Plaque Rupture and Plaque Erosion

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Summary

There are multiple substrates for coronary thrombosis overlying an atherosclerotic plaque. The most common, plaque rupture, consists of an interruption of a thin fibrous cap overlying a lipid rich core. Plaque rupture is a result of macrophage infiltration and matrix degradation, is often seen in calcified plaques, and is highly associated with hypercholesterolemia. A less common substrate, plaque erosion, is not associated with elevated cholesterol and is the prime cause of coronary thrombosis in premenopausal women. The characteristic histologic features are abundant surface smooth muscle cells and proteoglycans, and a small or absent lipid rich core. The mechanisms of plaque erosion are unclear, and there are no consistent risk factors, although patients are often smokers.

Introduction

Atherosclerosis is a life-long disease that begins in childhood and becomes manifest only in adult life. The early lesions of atherosclerosis consist of the adaptive lesion, fatty streak, and the fibrous plaque. These lesions generally do not give rise to symptomatic disease. The complicated lesions, namely hemorrhage into a plaque, ulceration and luminal thrombosis, and calcification, are responsible for the development of symptomatic heart disease and occur rarely before the fourth decade (1-3). Inflammatory cells of the fibrous cap, foamy macrophages, T-lymphocytes and smooth muscle cells transform the lesion from a stable plaque into an unstable plaque via growth factors and cytokines (4). Until recently, it was thought that coronary thrombi occur only at the site of plaque rupture (5, 6), defined as a disruption of a fibrous cap over a lipid core with contact of the acute thrombus with the lipid pool (7, 8). It is only within the past few years that another substrate for coronary thrombosis, the plaque erosion, has been fully described.

Definition of Plaque Erosion

van der Wal et al. studied 20 patients with acute myocardial infarction, with histologic studies of the site of coronary thrombosis. They reported that plaque rupture occurred in 12 (60%), but in the remaining 8 (40%) cases, the cause of the thrombosis was intimal erosion without plaque rupture. These authors characterized intimal erosion as a thrombus overlying a plaque that is a mixture of macrophages and T cells with an absence of smooth muscle cells. The definition of intimal erosion included a heterogeneous group of lesions, however. It included two lesions that were lipid rich with a thin attenuated fibrous cap, three cases with a solid fibrous cap rich in macrophages and T cells covering a lipid core, and another three that had a fibrocellular plaque rich in smooth muscle cells without a clear lipid core. The dominant cells were described as macrophages and T cells in 2, and smooth muscle cells in 2 (9). In 3 of the 4 remaining cases, the lesions were rich in macrophages, T cells, smooth muscle cells and collagen. The last case had a solid cap infiltrated by macrophages, T cells, smooth muscle cells and collagen overlying a lipid core (9). The description of plaque erosion offered by van der Wal et al, although offering evidence of the complexity of the morphologic substrates of coronary thrombosis, did not give a unifying picture of coronary thrombi that do not occur as a result of rupture.

We have recently reported our findings on the type of atherosclerotic lesion underlying a luminal thrombus in patients with sudden coronary death (10). Of 96 cases of sudden coronary death, 50 (52%) had coronary thrombi. Sudden coronary death was defined as witnessed sudden unexpected death within 6 h of the onset of symptoms or death of an individual who had been seen in stable condition less than 24 h antemortem. To confirm that death occurred from coronary disease, at least one major coronary artery had a histologically confirmed acute luminal thrombus (10).

In this study, coronary artery thrombi were separated into two categories based on the morphology of the underlying plaque. Coronary plaque rupture was defined as described above, and plaque erosion (superficial erosion) was characterized as a thrombus having direct contact with the intimal plaque without rupture into a lipid pool. The lipid pool was either absent or formed an insignificant part of the plaque and did not communicate with the thrombus on serial sectioning. The plaque underneath the thrombus was rich in smooth muscle cells, with variable numbers of macrophages and T cells. Using these definitions, 28 (56%) thrombi were secondary to plaque rupture and 22 (44%) from plaque erosion (10).

Characteristics of Plaque Rupture versus Superficial Erosion

In our study, there were striking differences in clinical and morphologic findings between the erosion and rupture groups (Table 1). The mean age in cases of coronary thrombosis due to plaque rupture was 53 ± 10 years versus 44 ± 7 years in erosion (p < 0.003) (10). In the plaque rupture group, 5 of 28 (18%) were women versus 11 of 22 (50%) in eroded plaques (p = 0.03). The mean percent cross-sectional area stenosis (excluding the thrombus itself) was greater in plaque ruptures (78 ± 12%) versus erosions (70 ± 11%, p < 0.03). Thirteen ruptured...
arteries were concentric (46%), and 15 (54%) were eccentric. Only 4 eroded arteries without lipid core rupture were concentric (18%) while the remaining 18 (82%) were eccentric (p = 0.07 versus rupture into a necrotic core). Plaque calcification was present in 19 ruptures (69%) compared with 5 erosions (23%; p = 0.002). These data indicate that plaque erosions, in contrast to ruptures, occur in younger patients, often female, are relatively less occlusive, and are much less frequently concentric and calcified.

The nature of the thrombus itself, and frequency of myocardial infarction, was not significantly different between the erosion and rupture groups (10). The thrombus was occlusive in 12 rupture cases (43%) and non-occlusive in 16 (57%); only 4 eroded plaques (18%) demonstrated complete thrombotic occlusion (p = 0.08 versus rupture into a necrotic core). Thrombi were predominately composed of platelets in 13 (48%) plaque rupture cases and fibrin in 15 (52%), a similar distribution to the eroded plaque group in which 14 (52%) were predominately composed of platelets and 8 (35%) were predominately fibrin (p = 0.26). Increased fibrin content may represent early organization of the thrombus progressing from initial platelet deposition to infiltration and stabilization by fibrin. An acute myocardial infarction was present in 10 coronary rupture cases (36%) compared with 6 erosion cases (27%, p = 0.56). The frequency of healed myocardial infarction was similar in coronary ruptures and erosions [11 (39%) ruptures and 7 erosions (32%), p = 0.77] (10).

Immunohistochemical stains demonstrated several differences between ruptures and erosions (Table 1, Fig. 1). Foci of macrophages, identified by anti-KP-1 staining, at the luminal surface adjacent to the thrombus were present in all 28 plaque rupture cases versus 11 (50%) erosion cases (p < 0.0001). In plaque ruptures, macrophages typically infiltrated the thin fibrous cap and were present at the margins of the rupture site. When present in eroded plaques without lipid core rupture, macrophages were sparsely distributed in the upper layers of the plaque near the luminal surface. Clusters of spindle-shaped cells, identified as smooth muscle cells by actin staining, were seen at the luminal surface adjacent to the thrombus in 21 plaque erosions (95%) compared with 11 cases (33%) with smooth muscle cells in the fibrous cap adjacent to the plaque rupture (p < 0.0001). T-cells were present in 21 ruptured plaques (75%) at the luminal surface in the vicinity of the rupture site versus occasional scattered T-cells in 7 eroded arteries (32%, p < 0.004). Cell activation, indicated by HLA-DR staining, was identi-
fied in macrophages and T-cells in 25 (89%) plaque ruptures and in macrophages in 8 (36%) plaque erosions (p = 0.0002) (10).

Our results are dramatically different from those published by van der Wal et al., as we observed HLA-DR positively predominantly in macrophages and T-cells and only occasionally in smooth muscle cells (9). We have recently quantitated the number of macrophages and T-cells in the plaque rupture and plaque erosion (unpublished observations), and observed marked differences in cellular content. Adjacent to the site of plaque disruption, we found that plaque erosion cases were far richer in smooth muscle cells (794 ± 334/mm²) than were plaque ruptures (164 ± 177/mm², p <0.0001). Conversely, the number of macrophages was significantly greater in rupture than in erosion (585 ± 219/mm² versus 251 ± 159, p = 0.0007). However, there were no significant differences in the number of T-cells in the two groups. Thus it appears that what we describe as plaque erosion may be morphologically different from what has been described by van der Wal et al. (9).

Role of Risk Factors and Underlying Plaque Morphology in Culprit Lesions in Men and Women

In both men and women, traditional risk factors appear to play a role in culprit plaque morphology and frequency of vulnerable plaques in patients dying suddenly. Vulnerable plaques were defined as a plaque with a large necrotic core, a thin fibrous plaque (<65 mm) which is heavily infiltrated by macrophages (11).

In a series of men dying suddenly with severe coronary atherosclerosis, we observed that traditional risk factors were present in 96.5%. Smoking was a predictor of acute thrombosis, and thrombi from plaque rupture correlated with high total cholesterol (TC) (262 ± 58 mg/dl), low HDL-cholesterol (35.8 ± 13.5 mg/dl), and a high TC/HDL-cholesterol ratio (8.5 ± 4.0) (11). We also observed that as the cholesterol rose (<210 mg/dl and TC/HDL ratio ≤0.5 was considered normal and high >210 mg/dl and TC/HDL ratio ≥0.5), so did the mean numbers of vulnerable plaques per heart increase (from 0.17 ± 1.43 to 1.69 ± 1.41).

In women, we have observed that plaque erosion is highly correlated with smoking and is generally seen in women <50 years. In contrast, plaque rupture is more frequent in women >50 years and correlated with elevated total cholesterol (270 ± 55 mg/dl). Vulnerable plaques are more frequently seen in women >50 years than <50 years. Stable plaque with healed myocardial infarction is seen more frequently in women with ≥10% glycohemoglobin (12).

It appears, therefore, that in both men and women, cigarette smoking demonstrates an association with acute thrombosis, but that elevated levels of cholesterol are associated exclusively with plaque rupture. Furthermore, the hormonal status of the patient appears to influence the morphology of the atherosclerotic plaque, as vulnerable plaques and acute plaque ruptures are infrequently observed in premenopausal women.

References

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