Incidence of Ovarian Fibromas and its Relation to Malignancy of the Skin in Gorlin Syndrome Patients

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Abstract

Gorlin syndrome (GS) is an autosomal dominant condition primarily caused by pathogenic variant in the PTCH1 tumor suppressor gene. It is characterized by numerous basal cell carcinomas, keratocystic odontogenic tumors, and other dysmorphic features. Women with GS may also develop ovarian fibromas (OF), which can significantly impact quality of life by causing heavy menstrual bleeding, frequent urination, and abdominal pain. To date, the incidence of OF and their relation to severity of skin disease in Gorlin patients are not well-defined. The goal of our study was to evaluate the prevalence and severity of OF among female participants in our GS Registry. We also analyzed its correlation with severity of cutaneous basal cell carcinoma (BCC).

Our data set consists of 141 GS patients, 85 female and 56 male. We utilized number of BCCs as an indicator of cutaneous disease severity. Of the female participants, 76 responded. Of the responders, 31 (40.8%) reported history of OF. The mean number of BCC's in patients with a history of OF was 388 compared to 226 in those without history of OF (p=0.053). Mean BCC's in females with no OF was comparable to the mean of 228 BCC's in males. Although it is borderline significant statistically, the study did demonstrate a higher mean number of BCC's in women with a history of OF. Our findings are consistent with previous literature demonstrating the role of estrogen in tumorigenesis and estrogen-responsiveness of the skin. We therefore conclude that there may be a potential role of estrogen in the development of BCC's in females with GS. Our study also showed high incidence of OF (40.8%) in women with GS, comparing to that from prior studies estimating

Introduction

Gorlin syndrome is also known as nevoid basal cell carcinoma syndrome. It is a rare genetic disease with a prevalence of approximately 1 per 31,000.[1] GS is a multi-organ disorder characterized by many cutaneous basal cell carcinomas, keratocystic odontogenic tumors of the jaw, as well as meningioma and medulloblastoma of the brain. Other abnormalities seen may include ophthalmologic manifestations, bone abnormalities, and cardiac/ovarian fibromas. Various tumor suppressor genes (*PTCH1, PTCH2, SUFU*) have been implicated in the pathophysiology of GS.

Due to the rarity of GS, there is limited data on this disease. Current literature on phenotypes associated with different mutations, screening guidelines, and treatment options are limited.

Photo from Gorlin Syndrome Alliance

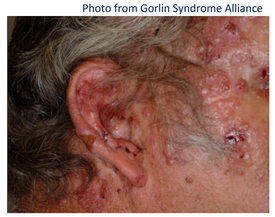

Figure 1. Gorlin patients frequently present with numerous BCC's.

Photo courtesy of Dr. Ed Urthman

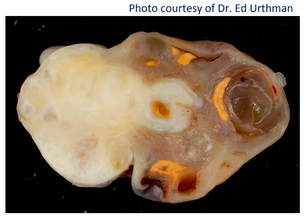

Figure 2. Ovarian fibroma which may be seen in female Gorlin patients.

Methods and Materials

The Gorlin Syndrome Alliance and Stanford University have collaborated to establish a national registry collecting information including demographic information, family history, and medical as well as surgical history, including disease manifestation/ progression, treatments, and genetic test results. A total of 141 GS patients were analyzed; of which 85 are female and 56 are male. Two-sample t-test was used to compare number of basal cell carcinoma in male vs. female patients and in female patients with and without a history of ovarian fibroma.

Results

The median age of the female patients was 57 yrs and median age of diagnosis was 17 yrs. Of the 85 females, 76 responded (those who responded unsure or not applicable were excluded from this analysis). Of the 76 responders, 31 (40.8%) reported history of OF. The mean number of BCC's in this group was 388 compared to 226 in those without a history of OF (p=0.053), which is comparable to mean of 228 BCC in male patients. Out of 85 females, 12 had a diagnosis of advanced or metastatic BCC. Out of the 73 females who responded either yes or no to having a diagnosis of advanced or metastatic BCC, there were 5 patients who had a history of OF (16.7%) and 5 who did not (11.6%).

Table 1. Demographics of our cohort and two-sample t-test results.

Total patients in registry (n=141)	Female	Male
Gender	85/141 (60.3%)	56/141 (39.7%)
Number of BCC's	275	228
Median Age (years)	57	56

Total female Gorlin patients (n=85)	Hx of Ovarian Fibroma	No Ovarian Fibroma
Responded yes/no to presence of OF (n=76)	31/76 (40.8%)	45/76 (59.2%)
Number of BCC's	388	226
Diagnosed with advanced or metastatic BCC (n=73)	5/30 (16.7%)	5/43 (11.6%)

Two-sample t-tests	t	p-value
Female vs. Male	1.656	0.211
Hx of OF vs. No Hx	1.678	**0.053**

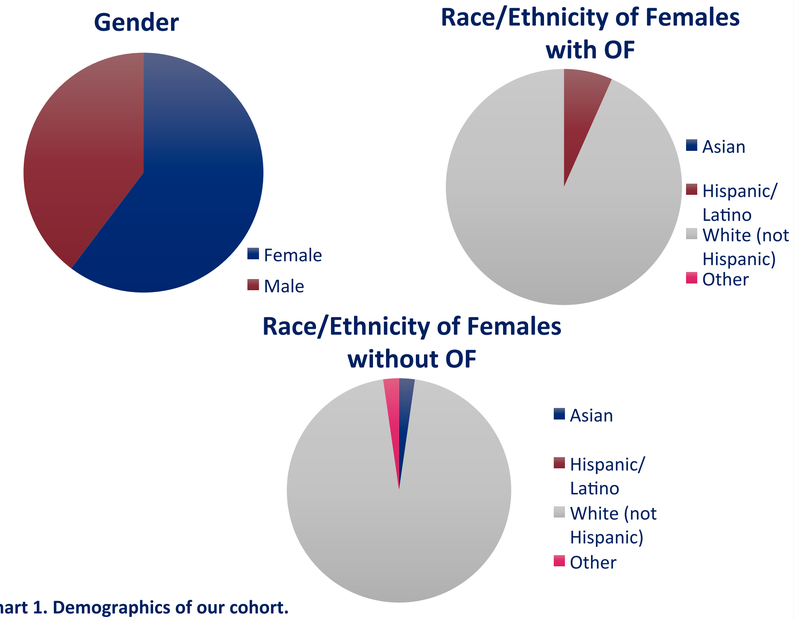

Chart 1. Demographics of our cohort.

Discussion

Contrary to prior literature suggesting equal incidence of BCC's in men and women,[2] our study demonstrates a difference in number of BCC's in women with OF versus men. We also found a near statistically significant difference in number of BCC's in women with ovarian fibroma versus those without. This may suggest a role of estrogen in the development of BCC's that is worth additional investigation. Of those patients with a history of OF, a greater percentage were diagnosed with advanced or metastatic or advanced BCC compared to those without a history of OF.

An alternative question to pose based on our findings would be whether or not the number of BCC's predicts risks of internal disease in GS patients, thus requiring close surveillance. Overall, our study showed a higher than previously demonstrated incidence of OFs in female patients with Gorlin syndrome, indicating potentially higher burden of disease for women.

Conclusions

It has been demonstrated that estrogen modulates tumorigenesis, and skin in particular is an estrogen-responsive organ.[3,4] Our study supports a possible role of estrogen in the development of BCC's in females with GS. These women may also be more susceptible to high risk BCCs. Our study showed 40.8% women with GS had ovarian fibromas, which is higher than the 15-25% incidence reported prior.[5-7]

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