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Original Article

Dermatology Section

# Skin Appendageal Tumours: An Institutional Experience from Northern India

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## ABSTRACT

**Introduction:** Skin Appendageal Tumours (SAT) are a heterogenous group of rare tumours having differentiation towards the skin appendageal structures and are rarely considered clinically as a differential diagnosis. A couple of studies and case series are available in literature from different parts of India but only meagre work is published from northern India.

**Aims:** To study the spectrum of clinicopathological features of SAT in northern India, classify them according to WHO classification and to compare the outcome with published data in literature.

**Materials and Method:** This retrospective and prospective study included 64 cases of histologically confirmed SAT at a tertiary care hospital located in northern India. The relevant clinical data including patient's age, gender, site alongwith histopathological features of the tumour were analysed. Tumours were classified as per WHO classification (2006). The data was then compared with the previous studies.

**Results:** Of the 64 cases diagnosed as skin appendageal tumour, 52 (81.25%) were benign, while 12 (18.75 %) were malignant. Male to female ratio was 1:1.29. People in third decade of life were more commonly affected closely followed by 6th and 7th decades. Head and neck was the commonest site (39/64; 60.93%), followed by upper extremities (10/64; 15.62%) and trunk (8/64;12.50%). Tumours with follicular differentiation formed the major group (33/64; 51.56%). Pilomatricoma (24/64; 37.5%) and proliferating trichilemmal tumour (6/64; 9.38%) were the commonest benign and malignant tumours respectively. One of the cases diagnosed as sebaceoma was associated with Muir Torre syndrome.

**Conclusion:** SAT should be suspected if there is a subcutaneous papulonodular lesion especially in head and neck region. Histopathological diagnosis and sub classification of SAT is often difficult, but following a widely accepted WHO classification system, may help to minimize conflicts and dilemma.


Keywords: Apocrine and eccrine tumours, Follicular tumours, Pilomatricoma, Proliferating trichilemmal tumour, Sebaceous tumours

## INTRODUCTION

Skin Appendageal Tumours (SAT) / Neoplasms (SAN) are uncommon group of tumours exhibiting differentiation towards normal skin appendageal structures. The exact aetiology behind their occurrence is still unclear. These tumours are classified according to their morphological differentiation towards one or more of the skin appendageal structures. Earlier, these were classified as tumours with follicular, sebaceous, apocrine and eccrine differentiation. This classification system included hyperplasia and hamartomas as well [1]. But, WHO classification system for SAT (2006) has classified SATs into three broad categories- tumours with apocrine and eccrine differentiation, tumours with follicular differentiation and tumours with sebaceous differentiation [2].

SAT are rarely encountered and even rarely suspected clinically. SATs are more frequently benign [3]. The benign SATs usually present as smooth surfaced, symmetrical papulonodular lesions while most appendageal carcinomas are irregular plaques with or without ulceration [2]. These tumours are rarely subjected to fine needle aspiration and the diagnosis is made primarily on histopathology. Histopathologic diagnosis is also not usually straightforward. This problem is encountered especially in tumours with an admixture of follicular, eccrine/apocrine and sebaceous differentiation [1]. Although a couple of case series and studies are published from different parts of India, however, not many studies are available from northern India [4,5]. We attempted to study the clinical and histomorphological spectrum of the SAT encountered in our institute.

## MATERIALS AND METHODS

This was a retrospective and prospective study conducted over a period of 10 years, from January 2007 to December 2017 (retrospective from January 2007 to December 2015 and prospective from January 2015 to December 2017), in a tertiary care hospital and teaching institute (Shri Guru Ram Rai Institute of Medical and Health Sciences) located in Dehradun, Uttarakhand, a state in northern India. The study

was approved by Institutional Ethical Committee. A total of 64 cases diagnosed as SAT and subtypes on histopathology during the study period, were included. All pseudotumours, appendageal cysts and hamartomas were excluded. The patients were from the department of general surgery, dermatology and plastic surgery. All relevant clinical details including patient's age, gender, site of tumour, any other systemic disorder, clinical diagnosis and any cytological diagnosis (if available) were recorded. The Haematoxylin and Eosin stained sections from the biopsy specimens of these cases were subjected to detailed histopathological examination for diagnosis. These were classified according to the WHO classification of SAT, 2006 as given below [2] [Table/Fig-1].

| Tumours with apocrine and eccrine differentiation | Tumours with follicular differentiation | Tumours with sebaceous differentiation |
|---|---|---|
| **Malignant tumours**<br>Tubular carcinoma<br>Microcystic adnexal carcinoma<br>Porocarcinoma<br>Spiradenocarcinoma<br>Malignant mixed tumour<br>Hidradenocarcinoma<br>Mucinous carcinoma<br>Digital papillary carcinoma<br>Adenoid cystic carcinoma<br>Apocrine carcinoma<br>Paget disease of breast<br>Extramammary Paget disease | **Malignant tumours**<br>Pilomatrical carcinoma<br>Proliferating trichilemmal tumour | Sebaceous carcinoma<br>Sebaceous adenoma<br>Sebaceoma<br>Cystic sebaceous tumour |
| **Benign tumours**<br>Hidrocystoma<br>Syringoma<br>Poroma<br>Syringofibroadenoma<br>Hidradenoma<br>Spiradenoma<br>Cylindroma<br>Tubular adenoma<br>Tubular papillary adenoma<br>Syringocystadenoma papilliferum<br>Hidradenoma papilliferum<br>Chondroid syringoma | **Benign tumours**<br>Trichoblastoma<br>Pilomatricoma<br>Tricholemmoma<br>Multiple tricholemmomas<br>Fibrofolliculoma/ trichodiscoma | |

**[Table/Fig-1]:** The WHO classification of SAT, 2006 [2].

Statistical analysis was done in terms of percentages and proportions.

## RESULTS

Only 64 cases were reported as SATs over a period of 10 years during which 37640 biopsy specimens were submitted for histopathology. Amongst these, 36 (56.25%) were females and 28 (43.75%) were males. Male to female ratio was 1:1.29. The age range was 7 months to 93 years. People in 3rd decade of life (10/64; 15.63%) were most frequently affected, followed by 6th and 7th decades (9/64; 14.06% each). There was an increasing incidence of malignant cases in later part of life. 7 of 12 cases (58.3%) of malignant appendageal tumours occurred in patients aged 60 years or more. The clinical diagnosis usually included- lipomas, lymphadenopathy, abscess/ inflammatory pathology, epidermal cysts and rarely, carcinoma. A primary clinical diagnosis of skin appendageal tumour and subtypes was suspected in only 9 (14.06%) cases. A preoperative cytodiagnosis of skin appendageal tumour was available in 8 (12.5%) cases, of which subtyping was possible in 3 (4.68%) cases. These were diagnosed as pilomatricoma on cytology.

Head and neck (39/64; 60.93%) especially, scalp (12/39; 30.77%) and periorbital region (10/39; 25.64%) was the commonest site. The anatomical distribution of cases is given in [Table/Fig-2]. Predilection for certain sites for specific tumour subtypes was observed- proliferating trichilemmal tumour in scalp (4/6; 66.67%) and sebaceous carcinoma in periorbital region (4/5; 80%). Of the nine SATs in cervical region, 8 (88.9%) were pilomatricoma.

| Site | No of cases (n=64) | Percentage |
|---|---|---|
| Head and neck | 39 | 60.93% |
| Upper extremity | 10 | 15.63% |
| Trunk | 8 | 12.5% |
| Pelvic region | 2 | 3.13% |
| Lower extremity | 5 | 7.81% |

**[Table/Fig-2]:** Anatomical distribution of cases.

There were 52 (81.25%) benign and 12 (18.75%) malignant tumours; ratio being 4.3:1. Of all the cases, tumours with follicular differentiation were commonest (33/64; 51.56%) followed by tumours with apocrine and eccrine differentiation (22/64; 34.38%) and finally, tumours with sebaceous differentiation (9/64; 14.06%). Pilomatricoma (24/64; 37.50%) was the commonest skin appendageal tumour, followed by chondroid syringoma (7/21; 33.33%). Of the malignant cases, proliferating trichilemmal tumour (tumour with follicular differentiation) was commonest (6/12; 50%) followed by sebaceous carcinoma (5/12; 41.67%). The distribution of cases according to histological diagnosis alongwith clinical features is given in [Table/Fig-3].

## DISCUSSION

SAT are uncommon, reported incidence of SAT in previous studies varies from 0.25% to less than 0.5% [6,7]. These tumours are rarely considered as differential diagnosis clinically and are diagnosed mainly on histology. This is attributed to uncommon occurrence of SATs and lack of awareness among clinicians about this group of tumours. SATs are often a diagnostic dilemma for pathologists as well. This is possibly because of long list of appendageal tumours and the uncertain origin of some of these tumours. It is crucial to diagnose the subtype SAT as some have malignant potential and some of the specific histological

| Histological diagnosis | No of cases (%) N=64 | M:F | Median age (years) | Head & neck | Upper limb | Trunk | Lower limb | Pelvic region and anogenital region |
|---|---|---|---|---|---|---|---|---|
| **Tumours with eccrine and apocrine differentiation** | 22 (34.38) | 1:1.75 | 50 | 10 | 5 | 3 | 2 | 2 |
| Chondroid Syringoma | 7 (10.94) | 1.33:1 | 30 | 5 | 2 | 0 | 0 | 0 |
| Hidradenoma papilliferum | 5 (7.81) | 1:4 | 65 | 1 | 0 | 1 | 1 | 2 |
| Hidradenoma | 3 (4.69) | 0:3 | 54 | 1 | 2 | 0 | 0 | 0 |
| Syringocystadenoma papilliferum | 3 (4.69) | 2:1 | 27 | 1 | 1 | 1 | 0 | 0 |
| Hidrocystoma | 1 (1.56) | 0:1 | 56 | 1 | 0 | 0 | 0 | 0 |
| Poroma | 1 (1.56) | 1:0 | 35 | 0 | 0 | 0 | 1 | 0 |
| Cylindroma | 1 (1.56) | 0:1 | 48 | 1 | 0 | 0 | 0 | 0 |
| Adenoid cystic carcinoma | 1 (1.56) | 0:1 | 63 | 0 | 0 | 1 | 0 | 0 |
| **Tumours with follicular differentiation** | 33 (51.56) | 1:1.06 | 30 | 22 | 5 | 4 | 2 | 0 |
| Pilomatricoma | 24 (37.5) | 1:1.4 | 24.5 | 15 | 4 | 4 | 1 | 0 |
| Trichilemmoma | 2 (3.13) | 1:1 | 57.5 | 1 | 0 | 0 | 1 | 0 |
| Trichofolliculoma | 1 (1.56) | 1:0 | 15 | 1 | 0 | 0 | 0 | 0 |
| Proliferating trichilemmal tumour | 6 (9.38) | 2:1 | 71 | 5 | 1 | 0 | 0 | 0 |
| **Tumours with sebaceous differentiation** | 9 (14.06) | 1:1.25 | 55 | 7 | 0 | 1 | 1 | 0 |
| Sebaceous adenoma | 1(1.56) | 0:1 | 55 | 1 | 0 | 0 | 0 | 0 |
| Sebaceoma | 3 (4.69) | 2:1 | 80 | 2 | 0 | 1 | 0 | 0 |
| Sebaceous carcinoma | 5 (7.81) | 1:1.5 | 53 | 4 | 0 | 0 | 1 | 0 |

**[Table/Fig-3]:** Distribution of cases according to histological diagnosis and clinical parameters.

subtypes are associated with certain syndromes eg Cowden syndrome–multiple trichilemmoma, Muir Torre syndrome-sebaceoma, Brooke-Spiegler syndrome – cylindroma and so on [2,8]. One of the cases, diagnosed as sebaceoma in present study had underlying Muir Torre syndrome [9].

Head and neck is the commonest site for SATs [3,4,8,10- 12]. The age at the time of presentation, as reported in various studies, falls between 20-40 years [8,10- 12]. However, Nair reported 11-20 years as the commonest affected age group and Sharma et al., reported them to be common in elderly (51-60 years) [3,4]. In present study, there was a bimodal age presentation, with peaks at 3rd decade closely followed by 6th and 7th decades. No significant gender preference was observed, which was in concordance with few previous studies [4, 8]. A comparison with previous publications has been shown in [Table/Fig-4] [3,4,8,10,11].

Most of the SATs are benign. The reported percentages of benign SATs varies from 77.1% to 100% [3,12]. Categorising a SAT as benign or malignant is at times difficult and can be a pitfall in their histodiagnosis. Always known, but lately emphasised architectural features at scanner view are also to be counted upon. The smooth contours, symmetry, V shape and stroma clefting are features of benign SATs while asymmetry, clefts between tumour cells and stroma and not shelling out completely favour malignancy [13]. The diagnostic criteria of appendageal carcinomas and benign SAT as mentioned in WHO blue book are helpful in distinguishing the two broad groups. The criteria for the diagnosis of appendageal carcinoma are- Irregular borders, asymmetry; horizontal orientation ; markedly irrregular aggregates of epithelial cells ; necrosis en masse; infiltration of the dermis or subcutis without the interposition of densely fibrotic stroma; frequent mitoses, can be atypical; irregular stroma, often scant, sometimes myxoid and pleomorphic nuclei (except microcystic adnexal carcinoma, which has monomorphic nuclei). Diagnostic criteria for benign epithelial adnexal neoplasms are- symmetric and smooth borders; vertically oriented with respect to the surface of the skin ; uniform aggregates of epithelial cells; no necrosis en masse (with the exception of poroma); variable mitoses, but typical; densely fibrotic stroma, rich in fibrocytes in the case of trichogenic; neoplasms forming a blunt, rounded interface with the native dermis (exception - poroma, which has vascular, myxoid stroma) and monomorphic nuclei (exceptions include atypical squamous nuclei in poromas) [2].

Co-existance of apocrine and eccrine lesions in hamartomas, presence of mixed differentiation and unclear origin of many of these lesions are the problem areas in diagnosis and

| | Present study N=64 | Nair [3] N= 33 | Sharma et al., [4] N=56 | Kaur et al., [8] N=110 | El Ochi et al [10] N=96 | Rajalaksmi et al., [11] N=21 |
|---|---|---|---|---|---|---|
| Age group Commonest | 21-30 yrs | 11-20 | 51-60 | 20-39 yrs | 31-40 yrs | 30-40 |
| M:F ratio | 1: 1.29 | 1:2.3 | 1.07:1 | 1.03:1 | 1.74:1 | 1.1:1 |
| Frequent location | Headandneck (60.93%) | Head and neck 46% | Head and neck 64.28% | Head and neck 78.18% | Head and neck 47.6% | Head and neck 47.6% |
| Percentage of benign cases | 81.25% | 100% | 80.36% | 82.73% | 97.9% | 90.48% |
| Percentage of tumours with eccrine and apocrine differentiation | 34.38 | 57.65% | 42,86% | 37.27% | 44.80% | 61.90% |
| Tumours with follicular differenti ation | 51.56% | 36.36% | 35.71% | 39.09% | 51% | 33.34% |
| Sebaceous differentiation | 14.06 | 6.06% | 21.43% | 23.64% | 4,2% | 4.76% |
| Commonest benign SAT | Pilomatricoma | Syringoma | Hidradenoma | Pilomatricoma | Pilomatricoma | Pilomatrcoma |
| Commonest malignant SAT | Proliferating trichilemmal tumor 6/64 (9.37%) | None | Sebaceous carcinoma 11/56 (19.6%) | Sebaceous carcinoma 13/110; 11.8% | Porocarcinoma 1/96 (1.1%), Eccrine sweat carcinoma 1/96 (1.1%) | Malignant dermal eccrine cylindroma 1/21;4.8% |

**[Table/Fig-4]:** Comparison with other studies.

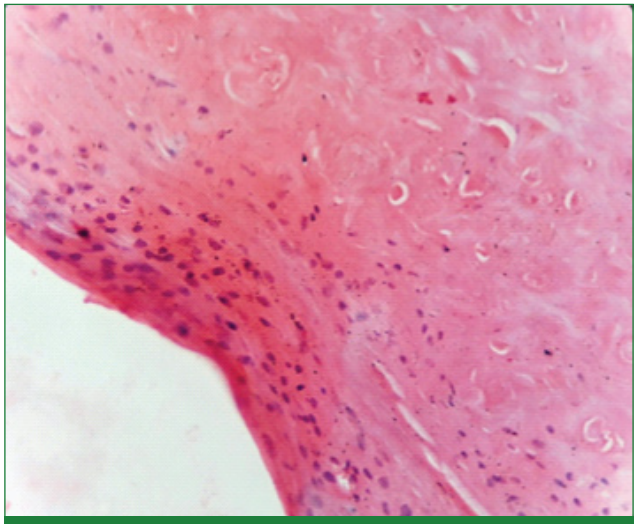
classification of SATs [14]. This favours the removal of entities like nevus sebaceous and the amalgamation of tumours of eccrine differentiation and tumours of apocrine differentiation into single broad category in WHO classification of SAT [2]. The present study as well as studies by Kaur et al., and El Ochi et al., reported tumours with follicular differentiation to be the commonest SATs [8,10]. On the other hand, some authors have found sweat gland tumours to be commonest [3, 4, 11].

## Benign tumours

Pilomatricoma (n=24/64; 37.5%), a tumour with follicular differentiation was the most common SAT in the present study. This was in concordance with the previous other studies [8,10,11]. Pilomatricoma is a common appendageal tumour which occurs as solitary nodules more frequently on hair bearing areas especially, head and neck in all age groups. In current study, 15/24 cases occurred in head and neck region. It was the only SAT encountered in <10 years age. Microscopically, these well circumscribed cystic lesions comprise of a peripheral zone of basaloid cells, followed by squamoid cells, shadow cells and keratin [Table/Fig-5].

There may be foreign body giant cell reaction or associated inflammation also. Calcification is seen often (70-85% cases). Surgical excision is curative, however recurrences may occur [15]. Rare cases of malignant transformation have been reported [16,17].

Chondroid syringoma (n=7/64), a tumour with eccrine/ apocrine differentiation, was the second most common

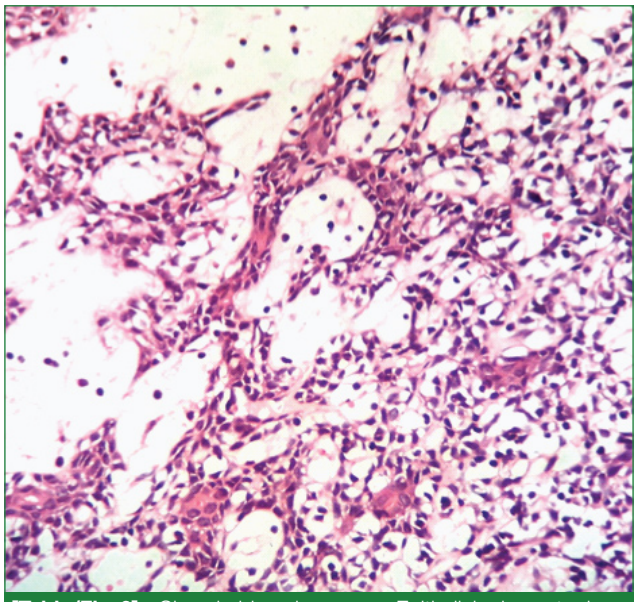


**[Table/Fig-5]:** Pilomatricoma : Basaloid cells followed by ghost cells and keratin (H&E, x400)

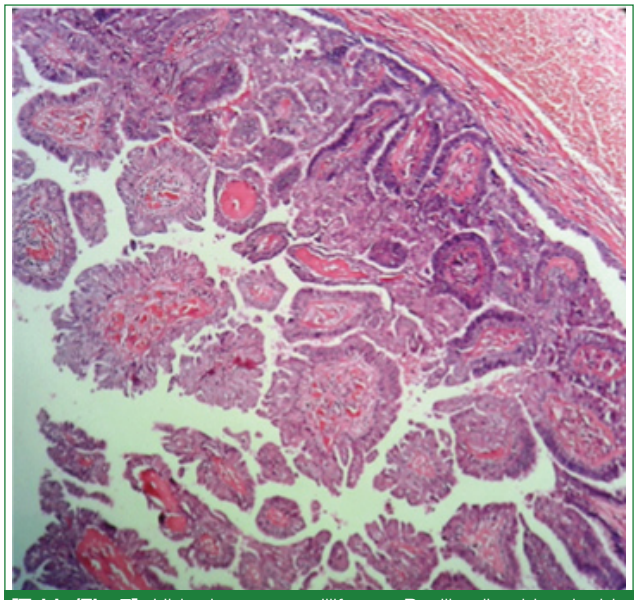
benign SAT in the present study. This tumour often occurs as nodule on head and neck region of young adults, more commonly males (3/4 cases). This well circumscribed tumour resembles pleomorphic adenoma of salivary gland histologically, comprising epithelial elements in a variable myxoid, chondroid or fibrous stroma [Table/Fig-6] [2].

Hidradenoma papilliferum (n=5/64), a tumour with apocrine/ eccrine differentiaton, appears as papulonodular lesion in perianal and vulval region of middle aged women, commonly

[2]. In concordance with this, two of the five cases were middle aged females in this study. There was one case of 38 years old male with a nodular lesion over trunk which was histologically diagnosed as hidradenoma papilliferum. Half of the non-anogenital or ectopic hidradenoma papilliferum are reported to occur in men [18]. Amongst the ectopic hidradenoma papilliferum, majority occur in head and neck region. Other rare sites of occurrence of ectopic hidradenoma papilliferum are arm, thigh, back and nipple [18-20]. Histologically, hidradenoma papilliferum has a complex papillary architecture. The papillae are lined by a double layer of epithelium and have no connection with the epidermis [Table/Fig-7] [1,2].

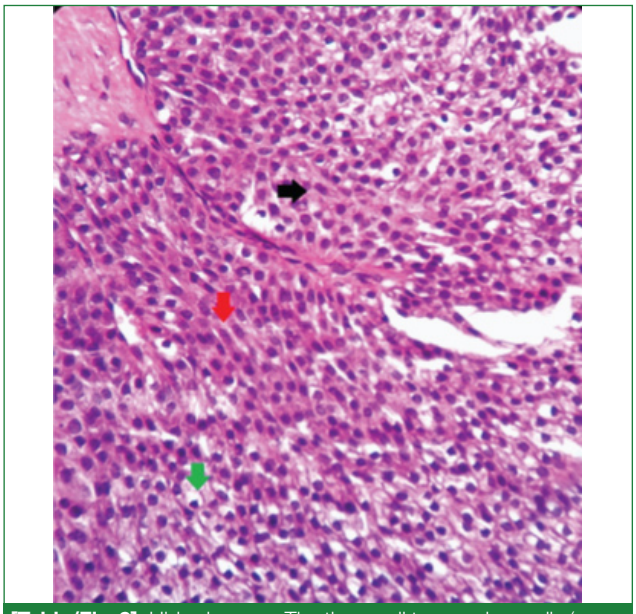


**[Table/Fig-6]:** Chondroid syringoma : Epithelial elements in a chondromyxoid stroma (H&E, x400).



**[Table/Fig-7]:** Hidradenoma papilliferum: Papillae lined by double layer of epithelium (H&E; x200)

Hidradenoma (n=3/64), a tumour with eccrine/apocrine differentiation is also known as clear cell hidradenoma, nodular hidradenoma or poroid hidradenoma. It occurs as subcutaneous nodules on upper extremity (n=2/3) and scalp (n=1/3). Microscopically, this well circumscribed tumour comprises of nodules and sheets of clear cells, squamoid cells, mucinous cells and cuboidal cells [Table/Fig-8]. Focal ductal/glandular formations and cystic changes are often seen [2].



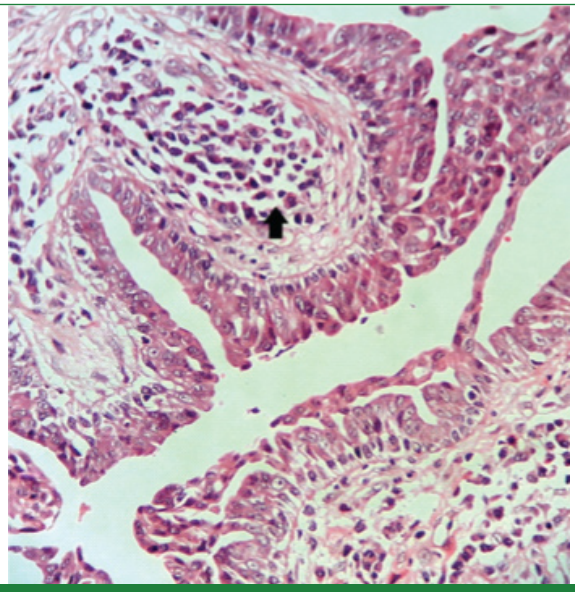
**[Table/Fig-8]:** Hidradenoma: The three cell types- clear cells (green arrow), cuboidal cells (red arrow) and squamoid cells (black arrow). (H&E;x400).

Syringocystadenoma papilliferum (n=3/64), another tumour with apocrine/eccrine differentiation, presents as solitary papule, preferentially on scalp and neck in young age and adults, especially males. Histologically, these are invagination of surface epidermis with endophytic papillary formations which are lined by double layered epithelium. The papillary cores often contain plasma cells [Table/Fig-9] [2].

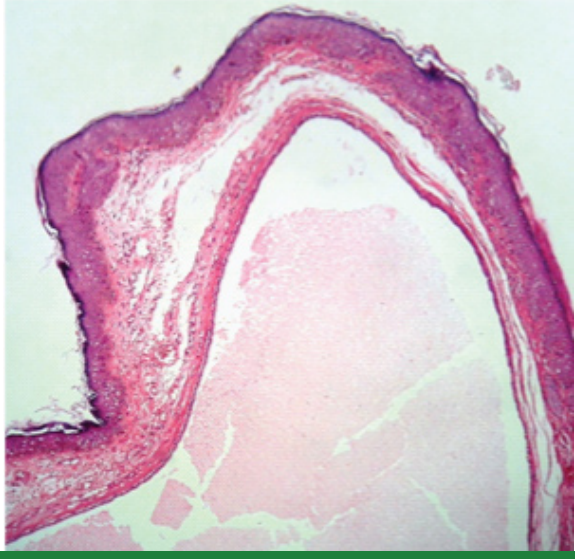
Hidrocystoma (n=1/64), a tumour with eccrine/apocrine differentiation, are rare cystic proliferations which more commonly occurs in periorbital region. Histologically, the cyst is lined by one or two layers of epithelium [Table/Fig-10] [2].

Trichilemmoma (n=2/64), a tumour with follicular differentiation, presented as solitary lesion on face of adults. Microscopically, there are lobules of pale, monomorphic cells with peripherally palisaded columnar cells. Epidermal continuity is present [2].

Sebaceoma or sebaceous epithelioma, a tumour with sebaceous differentiation, presents as solitary yellow-orange papule on face and scalp of the elderly. Histologically, it is composed of multiple lobules of uniform basaloid cells admixed with cells having microvesicular vacuolated cytoplasm. Interspersed ducts and cysts are often seen.



**[Table/Fig-9]:** Syringocystadenoma papilliferum: Papillae lined by double layer of epithelium and presence of plasma cells (black arrow) in the papillae cores (H&E; x400).

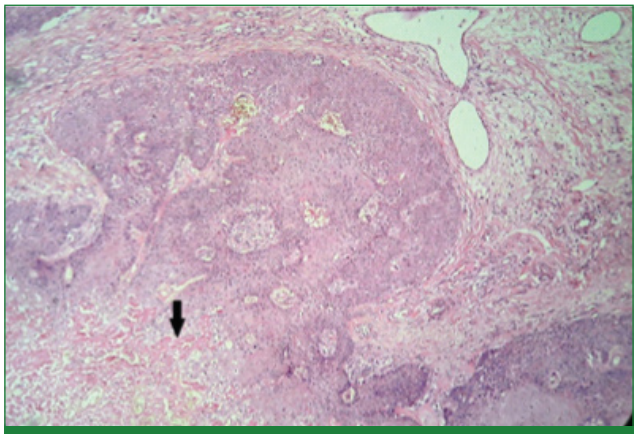


**[Table/Fig-10]:** 10 Hidrocystoma: Unicystic lesion lined by a single layer of cuboidal to flattened cells (H&E;x100).

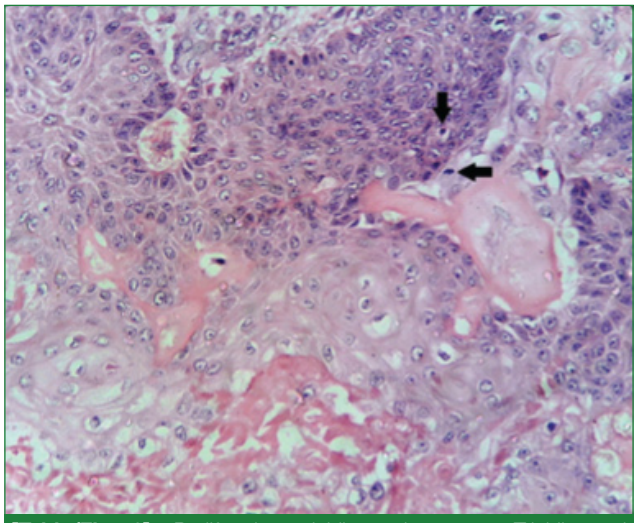
The only case encountered during the study period was associated with underlying Muir Torre syndrome. In Muir-Torre syndrome, there is presence of atleast one sebaceous skin tumour and an internal malignancy which is more frequently, colon carcinoma. Germline mutations in DNA mismatch repair genes (hMLH1 and hMSH2) are present in these patients [1].

## Malignant tumours

The commonest malignant SAT in the current study was proliferating trichilemmal tumour (50% of all malignant SATs) followed by sebaceous carcinoma (41.67%). Proliferating trichilemmal tumour cyst (PTT) (n=6/64) occurs as solitary lesion more often on scalp of elderly women. Grossly, these are multinodular solid-cystic lesions. Microscopically, PTT has a variable presentation. There is a multilobular architecture with lobules of neoplastic epithelium undergoing trichilemmal keratinization- i.e. from periphery to centre -palisaded basaloid cells, then large keratinocytes with abundant eosinophilic cytoplasm and abrupt keratinisation [Table/Fig-11,12].



**[Table/Fig-11]:** Proliferating trichilemmal tumour: Lobules of neoplastic cells undergoing trichilemmal keratinisation (black arrow) (H&E;x100).

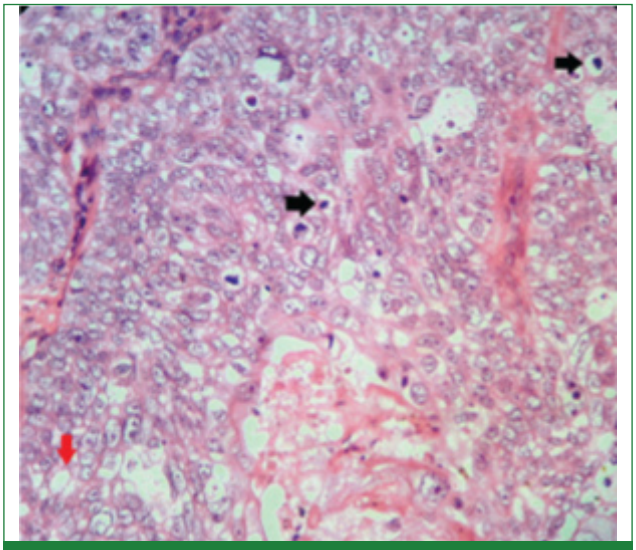


**[Table/Fig-12]:** Proliferating trichilemmal tumour: Trichilemmal keratinization and frequent mitotic figures (black arrows) (H&E;x400).

There may also be features of malignancy- invasion beyond the confines of cyst wall, nuclear atypia and high mitotic acitivity. Proliferating trichilemmal tumour is considered as borderline or tumour with uncertain behaviour. The tumours without atypical features have benign outcome while those with cytological atypia and evidence of invasion are likely to be locally aggressive, may recur or metastasise [2,21]. Hence, PTTs have been categorised under malignant tumours with

follicular differentiation as per WHO classification [2]. Ye J et al., has classified PTT into three groups- group 1- benign, 2- locally aggressive and, 3-malignant [21]. A complete surgical excision and a long term follow-up are recommended. Some authors have suggested chemotherapy and radiotherapy to prevent recurrence; however the role of adjuvant therapy is still unclear [22].

Sebaceous carcinoma (n=5/64) shows a female preponderance and often occurs as ocular or periocular lesions in adults [2]. It was the commonest malignant SAT in the study by Sharma et al. (19.6%), and Kaur et al. (11.8%) and second commonest in the present study [4,8]. Only one of the five cases encountered was extra-ocular (thigh). Histologically, it has a multilobular architecture with malignant cells exhibiting multivesicular cytoplasmic vacuolation [Table/Fig-13].



**[Table/Fig-13]:** Sebaceous carcinoma: Multiple lobules of malignant cells with a few cells showing sebaceous differentiation (red arrow). Frequent mitotic figures also present (black arrows) (H&E; x400)

## LIMITATION

Lesser number of cases in the study probably due to overall low incidence of SATs and their benign nature, rendering lesser number of lesions being subjected to excision and histopathological examination was the major limitation of the present study. General awareness about these tumours and a prospective inter-institutional study may give better data for analysis.

## CONCLUSION

Though rare, SATs should be suspected clinically if there is a subcutaneous nodule especially in head and neck region. It is important to excise and perform histopathological analysis to diagnose and subtype SATs because of the known association with certain syndromes and possible malignant transformation in some of the longstanding benign SATs. Some of the benign SATs are known to recur. On the other hand, malignant SATs need a more extensive surgery and adjuvant therapy. A more uniform and simplified classification system eg WHO classification, may be followed more widely to minimize conflicts and confusion in the diagnosis of SATs.

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