MULTIPLE TRICH EPITHELIOMA A REVIEW AND REPORT OF A CASE SHOWING UNUSUAL FINDINGS. (A NEW SYNDROME)

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INTRODUCTION:

Trichoepitheliomas (TEs) are small hamartomas or organoid lesions that consist of nests of basaloid keratinocytes with follicular differentiation [1].

Two forms of TEs are known: the multiple epithelioma adenoides cysticum which is also known as Brooke syndrome or multiple benign cystic epitheliomas. The second type is the solitary trichoepithelioma which is also known as trichoblastoma [2]. The multiple TEs usually appear in early childhood before the age of six [2] or at the age of 7 years [3] and also occur in early teens.

Clinically TEs, appear as small firm skin papules usually 2-5 mm in size. They may be flesh color, yellowish or bluish and often have a translucent sheen [2]. They usually have symmetric distribution and affect nasolabial folds, nose, preauricular region, forehead, upper lip, ears, and occasionally other body sites, as scalp, neck and trunk [2]. They are usually asymptomatic and grow slowly, and stabilize in size within few years, and clinically may mimic the appearance of basal cell carcinomas [1].

Rarely the multiple facial papules coalesce into a large hemifacial plaque taking a naevoid distribution [2] .

Epithelioma adenoides cysticum is usually an expression of a family trait and is of autosomal dominant inheritance [1, 4]. The gene for TE is mapped to chromosome 9P21 and the gene may be also a tumor suppressor one [5]. Solitary TE is non hereditary and rarely exceeds 0.5 cm in diameter and is usually seen on the face and is often mistaken for non pigmented cellular nevi. Few cases of solitary TE were described as being giant solitary trichoepithelioma that may reach a size of 3-4 cm x 2 cm [6] and has predilection to affect girdle particularly the perineum and is of rare incidence. It was also reported to affect groin, upper thigh, thigh and natal cleft. Desmoplastic TEs may be a variant of TE rather than a distinct entity and are characterized clinically by annular configuration with firm sclerotic border and may be solitary or multiple.[7] The relation between desmoplastic epithelioma and ordinary TEs is still disputable. It is postulated that a similar or identical genetic alteration could be responsible for both lesions but that other factors influence the phenotypic expression of a lesion as either a conventional TE or a desmoplastic one. [7] The trichoblastic fibroma differs from TE clinically as it is large solitary dermal or subcutaneous nodule of 1-8 cm in diameter without hereditary predisposition [8]. Trichoblastic fibroma is a benign trichogenic tumor which has epithelial and mesenchymal components and exhibit partial to complete follicular differentiation [9] and has been referred to as fibromatoid trichoepithelioma [10].

TE is a benign cutaneous epithelial-mesenchymal tumour with pilar differentiation and is best regarded as hair germ hamartoma [11,12]

Histologically TEs show well-circumscribed nodules that can occur either as solid islands and lobules or in an adenoid pattern. The tumor is composed of basaloid keratinocytes that connect with the epidermis and often palisade in the tumor's periphery. The tumor is surrounded by prominent fibrous stroma.

Trichoepitheliomas are relatively poorly differentiated follicular tumors that do not produce hair shafts. TE is characterized by formation of horn cysts with abrupt keratinization and by the papillary mesenchymal bodies, which indicate differentiation towards hair structures. It may be sometimes difficult to distinguish BCC from trichoepitheliomatous proliferations histopathologically. The presence of papillary mesenchymal bodies is characteristic of TEs. The formation of primitive hair bulb was observed in 30% of TEs but was not seen in any BCC [8] .

The papillary mesenchymal bodies are present in 93% of TE and only in 7% of keratotic BCC and 0% in all routine BCC. These papillary mesenchymal bodies are distinct fibroblastic aggregations that represent abortive attempts to form the papillary

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mesenchyme responsible for hair induction [13].

There is histopathological overlap between TE and BCC [9], and it may be difficult to differentiate desmoplastic trichoepithelioma from morpheaform BCC. BCC frequently shows clefts between tumor islands and stroma, such clefts are infrequent in TEs. Clinically BCC may ulcerate while TEs never do. Trichoepitheliomas and BCC can be differentiated immunohistochemically because BCC and trichoblastic fibroma show cytokeratin 7 expression while TE does not [8].

The TEs may coexist with multiple dermal cylindroma in a syndrome known as Brooke Spiegler syndrome [14,15] Both TEs and cylindromas are autosomal dominantly inherited [16].

TEs were reported in association with familial multiple eccrine spiradenomas in three generations of one family although it is known that spiradenomas do not have familial tendency [16].

Eccrine spiradenomas are usually solitary bluish red tender nodules dermal or subcutaneous mainly affecting young adults and develop most commonly on the upper dorsal aspect of the body [17].

Basal cell carcinoma occasionally arises from pre-existing lesions of TEs and observing genotypes obtained by polymerase chain reaction with microsatellite markers of chromosome 9P21 indicates that basal cell carcinoma gene on chromosome 9q may be directly responsible for development of BCC in patient with TEs [18] .

Trichoepitheliomas were described also in Rombo syndrome which is autosomal dominant and is characterized by atrophoderma vermiculatum, milia, hypotrichosis, trichoepitheliomas, basal cell carcinoma and peculiar peripheral vasodilation with cyanosis of the hands, feet, lips with progressive loss of eye lashes and eye brows[19,20,21].

Trichoepitheliomas were also reported to be part of Rasmussen's syndrome which is characterized by combination of TEs, milia and cylindromas. The milia were only found in areas of vellus hairs. Rasmussen's syndrome is autosomal dominant [22,23].

Case Report

Patient F.M.A.D. is 12 years old Qatari child who presented to Dermatology Clinic referred from Primary Health Care Center, with the diagnosis of multiple warts on the face which started to erupt at the age of one year. On examination the child was found to have asymptomatic multiple skin colored dome shaped smooth surface papules some with a brown tint, 1-2 mm in diameter distributed on the periorbital and nasolabilal fold bilaterally with the involvement of both cheeks, similar lesions were also found on the anterior and posterior trunk as well on both upper and lower limbs. (Fig. 1,2,3,4,5,6,7).It was observed that the patient had few ash leaf hypopigmented macules and few cafè au lait spots on the trunk and showed mild elasticity of the skin

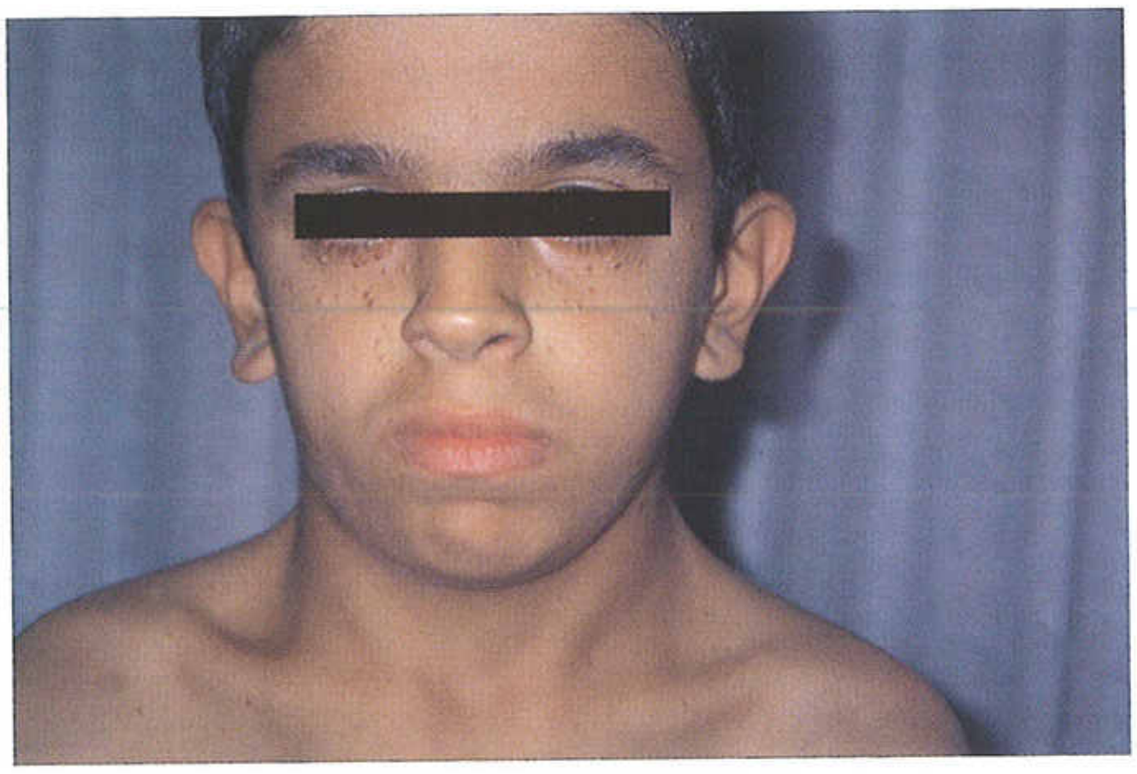

Fig 1.TEs of the face.

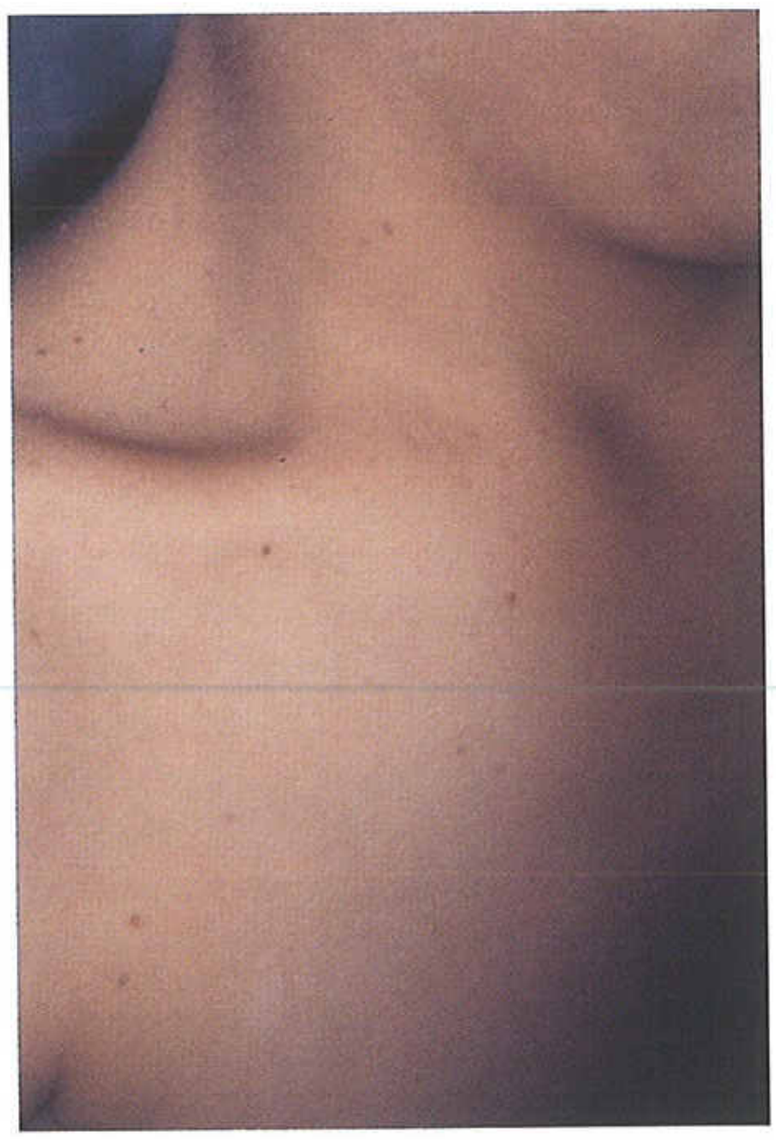

Fig 2. TEs of the neck and chest with ash leaf

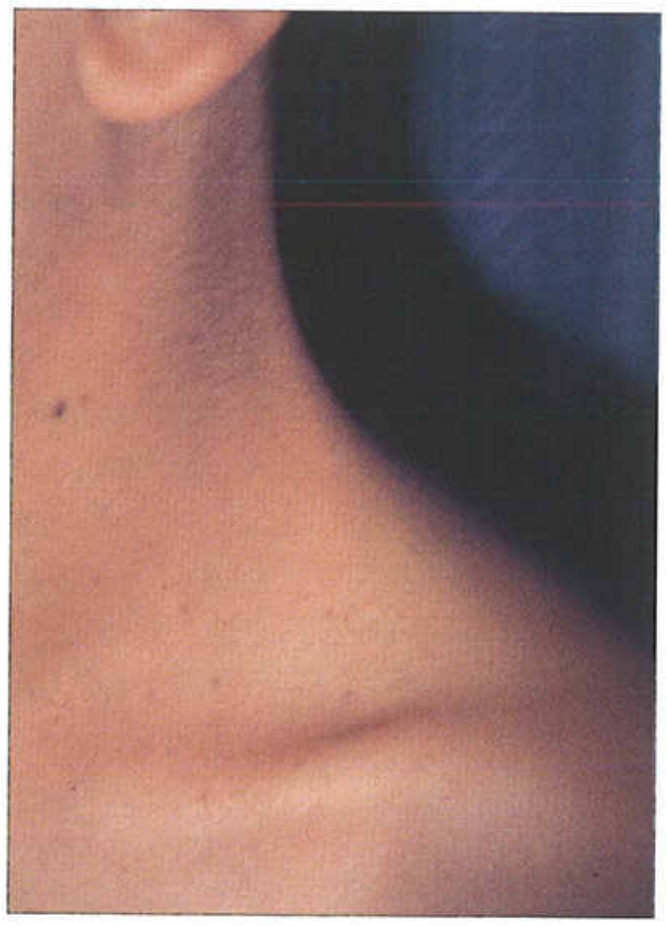

Fig3. TEs of neck and chest. Neck shows yellowish papules reminding of pseudoxathoma elasticum

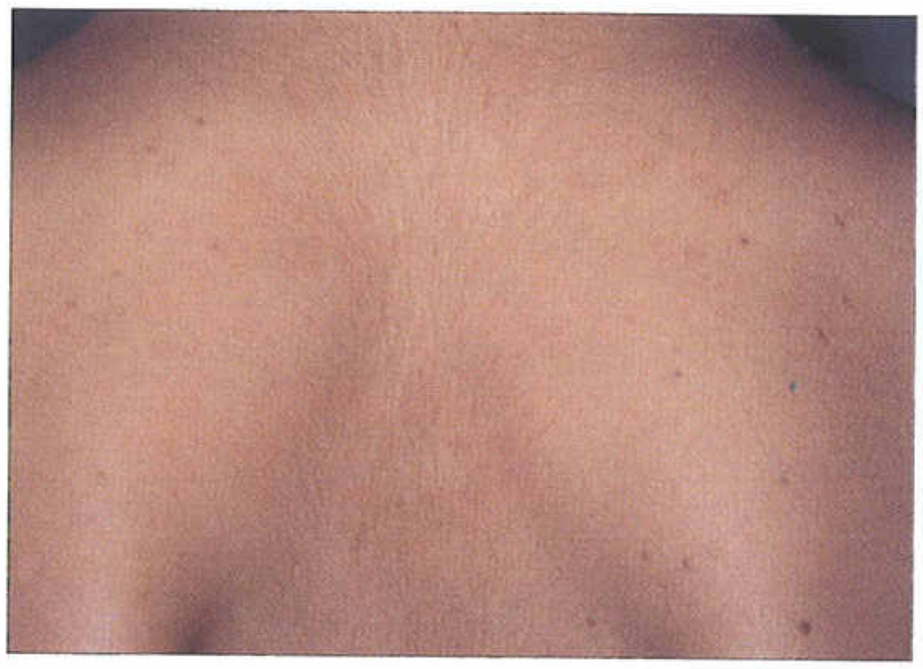

Fig4. TEs of the back

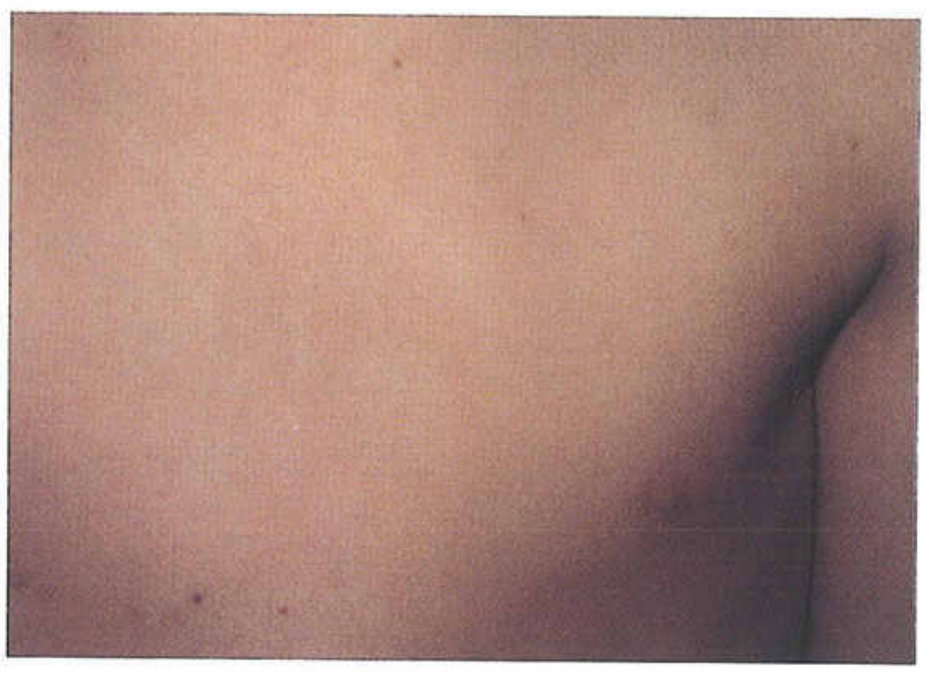

Fig5. TEs of the chest

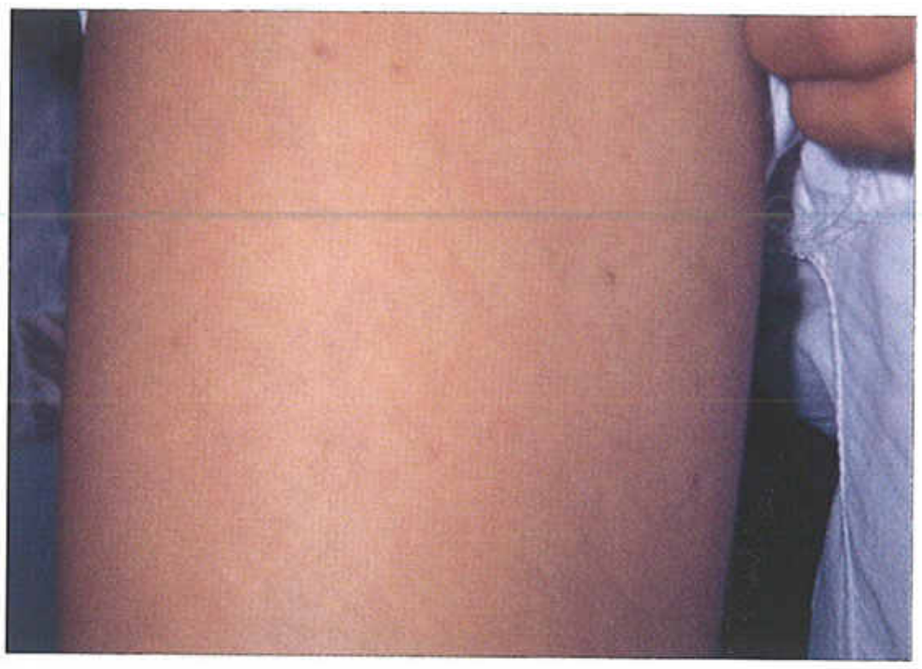

Fig6. TEs of the right thigh

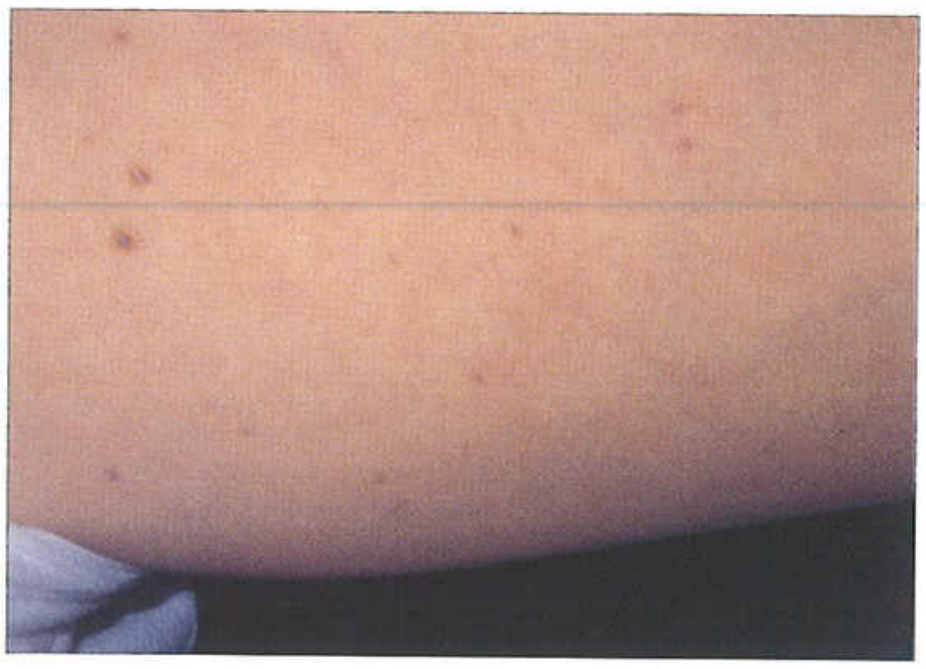

Fig7. TEs of the left thigh

with no laxity of the joints with normal teeth and nails.(Fig.8,9,10,11,12) . The child has low seated large prominent ears, high arched palate and webbing of the neck. [13,14], winged scapulae, wide carrying angle of the elbow joints (cubitus vulgus.) (Fig.15, 16), widely spaced hypoplastic nipples. (Fig.17). Genitalia were of normal development.

The child is below average intelligence and gave no history of fits.

Past history: Full term normal vaginal delivery, he had neonatal jaundice at the age of 3 days and U/S showed hydrocephalus at the age of 7 month with normal brain CT scan. His development was mildly delayed.

Family history: Parents are second degree relatives. Had a younger sister with Down syndrome who died at the age of two years because of cardiac problem. All other siblings are normal.

Investigations done included CBC, LFT, KFT, U/E, all within normal. X-ray skull was normal. Chest x-ray showed clear lung fields, scapula outline mildly hypoplastic, the first ribs both sides also hypoplastic. Xray pelvis: No significant abnormality. X-ray dorsolumbarspine AP and LAT were normal. EEG showed abnormal record because of occipital spike with wave, more active on the right side. These findings could be benign epilepsy of childhood with occipital spike.

Five skin biopsies were taken, one from facial papules, the second from a papule of the back. The

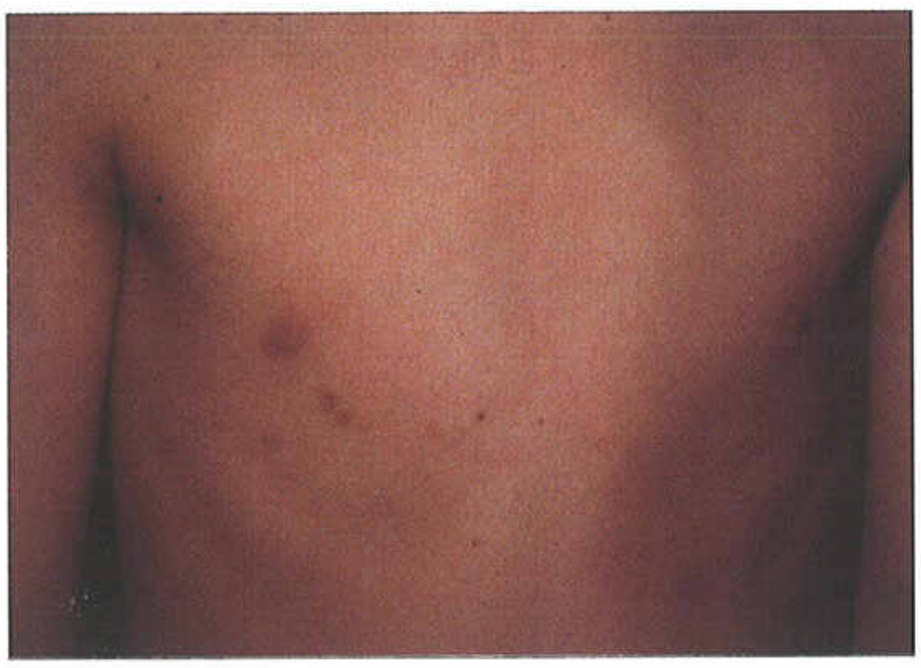

Fig8. Ash leaf hypopigmented macule and widely spaced hypoplastic nipples.

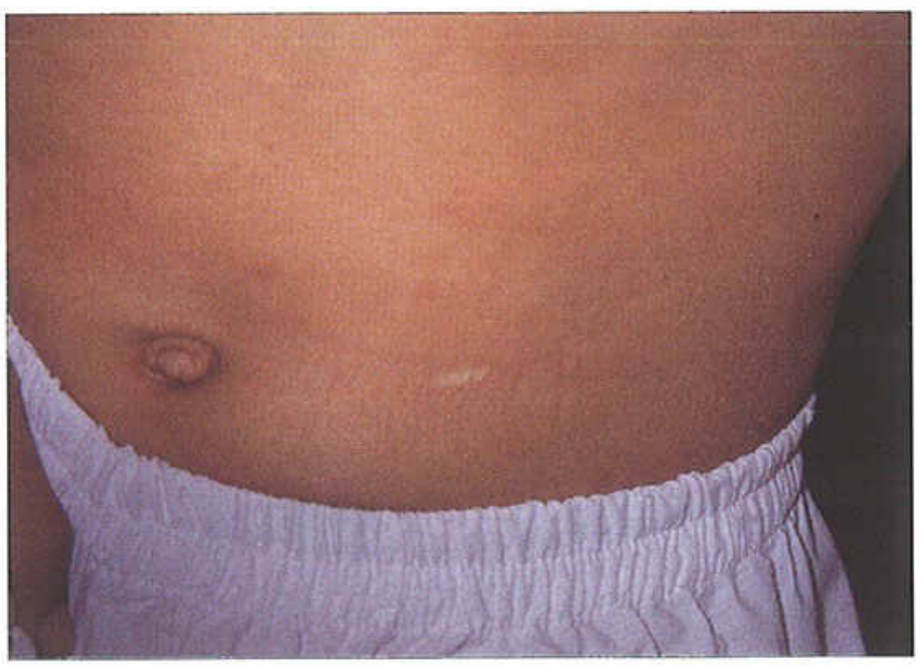

Fig9. Ash leaf Hypopigmented macule

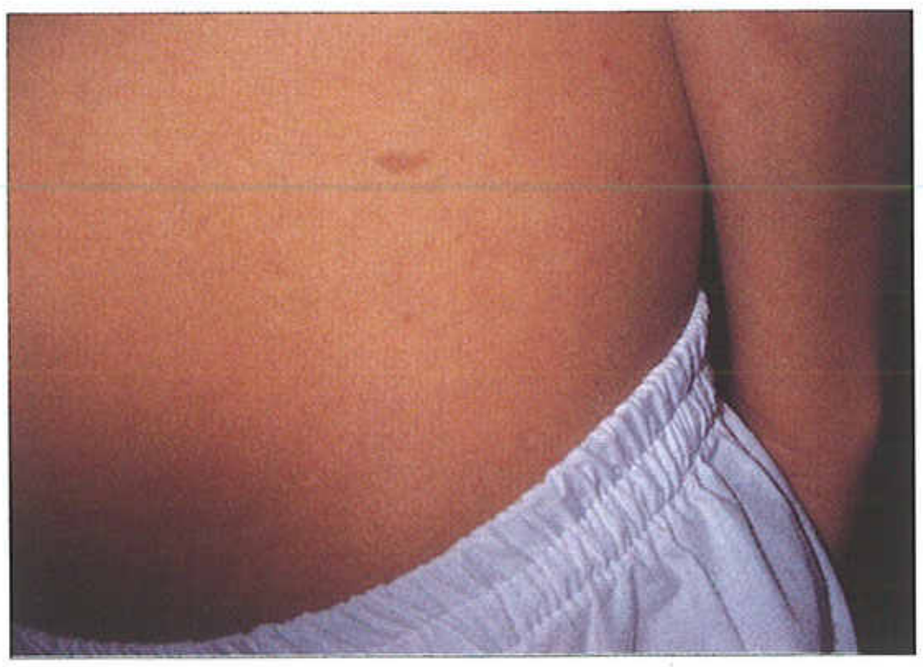

Fig10. Café au lait hyperpigmented macules

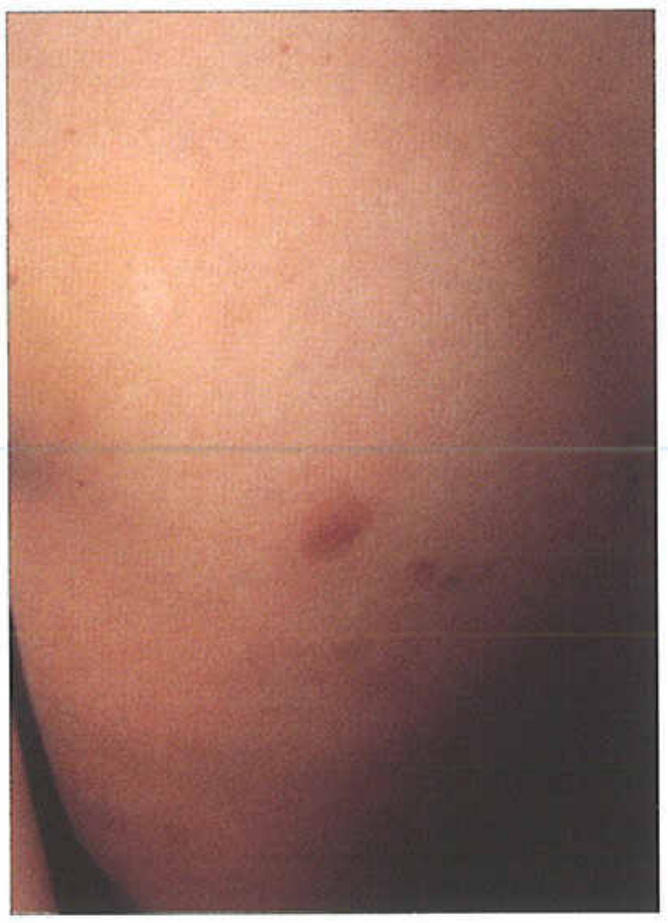

Fig11. Café au lait hyperpigmented macules

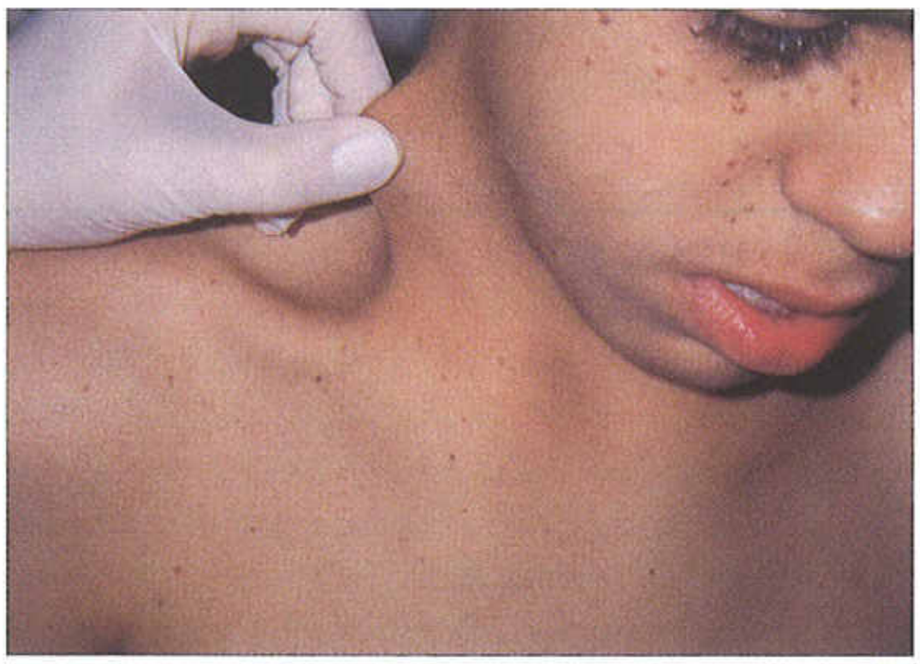

Fig12. Hyperelastic skin

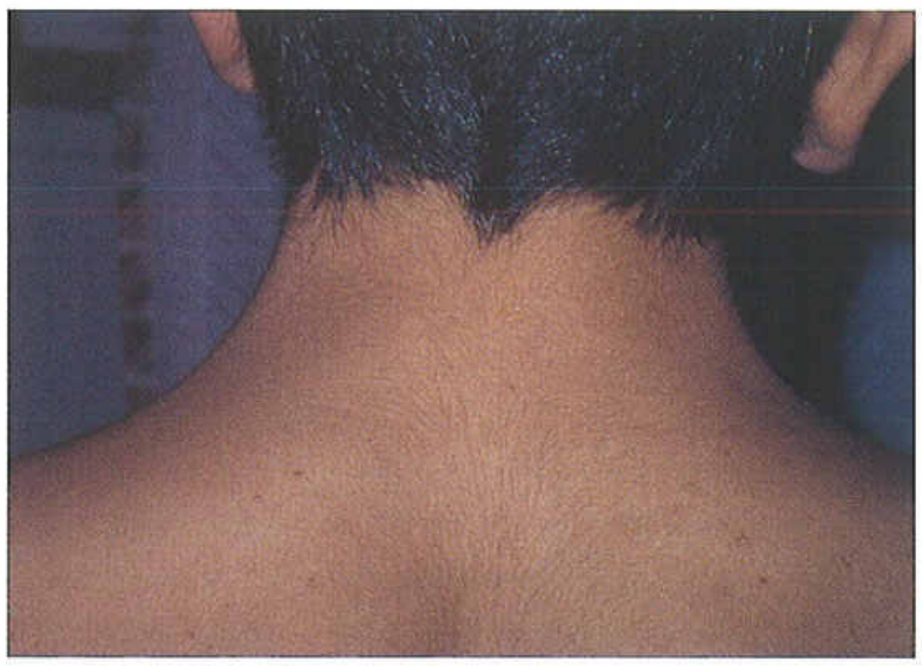

Fig13. Webbed neck

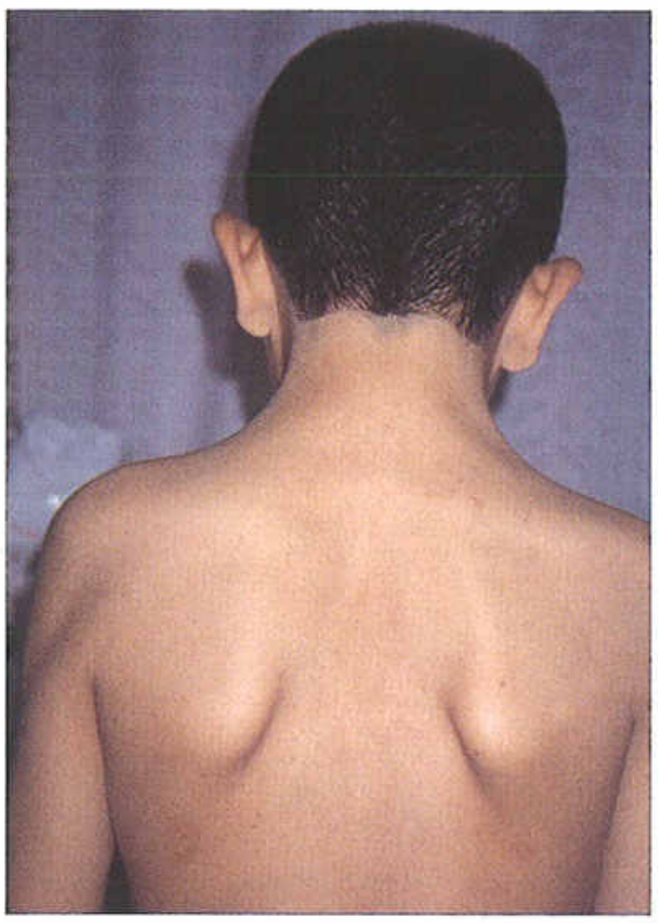

Fig14. Webbed neck, lowset ears, winged scapulae.

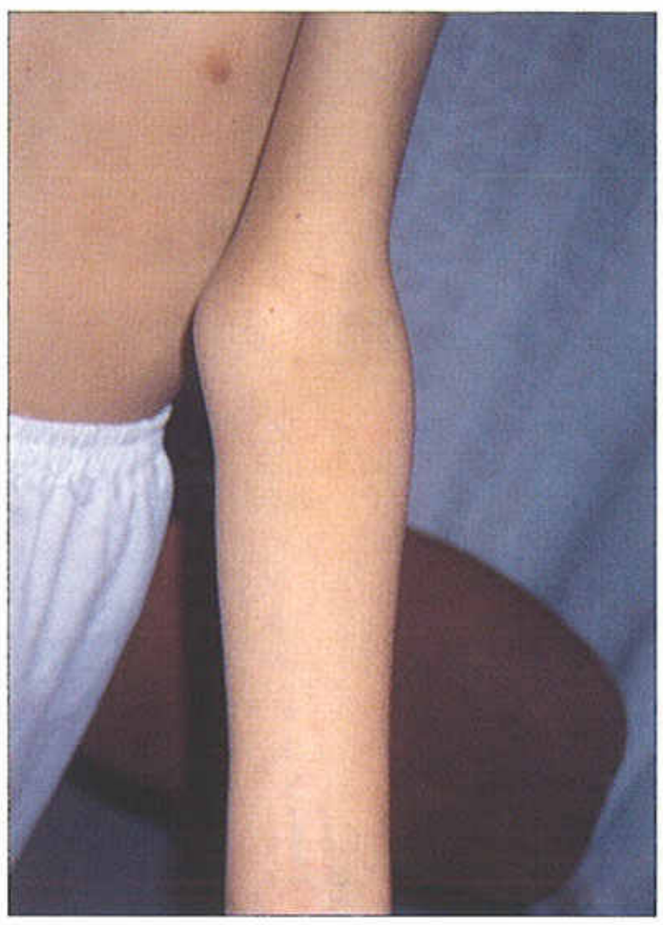

Fig15. Cubitus vulgus - left elbow joint

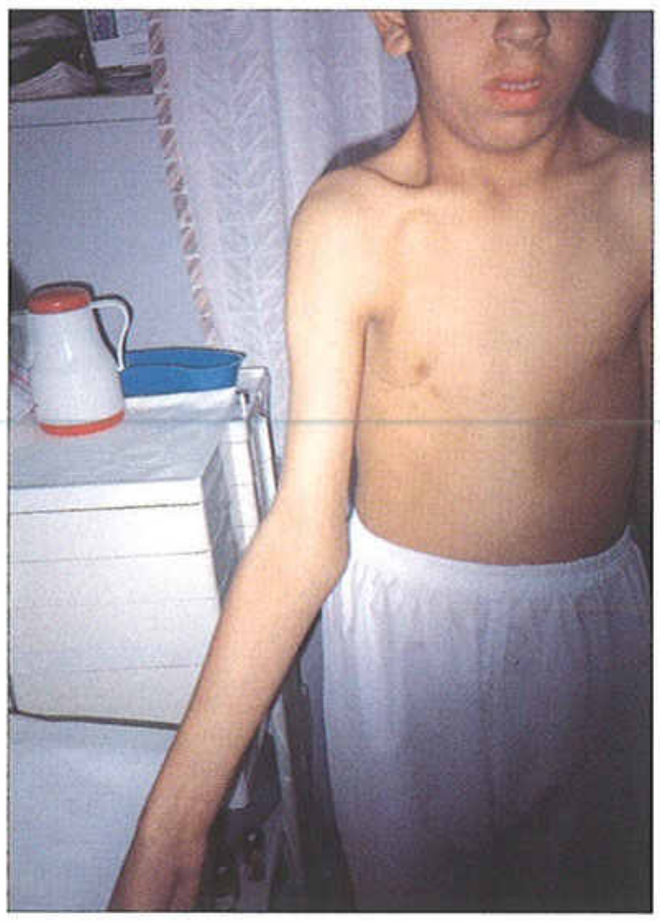

Fig16. Cubitus vulgus - right elbow joint

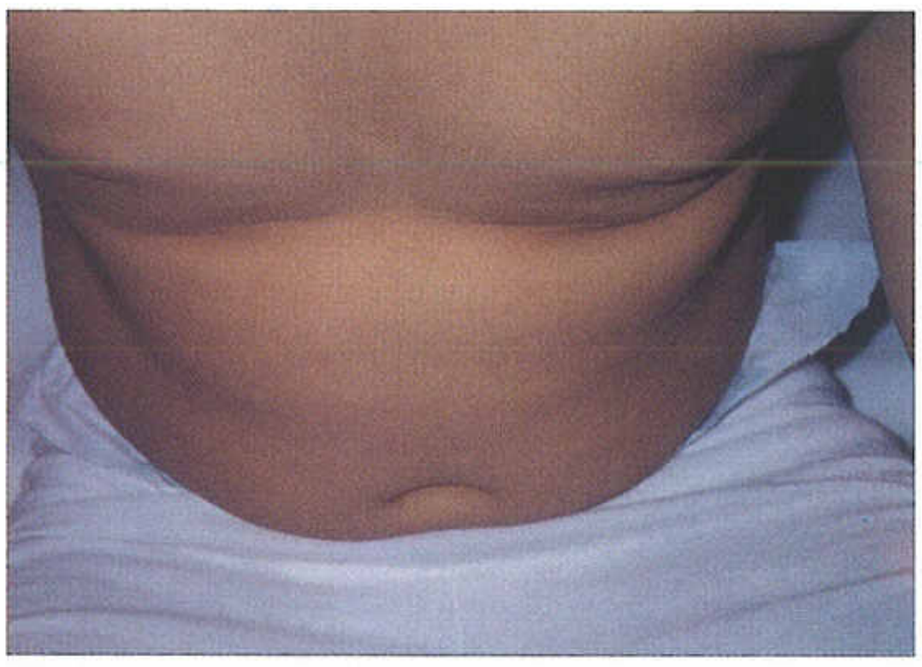

Fig17. Wide spaced hypoplastic nipples

third, fourth and fifth were taken from normal skin, ash leaf hypopigmented lesion and café au lait spots respectively.

Histopathology

Sections of the 3-mm skin punch biopsy from the face showed characteristic features of a trichoepithelioma. Multiple cords of basaloid cells in radiating and antlerlike branching pattern were present. Cells in the peripheries of the basaloid cord were arranged in palisade fashion, resembling basal cell carcinoma (Fig.18-20). However, there was no high-grade atypia or necrosis and mitotic figures were extremely scanty.

These epithelial nests were enveloped in a fibrotic stroma. Mucoid changes were present associated with slits and small spaces at the interface of the epithelial cords and surrounding stroma (Fig.20), but the "separation artifacts" of the type and magnitude commonly seen in basal cell carcinoma were absent. Some of the basaloid cords were connected to and continuous with the epidermal basal layer. A small nodule of smooth muscle was present, closely associated with basaloid nests recapitulating arrector pili muscle (Fig.21). Abortive hair follicles, some with minute horn cysts, as well as small foci of sebaceous differentiation (Fig.22) were noticed. Melanin pigment was relatively abundant both in the epithelial nests and in the connective tissue stroma. Sections of the 3-mm skin biopsy from the back also showed a trichoepithelioma essentially similar to the tumor seen on the face. Horn cysts were, however, more obvious compared to the first biopsy (Fig.23). Moreover, multinucleated epithelial aggregates were present in the center of the basaloid cells (Fig.24). Also inflammatory cells in the tumor stroma composed of mast cells, lymphocytes and occasional plasma cells were noticed.

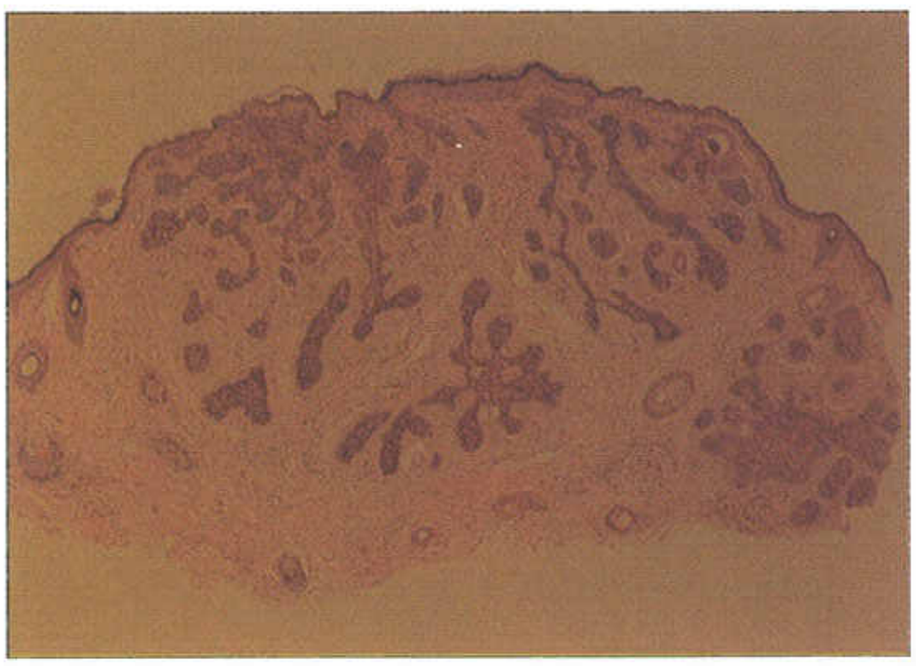

Fig18. Trichoepithelioma. Low power view of the biopsy from the face showing multiple nests of basaloid cell. (Hematoxylin & Eosin).

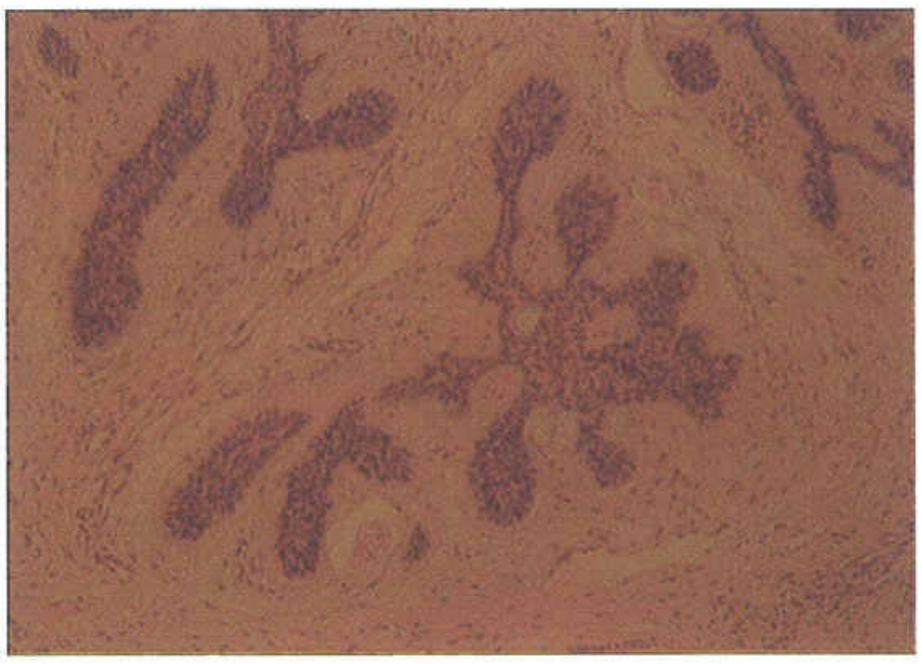

Fig19. Radiating and antlerlike basaloid islands surrounded by a fibrous stroma. (Hematoxylin & Eosin).

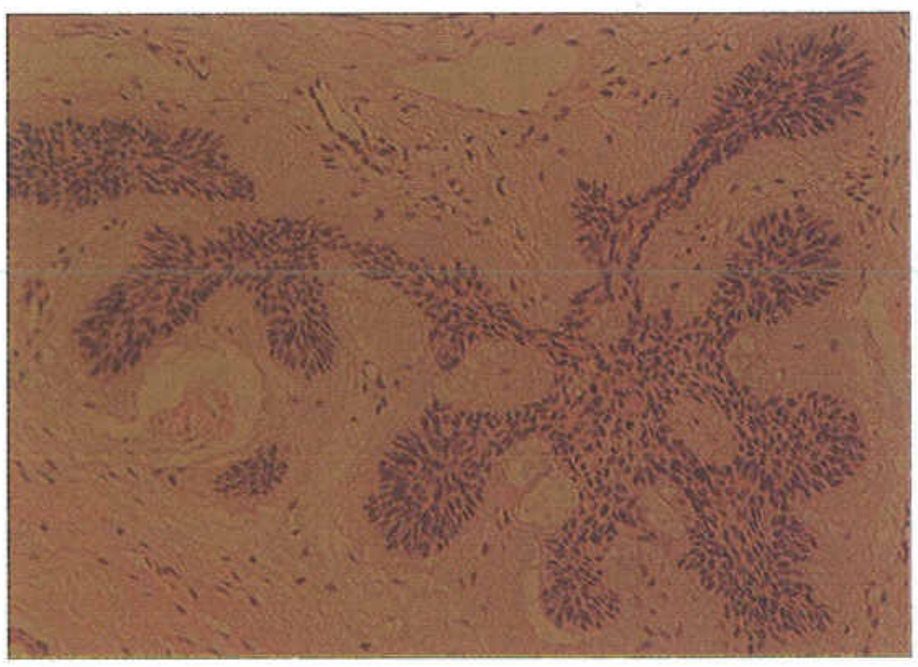

Fig 20. Note slits and small spaces separating epithelial nests from connective tissue stroma, caused by accumulation of mucopolysaccharides. (Hematoxylin & Eosin).

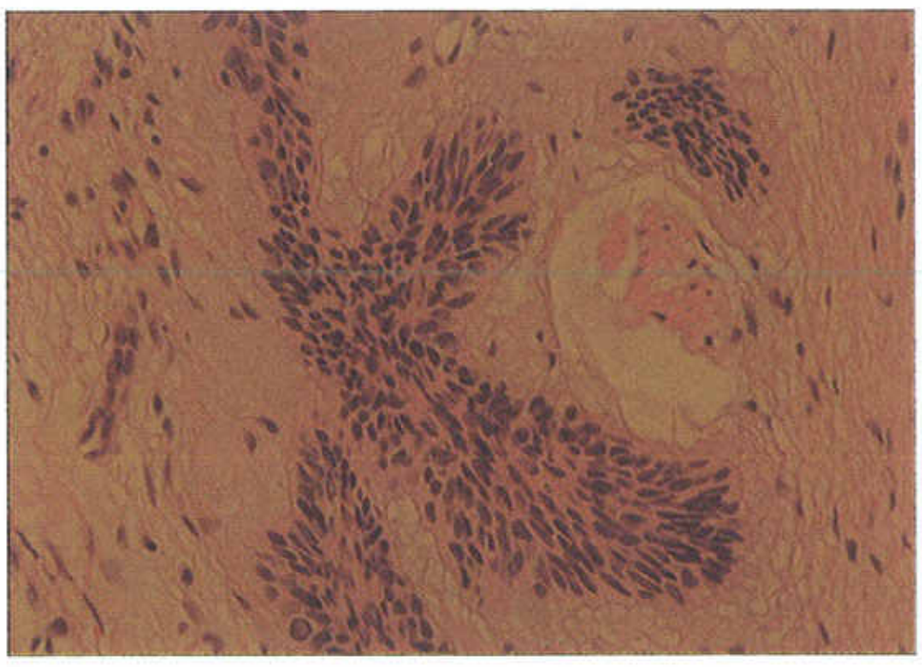

Fig 21. High power view to demonstrate a nodule of smooth muscle, simulating arrector pili muscle? (Hematoxylin & Eosin).

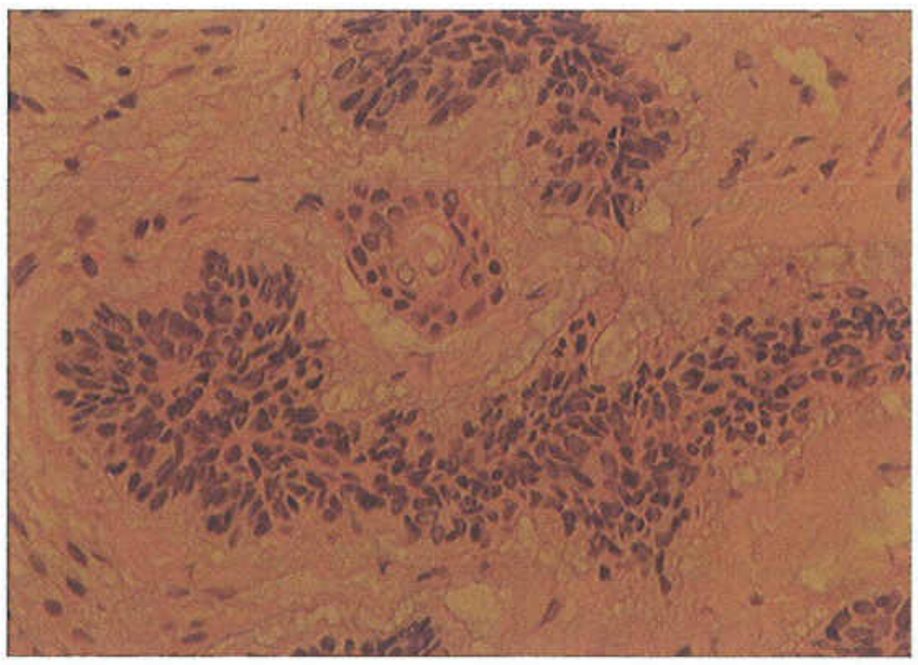

Fig 22.The small epithelial nest in the center shows features suggestive of sebaceous differentiation. (Hematoxylin & Eosin).

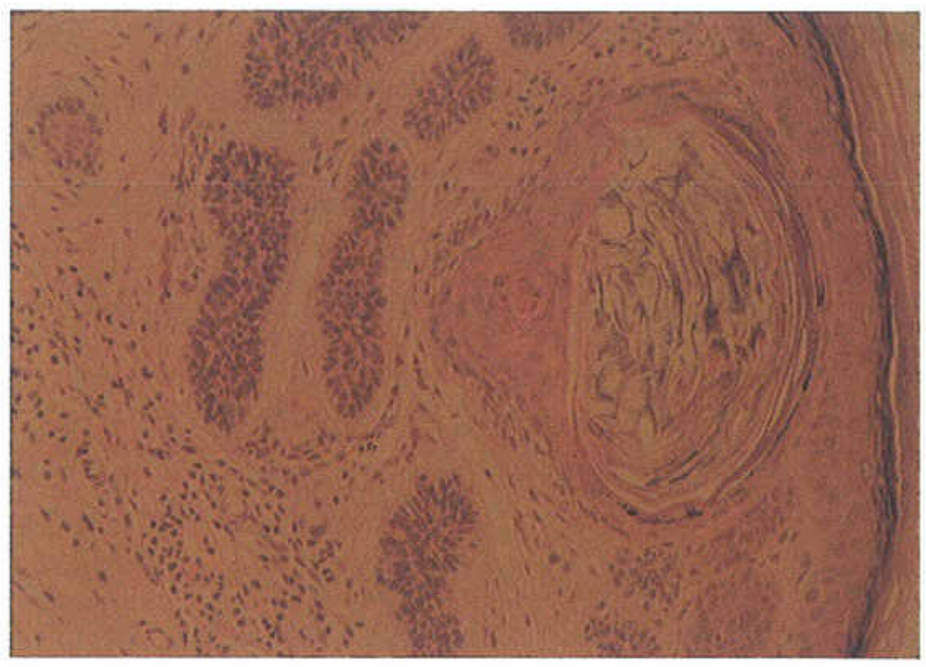

Fig 23. "Horn cyst" in trichoepithelioma. (Hematoxylin & Eosin).

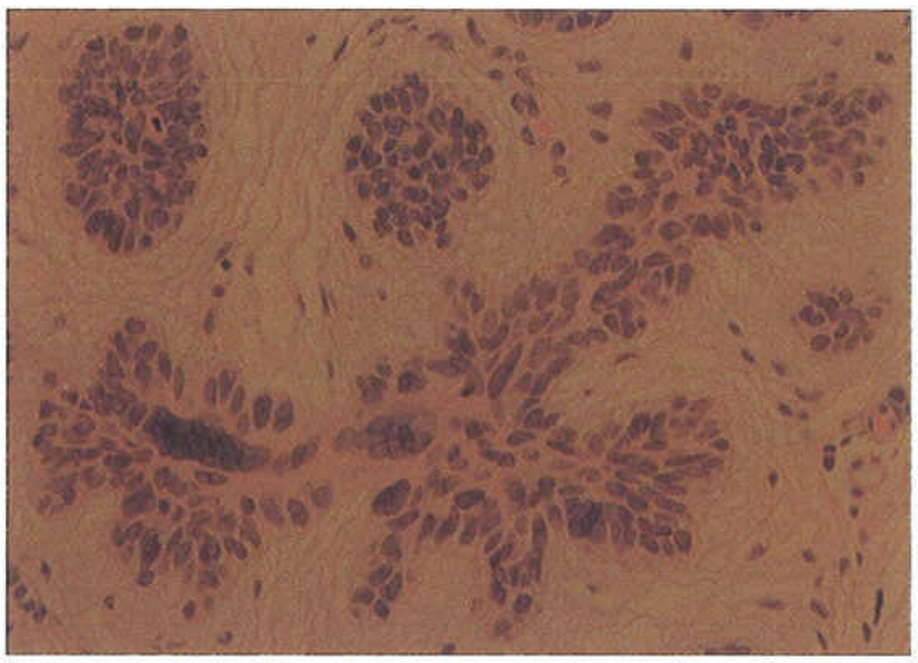

Fig24 Multinucleated epithelial cells in basaloid nests in trichoepithelioma. (Hematoxylin & Eosin).

Three 2-mm punch biopsies designated as "normal", "ash-leaf" and " cafè au lait spot" respectively, showed minor changes of sparse pigment-laden cells and a perivascular sprinkling of lymphocytes in papillary dermis.

There was no giant melanosome present in any of the biopsies.

Comment:

The benign nature of TEs has been emphasized. Patients with TEs may rarely develop BCCs which were reported to occur on upper lip; temple, nose, ear and forehead and it is probable that sun exposure predisposes to BCC development. [24] It was not possible to find out whether these BCCs developed from pre-existing TEs or the two tumors were coincidental.[24]

Histopathologically the desmoplastic epithelioma shows strands of basaloid cells, conspicious horn cysts, fibrotic stroma and more than 10% of cases are associated with intradermal nevus[25]. Melanocytic nevi have been associated with epidermal hyperplasia resembling seborrhoeic keratosis, follicular cysts, trichostasis spinulosa.[26] , syringomas, BCCs and hair follicle formation on the sole.[27]

Desmoplastic TE has to be differentiated from morpheoic basel cell epitheloma because the latter needs aggressive surgery. [28] Study of desmoplastic trichoepitheliomas using beta-2- microglobulin and a panel of anticytokeratin antibodies demonstrated that the tumor cells showed the phenotypes of keratinocytes of the infrainfundibular outer root sheath. [29] Cutaneous tumors often occur in multiple and solitary forms and have a genetic pattern. The multiple ones are generally autosomal dominant and are sometimes associated with other skin or internal lesions. The solitary ones have the same histology like the multiple and are non-hereditary[30]. The tumors that illustrate this genetic principles are:-

1. Adnexal tumors such as cylindroma, sebaceous adenoma, steatocystoma and epithelial tumors of hair follicle namely trichoepitheliomas, trichofolliculoma and trichilemmoma.
2. Some tumors of the perifollicular connective tissue which includes perifollicular fibroma, trichodiscoma and fibrofolliculoma.
3. Non adenexal tumors such as neurofibroma, leiomyoma, clear cell acathoma and tuberous sclerosis.

The trichoepitheliomas are to be differentiated from .[30]

1. Nevoid basal cell carcinoma syndrome which is autosomal dominant and is characterized by ge-

netic predisposition to develop multiple BCC. on sun exposed and non sun exposed areas at an early age. This syndrome is associated with odontogenic cyst, brain calcifications, skeletal abnormalities, pits on palms and soles and benign and malignant tumors such as ovarian fibromas and medulloblastomas.

2. Rombo syndrome characterized by vermiculate atrophoderma, hypotrichosis, trichoepitheliomas, milia, basal cell carcinoma and peripheral vasodilatation and is autosomal dominant.
3. Basex Dupre Christol Syndrome,[31] which is clinically characterized by vermiculate atrophoderma of the face, elbows and hands and is associated with hypotrichosis and basal cell carcinoma. It is rare genetic x linked or autosomal dominant.
4. Multiple tumors of the follicular infundibulum clinically characterized by papules on the face and is associated with basal cell carcinoma.
5. Multiple eccrine-pilar hamartomas which appear as multiple papules of the face showing differentiation toward pilar and sweat glands structure [32].

The main findings in the present case are:

Multiple trichoepitheliomata affecting mainly the face, neck, upper and lower limbs, front and back of the trunk. There is no family history of such lesions.2)The skin shows few ash leaf hypopigmented macules on the trunk .3)Few cafè au lait spots on the trunk .4)Hypoplastic nipples.5)Very high arched palate.6)Awide carrying angle of both elbows (Cubitus vulgus).7)Markedly webbed neck .8)Narrow shoulder; winged scapulae .9)The right knee region has a bigger circumference than the left.10)Superficial veins show prominantly through a thin skin allover the body surface with a mild degree of hyperelasticity but no joint laxity.11)Subnormal mentality and intelligence.12)EEG showed abnormal record.

Conclusion:

This patients shows skin manifestations of multiple trichoepitheliomas proved histopathologically with other cutaneous findings that are partly shared with tuberous sclerosis, neurofibromatosis, Noonan syndrome and laxity of skin. To the best of our knowledge these combined cutaneous findings were not previously reported and we wonder if this could be a new syndrome with multiple gene defects.

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