CASE REPORT

Birt-Hogg-Dubé syndrome: awareness is important!

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SUMMARY

Birt-Hogg-Dubé (BHD) is a rare syndrome of inherited renal cell carcinomas, characterised by cutaneous lesions and pulmonary cysts and pneumothorax in a vast majority of the patients. Awareness of this syndrome is important in order to refer patients for genetic counselling and personalised follow-up as soon as possible. We describe a case of a 30-year-old female referred to our institution due to incidental discovery of solid bilateral renal masses. Renal biopsies were consistent with chromophobe tumour, and bilateral nephrectomy was performed. Gross examination revealed deformed kidneys with 28 brown and solid lesions, size variable between 0.1 and 6 cm, histologically corresponding to renal cell carcinomas, chromophobe type. Genetic test was required that showed a c.573delG>insT frameshift mutation in heterozygosity at the folliculin gene, consistent with BHD diagnosis.

BACKGROUND

This case was written due to its rarity and in order to increase awareness of the entity. Birt-Hogg-Dubé (BHD) is a rare syndrome characterised by fibrofolliculomas, lung cysts and kidney tumours, the latter of extreme importance in the follow-up and survival of these patients. In our case, the syndrome manifested by renal tumours, but it can arise with pulmonary cyst or skin lesions, which should raise suspicion by the clinician and prompt

resort to a genetic test for folliculin (FLCN) providing the diagnosis.

CASE PRESENTATION

Thirty-year-old female patient referred to a urology consultation because of solid bilateral renal masses discovered incidentally in abdominal ultrasound due to back pain.

An abdominal and pelvic CT scan was performed and showed 10 solid masses on the left kidney and 5 lesions on the right kidney, with diameters ranging between 1.0 and 6.5 cm (figure 1). Considering this finding, the patient was sent to a urology consultation.

Physical exam revealed fibrofolliculomas and trichodiscomas predominantly on face and neck. Renal masses were not palpable. Patient's medical history revealed a lower lobar lobectomy held 5 years before in the context of a spontaneous pneumothorax. Her case was discussed in a multidisciplinary therapeutic meeting and was proposed to perform a biopsy of a solid mass from each kidney.

INVESTIGATIONS

Both biopsies showed epithelial neoplasia with morphologically and immunohistochemically compatible with chromophobe carcinoma.

Further discussion on the multidisciplinary meeting decided to propose the patient for bilateral nephrectomy.

Two days before surgery, the patient was subjected to a tunnelled dialysis catheter implant.

The bilateral nephrectomy was performed by single port laparoscopy without incidents.

On gross examination, the right kidney weighted 280g and the left 300g; both were markedly deformed and on cut section showed multiple nodular and intrarenal formations: nine in the right kidney and nineteen on the left kidney. All tumours were solid and brown, focally with yellowish areas, size variable between 0.2–6 cm (right) and 0.1–5.8 cm (left) (figure 2).

Remaining renal parenchyma and ureters without abnormalities.

Histological examination was performed on H&E stained slides observed in light microscope (Nikon Eclipse 50i), and images were obtained using a Nikon Digital Sight DS-Fi1 camera.

Microscopically, all the lesion corresponded to malignant epithelial neoplasia, composed of small nests, trabeculae and acinar structures, with well-defined boundaries, mainly with eosinophilic and granular cytoplasm (figure 3A,B); some cells occasionally had clear cytoplasm. The nuclei are round, sometimes with visible nucleoli on 100×

Figure 1 CT scan showed multiple kidney lesions (28), the larger with 6.5 cm in the right kidney.

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Figure 2 Gross examination revealed multiple nodular brownish lesions, well delimited and intrarenal, on the right (A and B) and left kidney (C and D).

magnification. Perinuclear halos were frequent (figure 3C). There was no vascular or capsular invasion, and necrosis was focal. Remaining kidney and ureters with no pathological

Figure 3 Microscopically, the lesion had well-defined boundaries (A), composed by small nest, trabeculae and acinar structures (B). The cells had eosinophilic and granular cytoplasm, some with clear cytoplasm (C). All tumours were positive for Hale's technique (D).

findings. Surgical margins, namely vascular and urothelial, were negative.

DIFFERENTIAL DIAGNOSIS

Histochemical studies were performed in one representative block of each lesion with Hale's colloidal iron.

Immunohistochemical studies were performed on one representative block of the bigger lesion in each kidney, resorting to avidin–biotin–peroxidase complex detection system and performed on Ventana Marker Platform Bench Mark ULTRA IHC/ISH using the following antibodies: CD10 (SP67, Ventana, Tucson, Arizona, USA), CD117 (9.7, Ventana), renal cell carcinoma (RCC; PN-15, Cell Marque, Rocklin, California, USA), cytokeratin 7 (SP52, Ventana) and vimentin (V9, Ventana).

All tumours were diffusely positive for Hale's technique (figure 3D). The tumours tested by immunohistochemistry were heterogeneously positive for CK7 and CD117, focal staining for CD10 and negativity for RCC and vimentin.

The combination of morphological, histochemical and immunohistochemical findings provided us with the definite diagnosis of multiple renal cell carcinomas, chromophobe type.

Tumour was staged using TNM staging (seventh edition) – T1b (m) Nx Mx.

TREATMENT

Surgical intervention was the main plan of treatment for this patient, which went without complications.

The patient remained hospitalised for 7 days to start dialysis and to prepare the ambulatory dialysis programme.

OUTCOME AND FOLLOW-UP

Follow-up has been normal, without tumour recurrence. Post-operative CT scan showed right pulmonary bullae, the bigger with 2.3 cm.

The patient underwent genetic study that showed a BHD syndrome with c.573delGAT frameshift mutation in heterozygosity at the FLCN gene, also identified in her father and sister.

She is currently under study for living donor kidney transplant.

DISCUSSION

Kidney cancer (KC) is the 7th most common cancer in men and the 10th in women¹ and represents the 10th most common cause of cancer-related death in the world.²

The majority of KC are sporadic, with well-known factors such as obesity, tobacco and hypertension, with a minority of KC arising in a familial context, being the Von Hippel-Lindau disease the most common.^{1,2}

BHD syndrome is one of the rare conditions that implies a high risk of RCC,³ first described in 1977 by Birt, Hogg and Dubé.⁴

BHD syndrome is characterised by cutaneous lesions, pulmonary cysts with or without spontaneous pneumothorax and RCC of diverse morphological types.⁵ It is caused by a mutation in the FLCN gene, with over than 30 variants described⁶; FLCN is a tumourous suppressor gene located on the short arm of chromosome 17 at position 11.2 that, through interaction with its partners FNIP1 and FNIP2, has a major role in metabolic pathways like activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR).⁷

The clinical picture in BHD syndrome is variable, with cutaneous lesions in up to 90%–92%, mainly fibrofolliculomas, but trichodiscomas and acrochordons may also occur;^{5,6} pulmonary cysts (number variable between 0 and 166) are present in up to

90% of the patients, and pneumothorax arises in 24%–38%;^{8,9} however, the main concern regarding follow-up and survival is the development of RCC in up to 27% of the patients.⁴ RCCs are normally solitary lesions⁶ and histologically are mainly of the chromophobe, oncocytic or hybrid oncocytoma–chromophobe subtypes, with less frequent cases of clear cell and papillary subtypes.^{3,5,6}

Patients usually are over 40–50 years old,^{6,8} and most of the time, the clinical and familiar history reveal cutaneous lesions, namely fibrofolliculomas, achrochordons, perifollicular fibromas, dermatofibromas and even lipomas;^{5–7} of all those lesions, only fibrofolliculomas are specific for BHD.⁹ However, the clinician must be aware that differential diagnosis must be made with cutaneous lesion from other syndromes namely tuberous sclerosis (TSC) and Cowden syndrome.⁹

Pulmonary cysts are also highly suspicious of BHD, especially in association with cutaneous lesions, but other syndromes have to be ruled out, namely TSC, Marfan syndrome, Ehlers-Danlos syndrome, vascular type and lymphangioleiomyomatosis (LAM).⁹

Other manifestations may include renal cysts and hepatic cysts/haemangiomas.⁶

Due to BHD wide clinical picture and the possibility of developing RCC, the recognition of this syndrome is of extreme importance in order to perform a genetic test, definitive for BHD diagnosis, and refer patient to adequate follow-up with regular clinical and imaging screening with annual MRI.^{3–6,9,10}

An algorithm for BHD has been proposed, considering clinical and pathological findings, with ‘Probable BHD’: two of the following: characteristic CT findings; familial/repeated history of pneumothorax; characteristic histology of pulmonary cysts; more than one oncocytic renal tumour; and at least five skin papules suggestive of or at least one histologically diagnosed as fibrofolliculoma; and ‘Possible BHD’ classification: one of the previous characteristics or the following: repeated episodes of pneumothorax with unspecific microcysts and excluded LAM; multiple unspecific pulmonary cysts, without LAM; multiple renal tumours without characteristic skin lesions and pulmonary findings, without TSC or familial RCC; and one histologically diagnosed fibrofolliculoma, without lung and renal lesions.⁶

Currently, RCC is the only malignancy recognised to be associated with BHD; however, there are some reports in the literature that highlight association with colorectal cancer, thyroid oncocytic carcinoma, salivary gland tumours of oncocytic type, adrenal gland adenoma and melanoma.^{6,9}

Our patient had a typical clinical history, despite absence of familiar history, with cutaneous lesions and pulmonary cysts and pneumothorax; however, the genetic study was never proposed, maybe due to lack of awareness of BHD syndrome by the fellow clinicians, so the patient was never in a specific follow-up.

Most patients develop unique RCC and in some cases a partial nephrectomy may be considered; however, in our patient, due to multiple bilateral tumours, a conservative approach could not be proposed, probably even if the patient was under a personalised

follow-up with regular screening, the high number of tumours would not allow kidney-sparing surgery.

Genetically, the mutation discovered—mut c.573_574delinsT (p.Lys192Argfs*31)—was already reported in literature.¹¹ The identification of the same mutation in the patient’s father and brother will allow to do a personalised follow-up on them.

Learning points

- Adnexal skin tumours and pulmonary cysts/pneumothorax can precede visceral manifestations in several years and should raise suspicion of Birt-Hogg-Dubé syndrome in the clinicians, keeping patients under surveillance.
- Birt-Hogg-Dubé is a rare syndrome characterised by fibrofolliculomas, lung cysts and kidney tumours.
- Kidney tumours are the main feature regarding survival and follow-up.
- Kidney tumours are normally solitary but can be multiple as in this case.
- Definite diagnosis is provided by genetic evaluation of the folliculin gene.

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