Atherosclerosis 229 (2013) 124–129

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Coronary calcification identifies the vulnerable patient rather than the vulnerable Plaque

Alessandro Mauriello [a,*], Francesca Servadei [a], Giuseppe Biondi Zoccai [b], Erica Giacobbi [a], Lucia Anemona [a], Elena Bonanno [a], Sara Casella [a]

[a] Anatomic Pathology, University of Rome Tor Vergata, Italy
[b] Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

ARTICLE INFO

Article history:
Received 21 September 2012
Received in revised form
11 March 2013
Accepted 11 March 2013
Available online 21 March 2013

Keywords:
Coronary calcification
Plaque vulnerability
Vulnerable patient
Histology

ABSTRACT

Objective: Presence of coronary artery calcium (CAC) is associated with a high risk of adverse cardiovascular outcomes. Nevertheless, although CAC is a marker of atherosclerosis it is still uncertain whether CAC is a marker of plaque vulnerability. Therefore, the aim of this study was to verify if calcification identifies a vulnerable patient rather than the vulnerable plaque.
Methods: A morphologic and morphometric study on 960 coronary segments (CS) of 2 groups of patients was performed: (i) 17 patients who died from AMI (510 CS); (ii) 15 age-matched control patients without cardiac history (CTRL, 450 CS).
Results: Calcification was found in 47% CS of AMI and in 24.5% CS of CTRL. The area of calcification was significantly higher in AMI compared to CTRL ($p = 0.001$). An inverse correlation was found between the extension of calcification and cap inflammation ($r^2 = 0.017$; $p = 0.003$). Multivariate regression analysis demonstrated that the calcification was not correlated with the presence of unstable plaques ($p = 0.65$). Similarly, the distance of calcification from the lumen did not represent an instability factor ($p = 0.68$).
Conclusion: The present study suggests that CAC score evaluation represents a valid method to define the generic risk of acute coronary events in a population, but it is not useful to identify the vulnerable plaque that need to be treated in order to prevent an acute event.
© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

It has been widely demonstrated that acute coronary syndromes (ACS) are related to rupture and acute thrombosis over a mildly stenotic plaque, rather than to a slow growth with final occlusion of a plaque encroaching the lumen [1–3]. Several studies highlighted the role of inflammatory cells (macrophages and T lymphocytes), metalloproteases and cytokines in the transformation of a stable plaque into a vulnerable one [4–6]. It has been suggested that calcific content of a plaque is another key factor for plaque destabilization, potentially modifying mechanical plaque's characteristics and predisposing it to rupture [7] (Fig. 1).

Indeed, calcification is the most frequent complication of atherosclerotic lesions [8]. There is a strong relationship between mortality and total coronary artery calcium (CAC) score evaluated by cardiac computed tomography (CT) [7,9,10]. Presence of CAC is a well-established marker of coronary plaque burden and is associated with a high risk of adverse cardiovascular outcomes [11,12]. Although coronary calcification is a marker of atherosclerosis, its effect on plaque instability seems to be less evident. It is still uncertain whether coronary calcification is a marker for plaque vulnerability.

The recent introduction of intravascular ultrasound (IVUS) provided conflicting results compared to CT-based studies [13,14], showing minor calcification in culprit lesions of ACS in respect to patients with stable angina [15].

Moreover, it is worth noting that in the modified AHA classification of coronary plaques the frequent fibrocalcific plaques are considered as stable lesions [16]. These findings are difficult to reconcile with those derived by CT.

In order to better define the role of calcification in coronary plaques destabilization we perform a detailed morphologic, morphometric and topographic study evaluating serial sections of the whole coronary tree of patients died from acute myocardial infarction (AMI) and non-cardiac causes.

* Corresponding author. Cattedra di Anatomia ed Istologia Patologica, Dipartimento di Biomedicina e Prevenzione, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Roma, Italy. Tel.: +39 06 2023751; fax: +39 06 20902209.
E-mail address: alessandro.mauriello@uniroma2.it (A. Mauriello).

0021-9150/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.03.010

2. Materials and methods

2.1. Patient population

We studied 960 coronary segments (CS) of 32 consecutive autopsies of 2 group of patients who have died at the Policlinico of the University of Rome Tor Vergata: 17 patients died from AMI (AMI group, 10 males/7 females, mean age 68.8 ± 9.5 years) and 15 age-matched control patients without positive cardiac history (CTRL group, 8 males/7 females, mean age 75.4 ± 12.6 years) who died from non-cardiac causes and in whom at least one coronary showed a cross-sectional luminal stenosis >50%. In the AMI group, the time interval between symptom onset and death was less than or equal to 72 h for all cases. Clinical history, electrocardiographic findings and positive cardiac enzymes defined the presence and the localization of acute myocardial infarction. This diagnosis was then confirmed by the histological analysis. All autopsies were performed within 12–24 h of death.

The study met the criteria of the code of proper use human tissue that is used in Italy for the use of human tissue.

2.2. Tissue handling and processing

The three major epicardial coronary arteries (left anterior descending, left circumflex and right coronary arteries) were carefully dissected for the entire length from the origin and fixed with buffered formalin. All CS were cut transversely at 5 mm intervals. Ten segments were examined for each coronary artery, in particular 510 CS of patients who died from AMI and 450 CS of patients of the control group. Coronary segments from patients died from AMI were subdivided into two additional groups, (a) infarct related coronary arteries and (b) non-infarct related coronary arteries.

The myocardium was macroscopically examined to detect the presence and extent of the infarcted area. In all cases, at least one complete transverse heart slice was sampled. Multiple myocardial samples were processed for histopathologic examination and the infarction confirmed by light microscopy.

All samples were paraffin-embedded. For histopathologic examination, arterial sections were stained with hematoxylin and eosin and Movat's pentachrome stain. A immunohistochemical study was also performed in order to characterize and quantify inflammatory cells of the plaques using CD68 (anti-human macrophages; Dakopatts, Denmark) and CD3 (anti-human T cell; Dakopatts) monoclonal antibodies.

2.3. Histopathologic and morphometric studies

Plaques were classified into three categories, according to the modified AHA atherosclerosis classification [16]: (1) unstable plaques, (2) stable ones and (3) pre-atherosclerotic lesions. Unstable lesions included both (a) "culprit" plaque characterized by the presence of an acute thrombus associated with plaque rupture or plaque erosion and (b) "vulnerable" plaques or "thin fibrous cap atheromata", characterized by a lipid-rich core covered by a less than 65 μm thick fibrous cap containing many lipid-laden macrophage foam cells (>25 per high-power magnification). In this group we also included the calcified nodule corresponding to a lesion characterized by an eruptive, dense area of calcium protruding in the lumen. Stable plaque included both fibrous cap atheromata and fibrocalcific plaques. Fibrous cap atheromata was characterized by a large lipid-necrotic core containing extracellular lipid, cholesterol crystals and necrotic debris, covered by a thick fibrous cap with few inflammatory cells. Fibrocalcific plaques consisted mainly of fibrous tissue with large calcification. Pre-atherosclerotic lesions included the diffuse intimal thickening (DIT) and the pathological intimal thickening (PIT).

Calcification was divided into (a) microcalcification if constituted only by spot <10 μm occupying <5% of cross-sectional plaque area and (b) macrocalcification if represented by large calcific plate ≥5% of plaque area.

In each CS the following variables were recorded: (a) lumen area (L); (b) internal elastic lamina (IEL) area; (c) plaque area [IEL − L]; (d) percentage of luminal stenosis [(IEL − L)/IEL × 100]; (e) cross-sectional of calcification (CA) and necrotic lipidic core (LC); (f) the relative area of calcification (%CA) as [CA/plaque area × 100] and that of necrotic lipidic core (%LC) as [LC/plaque area × 100]; (g) the minimum thickness of the cap; (h) the minimum distance of calcification from the lumen. Cross-sectional images were acquired by a Nikon digital camera connected to a computer. Areas were measured by using the Scion Image program (Scion Corporation) for morphometric analysis.

In order to determine hypertensive damage (irrespectively of type and amount of antihypertensive drug usage), arterial thickening was measured in the renal parenchyma [17]. Approximately 20 arteries 150–500 μm in diameter were analyzed from each kidney and the arterial histopathologic changes scored as following: 1: arteries and arterioles essentially free of intimal thickening; 2: focal mild intimal thickening; 3: concentric intimal thickening less than or equal to the thickness of the media; 4: concentric intimal thickening greater than the thickness of the media without concentric elastic duplication; 5: concentric intimal thickening greater than the thickness of the media with concentric elastic duplication in 3 or more vessels examined. Scores 4 and 5 were considered as indicator of chronic hypertensive status. The presence of other kidney diseases was also recorded.

2.4. Statistical analysis

Data were analyzed by SPSS 14.0 (Statistical Package for the Social Sciences) software. Continuous and categorical variables are expressed as mean ± SD or ±SE and as frequency values and proportions, respectively. Pearson's chi-square test and Fisher's exact test were utilized to assess possible differences of dichotomous variables between plaques of the various groups examined. The means of normally distributed data were compared with Student *t* test. In the other cases the groups were compared with Mann–Whitney's *U* test. Correlations between histologic measurements were made using a bivariate linear regression model. Multivariable linear regression analysis was performed to determine the morphological features associated to the presence of an unstable plaque and r^2 was computed using the unstable plaque as the only independent variable. A *p*-value of <0.05.

3. Results

3.1. General findings

No differences were observed between AMI and CTRL groups for age, gender, distribution of major risk factors (hypertension, hyperlipidemia, smoking, diabetes) and renal pathology (Table 1).

Myocardial histopathologic examination confirmed an acute transmural infarct as cause of death in all patients who died from AMI. Myocardium from CTRL group of patients showed neither infarct nor small necrosis in all cases. The cause of death in the CTRL group was bronchopneumonia in 8, bowel infarction in 2, pulmonary embolism in 4 and cerebral hemorrhage in 1 (Table 1).

The 960 analyzed CS were constituted by 201 pre-atherosclerotic plaques (20.9% of cases), 705 stable plaques (73.4%) and 54 unstable plaques (5.7%). In the latter group, 37 plaques were vulnerable and

Download English Version:

https://daneshyari.com/en/article/5947844

Download Persian Version:

https://daneshyari.com/article/5947844

Daneshyari.com