Series of Clinical and Medical Case Reports and Reviews

Case Report

Tuberous Sclerosis Complex (TSC) Identified by Genetic Testing After Histologic Diagnosis of Chromophobe Renal Cell Carcinoma

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Abstract

We report the case of a female patient with a histologic diagnosis of chromophobe renal cell carcinoma (ChRCC) after a left laparoscopic radical nephrectomy. Due to the unusual histologic diagnosis, a genetic test was ordered identifying tuberous sclerosis disease.

Keywords: tuberous sclerosis complex, chromophobe renal cell carcinoma, tumor, carcinoma

Abbreviations: ChRCC: chromophobe renal cell carcinoma, TSC: tuberous sclerosis complex, RCC: renal cell carcinoma, TSC-RCC: TSC-associated renal cell carcinoma

1. Introduction

Tuberous sclerosis complex (TSC) was described in the 19th century by Von Recklinghausen [1]; it's an autosomal dominant [2], a multi-organic disease that can affect skin, brain, kidneys, lungs, and heart, replacing normal parenchyma by different cell types. Development of tumors in TSC follows the inactivation of TSC1 (encoding hamartin) or TSC2 (encoding tuberin) [3, 4] genes [2], which leads to alterations of the TSC1-TSC2 intracellular protein complex, causing overactivation of the mammalian target of rapamycin (mTOR) protein complex [5], which is the cause for the development of tumors in different organs [3]. TSC has an incidence of 1/6000 to 1/10,000 live births.

Chromophobe renal cell carcinoma (ChRCC) is the third most common renal cancer after clear cell and papillary renal cell carcinoma, comprising 5% of all renal tumors, with an incidence of metastatic disease of 7% [6]; Casuscelli et al. [7] identified enrichment of TP53 and PTEN mutations in metastatic ChRCC. Under-expression of gamma-glutamyltransferase 1 (GGT1) has been identified as a risk factor for the development of ChRCC [6]. Oncocytomas and ChRCC share a common origin in the collecting system, which can make a histological diagnosis difficult [8]; looking for deletions in RB1 and ERBB4, which subsequently distinguishes ChRCC from oncocytomas [8]. ChRCC can occur in two autosomal dominant genetic alterations: Birt-Hogg-Dube syndrome and TSC [6].

TSC-associated renal cell carcinoma (TSC-RCC) has been identified as a subtype of RCC [2, 9]. It is associated with TSC, female predominance, young age at onset, and indolent evolution [9]. TSC-RCC can lead to the development of angiomyoadenomatous tumors [2, 9], TSC-associated papillary RCC, ChRCC or oncocytic/chromophobe tumors, eosinophilic/macrocystic and unclassified RCC [9]. The mTOR pathway activation and TSC2 mutations have been identified in TSC-RCC [9].

2. Case Report

A 39-year-old female patient with a history of gestational diabetes and hypothyroidism for four

years, with an incidental finding on an abdominal CT scan ordered for gastric complaints, demonstrated the presence of two contrast-enhancing tumors on the left kidney, one in the posterior interpolar region measuring 2 × 2 cm, and another one in the lower pole measuring 3.5 × 3.2 cm **(Figure 1)**. Due to the presence of multifocal tumors, a left laparoscopic radical nephrectomy was performed, with a histologic diagnosis of a multicentric Fuhrman 3, ChRCC, with other nodules composed of oncocytic cells disposed in groups, and a capsular leiomyoma **(Figure 2)**. Due to the unusual histologic diagnosis, a genetic profile was ordered, together with follow-up labs, chest X-ray, and abdominal ultrasound. Genetic sequence analysis and deletion/duplication testing of 83 genes (Invitae Multi-Cancer Panel) was performed by Invitae Genetic Testing (1400 16th Street, San Francisco, CA 94103), reporting a pathogenic heterozygous variant, c.2605A>T (p.Lys869*) identified in the TSC1 gene, consistent with a diagnosis of TSC. With this result, genetic testing was ordered on her offspring, and she was scheduled for follow-up visits.

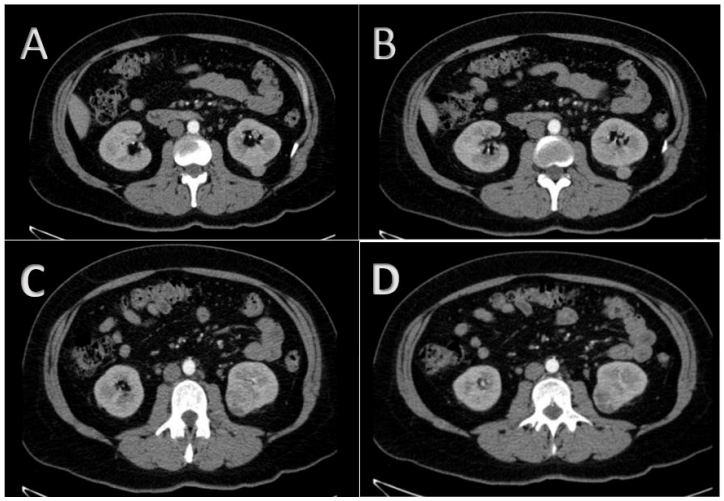

Figure 1: A and B) An enhancing, smooth-walled, round tumor in the left kidney's posterior capsular interpolar region. C and D) Left lower pole heterogeneous, strongly enhancing mass arising from the cortex.

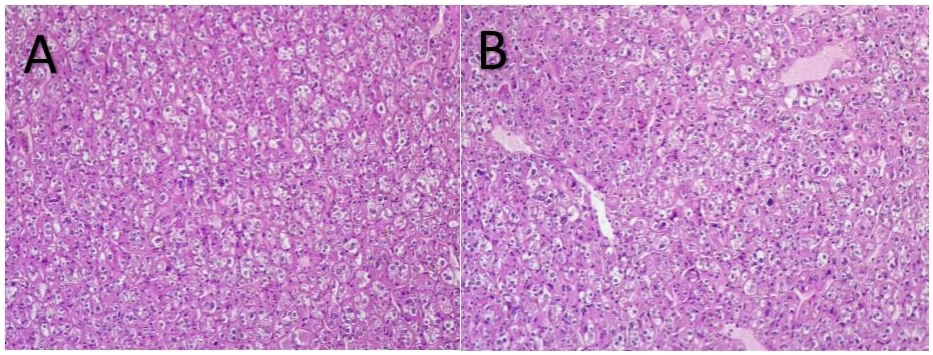

Figure 2: A) Classic type kidney chromophobe carcinoma with polygonal cells with clear and finely reticular cytoplasm with perinuclear halo and with pleomorphic cells. B) Classic type kidney chromophobe carcinoma with cells with central or eccentric nucleus with dense chromatin with cellular disposition around blood vessels.

3. Discussion

TSC is highly variable in clinical presentation. Elements required for a proper diagnosis include genetic and clinical criteria. It is recommended to identify mutations in TSC1 and TSC2 regardless of clinical findings [1]. Clinical diagnostic criteria include dermatologic, dental, ophthalmic, neurological [3], cardiovascular, pulmonary, endocrine, gastrointestinal, and renal alterations [1, 5]. Kidney angiomyolipomas are frequently associated with TSC and have been observed in up to 80% of these patients, and they can be observed in other organs as well [1, 2]. Although multiple renal cysts are infrequent in the general population, they are relatively common in TSC as the TSC2 and PKD1 genes are adjacent and transcribed in opposite directions on the same chromosome, and both genes can present deletions. RCC and oncocytoma [4] in TSC patients have been recognized for many years, and they develop by inactivation of TSC2 [2]. Renal tumors are often multifocal [4], and it was not clear if patients with multiple RCCs had intrarenal metastasis of a single tumor clone or multifocal tumor development [2]; however, the recent understanding of the genetic pathogenesis of TSC-related RCC concluded that RCCs arise independently [2].

4. Conclusion

ChRCC is an uncommon variant, and if identified without a previous history of genetic problems, the patient should be referred for genetic counselling in order to rule out the involvement of other organs.

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