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Case Series

Pathology Section

Clinical and Histomorphological Features of Cutaneous Adnexal Neoplasms: A Series of Eighteen Cases

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ABSTRACT

Cutaneous Adnexal Neoplasms (CAN) are rare skin tumours with varied morphology that are often misdiagnosed clinically. The definitive diagnosis of these tumours can only be made by Histopathology (HP) based on their appendage differentiation. Though rare in occurrence, diagnosing these tumours is of prime importance, as they can mimic primary cutaneous carcinomas, cutaneous metastasis of a primary tumour, or can serve as markers of internal malignancy. Excision is mostly curative in benign tumours, and wide local excision needs to be performed to prevent recurrences. The aim of the present case series study was to investigate the histopathological spectrum of different CANs based on their appendage differentiation in a hospital-based study. A retrospective analysis was conducted over a period of 4.5 years, and all CAN cases diagnosed on HP were classified according to their appendage differentiation. The concordance between histopathological diagnosis and clinical diagnosis was calculated. Additionally, the frequency distribution of CAN in relation to demographic data was analysed. In the present case series, 18 cutaneous adnexal tumours were reported, showing a female predominance. The majority of the tumours 12 (66.67%) cases were observed in the head and neck region and exhibited a predominance of sweat gland differentiation 12 (66.67%) cases. The most common CANs were eccrine spiradenoma and pilomatrixoma, with 3 (16.67%) cases each. Sebaceous carcinoma and a rare case of Malignant Proliferating Trichilemmal Tumour (MPTT) accounted for 2 (11.11%) cases, being the only malignant tumours reported. The present study demonstrated only concordance of 4 (22.22%) cases between clinical and HP diagnosis. Therefore, the present series emphasises the importance of appendage differentiation in HP, which plays a crucial role in the definitive diagnosis, treatment planning and prognosis in CAN.

Keywords: Appendage, Hair follicle, Malignant proliferating trichilemmal tumour, Sebaceous carcinoma

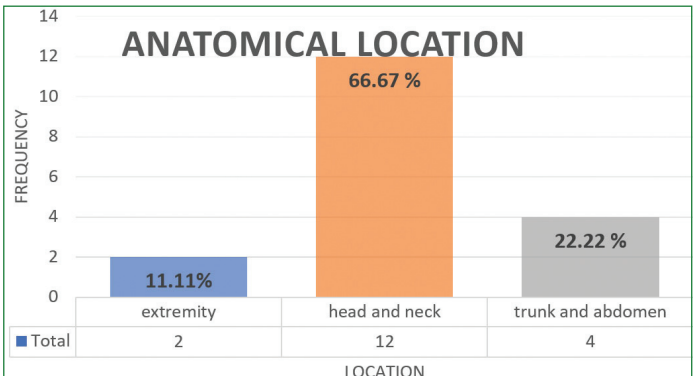
INTRODUCTION

Cutaneous adnexal neoplasms are rare tumours that exhibits either eccrine, apocrine, follicular, or sebaceous differentiation or a mixture of one or more differentiations based on their cell of origin [1]. These tumours typically originate at sites where their cells or glands of origin are normally located, such as the axilla (sweat glands), scalp (hair follicles) head and neck (sebaceous glands), and extremities. Clinical diagnosis of CAN is challenging because they do not have any distinct clinical appearance and can be mistaken for soft tissue tumours or lymph nodes. HP is considered the gold standard for diagnosing CAN. A definitive diagnosis of CAN is crucial, and they need to be differentiated from primary cutaneous carcinomas and cutaneous metastases of primary tumours [2]. These tumours may serve as markers of internal malignancies, such as sebaceous tumours in Muir-Torre syndrome and follicular tumours in Cowden syndrome [3]. Therefore, the objectives of the present study were to determine the concordance between clinical and HP diagnosis and to investigate the frequency distribution of CAN in relation to demographic data (age, gender and anatomical location) to identify any recent changes in presentation patterns.

CASE SERIES

A retrospective descriptive study was conducted for a period of 4.5 years from January 2018 to June 2022 in the Pathology Department of a tertiary care hospital. Clinical data was extracted from the patients' medical records. HP reports and slides were retrieved from the Pathology Department and reviewed. The histomorphology of tumours were examined, and classification was performed according to the World Health Organisation (WHO) Classification of Cutaneous Adnexal Tumours 2018 based on appendage differentiation [4].

Only 18 CAN cases were reported during the 4.5 year study period. CAN cases spanned a wide age range, from 8-76 years. The majority of CAN cases (n=6) were observed in the younger age group of 20-29 years, with a female preponderance in 10 (55.55%) cases, while the remaining 8 (46%) cases were seen in males. The head and neck region was the most common site for CAN in the present study, accounting for 12 (66.67%) cases [Table/Fig-1].



[Table/Fig-1]: Anatomical location.

In the present case series, only 2 (11.11%) cases were malignant, while the remaining 16 (88.89%) cases were benign. Malignant PTT and sebaceous carcinoma were the only reported malignant tumours. The most common subtype of appendage differentiation was apocrine/eccrine in 12 (66.67%) cases, followed by follicular in 5 (27.77%) cases. Overall, the most common CANs were eccrine spiradenoma and pilomatrixoma, each accounting for 3 (16.67%) cases. Among apocrine/eccrine (n=12) differentiation, eccrine spiradenoma was the predominant tumour in 3 (25%) cases, while among follicular differentiation (n=5), pilomatrixoma was

predominant in 3 (60%) cases [Table/Fig-2]. Sebaceous carcinoma was the only case with sebaceous differentiation (n=1), and only apocrine hidrocystoma showed apocrine differentiation.

Out of 18 cases, clinical diagnosis correlated with HP diagnosis in only four cases, all of which were present on the face, while the remaining 14 cases were diagnosed solely based on HP. The majority of the lesions were clinically diagnosed as sebaceous cysts (n=6). Only 3 cases of syringoma, trichoepithelioma and clear cell hidradenoma were presented as multiple lesions. Most of the tumours were less than 2 cm in size [Table/Fig-3].

Case 1

Eccrine Spiradenoma (ES)

All three cases (39-year-old and 21-year-old males and, 48-year-old female) presented as solitary painful swellings over the right foot, scalp and back. There was no significant medical or family history. Ultrasonography (USG) was performed in only two cases, both of which were reported as infected sebaceous cysts. The HP of all excised specimens revealed features of ES, with tumour cells arranged in discrete nodules composed of two types of cells: cells with scant cytoplasm, round to oval hyperchromatic dark nuclei and cells with pale nuclei. Cyst formation filled with eosinophilic decapitation secretion was seen in one case [Table/Fig-4a]. Pale cells were observed in a rosette arrangement around eosinophilic material [Table/Fig-4b]. The stroma showed lymphocytes within the tumour. Only the female patient returned for a follow-up for six months but was later Lost To Follow-Up (LTFU). The other patients did not show up for follow-up.

Case 2

Clear Cell Hidradenoma (CCH)

Among the three cases (52-year-old and 40-year-old females and, 62-year-old male), two presented as a solitary nodule over the scalp and neck, while one case presented with multiple hard swellings over the abdominal flank. The patient with the neck swelling had a recent history of discharge from the surface and pain, for which the patient sought consultation. There was no significant past medical or family history. USG was performed in two cases, and both were

Appendage differentiation	Cutaneous appendageal tumours	Frequency (n)	Percentage (%)	Frequency of appendage differentiation (n)	Percentage of appendage differentiation (%)	Percentage of individual appendage differentiation (%)	
Eccrine/Apocrine	Apocrine hidrocystoma	12	66.67	1	5.56	66.67	8.33
	Clear cell hidradenoma			3	16.67		25
	Cylindroma			2	11.11		16.67
	Eccrine poroma			2	11.11		16.67
	Eccrine spiradenoma			3	16.67		25
	Syringoma			1	5.55		8.33
Follicular	Pilomatrixoma	5	27.77	3	16.67	27.77	60
	Malignant Proliferating Trichilemmal Tumour (MPTT)			1	5.55		20
	Trichoepithelioma			1	5.55		20
Sebaceous	Sebaceous carcinoma	1	5.56	1	5.56	5.56	100
Total		18	100	18	100	100	

[Table/Fig-2]: Frequency distribution of appendage differentiation.

Case no.	Age/Gender	Site of lesions	Lesion no.	Size	Clinical diagnosis	Histopathology (HP) diagnosis	Tumour type	Treatment/ follow-up
1	25/F	Face	Multiple	0.3×0.3 cm	Syringoma	Syringoma	Benign	Excision/2 years
2	28/M	Eye canthus	Single	0.8×0.8 cm	Eccrine hidrocystoma	Apocrine hidrocystoma	Benign	Excision
3	58/F	Preauricular region	Single	2×2 cm	Lipoma	Cylindroma	Benign	Excision
4	23/M	Eyelid	Single	0.5×0.5 cm	Wart	Eccrine poroma	Benign	Excision
5	39/M	Right foot	Single	1.2×0.5 cm	Ganglion	Eccrine spiradenoma	Benign	Excision
6	33/M	Scalp	Single	0.5×0.5 cm	Appendage tumour	Cylindroma	Benign	Excision/1 year
7	52/F	Neck	Single	6.5×5.4 cm	Sebaceous cyst	Clear cell hidradenoma	Benign	Excision
8	24/M	Upper lip	Multiple	0.5×0.5 cm	Trichoepithelioma	Trichoepithelioma	Benign	Excision/2 years
9	76/F	Scalp	Single	6.5×3×3.5 cm	Squamous Cell Carcinoma (SCC)	Malignant Proliferating Trichilemmal Tumour (MPTT)	Malignant	Wide local excision/1 year
10	62/M	Scalp	Single	3.5×1.5 cm	Sebaceous cyst	Clear cell hidradenoma	Benign	Excision
11	29/F	Scalp	Single	1×1 cm	Pyogenic granuloma	Eccrine poroma	Benign	Excision
12	8/F	Arm	Single	1×0.5 cm	Sebaceous cyst	Pilomatrixoma	Benign	Excision
13	52/M	Abdomen	Single	4.5×4.5 cm	Lipoma	Pilomatrixoma	Benign	Excision
14	21/M	Scalp	Single	3×2 cm	Sebaceous cyst	Eccrine spiradenoma	Benign	Excision
15	40/F	Abdomen	Multiple	5.5×4.5×2.5 cm	Guinea worm calcification	Clear cell hidradenoma	Benign	Excision
16	48/F	Back	Single	1.9×1.5 cm	Sebaceous cyst	Eccrine spiradenoma	Benign	Excision/ 6 months
17	49/F	Back	Single	1.2×1.2 cm	Sebaceous cyst	Pilomatrixoma	Benign	Excision
18	47/F	Eyelid	Single	0.8×0.8 cm	Sebaceous hyperplasia	Sebaceous carcinoma	Malignant	Excision/ 1.5 years

[Table/Fig-3]: Clinical and histopathological findings.

reported as sebaceous cysts. The USG of the abdomen for the abdominal wall swelling was normal. In the scalp nodule, Fine Needle Aspiration Cytology (FNAC) was conducted at an outside hospital and reported as benign Cutaneous Adnexal Neoplasm (CAN), but details were not available. The HP of all excised specimens revealed a well-circumscribed tumour arranged in nests, nodules, and lining cystic spaces, consisting of two cell types. The predominant cells were clear cells with distinct borders, abundant clear cytoplasm, round central to eccentric nuclei with bland chromatin, and the other cells were polyhedral cells with eosinophilic cytoplasm and the same nuclear features as clear cells [Table/Fig-4c]. Numerous branching, hyalinised vessels were noted, and the histopathology was reported as Cutaneous Clear Cell Hidradenoma (CCH). None of the patients returned for long-term follow-up.

Case 3

Syringoma

A 25-year-old female presented with multiple non tender, skin-coloured nodules over the periorbital region of the face, which were increasing in number over time. There was no significant medical or family history. The histopathology of the excised specimen revealed a tumour composed of small ducts lined by a double layer of cuboidal cells; a few ducts showed a comma-like arrangement of epithelial cells within a fibrous stroma and were reported as syringoma [Table/Fig-4d]. The patient was followed-up for two years during which no new lesions developed.

Case 4

Cylindroma

A 33-year-old male and a 58-year-old female presented with single skin-coloured, non tender nodules over the scalp and preauricular region, respectively. Ultrasonography (USG) was performed in only one case, which was reported as a sebaceous cyst. There was no significant medical or family history. The histopathology of both excised specimens showed cylindroma, with tumour cells arranged in nests of epithelial cells, each surrounded by thick hyaline basement membrane material that appears like pieces of a jigsaw puzzle [Table/Fig-4e]. Within the nests, two types of cells were noted: cells with small dark nuclei and pale nuclei [Table/Fig-4f]. The male patient was followed-up for one year, while the female patient did not return for follow-up.

Case 5

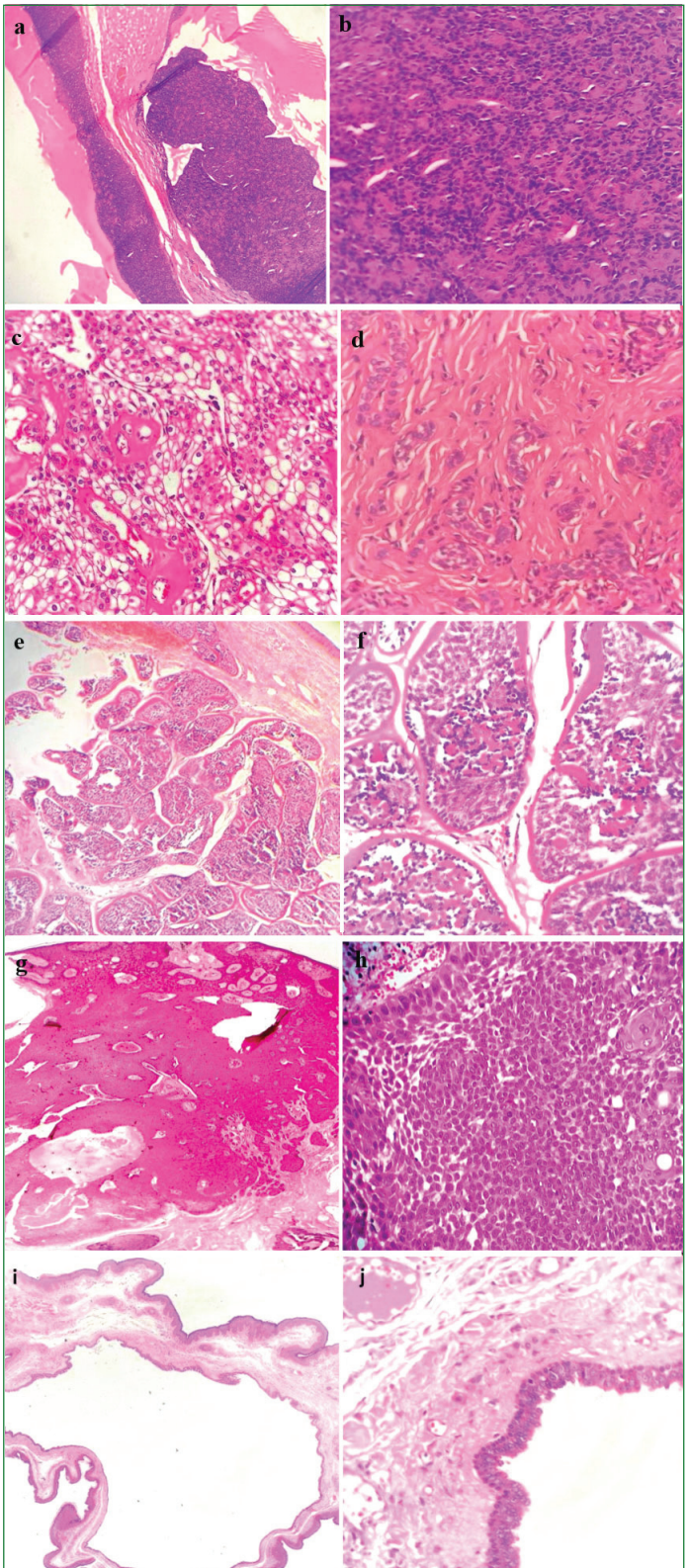
Eccrine Poroma

A 29-year-old female and a 23-year-old male both presented with solitary pedunculated nodules over the scalp and eyelid, respectively. The scalp swelling showed a recent increase in size and a history of intermittent bleeding over one month. There was no significant family history. The histopathology of both excised specimens showed poroma composed of large sheets and nests of cells in the dermis extending into the epidermis [Table/Fig-4g]. The cells were monomorphic, small, cuboidal with round nuclei and inconspicuous nucleoli [Table/Fig-4h]. The poroma cells were distinct from the basal cells of the epidermis. Thin fibrovascular stroma was observed along with cystic spaces filled with eosinophilic material. Follow-up details were not available.

Case 6

Apocrine Hidrocystoma

A 28-year-old male presented with a single cystic swelling over the right eye canthus. Excision was performed, and histopathology revealed a dermal cyst [Table/Fig-4i] lined by apocrine cells [Table/Fig-4j] with densely eosinophilic cytoplasm. The cells had round to oval nuclei showing nuclear stratification, which was reported as apocrine hidrocystoma.



[Table/Fig-4]: Sweat gland tumours microscopy (H&E): Eccrine spiradenoma: a) Nodules with dark cells and cyst formation with secretion (20x); b) Pale cells in rosette (40x); CCH: c) Dual cell population with hyalinised vessels (40x); Syringoma: d) Comma-like arrangement of cells (40x); Cylindroma: e) Jigsaw puzzle tumour pattern (20x); f) Nests surrounded by hyaline basement membrane material (40x); Eccrine poroma; g) Tumour with epidermal connection (10x); h) Monotonous poroma cells (40x); Apocrine hidrocystoma; i) Dermal cyst (10x); j) Apocrine cell lining (40x).

Case 7

Pilomatrixoma (Pilomatricoma)

All three cases (8-year-old and 49-year-old females and, 52-year-old male) presented as firm to hard masses observed over the abdomen, back regions and left arm. There was no significant medical or family history. FNAC was performed in two cases. One

case showed only a few anucleate squamous cells, and in the other case, the aspirate yielded no material on repeated aspirations. On HP, all cases showed a well-circumscribed dermal tumour composed of two types of cells: basaloid cells in sheets and their transition to ghost cells (shadow cells) with the loss of nuclei and retained cell outlines with trichilemmal-type keratinisation, which was reported as pilomatrixoma [Table/Fig-5a]. The stroma showed a foreign body giant cell reaction [Table/Fig-5b]. Calcification was observed in two cases. Follow-up details were not available.

Case 8

Trichoepithelioma

A 24-year-old male presented with multiple skin-coloured raised lesions over the upper lip and cheek. The patient had similar multiple tiny swellings over the nose and bilateral cheeks for three years. Clinical differentials considered were appendage tumour trichoepithelioma or adenoma sebaceum. There was no past history of mental retardation, seizures, or any family history. The histopathology of the excised specimen showed a dermal tumour trichoepithelioma with a focal epidermal connection, composed of horn cysts with abrupt keratinisation in the center [Table/Fig-5c], surrounded by nests and islands of basaloid cells with scanty cytoplasm and hyperchromatic oval nuclei [Table/Fig-5d]. A foreign body giant cell reaction was also noted at one focus. The patient was followed-up for one year.

Case 9

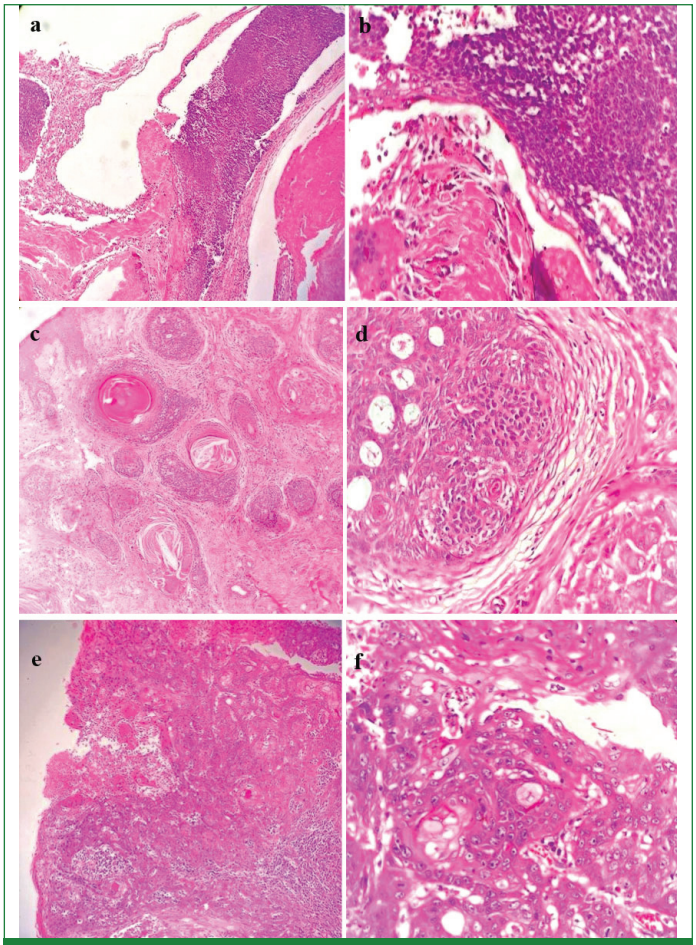
Malignant Proliferating Trichilemmal Tumour (MPTT)

A 76-year-old female presented with a recurrent painless swelling in the temporal region of the scalp of five months duration, which rapidly increased in size with postauricular lymph node enlargement. There was a past history of a similar swelling at the same site one year ago, which was excised, and the histopathology report was Proliferating Trichilemmal Tumour (PTT). The clinical diagnosis was Squamous Cell Carcinoma (SCC). A punch biopsy was taken, and the histopathology suggested a differential diagnosis of SCC and malignant cutaneous adnexal neoplasm. Wide local excision with lymph node excision was performed. The histopathology showed an ulceroinfiltrative tumour arranged in nests and sheets [Table/Fig-5e]. Individual tumour cells were round to polygonal, with moderate eosinophilic cytoplasm and pleomorphic hyperchromatic nuclei with prominent nucleoli and many abnormal mitotic figures [Table/Fig-5f]. The center of a few nests showed abrupt keratinisation. The intervening stroma showed diffuse, dense lymphoplasmacytic infiltrates. The histopathology was reported as low-grade MPTT, and the lymph node was free of tumour. Due to the risk of metastasis, the case was followed-up for one year, during which the patient was disease-free. Later, the patient was lost to follow-up.

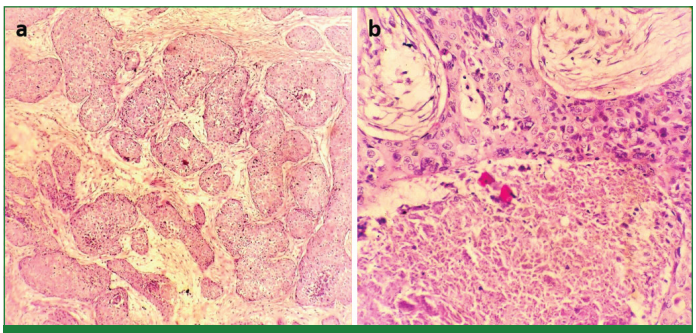
Case 10

Sebaceous Carcinoma (SC)

A 47-year-old female presented with a swelling over the left lower eyelid. The clinical diagnosis was sebaceous hyperplasia. Excision was performed, and histopathology revealed a tumour arranged in varying-sized nests and islands with infiltrative borders [Table/Fig-6a]. Individual cells had foamy cytoplasm [Table/Fig-6b] with pleomorphic vesicular nuclei and numerous abnormal mitotic figures. The center of the tumour nests showed areas of necrosis. The tumour was reported as sebaceous carcinoma, and the margins were free of tumour. The patient was followed-up for 1.5 years and remained disease-free during that period.



[Table/Fig-5]: Hair follicle tumours microscopy (H&E); Pilomatrixoma: a) Basaloid cells and ghost cells with trichilemmal type keratinisation (20x); b) Foreign body giant reaction (40X); Trichoepithelioma: c) Horn cysts with abrupt keratinisation (10x); d) Basaloid cells in nests (40x); MPTT: e) Ulceroinfiltrative growth with lymphoplasmacytic stromal infiltrates (10x); f) Tumour cells with atypia and many mitotic figures (40x).



[Table/Fig-6]: Sebaceous carcinoma microscopy (H&E): a) Varying-sized nests and islands of tumour cells (20x); b) Foamy cells with cytological atypia and areas of necrosis (40x).

DISCUSSION

The CANs are rare tumours, and their incidence is low in the present series, similar to other studies, as only 18 CAN cases were reported over a period of 4.5 years [2,5,6]. The neoplasms were predominantly seen in the younger age group of 20-29 years, comparable to two studies [1,7]. But other studies showed 51-60 years as the common age group [2,5]. The male to female ratio was 1:1.25, similar to the study by Pujani M et al., but most studies showed male predominance [2,3,7]. Head and neck were found to be the most common site, with 12 out of 18 cases (66.67%), similar to the studies by Pujani M et al., (72%) and Kamyab-Hesari K et al., (83.5%) [7,8]. The predilection for the head and neck was proposed due to the abundance of pilosebaceous units and sweat glands in this region [8]. Sun exposure was also postulated to be a risk factor in the development of these tumours [8]. In the present series, only syringoma, trichoepithelioma and CCH cases presented with multiple swellings. Multiple swellings may indicate a familial

syndrome association, such as spiradenomas, cylindromas, and trichoepitheliomas in Brooke-Spiegler syndrome, trichilemmomas in Cowden syndrome, pilomatrixomas in Gardner's syndrome and sebaceous tumours in Muir-Torre syndrome [3]. These tumours can be cutaneous signs of internal malignancy, as in Muir-Torre syndrome with colon tumours, hence warrant long-term patient follow-up [3].

The CAN showed predominant sweat gland differentiation, similar to other studies [2,5,7], unlike a few studies where follicular differentiation was predominant [1,3]. In this case series, the most common tumours were ES and pilomatrixoma, similar to other studies [3,9]. The present study showed a concordance of 4/18 (22.22%) cases between clinical and HP diagnosis, unlike two other studies, which showed concordance of 50% and 64%, respectively [7,8]. The majority of the CAN cases were diagnosed clinically as sebaceous cysts in 6 out of 18 cases. As appendage tumours have no specific clinical appearance, they are often misdiagnosed. The location of the neck or back with a dimple on the skin surface may sometimes be mistaken as the punctum of a sebaceous cyst. In 11/18 (61%) cases, CAN tumours were less than 2 cm in size, similar to other studies [7,10].

The CAN may show more than one appendage differentiation due to the proliferation and differentiation of pluripotent and multipotent stem cells [3]. Owing to their varied or hybrid morphology, they can sometimes pose diagnostic dilemmas. In the present series, one case of the relatively rare tumour ES presented with a painful swelling with decapitation secretion, indicating apocrine differentiation, similar to one study [3]. Stromal lymphocytes in ES, similar to one study, help differentiate it from cylindroma in cases with diverse morphology [2]. The syringoma case did not show any chondromyxoid stroma as seen in other studies [2,7]. One case of CCH presented as an abdominal wall swelling; hence, metastatic clear cell Renal Cell Carcinoma (RCC) was also considered as a differential, but the absence of mitotic figures and the presence of normal kidneys in USG helped us rule out this differential. Immunohistochemical (IHC) markers specific for RCC can also be performed to distinguish these tumours. Poroma showed an epidermal connection similar to other studies [3,9]. Pilomatrixoma cases showed a foreign body giant cell reaction, similar to one study [7], which was not seen in other studies [2,3,5]. Pilomatrixoma can turn malignant into pilomatrix carcinoma, which is more cellular with infiltrative borders, and shows nuclear atypia with numerous mitotic figures, requiring a wide local excision [2].

Cutaneous adnexal neoplasms were mostly benign in the present study, similar to other studies [3,5,9]. Malignant CAN, though rare, are not uncommon and were seen in the elderly. The malignant tumours in this series were SC and MPTT. In the present series, an ocular type of SC was seen, similar to other studies [2,6,7]. HP showed areas of necrosis, similar to one study [11], which was not seen in two other studies [2,7]. MPTT reported in this case series is a very rare tumour, and in the literature, only less than 40 cases have been reported, so far [12]. MPTT presented as a scalp lesion in an elderly female above 50 years, similar to two other studies [12,13]. PTT arises from a trichilemmal cyst, which later undergoes malignant transformation to form MPTT [12,13]. MPTT is further classified into low-grade and high-grade tumours. Low-grade tumours show local recurrence, and high-grade tumours show metastasis; hence, these tumours should be followed-up for a long time [11,13]. In the present case series, PTT underwent a malignant transition to develop MPTT. There was an absence of necrosis, lymphovascular invasion, similar to Alici O et al., study, which were seen in another study [13,14]. Due to its high-grade histomorphology, MPTT needs to be differentiated from SCC. MPTT has a tendency to recur and metastasise more frequently than SCC [12]. Trichilemmal keratinisation is an important point in differentiating MPTT from SCC [13].

Also, CAN have to be differentiated from cutaneous metastasis of solid primary tumours at other sites. There is a 0.7% to 9% chance of developing cutaneous metastases from solid tumours [15]. Tumours that can metastasise to the skin are breast tumours, which are the most frequent ones, followed by kidney, ovary, lung, bladder, colorectal, and prostate tumours [15]. Primary cutaneous neoplasms can also develop metastases to the skin, with the most frequent being melanoma; and others include SCC, Merkel cell carcinoma, pilomatrix carcinoma [15]. Cutaneous metastases show similar histomorphology and IHC markers of the primary tumour. But sometimes, even after an extensive IHC marker panel, it is difficult to identify the site of the primary tumour for which a radiological investigation such as Positron Emission Tomography and Computerised Tomography scan (PET CT) can be helpful [15,16].

CONCLUSION(S)

Cutaneous adnexal neoplasms are rare, mostly benign tumours with a female preponderance and can be seen at any age. The head and neck region is found to be the most common site. Malignant CAN is rare but must be differentiated from primary cutaneous tumours such as SCC and cutaneous metastases of solid tumours. Clinical diagnosis alone has a very low rate of diagnosing CAN. Therefore, the identification of appendage differentiation of CAN in HP plays a key role in accurate diagnosis and thus helps in planning treatment. Tissue biopsy must be performed wherever possible before complete excision to prevent recurrence. Periodic patient follow-up can help in identifying any familial syndrome association of these tumours.

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