Clinicopathological Study of 1016 Consecutive Adnexal Skin Tumors

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Abstract- Adnexal tumors (ATs) are primary skin tumors with benign or rarely, malignant behavior. They have been classified based on differentiation towards hair follicle, sebaceous, apocrine or eccrine gland. Few large-scale studies have focused on ATs. To determine the prevalence of ATs and to assess clinical and histopathological trend of ATs. A retrospective descriptive study of all ATs diagnosed in Razi hospital between 2006 and 2010 was performed. A total of 30,000 pathology records were reviewed, and 1016 ATs were included. The prevalence of ATs was 3.3%. 518 patients (51%) were female, with a mean age of 34.5 years. 953 tumors (93.8%) were benign. ATs were most commonly located in the head and neck area (822, 83.5%). The most common histopathological origin of ATs was sebaceous gland (536, 52.7%). Sebaceous nevus of Jadassohn was the most prevalent single tumor type (40.6% of all ATs). In 63.6% (646) of tumors, ATs were clinically suspected by the clinician prior to biopsy. The most common malignant AT was sebaceous carcinoma (23, 36.5% of all malignant ATs). ATs are infrequent lesions, most commonly occurring in 3rd and 4th decade of life. Diagnosis of ATs is made by histopathological studies as they often express indistinctive clinical features. Malignant ATs are rare, occur at an older age, and are often hard to recognize clinically.

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Introduction

Adnexal tumors (ATs) are a heterogeneous group of primary skin tumours with benign or rarely, malignant behavior. They have been classified based on histopathological differentiation towards hair follicle, sebaceous, apocrine or eccrine gland-like structures (1). Although they are often seen as single sporadic lesions, multiple tumours of the specific type may herald complex genetic syndromes and significant association with internal malignancies may occasionally be observed (2). Malignant ATs are rare; however, local destruction and distant metastasis can occur. Early diagnosis of tumors with malignant behavior bears therapeutic and prognostic significance (3). ATs may occasionally display more than one line of histological differentiation (hybrid /composite tumors) (4). These histological overlaps along with a wide variety of tumors, developmental and embryonic controversies regarding their lineage, and the complicated nomenclature have made the classification of ATs difficult and contradictory (5).

Adnexal tumors are generally infrequent. Diagnosis of these tumors is based on histopathological studies as clinical presentation is often not distinctive. Comprehensive large-scale clinicopathological review of ATs focusing on the overall prevalence of ATs, prevalence of each subtype is lacking. Data on malignant ATs are even scarcer due to their rarity. In addition, varied classification methods have been adopted by different authors rendering further comparisons difficult (6). Therefore, we designed this retrospective clinicopathological review in an attempt to re-classify ATs based on the World Health Organization criteria and to determine the true incidence of benign and malignant ATs. Correlation between clinical and histopathological assessments and epidemiological trends in Iranian patients with ATs were identified.

Materials and Methods

All adnexal tumors diagnosed in the Dermatopathology

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Department of Razi hospital, Tehran University of Medical Sciences between 2006 and 2010 were retrospectively studied. Clinical data and histopathology slides were retrieved from the archive of the Dermatopathology department.

All biopsies were reviewed by two board-certified dermatopathologist blinded to patient identification and previously reported results. Cases with insufficient documentation or incomplete data were excluded. A total of 30,000 records were reviewed, and 1016 consecutive specimens with confirmed final diagnosis of ATs were included. The clinical data including age at the time of diagnosis, sex, location, and the primary clinical diagnosis of the lesion were extracted.

Histopathological re-classification of ATs arising from sebaceous, hair follicle, and sweat glands was done after a meticulous review of the routine hematoxylin and eosin sections. Prevalence and histologic pattern of each type including benign and malignant tumors were collected. The concordance of clinical and histopathological diagnosis was also assessed. If ATs were suspected by the clinician prior to the biopsy, clinical and histopathological diagnoses were considered 'concordant'.

Results

30,000 pathology records from 2006 to 2010 were reviewed, and 1016 specimens (3.3%) with confirmed final diagnosis of ATs were included. In patients with ATs 518 (51%) were female, with a mean age of 34.5 years. Overall, 953 tumors (93.8%) were benign. ATs were most commonly located in the head and neck area (822, 83.5%). The most common histopathological origin of ATs was sebaceous gland, followed by the hair follicle; eccrine/apocrine glands being the least common origin (Table 1). In 63.6% (646) of tumors, ATs were clinically suspected by the clinician prior to excision/ biopsy while in 36.4% (370) of lesions, biopsy revealed a clinically unsuspected AT.

ATs with sebaceous differentiation

As noted, sebaceous glands were the most common histological origin of ATs (536, 52.7%). Among these, sebaceous nevus of Jadassohn was the most common tumor (413, 77%), followed by sebaceous hyperplasia (73, 13.6%) and sebaceous carcinoma (23, 4.3%). Sebaceous nevus of Jadassohn was the most prevalent single tumor type in this study (40.6% of all ATs).

The mean age of diagnosis in sebaceous nevus was 23 years. These tumors are frequently located on the head and neck (95.1%), however, 17 tumors (4.1%) have been identified on the truck and extremities. Sebaceous carcinoma is the most common malignant AT (23, 36.5% of all malignant ATs). The mean age of diagnosis is 64 years, most commonly seen in men (65.3%) and almost always in the head and neck area. This tumor was suspected by the clinician in only 21.7% of cases. Clinical and histopathological data of ATs with sebaceous differentiation including frequency of each type, mean age, sex, location and concordance of clinical and histopathological diagnosis has been summarized in Table 2.

ATs with follicular differentiation

Hair follicle differentiation was noted in 26.1% (265) of ATs with pilomatricoma being the most common tumor (96, 36.2%), followed by Inverted follicular keratosis (53, 20%) and trichoepithelioma (42, 15.9%).

Table1. Clinical and histopathological attributes of ATs, n=1016

Age	Mean	34.5 years
Sex (n, %)	Female	518 (51%)
Behavior (n, %)	Benign	953 (93.8%)
	Malignant	63 (6.2%)
Histopathlogic Origin (n, %)	Sebaceous gland	536 (52.7%)
	Hair follicle	265 (26.1%)
	Sweat gland	215 (21.2%)
Location (n, %)	Head and Neck	822 (83.5%)
	Extremities	118 (12%)
	Trunk	45 (4.5%)

Table 2. Clinical and histopathological attributes of ATs of sebaceous origin, n=536

AT with sebaceous differentiation	Frequecy (n, %)	Age (Mean, years)	Sex (Female)	Location	Concordance of clinical and pathological diagnosis
Sebaceous Nevus of Jadasson	413 (77%)	23	196 (47.5%)	Head&neck 393(95.1%) Trunk 17(4.1%) Extremities 3(0.8%)	345 (83.5%)
Sebaceous hyperplasia	73(13.6%)	46	29 (44%)	Head and neck 72(98.6%) Trunk 1(1.4%)	38 (57.5%)
Sebaceous carcinoma	23 (4.3%)	64	8 (34.7%)	Head & neck 22 (95.6%) Trunk 1 (4.3 %)	5 (21.7%)
Steatocystoma	18(3.4%)	23	5 (27.7%)	Head & neck 8(44.4%)	9 (50%)
Simplex	8 (1.4%)			Trunk 5 (27.8%)	
Multiplex	10 (2%)			Extremities 5(27.8%)	
Other Sebaceoma	5 (0.9%)	--	--	--	--
Sebaceous adenoma	4(0.8%)				

The most common tumor with malignant behavior was proliferating trichilemmal cyst (20, 7.5%). This tumor was most commonly seen on the head and neck (75%), and the mean age of diagnosis was 51 years. Proliferating trichilemmal cyst was clinically suspected in only 15% of cases.

Other rarely encountered malignant tumors are trichilemmal and trichoblastic carcinoma. Clinical and histopathological data of ATs with follicular differentiation including frequency of each type, mean age, sex, location and concordance of clinical and histopathological diagnosis has been summarized in Table 3.

Table 3. Clinical and histopathological attributes of ATs of hair-follicle origin, n=265

ATs of hair follicle origin	Frequecy (n, %)	Age (Mean, years)	Sex (Female)	Location	Concordance of clinical and pathological diagnosis
Pilomatricoma	96 (36.2%)	23	61(63.5%)	Head & neck 41(42.8%) Trunk 1 (o.9%) Extremities 54 (56.3%)	58 (60.1%)
Inverted Folliccular keratosis	53 (20%)	50	33(62.2%)	Head & neck 42(79.2%) Trunk 4 (7.6%) Extremities 7 (13.2%)	14 (26.4%)
Trichoepithelioma	42 (15.9%)	43	15(35.7%)	Head & neck 42(100%)	35 (83.3%)
Proliferatin pilar cyst	20 (7.5%)	51	10, (50%)	Head & neck 15(75%) Trunk 3 (15%) Extremities 2 (10%)	3 (15%)
Tricholemmoma	11 (4.1%)	50	2, (18.1%)	Head & neck 10 (91%) Extremities 1 (9%)	5 (45.5%)
Dilated pore of Winer	9(3.4%)	35	3, (33.3%)	Head & neck 6(66.7%) Extremities 3(33.3%)	3 (33.3%)
Other					
Trichoblastoma	7 (2.6%)	--	--	--	--
Trichoadenoma	6 (2.3%)	--	--	--	--
Trichofolliculoma	6 (2.3%)	--	--	--	--
Basaloid follicular hamartoma	5 (1.9%)	--	--	--	--
Fibrofolliculoma	3 (1.2%)	--	--	--	--
Trichodiscoma	2 (0.7%)	--	--	--	--
Tricholemmal carcinoma	2 (0.7%)	--	--	--	--
Neurofollicular hamartoma	1 (0.4%)	--	--	--	--
Folliculosebaceous cystic hamartoma	1(0.4%)	--	--	--	--
Trichoblastic Carcinoma	1(0.4%)	--	--	--	--

Table4. Clinical and histopathological attributes of ATs of sweat gland origin, n=215

ATs of sweat gland origin	Frequecy (n,%)	Age (Mean, years)	Sex (Female)	Location	Concordance of clinical and pathological diagnosis
Hidradenoma	53(24.6%)	48	24(45.2%)	Head &neck 35(66%) Trunk 6 (11.4%) Extremities 12(22.6%)	20 (37.7%)
Syringoma	32, 14.9%	27.3	32(100%)	Head&neck 28(87.5%) Trunk 1(3.1%) Extremities 3 (9.4%)	32(100%)
Hydrocystoma	26,12%	46	18, 69.2%	Head & neck	21 (80.7%)
Eccrine	12			26(100%)	
Apocrine	14				
Poroma	22(10.3%)	49	17, 77.2%	Head & neck 5 (22.7%) Trunk 1 (4.5%) Extremities 16 (72.8%)	11 (50%)
Syringocystadenoma-papilliferum	19, 8.9%	31	10, 52.6%	Head & neck 17 (89.5%) Extremities 2 (10.5%)	8 (42.1%)
Spiradenoma	13,6%	47	11, 84.6%	Head & neck 8 (61.5%) Trunk 1 (7.8%) Extremities 4 (30.7%)	
Paget ‘s disease (Extra-mammary)	14 (6.5%)	56	11(78.5%)	Vulvar/Scrotal 10 (71.4%) Perianal 4 (28.5%)	13 (92.8%)
Cylindroma	8(3.7%)	49	4(50%)	Head & neck 7(87.5%) Extremities 1(12.5%)	7(87.5%)
Other					
Angioeccrine hamartoma	5 (2.4%)	--	--	--	--
Eccrine carcinoma	4 (1.9%)	--	--	--	--
Mucinous carcinoma	3 (1.4%)	--	--	--	--
Porocarcinoma	3 (1.4%)	--	--	--	--
Cystic adenoid carcinoma	3 (1.4%)	--	--	--	--
Apocrine adenoma	2 (0.9%)	--	--	--	--
Papillary eccrine adenoma	2 (0.9%)	--	--	--	--
Microcystic Adnexal carcinoma	2 (0.9%)	--	--	--	--
Malignant spiradenoma	1 (0.5%)	--	--	--	--
Aggressive digital adenoma	1 (0.5%)	--	--	--	--

ATs with sweat gland differentiation

Sweat glands differentiation (eccrine and/or apocrine) was seen in 21.3% (215) of ATs; hidradenoma (53, 24.6%) was the most common biopsied AT in this group, followed by syringoma (32, 14.9%), hydrocystoma (26, 12%), and poroma (22, 10.3%). The most malignant AT with sweat gland differentiation was extra mammary Paget´s disease (14, 6.5%) including 11 women with a mean age of 56 years. Most cases (10, 71.4%) of Paget’s were seen in the vulvar/scrotal area. Paget’s disease was associated with adenocarcinoma in 2 patients (colorectal and ovarian cancer) and with malignant AT in 1 patient. Other rare malignant ATs in this group are adenoid cystic carcinoma (3, 1.4%),

microcytic adnexal carcinoma (2, 0.9%) malignant Spiradenoma (1, 0.5%) and aggressive digital papillary adenoma (1, 0.5%). Clinical and histopathological data of ATs with sweat gland differentiation including frequency of each type, mean age, sex, location and concordance of clinical and histopathological diagnosis has been summarized in Table 4.

Discussion

Few large-scale epidemiologic studies have focused on appendageal skin tumors. Most ATs are not common enough for pathologists to gain a ready familiarity with them. ATs, nevertheless, are not rare tumors. In this study, the histopathological prevalence of ATs over a 4-year-period among 30,000 pathology records was 3.3% (1016). Other authors have reported a lower prevalence; only 112 ATs were reported over a 13-year survey of consecutive biopsies in Malaya (7). In another study in Nigeria (8), 52 ATs were seen over a 16-year period, accounting for 0.9% of all cutaneous tumors. In a similar descriptive case series of 2637 dermatopathological cases in Paraguay, 36 ATs (1.4%) were identified (9). Whether this data is indicative of a higher prevalence of ATs in Iranian patients is not clear; this study was performed at Razi hospital, an academic dermatology tertiary care and referral center. It'spossible that patients with AT have more frequently undergone biopsy in this center as compared to a general dermatology clinic. However, the true clinical incidence of AT is believed to be higher than reported because many ATs are asymptomatic benign skin lesions that are usually not troublesome or cosmetically disfiguring for patients (e.g sebaceous hyperplasia) and are often treated with destructive modalities without prior biopsy (e.g electrodessication for syringoma).

Overall, no significant sexual predilection was found in ATs in this study as 51% of patients were female. Female predominance was noted in some types of ATs including syringoma (100%), poroma (77.2%), spiradenoma (84.6%), hydrocystoma (69.2%) and Paget's disease (78.5%). A high female to male ratio in syringoma has been reported in other studies. This fact may explain the overall female predominance observed in case series with a large number of syringomas (10). Male predominance is noted in sebaceous carcinoma (65.3%), steatocystoma (72.3%), trichoepithelioma (62.5%) and trichilemomma (81.9%). This finding is of great significant in sebaceous carcinoma; this tumor has been believed to be more common in women.

However, in the largest review of sebaceous carcinoma in the literature, it was found to be slightly more common in men (54%). However, it is not entirely clear whether these differences represent a true gender predilection or a biopsy selection bias due to cosmetic or social factors especially in female patients (11). Some ATs were present in small numbers (<20), rendering sexual comparisons difficult. Most ATs were seen in the third and fourth decade of life, and the mean age of diagnosis was 34.5 years. Some tumors appeared at an earlier age; the mean age of diagnosis for sebaceous nevus of Jadassohn, the most common AT in this study, was 23 years. Sebaceous Nevi are present at birth but are hardly discernible. Progressive thickening and verrucous growth occurs upon reaching adolescence. Therefore, patients often seek medical attention in their second and third decade of life when sebaceous nevi are in rapid growth phase. Syringoma and pilomatricoma were also seen in younger patients (mean age: 23 years). Malignant ATs were associated with advanced age; the mean age of diagnosis for sebaceous carcinoma and Paget's disease were64 and 56 years, respectively.

In this study, sebaceous glands differentiation was the most common histological pattern in ATs (52.7%). Sebaceous nevus of Jadassohn was the most prevalent single tumor type (40.6% of all ATs, 77% of ATs with sebaceous differentiation). These tumors are frequently located on the head and neck (95.1%), however, 20 tumors (4.9%) have been identified on the trunk and extremities. The diagnosis was clinically suspected in 83.5% of lesions. The main clinical differential diagnosis of sebaceous nevus was verrucous epidermal nevus. Some authors have proposed that sebaceous nevus and verrucous epidermal nevus are variants of the same disorder, those on the head and neck being more sebaceous and those elsewhere more verrucous (12).

Hair follicle differentiation was noted in 26.1% (265) of ATs in this study with pilomatricoma being the most common tumor (36.2%), followed by inverted follicular keratosis (20%) and trichoepithelioma (15.9%). Sweat glands differentiation (eccrine and/or apocrine) was seen in 21.3% of ATs. Hidradenoma (24.6%) was the most common biopsied AT in this group, followed by syringoma (14.9%), hydrocystoma (12%), and poroma (10.3%). In other studies in Nigeria (8), Paraguay (9) and India (10),sweat gland differentiation was the most common histopathological pattern in ATs with syringoma being the most prevalent type in India and Paraguay.

Syringomas are easily distinguished based on their clinical feature and periorbital/eyelid location. At our center, these lesions are often treated using

electrosurgical destruction or other modalities without prior biopsy unless they exhibit atypical features and/ location (trunk, genitalia, eruptive syringoma) or other differential diagnoses such as basal cell carcinoma are considered.

This study shows that the most common anatomic region for adnexal skin tumors was the head and neck area (83.5%). The predominance of ATs over head and neck area is well-documented and has been confirmed by other studies (7,8). Rich distribution of pilosebaceous apparatus,apocrine and eccrine sweat glands in the head and neck region provides a fertile field for development of ATs (13). Poroma was most commonly seen in extremities (72.8%) as acral presentation of this tumor as a sessile plaque surrounded by indented moats on the palm, and the sole is a classic feature. Notably, 56.3% of pilomatricomas appeared on the extremities. These tumors may develop on any non-glabrous skin, but have been mostly described on the head and neck and upper trunk. As a result of this novel finding, the authors suggest that the diagnosis of pilomatricoma should be considered by clinicians when a solitary firm skin-colored to faint blue nodule with or without overlying anetoderma appears on the extremities. ATs are generally benign, malignant types may infrequently be encountered. 6.2% (63) of ATs observed in this study showed malignant behavior. The most common malignant AT diagnosed in this center was sebaceous carcinoma (23, 36.5% of all malignant ATs). The mean age of diagnosis was 64 years, most commonly seen in men (65.3%) and almost always in the head and neck area. Importantly, this tumor was suspected by the clinician in only 21.7% of cases. The diagnosis of sebaceous carcinoma is generally delayed by 1 to 2.9 years. This delayed diagnosis may be associated with increased mortality (11). Therefore, It is wise to recommend that clinicians should be vigilant for the possibility of sebaceous carcinomas in periorbital or head and neck area, especially in the elderly. Proliferating trichilemmal cyst was the second most common malignant AT in this study (20, 31.7% of all malignant ATs). There is an ongoing controversy regarding the benign or malignant nature of these tumors. Nevertheless, local destruction and distant metastasis can occur. This tumor often occurs in the elderly; the mean age of diagnosis was 51 years in our study. It has been most commonly described in women; however, we found no sexual predilection. (10/20,50% female.) Proliferating trichilemmal cysts often occur on the scalp.

Notably, 25% of tumors in our study were located on the trunk or extremities. A higher rate of malignant behavior has been associated with lesions located in non-scalp areas (14). Extra-mammary Paget's disease was the third most common malignant AT in our study (14, 22.2% of all malignant ATs). In accord to the literature, Paget's disease was most commonly seen in women (78.5%) and in the vulvar area (71.4%). The mean age of diagnosis was 56 years, and unlike other malignant ATs, Paget's disease was suspected by the clinician in the majority of cases (92.8%). These lesions have been associated with adenocarcinoma and cutaneous adnexal malignancies in 10-33% of cases (15).

In this study, Paget's disease was associated with adenocarcinoma in 2 patients (colorectal and ovarian cancer) and with malignant AT in 1 patient. In 63.6% of ATs in this study, clinical diagnosis was consistent with pathological diagnosis. However, malignant ATs were less commonly suspected by the clinicians; the concordance of clinical and pathological diagnoses was 21.7% and 15% in sebaceous carcinoma and proliferating trichilemmal cyst, respectively. This low degree of suspicion in malignant ATs may result in delayed diagnosis of these tumors. In a study of head and neck ATs in India, 30 suspected lesions underwent histopathological examination. Diagnosis of AT was confirmed in 23 (76.67%) cases (16).

This confirms the fact that diagnosis of ATs is often made by histopathological studies as they often express indistinctive clinical feature.

ATs are infrequent lesions, most commonly occurring in third and fourth decade of life. ATs of sebaceous gland origin were the most common in this study with sebaceous nevus of Jadasshon being the most common single AT. Diagnosis of ATs is made by histopathological studies as they often express indistinctive clinical features. Malignant ATs are rare, occur at an older age, and are often hard to recognize clinically.

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