

Thoracic CT Findings in Birt-Hogg-Dubé Syndrome

Prachi P. Agarwal¹
 Barry H. Gross¹
 Ben J. Holloway²
 Jean Seely³
 Paul Stark⁴
 Ella A. Kazerooni¹

Keywords: Birt-Hogg-Dubé syndrome, CT, lung cysts, thoracic imaging

DOI:10.2214/AJR.10.4757

Received April 6, 2010; accepted after revision June 17, 2010.

P. P. Agarwal was awarded a grant from the GE-Radiology Research Academic Fellowship (GERRAF) program sponsored by the Association of University Radiologists and was awarded a grant from the National Psoriasis Foundation.

¹Department of Radiology, Division of Cardiothoracic Radiology, University of Michigan Health System, 1500 E Medical Center Dr., Ann Arbor, MI 48109. Address correspondence to P. P. Agarwal (prachia@med.umich.edu).

²Department of Radiology, University Hospital Birmingham, NHS Foundation Trust, Birmingham, UK.

³Department of Radiology, The Ottawa Hospital, Ottawa, ON, Canada.

⁴VA San Diego Healthcare System, San Diego, CA.

AJR 2011; 196:349–352

0361–803X/11/1962–349

© American Roentgen Ray Society

OBJECTIVE. Birt-Hogg-Dubé syndrome manifests in the thorax as lung cysts. The purpose of this article is to describe the CT characteristics of cysts in patients with Birt-Hogg-Dubé syndrome and to note other thoracic findings.

MATERIALS AND METHODS. The thoracic CT examinations of 17 patients with Birt-Hogg-Dubé syndrome were reviewed retrospectively for the presence, anatomic distribution (upper lung predominant, lower lung predominant, or diffuse), extent (size, number), and morphology (shape, wall thickness) of cysts. Any additional thoracic findings were also noted.

RESULTS. The study population consisted of 13 women (76%) and four men (24%) with a mean age of 50.2 ± 15.2 years. Two patients (12%) had normal findings on CT. Fifteen patients had cystic lung disease, all of whom had more than one cyst. Most patients had bilateral (13/15, 87%) and lower lung–predominant cysts (13/15, 87%). The cysts varied in size from 0.2 to 7.8 cm. The largest cysts were located in the lower lobes of 14 of 15 patients (93%). Of the nine patients with large cysts, most had at least one multiseptated cyst (7/9, 78%). Five of 15 patients (33%) had more than 20 cysts. Cyst shape varied among the 15 patients and also within individual patients (10/15, 67%) ranging from round to oval, lentiform, and multiseptated. Cysts showed no central or peripheral predominance.

CONCLUSION. Discrete thin-walled cysts in patients with Birt-Hogg-Dubé syndrome are more numerous and larger in the lower lobes and vary in size and shape. Large lung cysts are frequently multiseptated. These features may aid in differentiating Birt-Hogg-Dubé syndrome from other more common cystic lung diseases.

First described in 1977, Birt-Hogg-Dubé syndrome is an autosomal-dominant multiorgan systemic disorder that manifests as cutaneous lesions, renal tumors, and spontaneous pneumothorax secondary to pulmonary involvement [1, 2]. The classically described skin findings are the triad of hamartomas of the hair follicles (fibrofolliculomas), tumors of the hair disk (trichodiscomas), and skin tags (acrochordons). Fibrofolliculomas are the most characteristic finding of Birt-Hogg-Dubé syndrome and typically appear as multiple, 2- to 4-mm, whitish, smooth, dome-shaped papules on the head, neck, face, and upper trunk in patients in the third to fourth decade of life [2, 3]. Skin tags alone are not diagnostic because they can be seen in the general population [3]. The renal tumors in patients with Birt-Hogg-Dubé syndrome are often multiple and bilateral and include hybrid chromophobe oncocytomas (50%), chromophobe carcinomas (34%), clear cell carcinomas (9%), on-

cocytomas (5%), and papillary renal cell cancers (2%) [4].

Birt-Hogg-Dubé syndrome is a rare entity, although the precise prevalence of this disorder is difficult to estimate. The relationship between cystic lung disease and pneumothorax in patients with Birt-Hogg-Dubé syndrome is well known and was first described by Toro et al. [5]. Lung cysts have been described in most patients, 77–89%, with Birt-Hogg-Dubé syndrome [6], whereas the incidence of pneumothorax has been estimated to be approximately 33–38% [6]. The Birt-Hogg-Dubé gene locus has been mapped to 17p11.2 [7]; the gene product is thought to be a tumor suppressor protein termed “folliculin” that may play an important role in lung tissue and is expressed in stromal cells and type 1 pneumocytes [8]. This could explain the propensity of these patients to form lung cysts. Although the association of Birt-Hogg-Dubé syndrome with lung cysts and pneumothorax is well established, few studies describe the

thoracic CT appearance of this uncommon entity, with the articles in the radiology literature limited to sporadic case reports or inclusion in review articles [9–13].

It is important for radiologists to be aware of Birt-Hogg-Dubé syndrome as a cause of spontaneous pneumothorax and lung cysts because the former may be the initial clinical manifestation of this entity and the latter may be found incidentally or in patients undergoing cancer staging evaluations for a renal mass. In this study, we describe the thoracic CT appearance of patients with confirmed Birt-Hogg-Dubé syndrome to elucidate features that may help differentiate this condition from other more well-known cystic lung diseases, such as lymphangiomyomatosis and Langerhans cell histiocytosis [14, 15].

Materials and Methods

A computerized medical record search of patients with a diagnosis of Birt-Hogg-Dubé syndrome was performed at our institution for the years 1999–2009, yielding four cases. Thirteen additional cases were contributed by colleagues from three other institutions who recalled seeing cases of Birt-Hogg-Dubé syndrome in their practice. This study was approved by our institutional review board, with a waiver of informed consent. The diagnosis of Birt-Hogg-Dubé syndrome was established in all patients by genetic testing.

Patient Characteristics

The mean age of the 17 patients, 13 women (76%) and four men (24%), at the time of the thoracic CT examination was 50.2 ± 15.2 years. Four patients were smokers or had a history of smoking, three patients had never smoked, and smoking history was not available in the remaining 10 patients.

Radiologic Evaluation

Because the study was retrospective, the imaging protocol was not standardized and a variety of CT scanners and techniques were used. The CT scans of the study group included nine conventional thoracic CT examinations and eight high-resolution CT (HRCT) examinations. Standard thoracic CT studies were performed using various slice thicknesses, ranging from 2.5 to 7 mm. Five were performed without and four were performed with IV contrast administration. The HRCT scans were obtained using volumetric technique and a 1.25-mm slice thickness in four patients and incremental scanning with a 10-mm interscan gap and 1-mm slice thickness in four patients.

Nine patients had a known diagnosis of Birt-Hogg-Dubé syndrome at the time of thoracic CT,

TABLE 1: Lung Cyst Characteristics on Thoracic CT of Patients With Birt-Hogg-Dubé Syndrome

Lung Cyst Characteristics	No. (%) of Patients (n = 15)
Bilateral distribution	13 (87)
Craniocaudal distribution	
Lower lung	13 (87)
Upper lung	1 (7)
No predominance	1 (7)
Axial distribution	
No predominance	15 (100)
Largest cyst distribution	
Lower lung	14 (93)
Costophrenic sulcus involved	8 (53)
Size	
Large (> 2 cm)	9 (60)
Medium (1–2 cm)	5 (33)
Small (< 1 cm)	1 (7)
Number	
Numerous (> 20)	5 (33)
Several (10–20)	3 (20)
Few (< 10)	7 (47)
Shape	
Multiseptated	7 (47)
Various shapes in individual patients	10 (67)

whereas two were scanned for other reasons (i.e., abnormal findings on an initial chest radiograph in one patient and cancer staging in a patient with known endometrial cancer without known renal malignancy). The clinical indication for the initial thoracic CT examination was not available for the remaining six patients. Chest radiographs were not available for review.

The CT examinations were reviewed by two thoracic radiologists, with specialized thoracic imaging experience of 6 years and more than 20 years, as a consensus panel for the presence, anatomic distribution, extent, and morphology of lung cysts.

Cyst distribution was classified for both craniocaudal distribution (as upper lung predominant, lower lung predominant, or diffuse) and axial distribution (as central, peripheral, or diffuse). Involvement of the costophrenic sulci was recorded. The total number of lung cysts in each patient was recorded as few if there were fewer than 10 cysts, several if there were 10–20, or numerous if there were more than 20. The size of the cysts was categorized as small if the cysts were less than 1 cm,

medium-sized if they were 1–2 cm, and large if they were greater than 2 cm. Size was measured as maximum diameter.

Cyst morphology, including the shape of the cyst (round, ovoid, and multiseptated) and the thickness of the cyst wall (wall: not identifiable, thin [< 3 mm], or thick [> 3 mm]), was recorded. Any other associated abnormalities such as nodules, ground-glass opacities, and pleural effusions or pneumothoraces were also noted.

Results

Thoracic CT Findings

The thoracic CT findings are summarized in Table 1. Cystic lung disease was present in 15 of 17 patients (88%), and two patients had normal findings on CT. Cysts were bilateral in 12 of 15 patients. Of the three patients with unilateral cysts, one had a surgical staple line in the opposite lung from a resected cyst, implying bilateral involvement. Hence, overall 13 of 15 patients, or 87%, had bilateral involvement. The cysts were lower lung predominant in 13 of 15 patients (87%) (Fig. 1). Of the two patients without lower lung predominance, one had unilateral upper lung cysts (1/15, 7%) (Fig. 2). This patient had a history of cyst removal at the same side, although the precise operative details regarding the site of cyst resection were not available. A definite staple line was not seen on CT, which was performed using incremental technique with a 10-mm interscan gap. The other patient had only two cysts, a large lower lung cyst and a small upper lung cyst, with no clear distribution predominance. If the largest cyst were interpreted as an indicator of predominant distribution, this case would be characterized as lower lobe predominant, increasing the lower lobe predominance to



Fig. 1—66-year-old woman with Birt-Hogg-Dubé syndrome. Coronal reformatted image from volumetric high-resolution CT of chest reveals lower lung-predominant thin-walled cysts that vary in size and shape.

CT of Birt-Hogg-Dubé Syndrome

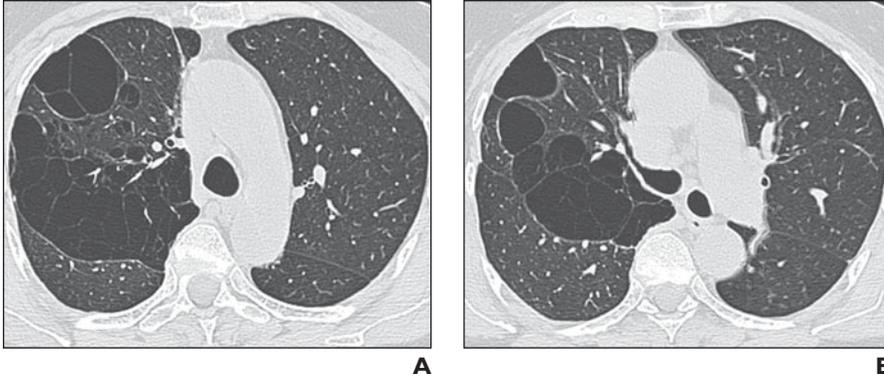


Fig. 2—68-year-old woman with Birt-Hogg-Dubé syndrome. Patient had history of prior cyst removal, but operative details were lacking. **A and B**, Axial high-resolution CT images show multiple confluent and multiseptated unilateral cysts in upper lung distribution.

14 of 15 patients, or 93%. With regard to the axial distribution, the cysts were diffuse with no central or peripheral predominance. The lung at the costophrenic sulci was involved in eight of 15 patients (53%) (Fig. 3).

In terms of the number of cysts, five of 15 patients (33%) had more than 20 cysts, three (20%) had 10–20 cysts, and seven (47%) had fewer than 10 cysts. The cysts ranged in size from 0.2 to 7.8 cm. The largest cyst in all cases except one case was found in the lower lobes (Fig. 2). One patient (1/15, 7%) had subtle CT findings, with cysts measuring up to only 0.7 cm; however, the largest cyst in all other patients was medium sized, measuring 1–2 cm (5/15, 33%), or was large, measuring more than 2 cm (9/15, 60%).

The morphology of the lung cysts was variable among the patients and also within individual patients (Fig. 1). Cyst morphology ranged from round to oval and lentiform. Large cysts, particularly those in the lower lungs, had a lobulated multiseptated appearance (Fig. 4). Of the nine patients with

cysts larger than 2 cm, seven patients had a multiseptated cyst. Cyst shape was variable in 10 of 15 patients (67%) and was relatively uniform (with round cysts) in five patients (33%). The cyst walls were perceptible, thin, and uniform in all patients.

No lung nodules, ground-glass opacity, septal thickening, honeycombing, or airway abnormalities were found. One patient presented with a pneumothorax that was seen on CT, and another patient had bilateral small pleural effusions.

Discussion

Few articles in the radiology literature describe imaging findings of patients with Birt-Hogg-Dubé syndrome and those that do primarily focus on the renal manifestations. However, it is important for radiologists to be aware of this syndrome because the skin manifestations are benign and may go unnoticed and the first clinical presentation might be a spontaneous pneumothorax or incidental lung cysts at the lung base found on an ab-

dominal CT examination for the assessment of a renal mass. Although Birt-Hogg-Dubé syndrome is a rare disorder, it may be under-recognized because of its variability of clinical expression [16].

The distribution and morphology of the lung cysts in Birt-Hogg-Dubé syndrome may be useful to differentiate this syndrome from other, better known cystic lung diseases. However, this hypothesis needs to be proven by additional studies directly comparing the patterns of different cystic lung diseases with those of Birt-Hogg-Dubé syndrome. The presence of ancillary findings such as renal tumors and clinical presentation of dermatologic findings can be helpful clues to the diagnosis. Other more commonly encountered cystic lung diseases include Langerhans cell histiocytosis, lymphangioleiomyomatosis, lymphocytic interstitial pneumonia (LIP), and *Pneumocystis jiroveci* pneumonia (PJP). The latter two conditions are usually suspected in specific clinical scenarios. For instance, a clinical history of an underlying immunologic process, such as Sjögren syndrome, raises the possibility of LIP, which may also show ancillary parenchymal abnormalities such as ground-glass opacity and small nodules [10]. A disease along the same continuum of abnormality as LIP and also associated with collagen vascular diseases is follicular bronchiolitis, which may manifest as lung cysts [17]. Patients with PJP typically are immunocompromised and have associated ground-glass opacities [18].

In previous reports, lymphangioleiomyomatosis, cystic lung disease associated with tuberous sclerosis has been suggested to be the closest mimic of Birt-Hogg-Dubé syndrome radiologically [10]. Both entities involve the lungs and kidneys, although in lymphangioleiomyomatosis the renal lesions



Fig. 3—58-year-old woman with Birt-Hogg-Dubé syndrome. **A–C**, Axial chest high-resolution CT images through upper lungs (**A**), through lower lungs (**B**), and at costophrenic sulci (**C**) show lower lung-predominant cyst with involvement of costophrenic sulci.

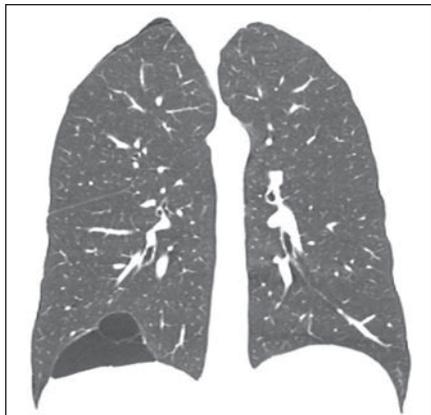


Fig. 4—38-year-old woman with Birt-Hogg-Dubé syndrome and tiny right apical pneumothorax. Coronal reformat image from volumetric high-resolution CT of chest shows unilateral lower lung involvement with large multiseptated cyst.

are fat-containing angiomyolipomas. Both conditions also tend to involve the lungs at the costophrenic sulci. Our data indicate that the cysts of Birt-Hogg-Dubé syndrome usually vary in size and shape and are lower lung predominant in distribution, whereas the cysts in lymphangiomyomatosis typically are described to be more uniform in size, round, and diffuse in distribution. This variability of shape and size as well as the lower lung predominance seen in our study population is similar to that described in the literature in a previous case series of 12 subjects with Birt-Hogg-Dubé syndrome [13]. The cysts in lymphangiomyomatosis are small to medium sized compared with the large cystic lesions, which are often multiseptated, seen in patients with Birt-Hogg-Dubé syndrome.

Distinction between Birt-Hogg-Dubé syndrome and Langerhans cell histiocytosis is relatively straightforward because Langerhans cell histiocytosis is an upper lung-predominant disease process that includes nodules in addition to lung cysts, both of which are usually irregular in shape [15].

Cystic changes have also been described in desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease [14]. These diseases share histologic features and often are considered to be along the same disease spectrum. Differentiation of these entities from Birt-Hogg-Dubé syndrome is straightforward because the cystic changes in these

diseases are accompanied by ground-glass opacities or centrilobular nodules and because the cysts lack a discernible wall [14].

Bullous lung disease with paraseptal emphysema can present with large and gas lucencies of various shapes, although it is typically associated with other manifestations of emphysema and is upper lung predominant. In our series, we found the largest cysts to be located in the lower lungs.

There are a few limitations to our study. Our study is limited by the small number of patients but the rarity of this syndrome makes it difficult to gather a larger series. Various scanning techniques and parameters were used, and the cases were acquired from multiple institutions utilizing different acquisition techniques. This limitation is inherent to the rarity of the disease and the retrospective nature of the study. Additionally, the clinical information regarding smoking and details about prior surgeries was lacking in some cases. The lack of operative details could potentially have influenced the perceived distribution of the disease process, resulting in incorrect categorization. Finally, we did not have chest radiographs to review, even though radiography is usually the first imaging test performed in most patients.

In summary, it is important to be aware of the thoracic CT findings of Birt-Hogg-Dubé syndrome: usually randomly scattered lower lung-predominant cysts of various sizes and shapes. The large dominant cysts tend to be located in the lung bases and may be multiseptated. Birt-Hogg-Dubé syndrome may manifest as a spontaneous pneumothorax or as lung cysts found at the lung bases in patients with a solid renal mass, in which case the interpreting radiologist may be the first to suggest the diagnosis and initiate workup.

References

1. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* 1977; 113:1674–1677
2. Toro JR, Glenn G, Duray P, et al. Birt-Hogg-Dubé syndrome: a novel marker of kidney neoplasia. *Arch Dermatol* 1999; 135:1195–1202
3. Choyke PL, Glenn GM, Walther MM, Zbar B, Linehan WM. Hereditary renal cancers. *Radiology* 2003; 226:33–46
4. Pavlovich CP, Walther MM, Eyler RA, et al. Renal tumors in the Birt-Hogg-Dubé syndrome. *Am J*

- Surg Pathol* 2002; 26:1542–1552
5. Toro JR, Pautler SE, Stewart L, et al. Lung cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dubé syndrome. *Am J Respir Crit Care Med* 2007; 175: 1044–1053
6. Toro JR, Wei MH, Glenn GM, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. *J Med Genet* 2008; 45:321–331
7. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet* 2001; 69:876–882
8. Warren MB, Torres-Cabala CA, Turner ML, et al. Expression of Birt-Hogg-Dubé gene mRNA in normal and neoplastic human tissues. *Mod Pathol* 2004; 17:998–1011
9. Ayo DS, Aughenbaugh GL, Yi ES, Hand JL, Ryu JH. Cystic lung disease in Birt-Hogg-Dubé syndrome. *Chest* 2007; 132:679–684
10. Souza CA, Finley R, Müller NL. Birt-Hogg-Dubé syndrome: a rare cause of pulmonary cysts. *AJR* 2005; 185:1237–1239
11. Grant LA, Babar J, Griffin N. Cysts, cavities, and honeycombing in multisystem disorders: differential diagnosis and findings on thin-section CT. *Clin Radiol* 2009; 64:439–448
12. Gupta P, Eshaghi N, Kamba TT, Ghole V, Garcia-Morales F. Radiological findings in Birt-Hogg-Dubé syndrome: a rare differential for pulmonary cysts and renal tumors. *Clin Imaging* 2007; 31:40–43
13. Tobino K, Gunjia Y, Kurihara M, et al. Characteristics of pulmonary cysts in Birt-Hogg-Dubé syndrome: thin-section CT findings of the chest in 12 patients. *Eur J Radiol* 2009 Sep 24 [Epub ahead of print]
14. Koyama M, Johkoh T, Honda O, et al. Chronic cystic lung disease: diagnostic accuracy of high-resolution CT in 92 patients. *AJR* 2003; 180:827–835
15. Hartman TE. CT of cystic diseases of the lung. *Radiol Clin North Am* 2001; 39:1231–1244
16. Menko FH, van Steensel MA, Giraud S, et al.; European BHD Consortium. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol* 2009; 10:1199–1206
17. Pipavath SJ, Lynch DA, Cool C, Brown KK, Newell JD. Radiologic and pathologic features of bronchiolitis. *AJR* 2005; 185:354–363
18. Boiselle PM, Crans CA Jr, Kaplan MA. The changing face of *Pneumocystis carinii* pneumonia in AIDS patients. *AJR* 1999; 172:1301–1309