Title

Age, Sex, and Anatomical Location Patterns in Cutaneous Pyogenic Granuloma Cases

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Manuscript Title: Distribution of cutaneous pyogenic granulomas by sex and anatomical location across age.

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Key Points

Question: What are the patterns of cutaneous pyogenic granuloma (PG) incidence across age, sex, and anatomical location?

Findings: In this retrospective study, we found that incidence of PGs varies by age, sex, and anatomical location with PGs on the head/neck and trunk being more common in males less than 20 years old and in females 20-50 years of age. We did not find any left-right laterality bias among upper extremity PGs.

Meaning: Trauma may not be a major etiologic factor for PGs. Further research is required to confirm this and understand the causes underlying the age-by-sex interaction observed in this study.

Structured Abstract

Importance: Cutaneous pyogenic granulomas (PGs) are commonly encountered, benign, vascular tumors whose epidemiologic factors have been variably reported, in part, due to sample size limitations and a focus on either adult or pediatric cases.

Objective: To assemble the largest current set of pathologically diagnosed PGs across the continuum of age and investigate for patterns of PGs by demographic factors, including age, sex, and anatomical location.

Design: Retrospective case series of pathologically confirmed PGs of cutaneous origin reported between 04/01/2010 to 03/31/2020.

Setting: Large tertiary academic center in the midwestern United States of America.

Participants: Individuals were included if they had a pathologically confirmed diagnosis of a PG. PG cases were excluded if they: included PG as part of the pathological differential; were recurrent; or were of non-cutaneous origin.

Main Outcomes and Measures: We evaluated for sex biases in frequency overall, by anatomical region, and by left-right laterality using exact binomial tests. We evaluated for differences in age-by-sex distribution overall and by anatomical region using Kolmogorov-Smirnov tests.

Results: We identified 1009 unique PG records from 987 individuals. There was an equal distribution of PGs between male and female individuals overall (p-value: 0.55) and for all anatomical locations except lower extremities, where females were more frequently impacted (p-value: 7.5×10^{-4}). The distribution of PGs by age was significantly different between male and female individuals (p-value: 2.2×10^{-16}), with this difference being driven primarily by the head

and neck (p-value: 3.7×10^{-7}) and trunk (p-value: 2.0×10^{-6}) but not upper extremity (p-value: 0.02) nor lower extremity (p-value: 0.56) anatomical locations. We did not observe a left-right laterality bias among upper extremity PGs (p-value: 0.86) nor anterior-posterior bias among truncal PGs (p-value: 0.08).

Conclusions and Relevance: There exists an age-by-sex interaction in the incidence of PGs with PGs on the head/neck and trunk being more common in males less than 20 years old and in females 20-50 years of age. Our findings suggest that trauma may not be a major etiologic factor for PGs. Future studies are necessary to confirm this and to understand the causes of the age-by-sex interaction.

Introduction:

Pyogenic granulomas (PGs) are benign, vascular tumors.[1] They typically present as solitary red cutaneous or mucosal papules that rapidly expand and readily bleed.[2] Histopathologically, they are well-circumscribed lobular arrangements of capillaries,[3] known as lobular capillary hemangiomas (LCHs). The etiology of PGs has been a subject of debate for centuries. In 1904, Legroux suggested that minor trauma preceded most PGs, though this was later clarified to be a slim majority by Lenoromant.[4] A history of preceding trauma has been inconsistently reported in subsequent studies.[3,5,6] Nevertheless, PGs as a reactive phenomenon remains a common explanation.[7] Harris et al., noted in their case series that neck PGs were twice as frequent in males whereas leg PGs were twice as frequent in females; hypothesizing that this may result secondary to shaving-related trauma.[8] Other case series have also noted sex differences with male predominance reported in some studies[6,9] and female predominance in others.[5,10] These differences are likely driven by varying numbers of pediatric cases as there exists evidence for an age-by-sex interaction.[3,8–10] Anatomical location may also explain the variation in reported sex differences, as mucosal lesions appear to be more common in females[9], particularly between ages 18-39[3] and during pregnancy.[7] Recent molecular studies of PGs have identified somatic variation associated with these lesions, suggesting that PGs may also arise spontaneously.[11,12]

We have assembled the largest current dataset of pathologically confirmed PGs across the continuum of age. Here we investigate for patterns of cutaneous PGs by age, sex, and anatomical location.

Methods:

For this retrospective study, after Institutional Review Board approval, we queried our institutional pathology database for case reports that included the term 'pyogenic granuloma' or 'lobular capillary hemangioma' from 04/01/2010 to 03/31/2020 (1902 pathology records). We filtered these records, removing: cases that did not include PG or LCH in the final pathological diagnosis (522); cases with non-cutaneous tissue origin (271); and cases for which there was pathological diagnostic uncertainty as represented by only including PG or LCH on the final pathological diagnosis differential (71). Following this filtration, 1038 pathologically confirmed PG records remained. We assigned an anatomical location category based on the Dermatology Lexicon Project[13] and further collapsed these into categories based on Giblin et al. 2007.[9] We annotated the cases with sex and age at lesion removal based on electronic medical record data. Recurrent lesions were identified as separate lesions from the same individual at the same anatomical location that were removed at a later date. We retained all first instance PGs and excluded recurrent lesions (29) as defined above. This yielded 1009 unique pathologically confirmed PG records. We identified individuals as having multiple PGs if they had more than one PG at different anatomical locations. Statistical analyses included exact binomial tests to evaluate for sex and left-right laterality biases in frequency of PGs as well as Kolmogorov-Smirnov tests to evaluate for differences between age-by-sex distributions.

Results:

Incidence of PGs by age, sex, and anatomical location.

We observed an overall equal distribution of PGs between male and female individuals (Table 1, p-value: 0.53). This equal distribution was consistent for most anatomical locations, except for the lower extremities where females were more frequently impacted (Supplemental Table 1, p-value: 7.5×10^{-4}). The distribution of PGs by age was significantly different between males and

females (p-value: 2.2×10^{-16}, Supplemental Table 2), with this difference being driven primarily by the head/neck (Figure 1A, p-value: 3.7×10^{-7}) and trunk (Figure 1B, p-value: 2.0×10^{-6}) anatomical locations. After correcting for multiple tests, we did not observe a significantly different age-by-sex interaction with the distribution of upper extremity (Figure 1C, p-value: 0.02) and lower extremity (Figure 1D, p-value: 0.56) anatomical locations. Overall, PGs on the head/neck and trunk are more common in males less than 20 years old and in females 20-50 years of age.

Investigating for duality bias among upper extremity and truncal PGs

Given that most traumatic injuries occur to the dominant limb, we hypothesized that if trauma was a major cause of PGs then we should observe a bias in the left-right laterality distribution among PGs of the upper extremity. However, we did not observe any statistically significant differences between the frequency of left versus right laterality among the upper extremity PGs (p-value 0.86) including in sub-anatomical regions (Table 2) or when only including individuals old enough to demonstrate consistent handedness[14] (Supplemental Table 3). We similarly did not observe evidence for anterior-posterior bias among the truncal PGs for which this information was available (130 anterior verses 103 posterior, p-value: 0.08).

Investigating for other PG-associations within our dataset

We investigated other associations reported in the literature. We identified 10 non-recurrent PGs from 9 pregnant females, representing 2.8% of the 321 adult females under age 65 in our dataset. We identified 13 non-recurrent PGs arising from, or in the field of, a vascular malformation in 9 individuals out of 987 (0.09%) individuals included in our dataset. We observed multiple, non-recurrent PGs among 17 of the 987 (1.7%) individuals in our dataset, including 6 out of the 9 individuals with vascular malformations and 1 pregnant female.

Discussion:

Here we present the largest dataset of pathologically diagnosed PGs to date, which is more than double the largest previously reported.[9] In addition to the pathological confirmation, a strength of this study is the inclusion of large numbers of both pediatric and adult cases. This enabled us to demonstrate an anatomical region-specific age-by-sex interaction in the incidence of PGs on the head/neck and trunk. We also replicated prior findings of female bias in lower extremity PGs, but did not observe an age-by-sex interaction, arguing against the etiological hypothesis of trauma.[8] The absence of upper extremity left-right laterality bias in PG incidence similarly suggests that trauma may not be a major etiological factor, though this remains to be replicated in future studies. Another future line of inquiry is the role of hormones in cutaneous PGs given the established association between mucosal PGs and pregnancy as well our findings of increased risk for cutaneous lesions in females between 20-50 years of age. Overall, sex differences in the anatomical distribution patterns of PGs are reminiscent of that observed for melanomas and thus may also reflect differences in sunlight exposure by anatomical region. This is compatible with recent studies identifying somatic variation within PG lesions[11,12], especially since the anatomical context of such variation is known to impact their functional consequences.[15] Interestingly, we observed several individuals with multiple PGs, a majority of whom did not have an associated vascular malformation, suggesting that other intrinsic factors may increase risk of developing PGs. These remain to be elucidated in future work.

A major limitation of this study is the retrospective nature. Potential associations such as pregnancy status are not always included in the documented history and thus may be undercounted. Similarly, inclusion in our study was predicated on being able to access care, which varies based on age, sex, and socioeconomic factors. Finally, we excluded many mucosal and conjunctival lesions. Some of these may have been cutaneous – for example, lip

or eyelid lesions – but were conservatively excluded unless a cutaneous origin was specified. Future studies contrasting cutaneous and non-cutaneous PGs, with a focus on somatic variants and hormonal influences, may help determine if these are indeed the same entity.

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Concept and design: Dube and Coughlin.

Acquisition, analysis, or interpretation of data: Dube and Coughlin

Drafting of the manuscript: Dube and Coughlin.

Critical review of the manuscript for important intellectual content: Dube, Corliss, Bowling, Heusel, and Coughlin

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Data Sharing Statement: to protect patient privacy, individual-level data will not be publicly available.

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Tables

Table 1. Demographic and Clinical Characteristics Based on Age at First Pyogenic Granuloma

	Pediatric (Age <18) (n = 376)	Adult (n = 611)
Female	122 (32.4)	364 (59.6)
Male	254 (67.6)	247 (40.4)
Pregnant	0 (0)	9 (1.5)
Multiple	7 (1.9)	10 (1.6)
Vascular Malformation*	6 (1.6)	3 (0.5)

* We identified 13 non-recurrent PGs arising from, or in the field of, a vascular malformation in 9 individuals out of 987 (0.09%) individuals included in our dataset

Table 2. Left-Right Laterality of Upper Extremity Pyogenic Granulomas

Upper Extremity Sub-Anatomical Location		Laterality			Exact Binomial P-value
		Left	Right	Unknown	
Finger, Thumb, Fingernails		59	63	1	0.79
	Digit 1	*20*	*9*	*0*	0.06
	Digit 2	*14*	*21*	*0*	0.31
	Digit 3	*7*	*13*	*0*	0.26
	Digit 4	*6*	*13*	*1*	0.16
	Digit 5	*12*	*7*	*0*	0.36
Forearm, Wrist		16	15	0	1
Hand Palmar		13	24	0	0.10
Upper Limb, Shoulder, Arm		45	35	0	0.31
Overall		133	137	1	0.86

Figures

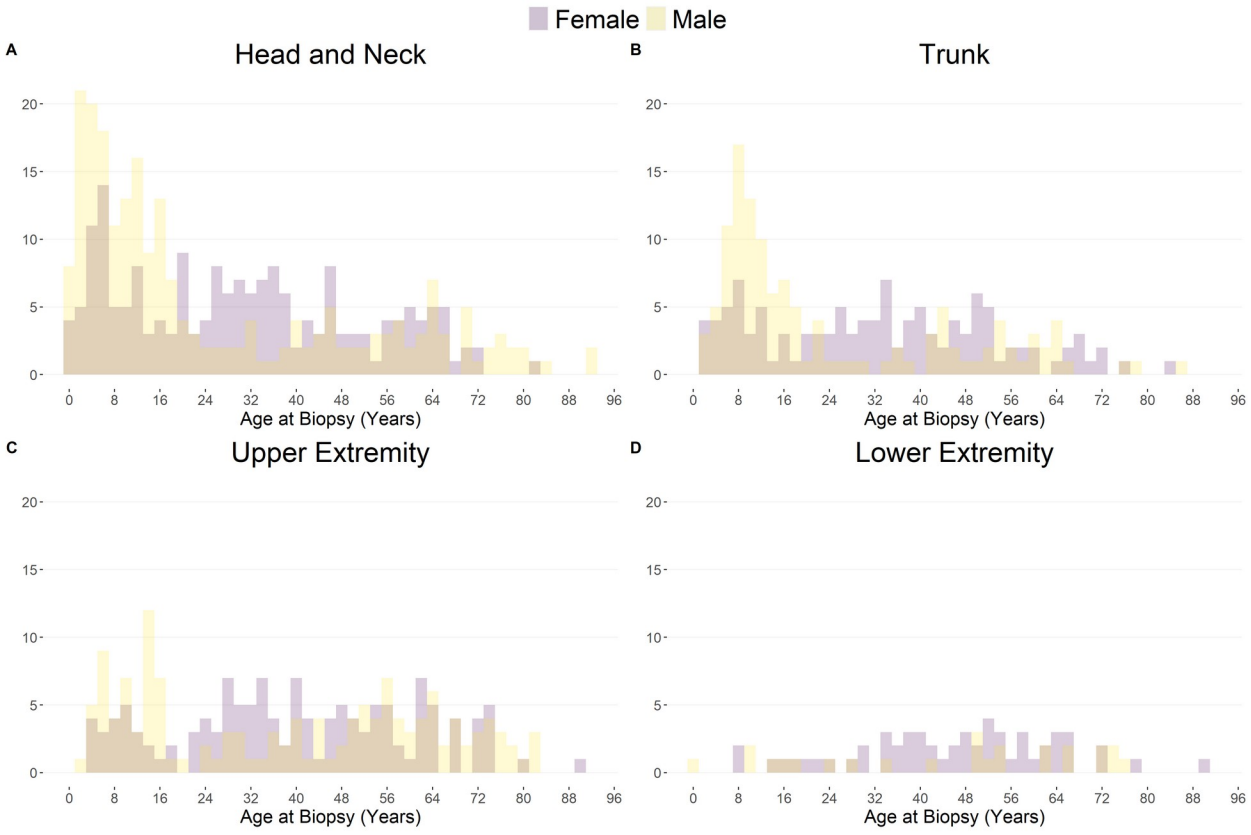

Figure 1. Different Distributions of Pyogenic Granuloma Incidence by Age, Sex, and Anatomical Location