Research Article

Four years retrospective study of skin adnexal tumors: Histomorphology and special stain study

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ABSTRACT

Background: Skin adnexal tumors (SATs) are uncommon and may cause diagnostic problems. **Objective:** The aim of this study is to determine the frequency of SATs with respect to their clinicopathological features over a period of 4 years. **Materials and Methods:** It was a retrospective, descriptive study. Formalin-fixed, paraffin-embedded sections were stained with hematoxylin and eosin for histopathological analysis and with special stains as Alcian blue/periodic acid–Schiff stain for confirmation. **Results:** A total number of cases that were diagnosed as SATs were 18; benign tumors were 17 (94.4%) and one malignant tumor (5.6%). Most tumors were of sweat gland origin (61.1%) followed by hair follicle origin (33.3%) then by sebaceous gland origin (5.6%). The age ranged from 3 to 51 years and male: female ratio was 1.57:1. The head-and-neck region was the most common location (44.4%). Hidradenoma (35.3%) was the most common benign tumor followed by pilomatrixoma (23.5%) and spiradenoma (17.6%) while sebaceous carcinoma was the only malignant tumor detected. **Conclusion:** The overall incidence of SATs was found to be very low. Benign SATs were more as compared with the malignant tumors. A careful histopathological assessment is essential for accurate diagnosis.

KEY WORDS: Skin Adnexal Tumors; Pilar Tumor; Sweat Gland Tumor; Sebaceous Tumor; Histopathology

INTRODUCTION

The skin adnexa are formed of different types of cells that give rise to a wide spectrum of tumors. They include sebaceous glands, eccrine and apocrine sweat glands, and hair follicles.[1] Skin adnexal tumors (SATs) commonly arise in head and neck, trunk, and extremities.[2] They can be solitary or multiple papulonodular or cystic lesions. The presence of multiple tumors can be considered as a marker for internal visceral malignancy.[3] Most SATs are benign but locally aggressive tumors can resemble primary cutaneous neoplasm. On the other hand, the malignant SATs are rare and have to be differentiated from cutaneous metastasis. They are usually of poor clinical outcomes and tend to recur and metastasize to lymph nodes.[4] SATs are quite challenging either in their classification, histogenesis, or diagnosis. This owed to overlap in their morphological features and their heterogeneous patterns of differentiation. They are supposed to arise *de novo* or originate from malformation in pluripotent stem cells in epidermal niches and one tumor type can show more than one line of differentiation.[5] Adnexal tumors of the skin differentiate toward pilar, sebaceous, eccrine, or apocrine structures. Moreover, they are rare tumors and their exact incidence is still unclear. The diagnosis of SATs is based mainly on histopathology with the limited role of immunohistochemistry.[5] The reported data regarding immunohistochemistry described a complex combination of cytokeratins, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA) to be assessed in cases with more than one line of differentiation. This is reported mainly for malignant SATs with potential pitfalls in diagnosis and in their origin either as malignant transformation of a previous benign SATs or malignancy for the 1st time.[5] Our study is

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a retrospective analysis of the histopathological microscopic features of SATs with respect to their morphological, clinical, and anatomic location in Minia University Hospital over a period of 4 years. The main aim is to determine the frequency of SATs in our hospital and to report their histopathological pitfalls in diagnosis using the routine stain and special stains.

MATERIALS AND METHODS

This retrospective study included all histologically diagnosed skin adnexal benign and malignant tumors in the hospital pathology department, Minia University Hospital, Egypt, over a period of 4 years from January 2015 to January 2019. All biopsies had been fixed in 10% formal saline, tissue processing was done to prepare paraffin-embedded sections then microtome sectioned at 5 μm and the resulting slides stained with hematoxylin and eosin. They are confirmed with special stains as Alcian blue/periodic acid–Schiff (PAS) stain Mowry where required.

Relevant data such as age, sex, anatomical location, and histopathological features were obtained from the histopathology request forms and duplicate copy of the histopathology reports. The corresponding histology slides were retrieved, reviewed and the tumors were classified based on their adnexal origin into sweat gland, hair follicle, and sebaceous gland tumors. Anatomical sites were categorized as head, neck, and face, upper extremity (including shoulder, arm, forearm, wrist, and hand), lower extremity (including the buttock, thigh, leg, and foot), trunk, and others (including the abdomen, back chest wall, and genitals). Slides were studied under light microscopy. A total of 18 cases of adnexal tumors were included in this study. All adnexal neoplasms were classified according to the World Health Organization Classification of Tumors 2018.[6] Correlation between gross and histopathological examination will be carried out.

For the malignant case (sebaceous carcinoma), ancillary studies were done outside the hospital and the tumor cells were positive with CK7, P63, CEA, and EMA but negative with CK20, GCDFP-15, and S100. Alcian blue/PAS was negative in the tumor cells.

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Institutional Ethical Committee. Since this study was a retrospective and descriptive study and the values were expressed in percentage, the individual parameters were not comparable to obtain a statistical significance. Hence, the data were analyzed using software Statistical Package for the Social Sciences, version 16.0 and the results were expressed in percentage.

RESULTS

A total of 18 SATs were diagnosed during the study period. The incidence of SATs was found to be 0.015% (18 out of 1221) of all skin biopsies. There were 11 males (61.1%) and 7 females (38.9%) with a male: female ratio of 1.57:1. Of the 18 cases documented, 17 were benign (94.4%) and 1 was malignant (5.6%).

The patients' age ranged from 3 to 51 years. The mean age ± standard deviation was 29.83 ± 13.93 and the median age was 34.5 years. The age distribution is mentioned in Table 1. Most of the cases were in the age group between the 4th and 5th decades (30–51 years, 72.2%; 13/18 cases). With respect to anatomical location, the head-and-neck region was found to be the most common (8/18; 44.4%) followed by extremities (6/18; 33.3%) and trunk (4/18; 22.3%). Clinical presentations varied from discrete swellings, nodules, and cysts. The tumors were further divided into hair follicle, sebaceous, and sweat gland differentiation. The most common tumors were of sweat gland origin (11/18, 61.1%) followed by hair follicle origin (6/18; 33.3%) then by sebaceous gland origin (1/18; 5.6%) [Figure 1]. Histopathologically, there were 17 (94.4%) benign to 1(5.6%) malignant lesions. The most common benign tumor was hidradenoma 35.3% (6/17) followed by pilomatrixoma 23.5% (4/17) and spiradenoma 17.6% (3/17). Malignant adnexal tumors were rare with only one case in our study, which was sebaceous carcinoma. The detailed clinicopathological data are shown in Table 1.

Diagnostic Patterns and Special Stain of Individual Lesions

Hidradenoma

Hidradenoma has variable histological patterns and accordingly, it was described in different terms as nodular hidradenoma, solid-cystic hidradenoma, clear cell hidradenoma, eccrine acrospiroma, and clear cell acrospiroma. Histologically, it is a lobulated dermal neoplasm with a nodular, circumscribed pattern with a pushy border at scanning magnification.[1] It has a biphasic cell population, eosinophilic cell type which is a large cell with abundant, eosinophilic, finely granular cytoplasm, and a clear cell type that has clear cytoplasm, (mostly due to glycogen content), and a smaller, more eccentrically placed nucleus [Figure 2a]. Some tumors were found to have an epidermal attachment. The intervening stroma is vascularized. Focal cystic spaces are commonly seen. Clear cell change [Figure 2c], squamous metaplasia, and focal apocrine components may be present. However, squamoid change does mean a worse prognosis.[7] The tumor cell cytoplasm shows positive stain for PAS (which may reflect the presence of glycogen) while the stroma shows positive Alcian blue staining (which may attribute to the presence of acid mucopolysaccharides) [Figure 2e and f]. A small amount of PAS-positive, diastase-resistant material was found in the clear cell areas.[8] Hidradenoma has a recurrence rate of about 12% if not fully excised and malignant transformation may be present in other areas of the

Table 1: Clinicopathological data of studied cases

Sr. No.	Age (years)	Se×	Site	Size (cm²)	Clinical history	Diagnosis
1	17	M	Elbow	2×3	Mass	Pilomatri×oma
2	9	M	Shoulder	1.5	Cyst lesion	Pilomatri×oma
3	6	M	Elbow	0.5×0.5	Painful cyst	Pilomatri×oma
4	3	F	Ear lobule	0.5×0.5	Cyst	Pilomatri×oma
5	31	M	Scalp	2×2	Multiple painful nodules	Proliferated trichilemmal cyst with atypia
6	37	M	Back	2×1.8	Painful cyst	Proliferated trichilemmal cyst
7	34	M	Leg	1.5	Mass	Nodular hidradenoma
8	44	F	Buttock	1.5	Mass	Nodular hidradenoma
9	15	M	Scalp	1.5×1	Nodule	Nodular hidradenoma
10	30	M	Groin	1.5×1.2	Mass	Clear cell hidradenoma
11	36	F	Back	1.5×1.2	Mass	Clear cell hidradenoma
12	39	F	Vulva	0.7	Cyst	Hidradenoma papilliferum
13	42	F	Cheek	0.3×0.2	Nodule	Chondroid syringoma
14	37	F	Scalp	1.2×1	Cystic lesion	Syringocystadenoma papilliform
15	35	M	Neck	1.5×1.5	Painful cyst	Spiradenoma
16	41	M	Cheek	0.5	Painful cyst	Spiradenoma
17	30	F	Shoulder	0.7	Painful nodule	Spiradenoma
18	51	M	Chin	1.2×1	Painful nodule	Sebaceous carcinoma

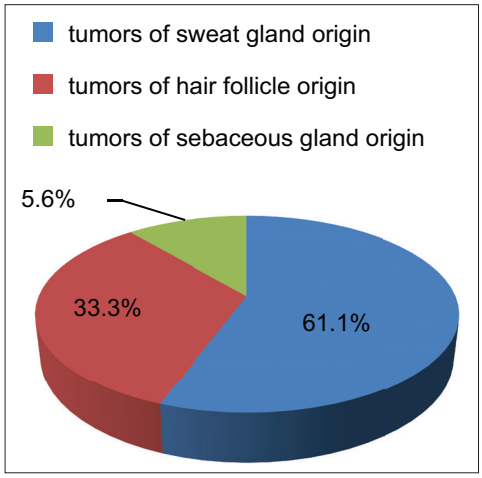

Figure 1: Distribution of lesions

lesion, especially if it has irregular peripheral margins, and hence, full excision is highly indicated.[9]

Hidradenoma papilliferum

Hidradenoma papilliferum is a well-circumscribed solid or cystic dermal nodular lesion that has no connection to the epidermis. It shows frond-like papillae or tubule-papillary structures lined by two cell layers: Luminal cuboidal cells or low columnar epithelial cells with apical secretions (positive for PAS stain) and an outer myoepithelial cell layer [Figure 2b and d]. The epithelial cells have histochemical characteristics of apocrine cell origin but lack cytonuclear atypia, mitotic activity, or tumor necrosis. Sometimes, it has a morphological feature analogous to benign breast diseases including sclerosing adenosis-like changes, oxyphilic (apocrine) metaplasia, atypical apocrine adenosis, ductal epithelial hyperplasia, myoepithelial cells with clear cell change, foamy histiocytic reaction, and stromal fibrosis.[7,10]

Pilomatrixoma (pilomatricoma, calcifying epithelioma of Malherbe)

Pilomatrixoma is a benign lesion with differentiation toward the hair follicle matrix. It has a different histomorphology according to the age of the lesion. It is recognized by the triad of basophilic cells, eosinophilic shadow cells (ghost cells/mummified), and calcification. These shadow cells arise from the basophilic cells and they consist of eosinophilic keratinized cytoplasm without nuclei, this transition may be abrupt or may take place over several layers of cells [Figure 3a and b]. It can express a more aggressive behavior and shows the following features: Proliferation edge, invasion of fat and skeletal muscle, and even vascular invasion, but distant metastases have not been reported. The local recurrence after excision is about 3% of cases even in the usual form of pilomatrixoma.[1,7]

Proliferating trichilemmal tumor (PTT)

PTT is a solid-cystic well-defined mass that presents in the dermis and may extend to the subcutaneous cellular tissue. The neoplastic epithelium shows a trichilemmal keratinization with a characterized peripheral palisade of basaloid cells and bulky eosinophilic squamous cells with abrupt keratinization [Figure 3c]. There are epithelial invaginations into the cystic lumen, calcification, and abundant cholesterol crystals. Epithelial cells may be

monotonous without any atypia or pleomorphic with atypia [Figure 3d], and these areas with atypia sometimes indistinguishable from squamous cell carcinoma. Furthermore, ghost cells that represent the expression of matrix differentiation, apocrine differentiation, and spindle cells are also observed.[7,10,11] PTT may have aggressive clinical behavior with recurrence and/or metastasis, and this is more common in tumors located in the scalp when exhibiting these features fast growing, infiltrative, tumors larger than 5 cm, presence of atypia and mitotic activity.[12,13]

Syringocystadenoma papilliferum

Syringocystadenoma papilliferum is a benign tumor that showed varying degrees of papillomatosis with several cystic invaginations that extend downward from the epidermis and lined by squamous keratinizing cells [Figure 3e]. Both the papillary projections and the lower portion of invagination lined by glandular epithelium that formed of two rows of cells with oval nuclei and eosinophilic cytoplasm, and some cells showing active decapitation secretion. The papillae show dense chronic inflammatory cells infiltrate.[14]

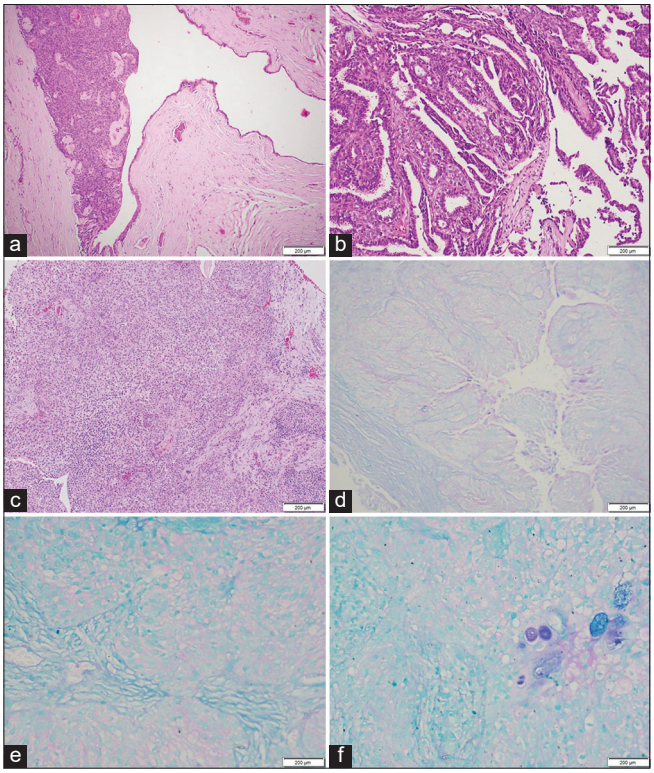

Figure 2: (a) Nodular hidradenoma: Well-circumscribed lobule with cystic changes (hematoxylin and eosin [H and E], × 100). (b) Hidradenoma papilliferum: Papillary structures lined by luminal cuboidal cells and an outer myoepithelial cell layer (H and E, × 100). (c) Clear cell hidradenoma: Abundant clear cells with clear cytoplasm (H and E, × 200). (d) Hidradenoma papilliferum (Alcian blue/periodic acid–Schiff stain, × 100). (e) Clear cell hidradenoma (Alcian blue/Periodic acid–Schiff stain, × 400). (f) Clear cell hidradenoma with calcification (Alcian blue/Periodic acid–Schiff stain, × 400)

Chondroid syringoma

Chondroid syringoma by histomorphology shows a chondroid matrix, ductal structures lined by a single epithelium, tubule-alveolar structures lined by double epithelium, nests of polygonal cells, and keratinous cysts [Figure 3f]. It was found that tubular lumina have eosinophilic PAS-positive material [Figure 4c]. The appearance of neoplastic cells in syringoma as singles due to small tubules lacking lumina is one of the challenging factors in the diagnosis.[7,10,15]

Spiradenoma

Spiradenoma is a benign neoplasm that shows either eccrine or apocrine differentiation. It is mainly presented clinically with pain. Microscopically, it consists of one large, sharply demarcated lobule, but more commonly there are more lobules within the dermis without any connections to the epidermis [Figure 4a]. Spiradenoma consists of two distinct cell types: Cells with small, dark nuclei (located at the periphery of the cellular aggregates) and the other cells with

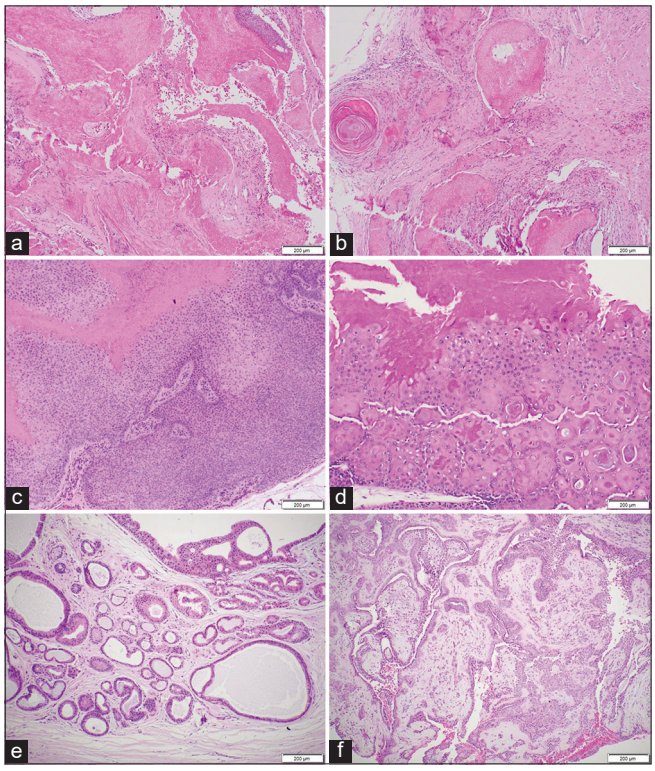

Figure 3: (a) Pilomatricoma: Islands of basophilic cells, shadow (ghost cells) that consists of eosinophilic keratinized cytoplasm without nuclei (H and E, × 200). (b) Pilomatricoma: Circumscribed islands of epithelial cells composed of basaloid cells transforming into ghost cells (H and E, × 200) (H and E, × 100). (c) Proliferated trichilemmal tumor: Well-defined lobules of squamous epithelium with keratin (H and E, × 200). (d) Proliferated trichilemmal tumor with atypia shows well-defined lobules of squamous epithelium with atypia (H and E, × 400). (e) Syringocystadenoma papilliferum: Varying degrees of papillomatosis with several cystic invaginations (H and E, × 200). (f) Chondroid syringoma: Tubules and ducts in chondromyxoid matrix (H and E, × 100)

large, pale nuclei (located in the center of the aggregates). The stroma usually shows many lymphocytes [Figure 4b]. Throughout the tumor, PAS-positive deposits were found [Figure 4d].[7]

Sebaceous carcinoma

Sebaceous carcinoma has been traditionally classified into ocular and extraocular types. The ocular type most frequently occurs on the eyelids while the extraocular sebaceous carcinoma mostly found in the head-and-neck region. Microscopically, it shows irregular variable-sized lobules, consists of undifferentiated cell types, but the center of most of the lobules shows sebaceous differentiation with foamy cytoplasm [Figure 4e]. It was found that some carcinomas may be formed mainly of neoplastic cells with a squamous or basaloid appearance and sebaceous differentiation was observed only focally.[1,7] Sebaceous carcinoma characterized by asymmetry, poor circumscription, and infiltrative growth pattern by solid sheets of cells with atypia and high mitotic activity [Figure 4f] which differs from sebaceous adenoma and sebaceoma. For the confirmation of sebaceous differentiation, EMA immunoperoxidase staining remains the best test to be used.[5,9]

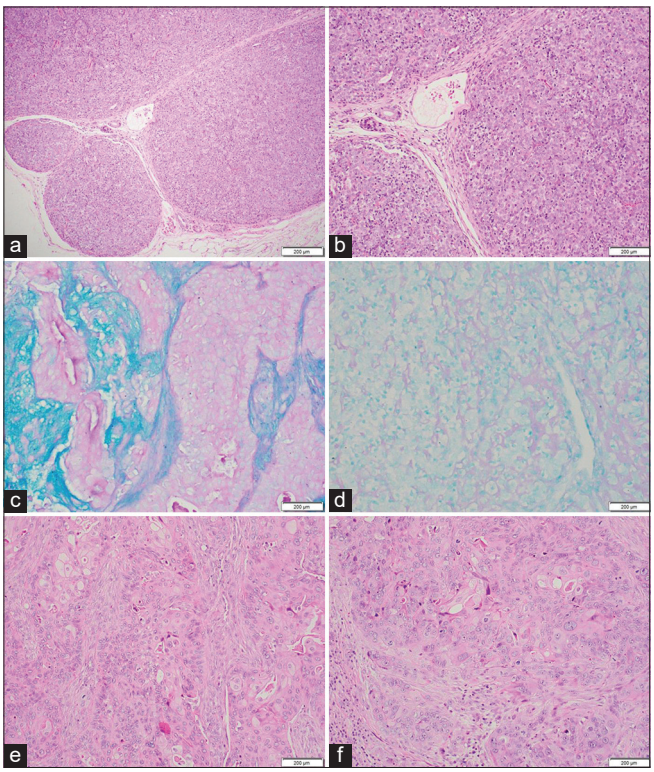

Figure 4: (a) Eccrine spiradenoma: Lobules of intertwining cords of cells with lumina lined by cuboidal or columnar cells, cystic spaces (H and E, × 100). (b) Eccrine spiradenoma: Stroma with dilated vessel and lymphocytic infiltrate (H and E, × 200). (c) Chondroid syringoma (Alcian blue/Periodic acid–Schiff stain, × 400). (d) Eccrine spiradenoma (Alcian blue/Periodic acid–Schiff stain, × 200). (e) Sebaceous carcinoma: Irregular variable-sized lobules of undifferentiated cell types and the center of most of the lobules shows sebaceous differentiation with foamy cytoplasm (H and E, × 200). (f) Sebaceous carcinoma: Lobule of undifferentiated cells (H and E, × 400)

DISCUSSION

Adnexal tumors of the skin are relatively rare and uncommon in routine pathology practice. Our study revealed low incidence of SATs (0.015%) and 94.4% were benign while 5.6% were malignant tumors. Most tumors were of sweat gland origin (61.1%) followed by hair follicle origin (33.3%) then by sebaceous gland origin (5.6%). The patients' age ranged from 3 to 51 years and the incidence of male: female ratio was 1.57:1. Most of the cases were found in the head-and-neck region (44.4%). Hidradenoma (35.3%) was the most common benign tumor followed by pilomatrixoma (23.5%) and spiradenoma (17.6%) while sebaceous carcinoma was the only malignant tumor detected. Most SATs have an endless morphologic spectrum, which is compounded by incomplete knowledge of their histogenesis.[16,17] The rich distribution of apocrine and eccrine sweat glands and pilosebaceous apparatus in the head-and-neck region is the reason why the majority of adnexal tumors are reported from the head-and-neck region.[18] Moreover, sun exposure is postulated as a definitive triggering event in the majority of these tumors.[5] Our study found that the head-and-neck region was the most common (44.4%) site for SATs followed by extremities (33.3%) and trunk (22.3%). This result concord with the previous studies which have found that the head-and-neck (ranged from 52% to 78.26%) was the most common site involved in both males and females with a predominance in the facial region (57.44%).[3,5,19-21]

In general, SATs have a wide range of age distribution. In the present study, the mean age was 29.83 ± 13.93 years with a maximum age distribution between 31 and 40 years (38.9% of cases). This result has concurred with the previous studies that reported the third decade to be the most common for SATs.[1,20] While other studies[21,22] found that the age group of 41–50 years was the maximum for skin adnexa tumors (21.56% and 34.78%, respectively). On the other hand, the age group of 51–60 years was reported as the most common for SATs in another study.[23] In the current study, SATs were more prevalent among males with an male: female ratio of 1.57:1. Furthermore, other studies reported similar results[20,23,24] who found that male: female ratio was 1.44:1, 1.07:1, and 1.8:1, respectively. While female predominance was reported by several other studies[2,3,5,21,22,25] with a male: female ratio of 1:1.88, 1:1.09, 1:1.47, 1:3.53, 1:1.68, and 1:2.3, respectively.

All the earlier studies report that the incidence of benign adnexal tumors as more prevalent compared to the malignant ones. The incidence of benign tumors in our study is 94.4%, which is in tandem with other studies[1,3,22,26,27]

who reported that 77.14%, 98.4%, 74.50%, 88.5%, and 82.73% were benign SATs, respectively. In the present study, only one malignant tumor was reported. No tumor with malignant change was reported previously in a 3-year clinicopathological study.[25] In our study, tumors of the sweat gland origin were the most common (55.6%) followed by hair follicle origin (33.3%) then by sebaceous gland origin (11.1%). This result is in concordance with other studies that found tumors of sweat gland origin to be the most common,[3,19,22-25] while others found the predominance of tumors with follicular differentiation to be 48.93%, 43.48%, 39.09%, and 64.29%, respectively.[5,21,27,28] This may be due to ethnicity and racial differences. Our study revealed that the most common benign tumor was hidradenoma 35.3% followed by pilomatrixoma 23.5% and spiradenoma 17.6%. Similarly, other studies found that hidradenoma was the most common benign tumor and pilomatrixoma was the second most common,[22,23] while others found that pilomatrixoma was the most common.[5,21,26,28]

The only diagnosed malignant adnexal tumor reported in our study was sebaceous carcinoma in a male patient 51 years old. Sebaceous carcinoma was reported as the most common malignant adnexal tumor in many studies[3,5,19,20,26] with occurrence in older age groups and they attribute their delayed diagnosis to the low degree of suspicion in malignant adnexal tumors and rare incidence. However, sweat gland carcinoma is the most common skin adnexal malignancy in another study.[26]

SATs are histologically challenging tumors to diagnose. Benign lesions need to be differentiated from their malignant counterparts and also from squamous cell carcinoma and basal cell carcinoma. Traditional criteria of cytological and nuclear atypia alone do not render a tumor malignant. This raised the importance of silhouettes/architectural attributes in the distinction between.[29] Benign tumors have symmetrical architecture, and vertical orientation of uniform collections of epithelial cells embedded in a dense fibrotic stroma. No necrosis, atypia, or mitosis are detected. Malignant tumors confer asymmetry, horizontal orientation of tumor cells, irregular arrangement of cells with infiltration, necrosis, atypia, mitosis, and diminished sclerotic stroma. Hence, it is important to examine each lesion under a scanner view to assess the silhouettes of SATs to differentiate benign and malignant tumors.[29,30]

The importance of special and/or immunohistochemical stains in the evaluation of SATs varies according to the case and can be used when necessary. PAS stain is usually used to demonstrate cytoplasmic glycogen contents and stromal hyalinized basement membranes that present in certain SATs and it was studied in the present work. Other stains as Hale's colloidal iron stain for acid mucin and Prussian blue for iron deposits within apocrine lesions are also reported. It was reported that immunohistochemistry and ultrastructural ancillary studies can be useful for tumors differentiation, but they have limited diagnostic value. In the literature, most SATs express different types of cytokeratins. Monoclonal CEA and EMA can be seen in tumors with ductal differentiation. EMA is expressed in tumors with sebaceous differentiation. GCDFP-15 and androgen receptors are seen in apocrine lesions, whereas estrogen and progesterone receptors are seen in different sweat glands lesions and are not considered specific. Hence, morphological evaluation is very important in evaluating SATs, and special and/or immunohistochemical stains may occasionally serve as ancillary tools.[5,17]

CONCLUSION

Our study confirms the fact that SATs are rare and histopathological studies are the gold standard to establish the diagnosis despite expanding use and dependability on special tests like immunohistochemistry. In today's time also, it is an intimidating task for pathologists to make a complete diagnosis and categorize the adnexal tumors, as they are still very rare.

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