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An index case of Birt Hogg Dube Syndrome

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ABSTRACT

A 46 year old lady presented to her general practitioner with recurrent urinary tract infections. She was subsequently diagnosed with a left sided exophytic renal tumour. Subsequent nephrectomy revealed a oncocytic renal tumour which raised a clinical concern for the hereditary syndrome of Birt Hogg Dube Syndrome (BHDS). The only family history of note was a cousin who has a history of renal cysts. Tumour genomic testing revealed somatic mutation in the folliculin gene. This was later confirmed as a germline mutation. Subsequent review of her pedigree discovered skin lesions suspicious for fibrofolliculomas in her father and brother. This history in conjunction with the germline testing confirmed a diagnosis of BHDS. BHDS is a rare hereditary syndrome characterised by fibrofolliculomas, spontaneous pneumothoraces, and renal neoplasms. Diagnosis and clinical management of these patients can be challenging requiring multidisciplinary input from respiratory physicians, urological surgeons and cancer geneticists.

Case presentation

A 45-year old female presented to her general practitioner with recurrent urinary tract infections and non-specific abdominal pain. She had a past medical history of nephrocalcinosis secondary to a parathyroid adenoma and had undergone a parathyroidectomy 20 years previously. She also has a history of gout and of a pancreatic pseudocyst which had ruptured spontaneously. The only family history of note was a cousin who has a history of renal cysts.

Imaging

Her GP referred her for abdominal ultrasound and a 6.3 cm heterogenous lesion was seen in the left kidney. A CT abdomen showed a contrast-enhancing, solid, exophytic lesion in the left upper renal pole (Fig. 1). The lesion had a maximum dimension of 6cm. There was also a 1.1 cm solid lesion at the lateral aspect of the middle pole. Cortical renal cysts were seen bilaterally.

Following patient review by the urology team, a left nephrectomy was performed. The post-operative course was uneventful.

Histology

The resected kidney measured 10 x 5 x 5 cm. There were four separate solid tumours and multiple fluid filled cysts. The tumours ranged in size from 0.8 to 5.1 cm. They had firm, cream cut surfaces and haemorrhagic areas were present focally in the largest tumour. The cysts contained serous type fluid. The background renal parenchyma was macroscopically unremarkable.

Microscopically, three of the four tumours were chromophobe renal cell carcinomas. These tumours had a compact tubular architecture. The cytoplasm was eosinophilic and focally clear. There was binucleation with round to wrinkled nuclear contours and prominent perinuclear halos were noted (Fig. 4). No necrosis or mitoses were seen.

The fourth tumour was a hybrid oncocytoma/chromophobe renal cell carcinoma. This tumour exhibited histological features similar to the other three tumours but it also had areas resembling oncocytoma, with rounded nuclei and nested architecture (Fig. 4). Immunohistochemical studies of this hybrid tumour showed focal CK7 positivity in the chromophobe areas and CK7 negative oncocytoma-like areas.

The background renal parenchyma contained multiple tiny collections of densely packed cell nests with eosinophilic and clear cytoplasm with similar morphology and CK7 positivity to that of the larger chromophobe tumours, consistent with oncocytosis.

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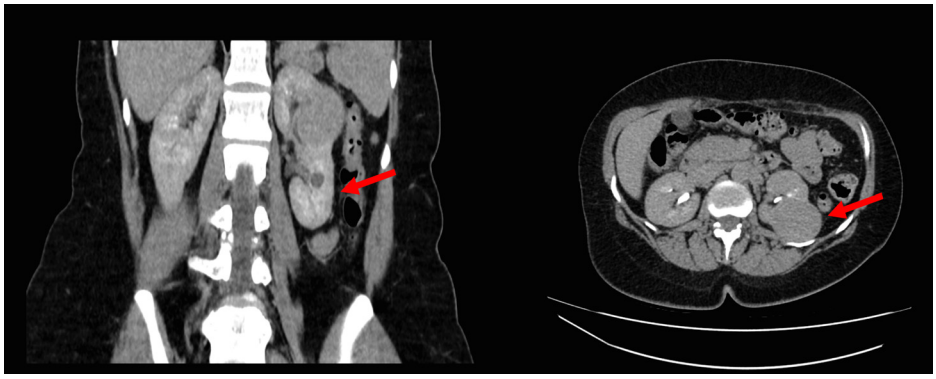

Fig. 1. Coronal and transverse planes of solid renal lesions on CT abdomen.

There was no invasion of the perirenal fat, Gerota's fascia or renal vasculature. The pathological TNM stage was therefore $pT1b_{(m)}$, pNx (UICC 8th edition).

Given the combination of the young age of the patient, the presence of multiple tumours and renal oncocytosis and her personal and family history of pancreatic and renal cysts, an inherited form of renal cell carcinoma was suspected and the possibility of Birt-Hogg-Dubé syndrome was raised. The case was referred to the Department of Cellular and Molecular Pathology in Dundee University for specialist opinion and genetic analysis.

Genetic analysis

DNA was extracted from the tumour and adjacent normal kidney and amplified by PCR for 40 cycles. Direct sequencing of all 14 exons of the folliculin gene was performed separately by bidirectional sequencing and these sequences were screened. Two heterozygous sequence variants were detected in the folliculin gene. The first variant was '*c.1285 duplication C*'. This variant alters the reading frame and introduces a premature stop codon in the folliculin protein and therefore, is pathogenic. As a folliculin mutation was confirmed in the tumour, it was highly likely that this patient had Birt-Hogg-Dubé syndrome.

Blood was drawn for confirmation of the germline mutation. The National Centre for Medical Genetics reported that there was a pathogenic mutation of the folliculin gene, namely *'c469_471delTTC'* in exon 6 of the FLCN gene. The somatic *c.1285 duplication C* mutation detected in the tumour was not present in the germline. This confirmed a diagnosis of Birt-Hogg-Dubé syndrome.

These data confirm that the patient has a germline mutation (*c469_471delTTC*) but that the 'second hit' occurring in the renal parenchyma and leading to tumour formation is heterozygosity for a second independent mutation (*c.1285 duplication C'*). Constitutional heterozygosity for independent folliculin mutations has not been described presumed to be due to embryonic lethality (Tomassetti et al., 2011)

Follow up

A CT thorax was performed and multiple pulmonary cysts were present, bilaterally. There were also small peripheral subpleural areas of subsegmental scarring. Fibrofolliculomas were diagnosed on examination by the genetic services.

Her father also has this skin pathology (a photograph showed this but was too poor quality to be included in this paper). Her sister is asymptomatic but she has a brother with a history of skin lesions which he has never had investigated. Her first cousin once removed has a history of previous lung collapse and skin lesions and he too has undergone genetic testing and been diagnosed with Birt-Hogg-Dubé syndrome.

Discussion

Clinical features

In 1977, Arthur Birt, Georgina Hogg and William Dubé described a skin syndrome of fibrofolliculomas in multiple family members who were over the age of 25yrs (Birt et al., 1977). Years later, this syndrome known as Birt-Hogg-Dubé (BHDS) was further characterized by an association with lung cysts, spontaneous pneumothorax and renal neoplasms (Schmidt et al., 2005). Birt-Hogg-Dubé syndrome is characterised as a triad of hair follicular hamartomas, pulmonary cysts/spontaneous pneumothorax and renal tumours. The clinical presentation of this case does not include all three features and so, not having a full complement does not out rule BHDS.

Studies published in the literature report the incidence of skin fibrofolliculomas in 90% of BHDS families (Toro et al., 2008), pulmonary cysts in 80% (Menko et al., 2009) and renal tumours in almost 30% (Toro et al., 2008, Chung et al., 1996).

Genetics of Birt-Hogg-Dube Syndrome

BHDS is a genetic disorder which exhibits autosomal dominant inheritance. It is caused by a germline mutation in the folliculin (FLCN) gene that has been mapped to chromosome 17p11.2 by genetic linkage analysis (Khoo et al., 2001). The exact normal function of the folliculin gene is as yet undefined; however, the folliculin protein does exhibit characteristics of tumour suppression (Nickerson et al., 2002).

Our index patient had a first cousin who has multiple renal cysts. Her father had multiple cutaneous cyst like lesions over his face which were never investigated. She had no past history of dermatology or pulmonary pathology. She had a parathyroidectomy at the age of 24yr after presenting with nephrocalcinosis secondary to a parathyroid adenoma. Parathyroid adenoma has been reported as a rare manifestation in BHDS and so this potentially may have been a phenotypic expression of her genetic disorder (Chung et al., 1996).

There is wide variability in the clinical presentation of this genetic disorder and therefore, this syndrome can be under diagnosed. This clinical variation seen is most likely due to the multiple mutation types. At present, studies have demonstrated race differences in the distribution of these mutations (Kunogi et al., 2010) but phenotype-genotype correlations have not yet been established (Schmidt et al., 2005; Toro et al., 2008). Mutations have been described throughout the gene. A second hit has been seen in the great majority of renal tumours. These second events have been most frequently mutations leading to a truncation of the folliculin protein (57%) or loss of the region of chromosome 17p carrying the folliculin gene.

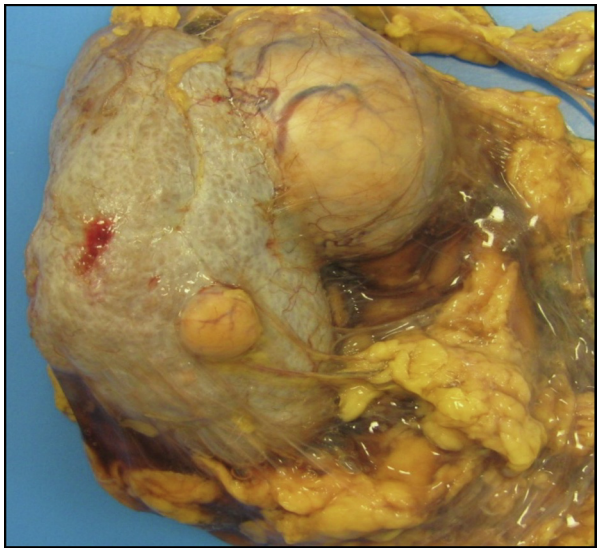

Fig. 2. Nephrectomy specimen with attached perirenal fat. Note the upper and mid pole lesions, as detected on imaging.

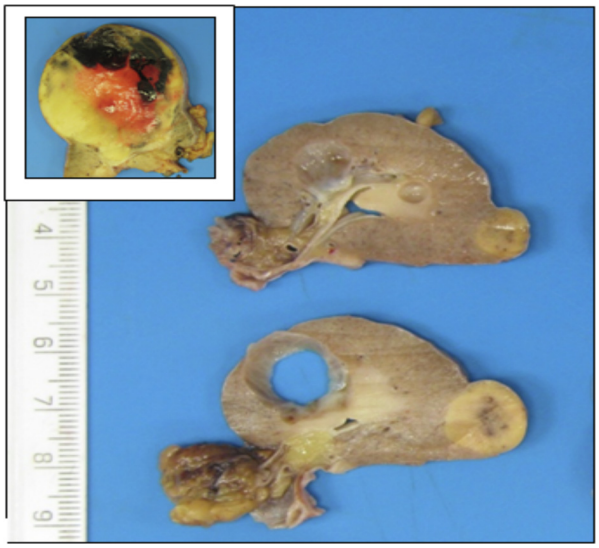

Fig. 3. Transverse sections of kidney with solid and cystic lesions Insert – Haemorrhagic foci in the largest solid lesion.

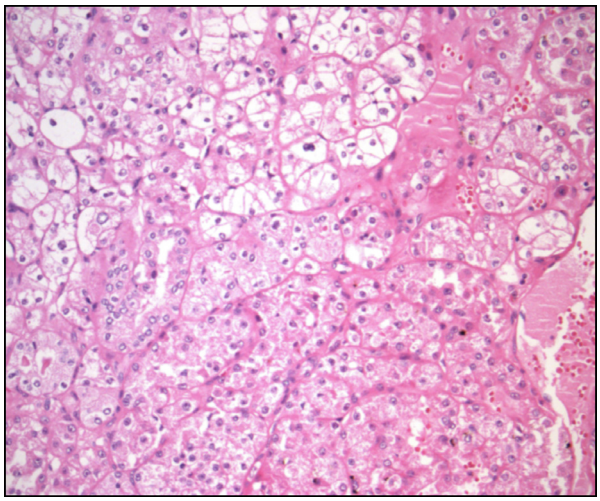

Fig. 4. Hybrid tumour comprising chromophobe-like areas with clear cytoplasm in the top half of the image and nested oncocytoma-like component below (20x magnification).

Renal tumours

Renal tumours arise in approximately 30% of BHDS patients; have a male predominance and a median age of diagnosis of 48–52 years (Schmidt and Linehan, 2015). These tumours are predominantly multifocal but unifocal lesions are also seen. They may be unilateral or bilateral. There are multiple histological subtypes documented including hybrid oncocytic tumours (50%), chromophobe renal cell carcinoma (34%), oncocytoma (5%), as well as clear cell and papillary renal cell carcinomas (Khoo et al., 2001). Typically, BHDS tumours are not aggressive and metastatic disease is rare. The detection of this genetic disorder is paramount in monitoring and screening those families at risk. BHDS diagnostic criteria proposed by Menko et al. (2009) included a minor criterion of "early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology".

Renal oncocytosis was first described by Warfel and Eble (1982) as 'Renal oncocytomatosis' and is characterised by the presence of numerous tiny oncocytic nodules within the renal parenchyma. These nodules can arise in non-BHDS kidneys, but this is rare. These changes can range from single to clustering oncocytic cells, oncocytic-lined cysts and oncocytic change in non-neoplastic tubules. In addition, nodules with a morphology and immunophenotype resembling chromophobe RCC can also be found, as in this case. The finding of oncocytosis should therefore always prompt consideration of a possible diagnosis of BHDS.

Pulmonary manifestations

The majority of patients with BHDS (80%) present with bilateral pulmonary cysts (Gupta et al., 2013), which demonstrates the atypical phenotype in our case. These patients have a significant 50-fold increased risk of spontaneous pneumothorax (Tomassetti et al., 2011). The recurrence rate is in the range of 75–80% demonstrating the significant morbidity associated with this condition (Toro et al., 2007). Risk factors for pneumothorax include pulmonary cysts including the size and total number and family history of pneumothorax (Figs. 2 and 3).

Other manifestations

In their initial report, Birt et al. (1977) reported cutaneous manifestations including fibrofolliculomas, trichodiscomas and acrochordons as the primary lesions associated with BHDS. These lesions are most commonly found on the face and forehead. They are typically painless, skin-colored papules which are typically < 0.5 cm in size and there may be many. They generally are asymptomatic and thus rarely require intervention. They are however clinically significant to aid diagnosis and guide appropriate genetic testing**.** There are reports of association with other cutaneous manifestations including lipomas, angiolipomas, melanomas and collagenoma (Palmirotta et al., 2010).

Management

Cutaneous lesions of BHDS are generally asymptomatic and do not require active clinical management except for aesthetic purposes.

It is recommended that patients undergo baseline renal imaging from the time of diagnosis or at age 20 (Pavlovich et al., 2005). This can be repeated every 3 to 4 years. MRI is considered the ideal modality to limit radiation dose while maintaining a high sensitivity and specificity. In the case of resectable tumours, a nephron sparing strategy may be preferable in the event that a patient develops further lesions (Pavlovich et al., 2005)

The management of pulmonary disease is primarily focused on the symptomatic management of pneumothoraces. Given that there is a high recurrence rate, it is generally recommended that pleurodesis is considered after the first episode of pneumothorax (Gupta et al., 2013). It is recommended that patients with BHDS avoid diving and smoking.

At present, children of our patient are under the age of 18yrs. The clinical features of BHDS do not usually present until after the age of 20yrs. Current standard practice is for the offspring of these patients to wait until they are of age of consent to decide if they wish to be genetically screened. However, spontaneous pneumothoraces in the children of BHDS families has been reported in the literature (Warfel and Eble, 1982) and the possibility of this occurring had been discussed with this patient.

Conclusions

1 BHDS is a syndrome of pulmonary cysts/pneumothoraces, fibrofolliculomas and renal tumours.
2 Diagnosis typically require multidisciplinary input to identify clinical and histopathological features consistent with the hereditary syndrome.
3 Oncologists (surgical/medical/radiation) should be aware of the possibility of inherited syndromes when dealing with rare multifocal tumours in a young patient. The identification of a genetic syndrome dictates management of the patient and has significant implications for the extended family.

Author contribution section

DOR wrote the initial draft of the manuscript and prepared the submission. SF and NM provided expert input to the pathological and genomic components of the case and reviewed the draft of the manuscript. PS provided expert input into the surgical management of the case and reviewed the draft of the manuscript. DP conceived the idea of the case report and edited the final draft of the manuscript.

Statement

The patient has provided full, informed consent to allow the submission and subsequent publication of this manuscript for educational purposes. The authors are very grateful for the patient's generosity in this regard

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Declaration of Competing Interest

None to declare

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