LEUKOCYTURIA AND CORONARY ARTERY DISEASE: FURTHER EVIDENCE TO THE PRESENCE OF INFLAMMATORY PROCESSES IN ACUTE CORONARY SYNDROME

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Abstract

INTRODUCTION: Cardiovascular disease is the main cause of mortality in developing countries. Because the major classic risk factors fail to explain the disease's epidemiologic diversity, other risk factors such as inflammation and systemic infections are being investigated, although no cause and effect relation between these infections and acute coronary syndrome (ACS) has yet been decisively proven. In view of the possible role of local and systemic infections in the occurrence of ACS, as well as leukocyturia and hematuria, the present study was designed and carried out.

METHODS: This was a prospective case-control study of all patients diagnosed as having ACS and hospitalized at the CCU of Fatemiyeh Hospital in Semnan. Urine analysis and culture were performed in all patients and the control group in the early stage of admission to the CCU. After collecting data, we examined the associations and the differences between the two groups by using t-test and chi-square test.

RESULTS: The case and control groups did not show any significant difference based on age and sex (age 60.03±19.32 years in cases and 59.9±17.2 years in controls, female prevalence was 40.5% in both groups). Hematuria was seen in 18.5% of cases and 5% of controls ($P<0.0001$). Leukocyturia was seen in 28.5% of cases and 12% of controls ($P<0.0001$). Albuminuria was seen in 6% of cases and 7% of controls ($P>0.05$).

CONCLUSIONS: These findings indicated the presence of sub-clinical underlying infection process due to uncommon pathogens or leukocyturia and hematuria in a systemic inflammatory process that can predispose to ACS by systemic inflammation.

Keywords: Hematuria, leukocyturia, acute coronary syndrome.

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Introduction

Coronary artery disease is the most common cause of mortality in developed countries and several factors are suggested as risk factors for this disease, some of which, including high blood pressure, hyperlipidemia, smoking and obesity, are proven to have such a role.[1-3] Since these classic major risk factors have not been able to explain the disease's epidemiologic diversity, other risk factors such as inflammation and systemic infections are being investigated, although no cause and effect relation between these infections and acute coronary syndrome has yet been decisively proven.[4,5]

Inflammatory factors like CRP, ICAm-1 and cytokines like IL-1, IL-2 and LL-6, and fibrinogen are associated with higher risk of cardiovascular diseases and acceleration of the atherosclerotic process.[6-9] The source of stimulation for production of these inflammatory factors may be within, or outside the vessels, e.g. chronic bronchial and urinary infections.[10] Infectious agents can play a significant role in the pathogenesis of atherosclerosis, which may be a result of a chronic infectious and/or inflammatory process of low intensity which may cause endothelial dysfunction[11] and occasionally there have been

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reports of overlaps between pathologic changes seen in obstructive vascular diseases and those seen in infectious diseases.[12]

Chronic infections with Chlamydia pneumoniae and Helicobacter pylori,[13-16] CMV,[8,17] gingival chronic infection,[14] bronchial infection,[10] urinary infection,[17] hepatitis A,[11] and HSV,[11,13] may lead to systemic infection which supports the theory on the role of infections in coronary disease.

Development of atherosclerosis has been described as a response to damage, and is indeed a mild chronic inflammatory process. Whether these infections play a role in atherogenesis or in changing a stable angina into an unstable angina and myocardial infarction is a controversial issue.[18,19]

Inflammatory processes can aggravate the process of atherosclerosis and systemic infection and these mild infections which have no apparent clinical signs, cause the acute coronary syndrome (ACS).[20, 21].

Another evidence of the role of infections in atherosclerosis comes from completed or ongoing studies that indicate a significant decrease in cardiovascular accidents following antibiotic therapy of patients after myocardial infarction.[20,21]

Considering the possible role of local and systemic infections in the occurrence of ACS, as well as leukocyturia and hematuria observed without urinary symptoms in a significant number of patients admitted for ACS, the present study was designed and carried out to compare the results of urine culture and prevalence of leukocyturia, hematuria and albuminuria between patient and control groups.

Materials and methods

This was a case-control study of all patients diagnosed as having ACS (unstable angina and myocardial infarction, hospitalized at the CCU of Fatemiyeh Hospital in Semnan, who were enrolled after giving informed consent. Data collection took nearly one year.

The diagnosis of ACS was based on classic criteria, including clinical signs of unstable angina:

1. Stress and/or exercise-induced chest pain which goes away after 5-10 minutes with rest and TNG
2. Pain at rest or with mild activity
3. Incremental pain

Myocardial infarction (MI) is characterized with pain of long duration and increase in myocardial enzymes, such as troponin, CKMB and CPK (indicating necrosis).[3]

Changes in RBC, WBC and albumin content of urine samples where studied on the basis of the following criteria:[3]

1. More than 3 erythrocytes in HPF in a urine sample
2. More than 8 leukocytes in HPF in a urine sample
3. More than 1+ albumin in dipstick test of a urine sample
4. Positive urine culture

Patients hospitalized due to unstable angina or MI within the last two weeks, patients whose urinalysis and urine culture samples were not taken during the first 2 hours of admission, patients with a history of renal diseases (e.g. renal failure), patients with signs of systemic or urinary infections, and patients who had undergone antibiotic therapy within the last two weeks in either group were excluded from the study.

The control group consisted of patients hospitalized for non-infectious and non-febrile conditions who had no history of taking antibiotics within the last two weeks.

Urine samples were taken in sterile conditions from all patients prior to heparin instillation (at most 1-2 hours after admission) for analysis and culture. The patients were enrolled in the study after giving their informed consent. This procedure was repeated for all members of the control group.Urine samples were centrifuged with cobota-KN70 for 10 minute at 3000 rpm and examined for WBC, RBC and albumin with Olympus microscope BH2; culture was performed in EMB-blood media.

All relevant data (results of urinalysis and urine culture, etc) analyzed by SPSS/11.5 to be evaluated by t-test and chi square statistical test with $\alpha=0.05$, to reveal differences or relations between selected variables.

Results

The patients had a mean age of 60.03±19.32 years and 40.5% were female. The control group had a mean age of 59.9±17.20 years and 40.5% were female. The two groups were not significantly different in terms of mean age and sex distribution ($P>0.05$).

Major cardiovascular risk factors in the two groups are shown in Table 1.

Hematuria was seen in 37 patients with ACS (18.5%) and in 10 members of the control group (5%). ($P=0.0001$, OR=4.31, CI 95%: 2.08-8.94).

Leukocyturia was detected in 28.5% (57) of patients and 12% (24) of controls. ($P=0.001$, OR=2.92, CI 95%: 1.73-4.94).

TABLE 1. Major Coronary Risk Factor in Cases and Control Groups

variable	Mean age	Male	Diabetes mellitus	Hypertension	Smoking	Hyperlipidemia
Unstable angina	58	54%	17%	45%	25%	35%
myocardial infarction	60	67%	18%	47%	28%	40%
control	59.9	59.5	6%	20%	20%	25%

Albuminuria was seen in 6% (12) of patients and 7% (14) of controls. (P<0.05, OR=0.86, CI 95%: 0.39-1.90). None of the patients had positive urine culture, while 1.5% of controls did; this is not a significant difference (P>0.5).

In the patients group, 174 had unstable angina and 26 had MI, and 19.2% of those with MI and 18.2% of those with unstable angina had hematuria (P>0.5, OR=1.65, CI 95%: 0.56-4.81).

Leukocyturia was seen in 22.9% of MI patients and 29.4% of unstable angina patients, with no significant difference (P>0.5, OR=0.72, CI 95%: 0.27-1.91). Albuminuria was also seen in 3.8% of MI patients and 6.3% of unstable angina patients which is not statistically significant (P>0.5, OR=0.59, CI 95%: 0.7-4.79).

Discussion

This case-control study showed that evidence of mild urinary infection, i.e. leukocyturia and hematuria in patients with ACS was more common than in controls, although none had positive urine cultures. These findings may indicate a mild underlying infection, infection with uncommon pathogens, or leukocyturia and hematuria due to a systemic inflammatory process. All of these can predispose an individual to ACS through a systemic inflammation. Most coronary thromboses result from a tear in a fibrous cap in vascular plaque, which has a dynamic state and its shape is constantly changing. Evidence shows that the balance between synthesis and degeneration of collagen content of a fibrous cap is controlled by inflammatory mediators.[22]

Pre-inflammatory cytokines can break the proteases that make the extracellular matrix and cause damage to the intimal layer, subsequently causing the exposure of the sub-endothelial area and release of endothelial cell tissue factors, which in turn lead to the activation of pre-coagulation pathways and finally local thrombosis.[19]

On the other hand, fibrinolytic pathways can change and cause a pre-coagulation state in patients with subclinical infections. Leukocyturia can decrease the epicardial blood flow and myocardial perfusion and cause an increase in thrombosis formation at the site of torn plaque.[23]

A urinary infection occurs when a bacterium binds to mucosal loci in the urinary pathways and involvement of the urinary pathways leads to bacteremia, which is seen in 30% of patients with urinary infections and causes systemic responses in these patients.

Adherence of bacteria to urinary epithelial cells begins the consecutive cytokine process and release of interleukins 1, 6, 8 and increase in neutrophils and inflammatory cells. If this process continues, a stable atherosclerotic plaque, which may have resulted from infection with germs that do not grow in ordinary culture media may rupture, or the infection may be too mild to give a positive culture.

A recent study in Dallas showed that the prevalence of urinary infection in ACS patients who were in hospital for coronary bypass surgery was 3 times as high as in the control group.[19]

It was observed in a survey that markers of mild inflammation, such as elevated CRP, leukocytosis and interleukins, increase in patients with ACS. An increase in white blood cells (WBC) can also cause MI.[13] Monocytes can cause an increase in pre-coagulation activity through increasing interleukins 6 and 8; a relation between infection, inflammation and thrombosis formation in ACS has also been suggested.[15]

Various infectious agents such as Chlamydia and CMV (cytomegalovirus) are associated with a higher risk of atherosclerosis and early myocardial infarction, supporting possible involvement of inflammatory processes in the occurrence of ACS.[10,13]

Another survey revealed that the rate of cardiovascular accidents increases following respiratory infections, with its peak in the first 3 days of infection; the study also showed that urinary infections increase the risk of these accidents.[15]

Another study has shown a significant decrease in cardiovascular accidents following antibiotic therapy in patients with MI.[20,21] These patients had negative urine cultures despite leukocyturia and hematuria; this raises the question of whether uncommon urinary infections have a role, or if consumption of quinolones by patients with leukocyturia can cause a decrease in cardiovascular accidents. Broader studies are required to address these questions.

The limitations of this study were that it was not possible to have a simultaneous blood culture to rule out systemic infections, and to have urine cultures for those pathogens that do not grow in ordinary culture media.

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