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CASE REPORT

Birt-Hogg-Dubé Syndrome Incidentally Identified in a Potential Liver Donor

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Abstract: ***Background*:** Birt-Hogg-Dubé Syndrome (BHDS), an autosomal dominant hereditary condition, occurs due to mutations in the gene encoding folliculin (FLCN) in the short arm of the 17th chromosome characterized by lung cysts with specific skin findings and renal cell carcinoma. Patients have usually complaints related to dyspnea and chest pain due to pneumothorax but they may be asymptomatic due to wide phenotypic heterogeneity. Herein, we report the imaging findings of a case 32-year-old male with BHDS without any symptom who was diagnosed incidentally by computed tomography (CT) due to organ donation.

***Case Report*:** In a 32-year-old male patient evaluated as a potential liver donor, CT was performed for preoperative preparation. The patient's medical history was unremarkable. In the CT examination, multiple air cysts of different sizes in both lungs were observed and also, a 7-cm solid renal mass of the right kidney was observed in the dynamic examination. Due to alarge number of lung cysts and the presence of solid renal tumors at a young age, BHDS was considered. The patient underwent partial nephrectomy, and the pathology result was hybrid oncocytic-chromophobe renal cell carcinoma. In the genetic examination, a heterozygous germline mutation was detected in the 11th exon of the FLCN gene.

***Conclusion*:** While potential organ donors are generally healthy and asymptomatic individuals, incidental lesions can be detected in the donor organ or other organs in the examination area during radiological imaging. Although most incidental lesions are benign, important clinical conditions can rarely be observed, as in our case. Familial and syndromic conditions should also be consideredfor the presence of solid renal masses incidentally detected at a young age. To the best of our knowledge, this is the first reported case of BHDS in English literature who was diagnosed incidentally on computed tomography for being a living liver donor.

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1. INTRODUCTION

Birt-Hogg-Dubé Syndrome (BHDS), first introduced by Birt *et al.* in 1977 [1], occurs due to mutations in the gene encoding folliculin (FLCN) in the short arm of the 17th chromosome and shows an autosomal dominant hereditary pattern [2]. It is known that FLCN is a tumor suppressor gene and plays a role in cell growth and differentiation [2]. Some of the mutations occurring in this gene cause the formation of various neoplasms that affect the multi-organ system, some of which are benign while others are malignant [3]. The prevalence of BHDS is considered to be 1-9/1,000,000. However, due to lack of awareness, the BHDS remains to be underdiagnosed [4].

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BHDS is a rare genodermatosis characterized by fibrofolliculomas and/or trichodiscomas, renal tumors and lung cysts [2]. The majority of patients with BHDS present dermatological manifestations and 90% are cutaneous fibrofolliculomas [5]. Individuals with BHDS are 32 to 50 times more likely to develop spontaneous pneumothorax than the unaffected population because of lung cysts [5]. Therewithal, patients with BHD have a 7-fold increased risk of developing renal cancer [6]. Renal tumors occur in 25 to 35% of the cases during their lifetime, and the most frequent type of neoplasm is the hybrid or chromophobe oncocytic tumor, which can be multiple and recurrent [5]. Skin findings are usually seen after the age of 20 years, lung cysts at 20-30, and kidney tumors mostly after the age of 40 [2].

In this paper, we present a 32-year-old male patient that underwent CT as a potential liver donor, suspected of BHDS due to the detected solid renal mass and multiple lung cysts, and subsequently diagnosed based on examination and radi-

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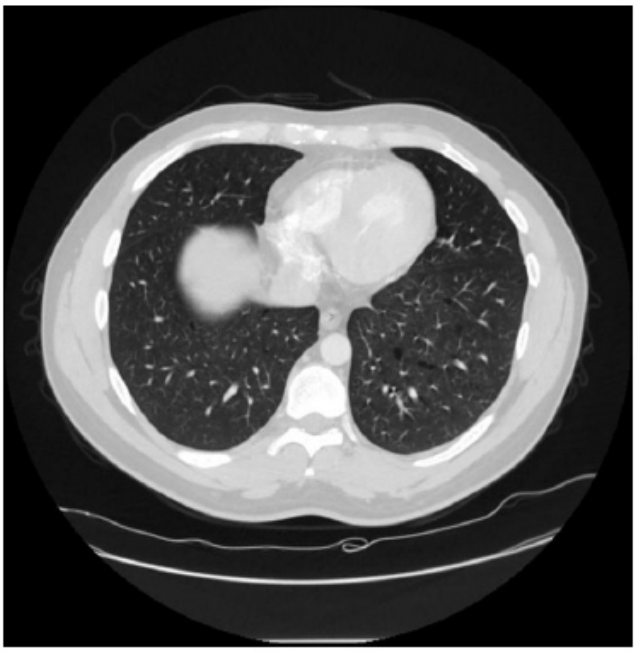

Fig. (1).) Computed Tomography (CT) showing ovoid and spherical shaped, small air cysts scattered in basal segments of the both lungs.

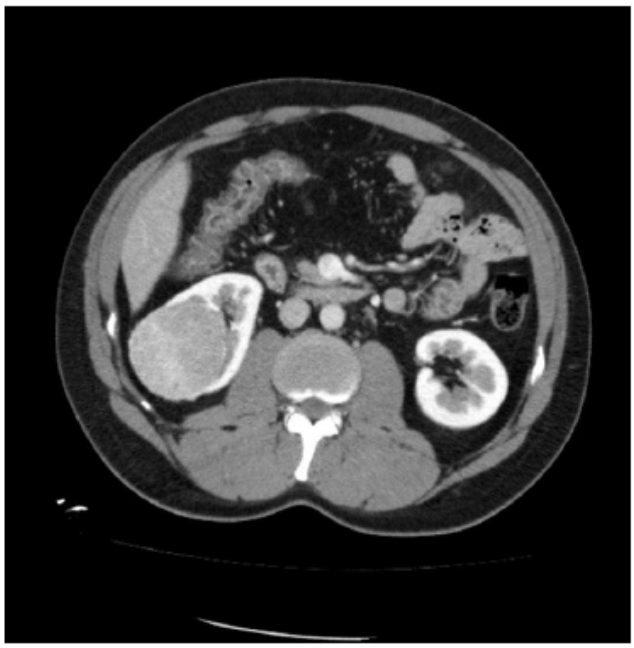

Fig. (2).) Computed Tomography (CT) showing solid renal mass with an exophytic extension in the right kidney. The tumour was removed by partial nephrectomy and the pathology result was hybrid oncocytic-chromophobe renal cell carcinoma.

ological findings. To our knowledge, this is the first report of a patient with BHDS diagnosed radiologically while preparing as a liver donor in English literature.

2. CASE REPORT

In a 32-year-old male patient evaluated as a potential liver donor, CT was performed for preoperative vascular mapping and volumetry examination. In the CT examination, air cysts of different sizes were observed in spherical and others in the ovoid configuration in basal segments of both lungs (Fig. **1**). No accompanying pneumothorax was detected. In the abdominal region, a 7-cm solid renal mass of the right kidney with an exophytic extension and progressive contrast enhancement in the dynamic examination was observed (Fig. **2**). No other focal lesions were detected in the left and right kidneys. Due to a large number of paramediastinal and costophrenic lung cysts and the presence of solid renal tumors at a young age, BHDS was considered. It was determined from the patient's history that he did not have a history of pneumothorax. There was also no remarkable characteristic in his family history, and no pathology was detected in the CT examination of his sister as another potential donor. When the patient was questioned in terms of skin findings, it was found that he previously had skin lesions that lasted for about five to six years, which he had thought were acne scars. The patient was referred to the dermatology department; his examination revealed white or skin-colored papular lesions of several millimeters in diameter on the face and neck. Based on the radiological and dermatological findings, the patient was diagnosed with BHDS. He was referred to the relevant clinics to resolve his current health problems and the genetics department for counseling and analysis. For the renal tumor, the patient underwent partial nephrectomy, and the pathology result was hybrid oncocytic-chromophobe renal cell carcinoma. In the genetic examination, a heterozygous germline mutation was detected in the 11^{th} exon of the FLCN gene.

3. DISCUSSION

The definitive treatment method of end-stage liver and kidney failure is organ transplantation. Organ transplantation is usually performed from living donors since cadavers are globally not at a level that can meet the need, although cadaver donors are more common in developed countries. Evaluating the anatomy before the transplant operation is crucial for both surgical planning and the prediction of possible intraoperative difficulties [7]. It is also important in preventing postoperative complications and protecting donor health [7]. Preoperative radiological examinations are used for this purpose. Radiologists play an important role in filtering potential donors by providing surgeons with the necessary information [8]. They can identify unsuitable donors without the need for unnecessary and invasive procedures [8].

In the selection of donor organs, CT is an effective non-invasive imaging method with high accuracy [7]. In liver and kidney donors, the abdominal region, including the basal segments of the lung, is included in the scanning area and evaluated. Therefore, in all the structures included in sections other than the target donor organ, various abnormal findings can be detected, some of which are clinically silent

but may prevent transplantation [9]. In studies evaluating potential renal donors, 61-75% of the study population are reported to have incidental findings. Similarly, these studies show various malignancies at a rate of 0.1%-0.3% [7, 9]. It is important to characterize these incidental findings, which may be important, albeit rarely, considering that they may affect both the organ transplantation decision and the health of the donor [9]. The Incidental Findings Committee was established for the practical and medically appropriate management of incidental findings detected in the abdominal region by the American College of Radiology (ACR) with the participation of various radiological organizations [10]. The recommendations of this committee are used in the management of incidental preoperative findings of the abdomen.

In the potential donor presented in this case report, multiple cysts in the basal of both lungs and a 7-cm solid renal mass were incidentally detected. When evaluating donor CT examinations, particular importance is given to the target organ. However, all structures included in the scan area must be evaluated in detail. In our patient, the risk of RCC was high according to the recommendations of ACR, and thus surgical excision was already indicated for the detected kidney mass [10]. However, detecting the presence of lung cysts was also effective in patient management. Unlike sporadic RCCs, patients with BHDS are at risk of developing multiple RCCs. In addition, there is an increased risk of spontaneous pneumothorax and some malignancies in these patients. Genetic counseling and analysis of risk-bearing family members gain importance due to the autosomal dominant hereditary pattern of the condition. Due to the existing renal mass, the patient underwent partial nephrectomy in accordance with the recommendation of the urologist. Genetic counseling was planned for other family members through a gene analysis. The patient was informed about the risk of pneumothorax and was included in a follow-up program for the operated RCC. In addition, his sister, another potential donor, was recommended to undergo genetic analysis.

It is known that solid renal masses detected in young individuals (angiomyolipomas, oncocytomas, RCC and its subtypes) may be associated with syndromes, such as Von Hippel Lindau, BHDS and tuberous sclerosis, or occur as familial conditions. In tuberous sclerosis and BHDS, lung cysts can accompany renal masses; therefore, these diseases should be considered in the presence of accompanying lung cysts when solid renal masses are detected in patients at a young age.

BHDS is a rare inherited autosomal dominant disorder caused by germline mutations in the tumour suppressor gene FLCN, encoding the protein folliculin [11]. Mutations are often inherited from one affected parent but can also occur de novo in individuals with no prior family history, as in our case [12]. Its clinical manifestation typically includes recurrent spontaneous pneumothoraces due to pulmonary cysts, cutaneous fibrofolliculomas and renal tumours of various histological types [11]. But the disease is characterised by a wide phenotypic heterogeneity. Carriers of FLCN gene mutations may be asymptomatic, or exhibit varying degrees of cutaneous, pulmonary or renal features. In our case, the patient was asymptomatic and incidentally detected by CT.

Lung cysts in BHDS are usually well defined, thin-walled, oval and lentiform shaped, typically multiple and bilaterally located in the lower basal zones of the lungs [13]. The main radiological differential diagnosis of BHDS are other cystic lung diseases such as Langerhans cell histiocytosis (LCH), lymphangioleiomyomatosis (LAM), centrilobular emphysema and lymphocytic interstitial pneumonitis (LIP). Centrilobular emphysema occurs in the upper lobes of smokers has no discernable walls [14]. LAM is characterized by multiple thin walled, round and well-circumscribed cysts, which are distributed diffusely throughout the lungs usually with a uniform distribution in reproductive women. LAM can occur either sporadically or in association with tuberous sclerosis. LCH may present with a combination of both nodules and irregular contoured cysts, and it tends to spare lung bases and costophrenic angles. It usually seems in young adults with a history of heavy cigarette smoking [14]. A few scattered perivascular smooth cysts associated with ground-glass opacities and nodules are seen in LIP, usually related associated with other autoimmune diseases [14].

Renal cancer constitutes the most severe manifestation of BHD [11]. The histology of renal tumors in BHDS is different from sporadic renal tumors. Normally, 85% of renal tumors are of clear cell histology, 5-10% are papillary, 5-10% chromophobe and 3-5% are oncocytomas [15, 16]. In BHDS, 50% of the renal tumors are hybrid clear cell RCC/oncocytoma and 33% are chromophope. The more aggressive clear cell RCC account for 9% and the benign oncocytomas account for 5% [16, 17]. BHDS patients may present with more than one tumor histology, as in our case (hybrid oncocytic-chromophobe renal cell carcinoma). Subtypes RCC cannot be differentiated by imaging in BHDS.

Diagnostic criteria for BHDS are based on a combination of clinical features, family history, and confirmation of germline FLCN mutation [18]. Once a diagnosis is confirmed, the appropriate follow-up and periodic kidney imaging for early detection of renal cancer are needed. Radiological evaluation is important in both diagnosis and follow-up of the disease.

CONCLUSION

While potential organ donors are generally healthy and asymptomatic individuals, incidental lesions can be detected in both donor organs and others in the scan area during radiological imaging performed for the target donor organ. Although most incidental lesions are benign, important clinical conditions can be rarely observed, as in our case. Therefore, systematic assessment is important when evaluating radiological images. Familial and syndromic conditions should also be considered in the presence of solid renal masses incidentally detected at a young age. The presence of lung cysts and renal solid tumors in a patient should raise the suspicion of BHDS. A prompt and accurate diagnosis is necessary for appropriate management of patients and genetic counseling.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Written and informed consent from the patient was obtained for publishing this case report.

STANDARDS OF REPORTING

CARE guidelines were followed in this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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