Cherry angioma: A case–control study

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Abstract:

BACKGROUND: Cherry angiomas (CAs) are very common asymptomatic vascular skin lesions. There are only a few studies on CAs in the literature and those assessing risk factors of CAs are scarce. The aim of our study was to determine risk factors for the development of CAs.

MATERIALS AND METHODS: A case–control study was conducted at a tertiary care center in Riyadh, Saudi Arabia. Patients underwent a full-body examination for CAs. Demographics and other data including medical history and medications were extracted from electronic medical records.

RESULTS: A total of three hundred patients were enrolled: one hundred cases with at least five CAs and two hundred controls without CAs. Bivariate analysis identified benign prostatic hyperplasia (odds ratio [OR]: = 2.591), malignancy (OR = 2.567), tamsulosin (OR = 3.171), and clopidogrel (OR = 0.321) as statistically significant associations. After multivariate logistic regression analysis, only tamsulosin (OR = 3.475, $P = 0.009$) and clopidogrel (OR = 0.281, $P = 0.028$) were found to be independent risk factors for CAs. Malignancies tended to be more associated with CAs, but this did not reach statistical significance ($P = 0.07$).

CONCLUSION: Tamsulosin is a possible risk factor for the development of CAs. Clopidogrel seems to have a protective role preventing the development of CAs.

Keywords:

Campbell de Morgan spots, cherry angioma, cherry hemangioma, senile hemangioma

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Introduction

Cherry angiomas (CAs) or "Campbell de Morgan spots" are one of the most common benign cutaneous vascular lesions. They present as asymptomatic, small, bright-red papules usually on the trunk and extremities of older individuals.[1] The frequency of CAs increases with age, but have no reported clinical consequences.[2] The incidence of CAs was 49.5% in males, who seem to be more commonly affected than females.[3] The treatment of CAs is cosmetic because they are benign and asymptomatic.[1]

The pathogenesis of CAs is not entirely known. Reduced expression of miR-424 in CAs was found to be associated with

abnormal angiogenesis through MEK1 or cyclin E1.[4] Human herpesvirus 8 has a possible role in eruptive CAs.[5] Some somatic genetic mutations have been identified in CAs.[6]

Risk factors associated with the development of multiple CAs could include age, chronic immunosuppression, chronic graft-versus-host disease, and malignancy.[7,8] Some studies suggest an association between CAs and the exposure to certain chemicals and drugs such as cyclosporine,[9] sulfur mustard,[10] nitrogen mustard,[11] and bromides.[12]

Studies on risk factors associated with CAs are few and limited mainly to case reports and uncontrolled studies. Controlled studies, which explored a limited number of variables, are surprisingly very few for this common condition. This study was done

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to explore risk factors associated with the occurrence of CAs.

Materials and Methods

This was a case–control study conducted at King Abdulaziz Medical City, one of the largest tertiary care centers in Riyadh, Saudi Arabia. Ethical approval was obtained from the Institutional Review Board of King Abdullah International Medical Research Center and informed written consent was obtained from all participants.

Cases were defined as patients with five or more CAs. Controls were age- and gender-matched patients who did not have any CAs. Only Saudi patients aged ≥18 years and admitted to the hospital were included in the study. Patients who refused a full body examination, or had received previous treatment for CAs, or had 1–4 CAs were excluded from the study.

The target case-to-control ratio was 1:2. The sample size was estimated as hundred cases and two hundred controls using OpenEpi sample size calculator. The calculation was based on an estimated 30%–40% exposure to the risk factor in the control group, to detect an odds ratio (OR) of 2.0 or more at the 95% confidence level and power of 80%. A nonprobability consecutive sampling was used to select the cases, while the selection of controls was based on matching for age and gender.

Full-body skin examination was performed on all patients. Variables consisted of demographics, Fitzpatrick skin phototype, and region of residence. Furthermore, the duration of CA, body site, and diameter were documented. Data regarding family history, medical conditions, malignancies, and environmental triggers were collected. Details of current medications were gathered from the electronic medical record.

Statistical analysis was done using Statistical package for the Social Sciences (SPSS) version 24 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages and were compared using the Chi-square test. Numerical variables were reported as means with standard deviation and were compared by Student's *t*-test. Skewed numerical data were presented as median and inter-quartile range. Step-wise multivariate logistic regression analysis was performed to determine any associated risk factors, if any, for the development of CAs. Variables entered in the model were those with $P < 0.2$ between cases and controls in the bivariate analysis. The results of regression analysis were presented as OR with 95% confidence interval. For all the statistical tests, $P < 0.05$ was considered statistically significant.

Results

A total of hundred cases and two hundred controls were enrolled in the study. The most common site of CAs was the trunk (mainly the chest) followed by the proximal extremities, head and neck, distal extremities, hands, and feet [Figure 1]. Similarly, the trunk had the highest number and CAs with the largest diameter [Table 1].

Patient characteristics are summarized in Table 2. No statistically significant difference was found between cases and controls with regard to age and gender. Similarly, no difference was found in body mass index, region of residence, job, and history of smoking. A family history of CA was positive in 12% of cases. The median duration of CAs was 6 years (interquartile range 3–20).

Bivariate analysis identified benign prostatic hyperplasia (OR = 2.591), malignancy (OR = 2.567), tamsulosin (OR = 3.171), and clopidogrel (OR = 0.321) as statistically significant associations [Table 3]. After multivariate logistic regression analysis, only tamsulosin and clopidogrel were found to be independent risk factors for CAs [Table 4]. Patients on tamsulosin were more likely to have CAs (OR = 3.475, $P = 0.009$), while those on

Table 1: Characteristics of cherry angiomas based on body site (*n*=100)

Body site	Number of lesions Mean±SD	Smallest diameter (mm) Mean±SD	Largest diameter (mm) Mean±SD
Head and neck	1.86 (1.21)	0.6 (0.3)	1.8 (1.1)
Chest and axillae	3.61 (2.67)	0.7 (0.5)	1.9 (1.3)
Abdomen	3 (2.0)	1 (0.3)	2.3 (2.1)
Back	3.73 (2.87)	0.74 (0.56)	1.9 (1.3)
Arms	3 (2.0)	0.6 (0.3)	1.3 (0.8)
Forearms	2 (1.0)	0.8 (0.6)	1.5 (0.8)
Hands	1 (0)	0.9 (0.7)	0.9 (0.7)
Thighs and buttocks	2.29 (1.29)	0.7 (0.3)	2 (1.0)
Legs	2 (1.0)	0.7 (0.4)	1 (0.5)
Feet*	2 (0)	1 (0)	1 (0)

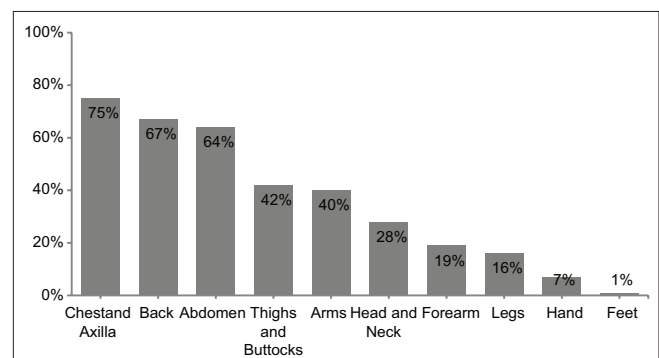*Only one patient had cherry angioma on the foot. SD=Standard deviation

Figure 1: Distribution of cherry angiomas based on the body site (*n* = 100)

Table 2: Bivariate analysis of patient characteristics

Characteristic	Control (*n*=200)		Cases (*n*=100)		*P*-Value
	n	**Mean±SD**	*n*	**Mean±SD**	
Age (years)	200	54.0±19.0	100	57.0±19.0	0.155
BMI	200	28.89±8.98	100	28.26±8.10	0.540
Characteristics	**Cases (*n*=100)**		**Controls (*n*=200)**		**_P_-Value**
	N (%)		**N (%)**		
Gender					
Male	100 (50.0)		51 (51.0)		0.870
Female	100 (50.0)		49 (49.0)		
Region of residence					
Central	158 (79.0)		82 (82.0)		0.949
North	12 (6.0)		6 (6.0)		
South	8 (4.0)		4 (4.0)		
East	12 (6.0)		4 (4.0)		
West	10 (5.0)		4 (4.0)		
Job					
Physician	0 (0)		1 (1.0)		0.330
Teacher	4 (2.0)		5 (5.0)		
Military	20 (10.0)		7 (7.0)		
Homemaker	88 (44.0)		43 (43.0)		
Retired	58 (29.0)		35 (35.0)		
Governmental	4 (2.0)		3 (3.0)		
Student	9 (4.5)		3 (3.0)		
None	5 (2.5)		1 (1.0)		
Other	12 (6.0)		2 (2.0)		
Smoker					
No	176 (88.0)		92 (92.0)		0.290
Yes	24 (12.0)		8 (8.0)		
Family history*	-		12 (12.0)		
Duration of cherry angiomas in years*, median (IQR)	-		6 (3-20)		

*Cases only. BMI=Body mass index, SD=Standard deviation, IQR=Interquartile range

clopidogrel seem to be less likely to have CAs (OR = 0.281, *P* = 0.028). Malignancy tended to have more association with CAs, but this was not statistically significant (*P* = 0.07).

Discussion

Studies on CAs are generally limited. Trunk was the most common site affected with CAs in our cases, which is in agreement with the literature and clinical observation.[1] The pathogenesis of CAs is still poorly understood. Genetic factors could play a role in the development of CAs. Family history of CAs was found in 12% of our cases. Somatic mutations in GNAQ and GNA11 genes were recently identified in CAs.[6] These genes are also known to be involved in the pathogenesis of other cutaneous vascular conditions such as capillary malformations.

Controlled studies on the risk factors of CAs are scarce. Borghi *et al*. assessed the risk factors of eruptive CAs in a total of 1032 patients.[13] Those with eruptive CAs had ≥30 CAs. The comparative group had either no or <30 CAs. Age, immunosuppressive therapy, and malignancy were identified as independent risk factors for eruptive CAs. Malignancy in our study had a

tendency of having statistically significant association with CAs., The number of CAs was significantly more on the skin of the affected breast in patients with unilateral breast cancer.[14] Serum lipids were shown to be more elevated in patients with CAs in a case–control study.[15] The lipid profile was not assessed in our study.

Tamsulosin and clopidogrel were identified in our study as independently significant associations with CAs. To the best of our knowledge, this association has not been previously reported. We found that patients on tamsulosin were more likely to have CAs. Tamsulosin is a selective alpha1A and alpha1D-adrenergic receptor blocker that is used in the treatment of BPH.[16] Alpha-1 adrenergic receptors are mainly found in the prostate and bladder. Tamsulosin works by relaxing smooth muscles in the prostate and bladder and therefore, improves urinary symptoms in patients with BPH. Although tamsulosin primarily works on the lower urinary tract, it has been shown to have some effect on the blood vessels, leading to vasodilation.[17] This might explain the association between tamsulosin and CAs found in our study.

Table 3: Bivariate analysis: Factors associated with cherry angioma

	Controls (*n*=200) N (%)	Cases (*n*=100) N (%)	Crude OR	*P* -Value	aOR	*P* -Value	95% CI for aOR
Diabetes	86 (43.0)	47 (47.0)	1.176	0.511	0.925	0.806	0.496-1.726
Hypertension	94 (47)	55 (55.0)	1.378	0.192	1.388	0.312	0.734-2.625
Dyslipidemia	36 (18.0)	18 (18.0)	1.000	1.0	0.980	0.956	0.476-2.018
Coronary artery disease	16 (8.0)	8 (8.0)	1.000	1.0	0.793	0.674	0.270-2.332
Stroke	13 (6.5)	8 (8.0)	1.251	0.632	1.544	0.413	0.546-4.367
Rheumatoid arthritis	3 (1.5)	4 (4.0)	2.736	0.193	4.802	0.133	0.620-37.192
Asthma	13 (6.5)	5 (5.0)	0.757	0.607	0.572	0.382	0.163-2.002
Hypothyroidism	12 (6.0)	7 (7.0)	1.179	0.737	1.020	0.970	0.362-2.878
Hyperthyroidism	1 (0.5)	2 (2.0)	4.061	0.255	3.791	0.349	0.233-61.716
Chronic kidney disease	14 (7.0)	8 (8.0)	1.155	0.754	0.929	0.890	0.328-2.635
Cirrhosis	2 (1.0)	2 (2.0)	2.020	0.485	1.174	0.896	0.107-12.916
Benign prostatic hyperplasia	10 (5.0)	12 (12.0)	2.591	0.033	0.333	0.402	0.025-4.363
Previous or current malignancies	11 (5.5)	13 (13.0)	2.567	0.028	3.419	0.019	1.219-9.590
Previous chemotherapy	4 (2.0)	1 (1.0)	0.495	0.632	0.192	0.234	0.013-2.905
Previous immunosuppression	16 (8.0)	10 (10.0)	1.278	0.562	0.509	0.385	0.111-2.338
Previous organ transplant	4 (2.0)	5 (5.0)	2.579	0.165	5.357	0.110	0.684-41.939
Tamsulosin	9 (4.5)	13 (13.0)	3.171	0.011	9.613	0.086	0.729-126.809
Clopidogrel	23 (11.5)	4 (4.0)	0.321	0.041	0.244	0.021	0.074-0.812
Fitzpatrick skin type							
II and III	78 (39.0)	36 (36.0)	1.038	0.848	0.975	0.907	0.640-1.487
IV	111 (55.5)	60 (60.0)					
V and VI	11 (5.5)	4 (4.0)					
Pregnancy	14 (7.0)	3 (3.0)	0.411	0.170	0.442	0.240	0.114-1.723

CI=Confidence interval, OR=Odds ratio, aOR=Adjusted OR

Table 4: Multivariate logistic regression analysis: Factors associated with cherry angioma

	SE	OR	95% CI		*P* -Value
			Lower	Upper	
Previous or current malignancies	0.443	2.232	0.936	5.323	0.07
Tamsulosin	0.480	3.475	1.357	8.899	0.009
Clopidogrel	0.576	0.281	0.091	0.870	0.028
Constant	0.139	0.462			0.000

CI=Confidence interval, OR=Odds ratio, SE=Standard error

Our findings indicate that clopidogrel seems to have a protective role against CA formation. Clopidogrel is an antiplatelet that prevents platelet aggregation through the inhibition of adenosine diphosphate.[18] It is used for the prevention of coronary artery disease and stroke. Clopidogrel has been recently shown to have an anti-angiogenic effect.[19] Both the number of microvessels and expression of vascular endothelial growth factor were significantly reduced by clopidogrel.

Our study has some limitations. *Post hoc* analysis showed the power of study as 60.45%, which could be due to the small sample size. The study was done at one center and therefore, its findings cannot be generalized. Another limitation is that our study design depended to some extent on patient recall of information. A better design would have been a prospective cohort but that would have been time-consuming and expensive.

Conclusion

We identified tamsulosin as a possible risk factor for the development of CAs. However, clopidogrel seems to have a protective role, possibly preventing the development of CAs. Future well-designed studies are needed to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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