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Mini-invasive Surgery

Case Report

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A rare cause of spontaneous pneumothorax: radiological findings and surgical approach

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Abstract

Birt-Hogg-Dubé Syndrome (BHDS) is a rare genetic condition that affects the connective tissue of kidneys, lungs, and skin, causing an aberration in the proteic folliculin (FLCN) pathway. In the lungs, the altered FLCN is found in the outer part of the alveoli, particularly in the lower lobes, causing parenchymal weakness and subsequent cystic degeneration. Because of its rarity, a comprehensive management protocol is not available yet. We present a case of a man with left recurrent pneumothorax due to bilateral multiple bullae, as revealed by a preoperative chest Computed Tomography (CT) scan. Given the characteristic radiological features of BHDS, the CT scan should always be considered for the differential diagnosis to exclude other more common cystic diseases, such as lymphoid interstitial pneumonia, Langerhans cell histiocytosis, or lymphangioleiomyomatosis. Considering the different options suitable for bullous diseases, we decided to treat the patient with a pleural abrasion through a biportal Video-Assisted Thoracic Surgery approach and sterile talc pleurodesis. No more spontaneous episodes were reported one year later. Bullectomy was not carried out because the diffuse cystic intraoperative pattern would never be solved by marginal parenchymal resections. Relapsing spontaneous pneumothorax could be a spy of a hidden genetic disease (such as BHSD), and a CT scan should be considered case-by-case because it may provide crucial information regarding the overall lung pattern. In such cases, pleural abrasion with talc pleurodesis is a considerably effective treatment.

Keywords: Birt-Hogg-Dubé syndrome, pneumothorax, computed tomography, pulmonary cysts

INTRODUCTION

Birt-Hogg-Dubé Syndrome (BHDS) is a genetic disease equally affecting men and women with a germline autosomal dominant mutation of the folliculin (*FLCN*) gene, a tumor suppressor gene coding for a protein called FLCN[1-3]. This modifies the normal signal of the mTOR growing pathway. BHDS commonly causes cutaneous alterations, renal tumors, and cystic lung lesions[1,3]. In fact, more than 80% of patients with BHDS develop bilateral pulmonary cysts during their lifetime, putting them at risk for recurrent spontaneous pneumothorax (estimated recurrence rate of 75%-82%)[4].

From a radiological point of view, BHDS is characterized by a predominant basal, subpleural distribution of the cysts, which are usually thin-walled and variable in size ranging from a few millimeters to several centimeters[1-4].

CASE REPORT

A 63-year-old male was transferred to the Emergency Department (E.D.) of our tertiary center because of dyspnea. A pneumothorax affecting the left apex and base was diagnosed at a chest X-ray [Figure 1A].

In his clinical history, two previous homolateral episodes of pneumothorax were reported and treated with drainage. Moreover, he referred to being affected by several comorbidities, such as previous colon cancer surgically treated, obstructive sleep apnea syndrome, obesity, hypertension, and hypothyroidism. He denied any drug abuse or tobacco smoke.

Two days after hospitalization, due to the worsening of the clinical conditions, a second chest X-ray was performed, and it demonstrated an increase of the pneumothorax with partial collapse of the left lower lobe [Figure 1B]. Generally, an X-ray showing a recidivant apico-basal episode of pneumothorax is sufficient to consider surgery to be strictly indicated, especially if the patient is symptomatic, as in the case we reported.

Therefore, to better characterize such findings, we preferred to execute a chest Computed Tomography (CT). The CT scan confirmed the severe pneumothorax, but it also revealed the presence of multiple bilateral cysts ranging from a few millimeters to 4 cm, mainly distributed in the lower lobes in the subpleural regions and along the fissures [Figure 2A-C]; the partial collapse of the left lower lobe was also clear [Figure 2A and C].

Given this evidence, a more thorough anamnesis was done, and it was revealed that the patient was previously diagnosed with BHDS through a specific genetic test. He came from another peripherical hospital and brought just a few clinical documents, so electronic files were unavailable.

Subsequently, the patient underwent surgical exploration through a biportal Video-Assisted Thoracic Surgery (VATS) approach. In this case of recidivant pneumothorax, we explored the chance to perform a bullectomy. Multiple strong pleuro-parietal and mediastinal adhesions involving the upper lobe and the presence of numerous diffuse cysts in both lobes, mainly affecting the lower segments, were identified [Figure 3].

Due to these findings, we did not remove the cysts because we could not have been resolutive. Moreover, no intraoperative air leak was registered. Consequently, electrical cauterization of the parietal pleura followed by the instillation of 2 gr of sterile talc was carried out. We carefully spread the sterile talc through an

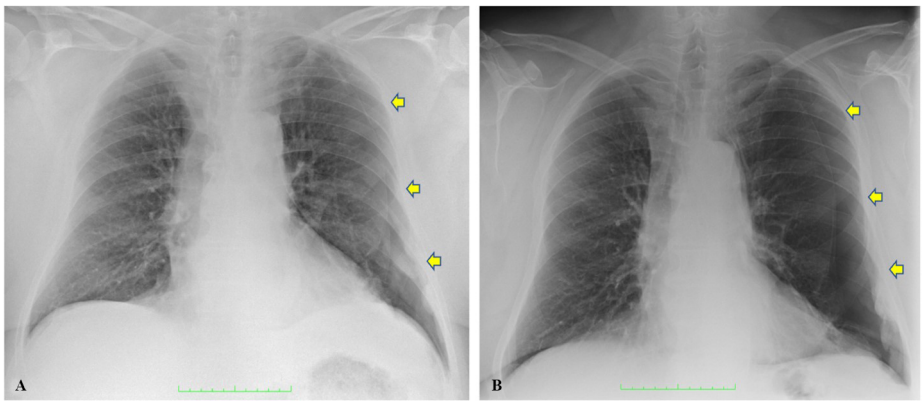

Figure 1. (A) The chest X-ray of the 63-year-old patient admitted to the E.D. well-showing the left pneumothorax extending from the apex to the base (yellow arrows); in (B), the chest X-ray performed two days later showed the increase of the pneumothorax.

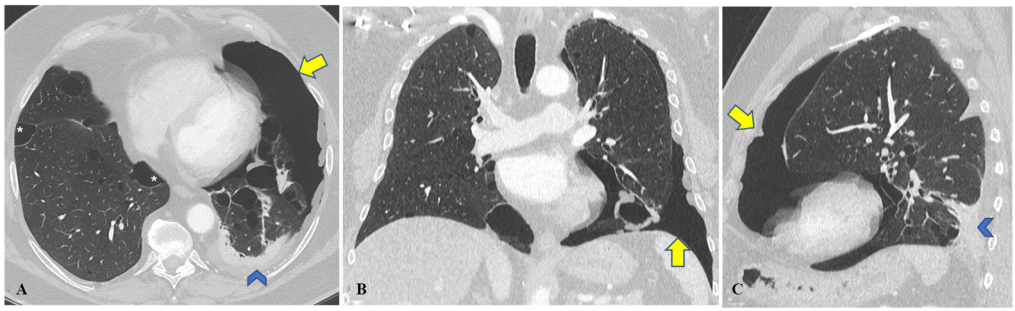

Figure 2. Axial (A), coronal (B), and sagittal (C) chest CT images of the 63-year-old patient confirm the great extension of the spontaneous left pneumothorax (yellow arrows in A, B, and C). Moreover, it is highlighted the partial collapse of the left lower lobe (blue arrowhead in A and C). It is shown multiple bilateral cysts with a predominant subpleural distribution in the lower lobes and along the fissures (white asterisks in A).

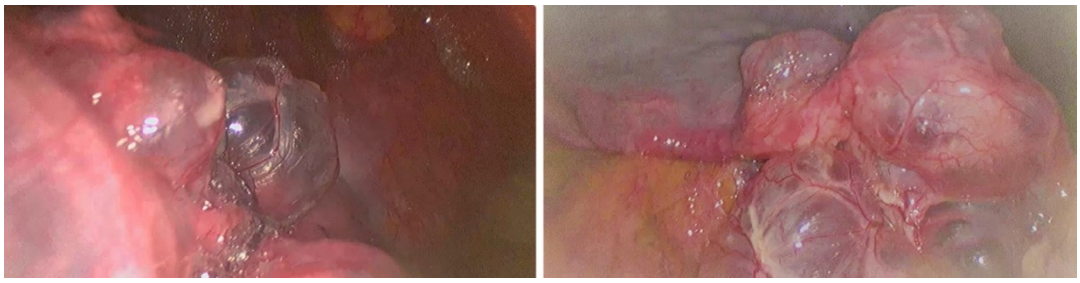

Figure 3. Intraoperative images of a cyst due to Birt-Hogg-Dubé syndrome: the frailty of lung parenchyma affected by folliculin (FLCN) mutation is related to the thin wall of the cysts.

aerosolizing device, which helped the ubiquitarian distribution in the pleural cavity and a homogenous inflammatory reaction. We especially avoided any talc accumulation during distribution in the pleural cavity because of the risk of granuloma formation.

After completing the hemostasis and pulmonary re-expansion, two apical drains were placed to gain better lung inflation in both chest sides (anterior wall and in the back) to ameliorate the mechanical adhesion of

pleural layers. We removed the drains on the third postoperative day; after two days of suction, there was no evidence of postoperative air leakage. The procedure has been well tolerated by the patient: no fever or any other inflammatory reaction was registered during the hospital length.

No postoperative complications occurred, and the patient was discharged after five days. One year later, the patient is in good health. He did not have any further episodes of pneumothorax or any other signs or symptoms of lung function decreasing, so we did not further investigate his lung capacity. Moreover, it was previously reported that BHDS does not deteriorate lung function in terms of lung capacity (FEV1, FVC, Tiffenau's ratio)[5]. We decided to postpone a contralateral treatment because no previous episodes of pneumothorax were reported there. Moreover, the patients did not develop any other complications, especially no tumors were discovered in one year of follow-up; we are continuing to follow them with other Specialists. We discharged the patients with a personalized surveillance plan, as guidelines suggest. The plan is shown in Table 1. The thyroid, colon, kidneys, and cutis need to be investigated (to avoid the risk of cancer development). In particular, the cutis could hide a growing melanoma.

DISCUSSION

Thus, we hereby report the clinical, radiological, and surgical findings of a case of successful surgical treatment of pneumothorax due to BHDS. The rupture of lung cysts is the base mechanism causing recurrent pneumothorax (RP) in such cases. The high prevalence of RP must be discussed, considering the role of FLCN germline mutation in the lung parenchyma. FLCN is a classic tumor suppressor gene involved in the AKT-mTOR pathway, and it is also implicated in the dysregulation of cell-to-cell interaction, decreasing the adhesion between epithelial cells[10]. It has been previously assessed that the aberrant expression of E-cadherin and claudin-1 induced a weaker intercellular interaction. Notably, in FLCN-deficient murine models, the aberrant FLCN induces an impaired lung structure due to monolayer Alveolar Epithelial Cells type II apoptosis and alveolar space enlargement. In addition, cell apoptosis decreases alveolar phospholipids, increasing alveolar surface tension and progressively maintaining this pathogenetic enlargement mechanism[10,11].

Lung bullous diseases encompass several different diagnoses that must be taken into consideration.

In fact, among the main differential diagnoses, lymphoid interstitial pneumonia, Langerhans cell histiocytosis, and lymphangioleiomyomatosis (LAM) should certainly be considered[12-14]. The main characteristics allowing the distinction of these diseases are summarized in Table 2.

In BHDS and other cases of spontaneous pneumothorax, while the first episode of pneumothorax is usually conservatively treated, surgery is mostly recommended for patients with a second episode. There are several treatments to manage these cases. According to the literature reported [Table 3], different and valuable experiences have been previously published, and the optimal management for each case must be calculated in a case-by-case discussion between Specialists. The most diffused procedures, with advantages, disadvantages, and recurrence percentages, are reported in Table 3.

The VATS approach is certainly a standard validated treatment. Mini-invasive surgery usually resolves pneumothorax with a lower incidence of postoperative morbidity and a good response compared to thoracotomy.

Table 1. Proposed follow-up

Organ	Surveillance
Kidney[6-8]	MRI every two years
Fibrofolliculomas[6]	Annual full skin examination
Thyroid[6]	Annual endocrinological examination
Gut[9]	Annual colonoscopy

Despite this, in bullous disease, surgeons must also consider impaired lung parenchyma. Because of the frailty of lung tissue and the high number of cysts, bullectomy is poorly effective, so it is generally not performed or, when adopted, it is not definitive.

Intraoperative chemical pleurodesis could be used to enforce the attachment of pleural layers reducing further episodes of pneumothorax, and this procedure, alone or in combination with surgery, has already been employed in BHDS[28,29]. Pleurodesis is commonly obtained with the instillation of sterile talc in the cavum after pleural abrasion[30]. A more recent treatment available is the total pleural coverage, employed especially in LAM. An oxidative regenerated cellulose mesh or a polyglycolic acid felt is placed in the visceral pleura covering the entire lung surface. Then a fibrin glue attaches the layers[31,32]. This treatment was not suitable in our center, so we decided to use pleurodesis.

There is a large expertise among tertiary centers on pleurodesis. Caustication is usually adopted in RP. Talc pleurodesis is diffused as a technique that prevents malignant pleural effusion. In our case, electrical caustication and talc pleurodesis are diffusely and successfully adopted. In this case, one year after surgery, with no recurred episodes, we can maybe be confident to conclude that the selected procedure was correctly suitable for our patients.

In conclusion, although rare, BHDS should be considered among the differential diagnoses in patients with multiple cysts at imaging, especially in the case of spontaneous pneumothorax. Radiologists should support clinicians and surgeons in the identification of this entity, and the proper therapeutic approach should be decided on a case-by-case basis according to the severity of the pattern. When bullectomy appears to be non-resolutive, and there is no evidence of intraoperative air leak, marginal resection could be superseded. In such cases, a mini-invasive electrical caustication and talc pleurodesis might be taken to be considered as a valuable treatment.

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Table 2. Main characteristics of BHDS and its principal differential diagnoses

Main cystic pulmonary diseases	Age (years)	Gender (F:M)	Cyst features and distribution	Additional pulmonary findings	Additional extrapulmonary findings
BHDS[1-4]	20-40	1:1	Lower lobes; subpleural also along fissures	/	Cutaneous fibrofolliculomas; renal cancer
LIP[12]	50-60	2:1	Mid to lower lobes	Interstitial thickening; pulmonary nodules; ground-glass areas	Association with autoimmune diseases such as Sjogren, SLE, RA
LCH[13]	20-40	1:1	Upper lobes	Nodules; ground glass; mosaic attenuation; interstitial thickening	Association with ALL and AML
LAM[14]	Early 30	Basically, a female disease	Scattered	Small nodules; pleural effusion; pericardial effusion	Lymphangioleiomyomas and renal angiomyolipomas
LCDD[15]	40-60	Slight male predominance	Diffuse; perivascular with thin vessels crossing the cysts or their walls	Nodules	Renal, hepatic, and cardiac involvement
Pneumatoceles due to prior Infections[16,17]	All age groups (more frequent in infancy)	Unspecific	Cysts may contain fluid; no specific distribution	/	/
Cystic metastases[18-20]	According to the age group of the primary tumor	According to the gender distribution of the primary tumor	/*	Potential additional findings related to the primary tumor	The main primary tumors include colorectal cancer and soft tissue sarcoma
Neurofibromatosis type I[21,22]	< 10 (age at diagnosis ft the primary disease)	1:1 (distribution ft the primary disease)	Sharply defined	Ground glass opacities, reticulation, bullae	Skin, nervous system, eyes, and bones
Recurrent respiratory papillomatosis[23,24]	Juvenile (< 20) or adult (> 20) form of the primary disease	More common in males (1:1.6)	Thin-walled cysts close to nodules	Nodules, atelectasis, bronchiectasis	Signs associated with mucosal HPV infection

AML: Acute myeloid leukemia; ALL: acute lymphatic leukemia; BHDS: birt-hogg-dubé syndrome; HPV: human papilloma virus; LAM: lymphangioleiomyomatosis; LCDD: light chain deposit disease; LCH: langherans cell histiocytosis; LIP: lymphocytic interstitial pneumonia; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; *: rare finding not allowing to draw specific conclusions.

Table 3. Surgical suitable treatments in recurrent pneumothorax episodes

Author, Year	Procedure	Advantages	Disadvantages	Recurrence %
Kurihara *et al.*, 2020[25]	VATS TPC	No restrictive lung impairment Low recurrence** Less parietal impairment	Need time (learning curve) Not suitable in all centers	19.2% at 2.5 years
Fung *et al.*, 2022[26]	Bullectomy	Air-leak management	If multiple resections need, impaired lung function	15% at 1 year
	Bullectomy and pleurodesis			13% at 1 year
Hallifax *et al.*, 2017[27]	VATS abrasion + chemical (talc) pleurodesis	Diffused expertise	Chest pain, fever, inflammation discomfort, ARDS Not suitable for all patients	0%-3.2%*
	VATS talc poudrage only			5.6%-16.1%*
Hallifax R *et al.*, 2017[27]	Conservative	Lower compl. rate Lower hospital length	Higher recurrence	26.1%-51%*

ARDS: Acute respiratory distress syndrome. compl.: complications; Talc poudrage only: neither bullectomy nor caustication. TPC: total pleural covering; VATS: video assisted thoracic surgery. Parietal impairment means strength adherences which makes it extremely difficult to perform a second lung surgery (recurrence treatments or transplants). *: no timeline available. **: no large case series are available to assess TPC as a competitive treatment compared to others shown in the Table. The learning curve is related to the time that surgeons need to learn how to correctly and independently perform TPC.

DECLARATIONS

Authors' contributions

Conceptualization of the study: Bonis A, Giraudo C
Collected clinical and pathological notices: Verzeletti V, Zambello G
Reviewed and selected radiological resources: Giraudo C
Review and editing: Bonis A, Giraudo C
Supervision: Zuin A, Dell'Amore A, Rea F

Availability of data and materials

not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

A protocol number is not requested to be received from the local Ethical committee due to the single case report experience and the agreement to participate in our department's research activity. For this reason the ethical committee was not involved.

Consent for publication

Written informed consent has been obtained from the patient to publish this paper.

REFERENCES

1. Daccord C, Good JM, Morren MA, Bonny O, Hohl D, Lazor R. Birt-Hogg-Dubé syndrome. *Eur Respir Rev* 2020;29:200042. DOI PubMed PMC
2. Dal Sasso AA, Belém LC, Zanetti G, et al. Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary

involvement. *Respir Med* 2015;109:289-96. DOI PubMed

3. Jensen DK, Villumsen A, Skytte AB, Madsen MG, Sommerlund M, Bendstrup E. Birt-Hogg-Dubé syndrome: a case report and a review of the literature. *Eur Clin Respir J* 2017;4:1292378. DOI PubMed PMC
4. Ghosh S, Farver CF. Birt-Hogg-Dubé Syndrome. *Radiology* 2022;302:514. DOI PubMed
5. Daccord C, Cottin V, Prévot G, et al; OrphaLung network. Lung function in Birt-Hogg-Dubé syndrome: a retrospective analysis of 96 patients. *Orphanet J Rare Dis* 2020;15:120. DOI PubMed PMC
6. Sattler EC, Steinlein OK. Birt-Hogg-Dubé syndrome. 2006 Feb 27 [updated 2020 Jan 30]. In: GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://pubmed.ncbi.nlm.nih.gov/20301695/. [Last accessed on 25 Jun 2023].
7. Hasumi H, Baba M, Hasumi Y, Furuya M, Yao M. Birt-Hogg-Dubé syndrome: clinical and molecular aspects of recently identified kidney cancer syndrome. *Int J Urol* 2016;23:204-10. DOI PubMed
8. Menko FH, van Steensel MA, Giraud S, et al; European BHD Consortium. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol* 2009;10:1199-206. DOI PubMed
9. Sattler EC, Syunyaeva Z, Reithmair M, Dempke W, Steinlein OK. Colorectal cancer risk in families with Birt-Hogg-Dubé syndrome increased. *Eur J Cancer* 2021;151:168-74. DOI PubMed
10. Schmidt LS, Linehan WM. FLCN: the causative gene for Birt-Hogg-Dubé syndrome. *Gene* 2018;640:28-42. DOI PubMed PMC
11. Goncharova EA, Goncharov DA, James ML, et al. Folliculin controls lung alveolar enlargement and epithelial cell survival through E-cadherin, LKB1, and AMPK. *Cell Rep* 2014;7:412-23. DOI PubMed PMC
12. Panchabhai TS, Farver C, Highland KB. Lymphocytic interstitial pneumonia. *Clin Chest Med* 2016;37:463-74. DOI PubMed
13. Ahuja J, Kanne JP, Meyer CA, et al. Histiocytic disorders of the chest: imaging findings. *Radiographics* 2015;35:357-70. DOI PubMed
14. Pallisa E, Sanz P, Roman A, Majó J, Andreu J, Cáceres J. Lymphangioleiomyomatosis: pulmonary and abdominal findings with pathologic correlation. *Radiographics* 2002;22:S185-98. DOI PubMed
15. Colombat M, Gounant V, Mal H, Callard P, Milleron B. Light chain deposition disease involving the airways: diagnosis by fibreoptic bronchoscopy. *Eur Respir J* 2007;29:1057-60. DOI PubMed
16. Natarajan P, Skidmore J, Aduroja O, Kunam V, Schuller D. Bilateral pneumatoceles resulting in spontaneous bilateral pneumothoraces and secondary infection in a previously healthy man with COVID-19. *Proc* 2021;34:590-2. DOI PubMed PMC
17. Quigley MJ, Fraser RS. Pulmonary pneumatocele: pathology and pathogenesis. *AJR Am J Roentgenol* 1988;150:1275-7. DOI PubMed
18. Chan DP, Griffith JF, Lee TW, Chow LT, Yim AP. Cystic pulmonary metastases from epithelioid cell sarcoma. *Ann Thorac Surg* 2003;75:1652-4. DOI PubMed
19. Hasegawa S, Inui K, Kamakari K, Kotoura Y, Suzuki K, Fukumoto M. Pulmonary cysts as the sole metastatic manifestation of soft tissue sarcoma: case report and consideration of the pathogenesis. *Chest* 1999;116:263-5. DOI PubMed
20. Traweek T, Rotter AJ, Swartz W, Azumi N. Cystic pulmonary metastatic sarcoma. *Cancer* 1990;65:1805-11. DOI PubMed
21. Zamora AC, Collard HR, Wolters PJ, Webb WR, King TE. Neurofibromatosis-associated lung disease: a case series and literature review. *Eur Respir J* 2007;29:210-4. DOI PubMed
22. Lorentzen T, Madsen H, Lausten-Thomsen MJZ, Bygum A. Spontaneous pneumothorax as a clinical manifestation of neurofibromatosis type 1. *BMJ Case Rep* 2021;14:e238694. DOI PubMed PMC
23. Fortes HR, von Ranke FM, Escuissato DL, et al. Recurrent respiratory papillomatosis: a state-of-the-art review. *Respir Med* 2017;126:116-21. DOI PubMed
24. Seedahmed KMS, El-haj AH, Bashir AMA. Recurrent respiratory papillomatosis: clinical presentation, treatment modalities, and outcomes in Khartoum state. *Egypt J Otolaryngol* 2022;38:38. DOI
25. Kurihara M, Mizobuchi T, Kataoka H, et al. A total pleural covering for lymphangioleiomyomatosis prevents pneumothorax recurrence. *PLoS One* 2016;11:e0163637. DOI PubMed PMC
26. Fung S, Kivilis M, Krieg A, et al. Video-assisted thoracoscopic surgery with bullectomy and partial pleurectomy versus chest tube drainage for treatment of secondary spontaneous pneumothorax-A retrospective single-center analysis. *Medicina* 2022;58:354. DOI PubMed PMC
27. Hallifax RJ, Yousuf A, Jones HE, Corcoran JP, Psallidas I, Rahman NM. Effectiveness of chemical pleurodesis in spontaneous pneumothorax recurrence prevention: a systematic review. *Thorax* 2017;72:1121-31. DOI PubMed PMC
28. Thakare PH, Utpat K, Desai U, Joshi J, Nayak C. Birt-Hogg-Dubé syndrome - an unique case series. *Adv Respir Med* 2021;89:55-9. DOI PubMed
29. 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;175:1044-53. DOI PubMed PMC
30. Tschopp JM, Rami-Porta R, Noppen M, Astoul P. Management of spontaneous pneumothorax: state of the art. *Eur Respir J* 2006;28:637-50. DOI PubMed
31. Oshima K, Mizobuchi T, Nagato K, Ishibashi F, Sugano I, Kumasaka T. Uniportal video-assisted thoracic total pleural covering for refractory pneumothorax in a patient with lymphangioleiomyomatosis: a case report. *Video-assist Thorac Surg* 2020;5:10. DOI
32. Mizobuchi T, Kurihara M, Ebana H, et al. A total pleural covering of absorbable cellulose mesh prevents pneumothorax recurrence in patients with Birt-Hogg-Dubé syndrome. *Orphanet J Rare Dis* 2018;13:78. DOI PubMed PMC