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Case report

HEMOPTYSIS AFTER COVID-19 AND THE IMPORTANCE OF DIFFERENTIAL DIAGNOSIS: BIRT-HOGG-DUBÉ SYNDROME

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Abstract

Birt-Hogg-Dubé syndrome is a genodermatosis of autosomal dominant inheritance characterized by mutations in the folliculin (*FLCN*) gene. There is an inappropriate inhibition/activation of a protein, the foliculin, which may cause tumor lesions in skin, renal and lung lesions; they could have more risk of developing pneumothorax compared to the normal population. A 38-year-old male patient with bronchial asthma who consulted for hemoptysis three weeks after recovery from COVID-19 infection. A chest tomography was requested, showing an air cyst in the left lower lobe. Physical examination shows evidence of thoracic skin lesions which a skin biopsy was performed on. The results were compatible with fibrofolliculoma. Differential diagnoses were proposed. A genetic disorder associated with skin lesions was suspected. A multi-genetic panel that includes BRCA1, BRCA2, TP53 and FLCN genes was requested, which reported the mutation of the *FLCN* gene in heterozygosis classified as pathognomonic of Birt-Hogg-Dubé syndrome. Patient is currently under clinical follow-up while genetic counseling was requested for relatives.

Key words: Birt-Hogg-Dubé syndrome, fibrofolliculoma, spontaneous pneumothorax

Resumen

Hemoptisis luego de COVID-19 y la importancia de los diagnósticos diferenciales: Síndrome de Birt-Hogg-Dubé

El síndrome de Birt-Hogg-Dubé es una genodermatosis de herencia autosómica dominante caracterizada por mutaciones en el gen foliculina (*FLCN*), donde existe inhibición/activación inapropiada de una proteína, la foliculina, que puede causar lesiones tumorales sistémicas, principalmente a nivel de la piel, renal y lesiones pulmonares, presentando mayor riesgo de desarrollar neumotórax en comparación con la población normal. Comunicamos el caso de un varón de 38 años con asma bronquial que consultó por hemoptisis 3 semanas después de la recuperación de la infección por COVID-19. Se solicitó una tomografía de tórax, que mostró un quiste aéreo en el lóbulo inferior izquierdo. Además, presentaba en el examen físico una lesión cutánea que fue biopsiada, presentando diagnóstico de foliculoma. Se plantearon diagnósticos diferenciales y ante la sospecha de probable desorden genético, un panel genético fue solicitado. Se confirmó síndrome de Birt-Hogg-Dubé ante el hallazgo de la deleción heterocigota que comprende el exón 1 del gen *FLCN* clasificada como patogénica. Actualmente el paciente se encuentra en seguimiento clínico mientras se solicitó estudio genético para familiares.

Palabras clave: síndrome de Birt-Hogg-Dubé, fibrofoliculoma, neumotórax espontáneo

Birt-Hogg-Dubé (BHD) syndrome is a genodermatosis of autosomal dominant inheritance characterized by genetic mutations in the *FLCN*

gene located in chromosome 17p11.2[1,2]. It encodes foliculin, a protein that through an inappropriate either inhibition or activation of the mTOR pathway may cause skin lesions, renal cancer, and characteristic lung lesions[3].

Clinically, it can be observed in the skin as fibrofolliculomas. Histologically, this is a lesion typically vertical or perpendicular to the epidermis, centered in the hair follicle, and that presents thin epithelial projections[4]. It should be noted that despite the fact that skin lesions are a warning sign for a dermatologist, not all patients with Birt-Hogg-Dubé syndrome present them.

Within the extracutaneous manifestations, there is a predisposition to present renal tumors which are characteristically bilateral and multifocal, mostly of the histological type of hybrid forms of oncocytoma and chromophobe carcinoma[4, 5].

Regarding pulmonary compromise, up to 80% of patients with this syndrome have lung cysts which may be asymptomatic but that could have up to 50 times more risk of developing pneumothorax compared to the normal population. The location of the cysts is mainly in the lung bases and at the subpleural level.

Clinical case

We present the case of a 38-year-old male with bronchial asthma treated with budesonide (160 mcg) and formoterol (4.5 mcg) and no history of smoking, who consulted for isolated hemoptysis event, three weeks after recovery from COVID-19 infection, with a presumptive diagnosis of post-COVID-19 pulmonary complication.

A chest tomography was requested, showing multiple bilateral, basal and adjacent to mediastinum air cyst. The biggest one (28 × 27 mm) in the left lower lobe (Fig. 1A). The lesions were followed up for 3 months, a period in which did not show changes in its size, nor association with interstitial lesions. Neither was evidence of compromise in computed tomography of the abdomen and pelvis with intravenous contrast, excluding kidney affectation. In this context, different diagnoses were proposed, such as Langerhans cell histiocytosis, lymphangioleiomyomatosis, lymphocytic interstitial pneumonia and BHD syndrome (Table 1).

During the follow-up of the patient, physical examination revealed firm, whitish, papular skin lesions 2 to 4 mm in diameter, asymptomatic throughout the thorax. An interconsultation with Dermatology was requested, who biopsed this lesion, resulting in a circumscribed tumor lesion with a central cystic cavity surrounded by concentrically arranged collagen fibers, compatible with the diagnosis of fibrofolliculoma (Fig. 1B).

Within the family history of the patient, there was a maternal aunt who presented spontaneous pneumothorax on three occasions; a maternal grandmother with recurrent adrenal carcinoma; and maternal grandfather with leukemia.

Given the suspicion of a genetic disorder associated with skin lesions and cystic lung lesions, a multi-genetic panel was requested (*BRCA1/BRCA2/TP53/FLCN*) resulting in a pathological variant of the *FLCN* gene (exon 1 deletion, heterozygous) associated with autosomal dominant BHD syndrome. This variant is a large deletion that occurs in

Figure 1 | A: Chest tomography. Left lower lobe air cyst (28 x 27 mm) B: Skin biopsy (Hematoxylin/eosin stain x40): circumscribed tumoral lesion with central cystic cavity surrounded by concentrically arranged collagen fibers

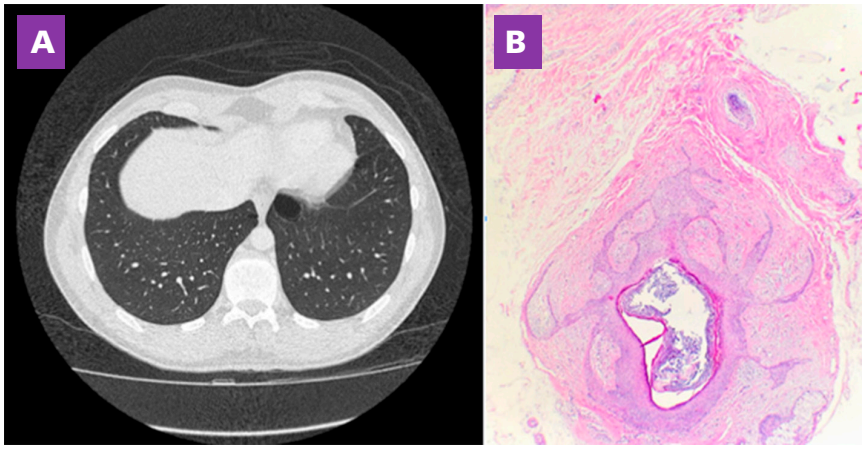

Table 1 | Differential diagnosis of Birt Hogg Dube syndrome

Disease	BHDS	LAM	LIP	Pulmonary LCH
Demography	Autosomal dominant disorder	Childbearing women	40-60 years old women	20-40 years old
Associated conditions	-	* No (sporadic-LAM) * TSC (tuberous sclerosis complex)	* Autoimmune disorders (Ej: Sdo. Sjogren, etc)	* Smoking *Tumours (Hodgkin's lymphoma)
Features of the cysts	*Variable size * Thin-walled * "Air-cuffing sign"	* Size <3 cm * Thin-walled * Rounded/oval	* Size <3 cm * Thin-walled * Variable shape	* Variable size and wall-thickness * Bizarre shapes
Distribution of the cysts	* Basis and adjacent to mediastinum +++	*Homogeneous	*Random, subpleural, basilar, perivascular	*Superior lobes +++
Other thoracic findings	* Pneumothorax	* Septal thickening * GGO *Lymphadenopathy * Pleural effusion * Pneumothorax	* Septal thickening * GGO * Centrilobular and subpleural nodules Lymphadenopathy	*Centrilobular and Peribronchial nodules *Cavitating nodules *Lymphadenopathy * Pneumothorax
Extrathoracic findings	* Cutaneous fibrofolliculomas * Renal tumours	*Retroperitoneal lymphadenopathy * Renal angiomyolipomas * Chylous ascites * Uterine fibroids * TSC (tubers, etc.)		* Only in systemic LCH (lytic lesions in flat bones, etc.)

LCH: Langerhans cell histiocytosis; LAM: lymphangioleiomyomatosis; TSC: tuberous sclerosis complex; LIP: lymphocytic interstitial pneumonia; BHDS: Birt Hogg Dube syndrome; AIDS: acquired immune deficiency syndrome; GGO: ground-glass opacities
The differential diagnosis in our patient led us to think of BHDS, as he was a non-smoker young man, with pulmonary cysts of variable size, thin wall, bilateral, with basal perimediastinal location, without any associated conditions as TSC, autoimmune disorders or tumors

a non-coding region of the *FLCN* gene. It does not change the encoded amino acid sequence of the *FLCN* protein. Studies have shown that a similar copy number variant alters *FLCN* gene expression[6]. For these reasons, this variant has been classified as pathogenic. In this context, the molecular finding explained the clinical condition. Genetic counseling was requested from relatives: both the grandmother and the aunt were diagnosed with the disease. His mother, during the follow-up process, underwent a chest tomography that showed cystic lesions in the lungs, but the genetic study is still in process. These patients are currently under clinical follow-up, and family screening is going on.

The patient did not repeat new episodes of hemoptysis.

Discussion

The follow-up of patients after suffering from SARS-CoV-2 virus disease has led us to carry out imaging studies that can generate the diagnosis of incidentalomas, which require a differential diagnosis approach and follow-up to carry out an early treatment if necessary[7].

The management of BHD syndrome must be carried out by a multidisciplinary group of physicians. The two essential components of

the clinical follow up of the BHD syndrome are the management of recurrent spontaneous pneumothorax and screening of kidney tumors. The high probability of pneumothorax is well known, nearly 30% will have it as personal medical history before 40 years old. The optimal method and timing of treating BHD associated pneumothorax is unclear and controversies exist as randomized prospective trials are lacking. Some reviews suggested that BHD-associated pneumothorax should be managed in the same way as in the general population; others argue that with the lower likelihood of spontaneous resolution and recurrence, pneumothoraxes should be managed more aggressively[8, 9].

Renal tumors are usually multiple and bilateral, frequently appearing at a median age of 30 to 40 years. In comparison with most inherited renal cancers syndromes, that are commonly related to a single histologic tumor type, BHD syndrome is related to a wide range of tumor histologies, most typically chromophobe tumors and hybrid chromophobe/oncocytic tumors. Clear cellular carcinoma, papillary carcinoma, and blended-kind carcinoma can also occasionally be seen. Some experts recommend abdominal imaging starting at age 21 (or following diagnosis) and at least every 36 months until a mass is identified, at which time interval imaging is determined in the individual patient based upon the size and growth rate of the tumor. Ultrasonography may miss small isoechoic renal masses, and, therefore, computed tomography imaging or magnetic resonance imaging to minimize radiation exposure should be used when possible[5]. Favorably, the reported patient did not present pneumothorax or renal involvement.

In conclusion, a new medical paradigm has emerged as a result of the SARS-CoV-2 virus pandemic in a number of ways. The increased neumological follow-up made possible early diagnosis of pathologies less common in everyday practice. This case serves as an illustration of dealing with a challenging pathology in terms of the differential diagnosis of cystic lung diseases. The patient and his family should be treated in a multidisciplinary manner focusing on the treatment of potential complications, avoiding late diagnosis of possible oncological pathology, and providing genetic counseling for the patient and his family[10].

It is interesting to note that neither Argentina's epidemiological statistics nor international management guides specify the screening method, frequency, or ideal age for this condition; which provides an excellent opening for future research.

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Conflict of interest: None to declare

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