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Flugelman MY, Fischer L, Halon DA, Lewis BS

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Studies of Atherectomy Specimens in Patients with Acute Coronary Syndromes

M. Y. Flugelman, D. A. Halon, L. Fischer, B. S. Lewis

The concept of plaque rupture and thrombosis has occupied a central role in our understanding of the pathogenesis of acute coronary syndromes. This paper reviews the evidence provided by atherectomy studies in this regard. The cellular composition of unstable plaques varies widely. In many instances smooth muscle cells predominate while in others there is an inflammatory response, including macrophages and T-lymphocytes. Thrombosis was reported in 19–83% of atherectomy studies from patients with unstable angina pectoris, but is not a universal finding. The data presently available imply that there is more than one mechanism underlying the pathogenesis of the acute coronary syndromes, with an interplay between inflammation, smooth muscle cell proliferation and thrombosis. J Clin Basic Cardiol 2000; 3: 91–4.

Key words: atherectomy, thrombosis, smooth muscle cell proliferation

The concept of plaque “rupture and thrombosis” as the primary mechanism for unstable transformation of atherosclerotic plaque has prevailed for many years in the cardiology community [1–5]. Despite substantial evidence for this mechanism, however, alternative data, including the failure of thrombolytic therapy in unstable patients, raised significant questions regarding the pathophysiology of acute coronary syndromes [6–8]. Failure of thrombolytic therapy to improve the prognosis of patients with unstable angina led to a search for more effective therapeutic modalities. A better understanding of the pathophysiology of acute coronary syndromes would facilitate the development of new treatment protocols.

The advent of directional coronary atherectomy allowed, for the first time, an analysis of coronary tissue in living patients with acute coronary syndromes, as opposed to the information till then available from pathologic reports of patients succumbing to the disease.

In this review we will describe the studies of atherectomy specimens from patients with acute coronary syndromes in general and specifically in unstable angina. The pathologic information gained from these studies may contribute new information regarding the pathophysiology of unstable angina pectoris.

Atherectomy studies

The information regarding the composition of atherectomy specimens in acute coronary syndromes can be classified into 3 major categories: cellular composition, presence of thrombus and cellular and extracellular content.

1. Cellular composition

The cellular content of atherectomy specimens was the focus of several studies. Smooth muscle cell predominance was greater on a 0–3 scoring system in unstable angina patients compared with stable (1.4 ± 0.9 vs. 0.7 ± 0.6) in a study by Flugelman et al. [9]. Neointimal hyperplasia was reported in 38% of unstable angina patients in a study by Arbustini et al. [10]. Mann et al. found a pattern of smooth muscle cell proliferation in 64% of Braunwald class IIIb, and 100% of patients with Braunwald class IIb unstable angina [11]. The resemblance of some atherectomy specimens from unstable angina patients to atherectomy specimens from patients with post angioplasty restenosis lesions was first described by Safian et al. [12]. In a recent study by Chen of specimens from patients with unstable angina and post angioplasty restenosis, the morphology of smooth muscle cells was similar [13]. Using electron microscopy, these researchers showed that synthetic organelles occupied a large proportion of smooth muscle cells cytoplasm in specimens from patients with unstable angina. In a study by Depre et al. greater cellularity with stellar-shaped smooth muscle cells in atherectomy specimens was associated with more severe anginal syndromes [14]. The similarities of the findings of this study to the findings of Flugelman et al. [9] are striking. The definite identification of the synthetic cells observed within loose extracellular matrix is the focus of a study by Tjurmin et al. [15]. In this study multiple antibodies were used to characterize the stellate-shaped cells often found in loose stroma. Although the authors of this study concluded that these cells are probably pericytes, the heterogeneous staining with a smooth muscle actin antibodies amongst other antibodies, indicates that a significant proportion of these cells may be synthetic smooth muscle cells.

The second major field of interest of atherectomy related research of living patients in unstable angina is the establishment of the pivotal role of inflammation in general and specifically of lymphocytes and macrophages in unstable transformation. The presence of T-lymphocytes, identified by immunohistochemical staining for interleukin 2 receptor (IL-2R) (CD25) [16], was increased in patients with unstable angina and acute myocardial infarction. While only 52% of lesions of stable angina patients contained T-lymphocytes, 90.9% of those of patients with refractory angina and 89.4% of lesions of patients with myocardial infarction contained T-lymphocytes as an indication for immune response activation [16]. Kaarinen et al. showed that higher numbers of mast cells and T-lymphocytes were found in atherectomy specimens of patients with unstable angina when compared to specimens of stable angina patients [17]. In this study, specimens of patients with Braunwald class III angina contained the largest numbers of TNFα positive mast cells and 92kD gelatinase positive macrophages. These findings again indicate the presence of active inflammatory process in coronary atheroma of unstable angina patients.

Moreno et al. found that plaques rich with macrophages were more prevalent in patients with unstable angina and...
non-Q wave myocardial infarction than in patients with stable angina and implied that the presence of macrophages is an evidence of propensity for plaque rupture as macrophages secrete matrix metalloproteinases that degrade collagen and render the plaque liable for rupture [18]. Other cell types were also described in atherectomy studies. Neovascularization, determined by immunohistochemistry with CD34 and factor VIII related antigen specific antibodies, was observed in higher proportions in patients with unstable angina [19].

All in all, it is clear that unstable angina is associated with a striking increase in cellularity in the region of the plaque, including smooth muscle and inflammatory cells. These findings are illustrated in Figure 1.

2. Thrombosis

The prevalence of thrombus in coronary atherectomy specimens taken from unstable patients is presented in Table 1. The frequency of thrombosis was higher in patients with more severe angina according to the Braunwald classification [11, 22].

These data clearly show that thrombus is a frequent but not universal finding in atherectomy specimens from unstable patients, albeit atherectomy specimens are not taken at the onset of the syndrome and may miss thrombus, especially recent friable or mobile thrombi which may be dislodged.

3. Extracellular and cellular protein content

Dangas et al. showed that in patients with unstable angina specimens contained higher quantities of lipoprotein (a) [24]. Lipoprotein (a) is a thrombogenic and atherogenic lipoprotein and its presence was associated in this study with the presence of macrophages and smooth muscle cells. The expression of 92-kD gelatinase, a member of the matrix metalloproteinase family, was identified both in atherectomy specimens from stable and unstable angina patients. In patients with acute coronary syndromes, the 92-kD gelatinase was localized inside macrophages and smooth muscle cells while in patients with stable angina it was found only in the extracellular space [25]. The authors postulate that intracellular localization indicates active synthesis and that active synthesis of gelatinase is related to plaque rupture.

A higher proportion of cells expressing growth factors and the presence of growth factors in the extracellular space were found in patients with unstable angina [9, 10]. Platelet derived growth factor (PDGF AA, AB, αβr) and basic fibroblast growth factor (bFGF) were reported in 18–30 % of cells in atherectomy specimens of unstable angina patients and in only 1.7–7 % in stable angina [10]. In most specimens of unstable angina patients studied by Flugelman et al. evidence of acidic and basic FGF was found [9]. Furthermore, in a study by Abe et al., tyrosine phosphorylation of the PDGF β receptor was highly associated with unstable angina pectoris [26].

Tissue factor expression was detected in 43 % of specimens of unstable angina in comparison to 12 % in stable angina patients [27]. Moreno et al. found that tissue factor content was higher in patients with unstable angina when compared to stable angina (42 % vs 18 %) [18]. Similar findings were described by Ardissino et al. who also measured an increased tissue factor activity in atherectomy specimens of patients with unstable angina [28]. Increased expression of P-Selectin on endothelial cells was observed in patients with unstable angina while no differences were observed in expression of E-Selectin and ICAM-1 between unstable and stable angina patients [29].

In a series published by Kol et al. the presence of immediate-early genes of cytomegalovirus was sought by RT-PCR in atherectomy specimens from stable and unstable angina patients [30]. Despite meticulous methodology no evidence of viral gene expression was found. This study provided evidence that CMV infection did not contribute to unstable transformation.

**Discussion**

Observations made by a number of groups led to the understanding that several mechanisms are operative in the development of the syndrome of unstable angina pectoris. Such understanding is echoed in a recent editorial by Braunwald relating to 5 different co-mechanisms of transformation from stable to unstable angina [31].

The relevance of smooth muscle cells to the development of unstable angina was consolidated by observation of coronary pathology of patients who died suddenly [32, 33]. Two new concepts emerged as a result of these observations: a) plaque erosion [32] which refers to “shaving” of the fibrous cap without complete rupture and which may lead to local thrombosis and acute coronary syndromes, and

**Table 1. Prevalence of thrombus in coronary atherectomy specimens, unstable patients**

<table>
<thead>
<tr>
<th>Series (ref. No.)</th>
<th>Specimens with thrombus in unstable angina</th>
<th>Angina classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escaned et al. [20]</td>
<td>10/45 (22 %)</td>
<td>Not available</td>
</tr>
<tr>
<td>Flugelman et al. [9]</td>
<td>11/32 (34 %)</td>
<td>Not available</td>
</tr>
<tr>
<td>DiScaiocio et al. [21]</td>
<td>29/63 (46 %)</td>
<td>50 % rest angina, 41 % crescendo angina</td>
</tr>
<tr>
<td>Arbustini et al. [10]</td>
<td>14/40 (35 %)</td>
<td>Not available</td>
</tr>
<tr>
<td>De Servi et al. [22]</td>
<td>18/38 (47 %)</td>
<td>Higher prevalence in patients with inverted T wave on ECG</td>
</tr>
<tr>
<td>Haft et al. [23]</td>
<td>50/60 (83 %)</td>
<td>Not available</td>
</tr>
<tr>
<td>van der Wal et al. [16]</td>
<td>21/30 (70 %)</td>
<td>61 % Braunwald I &amp; II, 83 % Braunwald III</td>
</tr>
<tr>
<td>Moreno et al. [18]</td>
<td>24/50 (48 %)</td>
<td>Not available</td>
</tr>
<tr>
<td>Mann et al. [11]</td>
<td>12/25 (48 %)</td>
<td>27 % Braunwald IIb, 64 % Braunwald IIIb</td>
</tr>
<tr>
<td>Depre et al. [14]</td>
<td>7/38 (19 %)</td>
<td>21 % Braunwald b, 60 % Braunwald c</td>
</tr>
</tbody>
</table>

Figure 1. Atherectomy specimen in a patient with unstable angina pectoris (Movat’s pentachrome staining). Note hypercellularity with multiple smooth muscle and inflammatory cells and loose connective tissue (magnification ×160).
b) plaque expansion [9] or “accelerated progression pattern” [11] in which smooth muscle cell proliferation and extracellular matrix production lead to mechanical obstruction and transformation from the stable to an unstable syndrome. Plaque expansion may lead to secondary local thrombosis due to arterial narrowing and hyperreactivity with turbulent or diminished coronary flow or rupture or erosion of the endothelium following the rapid expansion of the subendothelial plaque volume. Evidence regarding the role of smooth muscle cells in unstable angina should not cancel out the possibility that smooth muscle cell proliferation may represent a recovery phase of plaques after local thrombosis or haemorrhage. Since organizing thrombi are rich in growth factors and inflammatory cells, recruitment of smooth muscle cells and other arterial cells may be presented after several weeks as neointimal proliferation dominated by smooth muscle cells. Of great interest is a recent study by Suzuki et al. which showed a high frequency (68%) of neointimal hyperplasia in atherosclerosis specimens of patients with variant angina [34]. Strong correlation between neointimal hyperplasia in primary lesions and vasospasm implies that hyperreactivity of plaque smooth muscle cells contributed to the clinical syndrome.

The role of inflammation in the progression of atherosclerosis is well established [35]. Atherectomy studies provided further evidence on the role of T-lymphocytes and macrophages in plaques of patients with unstable angina and myocardial infarction. Macrophages and lymphocytes express tissue factor and secretory MMPs and therefore contribute to fibrous cap degradation and local thrombosis. The exact timing of initiation of the inflammatory process is unknown but the use of symptoms as a time point of initiation of unstable transformation may be misleading. The process may well have started before the symptoms and our pathological findings may represent the peak or nadir of the inflammatory process.

The presence of thrombus varies between 19–83% in atherectomy specimens from unstable angina patients, the variation representing different patient populations. In most series the rate of thrombosis was below 50%, but this figure increased in patients with more severe angina. Although angiography has served as the gold standard for detection of thrombus in unstable angina, angiography fails to detect early or small thrombus plaques and therefore contributes to fibrous cap degradation and local thrombosis. The exact timing of initiation of the inflammatory process is unknown but the use of symptoms as a time point of initiation of unstable transformation may be misleading. The process may well have started before the symptoms and our pathological findings may represent the peak or nadir of the inflammatory process.

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