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Three cases of Birt-Hogg-Dubé syndrome treated with bullectomy and skipped pleural covering using polyglycolic acid sheets

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Abstract

Birt-Hogg-Dubé Syndrome (BHDS) is a rare autosomal dominant disorder characterized by pulmonary cysts, recurrent pneumothorax, skin lesions, and renal tumors. We report three cases of pneumothorax caused by BHDS that were treated with bullectomy followed by Skipped Pleural Covering (SPC) Using Polyglycolic Acid (PGA) sheets. All cases showed multiple cysts predominantly in the mediastinal pleura and interlobar fissures. Genetic testing confirmed FLCN variants in all cases. No recurrence was observed postoperatively. Selective application of PGA sheets using the SPC technique may effectively prevent recurrence in BHDS-related pneumothorax while minimizing pleural adhesion and preserving lung function.

Keywords: Birt-Hogg-Dubé syndrome; Pneumothorax; Skipped pleural covering; Polyglycolic acid sheets.

Abbreviations: BHDS: Birt-Hogg-Dubé syndrome; SPC: Skipped Pleural Covering; PGA: Polyglycolic Acid; ORC: Oxidized Regenerated Cellulose; CT: Computed Tomography; FLCN: Folliculin Gene.

Introduction

Birt-Hogg-Dubé Syndrome (BHDS) is an inherited autosomal dominant disorder characterized by a triad of multiple pulmonary cysts with recurrent pneumothorax, fibrofolliculomas of the skin, and renal tumors. The causative gene, FLCN, located on chromosome 17p11.2, was identified in 2002 and functions as a tumor suppressor gene potentially involved in the mTOR pathway. Pulmonary lesions of BHDS typically manifest as bilateral, multiple cysts with a high risk of pneumothorax recurrence. Effective surgical strategies to prevent recurrence remain a clinical challenge. This report presents three cases of BHDS-related pneumothorax treated with bullectomy and Skipped Pleural Covering (SPC) using PGA sheets.

Case presentations

Case 1

A 42-year-old woman presented with dyspnea. CT revealed a right pneumothorax and multiple bilateral mediastinal cysts (Figure 1). She had a prior history of left-sided pneumothorax and a family history of BHDS. Thoracoscopic bullectomy was

performed, followed by SPC using PGA sheets. The postoperative course was uneventful. Genetic analysis confirmed a pathogenic FLCN mutation (c.1285dupC, p. His429ProfsTer27). No skin or renal manifestations were noted.

Case 2

A 58-year-old woman presented with recurrent right pneumothorax. CT revealed large subpleural and mediastinal cysts bilaterally (Figure 2). Thoracoscopic bullectomy and PGA-SPC were performed. An FLCN variant (c.1063-2A>G) was identified. Facial papules suggested fibrofolliculomas, but biopsy was declined. The postoperative course was favorable, and no recurrence has been observed.

Case 3

A 45-year-old man with a history of recurrent pneumothorax was admitted with complete right lung collapse. CT showed large cysts along the mediastinal pleura and fissures (Figure 3). Thoracoscopic bullectomy and PGA-SPC were conducted. Genetic testing revealed a variant (c.780-2A>G) of uncertain pathogenicity, but the family history and radiological features supported a BHDS diagnosis. The postoperative course was favorable without recurrence.

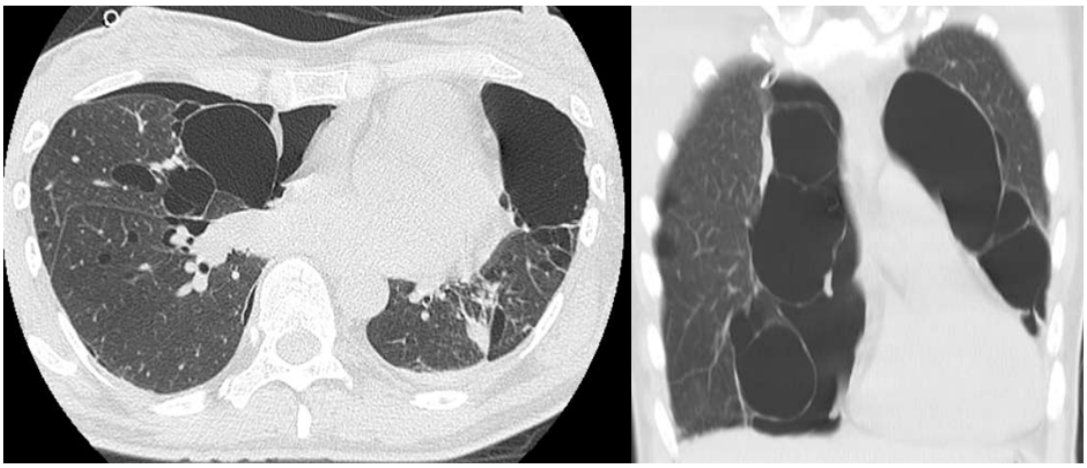

Figure 1: Diffuse distribution of thin-walled cysts is noted, predominantly along the mediastinal aspect.

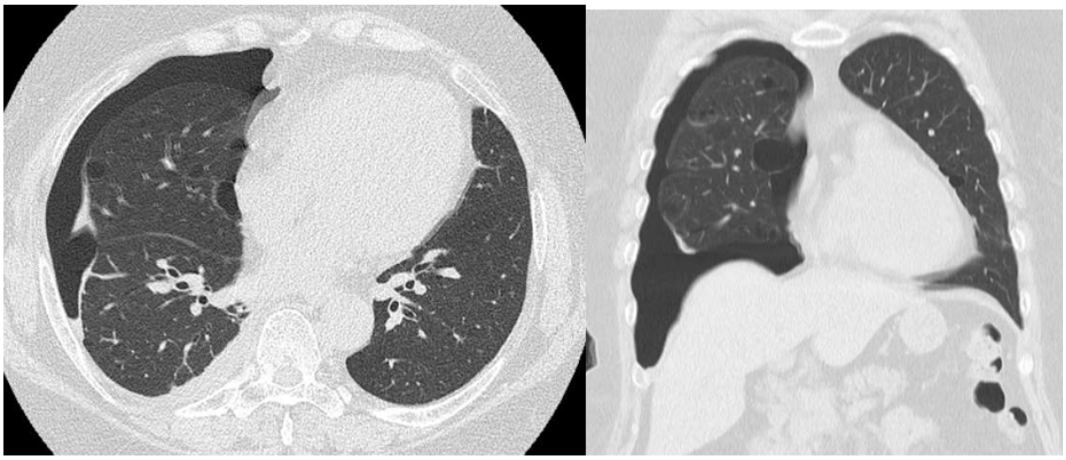

Figure 2: Despite the presence of a right-sided pneumothorax, thin-walled cystic lesions are also identified in regions adjacent to the pulmonary vasculature.

Discussion

BHDS is a rare genetic disorder first described in 1977, characterized by lesions in the lungs, skin, and kidneys [1]. The FLCN gene, identified in 2001, is implicated in the mTOR pathway [2,3]. Pulmonary manifestations include bilateral cysts and recurrent pneumothorax, which occur in approximately 24% of affected individuals. Diagnostic criteria include major criteria (histologically confirmed fibrofolliculomas or a pathogenic FLCN variant) and minor criteria (multiple pulmonary cysts, early-onset renal cancer, bilateral or multifocal renal tumors, or a first-degree relative with BHDS) [4]. Cases 1 and 2 fulfilled major criteria through genetic confirmation, while Case 3 met two minor criteria. FLCN mutations most frequently affect exon 11 in both Western and Japanese populations and are associated with a higher risk of renal tumors [5]. Understanding these mutation patterns may guide follow-up strategies. The mechanisms of cyst formation may involve defective alveolar adhesion (via the TGF-β pathway), dysregulation of type II pneumocyte proliferation through mTOR, impaired extracellular matrix integrity, and abnormal cellular stress responses, all of which contribute to alveolar fragility [6,7]. Various surgical strategies have been used to prevent recurrence, including pleural abrasion, bullectomy, and covering with materials like PGA or ORC sheets [8]. Skipped pleural covering (SPC) is an emerging technique especially suitable for diffuse cystic lesions. SPC not only acts as a physical barrier but also promotes localized in-

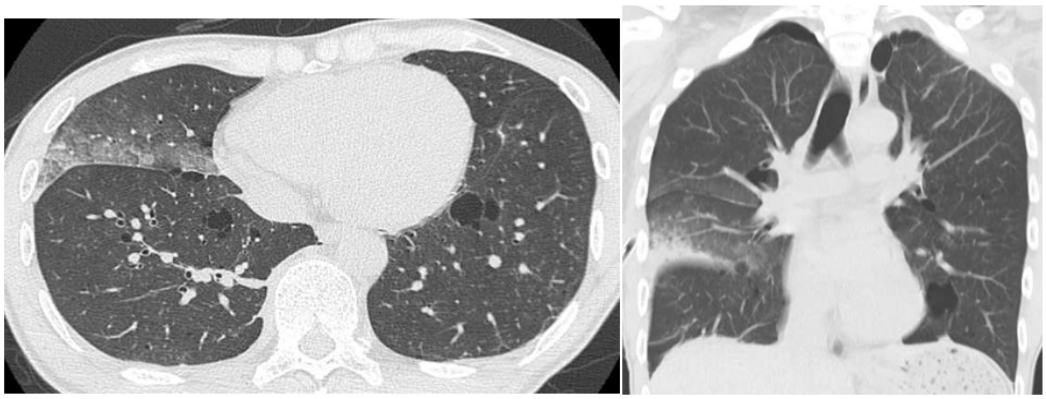

Figure 3: Right-sided pneumothorax is observed, accompanied by the presence of thin-walled bullae distributed in both lungs.

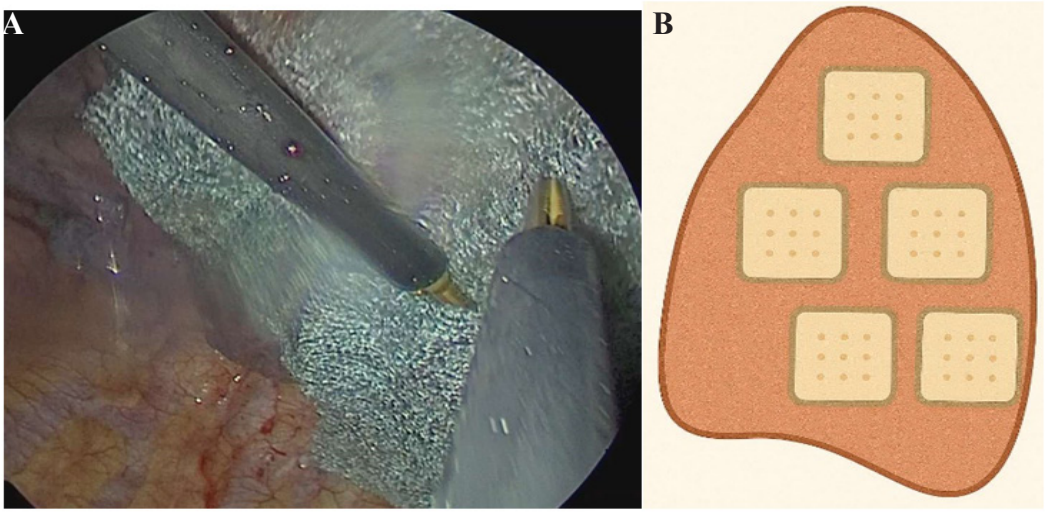

Figure 4: **(A)** Polyglycolic acid (PGA) sheets were applied contiguously over sites of cyst resection and regions with fragile cyst walls. **(B)** The remaining PGA sheets were placed with intervals to achieve the broadest possible coverage of the lung surface.

flammation and fibrosis, reinforcing the pleural surface. In this context, "skipped pleural covering (SPC)" refers to the strategic placement of PGA sheets in a discontinuous fashion, targeting regions of cystic vulnerability while avoiding unnecessary pleural adhesion in unaffected areas. In our cases, two 10 cm × 10 cm PGA sheets were trimmed and applied at 1-2 cm intervals over the visceral pleura, particularly over cyst-prone zones, to encourage selective thickening without restricting lung compliance. The choice of covering material is essential. PGA has demonstrated superior adhesion-inducing properties compared to ORC [9], which tends to resorb before inducing sufficient pleural remodeling. In all three cases, the postoperative course was uneventful, and no recurrence has been observed during follow-up, underscoring the potential of this technique. Tailoring the extent and pattern of pleural coverage to individual patient factors—such as cyst distribution, age, and baseline lung function—may optimize outcomes. Younger patients or those with extensive cystic disease may benefit from more aggressive coverage, whereas older or functionally limited individuals may require a more conservative approach. Preoperative imaging-based planning of "adhesion zones" could facilitate such precision. Additionally, the immunological milieu and fibroblast activity in BHDS-affected pleura are not well understood. Further research into the molecular effects of PGA-induced fibrosis could identify methods to enhance or fine-tune the therapeutic response. Multicenter studies integrating radiological, genetic, and histological findings are essential to establish standardized treatment protocols. According to the British Thoracic Society (BTS) 2023 guidelines [10], pleurodesis should be considered after surgical management of spontaneous pneumothorax. Given the high recurrence rate associated with BHDS, SPC using PGA sheets offers a rational compromise between maximizing recurrence prevention and preserving lung function. This balance is particularly important in younger patients and those with good baseline pulmonary capacity.

Conclusion

Skipped pleural covering using polyglycolic acid sheets following bullectomy effectively prevented pneumothorax recurrence in three cases of Birt-Hogg-Dubé syndrome. This technique supports targeted pleural adhesion, striking a balance between preventing recurrence and maintaining pulmonary function. Future research should focus on individualized "adhesion design" strategies tailored to cyst burden and recurrence risk.

Declarations

Conflict of interest: The authors declare that they have no competing interests.

Author contribution: Akira Naomi: Primary author of the manuscript, drafted and revised the paper. Kenichi Nishie, oshiyuki Oyama, Yasuo Kohashi, Yukiko Yoneda, Yuka Kitamura, Yoshinobu Hattori, Yuji Saitou: The attending doctors who treated

the patient on admission. All authors read and approved the final manuscript.

Ethics statement: The authors declare that appropriate written informed consent was obtained for the publication of the manuscript and accompanying images.

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