Evaluation of hepatic hemangioma in patients with cherry angioma

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Background
Cutaneous cherry angioma (CA) and hepatic hemangioma (HH) are the most common types of acquired vascular proliferations that develop during aging process with unknown etiologies. The role of angiogenic and hormonal factors has been proposed in inducing these vascular lesions.
Objective
To compare the frequency of HH in persons with and without CA.
Patients and methods
This case–control study consisted of 160 patients including 80 patients with CA and 80 patients without CA. Sex, age, history of contraceptive pills intake, number of pregnancies, BMI, number of the CA lesions, and liver ultrasound findings were collected for all participants.
Results
HH was detected significantly more frequently in the participants with CA ($P<0.001$), but there was no significant association between number of CA and number of HH ($P=0.837$). History of oral contraceptive pill intake was significantly more frequent in women with HH, but this history was not significantly more frequent in women with CA compared with control group.
Conclusion
HH was significantly more frequent in participants with CA. Thus, CA may be a cutaneous marker for HH.

Keywords:
angiogenic factors, cherry angioma, hepatic hemangioma

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Introduction

Cherry angioma (CA) is the most common type of acquired benign vascular proliferation which presents as asymptomatic red papule on the skin [1]. It has a polygenic mode of inheritance and could be seen in 50–75% of people aged older than 75 years [1–3]. Different causes have been proposed including aging, pregnancy, hyperprolactinemia, human herpesvirus 8 infection, sulfur mustard exposure, underlying malignancy, immunosuppression, some chemokines, and chemical agents [3–8]. People are usually concerned about the increasing number of CA, association with cancers and visceral involvement [1,5].

On the contrary, hepatic hemangioma (HH) is also the most common type of benign vascular tumor in the liver, which has been detected in more than 7% of patients. Incidence of these lesions has been estimated to be 0.4–20% [9,10]. HH is usually single, but multiple lesions and huge tumors are probable [10,11]. HH is two to five times more frequent in women compared with men, mainly between 30 and 50 years old. HH might grow with estrogenic pills and pregnancy. These lesions are mainly asymptomatic and could be detected incidentally during imaging for other reasons. However, larger tumors may result in abdominal pain, compressive effects, or even internal hemorrhage [9–12].

Association of infantile hemangioma with HH has been previously described [1,12–14], but to the best of our knowledge, association of CA with HH has not been evaluated in prior reports.

This research was performed to compare the frequency of HH in persons with and without CA.

Patients and methods

This study was designed as a case–control study that was performed at a tertiary referral hospital from June 2018 to February 2019.

This study included 160 volunteers, 80 persons with CA and 80 healthy participants without CA, consecutively selected from our patients who visited the hospital for esthetic reasons, including nevi, lentigo, and melasma. Both groups were frequency-matched in age groups and sexes. Written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki 2013 principles. This research project was approved by Ethics committee of Guilan University of Medical Sciences in 2018 (Approval Code: IR.GUMS.REC.1397.193).

All patients aged more than or equal to 30 years who gave consent for body examination and doing imaging evaluation were included. Owing to hair density on scalp region and some cultural limitations, scalp and genital area were examined only in participants who mentioned any skin lesions in these areas.

Some cases were excluded as follows: no consent for physical examination or ultrasound, pregnant women, and previous known liver disease through past medical history.

CA was diagnosed based on the physical examination performed by an individual dermatologist without skin biopsy; however, suspected lesions were evaluated using dermoscopy for more accurate diagnosis.

Abdominal ultrasound is the most common and cheapest method for detection of HH, so we selected this method for initial screening. It has 97% sensitivity and 60% specificity for diagnosis of HH, but suspected lesions should be evaluated with more accurate methods such as MRI or computed tomography with intravenous contrast material [12]. We only included suspected HH lesions on ultrasound if these cases had been followed up and confirmed with more accurate methods.

Ultrasonic imaging was done by a real-time Toshiba Aplio 300 ultrasound machine made in Japan with transducer of 5–7 Hz and B mode method. Upper abdominal ultrasound evaluation was done after 6-h fasting in supine and right anterior oblique position by an experienced radiologist who was not informed about which participants had CA. Typical HH has been defined as round hyper-echoic lesion with posterior enhancement but it may be present as an irregular or hypo-echoic lesion as well especially with fatty liver disease. HH lesions mainly have less than 4-cm diameter, and huge lesions have been defined as lesions larger than 4 cm [12].

Age, sex, BMI, number of the cherry lesions, history of oral contraceptive pills (OCP) intake, and number of previous pregnancies in women were recorded in the first visit. History of OCP intake was considered positive in this research if our patient was on estrogenic pills for at least 6 months continuously.

Abdominal ultrasound findings of the liver, including presence or absence of HH, size and number of these lesions, and presence or absence of fatty liver disease, were collected for both groups.

Statistical analysis

Quantitative variables with abnormal distribution were described using median and interquartile range and qualitative data were reported by number and percentage. For the comparison of frequency of qualitative data, the χ^2 test or Fisher's exact test was used, and for the comparison of continuous variables with abnormal distribution, Mann–Whitney test was applied in both groups. All statistical tests were performed using SPSS Software 18 (SPSS Inc., Chicago, Illinois, USA). All P values were two sided, and significance level was set at P value less than 0.05.

Results

A total of 80 cases with CA and 80 patients without CA were enrolled in this study. Baseline characteristics of the participants are shown in Table 1, which were not significantly different in the two groups.

HH was detected significantly more frequent in the group with CA compared with group without CA ($P<0.001$), but the frequency of fatty liver disease was not different between the two groups ($P=0.191$) (Table 2). Moreover, there was no significant association between the number of CA and the number of HH in cases with CA ($P=0.837$) (Table 3). History of OCP intake was significantly more frequent in women with HH compared with women without HH ($P=0.045$), but this history was not significantly different in women with and without CA ($P=0.157$).

There were no significant differences in BMI status of patients with CA and without CA ($P=0.063$) and BMI status of persons with HH and without HH ($P=0.861$) (Table 1).

We found no significant difference between number of pregnancies in women with and without HH ($P=0.844$), as well as in women with and without

Table 1 Characteristics of participants with and without cherry angioma

Variables	Without CA (*N*=80) Median (IQR)/*n* (%)	With CA (*N*=80) Median (IQR)/*n* (%)	Total (*N*=160) Median (IQR)/*n* (%)	*P* value
Age (years)	40.5 (32–50)	39.5 (32–47.75)	40 (32–49)	0.646*
Age groups (years)				
30–34	30 (37.5)	29 (36.3)	59 (36.9)	0.709**
35–39	7 (8.8)	11 (13.8)	18 (11.3)	
40–44	14 (17.5)	18 (22.5)	32 (20)	
45–49	7 (8.8)	6 (7.5)	13 (8.1)	
50–54	11 (13.8)	8 (10)	19 (11.9)	
55–59	4 (5)	5 (6.3)	9 (5.6)	
60–64	5 (6.3)	1 (1.3)	6 (3.8)	
65–69	2 (2.5)	2 (2.5)	4 (2.5)	
Sex				
Male	38 (47.5)	39 (48.8)	77 (48.1)	0.874***
Female	42 (52.5)	41 (51.2)	83 (51.9)	
BMI (kg/m^2)	26.5 (24–30)	26 (23–27)	26 (24–28.75)	0.063*
Categorized BMI (kg/m^2)				
Under-weight (≤18.5)	0	1 (1.3)	1 (0.6)	0.237**
Normal (18.6–24.9)	22 (27.5)	29 (36.3)	51 (31.9)	
Over-weight and obesity (≥25)	58 (72.5)	50 (62.5)	108 (67.5)	

IQR, interquartile range. *Mann–Whitney test. **Fisher's exact test. ***χ^2 test.

Table 2 Frequency of hepatic hemangioma and fatty liver disease in patients with and without cherry angioma

Variables	Group without CA (*N*=80) [*n* (%)]	Group with CA (*N*=80) [*n* (%)]	Total (*N*=160) [*n* (%)]	*P* value*
HH				
No	75 (93.8)	55 (68.8)	130 (81.2)	<0.001
Yes	5 (6.2)	25 (31.2)	30 (18.8)	
Fatty liver disease				
No	46 (57.5)	54 (67.5)	100 (62.5)	0.191
Yes	34 (42.5)	26 (32.5)	60 (37.5)	

CA, cherry angioma; HH, hepatic hemangioma. *χ^2 test.

Table 3 Assessment of association of number of cherry angioma with number of hepatic hemangioma in participants with cherry angioma

Number of CA	Number of HH [*n* (%)]			*P* value*
	≤5 lesions (*N*=12)	>5 lesions (*N*=68)	Total (*N*=80)	
Without lesion	8 (66.7)	47 (69.1)	55 (68.8)	0.837
1 lesion	4 (33.3)	18 (26.5)	22 (27.5)	
2 lesions	0	3 (4.4)	3 (3.7)	

CA, cherry angioma; HH, hepatic hemangioma. *Fisher's exact test.

CA (*P*=0.580) (Table 4). We had only two cases of HH lesions with a diameter more than 4 cm in patients with CA, so the association of HH diameter with CA count was not evaluated.

Discussion

Hemangiomatous lesions are common benign vascular tumors that develop owing to endothelial cell proliferation. Our results showed a significant association between CA and liver hemangioma. It may be explained by common pathogenic pathways such as angiogenic mediators, viral infections, hormonal factors, and metabolic state [13–18].

Disturbances in some chemokines such as vascular endothelial growth factor, interleukin-1, interleukin-17, and mast cell mediators have also been incriminated in the development of angiomatous lesions [15–18]. Role of viral infections such as polyomavirus and human herpesvirus 8 in endothelial cell proliferation has been reported [7,8,18], but we could not find an individual viral etiology for development of both CA and HH lesions in prior reports.

Vascular tumors and malformations have receptors for sex hormones, so the frequency and diameter of these lesions may increase with hyperestrogenic status including pregnancy, OCP intake, and obesity [16].

Table 4 Association of number of pregnancies in women of both groups (men were not included in this analysis)

Number of pregnancies	Without cherry angioma (*N*=42) [*n* (%)]	With cherry angioma (*N*=41) [*n* (%)]	*P* value*	Without hepatic hemangioma (*N*=65) [*n* (%)]	With hepatic hemangioma (*N*=18) [*n* (%)]	*P* value*
0	18 (42.9)	14 (34.1)	0.580	24 (36.9)	8 (44.4)	0.844
1	6 (14.3)	9 (22)		12 (18.5)	3 (16.7)	
≥2	18 (42.9)	18 (43.9)		29 (44.6)	7 (38.9)	

*χ^2 test.

Although we found a significant relation between HH and OCP, but no significant difference was detected between number of previous pregnancies and HH. Moreover, there was no association between BMI status with HH and CA. However, prior reports have shown that higher BMI and obesity could result in hyperestrogenic and hyperinsulinemic status and increased level of vascular endothelial growth factor, which result in vascular proliferation [19]. The role of sex hormones in development and increasing of CA and HH lesions has been discussed in the literatures, but there was no significant difference in frequency of CA lesions in both sexes in previous reports [2,19–22]. Estrogen levels may affect benign liver tumors without a clear mechanism. Increased exogenous estrogens or their receptors could result in benign tumor growth. HH may be affected by female hormones, but in rare cases, significant enlargements have occurred. Therefore, liver ultrasound follow-up in women with HH using estrogenic pills has been recommended [21–23].

According to ultrasound findings in the present research, frequency of fatty liver disease as an additional finding had no significant differences in patients with and without CA. However, Navabi *et al.* [24] showed CA could be a cutaneous marker of nonalcoholic fatty liver disease, and Darjani *et al.* [25] reported that hypercholesterolemia has been more common in patients with CA. These different findings in our study may be due to excluding of patients with a known previous liver disease to decrease confounding factors in ultrasonic evaluation.

Our limitations in this research were as follows: relatively small number of patients included in the study, which may not be fully representative of the general population; family history of CA or HH was not evaluated; scalp and genital examination was not done in all participants, which may result in some selection bias; and some suspected and not finally confirmed HH lesions, as well as known cases of previous liver diseases, were excluded.

More studies with a larger sample size and more accurate diagnostic imaging methods in the future are recommended. Moreover, evaluation of angiogenic factors and viral markers may be helpful to elucidate the pathogenesis of these vascular lesions in the future.

Conclusion

The exact causes of these acquired vascular tumors are unknown, but there is an association between CA and HH lesions, and CA lesions may be a cutaneous marker for HH.

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Conflicts of interest

There are no conflicts of interest.

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