STUDY

Prevalence of Pilomatricoma in Turner Syndrome

Findings From a Multicenter Study

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Importance: The absence of data on the prevalence of pilomatricoma among patients with Turner syndrome served as the catalyst for this multicenter investigation.

Objectives: To ascertain the prevalence of pilomatricoma among patients with Turner syndrome and to determine any association between the development of pilomatricomas and the use of exogenous hormones in patients with Turner syndrome.

Design: A retrospective medical record review from January 1, 2000, through January 1, 2010, was performed of all patients with Turner syndrome. Data on pilomatricomas and the use of hormone therapy were collected.

Setting: University of California–Davis Medical Center, University of Nebraska Medical Center, and The University of North Carolina at Chapel Hill.

Participants: Patients with a diagnosis of Turner syndrome.

Main Outcome Measures: Prevalence of concomitant pilomatricoma and diagnosis of Turner syndrome. Secondary outcome measures included the use of the exogenous hormones estrogen or recombinant human growth hormone (rhGH).

Results: In total, 311 patients with Turner syndrome were identified from these 3 institutions. Among them, 8 patients (2.6%) were diagnosed as having pilomatricomas. Before the development of pilomatricomas, 5 patients had been treated with rhGH but not estrogen, 1 patient had received estrogen but not rhGH, and 2 patients did not receive either therapy.

Conclusions and Relevance: Although the prevalence of pilomatricoma among the general population is unknown, this study demonstrates a high prevalence (2.6%) of pilomatricomas among patients with Turner syndrome. No apparent relationship was noted among our patients or in the literature between the use of rhGH and the development of pilomatricomas.

JAMA Dermatol. 2013;149(5):559-564.
Published online February 20, 2013.
doi:10.1001/2013.jamadermatol.115

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PILOMATRICOMAS (ALSO KNOWN as calcifying epithelioma, benign calcifying epithelioma of Malherbe, and pilomatrixoma) are benign cutaneous adnexal tumors that arise from the outer root sheath cells in the hair follicle.[1-3] These tumors have a 3:2 female predominance, with most manifesting on the head, neck, and upper extremities before age 20 years.[4-8]

The prevalence of pilomatricoma among the general population is unknown. Pilomatricomas typically appear as solitary, hard, mobile, nontender nodules, with bluish discoloration[2,4,9] (**Figure 1** and **Figure 2**). Classic histological findings may include central "shadow cells" surrounded by basophilic cells, as well as calcification[5] (**Figure 3** and **Figure 4**). Surgical excision remains the standard of care, and recurrence rates are between 0% and 6%.[2,10] Case series in the 1960s and 1970s reported that 97% of the lesions occurred in individuals of white race/ethnicity, but cases have since been published among individuals of black, Hispanic, and Asian races/ethnicities.[9,11,12]

Turner syndrome, first described by Henry Turner in 1938, has an incidence of 1 in 2500 live female births and is the most common sex chromosomal abnormality affecting girls and women.[13-15] By definition, individuals with Turner syndrome are female and lack part or all of the second sex chromosome. Many patients have classic 45,X karyotypes, but frequently patients have another cell line containing 2 normal Xs or a normal X and a structurally abnormal X or Y chromosome.[16] More than 90% of patients with Turner syndrome have short stature, mani-

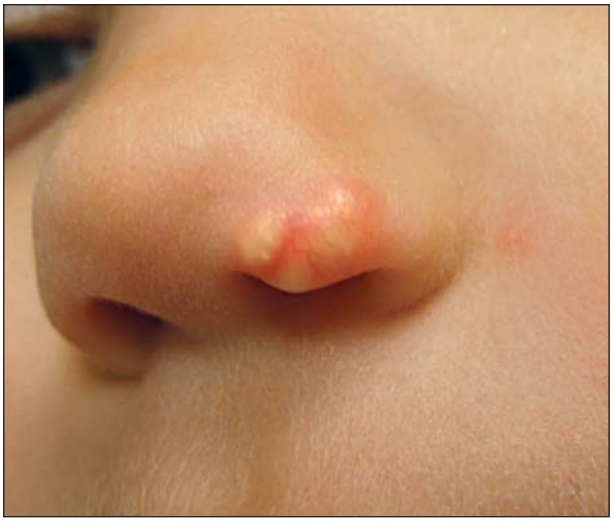

Figure 1. Child with pilomatricoma on the nose.

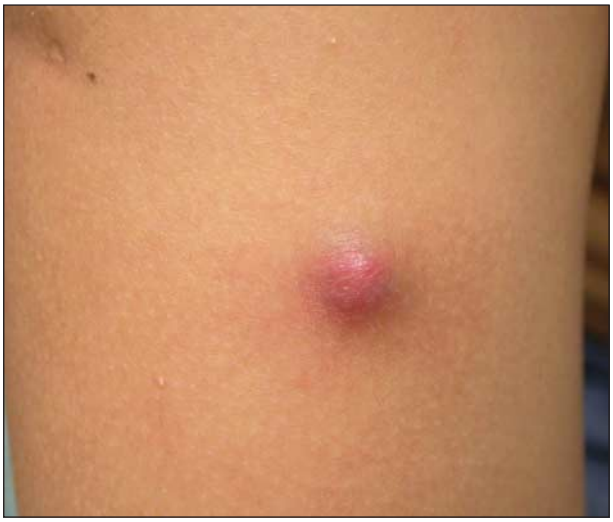

Figure 2. Pilomatricoma lesion on the lateral aspect of the bicep.

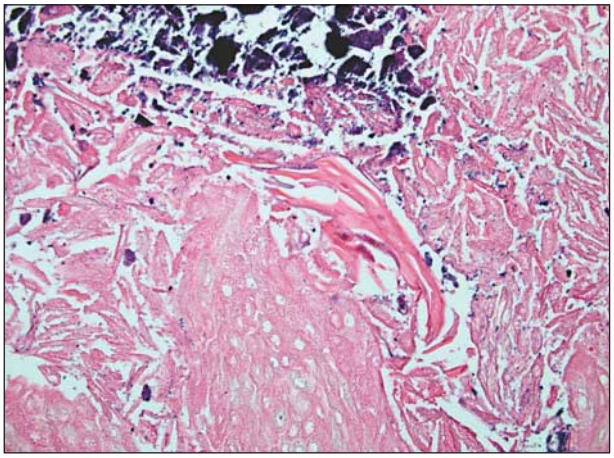

Figure 3. Sharply demarcated pilomatricoma tumor surrounded by a fibrous capsule (hematoxylin-eosin, original magnification ×5). Reproduced with permission from Maxwell Fung, MD.

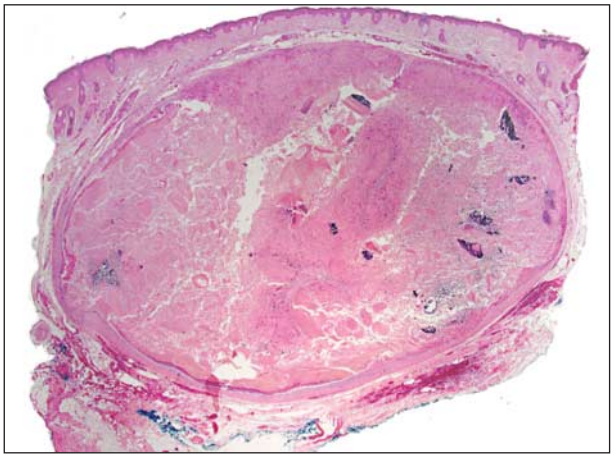

Figure 4. Pilomatricoma showing darkly stained basophilic calcium and shadow cells with missing nuclei (hematoxylin-eosin, original magnification ×40). Reproduced with permission from Maxwell Fung, MD.

fest premature ovarian failure, and are at high risk for various phenotypic abnormalities (eg, high palate, nail dysplasia, low posterior hairline, widely spaced nipples, webbed neck, and low-set or malrotated ears), as well as other medical problems such as cardiovascular defects, skeletal anomalies, and autoimmune disorders.[17] Patients with Turner syndrome frequently are prescribed recombinant human growth hormone (rhGH) therapy to increase their growth velocity and final adult height. Those who fail to undergo puberty or who develop premature ovarian failure are treated with estrogen.

Four case reports have described the initial development of pilomatricomas between the ages of 6 and 23 years in patients with Turner syndrome.[18-20] Three of the 4 patients had multiple lesions or recurrences, with 10 lesions developing over 7 years in 1 patient. Only 1 patient had reported the use of rhGH and estrogen, both before the lesion appeared. The absence of data on the prevalence of pilomatricoma among patients with Turner syndrome served as the catalyst for this multicenter investigation.

We performed a retrospective study of patients with Turner syndrome treated at University of California–Davis Medical Center, University of Nebraska Medical Center, and The University of North Carolina at Chapel Hill to ascertain the prevalence of pilomatricoma among patients with Turner syndrome. We also evaluated for any association between the development of pilomatricomas and the use of exogenous hormones in patients with Turner syndrome.

METHODS

The study was approved by the institutional review boards at University of California–Davis Medical Center, University of Nebraska Medical Center, and The University of North Carolina at Chapel Hill. The medical record databases were initially searched for *International Classification of Diseases, Ninth Revision* diagnoses of Turner syndrome and gonadal dysgenesis; Turner syndrome characterizes most of those with an *International Classification of Diseases, Ninth Revision* diagnosis of gonadal dysgenesis. The medical records were manually and individually reviewed to ensure the accuracy of the diagnosis

Table. Characteristics of Patients With Turner Syndrome

Variable	University of Nebraska Medical Center (n = 43)	University of California–Davis Medical Center (n = 73)	The University of North Carolina at Chapel Hill (n = 195)	Total (N = 311)
	Karyotype, No. (%)			
45,X	4 (9.3)	18 (24.7)	97 (49.7)	**119** (38.3)
45,X/46,XX	1 (2.3)	8 (11.0)	20 (10.3)	**29** (9.3)
45,X/46,X,idic(X)[a]	4 (9.3)	8 (11.0)	13 (6.6)	**25** (8.0)
45,X/ring(X)	1 (2.3)	2 (2.7)	18 (9.2)	**21** (6.8)
Other	8 (18.6)	9 (12.3)	35 (17.9)	**52** (16.7)
Unknown	25 (58.1)	28 (38.9)	12 (6.2)	**65** (20.9)
	Age, y			
Mean (SD)	10.5 (5.7)	20.5 (15.1)	12.4 (7.6)	14.0 (10.2)
Median	11	18	12	13
At initial pilomatricoma diagnosis[b]	NA	5, 15	3, 4, 4, 5, 7, 10	NA
	Hormonal Treatment With rhGH, Estrogen, or Both, No. (%)			
rhGH				
Received medication	35 (81.4)	30 (41.1)	136 (69.7)	**201** (64.6)
Did not receive medication	7 (16.3)	26 (35.6)	56 (28.7)	**89** (28.6)
Unknown	1 (2.3)	17 (23.3)	3 (1.5)	**21** (6.8)
Estrogen				
Received medication	15 (34.9)	41 (56.2)	97 (49.7)	**153** (49.2)
Did not receive medication	21 (48.8)	22 (30.1)	98 (50.3)	**141** (45.3)
Unknown	7 (16.3)	10 (14.0)	0	**17** (5.5)
rhGH and estrogen				
Received both medications	11 (25.6)	19 (26.0)	66 (33.8)	**96** (30.9)
Did not receive either medication	4 (9.3)	14 (19.2)	43 (22.1)	**61** (19.6)

Abbreviations: NA, not applicable; rhGH, recombinant human growth hormone.
[a] Isochromosomes include isocentric, dicentric, and pseudodicentric chromosomes.
[b] Among 8 patients with pilomatricomas.

of Turner syndrome. Patients were included if they had Turner syndrome and were seen by a health care provider between January 1, 2000, and January 1, 2010. The data collected included age, karyotype, pilomatricomas, and hormonal treatment with rhGH, estrogen, or both.

RESULTS

In total, 311 patients with Turner syndrome were identified from the combined data at 3 institutions from January 1, 2000, through January 1, 2010. The mean (SD) age of patients with Turner syndrome was 14.0 (10.2) years. Of the known karyotypes, 119 (38.3%) were monosomy 45,X. Of 311 patients, 201 (64.6%) had received rhGH and 153 (49.2%) had received estrogen. Only 96 patients (30.8%) had received both rhGH and estrogen, while 61 patients (19.6%) did not receive either therapy.

Eight of 311 patients (2.6%) were diagnosed as having pilomatricomas (case reports and **Table**). The mean (SD) age at initial pilomatricoma diagnosis was 7.0 (3.9) years (age range, 3-15 years). Four of 8 patients developed multiple pilomatricomas. Evaluation of karyotypes among the 8 revealed 3 to be monosomic 45,X. Two patients had Y chromosome material, both Y isochromosomes, 45,X/46,X,idic(Y) in one patient and 45,X/46,X,idic(Y)/47,X,idic(Y),idic(Y) in the other patient.

Of 8 patients with Turner syndrome, 5 had been treated with rhGH but not estrogen. One patient had received estrogen but not rhGH. Two patients did not receive either therapy.

In each case, the lesions were biopsied or excised. The diagnosis of pilomatricoma was pathologically confirmed.

CASE REPORTS

Patient 1

A 5-year-old girl of white race/ethnicity with 45,X Turner syndrome diagnosed at birth owing to lymphedema and coarctation of the aorta developed a 20-mm tender, nonpruritic, firm, mobile, bluish subcutaneous nodule on her right upper back over several months. She had begun rhGH treatment at age 3 years 1 month, 2 years 4 months before being seen with pilomatricoma.

Patient 2

A 15-year-old girl of white race/ethnicity with 45,X/46,X,idic(X) Turner syndrome developed a nodule over the eyebrow. The patient had noted the firm mass 8 months previously and stated that it had grown rapidly to its current 3-mm diameter. On examination, it was firm, mobile, and nontender with a dark discoloration. She had been started on conjugated estrogens 6 months before presentation but had not received rhGH therapy.

Patient 3

A 24-year-old woman of white race/ethnicity with 45,X Turner syndrome, hypothyroidism, obesity, multiple be-

nign nevi, chronic lymphedema, and a repaired coarctation of the aorta was seen at the clinic with 2 hard, tender nodules. She had a history of 14 pilomatricomas removed, the first 2 at age 3 years above the left eye and cheek. The recent nodules were tender and firm, one of 12-mm diameter on the posterior scalp and the other a 10-mm nodule on the left arm. She had used rhGH between the ages of 7 and 14 years and was taking oral contraceptive pills.

Patient 4

A 16-year-old girl of white race/ethnicity with 45,X Turner syndrome was seen with a slowly enlarging 9 × 9-mm bluish papule on the center of her forehead. She had a history of 6 excised pilomatricomas since age 7 years. Her dermatologic history also included recurrent verruca vulgaris on the hands and feet and removal of 3 compound nevi. The forehead lesion was monitored and underwent spontaneous regression. The patient had used rhGH between the ages of 2½ and 14 years, and she had never received estrogen therapy.

Patient 5

An 11-year-old girl of Hispanic race/ethnicity with Turner syndrome, in good health and taking no medications, was seen with two 3-mm asymptomatic nodules on the forehead and the right cheek. Her medical history was significant for having had 2 pilomatricomas removed at age 5 years and 3 removed at age 8 years. Owing to the multiple pilomatricomas, a karyotype was obtained at age 8 years, revealing 46,X,del(X)(p11.22) Turner syndrome. Dermatologic examination was also significant for keratosis pilaris and multiple telangiectatic macules 2 to 5 mm in diameter on the upper extremities. The patient's nodules were asymptomatic and were regularly monitored. The patient had not been receiving rhGH or estrogen.

Patient 6

A 9-year-old girl of white race/ethnicity diagnosed as having 45,X/46,X,idic(Y)(p11.3)/47,X,idic(Y)(p11.3),idic(Y)(p11.3) Turner syndrome at age 2 years was seen with an 11-mm nodule on the neck. Her medical history was significant for a 3 × 5-mm pilomatricoma removed at age 7 years from below her left eyelid, gonadectomy at age 3 years, and treated hypothyroidism. Physical examination revealed keratosis pilaris, sebopsoriasis, and 2 café au lait macules on the trunk and 2 on the lower extremities, as well as a large lightly hyperpigmented patch on the posterior right lower extremity. The patient had 10 nevi on the body, with acanthosis nigricans around the posterior neck. The neck nodule was excised, and pathological examination confirmed pilomatricoma. Since age 4 years, she had been treated with rhGH but had not received estrogen.

Patient 7

A 10-year-old girl of Hispanic race/ethnicity with 45,X/46,X,ring(X) Turner syndrome diagnosed at age 15 months because of gross motor delays was seen at the dermatology clinic for treatment of eczema and a nodule of less than 20-mm diameter on her face. The lesion was biopsied, and pathological examination confirmed the diagnosis of pilomatricoma. At that time, no excision was performed. Treatment with rhGH had begun at age 2 years 7 months. She had not received estrogen therapy.

Patient 8

A 4-year-old girl of white race/ethnicity with 45,X/46,X,psudic(Y)(p11.3) Turner syndrome was seen at the dermatology clinic with a nodule on her face. Her medical history included a horseshoe kidney, mild learning disability, and hypothyroidism. She had received rhGH for 2 months before presentation. The excised nodule was diagnosed as a pilomatricoma by pathological examination.

COMMENT

Within the cohort of 311 patients with Turner syndrome, 8 individuals developed at least 1 pilomatricoma, for a prevalence of 2.6%. The lack of pilomatricoma prevalence data among the general population prevents comparison with the prevalence among our cohort with Turner syndrome. In this study, patients with Turner syndrome developed pilomatricomas at a mean (SD) age of 7.0 (3.9) years, and most occurred on the head and neck. These findings are consistent with previous studies[4-6] of pilomatricoma sites and age at onset. The incidence of pilomatricoma was also examined in our cohort with Turner syndrome. During the observation period, the patients were followed up for 2634 patient-years, and 6 patients developed their first pilomatricoma, resulting in an incidence of 0.0022 cases per year. Unfortunately, the published data on the general population are limited to pathology reports of excised skin lesions, with a reported 0.12% case incidence per 35 years, or 0.000035 cases per year.[4] The methods used to determine incidence in this study differ, so comparisons are indirect.[4]

It has been hypothesized that growth hormone (or its effector molecule insulinlike growth factor 1) and estrogen may promote hair follicle growth, inhibit apoptosis, and produce pilomatricomas.[20-22] Although both rhGH and estrogen can promote tumor growth, there does not seem to be an association between their use and the development of pilomatricomas; 5 of 8 patients (62.5%)with pilomatricomas herein had received rhGH, which is comparable to the 64.6% who had received rhGH in our overall cohort with Turner syndrome. None of those with pilomatricomas had received estrogen therapy before the development of their first pilomatricoma.

Possible explanations for the increased prevalence of pilomatricoma among patients with Turner syndrome include effects from haploinsufficiency of gene expression in pseudoautosomal regions and mutations or imprinting on the X chromosome. A mouse model of Turner syndrome demonstrated a reduction of Gp3 (GPC3 in humans).[23] Low GPC3 levels result in increases of the transcription factor β-catenin.[24,25] Increased β-catenin is associated with decreased apoptosis and increased hair

follicle differentiation.[26] Error in expression of β-catenin (encoded by *CTNNB1*) has been attributed to pilomatricomas[27] and may lead to the development of pilomatricomas in other genetic disorders such as Gardner syndrome,[28] myotonic dystrophy,[29] Rubinstein-Taybi syndrome,[30] cerebral gigantism,[31] Kabuki syndrome,[32] gliomatosis cerebri,[33] glioblastoma,[34] and trisomy 9.[35-37] There may be an association between an upstream event that causes increased β-catenin expression and subsequent development of pilomatricomas.

Multiple studies[38-43] have reported tumor formation in individuals with Turner syndrome. Cohort studies[44-46] have demonstrated an increase in site-specific cancers above that among the general population. Girls and women with Y chromosome material have a 25% to 43% chance of developing gonadoblastomas, while those without Y chromosome material are not at risk.[47-50] Notably, 2 of 8 patients herein with pilomatricomas had karyotypes containing Y chromosome material, whereas in the overall cohort with Turner syndrome, only 18 of 311 patients (5.8%) had Y chromosome material. Whether there is an association between Y chromosome material and the development of pilomatricomas is unknown. Patients with Turner syndrome may have an increased risk for cancers of the colon or rectum,[44,45] as well as meningeal tumors, childhood brain tumors, and bladder and urethral cancer.[46] Individuals with chromosomal aberration are at increased risk for tumors. This may be due to a tendency for mitotic nondisjunction that may underlie the development of cancers.[51]

Our study has several limitations. The current prevalence rate of pilomatricoma is unknown for the general population. As a result, we can only speculate that the prevalence of 2.6% among patients with Turner syndrome is greater than that among the general population. There are limitations of medical record review; the number of lesions may be underreported because of the potential lack of accurate documentation of lesions on examination and the inability to access records of unaffiliated health care providers. Some patients may have had lesions that were undiagnosed, undocumented, or unevaluated by a pathologist. Given the predominance of pilomatricomas among girls younger than 20 years, it is possible that some of the effect is related to epidemiological factors that have yet to be explained, rather than being explained fully by factors related to Turner syndrome.

Physicians caring for patients with Turner syndrome should be aware of the prevalence of pilomatricoma among this population. Those treating Turner syndrome should suspect pilomatricoma in patients seen with solitary, hard, mobile, nontender, bluish nodular growths on the head and neck.

Accepted for Publication: July 1, 2012.
Published Online: February 20, 2013. doi:10.1001/2013.jamadermatol.115
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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Acquisition of data:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Analysis and interpretation of data:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Drafting of the manuscript:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Critical revision of the manuscript for important intellectual content:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Statistical analysis:* Handler, Derrick, Lutz, Morrell, Davenport, and Armstrong. *Study supervision:* Lutz, Morrell, and Armstrong.
Conflict of Interest Disclosures: None reported.
Additional Contributions: Figures 3 and 4 were provided by Maxwell Fung, MD.

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