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Inflammatory Mediators in Xanthelasma Palpebrarum: Histopathologic and Immunohistochemical Study

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Abstract

Purpose: To evaluate the expression of inflammatory mediators in xanthelasma palpebrarum.

Methods: In this retrospective histopathologic case-control study, xanthelasma specimens obtained from the private practice and pathology archives of 1 author (R.Z.S.) were analyzed and compared with the blepharoplasty tissues from age- and sex-matched controls. Paraffin-embedded tissue sections were stained with hematoxylin-eosin and CD3, CD20, CD163, cyclooxygenase-1, inducible nitric oxide synthase, matrix metallopeptidase-9, and myeloperoxidase antibodies. Immunostaining was quantified by light microscopy and with a computerized image analysis system of scanned images.

Results: Hematoxylin-eosin-stained preparations of xanthelasma specimens demonstrated significantly more intense chronic lymphocytic infiltrate when compared with the control blepharoplasty tissues ($p < 0.001$). Immunohistochemical studies revealed more intense CD3+T cell and CD163+ histiocytic infiltrate (11% vs. 5%; $p = 0.02$ and 28% vs. 5%; $p = 0.003$, respectively) and increased expression of cyclooxygenase-1 (44% vs. 20% expressing cells; $p < 0.001$ and 21% vs. 9% strongly expressing cells; $p = 0.008$) and inducible nitric oxide synthase (43% vs. 26% expressing cells; $p = 0.03$ and 42% vs. 25% strongly expressing cells; $p = 0.02$) in xanthelasma specimens compared with control tissues.

Conclusions: The inflammatory milieu in xanthelasma appears to be analogous to descriptions of the early stages of cardiac atherosclerotic plaque formation. These findings may contribute to the understanding of xanthelasma pathogenesis and to the development of potential targeted therapies.

Xanthelasma palpebrarum (XP) is the most common form of cutaneous xanthoma, occurring with an incidence of 1.1% in women and 0.3% in men.[1] Xanthelasma palpebrarum clinically

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presents as yellowish cutaneous plaques, typically near the medial canthus of the eyelid, in middle-aged and older adults.[2] It has been suggested that the appearance of xanthelasma before age 40 may be associated with an increased likelihood of familial hypercholesterolemia.[3] However, 25% to 70% of patients with XP are normolipid-emic.[4] Additionally, xanthelasmas do not develop in most patients with hypercholesterolemia, suggesting other pathogenic factors.[4]

In vitro lipogenesis studies demonstrate considerable in situ synthesis of all major lipid groups in xanthoma tissue from both hyperlipidemic and normolipidemic patients.[4–6] Decreased high density lipoprotein levels may also play a role in the for-mation of xanthelasma, even in normolipidemic individuals, via impaired cholesterol removal from the tissues.[4,5] In addition, trauma may be a potential factor influencing pathogenesis of XP. It has been demonstrated experimentally that the rate of capillary leakage of low density lipoprotein (LDL) is higher in the areas exposed to friction and constant movement, potentially explaining the predilection of XP for the eyelid skin.[5,7] Finally, upregulation of inflammatory cells and mediators in eyelid tissue has been suggested to play a role in xanthelasma formation, in a process analogous to atherogenesis.[8] However, to our knowledge, there have been no prior studies systematically assessing the inflammatory landscape in xanthelasma.

Xanthelasma palpebrarum can be recalcitrant to the currently available therapeutic modalities, thus presenting a considerable cosmetic challenge.[2] Current therapies revolve around the ablation or resection of the involved tissue, without clear understanding XP's pathophysiology.[2,9–15] Thus, elucidation of the mechanisms driving pathogenesis of xanthelasma may open avenues for development of noninvasive alternative or adjuvant therapies. The potential contribution of targetable inflammatory mediators to pathogenesis of XP prompted the authors to investigate the inflammatory milieu in xanthelasma tissue.

METHODS

Patients and Tissues

Approval of the California Pacific Medical Center Institutional Review Board/Ethics Committee was obtained. Oculoplastics records (pathology archives) were searched for all patients who underwent surgery for xanthelasma between 2014 and 2016. Following informed consent, age- and sex-matched patients who underwent a blepharoplasty procedure were selected as controls. Data collected included patient age, sex, and biopsy location.

Histochemistry and Immunohistochemistry

Five-micrometer-thick sections were cut from blocks of formalin-fixed, paraffin-embedded tissues, and stained with hematoxylin-eosin. Immunohistochemical staining was performed with primary antibodies against CD3, CD20, CD163, myeloperoxidase [MPO], inducible nitric oxide synthase (iNOS), metallopeptidase-9, and cyclo-oxygenase-1 (COX-1; Table 1) using a Dako (Agilent Technologies, Santa Clara, CA) automated immunostainer in accordance with the manufacturer's guidelines.

Hematoxylin-eosin stains were examined by light microscopy and scored semiquantitatively for intensity of inflammation as “0” (none), “1+” (sparse, 0–5 inflammatory cells/high power field), “2+” (mild, 6–15 inflammatory cells/high power field), “3+ (moderate, 16–50 inflammatory cells/high power field or scattered small inflammatory aggregates), an “4+” (intense, dense sheet-like infiltrate or multiple large aggregates). The immunohistochemical slides were scanned with an Aperio ScanScope CS2 (Aperio, Vista, CA) under 20× magnification, viewed with the ImageScope program, and analyzed using Precision Analysis Software, Whole Cell Quantification Algorithm (Aperio), which calculates the percentages of cells in the tissue with staining intensities ranging from 0 (no staining) to 3+ (strong staining). The epidermis and dermis of each tissue were manually selected for this automated analysis.

Statistical Analysis

Among the subjects (n = 7) with data from both left eyelid and right eyelid, the authors first used the paired *t* test to evaluate the agreement in outcomes between left eyelid and right eyelid tissues of the same patient. Because the authors found no differences between the left and right eyes (see Table, Supplemental Digital Content 1, available at http://links.lww.com/IOP/A158), the authors used the average of left eye and right eye (for those with data from both left eyelid and right eyelid) for the subsequent analysis for the comparison between patients with xanthelasma and controls. The *t* test was used for comparison of means and χ^2 test was used to compare proportions between patients with xanthelasma and controls. A linear regression model with and without adjustment by age and gender was used to compare the measurements between specimens of xanthelasma and controls. All statistical analyses were performed in SAS V9.4 (SAS Institute Inc., Cary, NC) and 2-sided $p < 0.05$ was considered to be statistically significant.

RESULTS

Database search yielded 9 patients (10 specimens) with xanthelasma and 8 patients (14 specimens) who underwent a blepharoplasty One patient with xanthelasma and 6 patients with blepharoplasty had bilateral procedures. There were 4 males and 5 females with ages from 46 to 79 (median of 59, mean of 59.9) in the xanthelasma group. The control sample included 1 male and 7 females with ages from 55 to 74 (median of 66, mean of 65.5). There was no significant association between patients’ age and gender and the intensity of inflammation for each tissue type (Table 2).

Hematoxylin-eosin-stained preparations of xanthelasma biopsies demonstrated significantly more intense chronic lymphocytic infiltrate when compared with blepharoplasty tissues ($p < 0.001$; Table 3; Figs. 1–2). Immunohistochemical patterns of expression of the inflammatory cell and mediator antigens in the eyelid skin are summarized in Table 4 and illustrated in Figs. 1–4. When compared with controls, xanthe-lasma tissues contained a significantly greater percentage of CD3 immu-noreactive T lymphocytes (12% vs. 5%; $p = 0.02$; Table 5; Figs. 1–2) and CD163 immunoreactive macrophages (28% vs. 5%; $p = 0.003$; Table 5; Figs. 1–2). There was a greater percentage of MPO immunoreactive macrophages in the dermis of xanthelasma biopsies as compared with controls (22% vs. 3%; $p = 0.03$; Table 5; Figs. 3–4),

but this observation lost statistical significance when adjusted for patient's age and sex (p = 0.11). When compared with controls, xanthelasma biopsies demonstrated a significantly greater percentage of COX-1 immunoreactive dermal inflammatory cells, vascular endothelial cells, and fibroblasts (44% vs. 20%; $p < 0.001$; Table 5) and significantly stronger immunoreactivity in these cells (21% vs. 9%; $p = 0.008$; Table 5; Figs. 3–4). When compared with controls, xanthelasma biopsies had greater percentage of iNOS immunoreactive epidermal keratinocytes (43% vs. 26%; $p = 0.03$; Table 5) and stronger immunoreactivity in these cells (42% vs. 25%; $p = 0.02$; Table 5; Figs. 3–4). There was also a greater percentage of iNOS immunoreactive dermal lymphocytes and macrophages of xanthelasma tissues when compared with controls (21% vs. 7%; $p = 0.04$; Table 5; Figs. 3–4). There was no significant difference in the percentage of immunoreactive cells and strength of immunoreactivity for metallopeptidase-9 (Table 5; Figs. 3–4).

DISCUSSION

This study demonstrates upregulation of T-cells, macrophages, and the inflammatory mediators iNOS, COX, and MPO in xanthelasma. While the inciting events leading to these findings remain obscure, this inflammatory milieu is similar to descriptions of the early stages cardiac atherosclerotic plaque formation. Atheromagenesis is currently believed to be primarily an inflammatory process, driven by the oxidized LDL and elevated iNOS, COX, metallopeptidase, and MPO levels, resulting in recruitment of blood monocytes to the vessel wall, monocyte activation, and transformation into lipidized macrophages, or "foam cells," followed by potentiation of the inflammation by the macrophages.[16–18] T-cells are also believed to play an important role in atherosclerotic plaque formation, partially via modulation of iNOS and COX levels.[19–21]

Bergman et al.[22] found no evidence of intrinsic cellular cholesterol metabolism derangement in monocyte-derived macrophages. The authors hypothesized that the increased plasma lipid peroxidation might lead to accumulation of cholesterol in macrophages and formation of foam cells. The dermal monocyte-derived macrophages have been found to express scavenger or acetyl-LDL receptors that are not regulated by intracellular cholesterol levels and, therefore, can upregulate exogenous LDL uptake irrespective of cellular cholesterol content.[4,22,23] Thus, it is possible that increased vascular permeability in the easily traumatized or inflamed eyelid skin leads to the egress of LDL into the dermis.[4] Oxidized LDL, generated by free radicals or by the ultraviolet light, in conjunction with the elevated iNOS, COX, and MPO levels may, in turn, induce dermal monocyte activation and transformation into xanthoma cells.[24]

While the observations cannot prove causation, the presence of proinflammatory cytokines and chronic inflammatory cells in XP tissue suggests a potential role for inflammation-modulatory therapies in management of xanthelasma. Interestingly, recent in vitro and in vivo studies have shown that statins, in addition to the well-recognized hypocholes-terolemic activity, have direct anti-inflammatory effects that may contribute to their efficacy in management of hyperlipid-emia and atherosclerosis.[25,26] The newly discovered functions of statins include regulation of endothelial cell nitric oxide synthase, monocyte chemotactic protein-1, and lymphocyte function-associated antigen-1, and have led to an investigation of

potential utility of statins in modulating cutaneous wound healing and inflammation.[25–29] Based on the published literature, topical application of statins (currently investigational) may prove invaluable in the treatment of various inflammatory dermatological disorders, especially those characterized by skin ingress of activated leukocytes such as alopecia areata, vitiligo, erythema multiforma, toxic epidermal necrolysis, and psoriasis.[28,30,31] Thus, additional studies assessing the potential utility of statins in xanthelasma management may be of value.

This pilot study is limited by its retrospective design and small patient size. Despite these important limitations, it provides a glimpse into the potential pathophysiology of xanthelasma, which in turn, may yield alternative noninvasive therapies. Additional in vitro and animal studies are required to more precisely elucidate the mechanism of xanthelasma pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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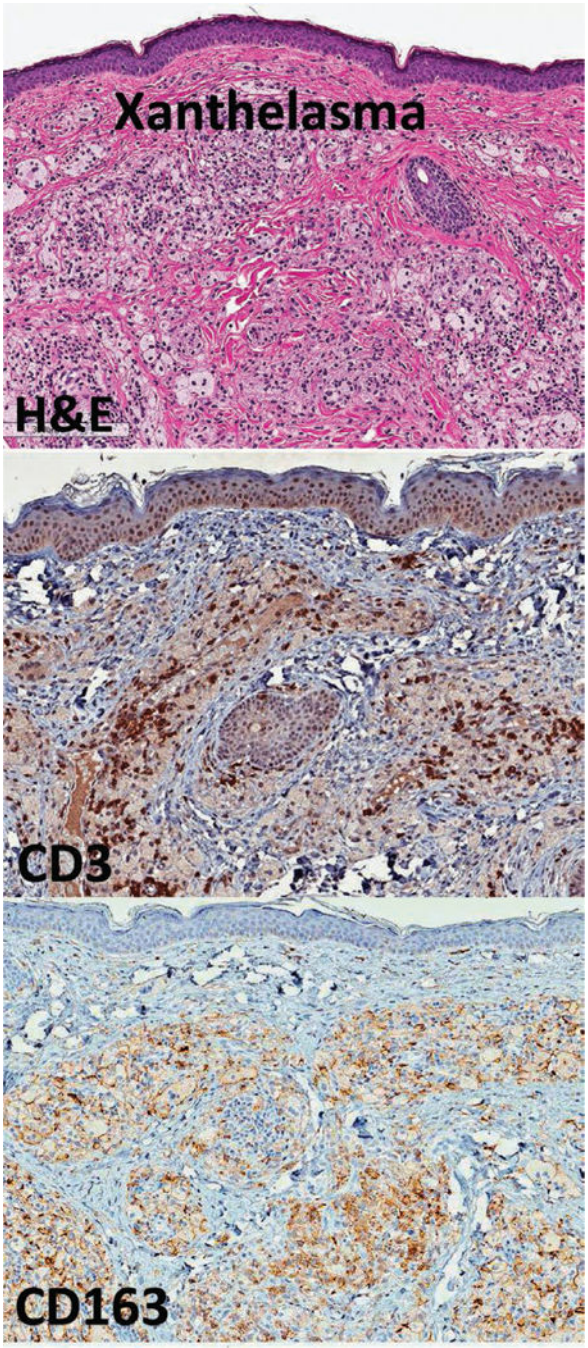

FIG. 1.

Histopathologic and immunohistochemical findings in xanthelasma. **Top row**, Hematoxylin-eosin stain shows a moderately intense lymphocytic infiltrate. **Second row**, CD3 immunostain highlights the numerous T lymphocytes. **Third row**, CD163 immunostain stains the cytoplasm of numerous lipidized macrophages (xanthoma cells) and few nonlipidized macrophages (all figures: original magnification ×25).

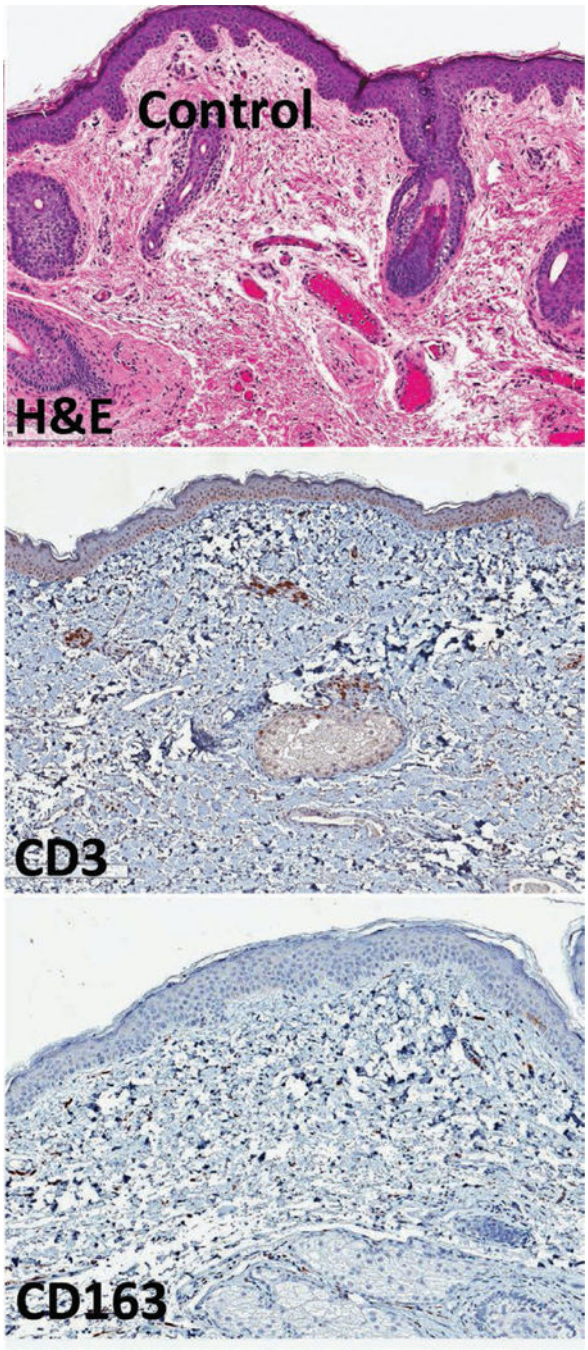

FIG. 2.

Histopathologic and immunohistochemical findings in blepharoplasty controls. **Top row**, Hematoxylin-eosin stain shows a sparse lymphocytic infiltrate. **Second row**, CD3 immunostain highlights the rare lymphocytes. **Third row**, CD163 immunostain stains the cytoplasm of rare CD163 immunoreactive macrophages (all figures: original magnification ×25).

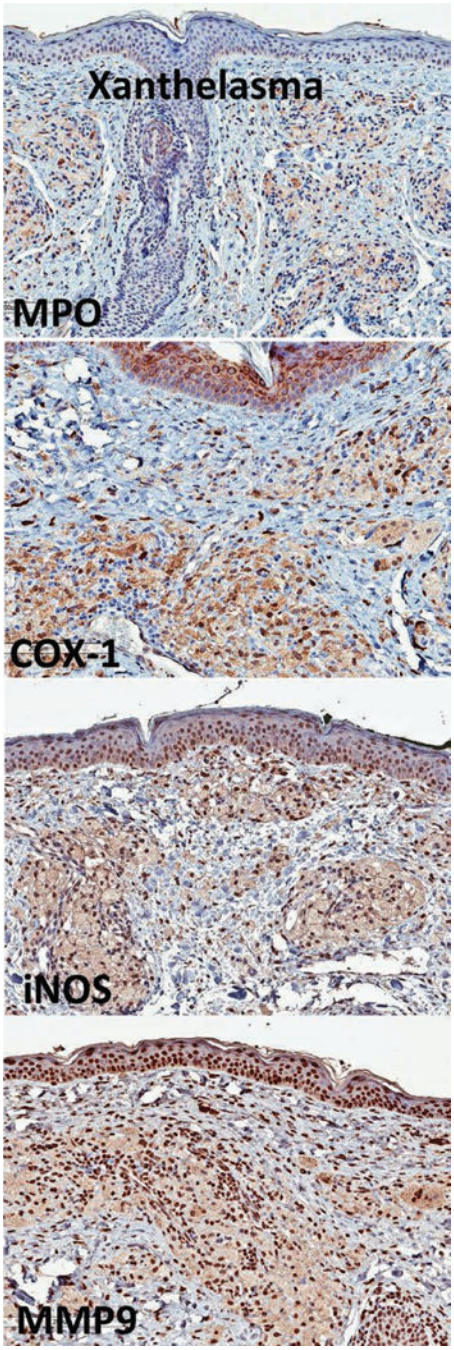

FIG. 3.

Immunohistochemical findings in xanthelasma. **First row**, Myeloperoxidase immunostain is weakly positive in the cytoplasm of xanthoma cells. **Second row**, COX-1 immunostain is diffusely positive in a perinuclear pattern in the dermal inflammatory cells, fibroblasts, and occasional vascular endothelial cells. **Third row**, iNOS immunostain demonstrates weak cytoplasmic staining (and nonspecific nuclear staining) in the epidermis and inflammatory dermal cells. **Fourth row**, MMP9 immunostain shows strong nuclear and weaker cytoplasmic staining in the epidermis, dermal inflammatory cells, and dermal fibroblasts (all

figures: original magnification ×25). COX-1, cyclooxygenase-1; iNOS, inducible nitric oxide synthase; MMP9, metallopeptidase-9.

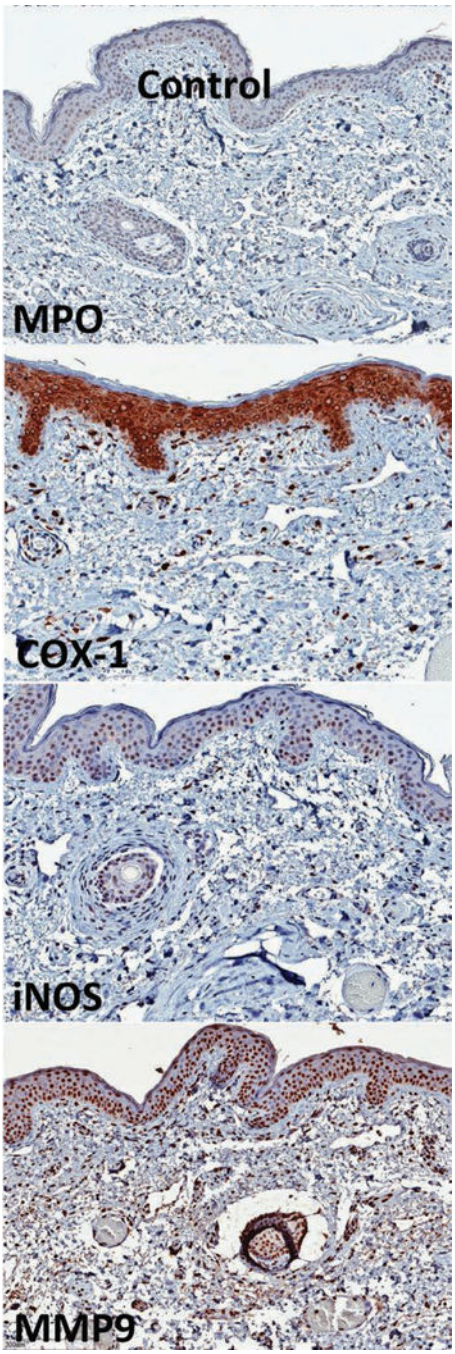

FIG. 4.

Immunohistochemical findings in blepharoplasty controls. **First row**, Rare macrophages in control tissue immunoreact with myeloperoxidase. **Second row**, COX-1 immunostain is positive in rare dermal fibroblasts and inflammatory cells. **Third row**, iNOS immunostain demonstrates weaker cytoplasmic staining for iNOS in fewer cells, when compared with xanthelasma tissues. **Fourth row**, MMP9 immunostain shows strong nuclear and weaker cytoplasmic staining in the epidermis, dermal inflammatory cells, and dermal fibroblasts (all

figures: original magnification ×25). COX-1, cyclooxygenase-1; iNOS, inducible nitric oxide synthase; MMP9, metallopeptidase-9.

TABLE 1.

Antibodies used in the study

Antibody	Clone	Dilution	Vendor	Positive control*
CD3	A0452	1:50	DAKO	Lymph node/tonsil
CD20	L26	1:400	DAKO	Lymph node/tonsil
				Lymph node
CD163	10D6	Ready to use	AbCam	Human placenta
MPO	A0398	1:600	DAKO	Bone marrow aspirate
iNOS	Ab53769	1:50	AbCam	Lung carcinoma
COX-1	Ab53766	1:200	AbCam	Human brain
MMP9	SB15C	1:100	AbCam	Human colon

*Substitution of primary antibody with nonantigenic serum was employed for all negative controls.

COX-1, cyclooxygenase-1; iNOS, inducible nitric oxide synthase; MMP9. metallopeptidase-9; MPO, myeloperoxidase.

TABLE 2.

Associations between inflammation, gender, and age

Inflammation intensity	**Male (n = 5)**	**Female (n = 12)**	***P***
1+	1 (20.0%)	6 (50.0%)	0.36
2+	1 (20.0%)	3 (25.0%)	
3+	3 (60.0%)	3 (25.0%)	
4+	0 (0%)	0 (0%)	
	Age ≤ 60 (n = 9)	Age > 60 (n = 8)	*P*
1+	2 (22.2%)	5 (62.5%)	0.23
2+	3 (33.3%)	1 (12.5%)	
3+	4 (44.4%)	2 (25.0%)	
4+	0 (0%)	0 (0%)	

TABLE 3.

Comparison of inflammation intensity on hematoxylin-eosin stain between xanthelasma biopsies and blepharoplasty tissues

Inflammation intensity	Xanthelasma (n = 9)	Control (n = 8)	*P*
1+	0 (0.0%)	7 (87.5%)	<0.001
2+	3 (33.3%)	1 (12.5%)	
3+	6 (66.7%)	0 (0.0%)	
4+	0 (0%)	0 (0%)	

TABLE 4.

Immunohistochemical patterns of expression of inflammatory cell and mediator antigens in the skin

Antigen	Cells expressing	Pattern of staining
CD3	T-cells	Cytoplasmic
CD20	Very rare B-cells	Cytoplasmic
CD163	Macrophages and xanthoma cells	Cytoplasmic
MPO	Macrophages (strongly) and xanthoma cells (weakly)	Cytoplasmic
	No neutrophils identified	
iNOS	Epidermis, lymphocytes, macrophages/xanthoma cells	Cytoplasmic
		Nonspecific nuclear staining
COX-1	Epidermis, lymphocytes, macrophages/xanthoma cells, endothelial cells, fibroblasts	Strong perinuclear
		Weak diffuse cytoplasmic
MMP9	Epidermis, macrophages, lymphocytes, fibroblasts	Nuclear and cytoplasmic

COX-1, cyclooxygenase-1; iNOS, inducible nitric oxide synthase; MMP9, metallopeptidase-9; MPO, myeloperoxidase.

TABLE 5.

Comparison of expression of inflammatory cell and mediator antigens between xanthelasma and control tissues by presence of expression (% cells with 1+, 2+, or 3+ expression) and by strength of expression (% of cells with 2+ and 3+ expression)

		Unadjusted			Adjusted for age and gender		
Inflammatory cells and mediators	**Presence of expression / Strength of expression**	**Xanthelasma (n = 9) Mean% (SE)**	**Controls (n = 8) Mean% (SE)**	***P***	**Xanthelasma Mean% (SE)**	**Controls Mean% (SE)**	***P***
CD3 dermis	Presence	12.6 (1.7)	3.9 (1.6)	0.002	11.8 (1.7)	4.8 (1.8)	0.02
	Strength	12.6 (1.7)	3.9 (1.6)	0.002	11.8 (1.7)	4.8 (1.8)	0.02
CD163 dermis	Presence	27.8 (4.9)	6.0 (1.2)	0.001	28.4 (4.1)	5.3 (4.3)	0.003
	Strength	12.0 (3.3)	3.7 (0.8)	0.03	12.8 (2.7)	2.8 (2.9)	0.03
MPO dermis	Presence	22.2 (6.9)	3.3 (1.9)	0.03	20.5 (5.7)	5.2 (6.1)	0.11
	Strength	3.0 (1.6)	1.4 (0.7)	0.40	2.9 (1.3)	1.5 (1.4)	0.52
COX-1 dermis	Presence	44.5 (3.8)	19.9 (1.6)	<0.001	44.3 (3.4)	20.2 (3.8)	<0.001
	Strength	20.9 (2.8)	8.4 (0.9)	0.002	20.8 (2.5)	8.6 (2.7)	0.008
COX-1 epidermis	Presence	79.4 (2.8)	72.5 (2.0)	0.08	79.6 (2.7)	72.3 (3.0)	0.11
	Strength	40.9 (3.6)	31.3 (2.1)	0.053	39.9 (3.1)	32.3 (3.5)	0.14
iNOS dermis	Presence	22.8 (5.3)	4.2 (1.2)	0.006	20.7 (4.1)	6.5 (4.4)	0.04
	Strength	2.3 (1.4)	0.3 (0.2)	0.20	1.7 (1.0)	1.0 (1.1)	0.66
iNOS epidermis	Presence	46.4 (5.7)	22.2 (4.1)	0.004	43.1 (4.6)	25.9 (5.0)	0.03
	Strength	45.2 (4.9)	22.1 (4.1)	0.003	42.3 (4.2)	25.3 (4.5)	0.02
MMP9 dermis	Presence	61.4 (7.6)	63.7 (6.7)	0.83	60.1 (7.8)	65.1 (8.3)	0.68
	Strength	32.5 (6.0)	28.3 (4.3)	0.59	31.3 (5.7)	29.6 (6.1)	0.85
MMP9 epidermis	Presence	70.6 (7.8)	76.5 (5.4)	0.55	68.8 (7.4)	78.4 (7.9)	0.41
	Strength	47.6 (3.8)	51.8 (2.3)	0.38	46.4 (3.3)	53.2 (3.6)	0.21

COX-1, cyclooxygenase-1; iNOS, inducible nitric oxide synthase; MMP9, metallopeptidase-9; MPO, myeloperoxidase; SE, standard error.

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