Dermatology Practical & Conceptual

Clinical Updates on Birt-Hogg-Dubé Syndrome and Atypical Presentations: Diagnosis and Management

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ABSTRACT Birt-Hogg-Dubé (BHD) syndrome is a rare hereditary genodermatosis associated with a mutation in the folliculin (FLCN) gene. Diagnostic criteria for this disease were first established in 2009; however, researchers have recently come across new germline mutations and resulting phenotypes. This review reassessed current guidelines by taking into consideration the incomplete forms of the syndrome as patients may have clinical features of BHD without a FLCN gene mutation. Individuals who share any characteristics of the syndrome should be screened for BHD since patient outcomes depend heavily on early detection.

Introduction

Birt-Hogg-Dubé (BHD) syndrome (OMIM #135150) is a rare autosomal dominant genodermatosis affecting multiple organs, including the skin, lungs, and kidneys. Patients typically present in early adulthood with dermatological lesions, spontaneous pneumothoraces, and bilateral multifocal chromophobe renal cancer. BHD has an estimated 2 cases per million, with an equal prevalence in males and females and a varied life expectancy depending on the severity of presentations (i.e., malignancy). For this reason, early diagnosis and genetic screening is critical. In 2009, official diagnostic criteria were established; however, new pathogenic variants and germline mutations have been described since then. Although previous criteria required individuals to have at least five fibrofolliculomas or trichodiscomas with histological

confirmation, this may no longer be the case. Thus, atypical manifestations of BHD require physicians to expand their knowledge of a previously well-defined syndrome.

Pathogenesis

BHD is associated with frameshift, nonsense, or splice site mutations in the highly conserved tumor suppressor gene *folliculin* (FLCN) on chromosome 17p11.2, which plays a critical role in regulating the rapamycin complex 1 (mTORC1) signaling pathway and activity of transcription factor B (TFEB) [1]. When FLCN is mutated, there is enhanced mTORC1 signaling and constitutional activation and nuclear localization of TFEB, leading to renal cystogenesis [2].

The latest research has shown that other novel mutations may be co-segregated with the FLCN gene. A paper by Schmidt et al. discussed a germline PRDM10 pathogenic variant found on the same codon as a family that reportedly had similar BHD phenotypes and a significant history of lipomas but that did not have the FLCN gene mutation. Researchers concluded that PRDM10 may be co-segregated with the clinical phenotype of this family, and BHD patients with cutaneous and renal manifestations who do not have FLCN mutation should be screened for PRDM10 germline variants, especially if lipomas are present [3].

Similarly, a study published by Zong et al. described a Chinese family with BHD syndrome that had a known history of spontaneous pneumothorax and pulmonary cysts; however, the family had a different novel frameshift mutation of FLCN (c.912delT/p.E305KfsX18), which had not been reported previously [4]. The absence of cutaneous lesions, which was previously required for diagnosis, may represent an incomplete form of BHD.

Scientists are still searching for a correlation between exhibited phenotype and FLCN genetic variation. Limited studies show FLCN mutations in exons 9 or 11 are linked to an increased presence of lung cysts or fewer renal tumors, respectively. Some races also have genetic variability in the FLCN mutation. Although Chinese BHD patients are more likely to have the exon 1 deletion, the data are sparse on how this affects specific BHD phenotypes seen in this subset population [5].

Clinical Manifestations

Fibrofolliculomas and trichodiscomas are the most common cutaneous manifestations of BHD. These lesions are hamartomas of the follicular mantle and perifollicular tissue, respectively. Clinically, they are described as asymptomatic flesh-colored, smooth papules and typically appear on the scalp, face, and neck (Figure 1). Acrochordons are also associated with BHD and can be found anywhere on the body, but they favor high friction areas such as the neck, axilla, and groin [6]. Physicians should also be aware of other inherited syndromes that present with facial papules to ensure proper diagnosis and disease management (Figure 2).

Other Manifestations and Complications

Systemic involvement related to BHD primarily affects the pulmonary and renal systems, leading to either an increase in recurrent spontaneous pneumothorax or the development of renal cysts and growths [7]. Genetic studies have linked the FLCN gene to familial pneumothorax (frequency up to 80%), with some mutations resulting in a lung-only phenotype [8,9]. Up to 65% of patients without a family history of pneumothorax experience a pneumothorax as their initial presentation. This should prompt additional workup and

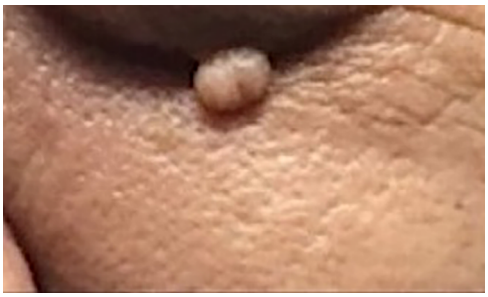

Figure 1. Flesh-colored domed shaped papule on the lower left eyelid consistent with fibrofolliculoma.

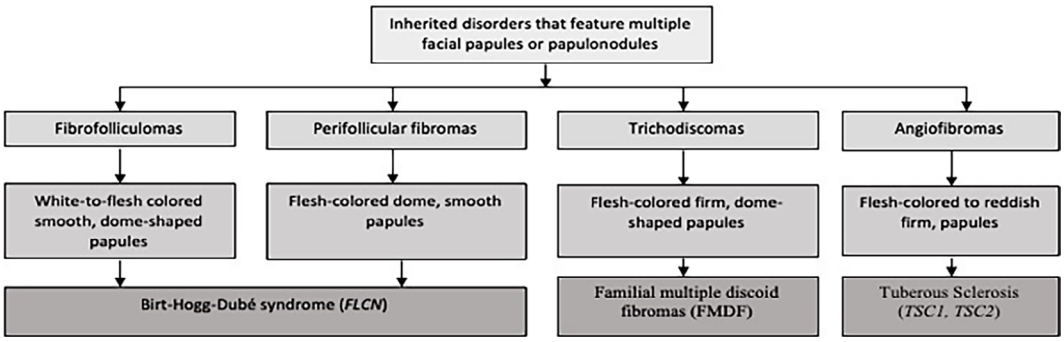

Figure 2. Inherited disorders that are associated with multiple facial papules or papulonodules.

further genetic testing, since other conditions, e.g., lymphangioleiomyomatosis (LAM) and pulmonary Langerhans cell histiocytosis (PLCH), can present with identical manifestations [10].

People with BHD are estimated to have a 50-fold increased risk of pneumothorax compared to the general population [11]. Pneumothorax can be fatal depending on the severity of lung collapse and pathophysiology. Minor pneumothorax may not require treatment as it will likely improve under careful observation if supplemental oxygen is deemed unnecessary. Severe pneumothorax is managed with either needle aspiration or insertion of a chest tube. While lung involvement does not usually result in respiratory impairment, BHD is one of the most important causes of cystic lung disease and associated malignancy (i.e., lung adenocarcinoma and atypical adenomatous hyperplasia) [11].

Renal tumors with mixed histological types develop in 12–34% of people affected by BHD, making it a common clinical manifestation [12]. It has been estimated that 50% of renal tumors are hybrid oncocytic tumors that contain histological features of renal oncocytoma and chromophobe renal carcinoma. Oncocytomas are benign neoplasms that arise from the proximal renal tubule and infrequently become malignant [13]. Comparably, chromophobe renal carcinomas are tumors that progresses from the intercalated cells of the distal tubules and have a 3–10% chance of metastasis [14]. Clear cell renal cell carcinoma is another renal neoplasm commonly seen [5]. Certain renal cancers are curative with surgery, but early diagnosis and treatment are critical, since renal cell carcinoma is associated with poor outcomes [15].

A few rare instances have been reported of uncommon patient clinical presentation that eventually led to a diagnosis of BHD. In one recent case report, a 38-year-old male with a history of bronchial asthma and COVID-19 presented with multiple 2–4 mm white firm papular lesions on the thorax, which biopsy confirmed to be a fibrofolliculoma [16]. Upon further investigation of the patient's family history, one maternal aunt had spontaneous pneumothoraces, and his maternal grandmother had had recurrent adrenal carcinomas [16]. Given these findings, he was worked up for BHD and found to have a confirmed genetic diagnosis of BHD. This case further emphasizes the importance of physicians being aware of BHD and how including it on the list of differentials can significantly improve patient outcomes in the long term. Similarly, a 64-year-old female with history of hypertensive emergency and a rapidly enlarging neck mass was discovered to have an FLCN genetic mutation after her initial workup for follicular thyroid cancer and paraganglioma [17]. The patient later received a colonoscopy, which confirmed the presence of stage 1 colon cancer [17]. Prior to her BHD diagnosis, she had no underlying familial or personal manifestations of this genetic disorder.

Colon polyps, breast cancer, and other lesions, including angiofibromas, rhabdomyomas, oral papules, and thyroid gland tumors, have also been reported in families with BHD [18]. Medullary thyroid carcinoma was found in six of the nine original BHD syndrome patients [19]. A case report by Dong et al. described a rare primary clear cell carcinoma of the thyroid in an individual with BHD [19]. The presence of these specific tumors should indicate further investigation of BHD in patients with no other explanations, but further research studies are required to definitively prove these associations with the syndrome [20].

Management of Patients with BHD and Similar Phenotypes

The management approach for patients with BHD should include a system-based analysis that involves early diagnosis of the disease, treatment of renal tumors, and prevention/treatment of pneumothorax. Family members should also be screened for organs that are commonly prevalent in BHD (i.e., pulmonary cysts and renal tumors). For renal involvement, initial imaging with either magnetic resonance imaging (MRI) or computed tomography (CT) should be performed starting at the age of 20, with repeat imaging every three to four years.[9] Patients are recommended to follow up with their primary care physician every three to five years for preventative purposes. The latest research suggests that those with BHD may have an early onset of colorectal cancer and should be screened at least 10 years earlier than the average population [21].

The main management of associated pulmonary involvement from BHD includes preventing and treating pneumothorax. After a primary spontaneous pneumothorax, mixed evidence shows that periodic chest CTs or pulmonary function tests are useful [9]. Additional management includes educating patients on pneumothorax symptoms (shortness of breath, sharp chest pain, etc.), since 25% of patients will have experienced one of them before the age of 25 [21]. Individuals with severe cystic lung disease and poor lung function should undergo recurring pulmonary function tests. Although strict data have yet to be published on the correlation between smoking and the risk of pneumothorax with BHD, patients should also be educated on the importance of smoking cessation to preserve lung health. They are also encouraged to obtain the annual influenza vaccine and pneumococcal vaccination.

Because BHD-associated skin findings are relatively benign, there is limited management recommendation. However, cases of melanoma have been reported in patients with BHD, with specific studies showing that those with the syndrome have a 10% increased risk of melanoma in comparison to the general population (2.1%). It has been hypothesized that the mutation of FLCN activates adenosine

monophosphate protein kinase, leading to increased melanocyte proliferation and tumor formation [22].For aesthetic reasons and psychological benefits, benign lesions can be removed using various surgical procedures i.e., cosmetic excision, debulking, and laser treatments [22].

Electrocautery, shave removal, dermabrasion, and topical rapamycin are considered additional therapies. In a recent report by Patel et al., a 55-year-old male with a history of known BHD had his fibrofolliculomas treated with non-fractionated ablative CO_2 laser. The authors reported a 92% decrease in the lesion count on the patient's face and ears at the 1-month follow-up. The lesion count decreased from 256 lesions to 21 after the final treatment [23]. Non-fractioned ablative classic mode (3 mJ) was used for the first round of treatment. At follow-up, the patient expressed partial satisfaction with his results and required a second round using a more intense non-fractioned laser (6 mJ), followed by a non-fractioned class mode (3 mJ). Although there was minimal recurrence reported at the patient's 6-month follow-up appointment, there was no procedural side effect. The patient noticed a significant improvement in texture and appearance [23].

Patients with incomplete forms of BHD may elect to have their facial papules and nodules removed for aesthetic reasons, as mentioned above. Those with the FLCN gene mutation and either a family history or past medical history of associated BHD complications should be screened using the same guidelines as those with BHD syndrome.

Re-Established Diagnostic Criteria

In 2009, Menko et al. published official diagnostic criteria for BHD that include the following: (i) At least five fibrofolliculomas or trichodiscomas, at least one of which must be histologically confirmed, and/or [24] (ii) pathogenic FLCN germline mutation on gene testing (although having a negative FLCN gene does not exclude one from the disease), and/or (iii) other criteria, including multiple lung cysts, renal cancer before age 50, multifocal or bilateral renal cancer or mixed chromophobe and oncocytic renal tumors detected on histology, and a first-degree relative with BHD syndrome [4].

The original diagnostic criteria do not include incomplete forms of BHD and therefore should be re-established to include controversial entities that researchers still classify as BHD syndrome.

1. At least five fibrofolliculomas, trichodiscomas, perifollicular fibromas, and at least one must be histologically confirmed, and/or
2. History of multiple lung cysts, spontaneous pneumothorax, renal cancer before age 50, multifocal or bilateral renal cancer, or mixed chromophobe and oncocytic detected on histology AND FLCN germline mutation.
3. Incomplete forms of this disease may appear as the presence of medullary thyroid carcinoma, parotid-gland oncocytoma, tonsillar carcinoma, parathyroid adenoma, rhabdomyoma, and BHD germline mutation [25].

Additionally, although Hornstein-Knickenberg syndrome was historically considered a different disease, it is now being classified as the same syndrome as BHD [26]. Both syndromes are autosomal dominant and have the same clinical features, i.e., lung, kidney, colon, and endocrine involvement and skin lesions commonly located on the head, neck, and trunk. The only difference between them is the histological features of trichodiscomas and fibrofolliculomas in comparison with perifollicular fibromas. Fibrofolliculomas contain epithelial cells with components comprised of collagen, fibrocytes, and vessels (Figure 3). Trichodiscomas are similar but do not have as much epithelial involvement and are more likely to have prominent sebaceous lobules. Perifollicular fibromas show hair follicles with concentric proliferation of collagen fibers around a fibrous sheath. The histological characteristics often overlap with fibrofolliculomas, making it difficult to distinguish between them (Figure 4) [27]. Researchers consider Hornstein-Knickenberg syndrome and BHD as the same entity, since many believe that fibrofolliculomas and perifollicular fibromas are indistinguishable. The only difference in syndromes was that doctors Hornstein and Knickenberg did not mention any extracutaneous cancer propensities seen with their previously described syndrome [4]. There needs to be updated diagnostic criteria taking this new establishment into consideration.

Differential Diagnosis

Fibrofolliculomas, trichodiscomas, and perifollicular fibromas can also be associated with other hereditary conditions, including tuberous sclerosis and familial multiple discoid fibromas (FMDF). Tuberous sclerosis is an autosomal dominant disorder due to mutations in the genes TSC1 and TSC2. Patients can have various cutaneous findings including hypomelanotic macules, Shagreen patches, and angiofibromas /perifollicular fibromas, which are characterized as skin-colored papules that can occur in BHD, although they

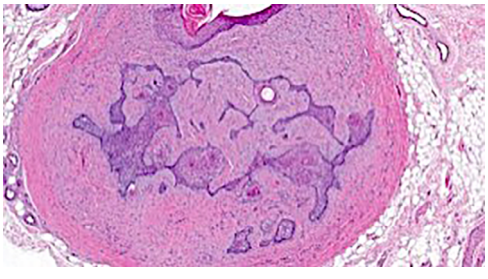

Figure 3. Fibrous pink orb containing a central follicle surrounded by epithelial cells.

are not officially included in the diagnostic criteria [28]. A recent case report of four patients with BHD discussed the presence of perifollicular fibromas-like lesions that appeared adjacent to fibrofolliculomas or showed identical histopathologic findings as fibrofolliculomas and trichodiscomas [26]. However, perifollicular fibromas lack the mantle that is commonly associated with fibrofolliculomas. Although perifollicular fibromas are not identical to fibrofolliculomas and trichodiscomas, some researchers believe this association is strong enough to be classified in the same category as these two lesions [26].

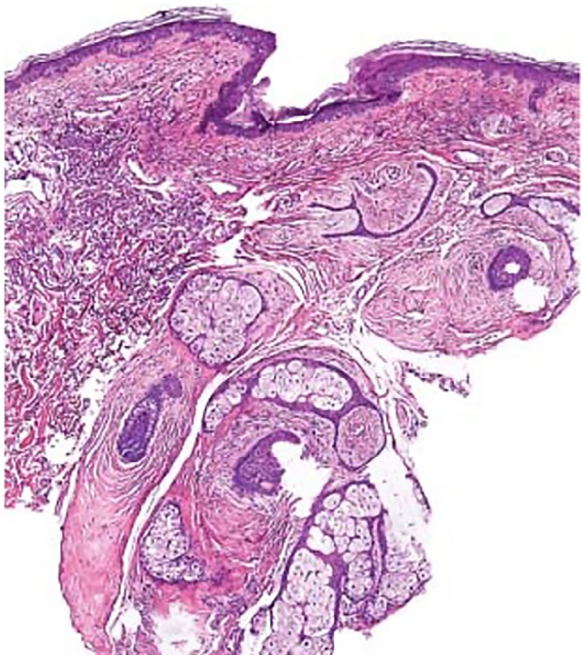

Figure 4. Epithelial strands inserted within connective tissue sheaths, which is consistent with fibrofolliculomas. Also present are hair follicles encompassed by dense connective tissue indicating the presence of perifollicular fibromas. (Granted permission by M. Shvartsbeyn)

Familial multiple discoid fibromas (FMDF) is another genodermatosis that shares similar skin findings with BHD, and patients of both can present with multiple trichodiscomas. However, FMDF differs from BHD syndrome due to the absence of the FLCN gene locus mutation and complications commonly associated with BHD (renal and pulmonary effects) [29]. In a study published by Van de Beek et al., genome-wide linkage analysis identified rare variants in the haplotype surrounding *FNIP1* on chromosome 5, including a missense variant in the *PDGFRB* gene that was found to be present in all tested patients with FMDF [30]. Similarly, other differential diagnoses to consider include Cowden syndrome and Brooke-Spiegler syndrome based on clinical features that resemble BHD (Table 1) [31,32].

When to Consider Screening for Birt-Hogg-Dubé Syndrome

Due to the increased risk of malignancies and mortality later in life, clinicians should have a low threshold to test for BHD early. Dermatologists should consider ordering genetic testing for patients that present with cutaneous findings consistent with fibrofolliculomas, trichodiscomas, or perifollicular fibromas and who have certain systemic features (i.e., recurrent pneumothorax or mixed histological renal tumors). Individuals with a known diagnosis should also be counseled to avoid smoking, have regularly scheduled imaging performed, and be routinely monitored for manifestations that pose great risk such as renal carcinoma and spontaneous pneumothorax.

Table 1. Differential Diagnoses to Consider for *Birt-Hogg-Dubé* Syndrome.

Condition	Common Genetic Mutation	Mode of Inheritance	Age at Onset	Clinical Features
Birt-Hogg-Dubé Syndrome	*FLCN*	Autosomal dominant	Adulthood	Fibrofolliculomas, trichodiscomas, perifollicular fibromas, spontaneous pneumothorax, lung cysts, renal cell carcinoma
Tuberous Sclerosis Complex	*TSC1, TSC2*	Autosomal dominant	Infancy	Angiofibromas, retinal hamartomas, rhabdomyomas, periungual fibromas, shagreen patch, liver and kidney angiomyolipomas, periungual fibromas
Familial Multiple Discoid Fibromas	*FNIP1*	Autosomal dominant	Childhood, adolescence, or adulthood	Multiple trichodiscomas, not commonly associated with systemic organ manifestations or malignancy
Cowden Syndrome	*PTEN*	Autosomal dominant	Early adulthood	Hamartomas, melanoma, trichilemmomas, breast cancer, endometrial cancer, colorectal cancer, developmental delay
Brooke-Spiegler syndrome	*CYLD*	Autosomal dominant	Adolescence or early adulthood	Spiradenomas, trichoepitheliomas, and cylindromas

Summary and Reappraisal

Although the diagnostic criteria for BHD were established in 2009, new clinical studies and reports have shed light on the discovery of incomplete forms of BHD that do not meet these standards. This review proposes that new updated BHD criteria should include the presence of perifollicular fibromas, lipomas, and tumors such as parotid gland oncocytoma, medullary thyroid carcinoma, and rhabdomyoma. Those who do not have the FLCN germline mutation should be screened for PRDM10 since it has been proven to be co-segregated with the FLCN gene. Similarly, if a patient has a family history of BHD phenotypes (i.e., pulmonary cysts), even if they do not have any associated cutaneous manifestations, we recommend that they be genetically tested for potential novel variants. New data emphasize the importance of having a low clinical threshold to screen for BHD, even if patients do not have "classic" symptoms or phenotypes. Likewise, these atypical individuals should have the same routine screening and management as those with BHD.

References

1. Schmidt LS, Linehan WM. FLCN: The causative gene for Birt-Hogg-Dubé syndrome. *Gene*. 2018;640:28-42. DOI:10.1016/j.gene.2017.09.044. PMID: 28970150.
2. Fenner A. Differential mTORC1 pathways in BHD. *Nat Rev Urol*. 2020;17(9):485-485. DOI:10.1038/s41585-020-0364-2
3. Schmidt LS, Vocke CD, Ricketts CJ, et al. PRDM10 RCC: A Birt-Hogg-Dubé-like Syndrome Associated With Lipoma and Highly Penetrant, Aggressive Renal Tumors Morphologically Resembling Type 2 Papillary Renal Cell Carcinoma. *Urology*. 2023;179:58-70. DOI:10.1016/j.urology.2023.04.035. PMID: 37331486.
4. Zong D, Li J, Liu X, Guo T, Ouyang R. Identification of a Novel Pathogenic Folliculin Variant in a Chinese Family With Birt–Hogg–Dubé Syndrome (Hornstein-Knickenberg Syndrome). *Front Genet*. 2020;11:565566. DOI:10.3389/fgene.2020.565566
5. Schmidt LS, Linehan WM. Molecular Genetics and Clinical Features of Birt-Hogg-Dubé-Syndrome. *Nat Rev Urol*. 2015;12(10):558-569. DOI:10.1038/nrurol.2015.206. PMID: 26334087.
6. Belgam Syed SY, Lipoff JB, Chatterjee K. Acrochordon. In: *StatPearls*. StatPearls Publishing; 2023. Accessed January 22, 2024. http://www.ncbi.nlm.nih.gov/books/NBK448169/
7. Muller ME, Daccord C, Taffé P, Lazor R. Prevalence of Birt-Hogg-Dubé Syndrome Determined Through Epidemiological Data on Spontaneous Pneumothorax and Bayes Theorem. *Front Med (Lausanne)*. 2021;8:631168. DOI:10.3389/fmed.2021.631168. PMID: 33987191.
8. Boone PM, Scott RM, Marciniak SJ, Henske EP, Raby BA. The Genetics of Pneumothorax. *Am J Respir Crit Care Med*. 2019;199(11):1344-1357. DOI:10.1164/rccm.201807-1212CI. PMID: 30681372.
9. Daccord C, Good JM, Morren MA, Bonny O, Hohl D, Lazor R. Birt-Hogg-Dubé syndrome. *Eur Respir Rev*. 2020;29(157):200042. DOI:10.1183/16000617.0042-2020. PMID: 32943413.
10. Ouellette DR, Parrish S, Browning RF, et al. Unusual causes of pneumothorax. *J Thorac Dis*. 2014;6(Suppl 4):S392-S403. DOI:10.3978/j.issn.2072-1439.2014.08.07. PMID: 25337394.
11. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev*. 2002;11(4):393-400. PMID: 11927500.
12. Adley BP, Smith ND, Nayar R, Yang XJ. Birt-Hogg-Dubé syndrome: clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med*. 2006;130(12):1865-1870. DOI:10.5858/2006-130-1865-BSCFAG
13. Perez-Ordonez B, Hamed G, Campbell S, et al. Renal oncocytoma: a clinicopathologic study of 70 cases. *Am J Surg Pathol*. 1997;21(8):871-883.DOI:10.1097/00000478-199708000-00001. PMID: 9255250.
14. Alaghehbandan R, Przybycin CG, Verkarre V, Mehra R. Chromophobe renal cell carcinoma: Novel molecular insights and clinicopathologic updates. *Asian J Urol*. 2022;9(1):1-11. DOI:10.1016/j.ajur.2021.11.010. PMID: 35198391.
15. Gupta S, Kanwar SS. Biomarkers in renal cell carcinoma and their targeted therapies: a review. *Explor Target Antitumor Ther*. 2023;4(5):941-961. DOI:10.37349/etat.2023.00175. PMID: 37970211.
16. Ruiz V, Bujan L, Kalfayan PG, Seehaus A, Carboni Bisso I, Las Heras M. Hemoptysis after COVID-19 and the importance of differential diagnosis: Birt-Hogg-Dubé syndrome. *Medicina (B Aires)*. 2023;83(2):311-314.
17. Lertdetkajorn K, Haw J, Paysour JE. THU514 Atypical Presentation Of Birt-Hogg-Dubé Syndrome With Poorly Differentiated Follicular Thyroid Cancer And Paraganglioma. *J Endocr Soc*. 2023;7(Suppl 1):bvad114.2142. DOI:10.1210/jendso/bvad114.2142
18. Balakumar R, Farr MRB, Fernando M, Jebreel A, Ray J, Sionis S. Adult-Type Rhabdomyoma of the Larynx in Birt–Hogg–Dubé Syndrome: Evidence for a Real Association. *Head Neck Pathol*. 2018;13(3):507-511. DOI:10.1007/s12105-018-0922-6. PMID: 29744825.
19. Dong L, Gao M, Hao W jing, et al. Case Report of Birt–Hogg–Dubé Syndrome. *Medicine (Baltimore)*. 2016;95(22):e3695. DOI:10.1097/MD.0000000000003695. PMID: 27258496.
20. Palmirotta R, Savonarola A, Ludovici G, et al. Association Between Birt Hogg Dubé Syndrome and Cancer Predisposition. *Anticancer Research*. 2010;30(3):751-757. PMID: 20392993.
21. Woodford MR, Andreou A, Baba M, et al. Seventh BHD international symposium: recent scientific and clinical advancement. *Oncotarget*. 2022;13:173-181. DOI:10.18632/oncotarget.28176
22. Nowsheen S, Hand JL, Gibson LE, el-Azhary RA. Melanoma in a patient with previously unrecognized Birt-Hogg-Dubé syndrome. *JAAD Case Rep*. 2019;5(11):947-952. DOI:10.1016/j.jdcr.2019.08.018. PMID: 31687461.
23. Patel R, Wesenberg J, Brammeier J. Fibrofolliculomas in Birt-Hogg-Dubé syndrome treated with nonfractionated ablative CO2 laser. *JAAD Case Rep*. 2023;40:96-98. DOI:10.1016/j.jdcr.2023.08.026. PMID: 37771352.
24. Menko FH, van Steensel MAM, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol*. 2009;10(12):1199-1206. DOI:10.1016/S1470-2045(09)70188-3. PMID: 19959076.
25. 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(6):321-331. DOI:10.1136/jmg.2007.054304. PMID: 18234728.
26. Shvartsbeyn M, Mason AR, Bosenberg MW, Ko CJ. Perifollicular fibroma in Birt-Hogg-Dubé syndrome: an association revisited. *J Cutan Pathol*. 2012;39(7):675-679. DOI:10.1111/j.1600-0560.2012.01929.x
27. Nam JH, Min JH, Lee GY, Kim WS. A Case of Perifollicular Fibroma. *Ann Dermatol*. 2011;23(2):236-238. DOI:10.5021/ad.2011.23.2.236
28. Zamora EA, Aeddula NR. Tuberous Sclerosis. In: *StatPearls*. StatPearls Publishing; 2023. Accessed December 2, 2023. http://www.ncbi.nlm.nih.gov/books/NBK538492/
29. Starink TM, Houweling AC, Doorn MBA van, et al. Familial multiple discoid fibromas: A look-alike of Birt-Hogg-Dubé syndrome not linked to the FLCN locus. *Journal of the American Academy of Dermatology*. 2012;66(2):259.e1-259.e9. DOI:10.1016/j.jaad.2010.11.039. PMID: 21794948.
30. van de Beek I, Glykofridis IE, Tanck MWT, et al. Familial multiple discoid fibromas is linked to a locus on chromosome 5 including the FNIP1 gene. *J Hum Genet*. 2023;68(4):273-279. DOI:10.1038/s10038-022-01113-1. PMID: 36599954.
31. Dubois A, Rajan N. CYLD Cutaneous Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. *GeneReviews*®. University of Washington, Seattle; 1993. Accessed November 18, 2024. http://www.ncbi.nlm.nih.gov/books/NBK555820/
32. Garofola C, Jamal Z, Gross GP. Cowden Disease. In: *StatPearls*. StatPearls Publishing; 2024. Accessed November 18, 2024. http://www.ncbi.nlm.nih.gov/books/NBK525984/