Transmural coronary inflammation triggers simultaneous multivessel rupture of unstable plaques

Emiliano Maresi, Rosalba Midulla, Valentina Cospite*, Nuccia Morici*, Rossella Tavormina**, Giovanni Fazio*, Elisabetta Orlando, Rosanna Porcasi, Caterina Trapanese, Paolo Procaccianti***

*Institute of Pathology, *Institute of Cardiology, **Institute of Pediatrics, ***Institute of Forensic Medicine, University of Palermo, Palermo, Italy*

Key words:
Acute coronary syndrome; Atherosclerosis; Inflammation; Plaque.

The authors describe a case of sudden cardiac death caused by the simultaneous multivessel rupture of unstable atherosclerotic plaques, triggered by a transmural inflammatory process (coronaritis).

Male subject, 44 years old, apparently in good health until 1 hour before death, when he complained of worsening dyspnea. At autopsy, it was found that the heart weighed 486 g. Evaluation of the coronary arteries revealed the presence of atherosclerotic plaques resulting in a lumen critical stenosis of the left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery, and acute occlusive thrombosis of the LAD and RCA. Transverse sections of the ventricular mass highlighted the presence of eccentric hypertrophy of the left ventricle associated with myocardiosclerosis of the posterior interventricular septum and of the posterior wall of the left ventricle. Histology revealed the presence of a coagulative myocytolysis ascribable to the free walls of the left ventricle, and a focus of lymphocytic-active myocarditis. All coronary arteries were sites of intima fibroatheromatous plaques complicated by rupture and thrombosis within the RCA and LAD and by a transmural infiltrate consisting of macrophages and T-lymphocytes associated with consensual medionecrosis and perineuritis.

In conclusion, the present case report confirms the hypothesis that inflammation plays a key role in the onset of acute coronary syndromes as it promotes the formation of an unstable plaque as well as its rupture.

(Ital Heart J 2003; 4 (7): 488-491)

Received December 19, 2002; revision received May 8, 2003; accepted May 19, 2003.

Address:

Prof. Emiliano Maresi

Via Gustavo Roccella, 61
90128 Palermo
E-mail: emilianomaresi@hotmail.com

Coronary thrombosis, an immediate cause of acute coronary syndromes (unstable angina, myocardial infarction, sudden death), is in most instances initiated by the rupture of an unstable (vulnerable) atherosclerotic plaque[1,2].

The morphological markers of an unstable plaque include a large lipid core and a thin fibrous cap containing numerous inflammatory cells (macrophages and T-lymphocytes)[3-5]. In atherosclerotic vessels, lymphocytic infiltrates can also be observed in the adventitia, with possible involvement of the vascular nerves[6], and less frequently in the tunica media[7]. Regardless of the location, inflammation occurs secondary to the continuous lipid deposition in the intima[8,9] and/or to various infectious stimuli, which overlay the atherosclerotic process[5,10]. Furthermore, the inflammatory infiltrate, just as conventional factors (hemodynamic stress, etc.), may determine the rupture of the unstable plaque[5].

In this study, the authors provide a *post-mortem* case description of a sudden cardiac death caused by the multivessel and simultaneous rupture of an unstable atherosclerotic plaque, triggered by a transmural inflammatory process (coronaritis).

Case report

Male subject, 44 years old, apparently in good health until 1 hour prior to death, when he complained of worsening dyspnea at rest. After consulting a clinician, he was urgently transferred to hospital; death occurred during transportation.

Autopsy revealed that the main medical findings were cardiac in nature. The heart weighed 486 g (normal range 270-310 g), its transverse diameter was 11.5 cm (normal range 9-11 cm), and its longitudinal diameter 10.5 cm (normal range 7-9 cm). The short-axis anatomic sections of the ventric-

ular mass highlighted the presence of left ventricular eccentric hypertrophy (interventricular septum 20 mm; left ventricle 17 mm; right ventricle 5 mm) and a focal intramural sclerosis located in the posterior interventricular septum and in the posterior wall of the left ventricle.

The coronary arteries were normal as to origin and course, with a dominance of the right circle; their opening by means of seriate transverse sections highlighted the presence of atherosclerotic plaques, partly concentric and partly eccentric, causing a lumen critical stenosis of the proximal segments of the left anterior descending (LAD), right coronary (RCA) and left circumflex arteries. These plaques were complicated by an acute occlusive thrombosis within the LAD and RCA.

Histology revealed the presence of myocardial contraction band necrosis (coagulative myocytolysis), located in the anterior and posterior walls of the left ventricle and of severe substitutive myocardial fibrosis involving the posterior interventricular septum and the posterior wall of the left ventricle. In the latter site, a small and isolated focus of active lymphocytic myocarditis was also visible.

The RCA, LAD and left circumflex arteries were found to contain unstable fibroatheromatous plaques in which lipid material was detected (Fig. 1). The fibrous caps of these plaques were found to have ruptured within both the RCA and LAD, causing acute occlusive thrombosis. In all three coronary vessels, there was a conspicuous transmural inflammatory infiltrate, consisting mostly of foamy macrophages at the intima plaque level and of lymphocytes at the media and adventitia levels (Fig. 1). At these sites, the lymphocytes determined a focal lysis of the smooth muscle cells and infiltrated the adventitial nerve endings (perineuritis) (Fig. 2A and 2B). Immunohistochemical investigation revealed that the inflammatory infiltrate consisted of T-lymphocytes (CD3+), helper (CD4+ and CD30+), cytotoxic (CD8+), and natural killer (CD57+) cells (Fig. 2C and 2D); additionally, the foamy macrophages were CD68+ (Fig. 2E and 2F).

Methods. Ventricular myocardial samples collected from the free wall of the left ventricle (3 samples), the interventricular septum (2 samples), and the right ventricle (2 samples) were fixed in formalin and subsequently included in paraffin for routine histological evaluation (hematoxylin-eosin; Veighert-van Gieson; Masson's trichromic). The immunohistochemical study of the coronary inflammatory infiltrate was carried out on 2-3 mm thick deparaffinized histological sections,

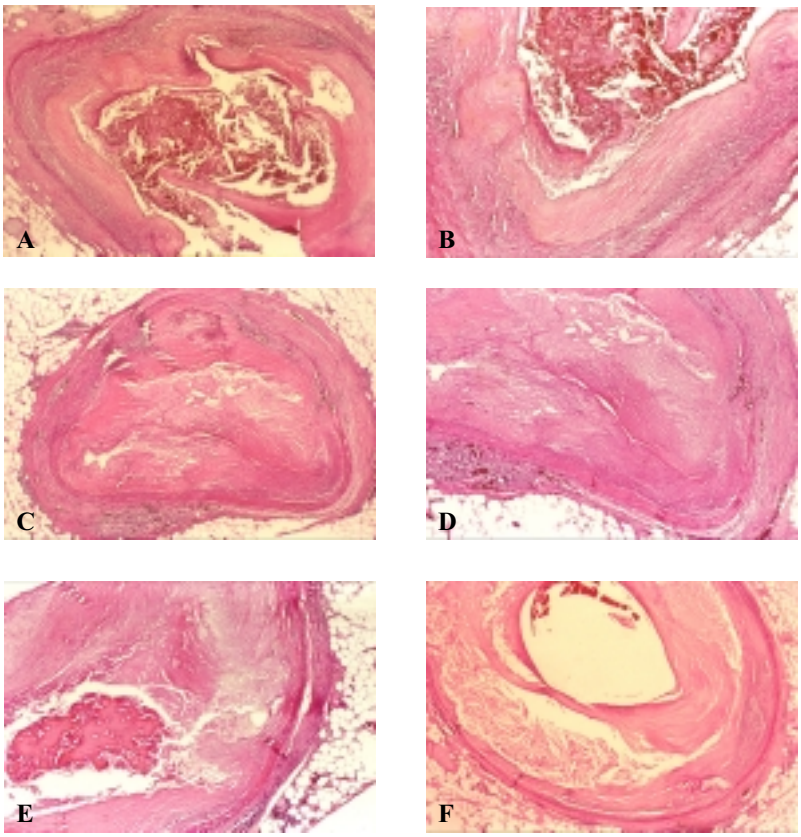

Figure 1. *Morphology of the unstable atherosclerotic plaques localized in the three main coronary arteries* (A-F)*: fibroatheromatous plaques, critically narrowing the coronary lumen, complicated by rupture of the fibrous cap within the left anterior descending* (A *and* B) *and right coronary arteries* (C-E). *All the coronary arteries showed a conspicuous lymphocytic infiltrate mainly involving the media and the adventitia.*

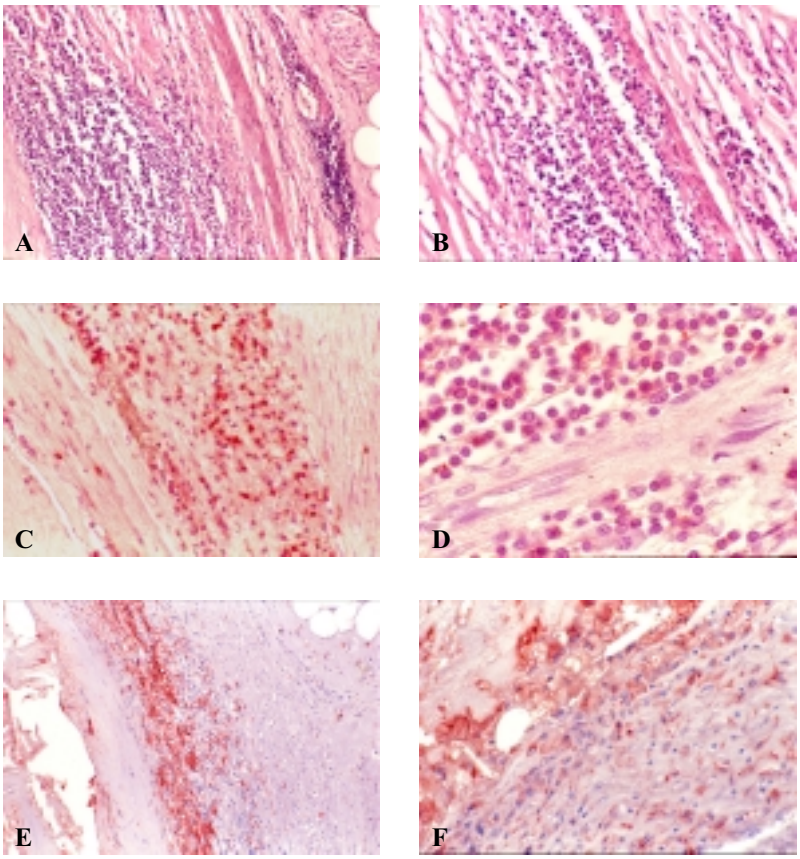

Figure 2. *Histology of the coronary inflammatory infiltrate* (A-F)*: media and adventitia inflammatory infiltrate* (A *and* B) *consisting of T-lymphocytes CD8+ and CD30+* (C *and* D) *with focal lysis of smooth muscle cells and perineuritis; note also the presence of foamy cells CD68+ mainly infiltrating the intima.*

pretreated with 0.01 M sodium citrate buffer solution (pH 6) and 3 MW cycles for antigenic exposure, and subsequently counterstained with Carazzi hematoxylin after having determined the presence or otherwise of antibodies against the CD3, CD4, CD8, CD30, CD57, and CD68 antigens.

Discussion

The presence of a lymphomonocytic infiltrate in an unstable coronary plaque suggests that inflammatory processes contribute both to the genesis of coronary atherosclerosis[5,11] and to its complications.

The inflammatory process involved in atherosclerosis does not differ from those occurring in chronic inflammatory fibroproliferative diseases such as liver cirrhosis, rheumatoid arthritis, glomerulosclerosis, pulmonary fibrosis, and chronic pancreatitis[10]. The fibroatheromatous plaque is the result of a series of highly specific cellular and molecular responses to various endogenous and exogenous antigenic stimuli[10,12]. These responses are mediated not only by endothelial and smooth muscle cells, but also by macrophages and specific subtypes of T-lymphocytes that determine the continuous remodeling of the plaque[3]. In fact, while the endothelial cells recruit the inflammatory ones (by expressing selective adhesion molecules, such as VCAM-1 that precisely binds monocytes and T-lymphocytes, on their surface, and by producing specific chemotactic molecules, such as MCP-1 that attracts monocytes) and smooth muscle cells produce matrix components (collagen, elastin and proteoglycans), macrophages ingest lipids (becoming foam cells) and T-lymphocytes stimulate them by producing interferon-γ and tumor necrosis factor-β[5,13]. However, macrophages and T-lymphocytes weaken the fibrous cap by two mechanisms: 1) producing proteolytic enzymes (a family of metalloproteinases that includes the collagenases, elastases, and stromelysins) and interferon-γ that respectively degrade collagen and inhibit its synthesis; 2) inducing the apoptosis of the smooth muscle cells[3,5,13-16]. In addition, macrophages ingest lipids and produce oxidized lipids that seem to be thrombogenic and also synthesize tissue factor, the major procoagulant: these macrophage products both lead to thrombosis when the plaque ruptures[5,13]. The prevalence of the fibroproliferative processes over inflammation contributes to the structural strength of the fibrous cap and induces the formation of a stable plaque; the imbalance between the inflammatory process and repair, in favor of the former, leads to destabilization of

the plaque (vulnerable plaque) and increases the risk of plaque rupture[17].

In the atherosclerotic coronary vessels, the inflammatory infiltrate may variably involve all three vascular layers[7] and represents a reactive phenomenon to the continuous deposition of modified lipid material and/or to various infectious stimuli (above all, *Chlamydia pneumoniae* and *Cytomegalovirus*)[10,13].

Besides damaging all three layers, the inflammatory process may involve other segments of the coronary tree. In fact, Buffon et al.[2] demonstrated, in a recent study, the widespread activation of neutrophils across the coronary vascular bed of patients with unstable angina, regardless of the location of the culprit lesion.

In the present case report, all three main coronary vessels were sites of unstable atherosclerotic plaques and the inflammatory infiltrate, mostly consisting of T-lymphocytes, was transmural. We believe that transmural inflammation of the coronary wall (coronaritis), and particularly the media and adventitia involvement, has triggered, via the induction of vessel hypertonia, the simultaneous rupture of the unstable atherosclerotic plaques located in the RCA and LAD[4,5].

In conclusion, the present case report confirms the hypothesis that inflammation plays a key role in the onset of acute coronary syndromes, as it promotes the formation of an unstable plaque as well as its rupture.

References

1. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000; 343: 915-22.
2. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. N Engl J Med 2002; 347: 5-12.
3. Virmani R, Frank D, Allen P, Farb A. Inflammation in coronary atherosclerosis - pathological aspects. In: Parnham MJ, ed. Progress in inflammation research. Basel: Birkhausre Verlag, 2001: 35-47.
4. Edwards W. Atherosclerotic plaque: natural and unnatural history. In: Schoen FJ, Gimbrone MA, eds. Clinicopathologic correlation and pathogenetic mechanisms. Augusta, GA, 1995.
5. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43.
6. Kohchi K, Takebayashi S, Hiroki T, Nobuyoshi M. Significance of adventitial inflammation of the coronary artery in patients with unstable angina: results at autopsy. Circulation 1985; 71: 709-16.
7. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN. Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. Circulation 2002; 105: 2504-11.
8. Berliner J, Leitinger N, Watson A, Huber J, Fogelman A, Navab M. Oxidized lipids in atherogenesis: formation, destruction and action. Thromb Haemost 1997; 78: 195-9.
9. Williams KJ, Tabas I. The response-to-retention hypothesis of atherogenesis reinforced. Curr Opin Lipidol 1998; 9: 471-4.
10. Schmitz G, Torzewski M. Atherosclerosis: an inflammatory disease. In: Parnham MJ, ed. Progress in inflammation research. Basel: Birkhausre Verlag, 2001: 1-34.
11. Biasucci LM, Liuzzo G, Angiolillo DJ, Sperti G, Maseri A. Inflammation and acute coronary syndromes. Herz 2000; 25: 108-12.
12. De Servi S, Mazzone A. Lymphocyte activation in acute coronary syndromes. In: Parnham MJ, ed. Progress in inflammation research. Basel: Birkhausre Verlag, 2001: 121-9.
13. Shah PK. Mechanisms of plaque vulnerability and rupture. J Am Coll Cardiol 2003; 41 (Suppl S): S15-S22.
14. Ihling C. Pathomorphology of coronary atherosclerosis. Herz 1998; 23: 69-77.
15. Libby P, Geng YJ, Aikawa M, et al. Macrophages and atherosclerotic plaque stability. Curr Opin Lipidol 1996; 7: 330-5.
16. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001; 104: 365-72.
17. Van der Wal AC, De Boer OJ, Becker AE. Pathology of acute coronary syndromes. In: Parnham MJ, ed. Progress in inflammation research. Basel: Birkhausre Verlag, 2001: 48-61.