Role of plaque inflammation in acute and recurrent coronary syndromes

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Inflammation plays an important role in the initiation, development, progression and complications of atherosclerotic vascular disease. Our present knowledge of the elementary role of inflammation for the onset of plaque rupture in atherosclerotic coronary lesions primarily stems from autopsy studies. However, the introduction of directional coronary atherectomy catheters has provided a unique opportunity to directly investigate the role of inflammation in coronary syndromes. In this report we describe the role of coronary plaque inflammation, as determined by immunohistochemistry, on the presentation of coronary syndromes and on the clinical outcome following percutaneous interventions. (*Neth Heart J* 2004;12:106-9.)

Key words: coronary syndromes, C-reactive protein, inflammation, plaque, restenosis

Recognition of the significant role of inflammation in development of atherosclerosis has dramatically changed our understanding of the pathophysiology of coronary artery disease during the last decade.[1-5] Basic research has established an elementary function of inflammation in all stages of atherosclerotic disease, starting from endothelial dysfunction and fatty streak formation to advanced complex and ruptured plaques and subsequently, thrombotic involvement.[3] Coronary atherosclerosis is initiated by endothelial dysfunction including upregulation of adhesion molecules and an increased permeability of the vessel wall to lipids, leucocytes and monocytes.[3] Macrophages and smooth muscle cells transform into foam cells by phagocytosis and accumulation of lipids. In addition, T lymphocytes and smooth muscle cells migrate into the neointima and contribute to the formation of a so-called 'fatty streak'. Expansion of the lipid core of the plaque is stimulated by death of lipid-laden foam cells. A large necrotic core with an overlaying fibrous cap is a characteristic feature of an advanced unstable lesion (figure 1A). Activated macrophages and T lymphocytes produce numerous growth factors and proteins with proteolytic activity such as metalloproteinases, which are capable of destabilising the fibrous cap. These inflammatory cells often accumulate in the shoulder region of the cap, the site where plaque rupture frequently occurs (figure 1B).[6] Involvement of procoagulant factors, which stimulate platelet adherence and aggregation, may lead to a superimposed clot formation and occlusion of the coronary artery.[1,7,8] The ensuing acute coronary syndromes or cardiac death are often the first manifestation of this chronic and progressive, and ultimately lethal disease. However, not all atherosclerotic lesions develop into unstable plaques. Abundant collagen synthesis and smooth muscle cell proliferation have stabilising effects, and determine whether a plaque will be stable or vulnerable (figure 1C).[4,9,10]

Our present knowledge of the elementary role of an inflammatory process for the onset of plaque rupture in atherosclerotic coronary lesions primarily stems from autopsy-based studies.[6] However, the introduction of directional coronary atherectomy catheters has provided a unique opportunity to directly investigate the role of inflammation in atherosclerotic

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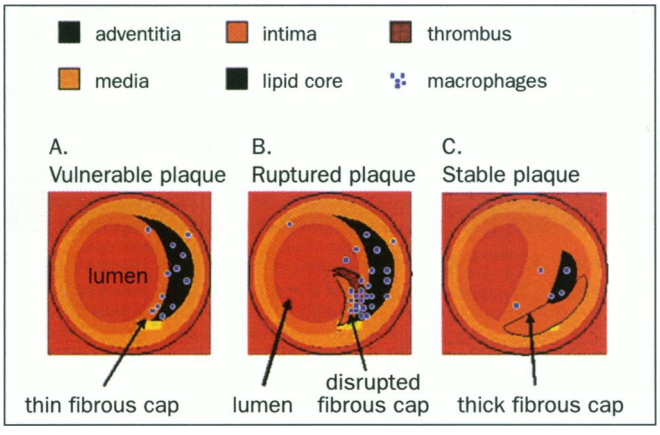

Figure 1. A. Schematic illustration of a cross-section of a vulnerable plaque. A large lipid core covered by a thin fibrous cap is a typical characteristic of a vulnerable plaque. The lumen of the coronary artery is often well preserved despite a large plaque volume, due to outwards growth of the vessel (positive remodeling).
B. Schematic illustration of a cross-section of a plaque rupture. The fibrous cap is disrupted at the shoulder site, where many inflammatory cells have infiltrated. The thrombus with large atheroma extends into the vessel lumen and may occlude the coronary artery completely. This is the typical lesion of unstable angina and myocardial infarction.
C. Schematic illustration of a cross-section of a stable plaque. A thick fibrous cap covers the lipid core, if present.

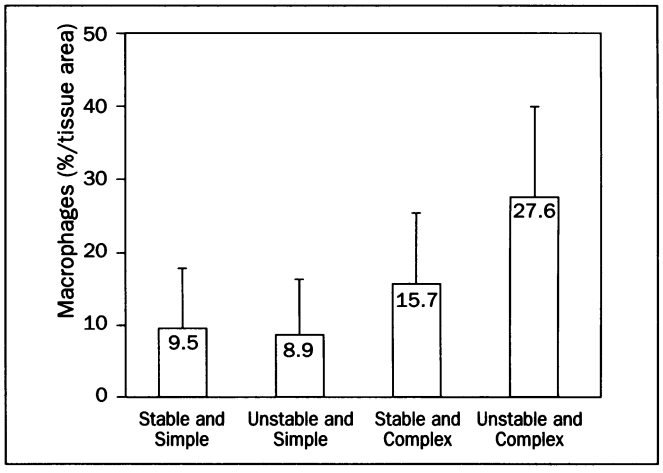

Figure 2. Bar graph showing the positive interaction between angiographic grading of coronary lesion complexity (complex vs. simple coronary lesions) and clinical presentation of the coronary syndrome (unstable vs. stable angina) on the extent of plaque macrophages.

plaques of patients. Initial studies have demonstrated significant differences in the extent of plaque inflammation between patients with stable and unstable angina.[11-13] Coronary lesions of patients with unstable angina or myocardial infarction contain more macrophages and T lymphocytes compared with coronary lesions of patients with chronic stable angina. These studies provided additional support to the hypothesis that infiltration of inflammatory cells is crucial for the onset of unstable coronary syndromes. Nevertheless, there is still limited information regarding the in vivo evaluation of this atherosclerotic process. In this study we describe the background and the role of plaque inflammation on the presentation of coronary syndromes and on the clinical outcome following percutaneous coronary interventions.

Clinical and angiographic correlates of plaque inflammation

Coronary angiography is used as the gold standard for evaluating symptomatic coronary artery disease. However, the angiographic severity of a coronary narrowing is not predictive for the clinical severity of acute coronary syndromes. Patients with unstable or stable angina pectoris may show narrowing with a similar percent diameter stenosis on coronary angiography.[14,15] Clinical studies by Ambrose et al. revealed a relation between qualitative angiographic characteristics of coronary narrowing and the clinical severity of coronary syndromes.[15,16] Irregular shaped eccentric coronary narrowings on angiography were related to unstable angina pectoris and were associated with ruptured atherosclerotic plaques with or without occlusive thrombus. In a study of 79 consecutive patients with symptomatic coronary artery disease we evaluated the relationship between angiographic complexity of coronary lesions (using the Ambrose classification)[16] and its inflammatory component. A multivariate model was used to evaluate which clinical and angiographic factors are associated with the amount of plaque inflammation. The degree of plaque inflammation of culprit coronary lesions was determined by immunohistochemical staining for macrophages and T lymphocytes. The results of this study showed that angiographically complex lesions and unstable anginal symptoms are positively associated with the amount of plaque inflammation.[17] The positive association between lesion complexity and macrophage content was more pronounced in patients with unstable angina than in patients with stable angina (figure 2). No other factors were positively associated with plaque inflammation.

Plaque C-reactive protein in acute coronary syndromes

Clinical studies have underlined the significance of serum C-reactive protein (CRP) for risk stratification in healthy individuals, in patients with stable and unstable angina and after percutaneous coronary intervention (PCI).[5] Furthermore, a positive relation between serum levels of CRP and the severity of manifestations of coronary syndromes was shown.[18] CRP is produced in the liver, in damaged tissues such as myocardial infarction and in atherosclerotic plaques causing catalysation of the inflammatory process.[19] CRP co-localises in the plaque with macrophages, cholesterol (oxidised LDL) and the membrane attack complex, which is involved in cell apoptosis and

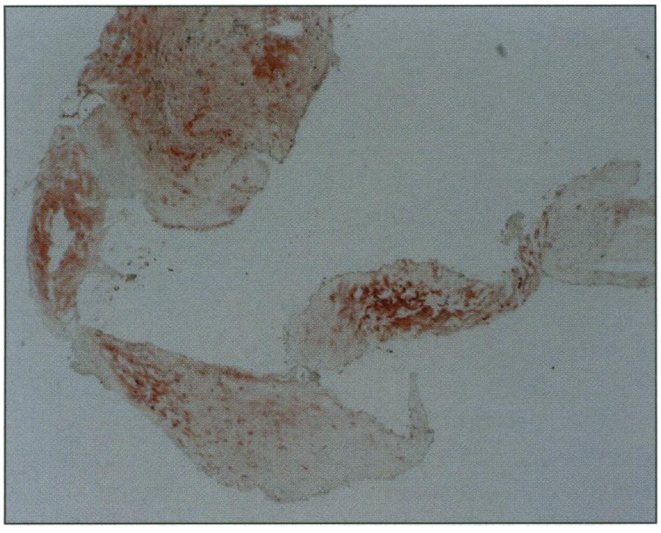

Figure 3. Part of an atherectomy specimen of a culprit lesion of a patient with unstable angina stained with anti-5G4, representing CRP.

thrombosis formation.[20,21] The coincidence of CRP, macrophages, oxidised LDL and terminal membrane attack complex of the complement cascade factors was more pronounced in atherosclerotic tissue of patients with an acute myocardial infarction or unstable anginal symptoms than in patients with stable anginal symptoms. The amount of plaque CRP was also significantly higher in patients with an acute myocardial infarction or unstable anginal symptoms compared with patients with stable anginal symptoms.[22]

Plaque inflammation and restenosis

The impact of atherosclerotic plaque associated inflammation remains controversial in the context of restenosis following coronary interventional procedures. The neointima, considered the dominant tissue component in restenosis lesions, generally contains little if any inflammatory cells. Instead, the tissue is composed mainly of smooth muscle cells (SMCs) and related extracellular matrix components[23] and, in fact, has been promoted as having a stabilising effect on restenosis lesions.[1] However, clinical experiences have shown that recurrences due to restenosis, following coronary interventional procedures, may still become manifest as unstable angina pectoris (UAP), although stable angina pectoris (SAP) occurs more frequently.[24,25] Since UAP is usually associated with intraplaque inflammation, surface erosions and mural thrombotic events,[11,13] these observations suggest a persistent role for a lesion-associated inflammatory process. We showed that despite the presence of a high density of smooth muscle cells in atherectomy specimens, a similar relation is present as in 'de novo' lesions between the presentation of the anginal symptoms and the amount of inflammation. Patients with unstable anginal symptoms due to restenosis have a large amount of plaque inflammation as reflected by the density of macrophages and T lymphocytes.[26] The conception is that a smouldering inflammatory wound after balloon angioplasty is responsible for recurrent plaque destabilisation and thereby, responsible for recurrent unstable anginal symptoms.

Figure 4. Macroscopic view of the retrieved specimen showing transparent blueish homogeneous tissue.

In-stent restenosis is characterised by an even more prominent smooth muscle cell proliferation compared with restenosis after balloon angioplasty (figure 4).[27]

Plaque inflammation and recurrent coronary syndromes

Clinical studies have suggested a relationship between the presentation of de novo coronary syndromes and the recurrent clinical manifestation of angina due to restenosis.[24,28] Foley et al. reported that half of the patients with initial unstable angina also expressed their restenosis as unstable angina, while patients with initially stable angina who developed restenosis usually presented again with stable angina. In general, coronary restenosis is considered to present more often with a stable pattern of angina.[25] However, no data concerning the relationship between plaque inflammation of the initial culprit lesion and the subsequent manifestation of coronary syndromes are available. We studied the predictive value of plaque inflammation on the incidence of cardiac events after angioplasty by evaluating the relationship between the extent of plaque macrophages and T lymphocytes and the recurrence of stable or unstable anginal symptoms and restenosis within one year after directional coronary atherectomy. No relationship between the extent of inflammation and the incidence of restenosis was found in this consecutive patient population. However, this study demonstrated a positive relation between the amount of initial plaque inflammation and the severity of recurrent anginal symptoms at long-term follow-up after directional coronary atherectomy.[29] Similar results were found in larger studies from De Winter et al.[30] in which plasma markers of inflammation (CRP) were measured. These observations strongly suggest that the inflammatory process at the site of the culprit lesion is not eradicated by atherectomy, so that the smouldering effects of the inflammation again may destabilise the repair tissues responsible for the severity of anginal symptoms at follow-up.

Conclusion

Inflammation plays an important role in the initiation, development, progression and complications of atherosclerotic vascular disease. Patients presenting with stable angina compared with patients presenting with unstable angina or acute myocardial infarction are characterised by marked differences in the extent of plaque inflammation of culprit coronary lesions. A similar positive association between the manifestation of anginal symptoms and the extent of plaque inflammation exists for patients with restenotic lesions. Restenosis is associated with abundant smooth muscle cell proliferation irrespective of the presentation as stable or unstable angina. Initial plaque inflammation is not predictive for the occurrence of restenosis. The presence of a large amount of plaque inflammation has prognostic value for the recurrence of unstable symptoms during one-year follow-up after PTCA, suggesting that a 'smouldering' process of inflammation is responsible for the recurrent destabilisation of coronary plaques. The inflammatory plasma marker CRP has an important predictive value for the occurrence of adverse cardiac events.[2,31,32] Recently, it was demonstrated that CRP is a useful guidance of medical treatment.[33] The decrease of CRP levels after statin therapy is a more sensitive parameter for the incidence of cardiac events compared with the decrease in cholesterol levels. Aspirin and ACE inhibitors[5,34] have proven to be effective in the treatment of atherosclerotic disease. Recent studies suggest that treatment with statins is particularly useful in patients with an elevated CRP level. Furthermore, it has been reported that a change in lifestyle using a modified diet and more exercise also decreases the plasma CRP levels.[35] These findings indicate that elevated levels of inflammatory markers such as CRP should be considered as an additional risk factor for of atherosclerotic disease. ■

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