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Original Research Article

Skin Adnexal Tumors: An Experience at Tertiary Care Centre

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Abstract

Background: Skin adnexal tumors are large and diverse group of uncommon neoplasms usually misdiagnosed clinically due to their large variety and variants. Histopathology usually helps in establishing the diagnosis. *Aims:* To study the spectrum and morphological features of skin adnexal tumors (SATs) at our centre. *Methods:* This is both retrospective and prospective descriptive study over a period of 5 years (June 2005 to June 2010). The study included all the biopsies and excision specimens submitted for histopathological examination. *Results:* Most of the SATs were benign (25/31) with head and neck being the most common location (67.74%). Male to female ratio was 1:1.8. There was equal occurrence of tumors of sweat gland and hair follicle differentiation (45%). The most common varieties of tumors encountered in the present study included proliferating trichilemmal tumor and hidradenoma. The concordance between clinical and histopathological diagnosis was found to be 6.45% approximately. *Conclusions:* SATs are relatively uncommon. As they are often clinically misdiagnosed, histopathology is mandatory for the diagnosis. Although they are not numerically important or therapeutically problematic, nevertheless they form the spectrum of interesting lesions.

Keywords: Adnexal tumor; Proliferating trichilemmal tumor; Hidradenoma; Pilomatricoma.

Introduction

Skin is a complex tissue with an intricate adnexae. Skin adnexae give rise to a perplexing number of neoplasms probably more than the accounted numbers. These tumors essentially differentiate in the line of hair follicles, sebaceous glands, eccrine and apocrine sweat glands [1]. Skin adnexal tumors (SATs) are rare lesions and in view of the fact that they are so infrequently encountered in practice, they may cause difficulty in diagnosis.

The embryological relations, anatomical distribution, combinations of neoplasms and the associations of SATs are all genuine biological phenomena [2]. Understanding the concept of histogenesis is essential for diagnosis of these tumors [3].

Apart from their rarity, difficulties in diagnosis also result due to their large variety, non specific clinical appearance, their frequent differentiation along two or more adnexal lines simultaneously and their complex nomenclature [1,4,5]. Benign SATs have a tendency to mimic malignant lesions and usually manifest in any age group. Malignant SATs are rare, locally aggressive and have the potential for nodal involvement and distant metastasis with a poor clinical outcome. Therefore establishing a diagnosis of malignancy in SAT is important for therapeutic and prognostic purpose [6].

There is scarcity of literature on the clinicopathological features of SATs. Histopathological study is mandatory to establish diagnosis which is the most valuable means of diagnosis in dermatopathology, inspite of its own limitations. Literature search showed very few studies from India, majority of them being isolated case reports. Keeping in view of these facts, the present study documents our experience with SATs with emphasis on clinical data, histomorphology, diagnostic approach and brief review of literature.

Materials and Methods

This was a descriptive study conducted at the department of Pathology in a tertiary care hospital over a period of 5 years from 2005 to 2010. The study included all the biopsies and excision specimens submitted for histopathological examination. Data was collected after a meticulous study of inpatient and outpatient dermatology, surgery records and histopathology records. The specimens were fixed in 10% formalin and the gross features were examined and sampled depending on the size of tumor. Tissue was routinely processed and sections of 3 to 5 micron thickness were taken and stained with hematoxylin and eosin. Wherever necessary relevant special stain was done. The facility for histochemical staining for enzymes was not available in our laboratory setup.

Results

During the 5 year study period, 135 skin tumors were noted, of which 31 were adnexal in origin. Prevalence of SATs compared to total surgical pathology specimens was found to be 0.12%. The tumors were categorized as per WHO classification. Majority of tumors in our series were benign (25 cases - 80.6%) with equal occurrence of hair follicle and sweat gland tumors (45%)(Table 1). Age range was wide from 11 to 80 years. One of the most notable findings in the present study was female predominance with male to female ratio of 1:1.8. Head and neck was the most frequently involved site for SATs accounting for 67.74%. The tumor size ranged from 0.5 cm to 7 cm. Most of the SATs (70.96%) were <2.5 cm in maximum dimensions. SATs were clinically suspected in 6.45% of patients before excision.

Tumors with Hair follicle differentiation

Hair follicle tumors had a female predominance and proliferating trichilemmal tumor (PTT) was the most common type. Next in frequency were pilomatricoma, trichoepithelioma and Malignant PTT (Table 2).

There were 7 PTTs among which 5 occurred in females and 2 in males. Age range was 14-60 years. Most common site was scalp (5 cases). Most common clinical diagnosis was sebaceous cyst. Histologically, all cases were well circumscribed and composed of squamoid cells showing trichilemmal keratinization and peripheral palisading. The tumor cells showed mild pleomorphism as well as dyskeratosis (Figs. 1,2). Calcification was noted in 4 of them. Presence of squamous eddies and cholesterol clefts were the other changes observed.

Four pilomatricomas were encountered in 3 females and 1 male subject. In one case, a 30 year old female presented with recurrence of axillary pilomatricoma despite wide surgical excision (Fig. 3). Histologically all 4 tumors were well

Table 1: Distribution of tumors according to line of differentiation and behaviour

	Benign	Malignant	Total
Tumors with Hair follicle differentiation	13	1	14
Tumors with sweat gland differentiation	11	3	14
Tumors with Sebaceous differentiation	1	2	3

Table 2: Tumors with hair follicle differentiation

No of cases	Age/sex	Site	Clinical details	Histopathological Diagnosis
1	30 yr/F	scalp	Swelling	Proliferating trichilemmal tumor
2	40 yr/F	Scalp	Non healing ulcer - SCC	Proliferating trichilemmal tumor
3	14 yr/F	Scalp	Sebaceous cyst	Proliferating trichilemmal tumor
4	60 y/F	Scalp	Sebaceous cyst	Proliferating trichilemmal tumor
5	45 yr/F	scalp	Ulcer - SCC	Proliferating trichilemmal tumor
6	55 y/M	Foot	Swelling - Sebaceous cyst	Proliferating trichilemmal tumor
7	60 y/M	Axilla	Cystic swelling Sebaceous cyst	Proliferating trichilemmal tumor with pilar cyst
8	18 y/F	Face	Swelling sebaceous cyst	Pilomatricoma
9	26 y/F	Suboccipital	Hard swelling - osteoma	Pilomatricoma with extensive calcification
10	30 y/F	Axilla	Recurrent bony hard swelling	Giant Pilomatricoma with extensive calcification
11	35 y/M	Leg	Mobile Swelling Sebaceous cyst	Pilomatricoma with giant cell reaction
12	86 y/F	Dorsum of nose	Asymptomatic nodule Adnexal tumor	Trichoepithelioma
13	28 y/F	Face	Multiple asymptomatic nodules - BCC	Trichoepithelioma
14	28 y/F	Scalp	Ulcerative lesion - SCC	Malignant proliferating trichilemmal tumor

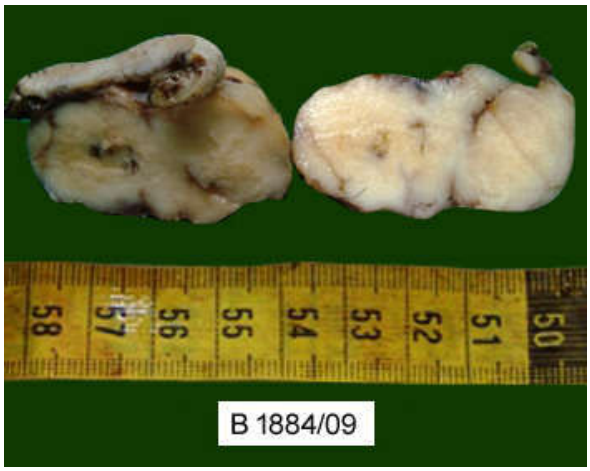

Fig. 1: Proliferating trichilemmal tumor: Scalp swelling measuring 4x3 cm

Fig. 3: Recurrent calcified Pilomatricoma: Axillary bony hard swelling measuring 7x4 cm

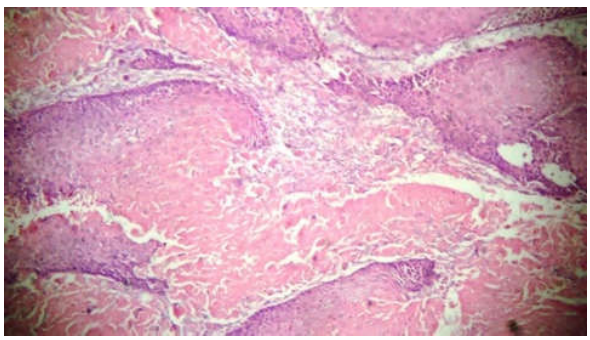

Fig. 2: Proliferating trichilemmal tumor: squamoid cells showing trichilemmal keratinisation (abrupt keratinization) and peripheral palisading. The tumor cells show mild pleomorphism as well as dyskeratosis (H&E 10X).

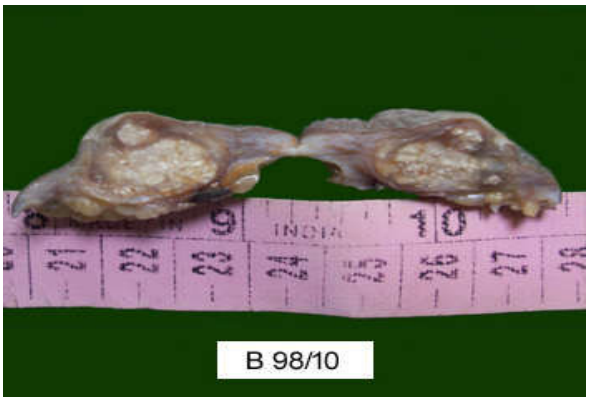

Fig. 4: Pilomatricoma: Leg Swelling measuring 2x1 cm.

circumscribed, composed of islands of basophilic cells and shadow cells (Figs. 4,5). Extensive calcification was seen in 2 of them and one tumor showed giant cell reaction to keratin.

Both trichoepitheliomas presented as nodular lesions over face. Histologically, showed islands of basaloid cells in the dermis with peripheral palisading (Fig. 6). Horn cysts, abortive hair follicles and presence of fibrous stroma were noted.

We came across one rare case of malignant PTT in 28 year old female who presented with an ulcer over scalp and the tumor had infiltrative margins composed of pleomorphic squamoid cell islands with areas of abrupt keratinisation and atypical frequent mitotic figures (Fig. 7).

Tumors with sweat gland differentiation

Benign sweat gland tumors comprised of hidradenoma, which formed the bulk of cases followed by one case each of cylindroma (Fig. 8), syringoma, Syringocystadenoma Papilliferum (SCP), apocrine hidrocystoma (Fig. 9) and chondroid syringoma (Fig. 10) (Table 3).

Hidradenoma was seen in 4 females and 2 males. Age range was 18-75 years. Three each were

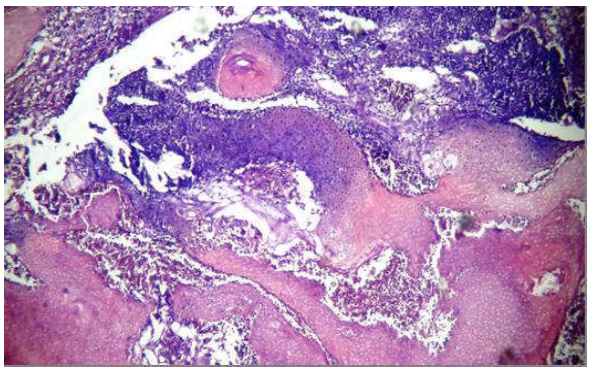

Fig. 5: Pilomatricoma: composed of islands of basophilic cells and shadow cells (H & E, 10X).

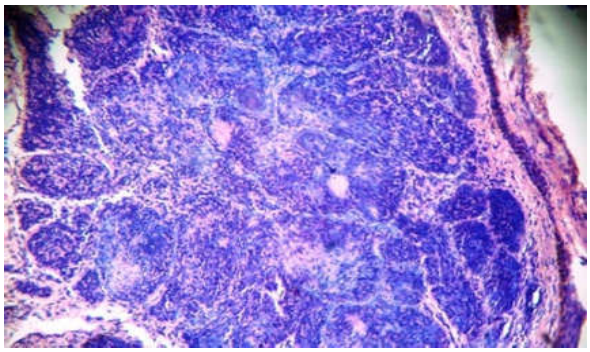

Fig. 6: Trichoepithelioma: Well circumscribed dermal tumor with islands of basophilic cells (H & E, 10X).

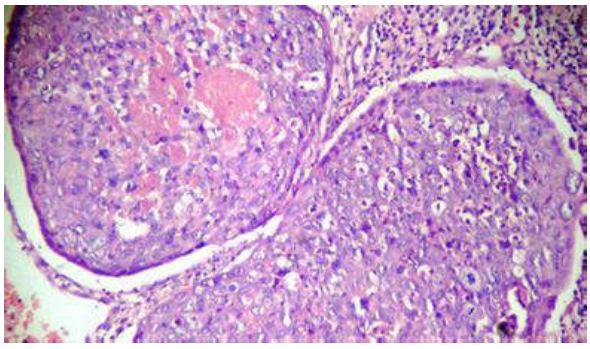

Fig. 7: Malignant proliferating trichilemmal tumor: pleomorphic squamous cell islands with areas of abrupt keratinisation and atypical frequent mitotic figures(H&E, 10X).

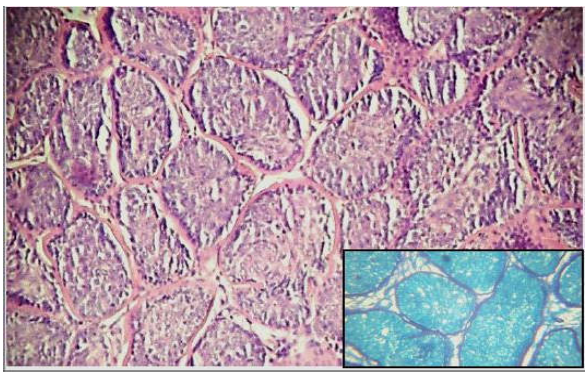

Fig. 8: Cylindroma: The tumor show dual population of cells with jigsaw puzzle pattern (H & E, 10X). Hyaline basement membrane showed PAS positivity (inset).

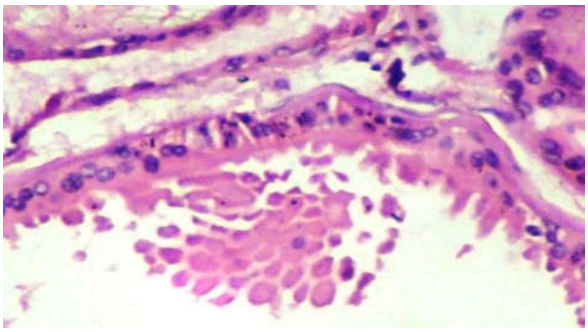

Fig. 9: Apocrine hidrocystoma: Multiloculated cystic lesion lined by columnar secretory cells showing decapitation (H & E,40X)

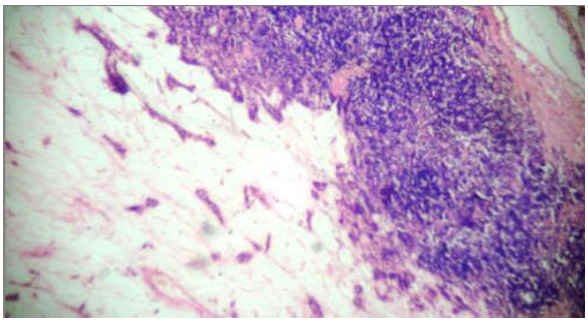

Fig 10: Chondroid syringoma: Epithelial cells arranged in solid sheets with formation of tubular lumina with abundant mucoid stroma (H & E,10X).

noted on the trunk and face. Common clinical presentations were swelling, ulcer and proliferative growth. All the tumors were well circumscribed lobular masses composed of clear cells and eosinophilic cells arranged in solid areas, tubule formations, with areas of cystic change. Cytoplasm of clear cells showed PAS positivity indicating presence of glycogen (Fig. 11). One of the tumor showed extensive squamous differentiation.

SCP was seen over back in a 38 year old male with epidermis showing papillomatosis and the cystic invaginations extending downward from epidermis lined by two layers of cells, the luminal cells being columnar showing apical snouting. Stroma of papillary core had dense lymphoplasmacytic infiltrate (Fig. 12).

Both hidradenocarcinomas mimicked metastatic adenocarcinoma histologically. One case was a recurrent swelling over the scalp in a 11 year old female (Figs. 13,14). Histologically the tumor cells were arranged in lobules and sheets and in tubular formations filled with secretions. Cells displayed mild nuclear pleomorphism with clear cytoplasm and brisk mitosis. In both cases detailed histomorphological study and complete clinical diagnostic workup was done to exclude metastasis to the skin. Apocrine carcinoma of axilla had infiltrating margins with tumor cells displaying cytonuclear pleomorphism and brisk mitosis (Figs. 15). The cells were arranged in sheets, islands, tubules and singles. Luminal cells showed decapitation secretion. PAS-positive diastase-resistant material was identified in the cells.

Tumors with sebaceous gland differentiation

Sebaceoma presented as nodule over nose in 55 year old female and showed extensive squamous differentiation (Fig. 16). Both sebaceous carcinomas were noted over lower eyelid with suspected clinical diagnosis of chalazion and basal cell carcinoma.

Table 3: Tumors with sweat gland differentiation

No of cases	Age/sex	Site	Clinical details	Histopathological Diagnosis
1	75 y/F	Cheek	Ulcer- BCC	Hidradenoma
2	18 y/F	Abdominal wall	Swelling	Hidradenoma
3	60 y/F	Forehead	Nodular ulcer	Hidradenoma
4	62 y/M	Scalp	Proliferative growth	Hidradenoma
5	32 y/F	Neck	Swelling	Hidradenoma
6	57 y/M	Back	Swelling - sebaceous cyst	Hidradenoma
7	32 y/F	Scalp	Swelling -Adnexal tumor	Cylindroma
8	38 y/F	Back	Papilloma	SCP
9	27 y/F	Eyelid	Asymptomatic nodule	Syringoma
10	48 y/M	Forehead	Swelling- Dermoid cyst	Chondroid syringoma
11	62 y/M	External auditory canal	Nodule	Apocrine hidrocystoma
12	11 y/F	Scalp	Recurrent swelling	Hidradenocarcinoma
13	45 y/M	Abdominal wall	Nodulo-ulcerative growth	Hidradenocarcinoma
14	60 y/M	Axilla	Cauliflower like growth	Apocrine carcinoma

Table 4: A comparative analysis of Indian literature with regard to the line of differentiation of adnexal tumors

Studies	Year	Total number of cases (N)	Tumors with Sebaceous differentiation	Tumors with Sweat gland differentiation	Tumors with Hair follicle differentiation
Vaishnavi and Dharkar [7]	1974	48	03	38	07
Kartha et al. [7]	1980	83	03	45	35
Reddy et al. [7]	1982	85	18	54	13
Solanki RL et al. [8,9]	1989	94	22	50	22
Nair PS [10]	2008	33	02	19	12
Saha A et al. [4]	2011	23	03	13	07
Jindal and Patel [11]	2012	25	01	13	11
Gayathri et al. [12]	2012	29	03	15	11
Radhika et al. [13]	2013	35	7	17	11
Pantola et al. [12]	2013	70	4	42	24
Sharma A et al. [14]	2014	56	12	24	20
Vani D et al. [15]	2015	51	10	22	19
Pujani M et al. [12]	2016	25	4	14	7
Present study		31	3	14	14

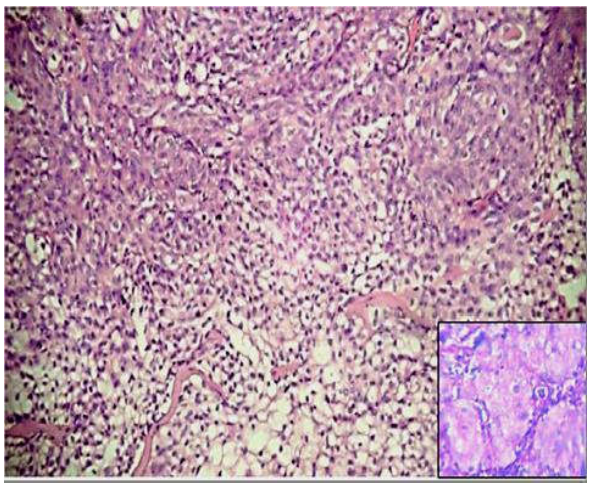

Fig. 11: Hidradenoma: solid areas composed of clear cells and eosinophilic cells (H&E,). Clear cells show PAS positivity (inset).

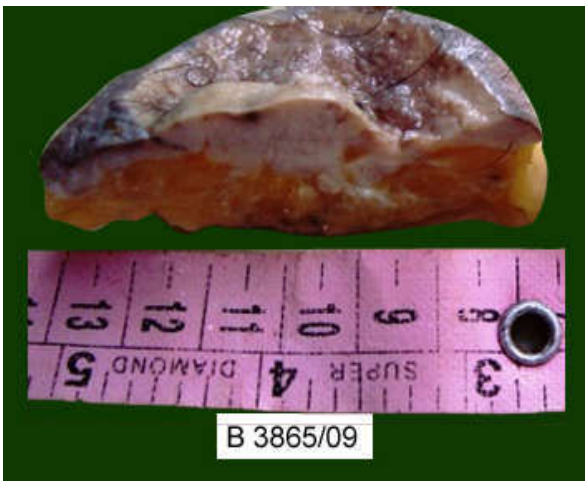

Fig. 14: Hidradenocarcinoma: Nodulo ulcerative growth measuring 7x6cm over abdominal wall

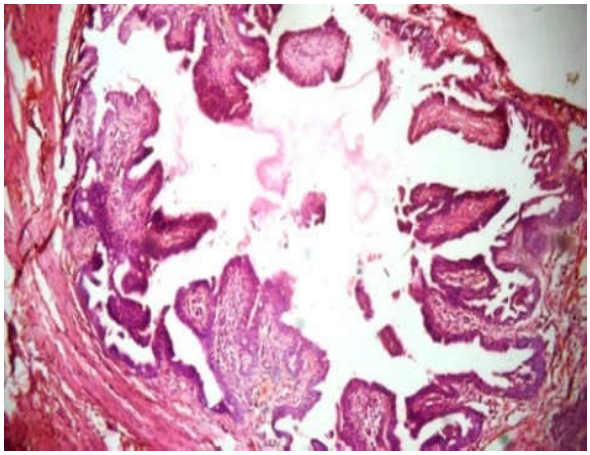

Fig. 12: Syringocystadenoma Papilliferum: Cystic invagination with by papillary projections lined by two rows of cells. Plasma cells seen in the core (H&E,10X).

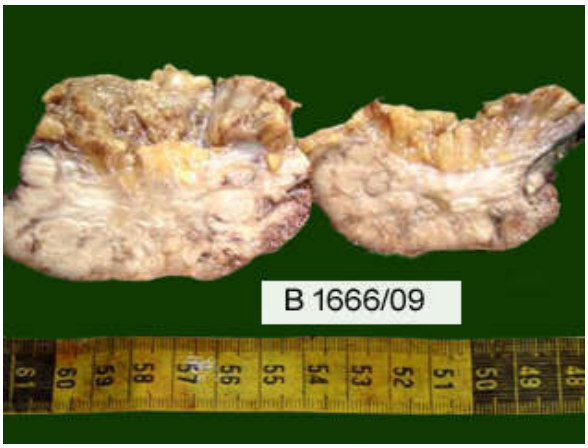

Fig. 15: Apocrine carcinoma: Cauliflower like growth measuring 7x6 cm in axillary region

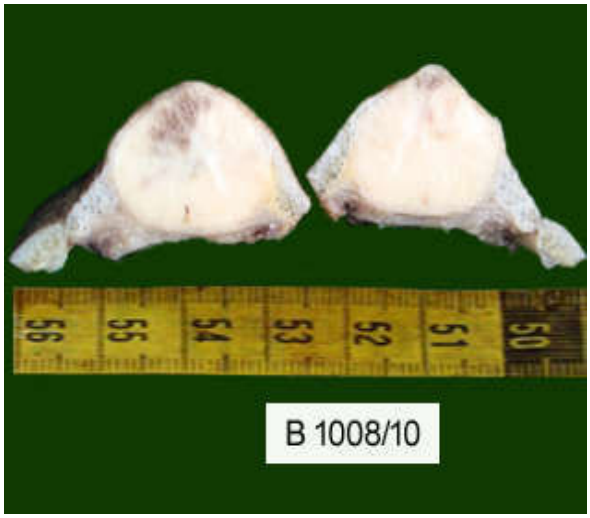

Fig. 13: Hidradenocarcinoma: Recurrent scalp swelling.

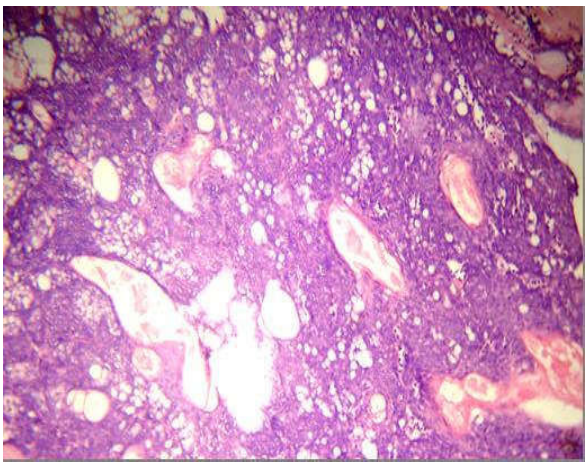

Fig. 16: Sebaceoma: well circumscribed mass with more than half of the cells being basaloid cells and few islands of mature sebaceous cells with extensive keratinization (H&E,10X).

Discussion

Only 31 cases seen in a 5 year period indicates that SATs are uncommon. A comparative analysis of many studies from Indian literature has been shown in Table IV with regard to the line of differentiation of SATs. In majority of Indian studies the most frequent line of differentiation encountered was sweat gland differentiation followed by hair follicle differentiation with the least frequent being sebaceous gland differentiation (Table 4). On the contrary present study showed equal occurrence of tumors of hair follicle and sweat gland differentiation (45%). In the present study 80.6% tumors were benign and 19.4% were malignant. Radhika et al., Reddy et al., Yaqoob N and Samaila have reported 77.14%, 69.41%, and 88.5% benign tumors respectively [7,13,15,16].

In our study SATs had a wide age range from 11 to 80 years with a female predominance. Female:male ratio was 1.8:1. Female : male ratio as observed by Nair PS and Saha et al. was 2.3:1 and 1.88:1 respectively [4,10]. Female predominance was noted in majority of Indian studies [6,13,14,17]. The higher frequency of SATs in females may be explained by the fact that they are cosmetically more conscious.

The predominance of SATs in head and neck region is a well documented fact supported by many studies which was also observed in our study (67.74%) [6,11,14,16,17]. This is accounted by the fact that this region is rich in adnexal units. In the present study, common SATs were PTT and hidradenoma. Radhika et al., Solanki RL et al., Reddy et al., Sharma et al. and Vani D et al. observed hidradenoma as the most common benign tumor [6,7,9,13,14].

PTT most commonly occur on the scalp and have a distinct predilection for women which concurs with our study [18]. Recently PTTs has been classified into benign, low grade, high grade and malignant tumors [18]. The usual clinical diagnosis of PTT is squamous cell carcinoma and sometimes PTTs may mimic SCC due to presence of cellular atypia [19]. Without paying closer attention to the trichilemmal type of keratinization, many of these lesions may be mistakenly diagnosed as SCC [20]. Presence of pre existing pilar cyst, good circumscription, trichilemmal keratinisation, absence of significant atypia, peripheral palisading and hyalinised basement membrane favour diagnosis of PTT [1]. Immunohistochemical positivity for CD34 and calretinin indicate the outer root sheath origin of PTT with low Ki 67 index [21]. Pilar cyst and PTT can occur together and lesions intermediate between pilar cyst and PTT have been evidenced. The key factor in proliferation may be vascularisation of cyst epithelium possibly secondary to focal injury [22]. There was one such lesion in our study in a 60 year old male who presented with scalp swelling and showed presence of both these lesions. Malignant PTT is an uncommon histopathological entity. No absolute clinical criteria can distinguish a benign PTT from a malignant PTT. Hence the entire lesion must undergo histopathological examination [20].

Pilomatricoma was first described in 1880 by Malherbe and Chenantais as a tumor of the sebaceous glands [23]. Pilomatricoma, although considered a tumor of hair matrical differentiation, is now believed to be a complex panfollicular neoplasm, in that it can exhibit signs of differentiation of the entire follicle that is towards inner sheath, infundibulum and isthmic epithelium [23]. In 75-79% of the times the clinical diagnosis is incorrect at the time of initial consultation [24]. Usual clinical diagnosis include calcified sebaceous cyst, osteoma, neurofibroma etc [25]. The term "giant pilomatricoma" has been used for lesions greater than 5 cm in diameter, although the term is very subjective [24]. Older lesions become solid with predominance of shadow cells, keratin debris, multinucleated giant cells and dystrophic calcification [1]. Calcification occur frequently and osseous metaplasia of stroma is occasionally found [22]. In our study calcification was seen in 2 cases.

Trichoepithelioma is a major histological differential diagnosis for keratotic BCC. Presence of well-formed horn cysts, papillary-mesenchymal bodies, lack of high-grade atypia and mitoses and absent epidermal connection favor the diagnosis of trichoepithelioma. Artifactual retraction is uncommon in trichoepithelioma [1]. Staining of the outermost epithelial layer with bcl-2 has been seen in trichoepitheliomas. In contrast, basal cell carcinomas frequently stain diffusely [10].

Hidradenoma shows differentiation towards intraepidermal and intradermal eccrine structures ranging from the poral epithelium to the secretory segment [1]. Hidradenomas occur as a solitary nodule at all ages and have variable histomorphological patterns, reflected by the various terms used to describe this entity. Occasionally some features show overlapping with those of poromas. Histological variants include epidermoid, oncocytic and pigmented. Clear cell change and squamous metaplasia may be prominent. However, squamoid change does not

appear to denote a worse prognosis [26]. These can occasionally redevelop even after excision [27].

Apocrine hidrocystoma is regarded as cystic adenomatous proliferation of apocrine glands rather than retention cyst. It can be differentiated from eccrine hidrocystoma by presence of decapitation and PAS positivity [1,27]. The largest series of SCP (100 cases) have been reported by Helwig and Hackney [28]. Clinically usually presents as raised warty plaque [27]. Most lesions exhibit both apocrine and eccrine differentiation. Positive immunoreactivity with gross cystic disease fluid protein-15 and 24 (GCDFP-15 and 24) is seen, indicating tumor of apocrine origin but electron microscopic features show evidence of eccrine origin.[1] Recent studies show loss of heterozygosity at chromosome 9q22 in cases of SCP [10]. Chondroid Syringoma is so named due to a mixture of proliferating ductular eccrine epithelium and a characteristic chondroid stromal matrix. It occurs mainly on the head and neck. Ultrastructurally, cells within its chondroid matrix show features of both epithelial and mesenchymal cells raising the possibility that both cell lines may be the neoplastic progeny of pluripotent cells which is expressed early in the development of this tumor [15].

Usually Hidradenocarcinomas arise de novo and also arise in pre-existing hidradenoma. Microscopic distinction between the benign and malignant forms is usually made based on the extent of invasion, asymmetry at scanning magnification, brisk mitotic activity and degree of nuclear atypia [29]. The tumor cells stain positively for LMWK, and the ductal structures/luminal surfaces are highlighted by EMA and CEA [26]. Apocrine carcinoma is a rare and highly aggressive adenocarcinoma, mostly occurs in areas rich in apocrine glands, especially the axilla. The tumor cells are positive for LMWK, and the luminal cells are reactive for CEA, EMA and GCDFP-15. Positivity to androgen receptors and GCDFP-15 is considered helpful but negativity of these tumors to ER and PR is more relevant. The use of calponin and SMA as markers for the peripheral myoepithelium is helpful in delineating invasion [26].

Occular sebaceous carcinomas are aggressive tumors and most commonly arise from meibomian and zeiss glands. Usual clinical diagnosis is chalazion. Presence of lymphovascular invasion, orbital extension and large size indicate poor prognosis. Tumor is positive for EMA and androgen receptor [27].

Malignant SATs often resemble their benign counterparts and attention has to be paid to features such as large size, rapid increase in size, infiltrative growth pattern, nuclear atypia, brisk mitosis and necrosis [1]. Some primary malignant SATs like hidradenocarcinomas mimic metastatic moderately to poorly differentiated adenocarcinomas. In such cases detailed histomorphological features and complete clinical diagnostic workup are pre-requisite to exclude metastasis to the skin. Two such tumors were present in our study. IHC may play an important role in distinguishing primary cutaneous adnexal carcinoma from metastatic carcinoma. P63 and CK 5/6 positivity favors a primary cutaneous adnexal carcinoma over a metastatic carcinoma [12].

The SATs encompassed a wide variety of clinical presentation, presenting as nodules, swelling and ulcerative growth with histologically distinct features. The most common clinical diagnosis for benign and malignant SATs were sebaceous cyst and squamous cell carcinoma respectively. The clinical appearance of appendageal tumor was mostly non-specific and diagnosis of SATs was not suspected clinically in most of the cases. Hence, the discrepancy between clinical and histopathological diagnosis was encountered. However, the location, single/multiple lesions, and their distribution can provide important diagnostic clues. In the present study, the concordance between clinical and histopathological diagnosis was found to be 6.45% approximately. Kamyab-Hesari et al. and Pujani M et al. found a higher (64% and 50%) concordance between clinical and histopathological diagnosis [12]. Sometimes more than one type of appendage give rise to combined tumors with varying degrees of maturation. However in our study, such combined tumors were not detected. Many a times it is only of academic interest to give a specific name for SATs because the surgeons pay more attention to the nature of tumor and its prognosis once it has been removed. Cytochemical stains such as PAS, mucicarmine, alcian blue, and reticulin may aid in establishing the diagnosis. The need for immunohistochemistry varies from case to case depending on histogenesis of SATs.

Conclusion

SATs are diverse group of neoplasms, with a nonspecific clinical appearance and their diagnosis primarily rely only on histopathology. However the location and distribution of lesions may provide diagnostic clues. Occasionally these tumors are difficult to classify and prognosticate. In our study the frequency of benign skin adnexal tumors was

more as compared to the malignant ones. SATs can occur anywhere in the body; however head and neck region constituted the most common site in our study. Most of the SATs occurred in younger age group but still showed a wide age variation. Most SATs are benign and local complete surgical excision is curative. Because these tumors are not frequently encountered, their diagnosis may be challenging even to an experienced pathologist. Dermatopathologists should employ a reliable criteria for accurate and reproducible diagnosis of SATs and make a foundation to determine the specific line of differentiation.

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