

INCIDENTAL RADIOLOGICAL FINDING OF A RENAL TUMOUR LEADING TO THE DIAGNOSIS OF BIRT-HOGG-DUBE SYNDROME

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Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant condition characterised by benign tumours of the hair follicle, renal cancer, pulmonary cysts and spontaneous pneumothorax. We report the diagnosis of a BHD syndrome achieved after incidental radiological finding of a renal tumour in a 24-year old man. The patient also displayed recurrent pneumothoraces and showed to have cysts in the basis of both lungs. The association of recurrent pneumothoraces and renal neoplastic disease should alert for the possible presence of this syndrome.

Key-word: Oncocytoma.

Case report

A 24-year-old man was admitted to the hospital for investigation of retrosternal pain suggestive of pericarditis. Initial investigations revealed a CRP level of 3.4 mg/dl and discrete ECG changes confirming the suspicion of pericarditis. A contrast enhanced computed tomography (CT) examination of the chest and the upper abdomen was performed to rule out conditions such as pulmonary embolism and aortic dissection, but the examination showed no abnormalities. However, it was incidentally noted that a solid contrast capturing nodule of 2 cm was present posteriorly in the interpolar region of the left kidney (Fig. 1A). The kidney otherwise appeared normal and no other abdominal abnormalities were seen. The patient subsequently underwent a gadolinium enhanced magnetic resonance imaging (MRI) study of the kidneys on which the presence of the nodule was confirmed. The mass was hypointense on the T1- and T2-weighted images (Fig. 1B), and showed slight enhancement after intravenous injection of gadolinium (Fig. 1C). A partial nephrectomy was performed. The anatomopathological analysis of the nodule showed an oncocytoma. Postoperatively our young patient surprisingly showed a left-sided pneumothorax. The pneumothorax resolved within 5 days after chest drain insertion.

The history of our patient revealed that one month prior to this admission, our patient was treated

for a primary left-sided pneumothorax with thorascopic pleurectomy and basal bullectomy after chest drainage had failed (Fig. 1D). The patient also had a known history of ulcerative colitis, for which he had been under treatment for several years. Furthermore, family history revealed that our patients father died at a young age due to renal cancer. Because of the wide variety of clinical problems present in a young patient and because of his family history of renal cancer, our patient was referred for genetic counselling. Molecular genetic research confirmed the diagnosis of Birt-Hogg-Dubé (BHD) syndrome, a rare autosomal dominant disorder.

Discussion

Birt-Hogg-Dubé syndrome is a rare autosomal dominant condition characterised by benign tumours of the hair follicle, renal tumours of different histological types, pulmonary cysts, and spontaneous pneumothoraces. The condition is caused by germline mutations in the FLCN gene, which encodes folliculin. At present about 200 families with BHD syndrome with pathogenic FLCN mutations have been reported worldwide. BHD syndrome is probably under-diagnosed because of the wide variability in its clinical expression. Patients might present with renal cancer or pneumothorax, conditions that generally occur sporadically. The skin lesions usually appear after the age of 20 years, as multiple dome-shaped, whitish papules on

nose and cheeks. About 25% of the FLCN-mutation carriers do not manifest skin lesions (1).

The most threatening complication of BHD syndrome is renal cancer. In a series of 124 individuals with BHD, 27% of the patients had renal tumours at a mean age of 50.4 years (range 31-74 years) (2). The earliest reported age at diagnosis of renal cancer in a patient with BHD syndrome is 20 years (3). A unique characteristic of this condition is the mixture of histological types of renal tumours seen in a single kidney or patient, with chromophobe renal cell carcinoma (RCC), clear cell RCC and oncocytoma respectively accounting for up to 34%, 9% and 8% of the cases (4). In addition to this, the presence of different cell populations within an individual tumour, the so-called hybrid oncocytic tumour (50%), is frequently observed in BHD patients. Furthermore, kidney tumours in BHD syndrome usually occur earlier than sporadic tumours and are generally multiple and bilateral (5). This is not the case in our patient. Therefore a familial history of renal cancer, the diagnosis of early-onset renal cancer (< 50 years), or the presence of multiple bilateral kidney tumours should raise suspicion of BHD syndrome, particularly if the predominant histological type is chromophobe renal cell carcinoma or hybrid oncocytic tumour. CT and MRI usually show multiple, bilateral, heterogeneous, solid renal masses that demonstrate heterogeneous enhancement after contrast administration. In our patient the family history of a malignant renal tumour and the discovery of a benign oncocytoma at the age of 24, were clues to the diagnosis of BHD syndrome.

On CT examination of the thorax, more than 80% of adult patients with BHD have multiple lung cysts. It is known that pulmonary cysts may rupture under the pressure of

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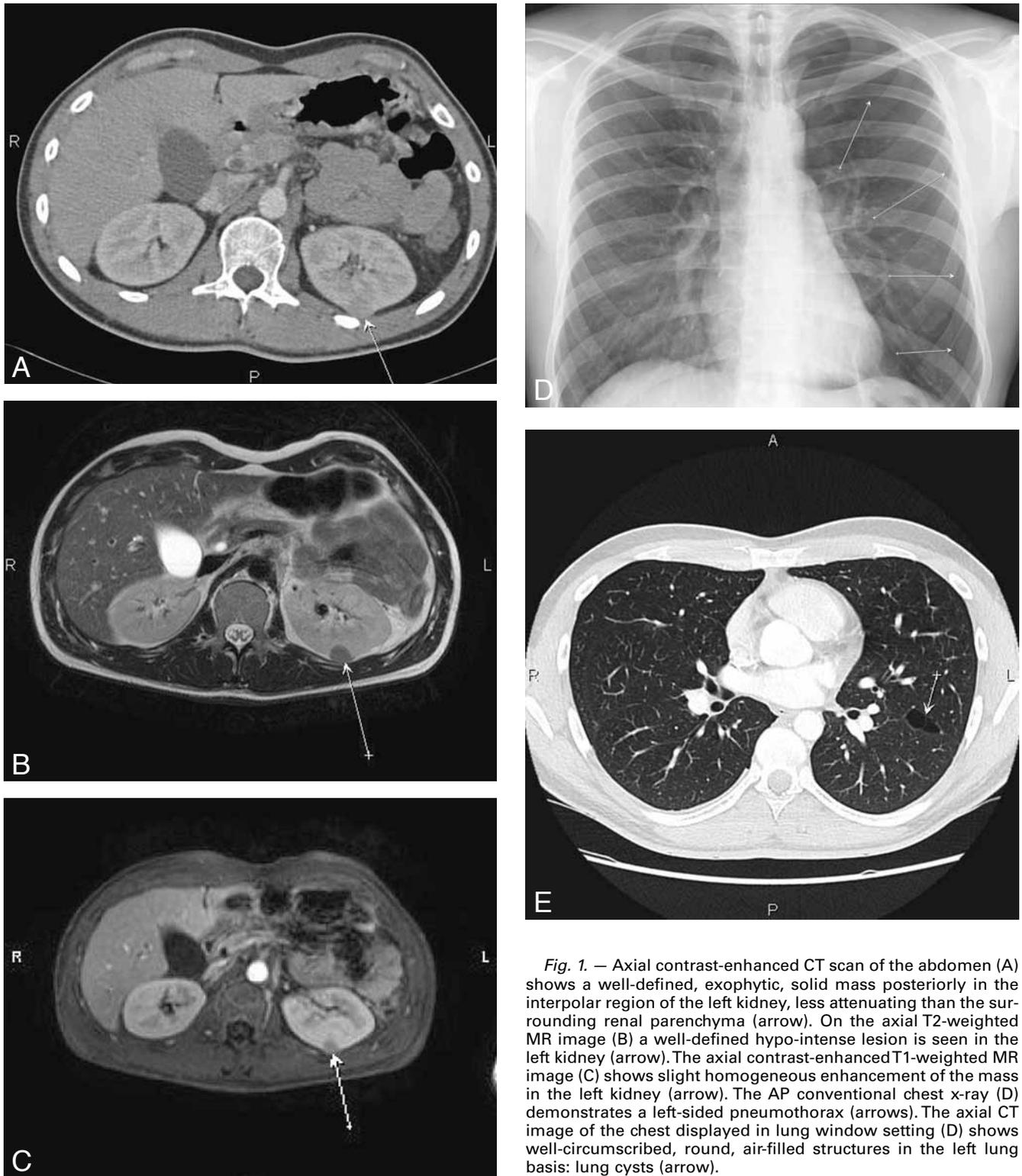


Fig. 1. — Axial contrast-enhanced CT scan of the abdomen (A) shows a well-defined, exophytic, solid mass posteriorly in the interpolar region of the left kidney, less attenuating than the surrounding renal parenchyma (arrow). On the axial T2-weighted MR image (B) a well-defined hypo-intense lesion is seen in the left kidney (arrow). The axial contrast-enhanced T1-weighted MR image (C) shows slight homogeneous enhancement of the mass in the left kidney (arrow). The AP conventional chest x-ray (D) demonstrates a left-sided pneumothorax (arrows). The axial CT image of the chest displayed in lung window setting (E) shows well-circumscribed, round, air-filled structures in the left lung basis: lung cysts (arrow).

ventilation and subsequently cause pneumothorax. On CT-scan the lung cysts are seen as well-circumscribed, round, air-filled structures. In contrast with sporadic primary pneumothorax, where pulmonary cysts are usually located in the apical

zones, the lung cysts in BHD are typically found in the basal lung regions (1). In our patient such cysts were seen in the basis bilaterally, with the largest one showing a diameter of 1.5 cm (Fig. 1E). Another clue to the diagnosis in our case was

therefore given by the finding of recurrent spontaneous pneumothoraces on radiographic imaging.

The typical skin lesions that are associated with BHD syndrome were in this case never used as a clue to the diagnosis of this rare clinico-

pathologic condition. Concerning the initial complaints, the retro-sternal pain was most likely the result of a viral pericarditis of which our patient steadily recovered. This pericarditis episode was probably unrelated to the syndrome.

Finally, since our patient is known with ulcerative colitis, we also searched for a possible link between ulcerative colitis and BHD syndrome, but as far as we know no other cases of BHD syndrome have been reported in combination with inflammatory bowel disease. Throughout the years, a number of pathological conditions have been linked to BHD syndrome. Intestinal polyps have been described more than once in combination with BHD syndrome, but no association was demonstrated so far. The general consensus now is that patients with BHD syndrome are not at risk for colon polyps or colonic adenocarcinoma (6, 7). Due to the risk of renal cancers for individuals who have a family history of BHD syndrome, different surveillance programs have been suggested aimed at early recognition and treatment of cancer. A yearly MRI scan of the kidneys starting at the age of 20 years is probably best, but the exact role of

CT and ultrasonography has not been fully investigated (1).

In conclusion, we describe the case of a patient with the rare Birt-Hogg-Dubé syndrome, a probably underdiagnosed syndrome that is passed on to following generations in an autosomal dominant fashion. Recurrent pneumothoraces with cysts in the basis of the lungs rather than in the apical regions in association with renal neoplastic disease should alert for the possible presence of this syndrome.

References

1. Menko F.H., van Steensel M.A., Giraud S., Friis-Hansen L., Richard S., Ungari S., Nordenskjöld M., Hansen T.V., Solly J., Maher ER.: Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol*, 2009, 10: 1199-1206.
2. Pavlovich C.P., Grubb R.L., Hurley K., Glenn G.M., Toro J., Schmidt L.S., Torres-Cabala C., Merino M.J., Zbar B., Choyke P., Walther M.M., Linehan W.M.: Evaluation and management of renal tumors in the Birt-Hogg-Dubé syndrome. *J Urol*, 2005, 173: 1482-1486.
3. Khoo S.K., Giraud S., Kahnoski K., Chen J., Motorna O., Nickolov R., Binet O., Lambert D., Friedel J., Lévy R., Ferlicot S., Wolkenstein P., Hammel P., Bergerheim U., Hedblad M.A., Bradley M., Teh B.T., Nordenskjöld M., Richard S.: Clinical and genetic studies of Birt-Hogg-Dubé syndrome. *J Med Genet*, 2002, 39: 906-912.
4. Pavlovich C.P., Walther M.M., Eyler R.A., Hewitt S.M., Zbar B., Linehan W.M., Merino M.J.: Renal tumors in the Birt-Hogg-dubé syndrome. *Am J Surg Pathol*, 2002, 26: 1542-1552.
5. Weirich G., Junker K., Salles P.G.O., Lim S.D., de Peralta-Venturina M.N., Alvarado-Cabrero I., Jimenez R.E., Cabras A.D., Höfler H., Schubert J., Amin M.B.: Comparative genomic hybridization analysis of renal oncocytomas (RO), chromophobe renal cell carcinomas (CHRCC) and tumors with hybrid histology – Hybrid Oncocytic Tumors (HOT). *Modern Pathology*, 2002, 15: 186.
6. Adley B.P., Smith N.D., Nayar R., Yang X.J.: Birt-Hogg-Dubé syndrome: clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med*, 2006, 130: 1865-1870.
7. Zbar B., Alvord W.G., Glenn G., Turner M., Pavlovich C.P., Schmidt L., Walther M., Choyke P., Weirich G., Hewitt S.M., Duray P., Gabril F., Greenberg C., Merino M.J., Toro J., Linehan W.M.: Risk of renal and colonic neoplasm and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev*, 2002, 11: 393-400.