

Epithelioma Adenoides Cysticum-Trichoepithelioma

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Abstract

Exceptional, benign neoplasm of pilo-sebaceous unit, the trichoepithelioma are engendered by the epithelial- mesenchymal cells of the hair follicle. Trichoepithelioma depicts three subcategories, the multiple familial trichoepithelioma (MFT), solitary non-hereditary trichoepithelioma and desmoplastic trichoepithelioma. A primary mutation on chromosome 9p21 and a concomitant mutation of cylindromatosis tumour suppressor (CYLD) gene, situated on chromosome 16q12-q13, is cogitated. Solitary or multiple, symmetric, skin coloured or pigmented, pink, brownish or blue-tinged, firm, spherical to oval, translucent or shiny, well defined, benign, asymptomatic papules or nodules are enunciated on the face, naso-labial folds, nose, forehead, eyelids and hair enriched zones. Dermascopy and histology is essential for categorizing the lesions.

Keywords: *Multiple Familial Trichoepithelioma (MFT); CYLD Gene*

Introduction

Trichoepithelioma is cogitated as an exceptional, benign tumour of pilo-sebaceous unit. The tumour emerges from the epithelial- mesenchymal cells of the hair follicle. The condition was simultaneously described in 1892 by Brooke as an “epithelioma adenoides cysticum” and by Fordyce as “multiple, benign cystic epitheliomas” [1,2]. Trichoepithelioma depicts three subcategories enunciated as multiple familial trichoepithelioma (MFT), solitary non-hereditary trichoepithelioma and desmoplastic trichoepithelioma. Currently enunciated as a variant of trichoblastoma, a terminology adopted in 1970, the nomenclature of trichoepithelioma is prevalent [3].

Disease Characteristics

Incidence of cutaneous trichoepithelioma remains undefined. MFT as autosomal dominant inheritance depicts an equal gender penetration and lacks a racial predilection. Multiple trichoepitheliomas predominantly affects adolescents, young females or individuals betwixt 10 to 20 years probably due to inadequate chromosomal penetration and minimal expression in males [3,4]. The disorder can appear in the 4th decade, though no age is exempt. Multiple familial trichoepithelioma with numerous lesions and an autosomal dominant penetration, encodes and annihilates the tumour suppressor gene situated on short arm of chromosome 9p21.

The solitary variant commences with a female preponderance at childhood or young age [3,4].

Desmoplastic trichoepithelioma can occur as a collision tumour with melanocytic nevus and manifests as an acquired condition or concurrent malformation.

Trichoepithelioma can follow a repetitive physical intervention for nevus eradication or excessive exposure to sunlight.

Trichoepithelioma characterizes an abrupt onset of pruritic lesions of amplifying magnitude.

Clinical elucidation of trichoepithelioma is non-confirmatory thus dermoscopic and histological analysis is essential for excluding cogent diseases such as basaloid epithelioma and basal cell carcinoma.

Dermoscopy is a beneficial technique which distinguishes benign from malignant proliferation. Trichoepithelioma on dermoscopy displays a pearly white exterior circumscribed by oval, hyper-pigmented tumour aggregates, multiple, superficial, centric keratinous cysts, a collagen envelop with arborizing peripheral blood vessels. On the contrary, basal cell carcinoma usually arises in elderly individuals above 50 years of age and demonstrates a pinkish-red backdrop with bluish-gray ovoid cysts and multiple globules. The lesions are translucent, pearl-tinted or pink red papules which progress gradually although significantly with central ulceration and superficial telangiectasia [4,5].

Cytokines and growth factors secreted by melanocytes can also activate the emergence of trichoepithelioma. An intensely hued, palpable nevus with pruritus and profound, intermittent sun exposure can stimulate melanocytes and induce trichoepithelioma [4,5].

Disease pathogenesis

Genetic mutations may concur with MFT. A primary mutation is localized on chromosome 9p21. A concomitant mutation of the cylindromatosis tumour suppressor (CYLD) gene, situated on chromosome 16q12-q13, is cogitated. CYLD gene is constituted by 20 exons with three un-translated exons, a configuration which induces genetic heterogeneity to MFT. However, MFT phenotype manifested with 9p21 genomic mutation is identical to the one arising from mutated CYLD gene. Brooke Spiegler syndrome (BSS) is associated with the CYLD gene [5,6]. MFT contingent to CYLD gene depicts a singular chromosomal mutation of the CYLD gene, as elucidated in BSS and familial cylindromatosis, a phenomenon known as “first hit”.

Sequential mutation/deletion of the CYLD gene occurs in the hair follicles instead of eccrine-apocrine cells incriminated in multiple cylindromas and is cogitated as a “second hit” [6,8].

Familial cylindromatosis, BSS and MFT can be cogitated as phenotypic variations of a singular entity. Tumour suppressor gene of CYLD encodes a deubiquitinating enzyme which coordinates the nuclear factor kappa light chain enhancer of activated B cells (NF κ B) and c Jun N-terminal kinase pathways. NF κ B is a predominant transcription factor incriminated in inflammation, immune reactions, genesis of tumours and apoptosis. Mis-sense mutation of CYLD gene modifies the amino acids within ubiquitin specific protease domain of CYLD protein. Therefore, de-regulated proliferation and differentiation of putative stem cells composing pilosebaceous-apocrine unit is initiated [5]. Numerous contemporary and novel mutations of CYLD gene can be identified in individuals with either MFT or BSS or in non-Caucasians. A minimum of 20 germ-line mutations of CYLD gene can be recognized in BSS, mutations exceeding 30 in familial cylindromatosis and an estimated 22 mutations in MFT [7,8].

Solitary trichoepithelioma is adjunctive to a genomic mutation at chromosome 9q22.3.

Clinical elucidation

Trichoepithelioma elucidates as a solitary, benign, asymptomatic skin tumour presenting skin coloured or yellowish papules or nodules with a refined, translucent surface and occasional telangiectasia measuring betwixt 2 - 8 millimetres. Lesions arise on the face, cheeks, nose, forehead, nasolabial groove, upper lip and cervical region [8,9].

MFT usually appears as multiple, symmetric, skin coloured or pigmented, pink, brownish or blue-tinged, firm, spherical to oval, translucent or shiny well defined papules or nodules. The nodules are preponderantly situated on the face (50%), naso-labial folds, nose, forehead, eyelids and hair enriched zones. Infrequently, lesions can be cogitated on the scalp, neck and upper trunk. The lesions vary from two to five millimetres in magnitude and may enhance up to 5 centimetres on the face or ears and 2 to 3 centimetres on adjunctive sites [4,5].

Trichoepitheliomas progress gradually with enhancing magnitude and quantification. Lesions can be centrally depressed or umbilicated.

Vascular dilatation with superficial telangiectasia is cogitated in larger lesions. The disorder often displays asymptomatic lesions devoid of ulceration and pruritus. Nodules can undergo malignant transformation and evolve into trichoblastic carcinoma or a basal cell carcinoma. MFT thus necessitates a vigilant monitoring of pre-existent lesions for expeditious growth or ulceration. Optimal sunlight protection can prevent or delay malignant conversion [6,7].

MFT can be associated with systemic disorders such as cerebellar infarction or cerebellar aneurysm, malignant lympho-epithelial lesion of the parotid gland, cheilognathopalatoschisis, jaw cysts, epilepsy, oligophrenia, bradykinesia, labyrinthine deafness, adipositas, Dupuytren's contracture and urinary disorders. Clinical significance of the concurrence remains unexplained [5,6].

Solitary trichoepithelioma is frequent in young adults and is situated on the mid-face and nasal region due to concentrated sebaceous glands. Mammoth trichoepitheliomas are exceptional, enlarge beyond one centimetre and localize on the neck, scalp or trunk.

Histological elucidation

Tumour histogenesis is variously described as the epidermis or epithelium of hair sacs or adult or embryonic pluripotent cells, embryonic rests or associated epithelial system, primary epithelial germ cell tumour or outer walls of the hair follicle and hair matrix [8,9].

A distinctive histological elucidation is paramount in demarcating trichoepithelioma from basal cell carcinoma. Characteristic histological attributes include horn cysts and tumour aggregates composed of basaloid cells. Horn cysts are constituted of completely hyalinised keratin centres circumscribed by basophilic cells devoid of atypia and mitosis. Keratinisation of horn pearls in trichoepithelioma is abrupt and complete, in contrast to keratinous horn cysts elucidated in squamous cell carcinoma. Primordial hair papillae and configurations akin to the hair shaft are sporadically enunciated. Tumour aggregates depict a peripheral palisade and augmented enveloping fibrous stroma [9,10].

Miniature clusters of mature sebocytes are demonstrated besides foci of ductal differentiation. It can be challenging to demarcate lesions of MFT or solitary trichoepithelioma from basal cell carcinoma in miniscule tissue specimens. Histological features supporting a diagnosis of trichoepithelioma are

- a) Symmetry and circumscription of the lesion
- b) Tumour islands displaying a smooth outline
- c) Clefts between stroma and epithelium
- d) Absence of retraction betwixt the tumour cell aggregates and enveloping stroma
- e) A fibrocystic stroma instead of a mucinous encompassment
- f) Minimal mitotic activity
- g) An element of mature follicular differentiation along with well defined, cornified cysts and papillary mesenchymal bodies [4-6].

An uninvolved epidermis with several dermal horn cysts circumscribed by minimal layers composed of cells with eosinophilic cytoplasm and elongated nuclei is cogitated. Tumours islands can be solid, comprising of miniature, monomorphic basaloid cells with pale-staining, vesicular nuclei, architecturally depicting a peripheral palisade. The aforementioned attribute is cogent in differentiating amidst lesions of trichoepithelioma and basal cell carcinoma.

Entirely keratinized horn cysts with a precipitous keratinisation demarcates the lesion from a squamous cell carcinoma. Solid tumour aggregates and branched cellular cords comprising of basaloid cells can about the horn cysts with the appearance of co-existent rudimentary hair follicles. The intervening stroma depicts abundant fibroblast like cells [9,10].

Trichoepithelioma depicts a cribriform pattern with distinct aggregates of germinating cells and a lightly-hued, fibrocystic stroma, papillary mesenchymal bodies interspersed with hair bulb like articulations. The epithelial-connective tissue islands are circumscribed by

cleft like spaces. In contrast, nodules of basal cell carcinoma display discrete aggregates of enlarged, basaloid cells with irregular outline, massive zones of necrotic stroma, mucin deposits and an artificial retraction of the stroma from cellular clusters with the emergence of clefts amidst germinating cell clusters and tumour perimeter [10,11].

Trichoepithelioma can exceptionally convert into basal cell carcinoma. Trichoepithelioma also requires a distinction from pigmented nevus.

Immune histochemistry

Distinction betwixt basal cell carcinoma and multiple familial trichoepithelioma can be ensured by employing immune antibodies such as Ber Ep4, CD34, CK20, bcl2, androgen receptors, transforming growth factor β (TGF β) and CD10. Additionally, p75 neurotrophin receptor (p75NTR) and pleckstrin homology like domain family A member1 (PHLDA1) can be utilized [3,4]. Trichoepithelioma is immune reactive to bcl2 as is basal cell carcinoma and immune reactivity to bcl2 appears to be diffuse within tumour cells and enveloping stroma of basal cell carcinoma. CD34 is immune reactive in blood vessels and stromal cells of trichoepithelioma and non-reactive in basal cell carcinoma. CD10 is varyingly immune reactive in peripheral basaloid or stromal cells of MFT and basal cell carcinoma. Instances where immune reactivity to bcl2, CD10 and CD34 remains indecisive application of androgen receptors, TGF β , p75NTR and PHLDA1 appears beneficial. However, tumour clusters and stroma may not react to Ber Ep4 and CK20 [4,5].

Immune reactivity of epithelial nests and keratinous cysts cogitated in classic solitary trichoepithelioma, desmoplastic trichoepithelioma, trichoblastic fibroma, trichogenic trichoblastoma and giant solitary trichoepithelioma are identical to the outer root sheath and infundibulum of normal hair follicles. Entire range of trichogenic tumours differentiate towards the external layer of exterior root sheath and associated components of the hair follicle. However, the spectrum of trichogenic tumours are devoid of specific immune reactivity [6,7].

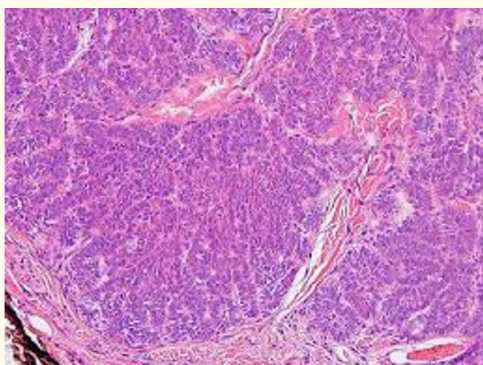


Figure 1: TE islands of basaloid cells with a fibrocystic stroma [16].

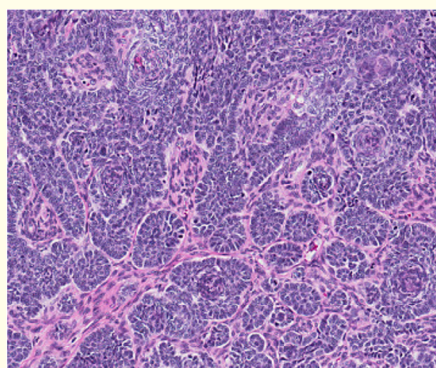


Figure 2: TE germinating hair follicular cell aggregates with circumscribing fibro-cellular stroma [17].

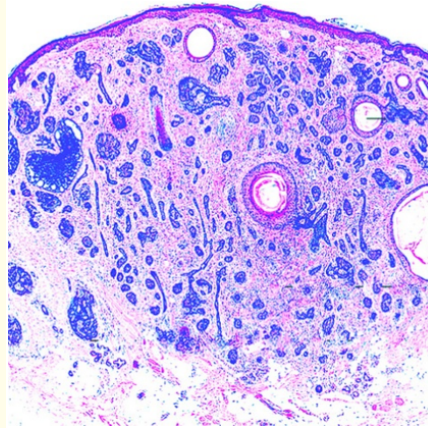


Figure 3: TE complete, abrupt, keratinized horn cysts with basaloid epithelial aggregates [18].

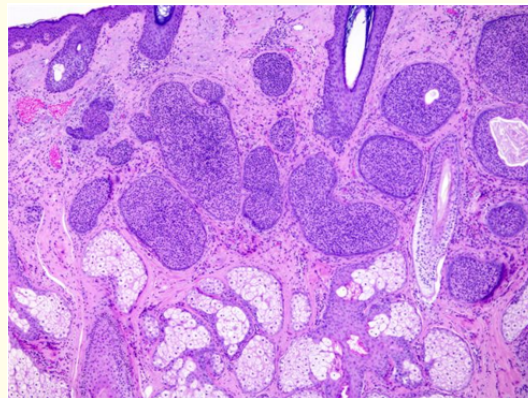


Figure 4: TE epithelial clusters of cells with minimal cytoplasm, peripheral palisading and large, hyperchromatic nuclei [18].

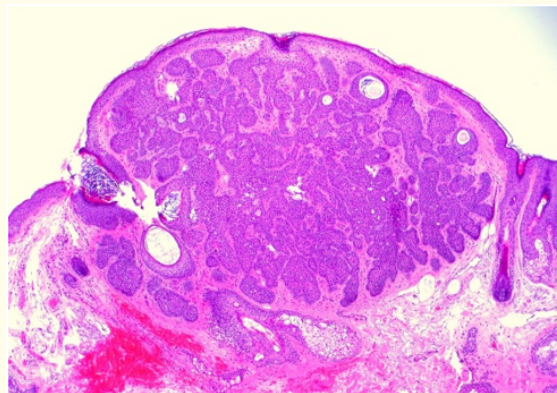


Figure 5: TE whole mount view of basaloid, hyperchromatic epithelial cords and strands with marginal palisade [19].

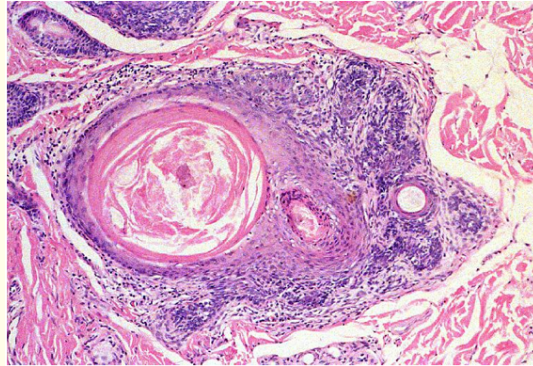


Figure 6: TE horn cysts with abrupt, comprehensive keratinisation and marginal, epithelial aggregates [20].

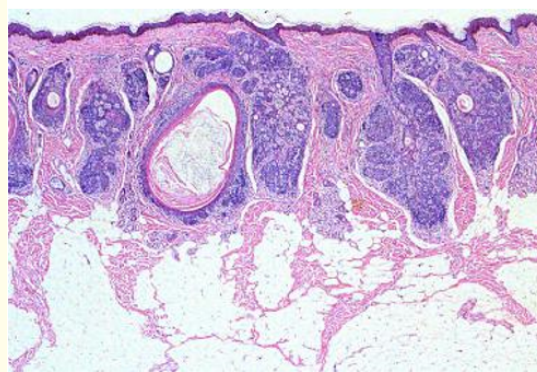


Figure 7: TE horn cysts with dispersal of cords and clusters of basaloid epithelial cells [20].

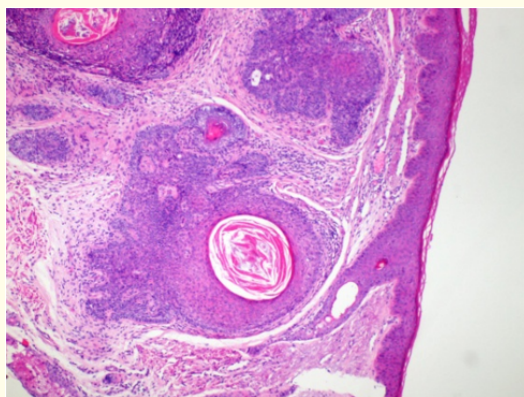


Figure 8: TE stratified squamous lining enveloping horn cysts and basaloid epithelial aggregates [21].

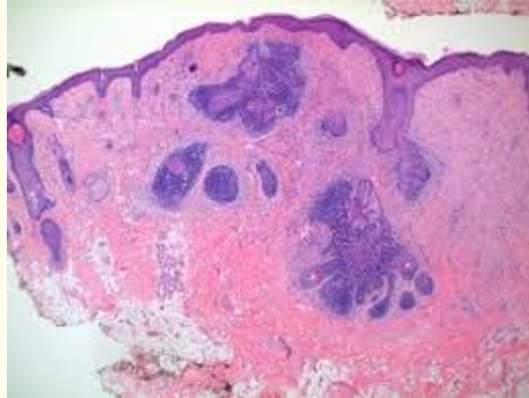


Figure 9: TE basaloid epithelium with a peripheral palisade and dense, fibrous connective tissue [22].

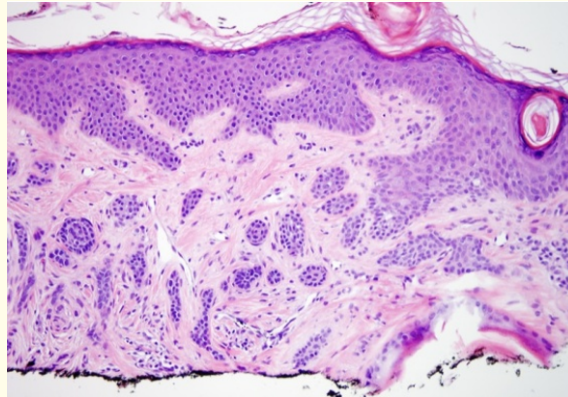


Figure 10: TE desmoplastic variant with horn cysts, basaloid accumulations and intense, fibrous connective tissue envelope [23].

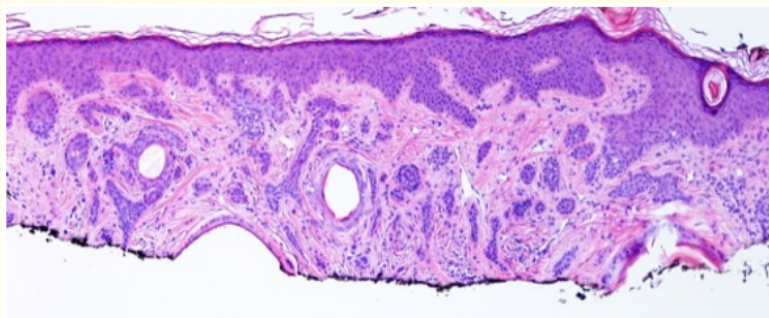


Figure 11: TE desmoplastic category with extravagant fibrotic stroma, horn cysts and epithelial cords [23].

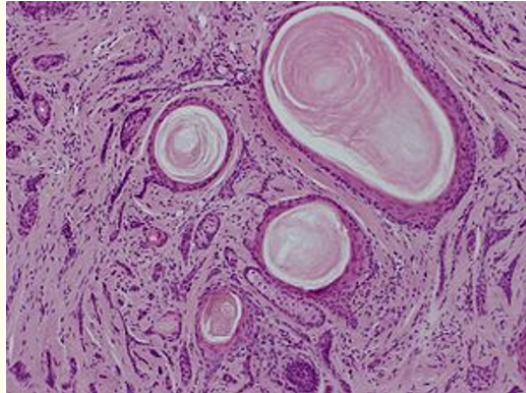


Figure 12: TE prominent horn cysts, dense stroma and strands of epithelium [24].

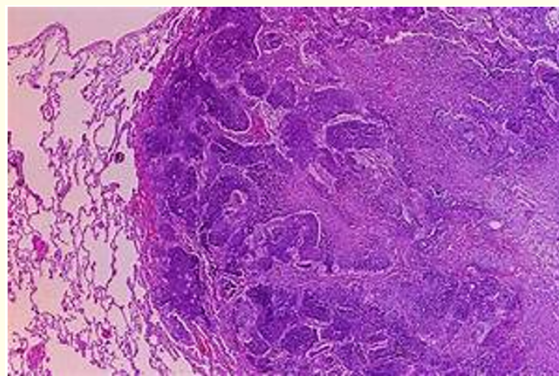


Figure 13: TE malignant with features of anaplasia, hyperchromasia, mitosis and rapid proliferation [25].

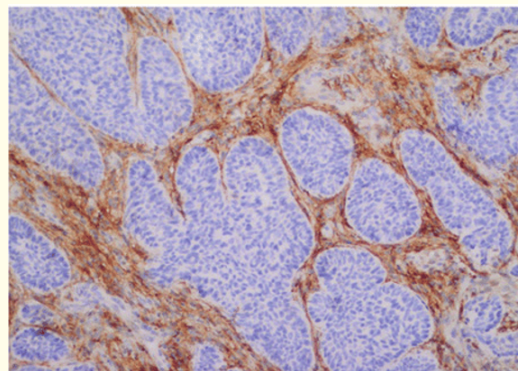


Figure 14: TE dense fibrous connective tissue stroma immune reactive to CD10 [26].

Therapeutic options

Therapeutic intervention is necessary in clustered and disfiguring lesions for favourable cosmetic outcomes. Preventive methodologies are currently undefined. Surgical excision is the optimal therapeutic strategy [1112].

Non-surgical options include laser resurfacing, electro-surgery, cryosurgery and dermabrasion. Utilization of erbium: Yag and carbon dioxide laser is associated with minimal scarring and reappearance of lesions within two years, in contrast to outcomes achieved with conservative therapies. A carbon dioxide laser appears as appropriate therapy and is devoid of pain, haemorrhage from the lesions and post-surgical oedema [12,13].

Complications of aforementioned strategies are reoccurrence of skin lesions, pain which necessitates the administration of local anaesthetic, haemorrhage, scarring and secondary malignancies of the skin.

Lesions of MFT tend to regress and grow less evident over an extended duration. Thus a policy of active surveillance with verbal reassurance can be advantageous in managing the patients [13,14].

Administration of oral 13 cis retinoic acid can prove to be inefficacious.

A 5% imiquimod cream is employed with partial clinical response. A therapeutic combination of tretinoin gel with 5% imiquimod cream is suitable and can be applied for a duration of up to three years without secondary scarring. Tretinoin as an agent can normalize the proliferation of epidermal cells and the thickness of trichoepithelioma is reduced with enhanced absorption of imiquimod. Therapeutically, imiquimod promotes epithelial maturation along with secretion of tumour necrosis factor alpha (TNF α) and interferon gamma (IFN- γ) which aids the evolution of T helper cell 1 (Th1) lymphocyte mediated immune response [3-5].

Agents such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) pharmacologically prohibit the activity of NF κ B and are efficacious in MFT.

Monoclonal antibodies such as adalimumab, when administered in conjunction with aspirin, appear competent in eliminating TNF α induced stimulation of NF κ B molecules [3,5].

Concordant conditions

Multiple familial trichoepithelioma (MFT) can appear as a component of Brooke Spiegler syndrome and Rombo syndrome.

Brooke Spiegler syndrome (BSS) displays an autosomal dominant mode of transmission. Mutation of the CYLD gene situated on chromosome 16q12-13 is cogitated. The gene functions as a tumour suppressor and inhibits unrestricted cell division and growth. The syndrome clinically manifests with multiple trichoepitheliomas, cylindromas and spriadenomas arising on the face and cervical zone [14,15].

Rombo syndrome is inherited as an autosomal dominant disorder and comprises of vermiculate atrophoderma, milia, hypotrichosis, basal cell carcinoma, trichoepithelioma and peripheral vasodilatation with cyanosis [13,15].

Conclusion

Trichoepithelioma displays a characteristic histology with horn cysts with completely hyalinised keratin centres and basaloid tumour nests. A cribriform pattern with aggregates of germinating cells, a fibrocystic stroma and papillary mesenchymal bodies with hair bulb like articulations are exemplified. Immune reactivity to Ber Ep4, CD34, CK20, bcl2, androgen receptors, transforming growth factor β (TGF β), CD10, p75 neurotrophin receptor (p75NTR) and pleckstrin homology like domain family A member1 (PHLDA1) is cogitated and utilized in the demarcation from basal cell carcinoma. Brooke Spiegler syndrome (BSS) and Rombo syndrome are concordant conditions

with an autosomal dominant inheritance. Surgical excision is the optimal therapeutic strategy. However, non-surgical options such as laser resurfacing, electro-surgery, cryosurgery and dermabrasion can be adopted.

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