Plasma cells in the carotid plaque: occurrence and significance

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Abstract. – OBJECTIVE: Atherosclerosis is one of the leading causes of disability and mortality worldwide. Inflammation, including monocytes, T and B cells, plays a key role in its pathogenesis. Our purpose was to evaluate plasma cells’ presence in a large series of carotid artery plaques and the clinical association.

PATIENTS AND METHODS: Forty-eight consecutive patients treated with carotid endarterectomy were retrospectively analyzed to assess plasma cells’ presence inside the plaque. A semiquantitative grading score was applied, ranging from absence, scattered, clusters of 5-10, and sheets of >10 plasma cells. Plasma cell’s location, as intraplaque, subendothelial or peri-adventitial, was also defined.

RESULTS: In 75% of plaques analyzed, plasma cells were detected: scattered in 63.9%, in clusters in 22.2%, and in sheets in 13.9% of cases. In all cases, plasma cells were observed only inside the plaque. In 13.9% and in 11.1% of cases, plasma cells showed, respectively, a concomitant subendothelial or peri-adventitial distribution. In 5.6% of plaques, there was a simultaneous distribution in subendothelial, peri-adventitial layer, and intraplaque. Association between the presence of symptoms and plasma cells infiltrate was found.

CONCLUSIONS: Our results suggest that plasma cells could be a key parameter linked to plaque instability. Some types of configurations are significantly associated with the occurrence of cerebrovascular symptoms.

Key Words: Atherosclerosis, Carotid, Plaque, Inflammation, Plasma cells.

Introduction

Atherosclerosis is one of the leading causes of disability and mortality worldwide. It is a chronic inflammatory disease, basically induced by the deposition of cholesterol-rich low-density lipoproteins (LDL) inside the intima of arterial vessels. Inflammation is a powerful trigger of the atherosclerotic process, monocytes, and macrophages representing the key players in atherosclerotic pathogenesis. Thus, monocytes and macrophages have been widely studied, and their interactions have been clarified. On the contrary, B cells only occasionally have been reported in atherosclerotic plaques. B cells may have a pro-atherogenic or an athero-protective effect, according to the type of B cell involved. B1 cells and IgM-producing plasma cells have been claimed to have a protective role, inhibiting foamy cell formation and promoting efferocytosis. On the other hand, B2 lymphocytes have been suggested to favor atherogenesis by releasing IgG and IgE.

The presence of B lymphocytes and plasma cells has been described in peri-adventitial lymphoid infiltrates. This finding has been related to advanced lesions. Conflicting results have been reported on IgG-producing plasma cells, which might have a pro-atherogenic effect or, alternatively, an anti-atherogenic behaviour. Given the scarcity of data regarding plasma cell occurrence inside the atherosclerotic plaque, this paper aimed to evaluate the presence of plasma cells in a large series of carotid plaques to evaluate their frequency and clinical significance.

Patients and Methods

Forty-eight consecutive carotid endarterectomies (33 males, 15 females, median age 73±7.4 years, age range from 50 to 86 years), analyzed at the Pathology Department of the University of Cagliari, were retrospectively analyzed to assess plasma cells’ presence inside the plaque.
Plasma cells in the carotid plaque

Table I. Plasma cells in carotid plaques of symptomatic and asymptomatic patients. Number of cases divided according to the presence or absence of symptoms and of plasma cells.

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With plasma cells</td>
<td>31</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Without plasma cells</td>
<td>2</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>15</td>
<td>48</td>
</tr>
</tbody>
</table>

Table II. Plasma cell grading score and distribution in symptomatic and asymptomatic patients. Number of cases divided according to the presence or absence of symptoms, to the semiquantitative plasma cells grading score and distribution of plasma cells.

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>2+</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3+</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1+</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2+</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3+</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0.16 square mm. The following semiquantitative grading score was applied: absence of plasma cells (0), scattered plasma cells (1+), clusters of 5-10 plasma cells (2+), and sheets of >10 plasma cells (3+). Later, we took into consideration plasma cells location, defined as intraplaque, subendothelial or periadventitial.

Statistical Analysis

The relationship between symptoms and the presence of plasma cells in the plaque infiltrate was tested by the Chi-square test.

Results

Plasma cells were detected in 36 out of 48 plaques analyzed (75%). In 63.9% (n = 23) of cases plasma cells were scattered (1+, Figure 1A and 1D). In 22.2% (n = 8) we observed clusters (2+, Figure 1B and 1E). In 13.9%, (n = 5) sheets of plasma cells (3+, Figure 1C and 1F) were found. In all positive cases (n = 36), plasma cells were localized inside the plaque, showing a concurrent subendothelial distribution in 13.9% (n = 5) or a peri-adventitial distribution in 11.1% (n = 4) of...
cases. In 5.6% (n = 2) of cases, there was a simultaneous sub endothelial, peri-adventitial and intraplaque location.

By applying a Chi-square test, we found a statistically significant ($p < 0.01$) association between the presence of symptoms and plasma cells in the plaque infiltrate. Indeed, the majority of symptomatic patients showed a plasma cells infiltrate (93.9%, n = 31), whereas in 66.7% (n = 10) of asymptomatic cases, no plasma cells were found. Interestingly, the finding of sheets of plasma cells was more represented in the symptomatic group.

**Figure 1.** Different degrees of plasma cell infiltrate in carotid plaques. A and D, Scattered plasma cells (grade 1+, arrows); B and E, Plasma cells in clusters (grade 2+); C and F, Sheets of plasma cells (grade 3+). A, B and C, H&E; D, E, and F, CD38.
Discussion

Atherosclerosis is a chronic inflammatory disease induced by the deposition of cholesterol-rich low-density lipoproteins (LDL) inside the intima of arterial vessels. Atherosclerotic plaque formation is a multi-step process. High levels of serum low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) induce the deposition of lipoproteins inside the arterial wall. In case of very high rates of deposition, the removal of lipoproteins from the vascular wall might be insufficient, leading to retention of LDL and triggering atherosclerosis.

Enzymatic and non-enzymatic modifications of LDL cause the release of bioactive phospholipids, which are able to modulate endothelial cell function ending with endothelial dysfunction. The activated endothelium expresses leukocyte adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1). Under these circumstances, blood cells expressing the receptor for VCAM-1, including monocytes and lymphocytes, may adhere to the endothelium. In the same way, also platelets may adhere to activated endothelium.

The role of inflammation has been debated in recent years. Atherosclerotic plaque evolution in 5 steps includes the recruitment of inflammatory cells. In particular, T cell subpopulations, B cells, plasma cells, macrophages, and mast cells have already been shown within the atherosclerotic plaques. Our preliminary data show that plasma cells infiltrate is a common finding in carotid plaques; besides, it is even more frequent in symptomatic patients. Whereas in the majority (63.9%) of cases, plasma cells were scattered and isolated, in some cases (13.9%), we observed sheets of plasma cells that were a major finding at histology. In the remaining cases (22.2%), clusters of plasma cells were detected.

Plasma cells have already been reported in atherosclerotic aneurysms of the abdominal aorta, suggesting a potential role of the immune response in atherosclerotic pathogenesis. Moreover, in clinical practice, the finding of plasma cells in clusters in other organs, including the liver, is considered a sign suggestive for activation of the immune system and a possible sign of autoimmunity. In recent years, the hypothesis that atherosclerosis might be considered an autoimmune disease has surfaced in the literature. Our data lay stress on the high frequency of plasma cells in carotid plaques and suggest the need for a re-evaluation of the role of autoimmunity in atherosclerosis.

Conclusions

From a practical point of view, the use of the anti-CD38 antibody could be important, in the pathological report of every carotid plaque, in order to reveal plasma cells isolated or in small clusters, which might be missed at histology.

Further investigations are needed to identify imaging specificities of plaques with high plasma cells infiltrate or other plaque histological elementary lesions. It would be interesting to study the different phases of the formation of atherosclerotic plaques in which has been observed the intervention of plasma cells and the correlation of the relationship between these cells and the behavior of cytokines interested in this process.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare that they have no conflict of interest. No founding is declared for this article.

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