Inflammation and Non-Atherosclerotic Coronary Artery Aneurysm

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ABSTRACT

Introduction: Coronary artery aneurysm is generally presented as an asymptomatic, incidental angiographic finding and is often associated with atherosclerosis. In this study we investigated the relation of non-atherosclerotic isolated coronary artery aneurysm with inflammation.
Patients and Methods: Data of 6845 coronary angiography were retrospectively evaluated. A total of 35 non-atherosclerotic isolated coronary artery aneurysms were diagnosed in 23 patients (0.34%). Patients follow-up charts were reviewed, demographic and hematologic parameters were determined and were compared with the results of 23 healthy subjects.
Results: Neutrophil to lymphocyte ratio was 2.44±0.88 in group I and 1.80±0.49 in group II, and the difference was found to be significant (p=0.01). Serum uric acid level was 6.37±1.80 mg/dL in group I and 4.91±0.99 in group II, and the difference was significant (p=0.008).
Conclusion: Present study indicates two important triggering factors in the pathogenesis of isolated coronary artery aneurysm; inflammation and oxidative stress. Antiinflammatory and antioxidant treatments may be a new approach in patients with coronary artery aneurysm.
Key Words: Inflammation; neutrophil to lymphocyte ratio; serum uric acid; coronary artery aneurysm; ectasia

Ateroskleroza Bağlı Olmayan Koroner Arter Anevrizması ve İnflamasyon İlişkisi

ÖZET

Giriş: Koroner arter anevrizması, genellikle asemptomatik, rastlantısal anjiyografik bir bulgudur. Büyük çoğunluğu ateroskleroza bağlıdır. Bu çalışmada, ateroskleroza bağlı olmayan izole koroner arter anevrizmalarının inflamasyon ile ilişkisini inceledik.
Hastalar ve Yöntem: Altı bin sekiz yüz kırk beş koroner anjiyografi verisi geriye dönük olarak incelendi. Toplam 23 hastada 35 koroner arter anevrizması saptandı (%0,34). Hasta takip kartları incelenerek demografik, hematolojik verilere ulaşıldı. Veriler koroner arterleri normal bulunan 23 olgunun sonuçlarıyla kıyaslandı.
Bulgular: Nötrofil lenfosit oranı grup 1'de 2,44±0,88, grup II'de 1,80±0,49 olup, fark anlamlı bulundu (p=0,01). Serum ürik asit seviyesi grup I'de 6,37±1,80 mg/dL olup, grup II'de 4,91±0,99 mg/dL olarak bulundu (p=0,008).
Sonuç: Sonuçlarımız, inflamasyon ve oksidatif stresin izole koroner arter anevrizması patogenezinde tetikleyici etkenler olabileceğini işaret etmektedir. Antiinflamatuar ve antioksidan tedavinin koroner arter anevrizması hastalarında yeni bir yaklaşım olabileceği kanaatindeyiz.
Anahtar Kelimeler: İnflamasyon; nötrofil lenfosit oranı; serum ürik asit; koroner arter anevrizması; ektazi

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Submitted: 03.11.2013
Accepted : 30.11.2013

INTRODUCTION

Coronary artery aneurysm (CAA) is generally an incidental angiographic finding with an incidence ranges of 1.5 to 5%[1]. Atherosclerotic coronary aneurysm formation is relatively more common in patients who underwent cardiac surgery and/or percutanous coronary intervention. Unfortunately non-atherosclerotic isolated cases' incidence and etiology are uncertain. Approximately half of CAA are associated with atherosclerosis.

Various studies revealed different findings about etiopathology of isolated CAA. Decreased collagen biosynthesis and increased collagenolysis may be the underlying pathologies in patients with CAA. Pathologic conditions effecting collagen turnover such as prolidase deficiency may effect arterial wall structure. Prolidase is an enzyme that catalyzes the final step of collagen breakdown by liberating free proline for collagen recycling[2]. Prolidase enzyme activity had been found severely decreased in patients with CAA in comparison with patients who have normal coronary arteries[3]. Similary increased secretion of elastase, matrixmetalloproteinases and oxygen free radicals may trigger collagenolysis and cause arterial wall weakness and aneurysm formation.

Recent data have shown that coronary artery aneurysm is associated with an inflammatory response presented with elevated inflammatory cytokines and markers[4-7]. In the last decade relationship of hematologic parameters and inflammation has been extensively studied. Association between chronic diseases and white blood cell count and subtypes in particular neutrophil to lymphocyte ratio (NLR) were well documented. Neutrophil related substances have critical role in inflammation. Previous studies showed strong correlation of cardiovascular diseases and increased NLR.

Serum uric acid (SUA) level has also been considered an independent cardiovascular disease marker. It is well known that hyperuricemia is associated with oxidative stress, endothelial dysfunction and atherosclerosis[8].

In our present study, we evaluated inflammation markers of patients with isolated CAA and those with normal coronary arteries.

PATIENTS and METHODS

Coronary angiographies of 6845 patients were evaluated retrospectively. A 1,5 fold increase of coronary artery diameter in any segment was accepted as coronary aneurysm. Angiographically detected atherosclerosis was accepted as an exclusion criteria regardless of stenosis percentage. A total of 35 non-atherosclerotic isolated CAA was diagnosed in 23 patients (0.34%). These patients were enrolled in the study. Twenty three healthy subjects whose coronary arteries had been found to be normal by angiography were included into the control group. Patients' follow-up charts were investigated, demographic and hematologic parameters were determined and compared statistically.

In laboratory analysis; hemogram was performed with ABX Pentra DF Nexus analyzer (Axon Lab AG, Baden, Germany), uric acid measurement was performed with AU680 Biochemistry System (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). CRP was measured by turbidimetric method.

Statistical Analysis

Statistical analysis was performed with the statistical package for the social sciences (SPSS) computer program, version 16.0 (SPSS, Inc., Chicago, III, USA). All data were expressed as mean±standart deviations. Shapiro wilk test was used to analyze variables in accordance to normal distribution. Results were analyzed with the Student t test or Mann-Whitney U test for quantitative data, and with the Chi-square or Fischer exact test (when Levene's test was significant) for categorical data. A p value of 0.05 was considered statistically significant.

RESULTS

Total 46 patients' follow-up charts were reviewed. Patients with CAA were enrolled in group I, and 23 patients with normal coronary arteries composed group II. Mean age was 57.43±11.54 years in group I and 56.63±15.27 years in group II. Seventeen patients were male in group I and 15 in group II (73.9% vs 65.2%). Although hypertension, diabetes mellitus and smoking history were found more common in group I, differences of these parameters were not statistically significant. Demographic features of patients were summarized in Table 1.

Patients white blood cell count, red blood cell distribution width, platelet count, mean platelet volume were found as similar between groups (Table 2).

NLR was 2.44±0.88 in group I and 1.80±0.49 in group II and the difference was significant (p=0.01). Pearson test was performed and revealed insignificant correlation between NLR and aneurysm count (R=-0.062, p=0.789).

C-reactive protein was found slightly higher in patients with coronary artery aneurysm (0.60±0.58 mg/dL in group I and 0.35±0.36 mg/dL in group II) but this difference was not statistically significant.

SUA levels were 6,37±1,80 mg/dL in group I and 4,91±0,99 mg/dL in group II and the difference was significant (p=0,008).

Receiver operating characteristics(ROC) Curve analysis showed that area under curve is 0.724 for SUA and 0.649 for NLR in diagnosis of CAA.

Table 1. Comparison of demographic features

Parameter	Group I	Group II	p value
Patient, n	23	13	NS
Age, years	57.43±11.54	56.63±15.27	NS
Male gender, %	73.9	65.2	NS
Hypertension	8	4	NS
Smoking history	11	6	NS
Diabetes Mellitus	6	4	NS
LDL	114.63±42.4	121.06±27.52	NS
HDL	44.34±8.2	49.37±7.363	NS

LDL: Low density lipid; HDL: High density lipid.

DISCUSSION

In the present study, we evaluated inflammation markers of patients with isolated CAA. We found significant correlation with NLR, SUA level and presence of CAA. We also analyzed the relationship of NLR, uric acid and disease severity but no correlation was found. C reactive protein which is another inflammation marker was also higher in group I but the difference was statistically insignificant. Our results may be considered to support the triggering effect of inflammation in CAA development.

CAA is usually an incidental finding in asymptomatic patients with an unknown etiology. Coronary atherosclerosis is one of the most frequent etiologic factor of aneurysm formation in adult patients[9]. The strong correlation between inflammation and atherosclerosis is well known. Atherosclerosis changes both histologic structure and flow dynamics of arteries. Histologically, inflammation between tunica media and intima may trigger aneurysm formation in patients with atherosclerosis and on the other hand atherosclerosis affects distribution of collagen type I and type III in arterial wall[3]. Additionally, post-stenotic flow disturbances may also contribute disease progression.

Neutrophil related substances play an important role in inflammation. Antoniadis et al. reported that inflammatory cell infiltration of the media layer by can be seen in ectatic coronary segments[10]. Neutrophils may cause tissue damage and aneurysm formation by secreting elastase, matrixmetalloproteinases (MMP) and oxygen free radicals. Akyel et al. found that neutrophil gelatinase-associated lipocalin (NGAL) which is secreted from activated neutrophils is higher in patients with isolated coronary artery aneurysm than normal population[11]. NGAL prevents MMP-9 degradation. MMP-9 causes degradation of gelation and collagen and indirectly leads to weakened artery wall and aneurysm formation. On the other hand neutrophil catalase activity was found to be decreased in patients with abdominal aortic aneurysm[12]. Although increased activated neutrophils play an important role, diminished antioxidant capacity may also be one of the major mechanisms in arterial wall damage.

Increased oxidative stress and decreased antioxidant capacity have been considered as important components of cardiovascular disease pathogenesis. Koc et al., showed that superoxide dismutase plasma activity can be decreased and that gamma glutamyl transferase activity can be increased in CAA patients[13]. Similary, Sezen et al. also showed that total oxidant status is increased and antioxidant status is decreased in patients with CAA[14]. Previous studies revealed that xanthine oxidase (XO) acts as a source of reactive oxygen species in the cardiovascular system. XO catalyzes purine degradation and converts hypoxanthine and xanthine to uric acid with concomitant generation of superoxide. Ramos et al., found increased superoxide levels in patients with abdominal aortic aneurysm[12]. Similary, role of increased oxidative stress was reported in ascending aorta aneurysm. Uric acid is the last product of purine metabolism and associated with H2O2 level. In this context, SUA may be considered reflecting oxidative stress. Previously, Esen et al. found significant correlation with SUA and oxidative stress in patients with ascending aorta aneurysm[15].

Both previous studies and our results demonstrate correlation of inflammation and coronary artery ectasia. Unfortunately neither NLR nor SUA levels may have spesific value in CAA diagnosis. In the last decade NLR has been found to be strongly associated with various pathologies. Koc et al. reported NLR in CAA diagnosis with a sensitivity of 77% and spesificity of 63%[13]. Similary SUA may be influenced in several processes and may have no prognostic value for coronary artery aneurysm diagnosis. NLR and SUA present new treatment targets rather than diagnostic modality. Antiinflammatory drugs may be an alternative in management of selected cases. In this sense simvastatin was found to possess preventing role in free radical formation by decreasing lipid peroxidation and TNF-α generation and also increasing catalase activity in human abdominal aortic aneurysm wall[16]. Recently Hasan et al. reported that acetylsalicylic acid attenuates inflammation in the walls of human cerebral aneurysms by decreasing expression of cyclooxigenase-2 (COX-2), microsomal prostaglandin E2 synthase-1 (mPGES-1) in macrophages[17]. In this regard, inflammation seems like a breaking point in aneurysm formation.

XO inhibitors have been widely studied in cardiovascular disease. Since XO is the major source of superoxide in vascular endothelium, XO inhibitors may decrease superoxide formation. Dopp et al. found that allopurinol, a XO inhibitor, attenuates chronic intermittent hypoxia related endothelial dysfunction in rats[18]. Allopurinol also directly scavenges free radicals and decrease oxidative stress[19]. In the last decade, another XO inhibitor Febuxostat has been used in uric acid lowering treatment and showed superior beneficial effects on oxidative stress compared to allopurinol[20].

In conclusion, previous studies and also ours indicate that inflammation and oxidative stress are important triggering factors of aneurysm formation in human coronary arteries. Antiinflammatory and antioxidant treatment may be new management targets to prevent aneurysm process.

Table 2. Comparison of hematologic markers

Parameter	Group I	Group II	P value
WBC	7347.62±2231.28	6717.65±2258.28	0.392
RDW	14.05±1.49	13.45±0.52	0.128
MPV	8.08±0.74	8.3±1.21	0.493
NLR	2.44±0.88	1.80±0.49	0.010
CRP	0.60±0.58	0.35±0.36	0.131
SUA	6.37±1.80	4.91±0.99	0.008

WBC: White blood cell count; RDW: Red blood cell distribution width; MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; CRP: C-Reactive protein; SUA: Serum uric acid.

Study Limitations

We could not investigate inflammatory cytokines and antioxidant status due to retrospective design and we could not perform cut off value analysis for both NLR and uric acid because of inadequate sample size.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

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