ARAŞTIRMA MAKALESİ / Research Article

Xanthelasma Palpebrarum is Associated with Higher Levels of Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratio

Ksantelazma Palpebrarum Artmış Nötrofil/Lenfosit ve Platelet/Lenfosit Oranı ile İlişkilidir

Selim Kul, Ali Rıza Akyuz

Saglik Bilimleri University, Trabzon Ahi Evren Cardiovascular and Thoracic Surgery Research and Application Center, Department of Cardiology, Trabzon, Turkey

Yazışma Adresi / Correspondence:
Selim Kul

Saglik Bilimleri University, Trabzon Ahi Evren Cardiovascular and Thoracic Surgery Research and Application Center, Department of Cardiology, Trabzon, Turkey

T: **+90 532 674 16 32** E-mail:selimkul@gmail.com

Geliş Tarihi / Received : **24.12.2017** Kabul Tarihi / Accepted : **02.03.2018**

Abstract

Objective According to many epidemiologic studies, Xanthelasma Palpebrarum (XP) is thought to be a determinant of an increased risk of atherosclerosis. Many studies have show that inflammation plays an important role in the progress of atherosclerosis. Platelet to lymphocyte ratio (PLR) and Neutrophil to lymphocyte ratio (NLR) is a marker of systemic inflammation that correlates with mortality and cardiac events in several cardiovascular diseases. We aimed to investigate the relationship between PLR, NLR and XP in this study.
(Sakarya Med J 2018, 8(1):63-69)

Material and Method Sixty-six subjects with XP and age and sex matched 66 control subjects were enrolled in the present study. Patients with known atherosclerotic vascular diseases were excluded. Baseline characteristics such as presence of hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking history, medications and hematological parameters were compared between the two groups.

Results Subjects with XP had higher levels of total cholesterol (217±54 mg/dl vs. 197±41mg/dl, p=0.04), low density lipoprotein cholesterol (143±45 mg/dl vs. 120±33 mg/dl, p=0.002), triglyceride levels (174±91 vs. 149±95, p=0.02), NLR (1.8±0.8 vs. 1.5±0.5, p=0.004) and PLR (117±35 vs. 100±29, p=0.004) than those in control subjects.

Conclusion In the present study we found that NLR and PLR levels, which are indicative of systemic inflammation and multiple adverse cardiovascular outcomes, were higher in the XP patients. This suggests that XP patients may need a close follow-up for cardiac risk factors.

Keywords Xanthelasma palpebrarum; inflammation; neutrophil to lymphocyte; platelet to lymphocyte Ratio

Öz

Giriş Epidemiyolojik çalışmalarda, ksantelazma palpebrarum (KP) artmış ateroskleroz riskinin belirleyicisi olduğu görülmüştür. Birçok çalışma, inflamasyonun ateroskleroz gelişiminde önemli bir rol oynadığını göstermektedir. Trombosit / lenfosit oranı ve nötrofil / lenfosit oranı, çeşitli kardiyovasküler hastalıklarda mortalite ve kardiyak olaylarla ilişkili olan sistemik inflamasyonun bir işaretidir. Bu çalışmada, trombosit / lenfosit oranı ve nötrofil / lenfosit oranı ile KP arasındaki ilişkiyi araştırmayı amaçladık.
(Sakarya Tıp Dergisi 2018, 8(1):63-69).

Metod Çalışmaya 66 KP olan ve yaş, cinsiyet eşleştirilmiş 66 kontrol hasta alındı. Bilinen aterosklerotik vasküler hastalığı olanlar çalışma dışı bırakıldı. Her iki grupta hipertansiyon, diabetes mellitus, hiperlipidemi, sigara kullanımı öyküsü, medikal tedavi öyküsü ve hematolojik parametreler gibi temel özellikler karşılaştırıldı.

Sonuç KP olan olguların total kolestrol seviyeleri (217 ± 54 mg / dl'a karşılık 197 ± 41 mg / dl, p = 0.04), düşük yoğunluklu lipoprotein kolesterol düzeyleri (143 ± 45 mg / dl'ye karşı 120 ± 33 mg / dl, p = 0.002), trigliserit düzeyleri (174 ± 91 karşı 149 ± 95, p = 0.02), nötrofil/lenfosit (1.8 ± 0.8'e karşı 1.5 ± 0.5, p = 0.004) ve platelet/lenfosit (117 ± 35'e karşı 100 ± 29, p = 0.004) kontrol gruptan daha yüksekti.

Tartışma Bu çalışmada, KP hastalarında sistemik inflamasyon ve istenmeyen kardiyovasküler sonuçların göstergesi olan nötrofil/lenfosit oranı ve platelet/lenfosit oranı düzeylerinin daha yüksek olduğunu bulduk. Bu, KP hastalarının kardiyak risk faktörleri için yakın izlem gerektirebileceğini göstermektedir.

Anahtar Kelimeler Ksantelazma palpebrarum; inflamasyon; nötrofil/lenfosit oranı; platelet/lenfosit oranı

Introduction

There are some dermatological stigmata indicative of an increased risk of early atherosclerosis. Among them, Xanthelasma Palpebrarum (XP) is a common variety of planar xanthoma, which is characterized by bilateral, soft, yellowish-orange plaques on/or around eyelids. The effect of XP on the risk of developing atherosclerosis is independent of that of other more common risk factors.[1-4] Although its exact physiopathology remains to be determined, xanthelasma is characterized by fatty areas mainly composed of cholesteryl esters containing macrophages.5 Accumulation of lipids and foam cell formation through their oxidation represents the basis of vascular inflammation in the atherosclerotic process.

As a marker of systemic inflammation, neutrophil to lymphocyte ratio (NLR) predicts mortality and cardiac outcomes in various cardiovascular (CV) disorders.6 Thrombocytes are responsible for the initiation of thrombotic events in blood vessels through an interaction with endothelial cells, components of coagulation cascade, and inflammatory cells. Platelet to Lymphocyte Ratio (PLR) and NLR are surrogate markers of inflammation and atherosclerosis. We aimed to investigate NLR, PLR relationship between with and without XP subjects.

Methods:

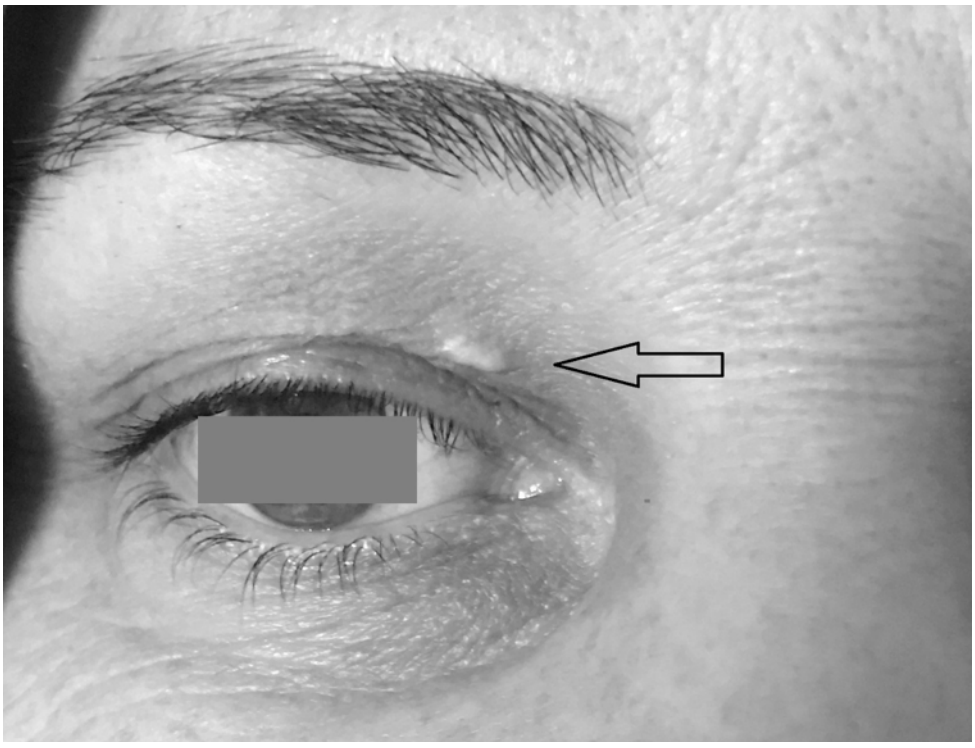
Study population

Asymptomatic subjects, who admitted to Akçaabat Haçkalı Baba State Hospital Preventive Cardiology Clinic for assessment of cardiovascular risk profile for screening and primary prevention purposes, were systemically screened for presence of cutaneous markers of cardiovascular disease, between January 2015 and January 2016. Among subjects screened, 66 XP cases were identified. A propensity score matched 66 subjects, according to age and sex, were selected as a control group from the same population pool. Patients were described to have XP if they had sharply demarcated yellow–orange plaques around their eyelids (Figure 1). None of them had any known CV disease. Patients with acute coronary syndrome and prior CV disease (history of myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, stroke and peripheral arterial occlusive disease); history of a cardiac valve disease or a cardiac valve operation; hematological, oncological, or inflammatory disorder; white blood cell count >10400 mm3; hemoglobin level <10 g/dL; using any anticoagulant drug; liver or thyroid dysfunction; thrombocytopenia or thrombocytosis and high body temperature >38° were excluded from the study.

All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Local ethical committe approved the study. Informed consents were obtained verbally and in writing from all participants.

Detailed anamnesis was obtained from all patients, and their demographic characteristics were recorded. Venous blood samples were taken from patients after an 8-to 10-h fast and were analyzed for complete blood count parameters, total cholesterol, Low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglyceride (TG) levels. The NLR and PLR were calculated by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count.

Patients were considered to have type II diabetes mellitus (DM) if they were previously diagnosed and treated for diabetes and/or if they had a fasting blood glucose level of ≥126 mg/dl. Patients were considered to have hypertension if they had previously known hypertension, or if they were on antihypertensive therapy, or if they had a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg, which were calculated as the mean of two measurements taken on each arm. Smoking was defined as "current smokers" or "nonsmokers". The patients were considered to have hyperlipidemia if they had a fasting total cholesterol level >200 mg/dl, a fasting LDL-c level >160 mg/dl, a fasting TG level >200 mg/dl, or were on anti-hyperlipidemia therapy.



(Figure 1)

Statistical Analysis

Statistical analysis was carried out using SPSS 17.0 statistical software. (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation or median and interquartile ranges where appropriate. Categorical variables were expressed as numbers and percentages. Analysis of the normality of the continuous variables was performed with the Kolmogorov-Smirnov test. The continuous variables were compared by using the Paired Samples t-test or the Wilcoxon Signed Rank Test and the categorical variables were compared using Pearson's x2-test or Fisher Exact x2-test for the two groups. P-value less than 0.05 was considered statistically significant for all tests.

Results

The patient characteristics are summarized in Table 1. There was no statistically significant difference between the ages and genders of the groups. HT was diagnosed in 26 patients of the XP group and in 29 patients of the control group (p=0.6). DM was diagnosed in 7 patients of the XP group and in 9 patients of the control group (p=0.6). HL was diagnosed in 11 patients of the XP group and in 5 patients of the control group (p=0.11). Cigarette smoking history was found in 3 patients

of the XP group and in 8 patients of the control group (p=0.11). Cardiovascular medications of both groups were similar.

Subjects with xanthelasma had higher levels of total cholesterol (221±58 mg/dl vs. 197±41 mg/dl, p=0.04), LDL-c (143±45 mg/dl vs. 120±33 mg/dl, p < 0.002), TG (174±91 vs. 149±95, p=0.02), NLR (1.8±0.8 vs. 1.5±0.5, p=0.004) and PLR (117±35 vs. 100±29, p=0.004) than those in control subjects. Xanthelasma subjects had lower lymphocyte count (2.16±0.6 x109/L vs. 2.48±0.7 x109/L, p = 0.003) than that in control subjects (Table 1).

Table 1. Comparison of clinical and laboratory characteristics between subjects with and without xanthelasma.

Age, years	50± 11	51 ± 11	0.7*
Sex, F/M	50/16	50/16	0.1**
BMI (kg/m²)	32± 6	31 ± 5	0.13*
Diabetes mellitus, n(%)	7(10,6)	9 (13,6)	0.6**
Hypertension, n(%)	26 (39)	29 (43)	0.6**
Hyperlipidemia, n(%)	11 (16,7)	5 (7,6)	0.11**
Current smokers, n(%)	3 (4,5)	8 (12,1)	0.11**
Cardiovascular medications			
ACE inhibitors or ARB, n(%)	17(25,8)	23(34,8)	0.26**
Calcium channel blockers, n(%)	5(7,6)	10(15,2)	0.17**
-Blockers, n(%)	6(9,1)	6(9,1)	1**
Cholesterol-lowering drugs, n(%)	8(12,1)	4(6,1)	0.23**
Oral antidiabetic drugs n(%)	6(9,1)	8(12,1)	0.6**
Biochemical and hematological parameters			
Total cholesterol (mg/dl)	217 ± 54	197 ± 41	0.04*
HDL-c (mg/dl)	47 ± 11	50 ± 10	0.14*
LDL-c (mg/dl)	143 ± 45	120 ± 33	0.002*
Triglyceride (mg/dl)	174 ±91	149 ±95	0.02*
Serum creatinine (mg/dl)	0.6/0.7/0.8	0.6/0.7/0.8	0.62***
White blood cell count (x109/L)	6.63±1.7	6.58±1.46	0.85*
Platelet count (x109/L)	242 ± 61	233 ± 56	0.3*
Mean platelet volume (fL)	8.9±1.0	8.9±1.0	0.96*
Lymphocyte count(x109/L)	2.16±0.6	2.48±0.7	0.003*
Neutrophil count(x109/L)	3.8±1.3	3.5±1.08	0.21*
Neutrophil-to-lymphocyte ratio	1.8±.8	1.5±.5	0.004*
Platelet-to-lymphocyte ratio	117±35	100±29	0.004*
Platelet-to-lymphocyte ratio	117±35	100±29	0.004*

* İndependent - Samples T test
** Chi-square test
*** Mann Whitney U test
ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body-mass index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NS, non-significant.

Discussion

XP is a form of planar xanthoma affecting eyelids. It has been reported that there is a tendency to develop atherosclerosis in patients with xanthelasma, particularly when they are hyperlipidemic although it can also occur in persons with normal lipid levels.[5,7] It is still unclear why persons with normal lipid levels develop XP and whether the latter is a risk factor for atherosclerosis. Montgo-

mery and Osterberg found a CV disease rate of 50% in patients with xanthelasma.[8] In a study by Vacca et al, 69% of patients with XP suffered atherosclerosis.[9] In contrast, a study with a control group, Segal et al. suggested that there is no significant association between XP and atherosclerosis. Özdöl et al. found no association between xanthelasma and either CV disease or Lp (a) level.[10] Several various reports have consistently confirmed an association between xanthelasma and hyperlipidemia by showing significantly higher total cholesterol and LDL levels in patients with xanthelasma compared to controls.[11,12] Our study also revealed higher TC and LDL levels in the XP patients compared to the control group. However, TG levels were also higher in the XP group whereas HDL levels were comparable in both groups.

Both normolipidemic and hyperlipidemic xanthelasma patients store cholesterol as the major lipid in their lesions. Experimentally, xanthomas and atheromas affecting vessel wall share the same mechanisms of cholesterol storage.[13] Inflammation is a key process for atherosclerosis from its beginning to plaque rupture. In this process, inflammatory mediators play a pivotal role by causing lipid accumulation and foam cell formation through lipid oxidation. NLR is a complete blood count parameter indicative of systemic inflammation and predictive of death and cardiac adverse events in a variety of cardiovascular disease states including stable and unstable coronary artery disease and acute decompensated heart failure.[14,15] Corriere at all showed that NLR is a strong predictor of the presence and the number of carotid atherosclerotic plaques.[16] SOLVD (An analysis of the studies of left ventricular dysfunction) study demonstrated a proportional increase in cardiovascular death with increasing neutrophil counts, and observed an exactly opposite correlation between lymphocyte count and death in left ventricular systolic dysfunction of ischemic and non-ischemic origin.[17] As previously indicated, neutrophils are responsible for the release of large amounts of inflammatory factors; furthermore, neutrophilia may indicate acute inflammatory response since the halflife of neutrophils is short. Neutrophils have recently drawn much attention owing to their contribution to tissue destruction in inflammatory disease states. Our study demonstrated that the XP group had a significantly higher NLR level, which is a marker of inflammation. Floudas et al. reported a case with XP lesion in association with Castleman's disease (hyperplastic disease of lymph nodes caused by a rare and atypical form of lymphoproliferation) characterized by a severe systemic inflammatory reaction, and the lesion shrunk after tumor removal and the elimination of the inflammatory state.[18] That report and the increased NLR level detected in our study may suggets that XP is a sign of enhanced inflammatory state.

Recently, a new inflammatory marker named PLR has been shown to predict major adverse cardiovascular outcomes in several cardiovascular disorders. Cells of vascular wall release some substances that activate thrombocytes which perpetuate vascular inflammation through proinflammatory substances such as chemokines and cytokines.[19-21] Our study also showed incresed PLR level in the XP group. This similarly points to the intensification of the inflammatory state in XP patients.

Study limitations

The major limitations of our study were its small sample size and cross-sectional observational design; we therefore did not investigate the correlation of NLR and PLR with short and long-term events. Moreover, other inflamatory markers were not explored in comparison with NLR and PLR for their predictive power. Lastly, we included and excluded study subjects by applying strict criteria and thus our results cannot necessarily be generalized to large patient populations.

Conclusion:

In the present study we found that NLR and PLR levels, which are indicative of systemic inflammation and multiple adverse cardiovascular outcomes, were higher in the XP patients. This suggests that XP patients may need a close follow-up for cardiac risk factors.

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