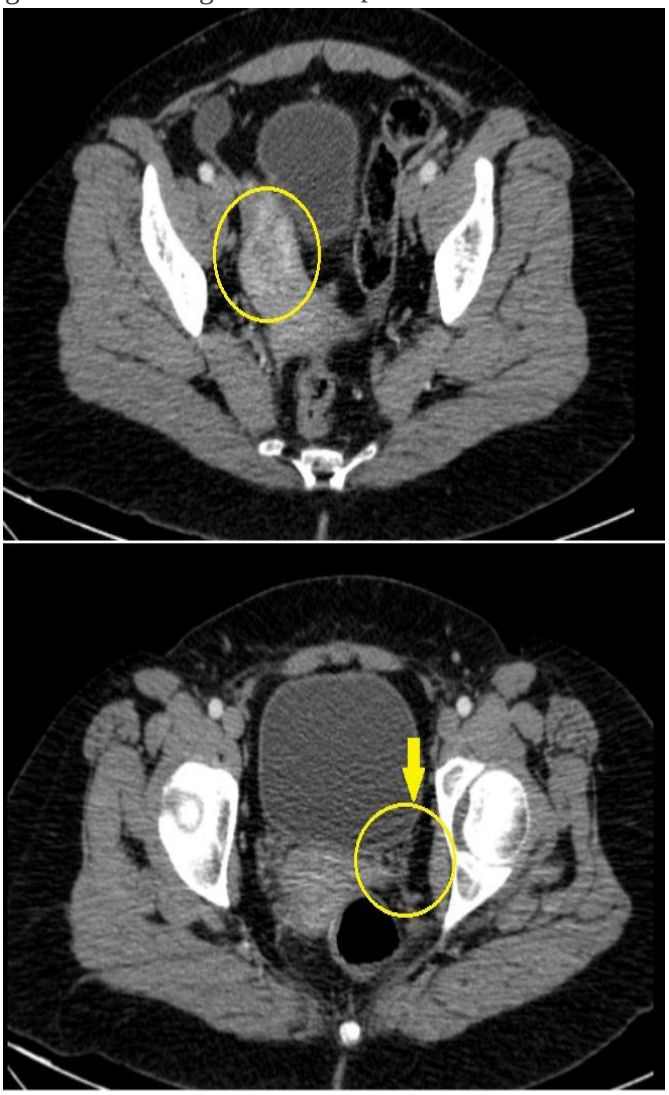

Figure 1. *Abdominal CT: Presence of right ovary and yellow arrow indicates absence of left ovary*

The patient has vitiligo, peripheral venous insufficiency, and depression, for which she takes metoprolol, calcium dobesilate, and escitalopram. Considering her medical history, there is a history of cesarean section and cholecystectomy; she is allergic to melon, spinach and thiocolchicoside. There was no history of smoking or alcohol use. Her mother

died due to kidney failure of unknown cause, and her father has a history of lung cancer. Additionally, the patient's father, brother, nephew, and her own son have a history of recurrent epistaxis and mucocutaneous telangiectasia.

Initial routine biochemical examinations, complete blood count and bleeding diathesis tests were within normal limits, and no pathological findings were found in platelet cells or other cell lines in the peripheral blood smear. Since no pathology was detected in the initial evaluation of the patient, platelet function tests, coagulation factor levels, bleeding time and vWF level were examined and all values were within normal range. These tests were repeated at 3-month intervals and were again found to be within the normal range.

Gastroscopy and colonoscopy were performed on this postmenopausal patient, whose laboratory findings were compatible with iron deficiency anemia, and no pathology was detected. Therefore, it was determined that the cause of anemia was epistaxis. Abdominal CT performed on the patient, who also had right upper quadrant pain, revealed a vascular lesion in the liver; Thereupon, a dynamic contrast-enhanced liver MRI was requested, which revealed a tortuous appearance in the intrahepatic branches of the hepatic artery. In addition, multiple lesions suggestive of follicular nodular hyperplasia, the largest of which was 3cm in size, were detected in both lobes of the liver. Biopsies were taken from these lesions and normal liver tissue was detected. Furthermore, surprisingly, incidental ipsilateral renal and adnexal agenesis was detected in the abdominal CT scan (Figure 1, Figure 2); However, on further examinations, no anomaly was detected in the uterus. On physical examination, there was widespread vitiligo on the skin, alopecia and telangiectasias all over the body (extremities, trunk and oral mucosa).

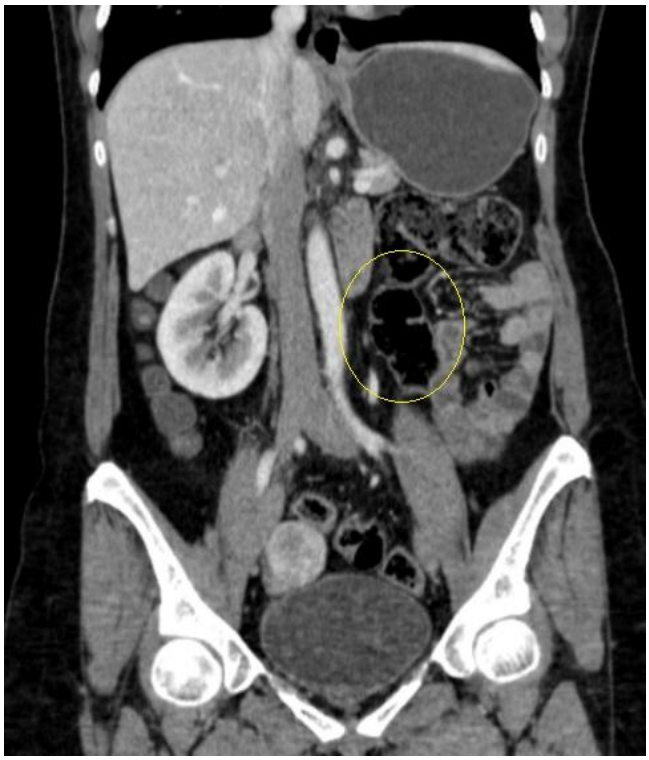

Figure 2. *Absence of left kidney on abdominal CT*

Considering the patient's clinical history, physical examination findings and the vascular anomaly in the celiac trunk (arteriovenous malformation) detected in the abdominal MRI, Osler-Weber-Rendu syndrome was diagnosed. Genetic counseling was given and follow-up was started. This incidentally found ipsilateral renal adnexal agenesis of a multiparous patient whose renal functions were found to be normal and she was asymptomatic.

3. DISCUSSION

The patient had a family history of recurrent epistaxis, which was genetically consistent with non-sex-selective autosomal dominant disorders in which generations cannot be skipped. Epistaxis is the first and most common finding of the disease; nevertheless, signs and symptoms of the disease are diverse including seizure, stroke, anemia, heart failure, hepatomegaly,

hemoptysis, pulmonary hypertension and gastrointestinal bleeding. Patients often have a history of recurrent epistaxis since childhood; however, frequency and severity of the epistaxis increase after the age of 40 [5]. The patient had epistaxis since childhood, and the aggravation of her symptoms in the last 10 years was consistent with the general characteristics of HHT.

HHT can involve almost all of the organs; however, neither renal nor adnexal involvement has been reported except for a few publications and it is extremely rare [6, 7]. These involvements are arteriovenous malformations that usually occur in the kidneys or ovaries. On the other hand, our patient had ipsilateral renal adnexal agenesis, which has not been reported in HHT patients.

Follicular Nodular Hyperplasia (FNH) is the most common type of liver involvement due to HHT, but multiple and multifocal lesions of FNH, as in our patient, are rare [8].

Unilateral ovarian agenesis usually occurs as congenital absence of the ovaries or ovarian torsion [3]. Since the ovaries, uterus, fallopian tubes and kidneys develop from the urogenital ridge, a combination of urogenital abnormalities is expected and there are well-known syndromes related to this: OHRIVA syndrome and Herlyn-Werner-Wunderlich syndrome [9, 10]. On the other hand, the number of publications regarding agenesis of the ovary and kidney on the same side without uterine anomaly is quite low [11, 12]. Our patient was multiparous and there was no abnormality in her uterus. She has ipsilateral renal adnexal agenesis.

In most patients, mutations in the ENG, ACVRL1, SMAD4 and GDF2 genes are responsible for HHT [13]. GDF2-related HHT, HHT type 5, has different characteristics from classical HHT, such as epistasis starting in childhood or extravascular findings due to 10q 11.21q11.23 deletions [14]. The human gene RET is localized on chromosome 10 (10q11.2), and mutation of the RET gene can cause renal agenesis [15]. RET and GDF2 genes are located in chromosome 10; therefore mutations in chromosome 10 could cause HHT and renal agenesis theoretically. In our case, we could not perform genetic analysis because advanced genetic tests could not be performed for several years due to some difficulties.

There is no established link between HHT and agenesis of the kidney and adnexa, but we hypothesized that defective blood walls in HHT may lead to agenesis of these organs in embryological life.

4. CONCLUSION

It is very important to consider HHT when investigating a complaint of recurrent nosebleeds, and family history is essential for diagnosis. The presence of a urinary or genital abnormality should alert us to investigate any abnormalities related to the other organs. We present the first HHT case with ipsilateral renal and adnexal agenesis in the literature.

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None

DECLARATIONS

Author Contribution

Hüseyin Döngelli wrote the first draft of the manuscript, and all authors commented on subsequent versions. All authors contributed to data collection, and patient follow-up. All authors read and approved the final manuscript.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Declaration of Conflicting Interests

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