 DOI: 10.5958/2394-6792.2016.00133.2

A clinico-pathologic analysis of cutaneous appendageal tumours

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Abstract

Background: Cutaneous appendageal tumours can arise from either the eccrine, apocrine, hair follicles or the sebaceous glands. Majority of the tumours are benign. Final diagnosis requires a good clinical as well as histpathological correlation.
The aim of the present study was to assess the clinicopathological characteristic of these tumours.

Materials & Methods: The present study was a retro-prospective study carried out in the department of Pathology, Rohilkhand Medical College & Hospital, Bareilly (Uttar Pradesh), a tertiary care hospital. The cases were noted, classified and studied according to their age, sex and site. A total of 29 cases were included in the present study over a period of three years. These cases were confirmed to have cutaneous adnexal neoplasm on histopathology. All the specimens were formalin fixed, processed and stained with routine Haematoxylin & Eosin method and special stains were applied wherever necessary. The tumours were classified as apocrine, eccrine, follicular and sebaceous type based on the histopathological report.

Results: It was observed that the incidence of skin adnexal tumours was very low in relation to the total number of surgical specimens received in the department of Pathology (0.093%). The mean age of presentation of adnexal tumours in this study was 37.66 years with patients ranging from 10 to 80 years. Females 18 (62.1%) outnumbered the males 11 (37.9%) in the present study. Among 29 cases, 23 cases were benign and 6 cases were malignant. 6 (20.7%) of these tumours were derived from eccrine & apocrine glands, 6 (20.7%) cases showed sebaceous differentiation and 17 (58.6%) cases were tumours of follicular differentiation. The commonest lesion observed was Pilomatricoma in 10 cases (34.4%).

Conclusion: Appendageal skin tumours have distinct histological characteristics which differentiates them from other cutaneous tumours. The clinical diagnosis may be difficult because they have overlapping presentations and thus can be differentiated using histopathological examination only.

Keywords: Apocrine, Eccrine, Pilomatricoma, Sebaceous, Cutaneous, Appendageal, Histopathology.

Introduction

Cutaneous appendageal neoplasms (CANs) include a large number of tumours that are mostly asymptomatic clinically and present as papule or nodule but histologically they have unique characteristics. They are commonly grouped depending on their appendageal differentiation based on embryologic, histological, ultrastructural and immunohistochemical features into follicular eccrine, apocrine or sebaceous types.[1] CANs develop from pleuripotent stem cells that are undifferentiated and present within the epidermis or the appendageal structures to finally differentiate into specific tumours influenced by genetics, local vascularity and the microenvironment of the dermis and epidermis.[1-7] Certain appendageal tumours have great significance since they serve as a marker for internal visceral malignancy such as multiple trichilemomma, which indicates underlying breast malignancy. This association is termed Cowden's disease.[8] Anatomic site, number and distribution of lesions help in diagnosing the nature of these tumours. They are later confirmed by histopathology. Immunohistochemistry may aid in confirming the diagnosis. Presence of multiple lesions serves as an important clue to the benign nature of the disease. Appendageal tumours may show a predilection for certain body parts such as eccrine poroma which is most commonly seen in the lower limbs. Since all cutaneous adnexa arise from a common source, it is likely that the tumours may share some common features. Malignant skin appendageal tumours are rare and locally aggressive and may spread to the lymph nodes or other distant sites carrying a poor prognosis. Diagnosing malignancy in CANs is important so as to start a proper treatment as well as assess the prognosis of the patient.[7]

The morphology of these tumours is variable. A clinical diagnosis may often be difficult, although most of these tumours behave in a benign manner. These tumours pose major diagnostic problems for both the dermatologist as well as the pathologist. The dermatologist is mostly interested in knowing whether the tumour is benign or malignant and furthermore the likely prognosis after it has been removed surgically. Only few studies on cutaneous appendageal tumours are available in the English literature, so the present study aims at analysing the clinico-pathological pattern of CAN in our Institute and to group them using the International Classification of World Health Organization (2006).

Materials and Method

The present study included patients with a confirmed histopathological diagnosis of appendageal tumours. Biopsy with histopathological examination of tumours was done in all the cases. All clinically suspected cases of appendageal tumours with a

confirmed histopathological diagnosis were included in the study. The clinical and histological findings in these cases were correlated and the classification of tumours based on their origin into hair follicle, sebaceous, apocrine or eccrine was done. An attempt was made to include the special stains and immunohistochemistry details supporting the histopathological diagnosis in clinically suspected appendageal tumours.

The present study was partly a retrospective and partly a prospective analysis conducted over a period of three years from January 2013to December 2015. The data was obtained from inpatient, outpatient and histopathological records of department of Pathology of our institute, a tertiary care teaching hospital. Cases clinically suspected to be CAN but not proved on histopathology and those not willing to give informed consent were excluded out from the present study. Formalin fixed, paraffin embedded tissue sections were stained with Haematoxyl in and Eosin stain in all the cases. Ackerman's diagnostic criteria's were used to label the tumour as malignant. These criteria's included: borders irregular or asymmetrical, horizontal orientation, irregular epithelial cell aggregates, presence of necrosis, infiltration of neoplastic cells into the dermis or subcutaneous tissue, atypical mitosis, stroma-irregular, scanty or myxoidand, presence of pleomorphic nuclei.

Results

The incidence of skin appendageal tumours as compared to the total surgical pathology specimens received was observed to be 0.093%. The tumours were further classified into hair follicle, sebaceous, eccrine orapocrine origin. The most common tumour arising from the hair follicles was pilomatricoma in 10 cases (34.5%) (Table 1).

Table 1: Showing distribution of Skin Adnexal Tumours

S.No	Age (Yrs)	Sex	Site of Biopsy	Presentation	Clinical Diagnosis	Diagnosis
I-Tumours with apocrine and endocrine differentiation: Malignant Tumour						
1	35	M.	Rt. Axilla	Swelling with sinus x 6 months. Tenderness present	Tubercular	Apocine Adeno carcinoma
2	24	F.	Left ear	Swelling x 6 months. Occasional pain	Epidermal cyst/Haemangioma	Malignant Nodular Hidradenoma
3	35	M	Right Axilla	Discharging sinus x 1 year	Tubercular lesion	Apocrine gland carcinoma
4	35	M.	Right Flank	Multiple, Progressive growth	Warts	Syringcystadenoma Papilliferum
5	50	M	Scalp	Swelling over occipital region CK, PAS; S-100 Focal pos; CEA Neg.	Infected Sebaceous cyst	Acrospiroma
6	28	M	Upper eyelid	Swelling x3 years. 8x5mm	#REF!	Eccrine Hidrocystoma
IIB- Tumours with follicular differentiation: Benign Tumours						
1	35	F.	Scalp	Swelling x 3 months. Well defined non-tender.	Sebaceous cyst	Pilomatricoma
2	16	M.	Rt. Forearm	Growth x 6 months. Swelling 2x2cm, hard Non-tender Mobile.	Sebaceous cyst	Pilomatricoma
3	40	F.	Swelling Scalp	Swelling. Non-tender, Firm, Mobile x 2 years	Lipoma	Pilomatricoma
4	30	F.	Rt. Thigh	Swelling Non-tender, Mobile	Sebaceous cyst	Pilomatricoma
5	16	F.	Back	Swelling	Sebaceous cyst	Pilomatricoma

6	60	F.	Scalp	Swelling x 8 months Mobile. Non - tender	Sebaceous cyst	Pilomatricoma
7	40	F.	Scalp	Swelling. Non fluctuant, Non-tender. No transillumination	Sebaceous cyst	Trichilemmal cyst
8	28	M.	Occipital Swelling	Swelling x 10 years. 3x3cm	Infected Sebaceous cyst	Trichilemmal cyst
9	35	F.	Forearm & Lt Leg	Multiple hypo-pigmented patches all over body.	Leprosy (MB HD)	Trichoepithelioma
10	17	F.	Neck	Multiple, yellowish Papules of variable sizes in front of neck x 3 years	Xanthoma /Syringoma	Trichoepithelioma
11	18	F.	Rt. Arm	Swelling 4 Months. Soft Non-mobile. Fixed to skin Non-tender	Abscess	Pilomatricoma
12	80	F.	Scalp	Swelling	Dermoid cyst	Pilomatricoma
13	50	F.	Scalp	Swelling	Sebaceous cyst	Pilomatricoma
14	10	F.	Left Cheek	Swelling x 4 years. Firm to Hard. Non-tender.	Sebaceous cyst	Pilomatricoma
15	50	F.	Scalp	Swelling	Sebaceous cyst	Trichilemmal Cyst
16	30	F.	Scalp	Swelling	Infected Sebaceous cyst	Trichilemmal Cyst
17	55	M.	Upper Back	Patch	Leprosy	Trichostasis Spinulosa.
III- Tumours with Sebaceous differentiation						
1	50	F.	Lt upper eyelid	Mass -Painful, fungating with blood tinged discharge	Squamous cell carcinoma	Sebaecous gland adenocarcinoma/ Meibomian gland carcinoma
2	65	M.	Eyelid	Nodular mass x 7-8 months. Painless. Progressive. Loss of eyelashes. 2x1cm. Lobulated, Vascular	Sebaceous carcinoma/ Merkel cell carcinoma/ Keratoacanthoma (FNAC: Adnexal tumours)	Sebaceous Cell Carcinoma
3	45	M.	Left Axilla	Sinus. CK**(+)**, S-100 (-) CEA (-) , Vimentin (-)	Sinus	Sebaceoma
4	45	M.	Lateral aspect of upper eyelid	Firm, Indurated growth. CK(+) ; S 100 (-)	Sebaceous gland carcinoma	Sebaceous Carcinoma
5	40	F.	Scalp	Painless Swelling. Soft. Non-tender. Punctum present in centre.	Sebaceous cyst	Pilar cyst

6	30	F.	Left upper eyelid	Growth x 2 years	Granuloma	Eccrine Syringioma

In the present study, CAT was observed in all the age groups with patients ranging from 10 to 80 years. The mean age was 37.66 years. However, the highest incidence was observed in the age group of 31 to 40 years followed by the 21-30 and 41-50 years groups. The male: female ratio was 11:18[Fig. 1] Head and neck has been reported to be the most affected site in 18 cases (62.1%) followed by upper extremities in 5 (17.2%). The Abdomen & Back were affected in 2 cases (6.9%) and lower extremities in 1 case (3.4%). Multiple sites were affected in 3 cases(10.3%) [Fig. 2].

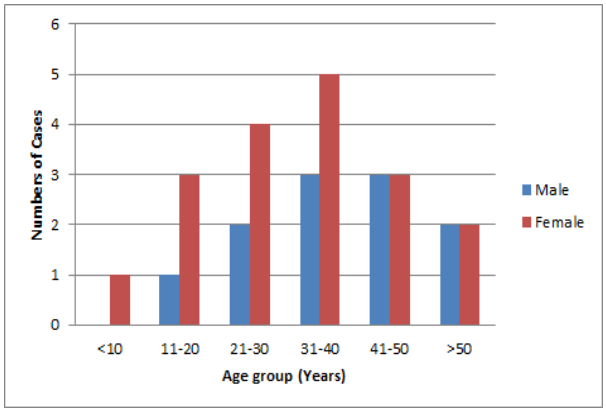

Fig. 1: Showing age and sex distribution of cases

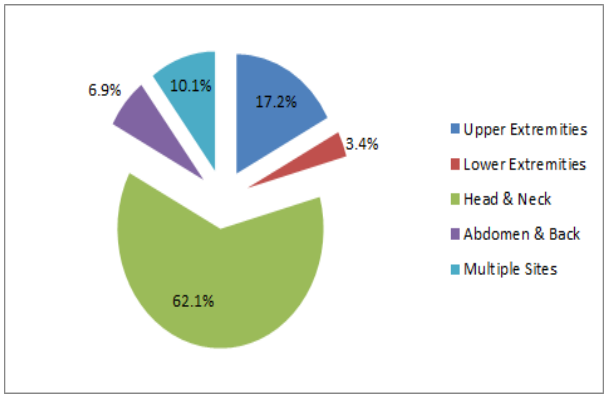

Fig. 2: Showing sites of involvement of Cutaneous Adnexal Tumours

Most of the tumours, 23 cases (79.3%) were benign. Incidence of malignancy was low 6 cases (20.7%). Most of the appendageal tumours were found to be less than 2 cm. number of tumours greater than 5 cm in diameter was less. The commonest presentation of these tumours was swelling or growth in 24 (82.8%) cases followed by patch or papule in 3 (10.3%) and discharging sinus in 2 cases (6.9%).

The duration of presentation was more than 2 years in 12 (41.4%) cases followed by 10 cases (34.4%) of 1 to 2 year duration, 5 (17.2%) of 6 months to 1 year duration and only 2 cases (6.9%) of less than 6 months duration. Of these 2 cases of shorter duration one was Apocrine adenocarcinoma and another Pilomatricoma.

Discussion

There are only few studies in the English literature on cutaneous appendageal tumours. We observed that the appendageal tumours are rare entities. Histopathological examination is required for establishing the diagnosis of appendageal neoplasms. Appendageal tumours are likely to differentiate into more than one cell line in the same tumour since they originate from the pleuripotent stem cells.[1,9,10]

In our study the incidence of CATs was 0.093%. Incidence of CANs observed in the present study was in concordance with previous other studies which ranged between 0.3-0.5%.[11-14] The male female ratio was 11:18. There has also been a female preponderance in the study carried out by Saha et al and Nair et al.[2,12] The male: female ratio as observed by Nair et al and Saha et al was 1: 2.3 and 1:1.88, respectively.[2,12] Radhika et al. also observed that females were more commonly affected than the males.[15] The present study also showed a female preponderance.

Skin appendageal tumours have a wide range of age distribution. Most cases in our study occurred in the younger age group which are similar to observations made by other authors in their studies.[3-5] Saha et al observed the mean age of onset of CATs was 24.15±8.44.[12] Nair et al reported the maximum number of cases to be affected in the 11-20 years age group; however, in the present study, the commonest age group affected was 31-40 followed by 41-50 and 21-30 years.[2] Saha et al observed that the commonest age of presentation was 51-60 years whereas Radhika et al found the third decade to be the most commonly affected.[12,15] In the present study in 19 (65.6%) cases head and neck region was involved. Previous studies have also indicated head and neck to be the commonest site affected.[2,12,15,16]

Incidence of benign tumours is more as compared to the malignant tumours as observed by previous authors. The benign: malignant ratio in this study was 11:3. In the present study 79.31% (23/29) cases were benign and 20.69% (6/29) tumours were malignant which have also been reported in studies by Radhika et al, Reddy et al, and Samaila at al who reported 77.14%, 69.41%, 88.5% benign and respectively 22.86%, 30.59%, 11.5% Malignant lesions.[15-17] Saha et al also reported that the incidence of benign tumours was much more as compared to the malignant cases.[12] Our results are comparable to the previous studies in respect to incidence of benign and malignant tumours and also in respect to the presentation of the tumours. Benign tumours are likely to present as multiple papules.26 tumours reported in our study were single lesions while

3 were multiple and none of the lesions was associated with any genetic syndrome. Nuclear and cytological atypia are not the only criteria to label malignancy in cutaneous appendageal tumours. Ackerman described a list of criteria to be applied to CANs to differentiate benign from the malignant appendageal lesions.[18] Benign tumours show a tendency for smooth borders, absence of ulceration of adnexae, vertical orientation with V-shape, uniform collection of epithelial cells with dense fibrotic stromal reactions around tumour cells and absence of necrosis, atypia and mitosis.[1,9,10,19] Malignant tumours are likely to have ulceration, necrosis, clefts between tumour cells and stroma.[19] Malignant CATs show asymmetry, horizontal orientation of tumour, Irregular cell arrangement with infiltration, necrosis, cellular atypia mitosis and sclerosis of stroma. Tirumalee et al have stressed the importance of examining under scanner view magnification to assess the silhouettes of SATs to differentiate benign and malignant tumours.[19] Malignant CANs are rare and occur predominantly in the region of trunk.

Clinical diagnosis of these tumours is often non-specific as most of them present with papules, plaques or nodules.[1,9,10,15] The long standing duration and their presentation as asymptomatic papules or nodules points more towards the benign nature of these tumours. Majority of the SATs are clinically mis-diagnosed as sebaceous cyst, dermoid cyst, haemangioma, granuloma and lymphadenopathy. Though anatomic location, number, distribution can provide a clue to the type of tumour it is only histopathology which is the gold standard in the diagnosis of CANs.[1] CANs differentiate towards different appendageal cell lines. Differentiation towards more than one cell type in the same tumour is also reported. This could probably be due to their origin from pleuripotent stem cells.[1,9,10] Owing to their common origin many tumours share overlapping features while some tumours may contain elements of two or more appendages in varying degree of maturation.[20] Many studies had described CANs with combined characteristics.[3,21] In the present study there was differentiation towards a single cell line only.

Follicular differentiation is identified by the proliferation of basaloid cells, peripheral nuclear palisading, adjacent papillary mesenchymal bodies and matricial ghost cells. Apocrine differentiation is identified by the presence of decapitation secretion, Eccrine differentiation by the presence of tubules and sebaceous differentiation is suspected by the presence of the mulberry cells with clear vacuolated cytoplasm.[1,9,10] Tumours showing pilar differentiation and sweat gland differentiation were the commonest tumours observed in all the previous studies. Among the sweat gland differentiation eccrine tumours were the commonest. Sweat gland tumours were the commonest appendageal tumours observed in some of the previous studies.[2,15,16] However, the second and third commnest tumour observed by Nair were hair follicle tumours and sebaceous gland tumours; whereas, Radhika and Samaila reported sebaceous gland tumours as the second commonest followed by hair follicle tumours.[15,16] Wong et al. observed that pilomatricoma was the most common benign tumour followed by dermoid cyst steatocystoma multiplex, syringoma, and trichilemmal cyst.[3] Radhika et al. observed that the most common benign tumour was nodular hidradenoma followed by nevus sebaceous.[15] In the present study, the most common tumour was pilomatricoma.

Among the follicular CANs the commonest tumour observed was pilomatricoma with majority of the cases distributed in the head neck region presenting as solitary nodule. 6 of the 10 cases (60%) included in the present study were reported in the head and neck region. Similar observations have been made in previous publications also.[5] In Pilomatricoma there has been a reported female preponderance as observed in the present study as well.[22] Of the 10 cases included in this study 9 were females and 1 was male. Pilomatrixoma, or calcifying epithelioma of Malherbe, are benign tumours arising from the sebaceous glands. The incidence is estimated to be 1 in 2000 histopathology specimens.[23] The most frequent anatomical location is the head and neck region, followed by the upper extremities, trunk and the lower extremities in that order.[24] In the head and neck the sites for occurrence of Pilomatricoma include cheek (36%), neck (20%) periorbital areas (14%), scalp (9%) and, the remaining involving multiple sites.[22-26] Reports of pilomatricoma involving breast are also available in the literature. Although pilomatricoma can occur at any age two peaks of presentation, the first and the sixth decades are reported to be affected. About 40% of cases occur in patients younger than 10 years of age and about 60% of cases in individuals less than 20 years of age.[24] Pilomatricoma mainly presents as a solitary cutaneous nodule with an average size of 1 cm rarely exceeding 2 cm in diameter and is covered by normal or hyperemic skin.[5] Mostly pilomatricoma remain asymptomatic. They are firm in consistency, mostly non-tender and deep seated with adherence to the overlying skin but not to the underlying structures. Grossly, they are well encapsulated and show fine, fibrovascular connective tissue stroma separating islands of cells comprising of two separate or biphasic cell populations with the ghost (shadow) cells surrounded by basaloid cells (darkly stained) along with foreign body giant cell reaction at some places in few of the cases(Fig. 3). As the tumour matures, the peripherally arranged basophilic cells acquire abundant cytoplasm and gradually lose their nuclei to become more eosinophilic resulting in a shadow type appearance. The ghost cells have well-defined cell borders, abundant pale eosinophilic cytoplasm with a central clear area. These shadow cells constitute the central portion of the tumour and may later calcify to give a bony hard consistency to the lesion. The basaloid cells are deep blue stained, round-to-ovoid cells with ill-defined cell borders having minimal cytoplasm.

The nuclei are vesicular mostly having prominent nucleoli. A transition of basaloid cells to ghost cells occurs in many areas. Secondary changes in the form of haemorrhage, keratinization, calcification, ossification, myxoid change, oedema, fibrosis, melanin deposition and focal lymphocytic infiltration along with a foreign body giant cell reaction in close proximity to the ghost cells can be present.[23]

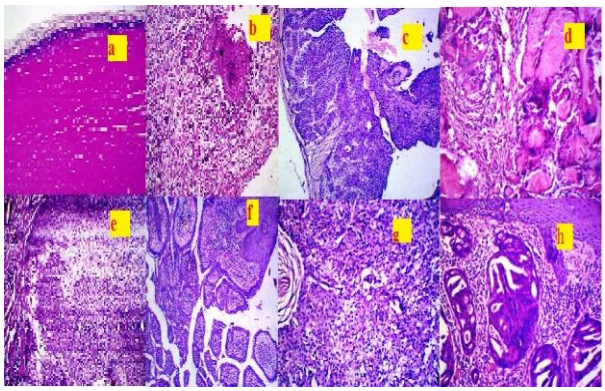

Fig. 3: Showing histopathology of various lesions (a) Trichilemmal cyst (b) Ruptured cyst with foreign body giant cells (c)Acrospiroma (d)Pilomatricoma with giant cells (e)Sebaceoma (f)Syringcystadenoma papilliferum (g)Malignant Nodular Hidradenoma (h) Apocrine adenocarcinoma (H&E x 100)

Nodular hidradenoma are circumscribed and solid tumours with few of them showing cystic changes. The tumour comprises of tubules of various sizes along with papillary projections that are lined by an outer layer of myoepithelial cells and inner layer of cuboidal cells. Solid portions of the tumour show nodules comprising of clear and polygonal cells. Microscopically, sebaceous carcinoma reveals irregular epithelial lobules with infiltration into the dermis. The neoplastic cells demonstrate marked cytologicatypia, mitotic activity and focal sebaceous differentiation. Syringocystadenoma papilliferum (Fig. 3) is a rare appendageal neoplasm. On microscopic examination, papillary projections with squamous epithelial lining and ductal invaginations were observed. The ducts were lined by an outer cuboidal cell layer and an inner columnar cell layer.[5]

Syringocystadenoma Papilliferum presents as solitary lesion. Multiple lesions are usually associated with Nevus sebaceus. It affects males and females equally. Majority of the cases have been reported to involve the head and neck areas. Different lesions are reported to be associated with it such as apocrine poroma, apocrine hidrocystoma, tubulopapillary hidradenoma, hidradenoma papilliferum, viral warts, nevus sebaceus, linear naevus verrucosus, naevus comedonicus, papillary eccrine adenoma, apocrine acrosyringeal keratosis, poroma folliculare, linear naevus verrucosa, atypical fibroxanthoma, clear cell syringoma, basal cell epithelioma, sebaceous epithelioma, trichoepithelioma and verruca of vulgaris variety.[26] Its association with verrucous carcinoma, sebaceous gland and ductal cells of breast has also been reported. The commonest association of syringocystadenoma papilliferum is with nevus sebaceous.[26] The most characteristic pattern is that of papillary projections. The glands are lined by two types of cells, the cuboidal cells present at the base and the columnar cells present at the luminal surface. The cuboidal cells are small in size, have a round nuclei with scanty cytoplasm, whereas the columnar cells have oval nuclei and cytoplasm which is faintly eosinophilic. Diastase resistant Periodic acid-Schiff (PAS) positivity secretions are invariably present at the luminal surface. The lesion is further characterized by the presence of mononuclear inflammatory cells comprising mainly of IgG and IgA class of plasma cells in the fibrous tissue of the papillary projections, along with presence of dilated capillaries.[26]

Conclusion

Cutaneous appendageal neoplasms are relatively less common neoplasms having distinct histological features. They are commonly distributed in the head and neck region with a female dominance as observed in the present study also. In the present study different appendageal tumours reported in a tertiary medical centre over a three years period has been highlighted. Majority of the benign tumours clinically presented as papules or nodules. A good clinic- histopathological correlation is vital to arrive at a final diagnosis of these entities. The clinical presentation of appendageal tumours is mostly vague and non-specific. Histopathology is the gold standard for making the diagnosis of these appendageal tumours. Hence, familiarity with the histopathological findings is mandatory for the surgical pathologists. Malignant SATs are rare and aggressive. It is always important to look for malignant features and the resected surgical margins before signing out the histopathology reports in skin appendageal tumours.

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