Anticentromere antibody in patients without CREST and scleroderma: association with active digital vasculitis, rheumatic and connective tissue disease*

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SUMMARY This paper looks at the problem confronting a doctor evaluating a patient with anticentromere antibody who does not have evidence of disease along the spectrum from CREST (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) to progressive systemic sclerosis. Of 33 people with anticentromere antibody, 21 had CREST and two had scleroderma. Of the other 10 with a positive anticentromere antibody, three had systemic lupus erythematosus (two with digital vasculitis), three very active seronegative polyarthritis, three Raynaud’s phenomenon, and one a claudication syndrome involving the legs. A positive antinuclear antibody test does not always indicate the presence of a connective tissue disease, but the presence of anticentromere antibody without systemic sclerosis or CREST often indicates the presence of another sometimes serious underlying rheumatic or connective tissue disease.

The presence of anticentromere antibody has usually been associated with the CREST (calcinosis cutis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) variant of scleroderma.1 Anticentromere antibody has also been described in scleroderma and in overlaps or mixtures of CREST and scleroderma.2-4 Various authors have described occasional people with other diseases, including Raynaud’s phenomenon alone or associated with systemic lupus erythematosus, rheumatoid arthritis, polyarthritis, or erythema nodosum.2,3 Other associations have included primary biliary cirrhosis, other chronic liver diseases, myositis, morphoea, linear scleroderma, Sjögren’s syndrome, and relatives of patients with scleroderma.3-9

The presence of anticentromere antibody is usually associated with a favourable prognosis, but some have not found this and have even described vasculitis.10,11 This study describes 10 people with anticentromere antibody who did not have CREST, scleroderma, or an overlap. Three had systemic lupus erythematosus, two with digital vasculitis and two with idiopathic thrombocytopenic purpura; three had seronegative polyarthritis; three Raynaud’s phenomenon, two of these having fibrositis/fibromyalgia; and one a claudication syndrome of the legs.

Patients and methods

Serum from the patients was examined for the presence of anticentromere antibody using HEP₂ cells. Positive results were confirmed by the Arthritis Foundation Center for Disease Control ANA Reference Laboratory.12 Positive serum samples were tested for antibodies to double stranded DNA by the Farr technique, Sm, RNP, SSA, and SSB.12 C3 and C4 were measured by nephelometry (Smith Kline Bio-Science Laboratories, Atlanta, Georgia). Circulating immune complexes were measured by 125I C1q binding and staphylococci binding assays carried out at the Center for Disease Control.13-15 The normal range for C1q binding assay is less than 8% and for the staphylococci binding assay less than 25. The patients admitted to the study had clinical or background information indicating the possibility of a connective tissue disease. Of patients who entered the practice in 1982 and whose details were placed on computer in 1985, 4500 were available for analysis. Each patient had a comprehensive history and physical examination and appropriate laboratory
and x ray studies. When available previous records and x rays were obtained and reviewed. From January 1987 all screening antinuclear antibody studies were carried out with HEP2 cells. When ant centromere antibodies were identified these were confirmed as noted above. Patients were classified as having scleroderma according to American Rheumatism Association criteria for the classification of systemic sclerosis (scleroderma).16 Those with CREST had three or more criteria.1

Table 2 Patients with positive anticentromere antibody who did not have systemic sclerosis or CREST

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Raynaud's syndrome</th>
<th>CAP*</th>
<th>Smoker</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Vasculitis, SLE*</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Vasculitis, ITP*, discoid SLE</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Cardiolipin, ITP, SLE</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>‘Dusky’ in cold</td>
<td>One vessel dilated</td>
<td>+</td>
<td>Seronegative polymyositis</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Seronegative polymyositis</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Seronegative polymyositis</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Raynaud’s phenomenon, fibrositis/ fibromyalgia</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>F</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Raynaud’s phenomenon, fibrositis/ fibromyalgia</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Leg claudication syndrome</td>
</tr>
</tbody>
</table>

*CAP= nail fold capillary microscopy; - = not present; + = present; SLE = systemic lupus erythematosus; ITP = idiopathic thrombocytopenic purpura.

Table 3 Serological studies in patients with positive anticentromere antibody

<table>
<thead>
<tr>
<th>Patient No</th>
<th>RF*</th>
<th>DNA</th>
<th>Sm</th>
<th>RNP</th>
<th>SSA</th>
<th>SSB</th>
<th>C3</th>
<th>C4</th>
<th>ClqBA* (%)</th>
<th>SBA*</th>
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<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>+/–</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>L*</td>
<td>L</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>L</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>101</td>
</tr>
<tr>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>30</td>
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<td>5</td>
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<td>-</td>
<td>-</td>
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<td>42</td>
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<tr>
<td>6</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>111</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>111</td>
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<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>29</td>
</tr>
</tbody>
</table>

*RF=rheumatoid factor; + = positive; – = negative; CIC= circulating immune complexes; ClqBA=Clq binding assay, normal <8%; SBA=staphylococci binding assay, normal <25; L=low.
Anticentromere antibody in patients without CREST and scleroderma

(Nos 1, 2, 3) had had antibodies to double stranded DNA during the course of their illness, two had had low complement levels, and one had antibodies to RNP and one to SSA. One woman with polyarthritis (No 4) had antibodies to SSA, and two with Raynaud's syndrome (Nos 8, 9) had antibodies to RNP and one of these also to SSA (Table 3). Eight of this group had circulating immune complexes identified by the staphylococci binding assay and four by the C1q binding assay.

Table 4 Patients with positive anticentromere antibody and systemic lupus erythematosus*

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Clinical and laboratory data</th>
<th>Allergies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Finger nail fold and toe nail fold digital infarction</td>
<td>None</td>
<td>Improvement with prednisone</td>
</tr>
<tr>
<td>2</td>
<td>Infarctions of the pulps of all of the toes, discoid lupus of scalp</td>
<td>Penicillin, sulphonamides</td>
<td>Improvement with prednisone</td>
</tr>
<tr>
<td>3</td>
<td>Strongly positive anticardiolipin antibodies (IgG, IgM, and IgG), false positive serological test for syphilis, psoriasis, positive lupus band test, 3-6 g proteinuria, previous cerebral vascular stroke</td>
<td>Piroxicam sulindac, hydroxychloroquine</td>
<td>Improvement with prednisone and etretinate</td>
</tr>
</tbody>
</table>

*These three people are from among 254 people with systemic lupus erythematosus—that is, about 1% of this group.

Table 5 Patients with positive anticentromere antibody and polyarthritis*

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Erosions</th>
<th>Other clinical or laboratory changes</th>
<th>Allergies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>None</td>
<td>Hypertension, obesity, lumbar stenosis, congenital syphilis</td>
<td>None</td>
<td>Prednisone, penicillamine</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Hypertension, thrombophlebitis, no cardioliens</td>
<td>Penicillin</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>Subchondal cysts of right tibia femur</td>
<td>Tetracycline</td>
<td>Prednisone, diclofenac</td>
</tr>
</tbody>
</table>

*These three people are from among 167 people with polyarthritis—that is, almost 2% of this group.

Table 6 Patients with anticentromere antibody and Raynaud's phenomenon*

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Additional clinical and laboratory data</th>
<th>Allergies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Mitral valve prolapse, fibrositis/fibromyalgia, hypermobile syndrome, vascular headaches</td>
<td>None</td>
<td>Cyclobenzaprine</td>
</tr>
<tr>
<td>8</td>
<td>Mitral valve prolapse, carpal tunnel syndrome</td>
<td>Sulphonamides</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Fibrositis/fibromyalgia, postpartum alopecia</td>
<td>Allergic rhinitis</td>
<td>None</td>
</tr>
</tbody>
</table>

*These three people are included among 55 with Raynaud's phenomenon—that is, about 5% of this group.

Table 7 Patient with anticentromere antibody and intermittent claudication of the legs

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Additional clinical and laboratory data</th>
<th>Allergies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Mitral valve prolapse, normal non-invasive arterial studies, borderline systolic hypertension</td>
<td>None</td>
<td>Oxpentifyline—could not tolerate</td>
</tr>
</tbody>
</table>
Discussion

Leon-Perez and Tiliakos described three anticentromere antibody positive men with necrotising digital vasculitis identified by biopsy or angiography. All were patients at the Veterans’ Administration Hospital, smokers, had Raynaud’s phenomenon, and were responsive to prednisone. Two had antecedent frostbite and two hypertension. Testing for a variety of other antinuclear antibodies was negative. Mitchell et al described a 62 year old Japanese-American ballet instructor who had granulomatous central nervous system vasculitis with anticentromere antibody and no features of a connective tissue disease except for alopecia areata. She was not hypertensive or a smoker. Most of the patients described here have clinical and serological findings indicating the presence of severe connective tissue and rheumatic disease. Migliaresi et al found positive anticentromere antibody ‘almost exclusively in patients with connective tissue disease and/or Raynaud’s phenomenon’. Six of their 31 anticentromere antibody positive patients had connective tissue diseases with unfavourable outcomes. Other risk factors in this group that need to be considered include smoking, as four of these people smoked and so did the patients of Leon-Perez and Tiliakos; allergic reactivity, as five of this group had allergic drug reactions and this has been described in people with connective tissue disease, hypertension and mitral valve prolapse, as there are three patients in each of these categories.

With the recent development of the solid phase enzyme linked immunosorbent assay (ELISA) to detect antibodies to the centromere protein, using a cloned fusion protein Cterm,CENP-B[β-gal] as antigen, one can now detect anticentromere antibody without using indirect immunofluorescence. The presence of other antinuclear antibodies may interfere with the identification of anticentromere antibody by immunofluorescence. In this paper we were able to identify anticentromere antibody in patients despite the presence of other antinuclear antibodies because of the different sensitivities of the techniques used. Using cloned CENP-B, we may be able to identify many more patients. We will see if the observations in this paper continue to be confirmed in people in whom anticentromere positivity is recognised earlier than by immunofluorescence.

This report indicates that finding a positive anticentromere antibody in a person without clinical data indicating scleroderma or CREST should alert the physician to the presence of a potentially serious underlying rheumatic disease process, whereas finding a positive antinuclear antibody may or may not indicate the presence of connective tissue disease. In this study only a small number of the people were found to have anticentromere antibodies —1% of those with systemic lupus erythematosus, nearly 2% of those with polyarthritis, and 5% of those with Raynaud’s phenomenon. Anticentromere antibodies have been described in 0-08% of female blood donors, but these subjects were not clinically evaluated. The patients described here will need to be followed up to see if eventually they develop scleroderma or CREST.

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References

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