Histopathological Analysis of Skin Adnexal Tumors: A Three Year Study of 110 Cases at A Tertiary Care Center

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Abstract

Background: Skin adnexal tumors (SAT) encompass wide spectrum of benign and malignant tumors that differentiate toward one or more adnexal structures found in normal skin. Overall incidence of SATs is low yet they can be challenging to diagnose. Aims: The aim of this study is to study the spectrum and microscopic features of SATs. Materials and Methods: It was a retrospective cross-sectional, descriptive study conducted over a period of 3 years. Formalin fixed, paraffin-embedded sections were stained with hematoxylin and eosin for histopathological analysis. Results: Out of the total 34,400 biopsies, 110 cases were diagnosed as SATs comprising 39.09% of tumors with follicular differentiation followed by tumors showing sweat gland differentiation (37.27%), and sebaceous differentiation (23.63%). The age ranged from 5 years to 85 years and male:female ratio was 1.03:1. Most of the tumors were benign (82.73%) while only 17.27% were malignant. Pilomatricoma (28.2%) was the most common benign tumor while sebaceous carcinoma (11.8%) was the most common malignant tumor. Conclusion: Architectural features are of great importance in differentiating benign tumors from malignant.

Key Words: Benign versus malignant, histopathology, skin adnexal tumors

Introduction

Adnexal tumors (ATs) includes a large spectrum of skin epithelial tumors including hamartoma, hyperplasia, benign, and malignant tumors that originate from or show differentiation toward adnexal epithelial structures, namely, pilosebaceous unit, eccrine, and apocrine. These tumors arise from multipotent stem cells present within epidermis or its appendageal structures. Therefore, during neoplastic transformation, these tumors may aberrantly express one or more lines of appendageal differentiation to varying degree.[1]

Diagnosis principally relies on histopathology as their clinical presentation is very nonspecific, and they are classified according to predominant morphological component. Exact categorization of benign tumors was believed to be purely academic and not affecting clinical management. However, some of these tumors can be markers of internal malignancy, for example, multiple trichilemmomas in Cowden syndrome, sebaceous adenomas in Muir–Torre syndrome.[2] Malignant tumors are rare compared to benign counterparts. However, they follow more aggressive clinical course and have potential of nodal and distant metastasis. Their diagnosis has important therapeutic implications. In this study, we have analyzed the frequency and microscopic features with differentiating features to avoid potential pitfalls between benign and malignant skin adnexal tumors (SATs).

Materials and Methods

The present study was a retrospective, cross-sectional descriptive study conducted over a period of 3 years from January 2013 to December 2015. A total of 110 cases diagnosed as SATs on histopathology were included in this study. Histopathological analysis was carried out on formalin fixed, paraffin embedded tissue sections which

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were stained with hematoxylin and eosin. Special stains such as periodic acid–Schiff with or without diastase and immunohistochemistry (IHC) were performed as and when required. The tumors were classified according to predominant pattern of differentiation into follicular, sebaceous, eccrine, and apocrine tumors.

**Results**

Out of a total of 34,400 biopsies which were received from January 2013 to December 2015, 110 cases were diagnosed as SATs comprising 56 males and 54 females (male:female ratio was 1.03:1). The age ranged from 5 years to 85 years. Most common age group affected was 20–39 years (40.91%, 45/110) followed by 40–59 years (26.36%, 29/110), >60 years (20%, 22/110), and 0–19 years (12.73%, 14/110), respectively. Malignant tumors mainly affected elderly age group of >50 years. However, malignant tumors of eccrine origin were reported in the age group of 20–40 years [Table 1].

Out of 110 cases, 82.73% (91/110) were benign ATs while 17.27% (19/110) were malignant. In the present study, tumors of follicular differentiation constituted the largest group with 39.09% (43/110) cases closely followed by tumors showing sweat gland differentiation both apocrine and eccrine with 37.27% (41/110) cases and sebaceous gland tumors in 23.64% (26/110) cases [Figure 1].

Tumors with follicular and sweat gland differentiation, most of the tumors were benign. However, in tumors with sebaceous differentiation, malignant forms were more common. Sebaceous carcinoma was the most common malignant tumor in this study with the prevalence of 11.82% (13/110). Other malignant tumors of follicular and sweat gland origin are extremely rare. We reported a single case of pilomatrix carcinoma, porocarcinoma, and apocrine adenocarcinoma each.

Pilomatricoma (28.2%, n = 31/110) was the most common benign tumor in this study and was observed affecting children and adults with a wide age range of 8–62 years. Nodular hidradenoma (15.45%) forms the second most common AT followed by nevus sebaceous (6.36%), syringoma (5.45%), and trichoepithelioma (5.45%).

**Table 1: Distribution of tumors of epidermal appendages with respect to age and sex**

| Tumor type and incidence | Male:female | Age |
|--------------------------|-------------|-----|
|                          |             | 0-19 years | 20-39 years | 40-59 years | >60 years |
| **Benign**               |             |       |       |       |       |
| Follicular               |             |       |       |       |       |
| Trichoepithelioma (5.45%, 6/110) | 1:1 | 1 | 4 | - | 1 |
| Pilomatricoma (28.2%, 31/110) | 0.7:1 | 11 | 15 | 4 | 1 |
| Proliferating trichilemmal cyst (2.72%, 3/110) | 2:1 | - | - | 2 | 1 |
| Trichofolliculoma (1.8%, 2/110) | 1:1 | - | 2 | - | - |
| Sebaceous               |             |       |       |       |       |
| Nevus sebaceous (6.36%, 7/110) | 6:1 | - | 7 | - | - |
| Sebaceous hyperplasia (4.55%, 5/110) | 0.66:1 | 1 | 1 | 1 | 2 |
| Sebaceous adenoma (0.9%, 1/110) | 1 male | - | - | 1 | - |
| **Apocrine**             |             |       |       |       |       |
| Syringocystadenoma papilliferum (0.9%, 1/110) | 1 male | - | 1 | - | 1 |
| Cylindroma (1.8%, 2/110) | 2 males | - | 1 | - | - |
| **Eccrine**              |             |       |       |       |       |
| Syringoma (5.45%, 6/110) | 1:1 | 1 | 2 | 3 | - |
| Eccrine poroma (3.63%, 4/110) | 1.33:1 | - | - | 2 | 2 |
| Eccrine spiradenoma (1.8%, 2/110) | 2 males | - | - | 1 | 1 |
| Nodular hidradenoma (15.45%, 17/110) | 1.8:1 | - | 9 | 6 | 2 |
| Chondroid syringoma (3.63%, 4/110) | 3:1 | - | 1 | 2 | 1 |
| **Malignant**            |             |       |       |       |       |
| Follicular               |             |       |       |       |       |
| Pilomatrix carcinoma (0.9%, 1/110) | 1 female | - | - | 1 | - |
| Sebaceous               |             |       |       |       |       |
| Sebaceous carcinoma (11.8%, 13/110) | 0.3:1 | 1 | 3 | 9 |
| **Apocrine**             |             |       |       |       |       |
| Adenocarcinoma (0.9%, 1/110) | 1 male | - | 1 | - | - |
| **Eccrine**              |             |       |       |       |       |
| Adenoid cystic carcinoma (2.72%, 3/110) | 0.5:1 | - | 2 | 1 | - |
| Porocarcinoma (0.9%, 1/110) | 1 female | - | 1 | - | - |
Anatomical distribution of tumors is given in Table 2. Head and neck (78.18%, 86/110) was the most common site of involvement followed by extremities (13.64%, 15/110) and trunk (8.18%, 9/110).

Discussion

ATs are relatively uncommon tumors comprising only 0.3% of all the biopsies (34,400) received over period of 3 years. Since this was a retrospective study, this data cannot reliably indicate the prevalence of SATs due to selection bias as only tumors sent for histopathology in our institution were included in this study. There are only few studies describing appendageal tumors in detail. Most of the tumors in this study were benign 82.73% while malignant was only 17.27%. This was in concordance with other studies [Table 3].

Most common tumors in our study were tumors of follicular origin with 39.09% (43/110) cases followed by tumors with sweat gland differentiation (37.27%) followed by sebaceous tumors (23.64%). Similar observation was in study of El Ochi et al while Nair and Sharma et al found sweat gland tumors to be most common followed by follicle and sebaceous tumors. It is because most common tumor in our study was pilomatricoma (28.2%).

SATs are histologically challenging tumors to diagnose. Apart from their malignant counterparts, benign lesions need to be differentiated from squamous cell carcinoma and basal cell carcinoma. Traditional criteria of cytological and nuclear atypia alone do not render

| Tumor type               | Benign                      | Malignant                  |
|--------------------------|-----------------------------|----------------------------|
| Follicular               | 6                           | 8                          |
| Sebaceous                | 7                           | 12                         |
| Apocrine                 | 1                           | 1                          |
| Eccrine                  | 5                           | 4                          |
| Malignant                | 12                          | 15                         |

Table 2: Distribution of tumors of epidermal appendages with respect to anatomical site

![Figure 1: Incidence of various skin adnexal tumors](image-url)
a tumor malignant. Bernard Ackerman first described importance of silhouettes/architectural attributes which can help in distinction between the two. Benign tumors are symmetrical, vertically orientated with V-shape with uniform collection of epithelial cells, dense fibrotic stromal reactions and absence of necrosis, atypia, and mitosis. Asymmetry, horizontal orientation of tumor, irregular arrangement of cells with infiltration, necrosis, atypia, mitosis, and diminished sclerotic stroma are sensitive indicators for the diagnosis of malignant lesions. Hence, it is important to examine under scanner view to assess the silhouettes of SATs to differentiate benign and malignant tumors. We applied these criteria while examining cutaneous adnexal neoplasms in this study.[10,11]

Pilomatricoma (n = 31/110) was the most common tumor in our study. Similar results were found in other studies but some also observed nodular hidradenoma and syringoma as the most common tumor.[3-9] Microscopically, pilomatricoma is a well-circumscribed dermal tumor characterized by islands of epithelial cells composed of ghost cells/shadow cells in the center surrounded by basoloid cells [Figure 2a].[1,4] However, under low power, these ghost cells can mimic necrosis, but high-power showed eosinophilic cells with empty nuclear spaces [Figure 2b].

Table 3: Comparison of prevalence of skin adnexal tumors in various published studies and present study

| Studies     | Samaila et al.[3] | Radhika et al.[4] | Saha et al.[5] | Sharma et al.[6] | Rajalakshmi et al.[7] | El Ochi et al.[8] | Nair.[9] | Present study |
|-------------|--------------------|-------------------|----------------|------------------|----------------------|-------------------|----------|---------------|
| Study period | January 1991 to December 2006 | January 1993 to December 2003 | June 2007 to May 2008 | June 2004 to June 2010 | 2009-2013           | January 2009 to December 2014 | 3 years | January 2013 to December 2015 |
| Total cases | 52                 | 35                | 23             | 56               | 21                   | 96                | 33       | 110           |
| Most common age group affected | 20-30              | 29.1±11.68        | 51-60          | 30-40            | 31-40                | 11-20             | 20-39   |
| Male:female | 1:1                | 0.7:1             | 1:1.9          | 1.07:1           | 1.1:1                | 1.7:1             | 1:2.3    | 1.03:1        |
| Most common site | Head and neck | Head and neck | Head and neck | Head and neck | Head and neck | Head and neck | Head and neck | Head and neck |
| Benign tumors (%) | 88.5               | 77.14             | 100            | 80.36            | 90.48                | 97.7              | 100      | 82.72         |
| Malignant tumors (%) | 11.5               | 29.63             | -              | 19.64            | 9.52                 | 2.3               | -        | 17.28         |
| Most common benign tumor | Eccrine acrospiroma (32.7%) | Nodular hidradenoma; nevus sebaceous (14.2% each) | Syringoma (39.13%) | Clear cell hidradenoma; pilomatricoma (21.43% each) | Pilomatricoma (19.04%) | Pilomatricoma (33.3%) | Syringoma (42.42%) | Pilomatricoma (28.2%) |
| Most common malignant tumor | Sweat gland carcinoma (11.5%) | Sweat gland carcinoma (11.4%) | -              | Sebaceous carcinoma (19.64%) | Aggressive digital papillary adenocarcinoma; malignant dermal eccrine cylindroma (one case each) | Porocarcinoma; Eccrine sweat carcinoma (one case each) | - | Sebaceous carcinoma (11.8%) |

Figure 2: (a and b) Pilomatricoma: Well-circumscribed islands of epithelial cells (H and E, ×100) composed of basoloid cells transforming into ghost cells (arrow) (H and E, ×400). (c and d) Pilomatricoma carcinoma: Irregular, asymmetrical infiltrating tumor (H and E, ×100)
containing keratin and few fragments of hair shafts. Various secondary hair follicles were seen radiating from cyst wall [Figure 3a].\textsuperscript{[1,12]}

Six cases of trichoepithelioma revealed well-circumscribed dermal tumors with epithelial and stromal components. It showed several horn cysts and basaloid epithelial cells with keratinized center. These tumor islands are surrounded by fibroblasts [Figure 3b]. The absence of clefting around these basaloid cells helps in differentiating these tumors from basal cell carcinoma.\textsuperscript{[1,3,12]}

Pilar tumor (proliferating trichilemmal cyst) was diagnosed in three cases of scalp swelling. Tumor showed irregular but well-defined lobules of proliferating squamous epithelium surrounded by thick basement membrane, abruptly merging into amorphous keratin in the central portions of the lobules [Figure 3c]. It can be mistaken for squamous cell carcinoma but circumscription and abrupt mode of keratinization helps in differentiation.\textsuperscript{[1,7]}

Nevus sebaceous \textsuperscript{(n = 7/110)} was characterized by hamartomatous collection of large sebaceous glands associated with papillomatous hyperplasia of overlying epidermis and dilated apocrine glands [Figure 4a].\textsuperscript{[1,3]} Sebaceous hyperplasia \textsuperscript{(n = 5/110)} consisted of single large sebaceous gland composed of numerous lobules lying near epidermis [Figure 4b].\textsuperscript{[1]} Sebaceous adenoma \textsuperscript{(n = 1/110)} composed of enlarged incompletely differentiated sebaceous lobules of varying size and shape. The lobules show basaloid cells at the periphery and mature sebaceous cells in the centre.\textsuperscript{[1]}

Syringocystadenoma papilliferum \textsuperscript{(n = 1/110)} showed marked papillomatosis of epidermis with cystic invaginations extending from epidermis as papillary projections [Figure 5a]. These papillary projections are lined by two rows of epithelium inner tall columnar and outer small cuboidal cells. Decapitation by luminal cells is considered an indicator of apocrine differentiation.\textsuperscript{[1,7]} Dense inflammatory infiltrate of plasma cells was noted in the papillary core [Figure 5b].

Cylindroma \textsuperscript{(n = 2/110)} composed of irregular islands of epithelial cells fitting into each other and are surrounded by hyaline sheath [Figure 5c].\textsuperscript{[1,3,4,12]}

Syringoma \textsuperscript{(n = 6/110)} were dermal tumors and are characterized by numerous ducts lined by two layers of cuboidal cells and embedded in dense collagenous stroma. Some of the epithelial cells have comma such as tails giving it tadpole appearance [Figure 5d].\textsuperscript{[1,4]}

Eccrine poroma \textsuperscript{(n = 4/110)} can be intraepidermal (hidroacanthoma simplex), juxtaepidermal involving both epidermis and dermis (eccrine poroma) and dermal also called as dermal duct tumor.\textsuperscript{[1]} Histology showed broad anastomosing bands of small cuboidal epithelial cells arising from lower portion of epidermis and extending into dermis [Figure 6a]. Tumor showed sharp demarcation from stroma. Tumor cells were small with deeply basophilic nuclei and were connected by intercellular bridges [Figure 6b].\textsuperscript{[1,7,12]}

Chondroid syringoma \textsuperscript{(n = 4/110)} were intradermal or subcutaneous nodular tumors. The cells were arranged in ductal and tubular pattern with areas of pseudo and true cartilage and cystic spaces filled with mucinous material [Figure 7b].\textsuperscript{[1,7]}

Eccrine spiradenoma \textsuperscript{(n = 2/110)} were a circumscribed basaloid tumor with fibrovascular component. It showed well-defined lobules with intertwining cords of epithelial cells [Figure 7c]. Biphasic cell population, one eosinophilic and other clear cell type along with collections of hyalinized material is seen. Stroma showed
heavy diffuse lymphocytic infiltrate and dilated blood vessels [Figure 7d].

Sebaceous carcinoma (n = 13/110) was the most common malignant tumor in this study. All the cases in this study presented as a painless mass on eyelids. It is characterized by irregular lobules of undifferentiated sebaceous cells with necrosis, infiltrative pattern, asymmetrical lesion and prominent atypia [Figure 4c and d]. It is important to differentiate from basal cell carcinoma with sebaceous differentiation and squamous cell carcinoma with hydropic change. IHC can be useful as these are found to be positive for cytokeratin (CK), epithelial membrane antigen (EMA), CAM 5.2, and antibreast carcinoma associated antigen-225 antibody but negative for carcinoembryonic antigen (CEA) and S100. EMA positivity is important in differentiating it from basal cell carcinoma. However, for distinction from squamous cell carcinoma, CAM 5.2 is more specific. CAM 5.2 and BRST-1 are not available in our institute but considering histomorphology and CK and EMA positivity, diagnosis of sebaceous carcinoma was given.

Pilomatrix carcinoma (n = 1/110) is an extremely rare tumor. This tumor has not been reported in other studies. We had a case of 50 years female presenting with 8 cm swelling on the forearm. On histopathology, tumor showed irregular-shaped aggregates of basaloid cells with mild atypia and ghost cells. However, due to asymmetry, poor circumscription, infiltrative pattern of growth and necrosis, it was diagnosed as malignant counterpart of pilomatrixoma [Figure 2c and d].

Figure 5: (a) Syringocystadenoma papilliferum: epidermis with cystic invaginations (H and E, ×100) (b) Syringocystadenoma papiliferum: papillary core showing plasma cells (arrow) (H and E, ×400) (c) Cylindroma: irregular islands of epithelial cells fitting into each other (H and E, ×100) (d) Syringoma: small ducts embedded in fibrous stroma (H and E, ×100)

Figure 6: (a) Eccrine proroma: Well-defined lobules of tumor cells (H and E, ×100) (b) Eccrine poroma: Uniform small cuboidal cells with deeply basophilic nuclei (H and E, ×400) (c) Porocarcinoma: Infiltrating bands of tumor cells (H and E, ×100) (d) Porocarcinoma: Tumor cells showing marked atypia and mitosis (H and E, ×400)

Figure 7: (a) Nodular hidradenoma: Well-circumscribed lobule with cystic changes (H and E, ×100). (b) Chondroid syringoma: Tubules and ducts in chondromyxoid matrix (H and E, ×100). (c) Eccrine spiradenoma: Lobules of intertwining cords of cells (H and E, ×100). (d) Eccrine spiradenoma: Stroma with dilated vessel and lymphocytic infiltrate (arrow) (H and E, ×400)

Figure 8: (a) Adenoid cystic carcinoma: Epithelial cells in cribriform pattern (H and E, ×400) (b) Apocrine adenocarcinoma: infiltrating tumor glands (H and E, ×100). Tumor cells were cytokeratin positive (c), epithelial membrane antigen positive (d) and carcinoembryonic antigen-positive (e)
Porocarcinoma (n = 1/110) was reported in 32 years female presented with ulceroproliferative growth on the scalp. Histopathology revealed irregular infiltrative pattern of tumor cells [Figure 6c]. Spiralling ductal structures indicated eccrine differentiation.[1,12] Tumor cells showed marked nuclear pleomorphism and atypical mitosis [Figure 6d].

Adenoid cystic carcinoma (n = 3/110) showed adenoid or cribriform pattern comprised many small epithelial islands containing amphophilic basement membrane-like material [Figure 8a].[1,12]

Apocrine adenocarcinoma (n = 1/110) was reported in 45-year male with supraclavicular swelling. It is an extremely rare tumor, only few cases have been reported in literature.[1,14] On histology, it was widely infiltrating tumor composed of neoplastic glands and cribriform pattern. On IHC, tumor cells were positive for CK, CEA, and EMA [Figure 8 b-e].[15]

The limitation of this study was the absence of facility of histochemistry for enzymes such as acid phosphatase, indoxyl acetate estrate, and succinic dehydrogenase to establish exact genesis of tumor.

**Conclusion**

Most of the tumors of epidermal appendages are benign with low incidence of malignant tumors. Clinical diagnosis is difficult in most of the cases as their presentation is very nonspecific. Histopathology is the gold standard in the diagnosis of SATs. It is important to look for the malignant features due to its therapeutic and prognostic implications. Scanner view is of utmost importance to assess the architectural features of irregular and infiltrative pattern of growth associated with necrosis to distinguish malignant lesions before evaluating cytological features.

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**Conflicts of interest**

There are no conflicts of interest.

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**What is new?**

Architectural features are of utmost importance in differentiating benign tumors from malignant tumors.