DOI: 10.4274/turkderm.galenos.2025.64928
Turkderm-Turk Arch Dermatol Venereol 2025;59(4):147-8

CYLD cutaneous syndrome presenting with multiple trichoepitheliomas

Multipl trikoepitelyomalarla seyreden CYLD kutanöz sendromu

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Keywords: CYLD cutaneous syndrome, multiple familial trichoepitheliomas, Brooke-Spiegler syndrome, cylindroma, trichoepithelioma

Anahtar Kelimeler: CYLD kutanöz sendromu, multipl ailesel trikoepitelyoma, Brooke-Spiegler sendromu, silindroma, trikoepitelyoma

To Editor,

CYLD cutaneous syndrome (CCS) encompasses a spectrum of hereditary adnexal tumor syndromes caused by germline mutations in the *CYLD* gene, a tumor suppressor that regulates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- B) pathway and epidermal differentiation[1]. Traditionally, these have been classified as Brooke-Spiegler syndrome (BSS), multiple familial trichoepithelioma (MFT), and familial cylindromatosis[2]. However, emerging evidence supports a unified classification, with phenotypic variability depending on the tumor type[3].

Here, we present the case of a 27-year-old woman with multiple trichoepitheliomas and a confirmed *CYLD* mutation but no family history, illustrating the challenges in differentiating between MFT and BSS and highlighting the importance of a broader classification framework within the CYLD CCS spectrum.

The patient presented with multiple asymptomatic papules on the nose, nasolabial folds, forehead, and scalp, which had appeared since adolescence (Figure 1). The patient reported that some of the facial lesions had been excised four years ago, but recurrence was observed soon after. Excision from the occipital scalp and nasolabial fold confirmed the diagnosis of trichoepithelioma histologically (Figure 2a-b). The scalp biopsy revealed a tumoral lesion in the dermis, consisting of multiple nodules of basaloid cells with keratin horn cysts and a fibrous cellular stroma closely associated with the epithelial components, without any connection to the surface epithelium (Figure 2a). The biopsy of the nasolabial region revealed a similar morphology without any evidence of cylindroma or spiradenoma (Figure 2b). Genetic testing identified a heterozygous pathogenic *CYLD* mutation (c.864del, p.Phe288Leufs*23) by SNV indel analysis. The patient had no family history of any other medical issues.

Trichoepitheliomas are benign adnexal tumors that can present as part of CYLD CCS, a genetic disorder encompassing BSS, MFT, and familial cylindromatosis[1-4]. These conditions, once considered distinct entities, are now increasingly recognized as phenotypic variations within a continuous clinical spectrum driven by germline *CYLD* mutations[1,3].

In this case, the patient exhibited multiple histopathologically confirmed trichoepitheliomas along with a pathogenic *CYLD* mutation (c.864del, p.Phe288Leufs23). This mutation was not among the 107 pathogenic variants previously reported in a comprehensive review of *CYLD* genetic testing. There was no evidence of cylindromas or spiradenomas, and there was no family history of similar lesions. This presentation is most consistent with an MFT-like phenotype; however, its sporadic occurrence challenges the traditional classification

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Received/Geliş Tarihi: 16.05.2025 **Accepted/Kabul Tarihi:** 01.10.2025 **Publication Date/Yayınlanma Tarihi:** 30.12.2025

Cite this article as/Atıf: Diremsizoğlu E, Demirbaş A, Vural Ç. CYLD cutaneous syndrome presenting with multiple trichoepitheliomas. Turkderm-Turk Arch Dermatol Venereol. 2025;59(4):147-8

Figure 1. Multiple skin-colored papules on the midface (nose, nasolabial folds, and forehead)

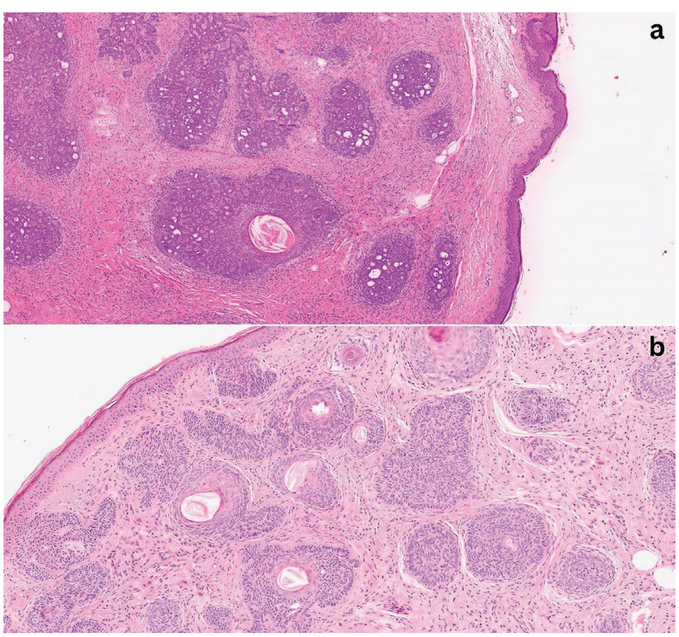

Figure 2 (a). Dermal basaloid tumor in the occipital region (H and E x 4), **(b)** Tumor consisting of basaloid multiple nodules containing small horn cysts in the nasolabial region (H and E x 10)
H and E: Hematoxylin and Eosin

of MFT as a strictly familial disorder[2]. The absence of additional adnexal tumors further differentiates this case from classic BSS; however, given the known phenotypic variability in CYLD mutation carriers, a potential future evolution into a broader CCS phenotype cannot be ruled out[4].

Although surgical excision is effective, it often leads to tumor recurrence, making the clinical management of *CYLD*-associated tumors challenging. Alternative approaches, such as laser therapy, topical treatments, and pharmacological interventions targeting the NF-κB pathway, are being explored; however, further research is required to establish their long-term efficacy[2,4].

Additionally, long-term follow-up is crucial because of the small but significant risk of malignant transformation. Studies suggest that approximately 5-10% of CYLD mutation carriers may develop basal cell carcinoma or other malignancies[5]. Therefore, genetic counseling and regular dermatological surveillance are strongly recommended for affected individuals, even in the absence of a family history, to monitor disease progression and potential malignancy development.

This case highlights the diagnostic ambiguity within CCS, illustrating the importance of a more flexible classification system that accommodates both familial and sporadic presentations of the disease. As our understanding of genotype-phenotype correlations continues to evolve, future research should focus on refining the diagnostic criteria and developing targeted therapies to improve patient outcomes.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of clinical images.

Footnotes

Authorship Contributions

Consept: E.D., A.D., Design: E.D., A.D., Data Collection or Processing: E.D., A.D., Ç.V., Analysis or Interpretation: E.D., A.D., Ç.V., Literature Search: E.D., A.D., Writing: E.D., A.D., Ç.V.

Conflicts of Interest: Authors declare that there are no conflicts of interest financial or otherwise related to the material presented herein.

Financial Disclosure: The authors declared that this study received no financial support.

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