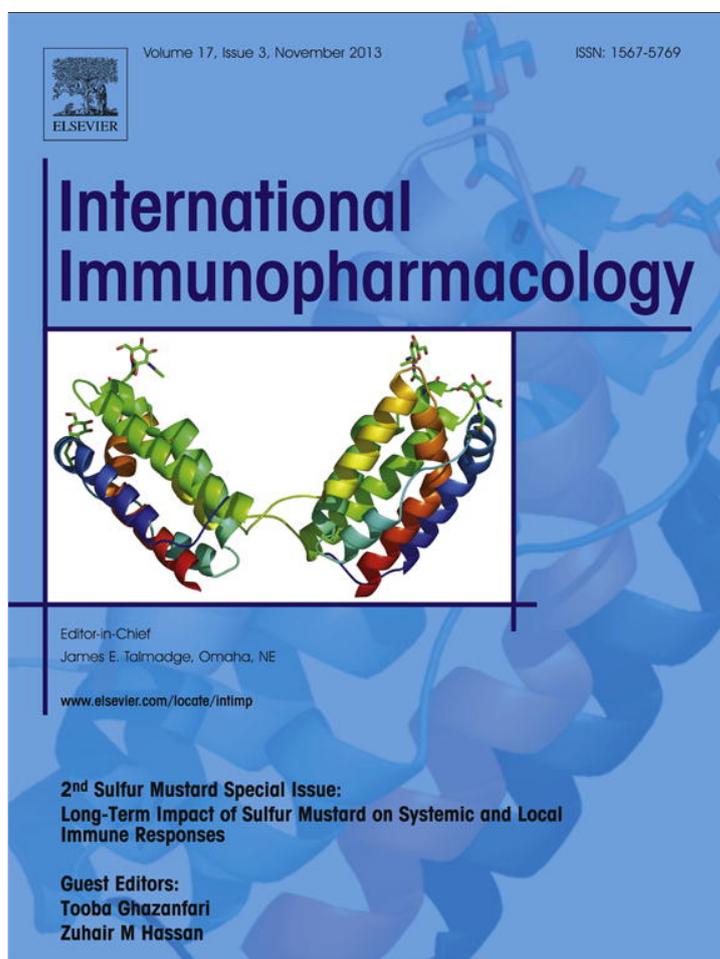


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Association of chemokines and prolactin with cherry angioma in a sulfur mustard exposed population – Sardasht-Iran cohort study

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ABSTRACT

Exposure to SM leads to short and long term adverse effects on various organs including the skin. Cherry angioma is one of the late skin disorders in SM exposed individuals. The pathogenesis of abnormal angiogenesis in cherry angioma is not well known but the role of inflammatory mediators and certain hormones, including prolactin, in the regulation of angiogenesis in other diseases has been reported. Alterations in serum levels of prolactin and chemokines in SM-exposed victims and the impact on angiogenesis are indications of the role in SM-induced cherry angioma. As part of the SICS, this study seeks to evaluate the possible association of prolactin and chemokines in the emergence of SM-induced cherry angioma. The serum concentrations of prolactin, IL-8/CXCL8, RANTES/CCL5, MCP-1/CCL2, and fractalkine/CX3CL1 were titrated using sandwich ELISA technique. There was a significant difference in the level of prolactin between the exposed subgroups (with cherry angioma $n = 72$; mean: 10.13) and without cherry angioma ($n = 268$; mean: 13.13, $p < 0.0096$). Median of the serum levels of CCL2 in the exposed patients with cherry angioma was significantly higher than exposed patients without cherry angioma (median = 203.5 pg/ml and median = 187.10 pg/ml respectively, $p = 0.035$).

There was no significant difference in the serum levels of IL-8, RANTES and CX3CL1 between the exposed subgroups with cherry angioma and without cherry angioma. This finding serves as a basis for further research on the molecular mechanisms and pathways involved in the pathogenesis of cherry angioma and other related disorders.

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1. Introduction

Sulfur mustard (SM) is an alkylating agent with cytotoxic, mutagenic, and vesicating properties with not yet fully understood mechanism(s) [1]. Exposure to SM leads to short- and long-term adverse effects on multiple organs especially the skin, the eyes, the respiratory tracts and the immune system [2]. There have been several studies on cutaneous complications of SM exposure in Iranian SM victims. The acute skin lesions are erythema, edema, blisters, pigmentation disorders, bulla, and ulceration, while the late skin lesions are pigmentation disorders, dry skin, eczema, cherry angioma, atrophy,

urticaria and vitiligo [2–4]. It was concluded that SM exposure causes significant delayed skin reactions. Cherry angioma is one of the late skin lesions in SM exposed individuals [3,5]. Cherry angioma is also known to be associated with exposure to chemicals such as ethylene glycol monobutyl ether and bromides [6,7].

A record of 19.9% for cherry angioma prevalence was reported by Moin et al. in Sardasht-Iran cohort study (SICS) [3]. However various records in different groups of Iranian SM exposed individuals were reported [8]. Little is known about the pathogenesis of abnormal angiogenesis in cherry angioma [9]. Angiogenesis, the growth of new blood vessels from pre-existing vessels is highly restricted in healthy tissues in part by the control of naturally occurring anti-angiogenic factors that prevent new vessel growth [10]. The role of inflammatory mediators [11] and certain hormones, including prolactin in the regulation of angiogenesis in other diseases, has been described [12].

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It has been reported that the major form of prolactin (23 kDa) promotes the growth of new blood vessels, induces angiogenesis [12], and is proteolytically cleaved to form a 16 kDa prolactin which is a potent anti-angiogenic [13–15].

Furthermore, we have previously reported a reduction in most of the inflammatory mediators in an SM-exposed population [16,17]. The role of inflammatory mediators in angiogenesis has been demonstrated [18]. Chemokines are small secreted proteins that have been shown to play a critical role in the regulation of angiogenesis during several pathophysiological processes [11,19,20].

Although no relationship has been discerned between cherry angioma and prolactin or chemokines, but according to the impact of these factors in angiogenesis and the alterations of chemokines in SM-exposed victims, it might be an indicative of possible role in SM-induced cherry angioma. As part of the SICS, the purpose of current study is to explore possible association between prolactin and chemokines in the development of SM-induced cherry angioma.

2. Materials and methods

2.1. Study design and participants

Details of the study design and methodology of the SICS have been reported previously [1]. Briefly, 372 male volunteers from Sardasht with a history of SM exposed in June 1987 and 128 unexposed sex/age matched as control from the unexposed town of Rabat have been recruited. SICS was initiated in 2006 and the clinical evaluations and samples collection were done in June 2007. The experiments were completed during 6 months. In this study all SICS participants were included and divided into 4 groups: 1) SM exposed group with cherry angioma disorder, 2) SM exposed group with no cherry angioma disorder, 3) control group with cherry angioma and 4) the control group without cherry angioma disorder. Complete methodological details of the SICS as well as demographic information were reported previously in the original methodology paper [1].

2.2. Ethical considerations

The study was approved by the Ethical Committee of Board of Research Ethics of Janbazan Medical and Engineering Research Center (JMERC), the Board of Research of the Ministry of Health and Medical Education, and Shahed University. Volunteer who signed an informed consent was recruited.

2.3. Clinical evaluation

Every volunteer was physically examined by a dermatologist [3]. Cherry angioma was diagnosed by the dermatologist based on clinical examination and an appearance of the lesion and SM-exposed and control groups were divided into two subgroups based on the presence of cherry angioma disorder.

2.4. Serum preparation

Blood drawn into non-treated Vacutainer tubes (BD Biosciences) was used for serum preparation. After clotting, sera were isolated, labeled, aliquoted and kept at -80°C until use.

2.5. Cytokine measurement

Human IL-8/CXCL8, RANTES, MCP-1, and fractalkine DuoSet® ELISA Development Kits (R&D Systems) were used to measure serum cytokine levels. This assay employs the quantitative sandwich enzyme immunoassay technique. Prolactin was also assessed using

ELISA method. The ELISA reader and washer of Stat-Fax 2100 and Stat-Fax 2600 (USA) were respectively used.

2.6. Statistical analysis

The statistical comparison of prolactin and chemokines between the two groups was performed using the ANOVA Tukey post hoc and Mann–Whitney respectively.

Difference of $p \leq 0.05$ was considered to be statistically significant. The data are presented as mean (SD) and median (first and third quartiles). Analyses of the data were performed using SPSS software version 16.0 (Chicago, Illinois, USA).

3. Results

The number of patients with cherry angioma disorder was 72 (19.9%) in SM exposed group and 12 (9.4%) in the control group of SICS [3] which was significantly different ($p = 0.007$).

3.1. Serum levels of prolactin

The serum level of prolactin in SM-exposed group (12.56 ± 8.20 ng/ml) was significantly ($p \leq 0.001$) higher compared with that in unexposed control group (10.23 ± 7.87 ng/ml).

As shown in Table 1, a significant ($p < 0.0096$) difference in the level of prolactin is seen between the exposed subgroups with cherry angioma $n = 72$; mean: 10.13 and without cherry angioma $n = 268$; mean: 13.13). There is no significant difference between the level of prolactin in individuals with cherry angioma from SM exposed group and unexposed. A significant ($p < 0.012$) difference is seen between the SM exposed and the control group with no cherry angioma.

3.2. Serum levels of IL-8 (CXCL8)

As presented in Table 2, the median of the serum levels of IL-8 in the SM exposed participants with no cherry angioma disorder (12.337 pg/ml) is significantly ($p < 0.001$) lower than the matched non exposed control group (15.586 pg/ml). There were no significant differences between the other subgroups.

3.3. Serum levels of CX3L1 (fractalkine)

There was no significant difference in the serum level of fractalkine, neither between the study groups nor between the subgroups (Table 3).

3.4. Serum levels of RANTES

As it is shown in Table 4, the serum level of RANTES in the SM exposed group with no cherry angioma (872.10 pg/ml) is significantly ($p < 0.01$) lower than the matched control group (1268 pg/ml). The serum level of RANTES in the SM exposed group who had cherry angioma (899.65 pg/ml) is significantly lower than the control group who did not have cherry angioma (1268.50 pg/ml) ($p = 0.027$). There was no significant difference between the serum level of RANTES in the presence and absence of cherry angioma within each group.

3.5. Serum levels of CCL2/MCP-1

As it is shown in Table 5, the median of the serum level of CCL2 in the SM exposed subjects diagnosed with cherry angioma (median = 203.5 pg/ml) is significantly ($p < 0.000$) higher than the exposed participants with no cherry angioma (median = 187.10 pg/ml).

Median of the serum level of CCL2 in the control subgroup with cherry angioma (149.65 pg/ml) was significantly ($p = 0.029$) lower than that of the control subgroup without cherry angioma (174.30 pg/ml) (Table 5).

Table 1
Association of serum levels of prolactin in SM exposed and control groups with cherry angioma.

Cherry angioma	Prolactin ng/ml								p-value ²	p-value ³
	Control				Exposed					
	N	Mean	SD	p-value ¹	N	Mean	SD	p-value ¹		
No	110	10.62	8.26		268	13.13	8.92		0.035^a	
Yes	12	7.73	2.92	0.651	72	10.13	4.91	0.030^a	0.782	0.979

The serum levels of prolactin in volunteers who had (Yes) and who did not have (No) cherry angioma were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups. p-value¹: comparison of the serum level of prolactin between participants who had (Yes) or did not have (No) cherry angioma within each group (ANOVA Tukey post hoc). p-value²: comparison of exposed with corresponding control groups (ANOVA Tukey post hoc). p-value³: comparison between exposed group who had cherry angioma and control who did not have cherry angioma (ANOVA Tukey post hoc).

^a Bold data shows significant differences with p value <0.05.

Table 2
Association of serum level of IL-8 (CXCL8) in SM-exposed and control groups with cherry angioma.

Study groups	Cherry angioma (Diagnosis)	IL-8 (CXCL8)						p-value ¹	p-value ²	p-value ³
		N	Median	Q1	Q3	Mean	SD			
		Control	No	111	15.586	10.981	23.182			
	Yes	12	11.873	8.619	24.212	20.147	23.322		0.539	
Exposed	No	272	12.337	7.373	21.875	19.255	22.882	0.163		
	Yes	72	14.014	9.993	21.721	20.735	22.393			

The serum levels of IL-8 in volunteers who had (Yes) and who did not have (No) cherry angioma were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups. p-value¹: comparison of the serum level of IL-8 between participants who had (Yes) or did not have (No) cherry angioma within each group (ANOVA Tukey post hoc). p-value²: comparison of exposed with corresponding control groups (ANOVA Tukey post hoc). p-value³: comparison between exposed group who had cherry angioma and control who did not have cherry angioma (ANOVA Tukey post hoc).

^a Bold data shows significant differences with p value <0.05.

There was a statistically significant (p = 0.000) difference between the SM exposed and the controls with cherry angioma disorder (median = 203.5 pg/ml, median = 149.65 pg/ml respectively).

The serum level of CCL2 in the SM exposed group who had cherry angioma (203.50 pg/ml) is significantly higher than the control group who did not have cherry angioma (174.30 pg/ml) (p = 0.003).

There was no significant difference between the control and exposed group without cherry angioma.

4. Discussion

Exposure to SM leads to many delayed skin complications including cherry angioma. The incidence of cherry angioma was reported to be 19.9% in SM-exposed group of Sardasht 20 years after SM exposure in SICS [3]. The pathogenesis of abnormal angiogenesis in cherry angioma is not clearly understood. It has been reported that prolactin and chemokines are associated with angiogenesis in different models [11,14,15,18] and alterations in some factors involved in angiogenesis such as inflammatory cytokines have been reported in SM exposed individuals [17].

In this study the possible association between serum prolactin level and inflammatory cytokines with the presence of cherry angioma in SM-exposed patients was evaluated and compared with control groups.

SM-exposed participants and control subjects were subdivided into different groups based on the diagnosis of cherry angioma.

Prolactin hyper secretion, albeit mild appears to be more frequent in SM-exposed patients than the control group. A significant association was seen between the enhancement of the serum levels of prolactin and the absence of cherry angioma in the SM-exposed group.

No significant difference in the serum level of prolactin was seen in SM exposed participants with cherry angioma and the control group with no cherry angioma disorder, while there was a significant difference between the prolactin level in SM exposed without cherry angioma and normal unexposed group or between exposed with cherry angioma and exposed group with no cherry angioma. In other words elevated levels of prolactin in SM-exposed group are related to those exposed group without cherry angioma and SM-exposed participants with cherry angioma did not show this alteration.

The major form of prolactin found in the pituitary gland is 23 kDa variants of prolactin and is characterized in mammals including human. Prolactin is biologically active and might even act as antagonist of 23 kDa human PRL. For example, intact PRL is known to have angiogenic properties; whereas 16K-PRL inhibits angiogenesis *in vivo* and *in vitro*. Various studies have confirmed the anti-angiogenesis role of 16K cleaved form of PRL which is derived from systemic and milk 23K-PRL in ocular neovascularization [13–15].

Table 3
Association of serum level of fractalkine (CX3CL1) in SM exposed and control groups with cherry angioma.

Study groups	Cherry angioma (Diagnosis)	Fractalkine (CX3CL1)						p-value ¹	p-value ²	p-value ³
		N	Median	Q1	Q3	Mean	SD			
		Control	No	109	0.724	0.483	0.953			
	Yes	12	0.618	0.416	0.705	0.551	0.209		0.494	
Exposed	No	273	0.667	0.439	1.011	0.871	1.368	0.304		
	Yes	72	0.628	0.412	0.868	0.693	0.479			

The serum levels of fractalkine in volunteers who had (Yes) and who did not have (No) cherry angioma were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups. p-value¹: comparison of the serum level of fractalkine between participants who had (Yes) or did not have (No) cherry angioma within each group (ANOVA Tukey post hoc). p-value²: comparison of exposed with corresponding control groups (ANOVA Tukey post hoc). p-value³: comparison between exposed group who had cherry angioma and control who did not have cherry angioma (ANOVA Tukey post hoc).

Table 4
Association of serum level of RANTES (CCL5) in SM exposed and control groups with or without Cherry Angioma.

Study groups	Cherry angioma (Diagnosis)	RANTES (CCL5)						p-value ¹	p-value ²	p-value ³
		N	Median	Q1	Q3	Mean	SD			
Control	No	112	1268.50	792.15	1812.00	1360.06	817.45	0.532	0.001^a	0.027^a
	Yes	12	1643.00	749.50	2289.50	1632.45	1091.12			
Exposed	No	273	872.10	661.10	1320.00	1150.25	859.95	0.677		
	Yes	72	899.65	666.25	1409.00	1193.51	892.65			

The serum levels of RANTES in volunteers who had (Yes) and who did not have (No) cherry angioma were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups. p-value¹: comparison of the serum level of RANTES between participants who had (Yes) or did not have (No) cherry angioma within each group (ANOVA Tukey post hoc). p-value²: comparison of exposed with corresponding control groups (ANOVA Tukey post hoc). p-value³: comparison between exposed group who had cherry angioma and control who did not have cherry angioma (ANOVA Tukey post hoc).

^a Significant value.

In the present study 23K systemic prolactin was assessed but previous reports indicated that the same form of 23K PRL is cleaved into anti-angiogenic 16K PRL in local tissues [13–15], this cleavage might occur in the skin as well. The findings of decreased prolactin levels in SM exposed with cherry angioma led to the assumption that prolactin may play a protective role against SM-induced cherry angioma. To investigate the role of PRL in preventing SM-induced angiogenesis, it is necessary to evaluate the concentration of PRL variants such as the anti-angiogenic 16K-like PRL fragments in the lesions of SM exposed patients.

The immune system regulates angiogenesis in cancer with both pro- and anti-angiogenic activities [11,21]. Chemokines are a family of small heparin-binding proteins mostly known for their role in the regulation of inflammatory and angiogenic responses. Members of the chemokines family have been shown to play a critical role in the regulation of angiogenesis during several pathophysiologic processes such as tumor growth, wound healing, inflammatory diseases and ischemia [21,22]. Chemokines may exert the regulatory activity on angiogenesis either by recruiting the pro-angiogenic immune cells and endothelial progenitors to the neo-vascular niche or directly regulating the endothelial functions, downstream of the activation of chemokine G-protein coupled chemoattractant receptors (GPCR) [23,24].

In the present study, the serum levels of four chemokines including MCP-1/CCL2, RANTES/CCL5, IL-8/CXCL8, and fractalkine/CX3CL1 in the SM exposed and control groups with or without cherry angioma were compared.

There was no association between the serum levels of fractalkine and RANTES with SM-induced cherry angioma. The serum levels of fractalkine and RANTES in the SM-exposed participants with or without cherry angioma showed to be the same patterns seen in other SM exposed participants which were previously reported by the same team [17].

Previously we have reported that the serum level of IL-8 is decreased in the same group of SM-exposed participants compared with the control group [17], herein it is found that there is no significant alteration in the serum level of IL-8 in exposed participants with cherry angioma compared to the control group with no cherry angioma. In other words decreased level of IL-8 in SM-exposed group is related to the

exposed group without cherry angioma but SM-exposed participants with cherry angioma did not show this decrement. IL-8 is considered to be an angiogenic factor [25] which showed that an association between lack of cherry angioma and decrement of IL-8 probably represents the angiogenic effect of this cytokine.

Previously we have reported an increased serum level of MCP-1/CCL2 in the same group of SM-exposed participants compared with the control unexposed group [17]. The results of the present study showed a significant association between enhancement of the serum levels of MCP-1/CCL2 and the occurrence of cherry angioma in the SM-exposed group. In other words elevated levels of MCP-1/CCL2 in SM-exposed group are related to those exposed group with cherry angioma and SM-exposed participants without cherry angioma did not show this alteration. The serum level of MCP-1/CCL2 in the exposed group with cherry angioma disorder was significantly higher than in the exposed group without cherry angioma. Altogether, these findings suggested that MCP-1/CCL2 elevation in the SM-exposed participants is associated with appearance of cherry angioma and may play a major role in SM-induced cherry angioma.

To our knowledge, there is no study in regard to the association of MCP-1/CCL2 with cherry angioma, but there are reports on MCP-1/CCL2 as a potent angiogenic factor which promotes vascularization *ex vivo* and *in vivo* [26,27]. Blocking MCP-1/CCL2 with using neutralizing antibodies showed to inhibit angiogenesis and led to decreased tumor metastases and increased survival in a mouse model [28].

The association between enhancement of the serum levels of MCP-1/CCL2 and the occurrence of cherry angioma is not shown in the control group. However a limited number subjects with cherry angioma (n = 12) in 128 control group is one of the restrictions of the present study. One interpretation for these differences between SM exposed and the unexposed controls might be due to the immune system of the SM-exposed toxicants which does not function normally; it seems that in the control group with an intact immune system, CCL2 is suppressed as a response of the body to control angiogenesis, but in the SM-exposed group, the elevation cannot be controlled by inhibitory mechanisms which may justify the angiogenic role of CCL2 in the diseases such as tumor. In addition, sometimes systemic chemokine levels might not reflect the local immune responses [29].

Table 5
Association of serum levels of MCP-1 (CCL2) in SM exposed and control groups with or without cherry angioma.

Study groups	Cherry angioma (Diagnosis)	MCP-1 (CCL2)						p-value ¹	p-value ²	p-value ³
		N	Median	Q1	Q3	Mean	SD			
Control	No	112	174.30	144.10	211.75	184.40	58.02	0.029^a	0.095	0.003^a
	Yes	12	149.65	129.40	162.50	149.46	32.17			
Exposed	No	273	187.10	153.60	224.30	195.39	66.86	0.035^a		
	Yes	72	203.50	163.65	241.55	210.66	65.82			

The serum levels of MCP-1 in volunteers who had (Yes) and who did not have (No) cherry angioma were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups. p-value¹: comparison of the serum level of MCP-1 between participants who had (Yes) or did not have (No) cherry angioma within each group (ANOVA Tukey post hoc). p-value²: comparison of exposed with corresponding control groups (ANOVA Tukey post hoc). p-value³: comparison between exposed group who had cherry angioma and control who did not have cherry angioma (ANOVA Tukey post hoc).

^a Bold data shows significant differences with p value <0.05.

Furthermore, multifunctional activities of MCP-1 might be in conflict with each other [30,31]. It should also be noted that angiogenesis is a multifactorial issue that a lot of elements may be involved in its establishment in a dependent or independent manner and many of these factors are affected by SM toxicity.

5. Conclusion

SM exposure may create a certain disorganization which could lead to cherry angioma if prolactin is also elevated and CCL2 correlation is observed. This finding on the alterations of prolactin and CCL2 could serve as a basis for further research on the molecular mechanisms and pathways involved in the pathogenesis of cherry angioma and other related disorders.

The etiology of cherry angioma in SM-exposed patients might be different from the patients with no history of SM exposure and although the unexposed patients do not have known history of exposure but they might have exposed to other toxic materials which induce the disease through the same or different mechanism(s).

Declaration of interest

The authors report no conflict of interest in this study.

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