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Phaeochromocytoma in a patient with a Birt-Hogg-Dubé syndrome phenotype

Alamin Alkundi [1], Rabiu Momoh [2]

[1]Diabetes and Endocrinology, East Kent Hospitals University NHS Foundation Trust, Ashford, UK
[2]Department of Intensive Care Medicine, William Harvey hospital, Ashford, Kent, UK

Correspondence to
Dr Rabiu Momoh; rabiu.momoh@nhs.net and Dr Alamin Alkundi; alamin.alkundi@nhs.net

AA and RM contributed equally.

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SUMMARY

A case of phaeochromocytoma in a female patient in her 50s with phenotypical expressions for the rare Birt-Hogg-Dubé (BHD) syndrome is presented. Whether this is an incidental finding or that there is a composite relationship between these two entities remains to be fully described. Less than 10 cases reporting likely association of BHD syndrome with adrenal tumours have been reported in the literature to date.

BACKGROUND

The Birt-Hogg-Dubé (BHD) Foundation, located in London, UK, approximates that there are about 600 families worldwide affected by this syndrome. However, this syndrome is likely underdiagnosed. The BHD syndrome, with an autosomal dominant inheritance pattern, has an estimated carrier frequency of 1:200 000. BHD syndrome results from the mutation of the folliculin (FLCN) gene (a tumour-suppressor gene) that codes for the FLCN protein. This syndrome shows variable expressivity. This condition presents with renal cysts, lung cysts and/or fibrofolliculoma (a unique skin finding).[1]

Additionally, the occurrence of benign or malignant renal tumours and pneumothoraces is a known complication of this syndrome. The description of phaeochromocytoma in relation to or association with BHD syndrome is scarce in the literature, hence the usefulness of this case report to shed light on this unexplored association. Other important differentials of BHD syndrome, as well as of phaeochromocytoma, have been reviewed in the Discussion section of this document for better clarity.

CASE PRESENTATION

A female patient in her 50s, with a medical history of hypercholesterolaemia, osteoporosis, past depressive episodes, recurrent atypical chest pain and mildly dilated aortic root (under surveillance), was investigated for a recurrent bilateral flank pain. Her regular daily medications included atorvastatin, ezetimibe, colecalciferol with calcium carbonate and as required sublingual glyceryl trinitrate spray. On radiological investigation, she was found with bilateral renal cysts and a right adrenal cyst (figure 1). She further required multiple percutaneous aspirations of symptomatic renal cysts. She smoked a pack a day of cigarettes since her 20s but had quit 4 years prior to this case submission and was an occasional alcohol user. The patient's daughter had recurrent spontaneous pneumothoraces and had bilateral renal cysts. The patient's brother also had bilateral renal cysts and had mildly dilated aortic root (under surveillance). The patient's mother (deceased) had emphysema and her father (deceased) had lung cancer.

Following assessment of the patient at a tertiary hospital's genetics clinic, a provisional diagnosis of BHD syndrome was made for her bilateral renal cysts and notable skin lesions (biopsy of one of these lesions however was reported as milia). Her CT of the chest study did not reveal lung cysts. Analysis of all the coding regions and exon/intron boundaries of the FLCN, fumarate hydratase (FH), myc-associated factor X (MAX), rearranged during transfection (RET), succinate dehydrogenase complex subunit A (SDHA), succinate dehydrogenase complex assembly factor 2 (SDHAF2), succinate dehydrogenase complex iron sulfur subunit B (SDHB), succinate dehydrogenase complex subunit C (SDHC), transmembrane protein 127 (TMEM127) and Von Hippel-Lindau (VHL) genes by targeted next-generation sequencing (Agilent custom capture V.6/Illumina NextSeq500) did not identify a pathogenic variant. The patient required further investigations for her recurrent episodic high blood pressure readings, anxiety, diaphoresis and headaches. Biochemical studies (table 1) done suggested phaeochromocytoma. Further investigation revealed a 2.4 cm right adrenal lesion that was metaiodobenzylguanidine avid. The patient then underwent a laparoscopic right adrenalectomy.

Histological study report of the right adrenal gland excisional biopsy is as follows: the cortex appears compressed by the presence of a medullary nodule, which was circumscribed, measuring 20 mm in maximum diameter. The nodular lesion was haemorrhagic in appearance and showed golden yellow areas in-between haemorrhages. There was low overt necrosis and there was no infiltration in the adrenal cortex.

On microscopic evaluation, the right adrenal gland showed an unencapsulated, well-circumscribed tumour, composed of polygonal cells with amphophilic to eosinophilic cytoplasm arranged in the nest within the vascular stroma. The tumour compressed the background adrenal tissue. There was no infiltration of the tumour through the capsule or involvement of the periadrenal brown fat. There were no increased or atypical mitoses, confluent necrosis, perineural or lymphovascular invasion. Myelolipomatous metaplasia was present in the cortex. Reticulin stain showed preserved architecture with no expansile nodules. No Periodic acid–Schiff or trichrome-positive intracytoplasmic inclusions were present. Immunostaining with SDHB was negative in the tumour cells. S100

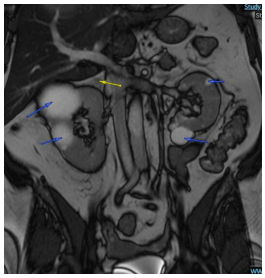

Figure 1 A coronal section of the abdomen seen on an MRI scan revealing the patient's bilateral renal cysts (blue arrows) and the enlarged right adrenal gland (yellow arrow).

highlighted occasional sustentacular cells. Ki-67 was less than 1%.

The patient reports that her notable skin lesions resolved post-right adrenalectomy surgery.

OUTCOME AND FOLLOW-UP

At a virtual endocrinology clinic, a year prior to this case report submission, she was noted with seated plasma metanephrine levels within normal range. She had gone on to have a partial right nephrectomy as a treatment for multiple symptomatic right renal cysts and clearance of adhesions from areas around the right kidney to the liver. She had no further episodic sweatiness or anxiety. She is being followed up with a tertiary centre's VHL syndrome clinic team due to the documented association between phaeochromocytoma and renal cysts. She has again been referred for urology unit's consideration of renal cyst decortication for her recurrent flank pain.

DISCUSSION

Three Canadian physicians (Dr Arthur Birt, Dr Georgina Hogg and Dr William Dubé) are widely credited to have first described the BHD syndrome in 1977.[2] In a 2012 publication by Happle, he suggested a change of the name of this syndrome to Hornstein-Birt-Hogg-Dubé syndrome to credit possible prior descriptions of this syndrome by Hornstein and Knickenberg for their publications in 1975 and 1976.[3]

Though the patient in this case report had the BHD syndrome phenotype (skin changes, bilateral renal cysts), as well as her daughter having bilateral renal cysts and recurrent spontaneous pneumothoraces, the patient's genetic mutation screens for FLCN, FH, MAX, RET, SDHA, SDHAF2, SDHB, SDHC, TMEM127 and VHL genes were negative studies. Although the diagnosis of BHD syndrome is made from genetic studies that confirm the presence of mutation affecting the FLCN gene, Leter *et al* described patients in their study who had phenotypical expressions for this syndrome but had no mutations detected on genetic study, as is the case with our index case report.[4]

Less than 10 cases exist in literature reviewing adrenal tumours in patients with BHD syndrome. Whether these cases were coincidental or that there is a causative or composite relationship between these clinical entities remains to be fully explained. A case report describing the presence of the FLCN and SDHB gene mutations (that causes BHD syndrome and hereditary paraganglioma-phaeochromocytoma syndrome) in a man in his 20s who had presented with haematuria, and CT study of his abdomen revealing a left renal tumour with nodal and liver metastasis as well as having left renal vein thrombosis with inferior vena cava extension, was published by Boland *et al* in December 2020. Pathological studies revealed a metastatic clear cell renal carcinoma post-cytoreductive surgery in the patient.[5]

A case description of a benign adrenocortical tumour (110×95×56 mm) in a woman in her 30s (with a family history of BHD syndrome), who had presented with urinary frequency, was published by Juszczak *et al*. The patient was found with a positive genetic screen result for this syndrome following her adrenalectomy surgery.[6] A histopathological finding of oncocytic tumour of the left adrenal in a man in his 30s with a prior diagnosis of BHD syndrome was published by Ramsingh and Watson.[7]

Another case describing the genetic study diagnosis of BHD syndrome in a woman in her 60s with trichodiscoma (a unique skin finding suggesting BHD syndrome) was published by Raymond *et al*. The patient was screened for renal tumours and a right adrenal tumour was found.[8] The diagnosis of BHD syndrome in a man in his 40s found with an incidental right adrenal nodule, which was non-secretory and oncocytic upon pathological study post-adrenalectomy, was published by MacFarlane *et al*.[9]

In the literature, there has been a lot of publication evidence to suggest the possible link of BHD syndrome with other organ pathologies other than the above-described signs of fibrofolliculoma, renal and lung cysts. Multiple neurilemmomas affecting nerves in a single extremity in a young woman with pre-existing BHD diagnosis were described by Renfree and Lawless in their 2012 publication.[10] A concurrent finding of bilateral parotid gland tumours in a patient found with skin changes and bilateral basal lung cysts that suggested BHD syndrome, which went on to be confirmed on genetic studies, was published by Lindor *et al*.[11] Bajwa *et al* published a case report identifying submandibular (extracardiac) rhabdomyoma in an elderly man who went on to be further evaluated with genetic screen that confirmed BHD syndrome.[12]

A case report describing an infant who had an out-of-hospital cardiac arrest and was also found to have two cardiac rhabdomyomas was published by Bondavalli *et al*. A genetic study revealing an FLCN gene mutation in this child was obtained afterwards. The genetic testing was done at the suggestion of the patient's known family history for this syndrome.[13] Sattler *et al* described possible association of BHD syndrome with early-onset

Table 1 Some relevant biochemical tests conducted while evaluating for the cause of recurrent episodic hypertension in the patient

Test	Result	Reference range	Comment
24-hour urine norepinephrine (nmol/24 hours)	2206	0–570	Elevated
24-hour urine dopamine (nmol/24 hours)	1906	0–2500	Within reference limits
24-hour urine cortisol (nmol/24 hours)	100	0–200	Within reference limits
24-hour urine creatinine (nmol/24 hours)	12.4	7–13	Within reference limits
Plasma renin activity (ng/mL/hour)	1.1	0.5–3.5	Within reference limits
Plasma aldosterone level (erect) (pmol/L)	220	90–700	Within reference limits

colorectal malignancy in their publication.[14] The association of BHD syndrome with endocrine tumours of the thyroid and parathyroid, melanomas, meningiomas and squamous cell carcinoma has been described in the literature.[15]

Renal cell cancer syndrome, VHL syndrome, hereditary leiomyomatosis and hereditary papillary renal cancer syndrome are some differential diagnoses of BHD syndrome. Histological and genetic studies may be used to distinguish BHD syndrome from them. Marfan syndrome, tuberous sclerosis complex, alpha1-antitrypsin deficiency, cystic fibrosis, Ehlers-Danlos syndrome, Langerhans cell histiocytosis and lymphangioleiomyomatosis are differential diagnoses of the pulmonary manifestations of BHD syndrome (lung cysts and pneumothorax). Other differentials for the skin findings in BHD syndrome include familial trichoepitheliomas, tuberous sclerosis complex, Cowden syndrome and multiple endocrine neoplasia type 1.[16]

In hereditary leiomyomatosis and renal cell cancer syndrome, FH gene mutation is found.[17] MAX, SDHAF2, SDHA, SDHB, SDHC, SDHD and TMEM127 gene mutations have been implicated in hereditary paraganglioma-phaeochromocytoma syndrome.[18] RET gene mutation is found in multiple endocrine neoplasia type 2a and familial medullary thyroid carcinoma.[19] SDHA gene mutation causes non-syndromic paraganglioma or phaeochromocytoma.[20] VHL gene mutation causes VHL syndrome (that is characterised by central nervous system haemangioblastoma, retinal angiomas, kidney, pancreatic or genital tract cysts). Phaeochromocytoma, clear cell renal carcinoma, endolymphatic sac and pancreatic neuroendocrine tumours are other tumours associated with VHL syndrome.[21]

Shave excision, curettage, laser ablation or skin resurfacing can be deployed to treat the skin manifestation of BHD syndrome. However, they commonly recur. Periodical general evaluation of the patient for the development of malignancy is recommended. If renal malignancy is excluded at the time of diagnosis of BHD syndrome, then renal MRI scans are recommended to be done every 36 months for lifelong surveillance.[22] Counselling of patients and their family is essential. Blood-line relatives of patients could be recommended for relevant organ assessments as well as genetic study for this syndrome. They should also be counselled about the dangers of smoking in progressing lung features of this syndrome. Partial or total nephrectomy may be surgical options to consider for kidney tumour(s) in this syndrome.[16]

Learning points

- More research into the association between Birt-Hogg-Dubé (BHD) syndrome and phaeochromocytoma needs to be done.
- Patient education can be better facilitated when one or both entities occur.
- Limited cases of phenotypical BHD syndrome have been described in the literature with negative folliculin gene mutation screens.

Twitter Alamin Alkundi @alamin_alkundi and Rabiu Momoh @RabiuMomoh3

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ORCID iDs
Alamin Alkundi http://orcid.org/0000-0003-0488-220X
Rabiu Momoh http://orcid.org/0000-0001-8412-0912

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