Prevalence and Genesis of Dystrophic Amyloid Deposits in Polymyalgia Rheumatica and In Temporal Arteritis

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Abstract

Aim: The aim of this study was to determine the prevalence of amyloid deposits in the temporal arteries, to identify the nature of amyloid in polymyalgia rheumatica (PMR) patients with or without temporal arteritis (TA).

Patients and Methods: Surgical biopsy specimens of the temporal artery of 299 patients with PMR were studied. PMR was clinically diagnosed at the National Institute of Rheumatology between 1991 and 2005 according to the criteria of Bird et al.

TA was diagnosed histologically, and classified according to Flood et al. Amyloid deposits were identified according to Romhányi by a modified (more sensitive) Congo red staining and confirmed by immunohistochemical techniques, and analysed histochemically according to Bély.

The link between amyloidosis and PMR (with or without TA) was analyzed by Pearson's chi-squared ($\chi^2$) test.

Results and Conclusions: Segmental or sectoral TA was associated with PMR in 71 (23.75%) of 299 patients, and was accompanied with amyloid deposits in 18 (25.35% of 71).

TA was "classic" in 11 (15.49 %), "atypical" in 44 (61.97 %), and "healed" in 16 (22.54 %) of 71 cases.

PMR existed without TA in 228 (76.25%) of 299 patients, and was accompanied with amyloid deposits in 37 (16.23% of 228).

PMR and TA are the same disease; TA represents a later and more severe stage of PMR. Amyloid deposits may vary the histology of temporal arteries of PMR patients with or without TA. In our biopsy population the amyloid deposits were exclusively localized, dystrophic and derived from the damaged internal elastic lamina.

Keywords: Polymyalgia rheumatic; temporal arteritis; amyloidosis;

Abbreviations: PMR–Polymyalgia rheumatica; TA–Temporal arteritis; Ath–Atherosclerosis; ACR–American College of Rheumatology

Introduction

Several authors suggested that based on the strong clinical association Polymyalgia Rheumatica (PMR) and Temporal Arteritis (TA) are essentially different stages of the same disease [1].

TA is a systemic disorder involving different size arteries and even veins with a predilection for branches of the temporal artery [2].

PMR and TA may be associated with amyloidosis which is probably derived from the disrupted, fragmented internal elastic lamina [3, 4].

The aim of this study was to determine the prevalence of amyloid deposits in the temporal arteries, to identify the nature of amyloid, and analyse the role of atherosclerosis (Ath) and inflammation in the genesis and origin of amyloid deposits in PMR patients with or without TA.

Patients and Methods

Surgical biopsy specimens of the temporal artery of 299 patients with PMR were studied. PMR was clinically diagnosed at the National Institute of Rheumatology between 1991 and 2005 according to the criteria of Bird, et al [5].

TA was diagnosed histologically, and classified according to Flood, et al [6]. Amyloid deposits were identified according to Romhányi [7] by a modified (more sensitive) Congo red staining [8] and confirmed by immune histochemical techniques using the streptavidin-biotin-complex/horseradish peroxidase method [9], and analysed histochemically according to Bély [10].

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [11]. The link between amyloidosis and PMR (with or without TA), furthermore its relation to Ath and to the stage of inflammation was analyzed by Pearson's chi-squared ($\chi^2$) test [11].

Glossary of definitions

“Prevalence" of amyloid deposits concerns the presence of amyloid in the wall of main (medium size) temporal artery or in accompanied blood vessels of different calibers.

Size of blood vessels in surgical specimens with branches of temporal artery

Arteriole (a) - no internal or external elastic membrane, <500 micrometers in diameter
Small artery (A) – only internal elastic membrane present, vessels 500-1000 micrometers in diameter

Medium size artery (AA) – internal and external elastic membrane are present – vessel <1000 micrometers in diameter

Venule (v), small vein (V), medium size vein (VV) – accompanying (a), (A) or (AA)

Atherosclerosis (Ath) – was diagnosed in PMR with or without TA patients only when sclerotic (calcified) plaques were present macroscopically and/or microscopically. Moderate changes like hyalin were not specified as “Ath”.

Histologic patterns of TA [6]

Classic – characterized by intimal thickening due to transmural inflammation with T-cells, histiocytes and multinucleated giant cells.

Atypical – is an intermediate stage of classic and healed TA, characterized by less dense inflammatory infiltrate composed predominantly of lymphocytes (with or without macrophages, and without giant cells). The inflammation tends to be most marked in the adventitia, and is accompanied by more or less pronounced structural changes (intimal proliferation, and fragmentation or distortion of internal elastic lamina).

Healed – (chronic stage) is characterized by moderate inflammation or its remnants. The intima is irregularly thickened (with stenosis or occlusion), and exhibits fibromyxoid change, with or without neovascularization. The internal elastic lamina has multiple lamellae, is fragmented and discontinuous. Media and adventitia are more or less fibrotic.

Results

Segmental or sectoral TA was associated with PMR in 71 (23.75%) of 299 patients, and was accompanied with amyloid deposits in 18 (25.35% of 71).

TA was “classic” in 11 (15.49 %) (Figure 1a-d), “atypical” in 44 (61.97 %) (Figures 2e-f and 3a-d), and “healed” in 16 (22.54 %) (Figures 4a-d, 5a-b and 6a-d) of 71 cases.

PMR existed without TA in 228 (76.25%) of 299 patients, and was accompanied with amyloid deposits in 37 (16.23% of 228).

Atherosclerosis was detected in 16 of 228 PMR patients without TA, and was associated with amyloid deposits in 2 of these (Ath was not associated with TA).

Demographics of PMR patient with or without TA, Ath and amyloidosis are summarized in table 1.

The relationship (“p” values of correlation) between female and male PMR patients with (n = 16 of 299) or without (n = 283 of 299) Ath, with (n = 55 of 299) or without (n = 244 of 299) amyloidosis, furthermore with (n = 71 of 299) or without (n = 228 of 299) TA is summarized in table 2.
Figure 2(a-f): Main branch of medium size temporal artery, atypical form of temporal arteritis
Lymphoid infiltration of the medium size main branch is accentuated adventitial and accompanied with adjacent arteriolitis and venulitis
(a) HE, x 20, (b) same as (a) x40, (c) same as (a) x40, (d) same as (a) x200, (e) same as (a) x40, (f) same as (a) x200

Figure 3(a-d) (same as Figure 2c): Main branch of medium size temporal artery with adjacent arteriole, atypical form of temporal arteritis
Intima is thickened, original lumen of medium size artery is stenotic, internal elastic lamina is multiple and fragmented.
(a) Light green-orcein combined staining, x40, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200, (e)
**Figure 4(a-d):** Main branch of medium size temporal artery, healed (chronic stage) of temporal arteritis
Cellular inflammatory infiltration is not present, intima is thick, original lumen of medium size artery is stenotic, internal elastic lamina is fragmented, homogenous and alternates with disrupted sections.
(a) HE, x 40, (b) same as (a) x100, (c) same as (a) x200, (d) same as (a) x600

**Figures 5(a-b) (same field as Figure 4c-d):** Main branch of medium size temporal artery, healed (chronic stage) of temporal arteritis
Fragments of internal elastic lamina are PAS negative, disrupted sections are PAS positive which complies with amyloid deposits.
(a) PAS, x 200, (b) same as (a) x600
Figures 6a-d (same artery as Figure 4a-d): Main branch of medium size temporal artery, healed (chronic stage) of temporal arteritis. Fragments of internal elastic lamina are congophil and stain with Congo red; disrupted sections do not stain with Congo red. Amyloid deposits localized at the vanished sections of the discontinuous internal elastic lamina. (a) Congo red staining, viewed with the light microscope, x 100, (b) same as (a) x200, (c) Congo red staining, viewed under polarized light, same as (a), x100, (d) same as (b) x200.

Table 1: Sex, average age (range) of 299 PMR in patients with TA (n = 71) or without TA (n = 228), with Ath (n = 16) or without Ath (n = 283) and amyloidosis (n = 55)

<table>
<thead>
<tr>
<th>Sex</th>
<th>N of patients</th>
<th>Average age (in years at biopsy)</th>
<th>Range (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMR patients</td>
<td>299</td>
<td>71.19</td>
<td>88 – 43</td>
</tr>
<tr>
<td>Female</td>
<td>250</td>
<td>71.3</td>
<td>88 – 43</td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>70.6</td>
<td>86 – 51</td>
</tr>
<tr>
<td>PMR with Ath</td>
<td>16</td>
<td>73.19</td>
<td>87 – 48</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>74.54</td>
<td>87 – 48</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>67.33</td>
<td>72 – 61</td>
</tr>
<tr>
<td>PMR without Ath</td>
<td>283</td>
<td>71.06</td>
<td>88 – 43</td>
</tr>
<tr>
<td>Female</td>
<td>237</td>
<td>71.1</td>
<td>88 – 43</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>70.85</td>
<td>86 – 51</td>
</tr>
</tbody>
</table>
PMR with TA | 71 | 73.25 | 88 – 53
---|---|---|---
Female | 61 | 73.47 | 88 – 53
Male | 10 | 71.43 | 82 – 58

TA Classic | 11 | 72.4 | 82 – 67
---|---|---|---
Female | 9 | 71.75 | 78 – 67
Male | 2 | 75.46 | 82 – 68

TA Atypical | 44 | 71.37 | 85 – 53
---|---|---|---
Female | 36 | 71.56 | 85 – 53
Male | 8 | 70 | 80 – 58

TA Healed | 16 | 79.36 | 88 – 68
---|---|---|---
Female | 16 | 79.36 | 88 – 68
Male | 0 | - | -

PMR without TA | 228 | 70.53 | 88 – 43
---|---|---|---
Female | 189 | 70.55 | 88 – 43
Male | 39 | 70.44 | 85 – 51

PMR with amyloidosis | 55 | 78.48 | 88 – 68
---|---|---|---
Female | 45 | 78.73 | 88 – 68
Male | 10 | 76.83 | 83 – 72

PMR without amyloidosis | 244 | 69.69 | 87 – 43
---|---|---|---
Female | 205 | 69.7 | 87 – 43
Male | 39 | 69.59 | 86 – 51

TA with amyloidosis | 18 | 71.5 | 88 – 55
---|---|---|---
Female | 15 | 71.86 | 88 – 55
Male | 3 | 69 | 76 – 62

TA without amyloidosis | 53 | 73.82 | 88 – 53
---|---|---|---
Female | 46 | 73.98 | 88 – 53
Male | 7 | 72.4 | 82 – 58

The average age of PMR patients with TA was significantly higher than the average age of PMR patients without TA \((p < 0.0164)\), and the average age of PMR patients with amyloidosis was significantly higher than the average age of PMR patients without amyloidosis \((p < 0.0000)\).

There was no significant difference between the average age of PMR patients with or without Ath \((p < 0.4222)\), and between the average age TA patients with or without amyloidosis \((p < 0.2995)\).

The relationship \((p\text{-values of correlation})\) between average age of female and male patients with classic, atypical and healed form of TA is summarized in table 3.

<table>
<thead>
<tr>
<th>p &lt;</th>
<th>Total (female &amp; male)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMR versus Ath</td>
<td>0.4494</td>
<td>0.2972</td>
<td>0.4217</td>
</tr>
<tr>
<td>PMR with Ath versus without Ath</td>
<td>0.4222</td>
<td>0.2703</td>
<td>0.0004</td>
</tr>
<tr>
<td>PMR with TA versus without TA</td>
<td>0.0164</td>
<td>0.0159</td>
<td>0.7951</td>
</tr>
<tr>
<td>PMR with amyloidosis versus without amyloidosis</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0037</td>
</tr>
<tr>
<td>TA with amyloidosis versus without amyloidosis</td>
<td>0.2995</td>
<td>0.3727</td>
<td>0.7228</td>
</tr>
</tbody>
</table>

Table 2
Comparing the healed stage of TA, the average age of the patients was higher than the average age of the patients with classic or atypical form of TA (the TA patients of healed stage were older than the TA patients of classic or atypical stage); the difference was significant (p < 0.005; p < 0.000 resp.).

Amyloid was detected in the wall of medium size vessels only (small arteries, arterioles or accompanying veins, without internal elastic membranes were not involved by amyloid deposits).

The localization, morphology, immunohistochemical and histochemical characteristics of amyloid deposits of the temporal arteries were the same in PMR patients with TA (Figures 7a-d and 8a-d) or without TA (Figure 9a-d).

Amyloid deposits were localized as small globular or linear deposits along the partially damaged internal elastic lamina where the elastic fibers have vanished.

Amyloid deposits were negative for anti-human amyloid A, β2 microglobulin (n=1), and AL β- or κ-light chain.

Histochemically the amyloid deposits localized to the temporal artery were resistant to performate pretreatment for 1 sec, and sensitive for 5-10 sec; resistant to KMnO4 oxidation for 1 min, resistant/sensitive for 3-5 min, and sensitive for 10 min or more (Table 4).

The relationship (p-value of correlation) regarding the prevalence of amyloid deposits in temporal arteries of PMR patients with or without TA, or Ath is summarized in Table 5.

The correlation between amyloidosis of PMR patients with TA or without TA was nearly significant (χ² = 3.0025; p < 0.083 – NS).

There was no significant correlation between amyloidosis and classic (χ² = 2.9776; NS) or atypical form (χ² = 1.4664; NS) of TA; the correlation between amyloid deposits and healed stage of TA was significant (χ² = 10.4193; p < 0.001).

Ath did not influence the prevalence of amyloidosis in PMR patients (χ² = 0.0863; p < 0.768 – NS).

The classic, atypical and healed form of TA is demonstrated on Figures 1-4.

Amyloid deposits in PMR patients with or without TA are demonstrated on Figures 7-8 and 9.

### Discussion

Our PMR patients with histologically diagnosed TA fulfilled the criteria of the American College of Rheumatology (ACR) for the classification of giant cell arteritis [12]. According to our interpretation TA represents a later and more severe stage of PMR, and we agree with the statement that giant cell arteritis (e.g. temporal or cranial arteritis) and polymyalgia rheumatica represent different clinical spectra of a single disease process [13].

The longer life span of our PMR patients with TA supports the assumption that TA develops later, and PMR with TA represent a later stage of the disease. In comparison with PMR without TA; the difference between the average age of the PMR patients with and without TA was significant (p < 0.0164).

This assumption is supported by the prevalence of amyloid deposits as well. The occurrence of amyloidosis in PMR patients without TA was lower (16.23%), then that in PMR patients with TA (25.35%); the increment may be caused by the longer life span of PMR patients.
Figures 7(a-d): Main branch of medium size temporal artery, PMR with atypical TA
Predominant lymphoid infiltration of the medium size main branch is accompanied by distorted, homogenous, and discontinuous internal elastic lamina.
(a) HE, x 20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200

Figures 8a-d (same field as Figure 7a-d): Main branch of medium size temporal artery, PMR with atypical TA
Predominant lymphoid infiltration of the medium size main branch is accompanied by distorted, homogenous, and discontinuous internal elastic lamina.
Amyloid deposits are localized along the homogenised and discontinuous internal elastic lamina.
(a) Congo red staining, viewed under polarized light, x 20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200
Figures 9(a-d): Main branch of medium size temporal artery, PMR without TA
Amyloid deposits localized at the vanished sections of the discontinuous internal elastic lamina.
(a) Congo red staining, viewed under polarized light, x 40, (b) same as (a) x100, (c) same as (a) x200, (d) same as (a) x200

There was no difference in localization, immunohistochemical and histochemical character of amyloid deposits of PMR patients with or without TA. This supports the assumption that PMR with TA or PMR without TA is identical disease.

Amyloid deposits of PMR patients proved to be an isolated phenomenon localized to the wall of medium size arteries only; small arteries, arterioles and veins were negative, which are not characteristic of systemic form of amyloidosis. The systemic AA, Aβ2M, and AL λ- or κ-light chain amyloidosis were excluded immunohistochemically as well.

Arth did not influence the prevalence of amyloid deposits of PMR patients, based on the negative association’s coefficient (-0.23461).

The localization of amyloid deposits in place of vanished sections of internal elastic lamina, and the close connection between them indicates that dystrophic amyloid deposits derive from the damaged internal elastic lamina in our PMR patients with or without TA (amyloid was not found in blood vessels without internal elastic lamina).

The genesis (origin) of amyloid deposits of temporal arteries can be regarded as dystrophic. Dystrophic amyloidosis is basically an ageing phenomenon. The high and significant value of correlations coefficient between dystrophic amyloidosis and healed stage of TA shows that the inflammation of the temporal artery contributes to the development of this type of amyloidosis by causing structural damage of the temporal artery.

Although TA is characterized by chronic inflammation, and it cannot be excluded a minimal or occasional inflammation in temporal arteries of PMR patients in the past (without actual inflammatory infiltration at biopsy), AA amyloidosis appears to be an exceptionally rare complication of this disorder [14-17]. Our results support this assumption as well; amyloid A deposition was not found in none of our 299 PMR patients with or without TA.

Systemic primary (myeloma-associated or B-cell dyscrasia related) immunoglobulin AL amyloidosis may mimick TA, conformed by several authors [18-25].

The lack of systemic primary AL amyloidosis in our biopsy population of PMR patients has been deceptive. Namely patients with clinically recognized lymphoproliferative disorders (with or without clinical symptoms of PMR) were transferred to an institution specialized in hematology.

Conclusion

PMR and TA are the same disease; TA represents a later and more severe stage of PMR.

Amyloid deposits may vary the histology of temporal arteries of PMR patients with or without TA. In our biopsy population the amyloid deposits were exclusively localized, dystrophic and derived from the demaged internal elastic lamellae.
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References


