Histologic Characteristics of Systemic Vasculitis: A Comparative Postmortem Study of 33 Rheumatoid Arthritis and 11 Progressive Systemic Sclerosis Patients

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Abstract

The aim of this study was to determine the histologic characteristics of vasculitis and other vascular changes in rheumatoid arthritis (RA) and systemic sclerosis (SSc) patients. Twelve organs of 33 RA and of 11 SSc with systemic vasculitis (SV) were studied microscopically. RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology. SV was observed in all of 33 RA and 11 SSc patients with variable prevalence and severity. Three types of vasculitis were detected: non-specific, fibrinoid necrotic and granulomatous with variable prevalence and severity in blood vessels of different calibers. Non-specific SV was the most frequent type of vasculitis in both of investigated autoimmune diseases. Fibrinoid necrotic SV may be present in RA and SSc, with higher prevalence and more excessively in SSc. Presence of granulomatous SV was never seen in SSc. Vessels of all sizes, mainly arterioles and small arteries may be involved in both autoimmune diseases. The relative frequent involvement of veins was present in SSc. Histological differences of vasculitis or vascular changes may help in identification of autoimmune disorders. Correct histological diagnosis is particularly important in early stages or in overlapping syndromes because of different prognosis and sometimes therapy.

Keywords — Rheumatoid arthritis, systemic sclerosis, systemic vasculitis, histologic characteristics

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I. INTRODUCTION

Autoimmune diseases may be characterized by the type, prevalence, severity and stages of vasculitis involving different size vessels.

Involvement of blood vessels in RA may be non-specific inflammation (Ns) and/or fibrinoid necrosis (Fn) or granulomatous transformation (Gr) of blood vessels in different (acute, subacute, subchronic, chronic) stages of the pathological process. The vasculitis may be accompanied by fibromuscular and/or intimal proliferation and successive adventitial fibrosis (FIP).

Involvement of blood vessels in SSc may be non-specific (Ns) and/or fibrinoid necrotic vasculitis (Fn) with or without fibromuscular and/or intimal proliferation and successive adventitial fibrosis (FIP) – in different (acute, subacute, subchronic, chronic) stages of the pathological process.

The aim of this study was to determine: (1) the prevalence and severity of vasculitis and vascular changes in RA and SSc, (2) the types of vasculitis and structural changes of the vessel walls in RA and SSc, (3) the size of blood vessels involved by vasculitis.

II. PATIENTS (AUTOPSY POPULATION)

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA and all of them were autopsied. SV of autoimmune origin complicated RA in 33 (20.49%) of 161 cases. RA: females 20, average age of 66.95 years, range 82-32, onset of RA: 58.5, disease duration: 10.89 years; males 13, average age of 67.46 years, range 83-53, onset of RA: 54.69, disease duration: 12.77 years at death. This non-selected autopsy population of 33 RA patients with SV was studied and compared with 11 autopsy patients suffering in SSc. SSc: females 10, average age: 53.6 years, range 62-37, onset of SSc: 43.3, disease duration: 10.0 years; male 1, age of 65 years, onset of SSc and duration of disease not known. RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology (ACR).

III. METHODS

Twelve organs (heart, lung, liver, spleen, kidney, pancreas, gastrointestinal tract, adrenal gland, skeletal muscle,
The prevalence (existence, incidence) and severity, the type of vasculitis, the size of the involved vessels (arteriole, small artery, medium size artery, venule, small vein, medium size vein), and the stages of vasculitis (acute, subacute, subchronic, chronic) were determined histologically.

Glossary of definitions
"Prevalence" concerns the presence of vasculitis in different vessels. "Prevalence" of vasculitis was determined based on the presence of vasculitis in blood vessels of different calibers.

"Severity" means different density of inflamed sections in vascular system. "Severity" of vasculitis was evaluated by semi-quantitative, visual estimation on a 0 to 3 plus scale (based on the number of involved vessels/light microscopic field x40 by Olympus BX51). Semi-objective score system of "severity": “0” – no vasculitis “1” – occasional blood vessels with vasculitis “2” – less than 5 involved blood vessels per microscopic field with a x20 objective. (In case of AA or VV it corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. less than five medium size vessels/tissue sample) “3” – Five or more involved blood vessels/microscopic field with a x20 objective (In case of AA or VV this corresponds to the absolute number of involved medium size vessels of tissue sample, e.g. 5 or more than five medium size vessels/tissue sample)

Types of vasculitis:
(Ns) Non-specific vasculitis is characterized by non-specific leukocytic, lymphocytic, plasmacytic infiltration. Fibrinoid necrosis is minimal or absent
(Fn) Fibrinoid necrotic vasculitis is dominated by fibrinoid necrosis (fresh or old fibrinoid changes in the vessel wall)
(Gr) Granulomatous vasculitis: the original structure of the vessel wall is replaced by granulomatous, more or less cellular infiltrate. In the early stages the infiltrate is dominated by histiocytes, with or without multinucleated giant cells, and later by fibroblasts. In the end stage of granulomatous vasculitis the vessel wall becomes less cellular and more fibrotic.

Size of blood vessels:
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)

IV. RESULTS
1. Histologic characteristics of SV according to the type of vasculitis and the size of blood vessels involved by vasculitis in RA are demonstrated in Tables I.I-I.II and Diagrams I.I-I.III.
Figure 1a-b
RA, stomach
Arteriole, non-specific, subacute-subchronic vasculitis
(a) HE, x 100, (b) same as (a) x200

Figure 2a-b
RA, duodenum, ileum
Small artery, fibrinoid necrotic, subchronic-chronic thrombo vasculitis
(a) HE, x 20, (b) same as (a) x40

Figure 3a-b
RA, ileum, duodenum
Arteriole, granulomarous, subacute-subchronic vasculitis
(a) HE, x 100, (b) same as (a) x200
severity of SV in 33 RA patients according to the type of vasculitis in involved vessels by size (in absolute value and in % of the total sum of severity N=594)

<table>
<thead>
<tr>
<th>Size of involved vessels</th>
<th>Non-specific n= (%)</th>
<th>Fibrinoid necrotic n= (%)</th>
<th>Granulomatous n= (%)</th>
<th>Total n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>arteriole (a)</td>
<td>204 (34,3)</td>
<td>73 (12,5)</td>
<td>45 (7,6)</td>
<td>322 (54,2)</td>
</tr>
<tr>
<td>small artery (A)</td>
<td>125 (21,0)</td>
<td>39 (6,6)</td>
<td>27 (4,6)</td>
<td>191 (32,2)</td>
</tr>
<tr>
<td>medium size artery (AA)</td>
<td>51 (8,6)</td>
<td>0 (0,0)</td>
<td>4 (0,7)</td>
<td>55 (9,1)</td>
</tr>
<tr>
<td>venule (V)</td>
<td>9 (1,5)</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>9 (1,5)</td>
</tr>
<tr>
<td>small vein (V)</td>
<td>6 (1,0)</td>
<td>5 (0,8)</td>
<td>2 (0,3)</td>
<td>13 (2,2)</td>
</tr>
<tr>
<td>medium size vein (VV)</td>
<td>0 (0,0)</td>
<td>2 (0,3)</td>
<td>2 (0,3)</td>
<td>4 (0,7)</td>
</tr>
<tr>
<td>Total</td>
<td>395 (66,5)</td>
<td>119 (20,0)</td>
<td>80 (13,5)</td>
<td>594 (100,0)</td>
</tr>
</tbody>
</table>

Diagrams I.I and I.II

Legends to Table I.I and Diagram I.I

Vessels of all calibers (arteriole, small artery, medium size artery, venule, small vein, and medium size vein) were involved with varying severity of vasculitis.

Three types of vasculitis or vascular changes were present, each with or without progressive fibromuscular and/or intimal proliferation and successive adventitial fibrosis (FIP). In most of the cases FIP was only moderate.

Vasculitis in RA was characterized by dominant involvement of arterioles and small arteries, and the veins were less severely affected.

Diagrams I.II

Legends to Table I.II and Diagram I.II

In RA the vasculitis was usually severe in the frequently involved blood vessels.

2. Histologic characteristics of SV according to the type of vasculitis and the size of blood vessels involved by vasculitis in SSc are demonstrated in Tables I.I-III and Diagrams II.I-III.

Prevalence of SV in 11 SSc patients according to the type of vasculitis in involved vessels by size (in absolute value and in % of the total sum of prevalence N=425)

<table>
<thead>
<tr>
<th>Size of involved vessels</th>
<th>Non-specific n= (%)</th>
<th>Fibrinoid necrotic n= (%)</th>
<th>Granulomatous n= (%)</th>
<th>Total n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>arteriole (a)</td>
<td>96 (22,6)</td>
<td>55 (12,29)</td>
<td>0 (0,0)</td>
<td>151 (35,5)</td>
</tr>
<tr>
<td>small artery (A)</td>
<td>81 (19,1)</td>
<td>35 (8,2)</td>
<td>0 (0,0)</td>
<td>116 (27,3)</td>
</tr>
<tr>
<td>medium size artery (AA)</td>
<td>41 (9,7)</td>
<td>10 (2,4)</td>
<td>0 (0,0)</td>
<td>51 (12,0)</td>
</tr>
<tr>
<td>venule (V)</td>
<td>25 (5,9)</td>
<td>7 (1,7)</td>
<td>0 (0,0)</td>
<td>32 (7,5)</td>
</tr>
<tr>
<td>small vein (V)</td>
<td>32 (7,5)</td>
<td>9 (2,1)</td>
<td>0 (0,0)</td>
<td>41 (9,7)</td>
</tr>
<tr>
<td>medium size vein (VV)</td>
<td>30 (7,1)</td>
<td>4 (0,9)</td>
<td>0 (0,0)</td>
<td>34 (8,0)</td>
</tr>
<tr>
<td>Total</td>
<td>305 (71,8)</td>
<td>120 (28,2)</td>
<td>0 (0,0)</td>
<td>425 (100,0)</td>
</tr>
</tbody>
</table>

Diagrams II.I

Legends to Table I.II and Diagram II.I

In SSc only two types of vasculitis or vascular changes were present, non-specific (Figure 4ab) and fibrinoid necrotic (Figure 5ab) vasculitis. Granulomatous type of vasculitis was not observed in SSc. In most cases vasculitis was accompanied by excessive fibromuscular and/or intimal proliferation and successive adventitial fibrosis (FIP).

Vasculitis and vascular changes involved a full segment or only a sector of the blood vessels alternating with intact segments of vessels.

Vessels of all calibers (arteriole, small artery, medium size artery, venule, small vein, and medium size vein) were involved, with varying incidence of vasculitis.

The prevalence of vasculitis was the highest in arterioles and small arteries, with prevailing participation of the veins.
SSc, kidney
Small artery and arteriole, non-specific vasculitis of chronic stage with fibromuscular intimal proliferation and total sclerotic (calcific) obliteration
(a) HE, x50, (b) same as (a) x200

Small artery and arteriole, sectorial fibrinoid necrosis of small artery, and fibromuscular intimal proliferation, fibrinoid necrotic preglomerular arteriole
(a) HE, x50, (b) same as (a) x200

### TABLE II.II

<table>
<thead>
<tr>
<th>Size of involved vessels</th>
<th>Non-specific n= (%)</th>
<th>Fibrinoid necrotic n= (%)</th>
<th>Granulomatous n= (%)</th>
<th>Total n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>arteriole (a)</td>
<td>171 (23,2)</td>
<td>92 (12,50)</td>
<td>0 (0,0)</td>
<td>263 (35,7)</td>
</tr>
<tr>
<td>small artery (A)</td>
<td>140 (19,0)</td>
<td>66 (9,0)</td>
<td>0 (0,0)</td>
<td>206 (28,0)</td>
</tr>
<tr>
<td>medium size artery (AA)</td>
<td>75 (10,2)</td>
<td>19 (2,98)</td>
<td>0 (0,0)</td>
<td>94 (12,8)</td>
</tr>
<tr>
<td>venule (v)</td>
<td>41 (5,6)</td>
<td>12 (1,6)</td>
<td>0 (0,0)</td>
<td>53 (7,2)</td>
</tr>
<tr>
<td>small vein (V)</td>
<td>51 (6,9)</td>
<td>16 (2,2)</td>
<td>0 (0,0)</td>
<td>67 (9,1)</td>
</tr>
<tr>
<td>medium size vein (VV)</td>
<td>47 (6,4)</td>
<td>6 (0,8)</td>
<td>0 (0,0)</td>
<td>53 (7,2)</td>
</tr>
<tr>
<td>Total</td>
<td>525 (71,3)</td>
<td>211 (28,7)</td>
<td>0 (0,0)</td>
<td>736 (100,0)</td>
</tr>
</tbody>
</table>

#### DIAGRAM II.II

Severity of Vasculitis with or without FIP in SSc (n=11)
Type of Vasculitis and Size of Involved Vessels

Legends to Table II.II and Diagram II.II

Blood vessels of all calibers were affected by two types (non-specific and fibrinoid necrotic) of vasculitis.

Dominant involvement of arterioles and small arteries (with prevailing participation of the veins) was characteristic
of SSc.

Pronounced fibromuscular intimal proliferation and adventitial fibrosis (FIP) accompanied both types of vasculitis in all size of involved blood vessels.

**Diagram II.3**

**Prevalence and severity of Vasculitis with or without FIP in SSc (n=11)**

According to the Size of Involved Vessels

Legends to Diagram II.3

In SSc the vasculitis was usually severe in the frequently involved blood vessels.

V. DISCUSSION

Vasculitis or vascular changes of autoimmune origin are considered a direct consequence (complication) of RA or SSc. In RA SV is generated by autoimmune processes (circulating immune complexes, antiendothelial, anticytoplasmic, antinuclear antibodies, etc.) 8-12. In SSc the immunological background is different 13-15; antinuclear, anti-RNA, anti-DNA topoisomerase etc. antibodies may play a role in SV of SSc 14-17, but the vasculitis in SSc is basically not immune complex mediated 2-17. The disparate prevalence and the differences regarding the type, frequency, severity and stages of vasculitis and vascular changes may be explained by differences in their pathogenesis.

Numerous papers discuss the histologic changes of blood vessels in SSc 18-24 or RA 25-26, but according to our best knowledge a detailed analysis of the prevalence and severity of vascular changes in various organs has not been available in the literature other than our earlier publications 27-29.

Differences in the histological appearance of vascular changes may help identifying autoimmune disorders. The correct histological diagnosis is particularly important in early stages or in overlapping syndromes because of different prognosis and sometimes therapy.

Non-specific SV was the most frequent type of vasculitis in both autoimmune diseases. Fibrinoid necrotic SV may be present in RA and SSc, with relatively greater dominance (higher prevalence and more excessively) in SSc. Presence of granulomatous SV excludes SSc, whereas pronounced structural changes of the blood vessels with fibromuscular, and/or intimal proliferation support it.

Vessels of all sizes may be involved in both of autoimmune diseases, most commonly arterioles and small arteries. Relatively frequent involvement of veins favors the diagnosis of SSc.

Incidence and severity of vasculitis are usually running parallel in both autoimmune diseases, and different stages may exist in both.

Blood vessels with a relatively more uniform advanced histologic changes support the diagnosis of SSc, while different types and different stages of changes in the same vessel, i.e. a more variegated histologic appearance in relatively less advanced stages of pathological processes favor RA 37-39.

**REFERENCES**


Miklós Bély (15 April, 1948). Miklós Bély qualified as a doctor of medicine (M.D.) at Semmelweis Medical University (SOTE), Budapest in 1972. He passed the Board Examination in Anatomic Pathology at the Postgraduate Medical School (HIETE), Budapest in 1976 and obtained a Ph.D. from the Hungarian Academy of Sciences in 1981. In 1994 the Semmelweis Medical University acknowledged him as Dr.med.habil, and in 2000 promoted him to Professor of Pathology. He obtained the degree of D. Sc. from the Hungarian Academy of Sciences in 1999. Dr. Bély spent one year (1975-76) as a General Pathologist in the Pathology Laboratory of the Majella Ziekenhuis in Bussum, the Netherlands. Since 1972 he has been working in the Department of Pathology of the National Institute of Rheumatology (since 1993 as Chairman). In 2001 the hospital of this institute has regained its former name, Hospital of the Order of the Brothers of Saint John of God. Dr. Bély has been interested in autoimmune disorders (organ involvement by autoimmune diseases, complications and disease modifying effects of associated conditions, etc.).

Ágnes Apáthy (23 May, 1949). Ágnes Apáthy qualified as a Medical Doctor at the Semmelweis Medical University (SOTE), Budapest in 1973. In 1978 she passed the Board Examination in Neurology at the Clinic of Neurology, Semmelweis Medical University, and the Board examination in Rheumatology at the Postgraduate Medical School (HIETE), Budapest in 1993. She worked as a rheumatologist and neurologist in the National Institute of Rheumatology (between 1973-2011), and since then as a rheumatologist in the Department of Rheumatology of St. Margaret’s Clinic Budapest. Her main fields of interest have been rheumatoid arthritis and disorders of the spine. She has been the author of well over 200 publications and many book chapters. She has been lecturing at scientific meetings in Hungarian, German and English. She is a Board Member of the Hungarian Association of Rheumatologists and a Board Member of Hungarian Spine Society).