Cerebral Amyloid Angiopathy Associated With Giant Cell Arteritis: A Case Report

MAURICE N. MURPHY, M.B., B. CH., M.SC, AND ANDERS A.F. SIMA, M.D., PH.D.

SUMMARY A case of cerebral amyloid angiopathy associated with granulomatous arteritis is presented with description of the microscopic, immunocytochemical and ultrastructural features. The amyloid proved to be of the AL-type, with failure to show reactivity with anti-AA, anti-prealbumin and anti-albumin. Antisera against SAP and IgG (AF) did show reactivity. Hence the immunologic characteristics of this amyloid differ from those of other known conditions and may therefore represent a new form of amyloid. The role of granulomatous arteritis in this case remains speculative.

CEREbral AMYLOID ANGIOPATHY (CAA) is seen in association with many conditions, such as Alzheimer’s disease,1-2 dementia pugilistica,3 adult monogolism,4 vascular malformations,5 generalized amyloidosis,6 radiation necrosis,7-8 hereditary cerebral hemorrhage9 and a multiple sclerosis-type demyelinating disorder.10 It is also noted within a significant proportion of aging brains.11,12 It is now recognized that CAA can occur without associated disease. Apart from the familial cases of CAA,13-15 there have been several reports of sporadic CAA associated with intracerebral hemorrhage.13-19 We report a patient with CAA and giant cell arteritis, an association not previously documented.

References
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Figure 1. Subarachnoid vessel showing chronic inflammation and multiple giant cells in close relationship to the elastic membrane. Note calcification of the elastic membrane, which also shows breaches. H & E Mag 48% of 200 → 96 ×.

Oared area with softening and flattening of the gyri was noted.

A cone-shaped section of tissue was readily separated from the underlying white matter. His post-operative course was uneventful with improvement of his neurological status. He was discharged and 9 months later he is doing well, the only neurological deficit being a left-sided homonymous hemianopsia.

Materials and Methods

Biopsied material was fixed in buffered 10% formalin and embedded in paraffin. Sections were stained with Haematoxylin and Eosin, Congo red and van Gieson stains. Immunocytochemical visualization of prealbumin (transthyretin), amyloid protein A (AA), and amyloid protein AP (SAP) was performed in the laboratory of Dr. Arnulf H. Koeppen, VA Medical Centre, Albany, New York. Antiserum against AA protein was made available to him by Dr. George G. Glenner, San Diego, California. Dr. Mark Pepys, London, made available anti-SAP. Anti-prealbumin was commercially available from DAKO Corp., Santa Barbara, California. The sections were also treated with antiserum against amyloid fibril whole protein from a patient with familial amyloid polyneuropathy.\(^{28}\) Antiserum against IgG, IgM, IgA, complement C\(_3\), and albumin were also used. Further sections were treated with potassium permanganate prior to Congo red staining, according to the method of Wright et al.\(^{20}\) Formalin-fixed material was washed, fixed in 2.5% cacodylate buffered glutaraldehyde and post-fixed in 1% osmium tetroxide, dehydrated and embedded in Epon. Ultrathin sections were stained with uranyl acetate and lead citrate and examined under the electron microscope.

Results

The tissue submitted for pathologic examination consisted of several pieces of red-yellow tissue aggregating 2.5 × 2.0 × 1.1 cms. On sectioning, the tissue was soft, hemorrhagic and necrotic. Light microscopic examination showed areas of infarction of various ages, ranging from one to several weeks duration. The overlying subarachnoid space showed an extensive chronic inflammatory infiltrate, which accompanied penetrating vessels. The patchy infiltrates consisted of lymphocytes, plasma cells and multinucleated giant cells in the subarachnoid arterial walls with destruction of the elastic membranes (fig. 1). Other vessels in the subarachnoid space showed intimal fibrosis with thick-
ening of their walls as well as deposition of calcium. Several vessel lumina showed fibrin occlusions. Congo red stained sections revealed amyloid in the walls of the subarachnoid vessels and vessels of the underlying cortex and white matter (fig. 2A, 2B). In sections pretreated with potassium permanganate the amyloid maintained its affinity for Congo red and birefringence under polarized light. No senile plaques or neurofibrillary tangles were demonstrated. The findings of the immunoperoxidase studies are summarized in table 1. Ultrastructurally, most vessels demonstrated fibrillary material outside the vascular basement membranes, consistent with amyloid. Adjacent to this material, plasma cells and macrophages were noted, the latter often showing multinucleation. No abnormalities of the vascular basement membrane were demonstrated (fig. 3). Some vessels showed marked endothelial swelling causing obliteration of their lumina. The cytoplasm of these cells contained an abundant and dilated endoplasmic reticulum.

Discussion

Several recent reports have identified CAA as an important cause of intracerebral hemorrhage.13-19 The incidence of intracerebral hemorrhage secondary to non-familial CAA varies. Among 1,214 autopsied cases of massive cerebral hemorrhage reported by Jellinger,21 0.2% were found to be directly related to CAA, while Hinton et al22 showed five cases of CAA in 84 hemorrhages. Lee and Stemmermann15 reported an incidence of 9.3% among their 75 cases of spontaneous intracerebral hemorrhage. CAA shows no sex preponderance and no greater incidence in patients with diabetes mellitus, cerebral atherosclerosis or hypertension. What does appear to be consistent is the site of involvement. In CAA, the parietal, temporal and occipital lobes are most commonly involved.

Giant cell arteritis is a generalized chronic granulomatous inflammation of medium-sized and large vessels.23 Granulomatous arteritis limited to the central nervous system (CNS) has been described and reviewed by Ojeda et al.24 The association with amyloid has been noted in temporal arteries25 and within the CNS26 in a case of an elderly patient with Down's syndrome. Furthermore, Mandybur27 in an autopsy study described three cases of CAA associated with chronic cerebral vasculitis. Two of these cases had rheumatoid arthritis, while the third patient had unspecified arthritis. The present case is, to the best of our knowledge, the first case of CAA directly associated with giant cell arteritis.

The amyloid in this case was of the immunoglobulin light chain-derived protein (AL) variety. Antisera against albumin, prealbumin and AA failed to show reactivity with the amyloid, whereas anti-SAP and anti-IgG (AF) did. It is of interest to note failure of reactivity with anti-prealbumin which is considered a common constituent of amyloid in the neuritic plaque, neurofibrillary tangle and the microangiopathic lesion.28 Our findings are similar to those of Koeppen and Mitzen29 in their study of prealbumin in familial amyloid polyneuropathy and may be explained by their suggestion that the tissue prealbumin differs from normal serum prealbumin. The absence of albumin within the vessel walls suggests that the presence of IgG, IgM and IgA is not secondary to an outpouring of serum. Ultrastructurally, Okoye and Watanabe30 described amyloid deposition surrounding electron dense alterations in vascular basement membranes, suggesting that these defects permitted protein deposition with subsequent amyloid formation. Our findings did not include such irregularities of basement membranes, which further argue against this hypothesis. Thus a pathogenetic role played by the granulomatous vasculitis in formation of the amyloid cannot be excluded.

In conclusion, we have described a patient with CAA and granulomatous arteritis. The amyloid appears to be of the AL-type without demonstrating reactivity with anti-prealbumin. This suggests that the amyloid in this case may represent a different phase in the evolution of amyloid of the Alzheimer type or in fact represents a different entity. We believe the latter to be the case and have classified this condition as a primary cerebral amyloid angiopathy.

Acknowledgments

We are indebted to Dr. Arnulf H. Koeppen for performing the immunocytochemical studies for prealbumin, amyloid protein A, amyloid

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### Table 1: Immunohistochemical Characteristics of Amyloid in the Present Case

<table>
<thead>
<tr>
<th>Antisera</th>
<th>Reactivity</th>
</tr>
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<tbody>
<tr>
<td>IgG</td>
<td>+</td>
</tr>
<tr>
<td>IgM</td>
<td>+</td>
</tr>
<tr>
<td>IgA</td>
<td>+</td>
</tr>
<tr>
<td>Complement C₃</td>
<td>+</td>
</tr>
<tr>
<td>Albumin</td>
<td>-</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>-</td>
</tr>
<tr>
<td>AA</td>
<td>-</td>
</tr>
<tr>
<td>SAP</td>
<td>+</td>
</tr>
<tr>
<td>IgG (AF)</td>
<td>+</td>
</tr>
</tbody>
</table>

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**Figure 3.** Electron micrograph of amyloid deposition (A) illustrating its typical fibrillary nature. Note the intact basement membrane (B.M.) of an endothelial cell (E). At the bottom of the figure two macrophage processes (M) are seen. Mag 45.5\% of 31,350 → 17,260 ×.
protein AP and amyloid fibril whole protein. We also wish to thank Ms. Beverly Welsh for skillful technical assistance.

References
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