Editorial comment
Multiple culprits in acute coronary syndromes: systemic disease calling for systemic treatment

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It is generally assumed that the same atherothrombotic plaque, the culprit lesion, is responsible for unstable angina and subsequent acute myocardial infarction (AMI), and this holds true also for AMI and early reinfarction. The evidence for this assumption is primarily based on the temporal association between presenting and recurring events. Emerging evidence indicates, however, that many complex and rapidly evolving coronary lesions exist indeed in many patients presenting with an acute coronary syndrome, challenging this "single culprit" concept in unstable patients.

Pathoanatomical evidence

Most acute coronary syndromes are caused by acute thrombosis, superimposed on a ruptured or eroded atherosclerotic plaque, with or without concomitant vasospasm[1,2]. Plaque rupture is not a rare event. It is followed by a variable amount of hemorrhage into the plaque and luminal thrombosis (often small and non-obstructive), causing sudden and rapid, but often clinically silent, growth of the lesion. It is probably the most important mechanism underlying the episodic (versus linear) progression of some coronary lesions observed by serial angiography[3]. Davies et al.[4] found ruptured coronary plaques without luminal thrombosis in 9% of persons who died suddenly of non-cardiac causes, increasing to 22% (including 5% with non-occlusive thrombosis) if an atheroma-related disease such as diabetes or hypertension was present. And many more ruptured plaques are found in patients dying of rather than with coronary atherosclerosis[3,5,6]. In 47 of such patients, we identified 103 ruptured coronary plaques (an average of 2.2/patient) of which only 40 had obstructive, and probably fatal, luminal thrombosis superimposed, while the remaining 63 ruptures were without luminal thrombosis or covered only by a small non-obstructive, and thus probably asymptomatic, thrombus[6]. None of these ruptured plaques were healed, suggesting they had developed within a relatively short period of time before death, though not necessarily simultaneously. Frink[5] identified 211 ulcerated plaques, of which many were judged to be chronic, in 83 cases of acute coronary death and concluded that ulcerated plaques without thrombosis are ubiquitous and multiple in such patients. Finally, a special non-uniform pattern of dense (older) and loosely arranged (younger) collagen, judged to represent the healed stage of subclinical plaque disruption, has recently been identified in many coronary plaques, particularly in those causing chronic high grade stenosis[3]. So, plaque rupture, causing episodic plaque growth, is not a rare event in the spontaneous progression of coronary atherosclerosis, and more than one ruptured plaque, with or without thrombosis superimposed, are usually present in persons dying of the disease. The temporal relation among multiple ruptured plaques, particularly whether they occurred simultaneously or not, remains, however, elusive because exact dating of acute coronary lesions is difficult if not impossible.

Regarding dating of acute coronary lesions *postmortem*, the pathologist has the advantage of being able to examine the le-

sion directly under the microscope. However, no reliable criteria exist for estimating the age of such lesions. The speed and completeness of healing of eroded or ruptured atherosclerotic plaques and/or luminal thrombi in severely diseased coronary arteries have never been, and probably never will be, determined. The sparse and indirect information we have suggests that acute plaque events do not heal rapidly. Coronary angioscopic examination of infarct-related arteries after AMI has revealed that healing of culprit lesions may take months[7], and both angiographic[8] and pathoanatomical[5] data indicate that some ruptured plaques never heal completely but persist as chronic ulcerations. The clinical history is not helpful for dating, because plaque rupture is asymptomatic, and if symptoms subsequently develop they are caused by the most dynamic and volatile components of the culprit lesion, thrombosis and vasospasm.

Clinical evidence

Some years ago cardiologists were puzzled by the fact that the number and severity of coronary stenoses were similar in patients with stable and unstable angina, despite the worse short-term prognosis of the latter[9]. Ambrose et al.[10] were the first to draw attention to the different angiographic morphology of culprit lesions, and it was soon realized that the behavior of culprit lesions also differed in the two syndromes. In unstable angina, a typical culprit lesion is angiographically complex (ruptured plaque), intraluminal filling defects (non-occlusive thrombosis) and vasospasm are frequent in the acute phase, and rapid progression to total occlusion (occlusive thrombosis) is impending[9]. Later it was realized, primarily thanks to a series of provocative angiographic observations by Kaski's group[11,12], that unstable patients often harbor multiple complex coronary lesions (an average of 2.6/patient)[13] of which only one is usually pointed out as the main culprit. And importantly, the more complex plaques the worse the prognosis[9]. These findings have recently been extended to patients with AMI. Goldstein et al.[14] identified multiple complex coronary plaques in as many as 40% of AMI patients undergoing angiographic examination, and the presence of multiple (versus single) complex plaques was associated with adverse clinical outcomes. This finding suggests multifocal disease activity with rapid progression of non-culprit lesions post-AMI, previously described by Guazzi et al.[15]. In the study by Goldstein et al.[14], patients with single and multiple complex plaques did not differ significantly in age, sex ratio, or the frequency of coronary risk factors, including current smoking, diabetes mellitus, and hypercholesterolemia. In non-Q wave AMI, 423 complex lesions were identified in 274 patients[16]. Although these figures for complex lesions are impressive, it should be remembered that angiography is able to identify only major plaque events and thus underestimates the real number of "active" coronary lesions. Overall, not only culprit lesions but also other complex, but not considered culprit, lesions progress rapidly during and shortly after an acute heart attack, indicating that multiple plaque ruptures and/or thrombosis occur simultaneously or within a relatively short period of time in the coronary arteries of clinically unstable patients.

Regarding dating of acute coronary lesions clinically, the information available is even more doubtful than that used by pathologists[17]. In non-fatal cases, the clinician has to rely on circumstantial evidence derived from a comprehensive evaluation of symptoms, ECG tracings and coronary angiography. The latter provides only a shadow of the complex and dynamic obstructive process and has limited ability to determine whether a given complex lesion is acute, subacute or chronic. Only the presence of intraluminal filling defects, by their propensity to resolve or become occlusive rapidly, appears to be a reliable angiographic marker of acute thrombosis.

Multiple coronary thrombosis

In contrast to the occurrence of multiple complex lesions, multivessel coronary thrombosis appears to be an exceptionally rare clinical finding, at least if judged by the lack of published cases. In this issue of the Journal, Garbo et al.[18] report their observations in 4 AMI patients and provide compelling clinical and angiographic evidence of multiple coronary thrombosis, developed simultaneously or, at least, within a very short period of time in all 4. Multiple coronary thrombosis, although apparently rarely observed by cardiologists, has been known by pathologists for years. In 1983, 51 recent coronary thrombi (and 29 old coronary occlusions) were identified in 44 patients who died of coronary atherosclerosis[6]. The year after, Davies and Thomas[19] published their landmark study on acute coronary lesions in sudden (< 6 hours) coronary death. In 100 cases examined *postmortem*, coronary thrombosis was identified in 74 cases of which 28 (38%) had more than one discontinuous segment with thrombosis. In all, 115 separate thrombi were found, and major coronary thrombosis, occluding more than 50% of the lumen, was present in 44 of the 74 cases[19]. That is, many of the thrombi identified in this thorough autopsy study were small and non-obstructive and thus probably asymptomatic. And finally last year, Arbustini et al.[20] reported their experience in a huge autopsy series of 298 AMI patients; they found multiple coronary thrombi in 29 (10%) of the cases, apparently unrelated to the integrity of the underlying plaque surface (whether it was ruptured or just eroded). So, multiple ruptured plaques, of which many are unhealed and probably ruptured recently, are frequently present in patients with an acute coronary syndrome, and multiple coronary thrombosis is found in more than 10% of autopsied cases. It seems likely that multiple

coronary thrombosis has often a rapid and fatal course which may explain why it is rarely recognized clinically.

Atherosclerosis: a systemic disease

The vital question is: why do multiple complex lesions (ruptured plaques), with or without filling defects (acute thrombosis), exist simultaneously in a chronic disease (atherosclerosis) that evolves slowly and silently over decades? If it is more than just a chance finding in an ongoing multifocal vessel wall disease, then simultaneous multifocal disease progression suggests a role for systemic factors. For example, 1) activation of the smoldering inflammation in plaques, with synchronized increase in thrombogenicity (e.g., tissue factor expression) and/or vulnerability (rupture-propensity); 2) simultaneous triggering of rupture-prone plaques[21]; and/or 3) simultaneous thrombosis on thrombosis-prone (e.g., eroded or unhealed previously ruptured) plaques, precipitated by a systemic thrombophilic state[22,23]. Regardless of the reason, multiplicity indicates that atherosclerosis is a systemic disease that needs systemic treatment. An invasive approach may be needed to obtain rapid, complete, and sustained reperfusion of infarct-related arteries (direct angioplasty) or to "passivate" one or a few complex lesions that pose a particularly high short-term risk in unstable angina, but a target lesion-based approach alone will not eliminate the threat posed by all the other existing coronary plaques, and their overall risk determines the prognosis at long term[24].

Atherosclerosis is an inflammatory disease[25], and inflammation is particularly frequent and intense in ruptured plaques beneath coronary thrombi[6,26]. The role of inflammation in plaque erosion is more questionable[26,27]. Similar to other chronic inflammatory diseases such as rheumatoid arthritis, a stable phase may suddenly be punctuated by an acute crisis in atherosclerosis, probably caused by activation of the disease[28,29]. Even if the chronic atherogenic stimuli are better, although not exhaustively, characterized than those stimuli that lead to or "precipitate" acute crises, some candidates are beginning to emerge[30,31]. Indeed, the frequent finding of more than one complex coronary lesion of which one is the main but not always the only culprit in unstable patients suggests that more generalized pathogenetic processes may precipitate an acute crisis. The observations by Garbo et al.[18] stress that systemic or global factors are important not only in the development of the underlying "chronic atherosclerotic background" for ischemic heart disease but also in the precipitation of the life-threatening thrombus-mediated acute coronary syndromes[32].

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