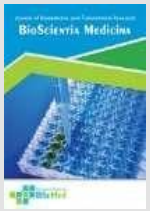
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Sporadic Coexistence of Multiple Trichoepitheliomas and Solitary Neurofibroma: Mimicking Brooke–Spiegler Syndrome

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ARTICLE INFO

Keywords:
Brooke–Spiegler syndrome
Dermoscopy
Resource-limited setting
Solitary neurofibroma
Trichoepithelioma

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i3.1522

A B S T R A C T

Background: The simultaneous presentation of multiple adnexal tumors and neural sheath tumors on the face typically heralds a genodermatosis, most notably Brooke–Spiegler syndrome (BSS) or neurofibromatosis type 1 (NF1). The sporadic, non-syndromic coexistence of these entities in the same anatomical region is a diagnostic pitfall that challenges the principle of parsimony. **Case presentation:** We report the case of a 24-year-old Asian female presenting with a 12-month history of 18 disseminated, skin-colored papules restricted to the centrofacial region, followed by the rapid development of a 3.0 cm solitary tumor on the right buccal region. Dermoscopic evaluation revealed a dichotomy in tumor morphology: the papules exhibited ivory-white backgrounds with multiple rosette signs and milia-like cysts, while the buccal tumor displayed a structureless pink pattern with absence of pigment networks. Detailed physical examination ruled out cutaneous stigmata of NF1. Histopathological analysis confirmed the diagnosis of multiple trichoepitheliomas and a solitary localized neurofibroma based on characteristic morphological features, including papillary mesenchymal bodies and mast cell presence. Immunohistochemistry was not utilized due to setting-specific resource limitations. **Conclusion:** This case underscores the potential for sporadic benign tumors to mimic syndromic phenotypes (phenocopies). It highlights the critical importance of recognizing key hematoxylin and eosin morphological markers and clinical signs to establish accurate diagnoses in resource-limited settings where molecular genetics and immunohistochemical staining are unavailable.

1. Introduction

The integumentary system serves as a complex biological landscape where a diverse array of neoplasms can arise, reflecting the intricate embryological origins of cutaneous structures.[1] Among the most diagnostically challenging are cutaneous adnexal tumors, a heterogeneous group of neoplasms deriving from the pilosebaceous unit, eccrine, or apocrine glands. These tumors occupy a unique niche in dermatopathology; while often benign, they present a formidable diagnostic labyrinth due to the significant morphological overlap between benign entities and their malignant counterparts. The accurate classification of these lesions is not merely an academic exercise but a clinical imperative, as misdiagnosis can lead to inappropriate surgical aggression or, conversely, the neglect of a malignant process.[2]

Within this spectrum, trichoepithelioma stands out as a prototypical benign adnexal neoplasm. It demonstrates differentiation toward the hair follicle, specifically targeting the germinative cells of the follicular bulge and papilla. Histologically, trichoepitheliomas mimic the structural complexity of the hair follicle, often presenting with islands of

basaloid cells and primitive hair germs. In the general population, solitary trichoepitheliomas are relatively common, presenting as sporadic, non-hereditary findings in adults. However, the clinical narrative changes drastically when these lesions appear in multiplicity. The presence of multiple facial trichoepitheliomas is a canonical feature strongly associated with autosomal dominant genodermatoses.[3]

The most prominent of these hereditary conditions is Brooke–Spiegler syndrome (BSS), a rare disorder characterized by a predisposition to form a triad of adnexal tumors: cylindromas, spiradenomas, and trichoepitheliomas.[4] The pathophysiology of BSS is intrinsically linked to germline mutations in the CYLD gene located on chromosome 16q12-q13. The CYLD gene encodes a tumor suppressor protein that functions as a deubiquitinating enzyme, acting as a critical negative regulator of the NF-kappaB signaling pathway. When the CYLD function is compromised, constitutive activation of NF-kappaB ensues, promoting cell proliferation and resistance to apoptosis, which manifests clinically as the eruption of multiple adnexal tumors. Thus, for the dermatologist, the observation of multiple trichoepitheliomas is rarely viewed in isolation; rather, it serves as a potential cutaneous marker for an underlying genetic diathesis.

In parallel to the epithelial complexity of adnexal tumors, the dermis also hosts neoplasms of neural origin. Neurofibromas are benign peripheral nerve sheath tumors comprising a heterologous mixture of Schwann cells, perineural cells, and fibroblasts, embedded within a collagenous and myxoid stroma.[5] While these tumors are histologically distinct from the epithelial-derived trichoepithelioma, they share a similar clinical dichotomy: they can exist as solitary, sporadic lesions or as hallmarks of a profound genetic syndrome.

Neurofibromas are the pathognomonic hallmark of neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease.[6] NF1 is a common autosomal dominant RASopathy caused by mutations in the NF1 gene, which encodes neurofibromin, a negative regulator of the RAS/MAPK pathway. The loss of neurofibromin leads to uncontrolled cellular growth and tumor formation. While solitary localized neurofibromas (SLN) occur sporadically in healthy individuals without any germline mutation, their anatomical distribution is non-random. Sporadic neurofibromas predominantly favor the trunk and extremities. Facial involvement in sporadic solitary neurofibroma is statistically uncommon, accounting for only a small fraction of reported cases. Consequently, the appearance of a neurofibroma on the face, particularly when large or deep-seated, often triggers a higher index of suspicion for NF1 or other phakomatoses.

The convergence of these two distinct tumor entities—multiple trichoepitheliomas and a facial neurofibroma—within the same anatomical territory is an event of extreme rarity. This presentation poses a significant intellectual and diagnostic challenge that strikes at the core of clinical reasoning: the tension between the principle of parsimony and the reality of stochastic biological events. The principle of parsimony, often referred to as Occam's Razor, posits that the simplest explanation—one that assumes the fewest distinct causes—is usually the correct one. In the context of a patient presenting with multiple facial papules and a larger facial tumor, the diagnostic heuristic immediately points toward a unifying genetic syndrome. Clinicians are trained to search for a grand unified theory of the patient's pathology. The coexistence of adnexal and neural tumors can mimic the phenotypic expression of mosaic RASopathies or CYLD-associated syndromes, creating a pseudo-syndromic clinical picture. For instance, patients with NF1 can develop various cutaneous tumors, and conversely, rare variants of BSS have been reported with diverse adnexal presentations. The initial clinical impression, therefore, leans heavily toward a syndromic etiology.[7]

However, clinical medicine is also governed by Hickam's Dictum, the counter-argument that a patient can have as many diseases as they please. It

is crucial for the clinician to distinguish between collision tumors and regional coexistence. A collision tumor is defined pathologically as two distinct neoplasms occupying the same microscopic space, often physically intermingled. In contrast, regional coexistence refers to independent tumors arising in the same anatomical field but separated by normal tissue. While less intimately connected histologically, regional coexistence on the face poses a greater diagnostic dilemma. The appearance of multiple tumor types in the centrofacial region forces the clinician to decide whether to pursue extensive, expensive, and potentially anxiety-inducing genetic testing or to treat the lesions as independent sporadic events.[8]

This diagnostic dilemma is magnified in resource-limited settings. In high-income healthcare environments, the resolution of such a case might rely on whole exome sequencing (WES) or extensive immunohistochemical panels to definitively rule out germline mutations or confirm the cellular origin of atypical cells. However, in many global health contexts, these advanced molecular tools are inaccessible. In these settings, the differentiation between a true syndrome and a sporadic coincidence cannot rely on genetic sequencing. Instead, it must rely heavily on rigorous clinical phenotyping and precise histopathological interpretation of standard Hematoxylin and Eosin (H&E) sections.

The back-to-basics approach becomes paramount. Clinicians must utilize physical examination maneuvers, such as the button-hole sign—where a neurofibroma invaginates into the subcutis upon pressure—to distinguish neural tumors from adnexal cysts or lipomas. Furthermore, dermoscopy has emerged as a non-invasive bridge between clinical examination and pathology. The identification of specific patterns, such as milia-like cysts and rosettes for trichoepithelioma, or the sparse vascular patterns of neurofibroma, allows for a morphology-first diagnosis.[9] The reliance on these fundamental skills is not merely a compromise; it is a critical competency for the astute dermatologist.

The danger in such cases lies in diagnostic anchoring, where the clinician fixates on the most obvious feature (multiple facial papules) and forces all subsequent findings to fit that diagnosis (assuming the buccal tumor is a large adnexal tumor associated with BSS). This can lead to misdiagnosis, as a neurofibroma requires a different surgical approach than a cylindroma or spiradenoma.[10] Furthermore, erroneous labeling of a patient with a genetic syndrome carries profound psychological and social implications, including syndrome anxiety, unnecessary screening for systemic malignancies, and concerns regarding family planning. Therefore, the identification of pseudo-syndromic presentations—where sporadic tumors mimic a genetic disorder—is of high clinical value. It validates the existence of statistical outliers where rare benign tumors coexist purely by chance, defying the principle of parsimony. Understanding this phenomenon prevents over-investigation and ensures that therapy is tailored to the specific pathology of each lesion rather than a presumed systemic defect.

In this comprehensive report, we document the rare non-syndromic, sporadic coexistence of multiple centrofacial trichoepitheliomas and a large solitary buccal neurofibroma in a young female. While individual case reports of trichoepitheliomas or neurofibromas exist, the specific convergence of these two distinct entities in the centrofacial region, mimicking a complex genodermatosis like Brooke-Spiegler Syndrome or Neurofibromatosis Type 1, represents a novel addition to the dermatological literature. The primary aim of this study is to dissect the diagnostic challenges posed by this phenotypic mimicry. We seek to demonstrate how a meticulous diagnostic algorithm—integrating the clinical button-hole sign, precise dermoscopic evaluation, and rigorous morphological analysis of H&E histopathology—can facilitate accurate diagnosis and management even in settings with limited laboratory resources. By presenting this unique case, we aim to provide a roadmap for clinicians encountering complex facial tumors, emphasizing that not all

clustered neoplasms equate to a genetic syndrome, and highlighting the enduring value of classical clinical and pathological correlation in the era of molecular medicine

2. Case Presentation

A 24-year-old Asian female presented to the dermatology outpatient clinic with a chief complaint of progressive cosmetic disfigurement affecting the central face. The patient provided a detailed chronological history of the lesions. The initial presentation occurred 12 months prior to consultation, characterized by the onset of asymptomatic, skin-colored papules on the nasolabial folds. These lesions progressively increased in number, disseminating to the glabella and periorbital regions over the subsequent six months. Figure 1 details a chronological representation of the patient's clinical course over a 12-month period prior to diagnosis. The timeline illustrates the distinct temporal evolution of the two tumor types: the gradual, stepwise dissemination of the trichoepitheliomas beginning at Month 0, contrasting with the delayed onset but rapid expansion of the solitary neurofibroma at Month 6. At Month 6, the patient noted a distinct, rapidly enlarging mass on the right buccal region. Unlike the smaller papules, this secondary lesion exhibited a rapid growth phase over a period of three months before stabilizing. This temporal dichotomy supports the hypothesis of two independent pathological processes (coexistence) rather than a single synchronous syndromic eruption. The patient denied pain, pruritus, paresthesia, or spontaneous bleeding from any lesion. A comprehensive systemic review was negative for neurological deficits, skeletal abnormalities such as scoliosis or tibial bowing, or visual disturbances (Table 1). A three-generation pedigree analysis was conducted. There was no family history of similar cutaneous tumors, turban tumors or cylindromas, epilepsy, or café-au-lait macules among first- or second-degree relatives. The patient had no history of environmental radiation exposure or chronic arsenic ingestion.

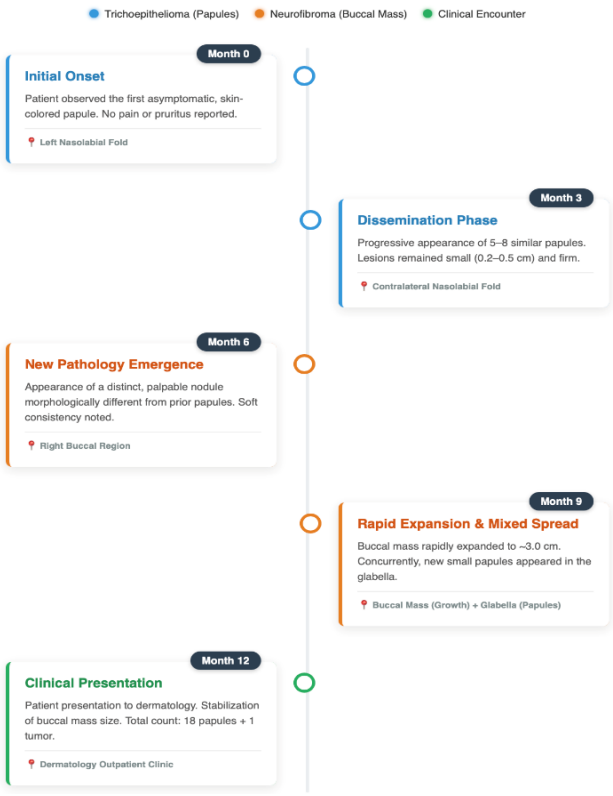

Figure 1. Timeline of disease progression.

On dermatological examination (Figure 2), two distinct morphological patterns were observed, suggesting a dual pathology: (1) Centrofacial Papules (Lesion Type A): A total of 18 firm, skin-colored to slightly translucent, dome-shaped papules ranging from 0.2 to 0.8 cm in diameter were distributed symmetrically across the nasolabial folds, glabella, and periorbital regions. No central dell, ulceration, or crusting was noted; (2) Buccal Tumor (Lesion Type B): A solitary, well-circumscribed, ovaloid mass measuring 3.0 cm by 2.4 cm was located on the right cheek. Palpation revealed a soft, compressible consistency. Crucially, the tumor exhibited a positive button-hole sign where the lesion invaginated into the subcutis upon vertical finger pressure, a clinical maneuver highly suggestive of neurofibromatosis or anetodermic changes. A full-body skin examination revealed no café-au-lait macules, axillary or inguinal freckling, or Lisch nodules, significantly reducing the clinical likelihood of classical NF1.

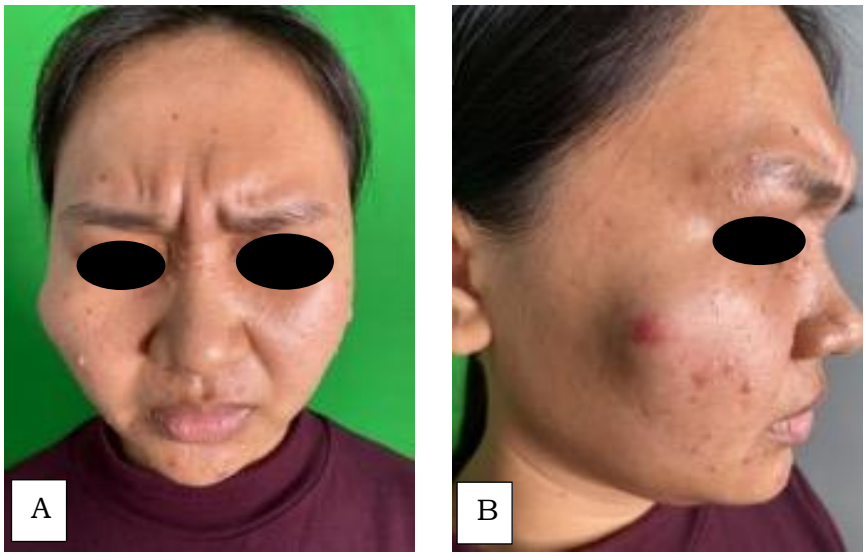

Figure 2. Dermatological examination. (A) Multiple trichoepithelioma lesions; (B) Solitary neurofibroma lesion on right cheek.

Dermoscopy (Figure 3) was utilized to differentiate the lesions non-invasively: (1) Lesion A (Facial Papules): Examination revealed a classical pattern consistent with trichoepithelioma. Key features included multiple white clods or milia-like cysts of varying sizes and rosette signs characterized by four white points arranged in a square visible under polarized light (Figure 3A). Fine, short telangiectasias were present but lacked the prominent arborizing character typical of basal cell carcinoma; (2) Lesion B (Buccal Tumor): Dermoscopy displayed a nonspecific pattern distinct from the papules, characterized by a pink-to-whitish structureless background with sparse, fine, curved vessels at the periphery (Figure 3B). Notably, there was an absence of the fingerprint pattern often seen in seborrheic keratoses or the arborizing vessels of basal cell carcinoma. The pigment network was absent, consistent with a non-melanocytic dermal tumor.

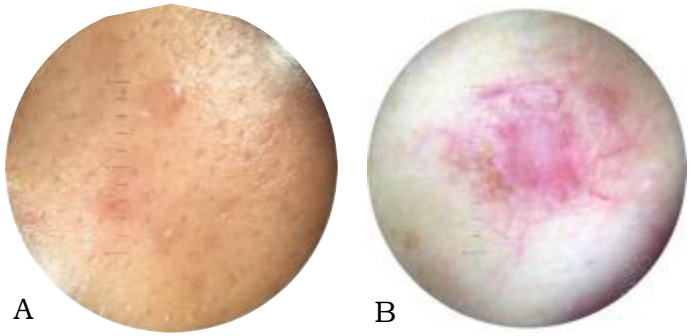

Figure 3. Dermoscopy examination. (A) Trichoepithelioma lesion; (B) Neurofibroma lesion.

To confirm the diagnosis and rule out malignancy, the patient underwent a shave biopsy of a representative nasolabial papule and an excisional biopsy of the buccal mass (Figure 4). Due to resource limitations in the setting, immunohistochemical staining was not available. Therefore, the diagnosis relied strictly on high-quality Hematoxylin and Eosin morphological analysis; (1) Specimen A (Papule): Staining revealed a symmetrical, well-circumscribed dermal tumor composed of islands of basaloid cells arranged in a cribriform and reticulated pattern (Figure 4A). Peripheral palisading of nuclei was present but was notably focal and lacked the retraction artifacts or clefting between the tumor and stroma that are characteristic of basal cell carcinoma. Numerous horn cysts or keratin-filled cysts were scattered throughout the tumor islands. The defining feature distinguishing this from basal cell carcinoma was the presence of papillary mesenchymal bodies—condensations of fibroblasts representing abortive hair papillae—within a fibrotic stroma that tightly integrated with the tumor islands. These findings were considered pathognomonic for Trichoepithelioma; (B) Specimen B (Buccal Mass): Histopathology demonstrated a non-encapsulated but well-circumscribed dermal neoplasm (Figure 4B). The tumor was composed of loosely arranged spindle cells with wavy, buckled, or serpentine nuclei set in a myxoid and collagenous stroma. The collagen bundles appeared thin and widely spaced, described as a shredded carrot appearance. Mast cells were frequently observed scattered throughout the stroma. No pleomorphism, nuclear atypia, or mitotic activity was observed. Based on the presence of wavy nuclei, myxoid stroma, and mast cells, the diagnosis of solitary localized neurofibroma was made.

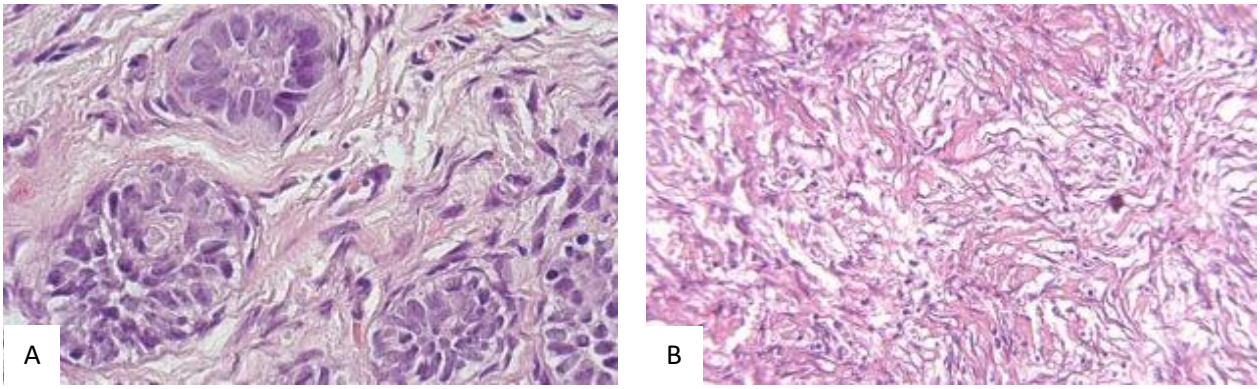

Figure 4. Histopathological results. (A) Histopathological examination on trichoepithelioma lesion showed basaloid nests with palisade peripherally; (B) Histopathological examination on neurofibroma lesion showed wavy spindle cells with wavy nuclei.

Table 1. Summary of Clinical, Dermoscopic, and Histopathological Findings on Admission

FEATURE DOMAIN	LESION TYPE A (Multiple Centrofacial Papules)	LESION TYPE B (Solitary Buccal Tumor)
Morphology & Size	Firm, dome-shaped, skin-colored to translucent papules. **Size: 0.2 – 0.8 cm**	Soft, compressible, ovaloid mass. Well-circumscribed. **Size: 3.0 cm × 2.4 cm**
Distribution & Count	Symmetric centrofacial distribution (Nasolabial folds, Glabella, Periorbital). **Count: ~18 lesions**	Asymmetric, isolated to the right buccal region (cheek). **Count: Solitary (1 lesion)**
Specific Clinical Signs	Negative for ulceration or central dell. No specific maneuvers positive.	POSITIVE SIGN **Button-hole sign** Invagination into subcutis upon vertical pressure.
Dermoscopic Features	• **Ivory-white background** • **Milia-like cysts** (white clods) • **Rosette signs** (polarized light) • Fine, short telangiectasias (non-arborizing)	• Pink-to-whitish structureless areas • Sparse, fine, curved vessels • **Absence** of pigment network • **Absence** of fingerprint pattern
Histopathology (H&E)	ADNEXAL ORIGIN Basaloid islands in cribriform pattern. **Papillary mesenchymal bodies** present. Horn cysts scattered. Focal peripheral palisading without retraction clefts.	NEURAL ORIGIN Non-encapsulated spindle cell neoplasm. **Wavy, buckled nuclei**. Myxoid stroma with shredded carrot collagen. Scattered mast cells.
Final Diagnosis	**Multiple Sporadic Trichoepitheliomas**	**Solitary Localized Neurofibroma**

Patient Systemic Review: Negative for café-au-lait macules, axillary freckling (Crowe's sign), Lisch nodules, or skeletal abnormalities. Family history negative for BSS or NF1 phenotypes.

Abbreviations: H&E = Hematoxylin and Eosin; BSS = Brooke–Spiegler Syndrome; NF1 = Neurofibromatosis Type 1.

Table 2 delineates the tailored therapeutic strategy and subsequent clinical outcomes, highlighting the necessity of a differential surgical approach for each tumor morphology. A dichotomous intervention plan was executed to balance oncological clearance with esthetic preservation in the cosmetically sensitive centrofacial region. The multiple trichoepitheliomas were managed via tangential shave excision combined with light electrodesiccation of the base. This modality was strategically selected to target the superficial exophytic components while preserving the reticular dermis, thereby minimizing the risk of permanent pitted scarring often associated with deeper resections. Conversely, the deep-seated buccal neurofibroma necessitated complete elliptical excision with layered closure. This more aggressive approach was mandatory to encompass the tumor's subcutaneous extension and prevent the local recurrence frequently observed with incomplete removal of peripheral nerve sheath tumors. Histopathological verification confirmed clear surgical margins for the neurofibroma. The six-month follow-up period demonstrated a favorable prognosis with no clinical evidence of recurrence for either lesion type. Cosmetic evaluation revealed excellent re-epithelialization of the shave sites and a fine, linearly healed scar on the cheek, congruent with relaxed skin tension lines (Vancouver Scar Scale score: 1). These physical outcomes translated into a significant restoration of the patient's psychosocial well-being, effectively resolving the syndrome anxiety associated with the initial presentation.

Table 2. Treatment Strategy, Follow-up, and Clinical Outcomes

DOMAIN	LESION TYPE A (Multiple Trichoepitheliomas)	LESION TYPE B (Solitary Neurofibroma)
Surgical Intervention	**Shave Excision + Electrodesiccation** Tangential shave removal of the exophytic papule followed by light electrodesiccation of the base to destroy follicular germinative cells.	**Complete Surgical Excision** Elliptical excision encompassing the entire tumor and deep dermal component, followed by layered closure (subcutaneous and cutaneous sutures).
Therapeutic Rationale	Chosen to maximize cosmetic outcome for multiple lesions while minimizing risk of pitted scarring. Targets superficial component.	Mandatory due to deep subcutaneous extension. Incomplete removal of neurofibromas carries a high risk of local recurrence.
Histological Clearance	Margins not evaluated (debulking procedure). Diagnosis confirmed via biopsy sample.	Clear surgical margins confirmed on final histopathology (deep and lateral borders free of tumor).
6-Month Outcome (Recurrence)	NO RECURRENCE No clinical evidence of papule regrowth or elevation at treated sites.	NO RECURRENCE No palpable mass or subcutaneous nodularity detected.
Cosmetic Result (Scarring)	**Excellent.** Complete re-epithelialization with minimal hypopigmentation. No hypertrophic scarring or keloid formation.	**Good.** Healed with a fine linear scar, congruent with Relaxed Skin Tension Lines (RSTL). Vancouver Scar Scale (VSS) score: 1.

Global Patient Outcome: The patient reported high satisfaction with the cosmetic results and significant alleviation of psychological distress ("syndrome anxiety"). Post-operative recovery was uneventful with no infection or dehiscence.

Note: VSS (Vancouver Scar Scale) ranges from 0 (normal skin) to 13 (worst scar). A score of 1 indicates near-normal pigmentation and vascularity with normal pliability.

3. Discussion

The primary clinical significance of this case lies in its deceptive presentation—a phenomenon best described as pseudo-syndromic phenotypic mimicry. In clinical dermatology, the simultaneous observation of multiple facial papules alongside a distinct, larger soft-tissue tumor acts as a powerful diagnostic trigger, immediately raising the specter of genodermatoses. This reflexive heuristic is grounded in the principle of parsimony, or Occam's Razor, which posits that a single underlying etiology is statistically more probable than the coincidental occurrence of two rare, unrelated pathologies in the same anatomical field. Consequently, the clinician is conditioned to search for a unifying genetic defect, such as a phakomatosis or an appendageal tumor syndrome, to explain the patient's constellation of symptoms.[11]

The initial differential diagnosis in such a scenario is heavily weighted toward Brooke–Spiegler syndrome (BSS) and neurofibromatosis type 1 (NF1). BSS is an autosomal dominant disorder characterized by a predisposition to form a triad of adnexal neoplasms: trichoepitheliomas, cylindromas, and spiradenomas.[12] The phenotypic expression of BSS is variable; while some patients present with the classic turban tumors (cylindromas), others may predominantly exhibit multiple facial trichoepitheliomas. Our patient's presentation of 18 centrofacial papules strongly mimicked the forme fruste of BSS. However, the unifying diagnosis fractured upon the evaluation of the larger buccal mass. In BSS, larger nodules are typically cylindromas

or spiradenomas. In this case, the buccal tumor was histologically confirmed as a neurofibroma—a neural sheath tumor distinct from the epithelial lineage of BSS.[13]

This histological discordance forces a reconsideration of the diagnosis towards NF1, the hallmark of which is the neurofibroma. It is well-documented that patients with NF1 can develop various cutaneous tumors, and rare instances of adnexal tumors have been reported in this population.[14] However, the rigorous application of the National Institutes of Health (NIH) diagnostic criteria for NF1 effectively ruled out this syndrome. The patient lacked the requisite café-au-lait macules, axillary or inguinal freckling (Crowe's sign), Lisch nodules, and skeletal dysplasias. Furthermore, sporadic neurofibromas typically favor the trunk; a solitary, large neurofibroma on the face of a patient without other stigmata of NF1 is a statistical outlier.[15]

Therefore, we are left with a diagnosis of exclusion: the sporadic coexistence of multiple trichoepitheliomas and a solitary neurofibroma. This represents a collision of diagnoses rather than a collision of tumors. Unlike a true collision tumor, where two neoplasms occupy the same microscopic space, this case represents regional coexistence—two independent neoplastic processes arising within the same dermatome. This presentation serves as a profound cautionary tale against diagnostic anchoring, reminding clinicians that common neoplasms can aggregate in rare patterns purely by chance, defying the standard rules of syndromic association.

To understand the genesis of these tumors, one must delve into the molecular biology of the pilosebaceous unit. Trichoepitheliomas are believed to arise from the follicular bulge, a repository of multipotent stem cells responsible for hair follicle cycling and repair. In syndromic cases like BSS, the pathophysiology is driven by germline mutations in the CYLD gene located on chromosome 16q12-q13.[16] The CYLD protein acts as a tumor suppressor by functioning as a deubiquitinating enzyme (DUB). Its primary role is to remove lysine-63-linked polyubiquitin chains from specific signaling molecules, thereby negatively regulating the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway. Loss of CYLD function leads to the constitutive, unchecked activation of NF-κB. This results in the upregulation of anti-apoptotic genes (such as Bcl-2) and varying degrees of cellular proliferation, manifesting as adnexal tumors. In our patient, who lacked a family history and systemic involvement, the lesions were classified as sporadic. However, the clustering of lesions in the centrofacial region necessitates a nuanced discussion of mosaicism. Cutaneous mosaicism occurs when a post-zygotic mutation arises during embryogenesis, creating two genetically distinct cell lines in an individual. It is theoretically possible that our patient represents a case of segmental mosaicism for a CYLD mutation.

Mosaicism in autosomal dominant skin disorders is typically categorized into two types. In Type 1 segmental mosaicism, a post-zygotic mutation occurs in a hemizygous embryo, leading to a segmental distribution of lesions (often following Blaschko's lines) in an otherwise healthy individual.[17] In Type 2 segmental mosaicism, a loss of heterozygosity occurs in a specific segment of an individual who already carries a germline mutation, resulting in a localized area of severe involvement superimposed on a milder, generalized phenotype. The strict localization of the trichoepitheliomas to the nasolabial folds and glabella in our patient could theoretically represent a Type 1 mosaic presentation. However, trichoepitheliomas in BSS typically appear in late childhood or puberty, driven by hormonal factors interacting with the genetic defect. The adult onset in this case, combined with the lack of strictly linear or Blaschkoid distribution and the presence of a distinct neural tumor (which involves a different germ layer origin—neural crest vs. ectoderm), favors a theory of independent somatic mutations. These somatic events may be driven by environmental factors, such as UV radiation, although the buccal mucosa is relatively

protected, adding to the enigma of the neurofibroma's location.

Perhaps the most critical dimension of this case is its management within a resource-limited setting. In the landscape of modern academic dermatology, the diagnostic standard of care for differentiating benign adnexal tumors from their malignant mimics (such as Basal Cell Carcinoma, or BCC) has increasingly shifted toward molecular genetics and immunohistochemistry (IHC). A typical panel for distinguishing trichoepithelioma from BCC would include CD34, Bcl-2, CK20, and Androgen Receptor markers. In trichoepithelioma, CD34 typically stains the fibrotic stroma surrounding the tumor islands, a feature absent in BCC. Bcl-2 expression in trichoepithelioma, is usually restricted to the peripheral basaloid cells (the pearl necklace pattern), whereas BCC typically shows diffuse, strong positivity throughout the tumor nest. CK20 highlights Merkel cells, which are often colonized within trichoepitheliomas but are rare or absent in BCC. Furthermore, to definitively rule out a mosaic form of BSS or NF1, Whole Exome Sequencing (WES) of tissue samples would be the gold standard. However, in our specific clinical context—and indeed in many global health settings—these advanced tools were unavailable due to cost and infrastructure constraints. This limitation forced a pivot from molecular reliance to classical clinical acumen—a back-to-basics or morphology-first approach.[18]

For the neurofibroma, we relied heavily on the button-hole sign. This clinical maneuver, where the tumor invaginates into the subcutis upon vertical pressure, is highly specific for neurofibromas (and anetoderma). It results from the herniation of the soft, myxoid stromal contents through a defect in the varying density of the dermal collagen. While not pathognomonic, in the absence of other findings, it is a robust clinical indicator. For the trichoepitheliomas, the diagnosis hinged on precise interpretation of Hematoxylin and Eosin (H&E) morphology. We specifically looked for architectural features that serve as reliable proxies for IHC findings. The most vital of these was the identification of papillary mesenchymal bodies—focal condensations of fibroblasts that represent abortive hair papillae. These structures are the histological hallmark of trichoepithelioma and are virtually never seen in BCC.[19] Additionally, we scrutinized the interface between the tumor and the stroma. BCC typically exhibits retraction artifacts (clefting) between the tumor islands and the stroma due to mucin deposition. In contrast, the stroma of trichoepithelioma is fibrotic and tightly integrated with the tumor islands, lacking these clefts. By prioritizing these subtle but pathognomonic architectural features, we were able to establish a diagnosis with a high degree of confidence, validating the utility of rigorous histomorphology in environments where advanced staining is not cost-effective.

Dermoscopy played a pivotal role in this case, acting as a non-invasive bridge that refined our pre-biopsy differential diagnosis and guided surgical planning. The dermoscopic evaluation revealed a clear dichotomy between the two lesion types, reinforcing the theory of dual pathology. For the facial papules (Lesion A), the dermoscopic findings were classic for trichoepithelioma. The observation of multiple white clods (milia-like cysts) on an ivory-white background is highly specific for adnexal tumors showing follicular differentiation. These clods correspond histologically to the keratin-filled horn cysts seen on H&E. Furthermore, the use of polarized dermoscopy revealed rosette signs—structures characterized by four white points arranged in a square, resembling a four-leaf clover. The rosette sign is an optical phenomenon caused by the interaction of polarized light with keratin-filled adnexal structures and concentric fibrosis at the level of the infundibulum. While initially described in actinic keratosis, rosettes are increasingly recognized as a key feature of trichoepitheliomas. Importantly, the vessels observed were fine and short, lacking the sharply focused, branching arborizing vessels that define BCC.[20]

For the buccal tumor (Lesion B), the findings were subtler but distinct. The lesion displayed a pink-to-

whitish structureless background with sparse, fine, curved vessels. The critical negative finding was the absence of a true pigment network. Instead, neurofibromas often display a pseudo-network or a reticular pigment pattern, which is actually caused by the transparency of the thinned epidermis revealing the dermal structures or the retention of melanin in the basal layer over the elevated dome of the tumor. The clear dermoscopic separation of these two tumor populations provided the confidence to pursue different surgical strategies: shave excision for the superficial trichoepitheliomas and deep excision for the neurofibroma.[19,20]

Despite the rigorous clinical and morphological approach, we must acknowledge the limitations inherent in a resource-constrained study. The primary limitation is the inability to perform immunohistochemical confirmation or genetic sequencing. While the histological features (papillary mesenchymal bodies, lack of retraction) were classic for trichoepithelioma, the lack of CD34 and Bcl-2 staining means that rare variants, such as desmoplastic trichoepithelioma or morpheaform basal cell carcinoma, cannot be excluded with the same statistical certainty as in a fully equipped reference laboratory. Desmoplastic trichoepithelioma, in particular, can be morphologically deceptive, sharing the infiltrative growth pattern of morpheaform BCC. However, the clinical context—specifically the stability of the lesions over 12 months, the multiplicity, and the lack of ulceration—strongly supports the benign diagnosis. Additionally, without genetic testing, we cannot definitively exclude low-grade mosaicism, although the clinical phenotype makes it unlikely. These limitations highlight the reality of practicing dermatology in diverse settings and underscore the need for adaptable diagnostic algorithms.

4. Conclusion

In conclusion, we have described a rare and instructive case of the coexistent, non-syndromic presentation of multiple centrofacial trichoepitheliomas and a solitary buccal neurofibroma in a young woman. This case serves as a vital educational vignette regarding the phenomenon of phenotypic mimicry, where sporadic benign tumors converge to simulate the presentation of complex genodermatoses like Brooke–Spiegler Syndrome or Neurofibromatosis Type 1. The diagnostic journey detailed here highlights several key takeaways for the clinician: (1) The Fallacy of the Unifying Diagnosis: While the principle of parsimony is a useful guide, clinicians must remain open to the possibility of regional coexistence, where multiple rare tumors appear purely by stochastic chance. Not all multiple facial tumors equate to a genetic syndrome; (2) The Power of Morphology: In an era increasingly dominated by molecular diagnostics, this case validates the morphology-first approach. In resource-limited settings, the astute integration of physical signs (the button-hole sign), dermoscopic features (rosettes and milia-like cysts vs. pseudo-networks), and definitive H&E histopathology (papillary mesenchymal bodies) remains the cornerstone of accurate diagnosis; (3) Holistic Patient Management: The distinction between a syndromic and sporadic diagnosis has profound psychological implications. By confidently ruling out a genetic syndrome through rigorous clinical phenotyping, we were able to alleviate the patient's syndrome anxiety and avoid unnecessary, expensive systemic screening. Successful treatment in such complex scenarios requires a tailored, multimodal approach. We advocate for a strategy that utilizes minimally invasive techniques (shave excision/electrodesiccation) for multiple superficial lesions to minimize scarring, while reserving radical excision for deeper neural tumors. This case stands as a testament to the efficacy of classical dermatological skills in navigating complex diagnostic landscapes.

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