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Leucocytoclastic vasculitis induced by prolonged exercise

Departments of Dermatology and *Pathology, Academisch Ziekenhuis, Maastricht, P. Debyeelaan 25, Postbus 5800, 6202 AZ Maastricht, the Netherlands
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Summary
Many people develop skin symptoms after long-distance walks, but little is known about the aetiology of these. In this study we took 11 biopsies from 10 long-distance walkers who walked 80 km. All biopsies originated from purpuric lesions on the lower legs, which had appeared during walking. In all 11 specimens, signs of a leucocytoclastic vasculitis were present with leucocytoclasis, exocytosis of erythrocytes and a granulocyte/mononuclear perivascular infiltrate. Immunofluorescence investigations showed deposition of C3c in many specimens and immunoglobulin M in some. The occurrence of a leucocytoclastic vasculitis after prolonged exercise may be explained by the existence of an exercise altered cutaneous microcirculation, complement activation and an altered immune function.

Worldwide there is a growing interest in sports and sports medicine. We have seen a patient who developed erythema, purpura and an histological proven leucocytoclastic vasculitis on the lower legs, which only occurred after walking at least 30 km. There have been several reports of exercise-induced purpura and urticarial lesions.1-4 These were mostly attributed to local pressure from shoes or clothing, or solar influences. However, purpura of the legs, in particular the lower leg region in association with sport, has not been described previously. To investigate this phenomenon we visited the finish of a long-distance walk to investigate the prevalence of skin symptoms such as erythema, urticaria and purpura, and to study venous function. The venous refilling time is known to be strongly reduced (mean 9-5 ± standard error 5-6 s; normal >25 s) as an indication of decompensation of the venous system.5 In this study we report the histological and immunohistological findings in skin biopsies taken from walkers directly after a long walk.

Patients and methods
Fifty-eight long-distance walkers (40 males, 16 females, sex in two not registered) were evaluated within 1 h following an 80 km march (Kennedy mars, Someren, the Netherlands). The participants were volunteers who gave verbal informed consent. Their legs were examined for erythema, urticaria, purpura and chronic venous insufficiency (CVI). Skin changes due to CVI were staged according to Widmer et al. and classified as either absent, or present in a mild or severe form.5 Fifty-four participants were evaluated for venous insufficiency by light reflection rheography using a Laumann 1000 Rheograph (Selb, Germany).6 None of the volunteers was examined before the walk and no data on medical history or medication were known.

Erythema, urticaria and purpura were described as absent or present. Erythema was defined as a transient local redness of the skin, disappearing after local pressure. Purpura was distinguished from erythema when it failed to blanch the lesion. In 10 participants, two 4 mm punch biopsy specimens were taken from a representative purpuric lesion on the lower leg; in one participant, two series of biopsies were obtained, one series of biopsies from each leg. No biopsies from other sites of the body nor from controls were taken. One of the two specimens was snap-frozen in liquid nitrogen and stored at −70°C. Cryostat cut 4 μm sections were stained with fluorescein-conjugated rabbit anti-human antibodies to Clq, C3c, immunoglobulin A (IgA), IgG and IgM and fibrin (Dako, Glostrup, Denmark). The other specimen was fixed in formaldehyde, embedded in paraffin and stained with haematoxylin and eosin. Both specimens were evaluated by one pathologist and one dermatologist. To standardize the histological features of leucocytoclastic vasculitis, grading criteria were used including the following: epidermal changes, specially...
necrosis; exocytosis of erythrocytes; depth of infiltrate; vessel wall invasion by neutrophils; amount of leuco-
cytoclasis and amount of fibrinoid necrosis. All criteria
were graded as absent, marginal or distinct.

Results

In 41 of the 58 volunteers erythema and/or purpura
was seen (Table 1). Coexisting urticarial lesions were
observed in eight cases. According to the volunteers, all
lesions had appeared during the walk, and were pain­
less. Some were palpable. The purpura were signifi­
cantly more frequent in participants who had distinct
oedema, saphenous vein varicosity, and/or severe skin
changes due to CVI. The occurrence of the purpura and
erythema was more frequent in females, but the skin
symptoms of CVI showed no sex difference.

All 11 biopsies showed leucocytoclastic vasculitis
(Table 2), with a mild to severe leucocytoclasia, granu-
locyes and mononuclear cells invading the vessels
(n = 11), marginal exocytosis of erythrocytes (n = 3),
and exocytosis of the infiltrate into epidermis (n = 2)
(Fig. 1). Fibrinoid necrosis, epidermal necrosis or libri
thrombus formation were not found. On immunofluor­
escence, all but one specimen revealed C3c deposition
in the subepidermal capillaries. In one case, granular C3c
was stretched out along the basement membrane. In
another, it was also found in the papillary dermis. C1q
was found, in two specimens, in the mid-dermis. IgM
distribution was seen in four: three times in the capil­
lar loop and once mid-dermal. One biopsy was nega­
tive for all antibodies. The infiltrate varied in depth from
being superficial and perivascular, involving mainly the
papillary dermis, to involving the subcutaneous fat with
vessel wall invasion by neutrophils.

Discussion

Leucocytoclastic vasculitis (syn: allergic vasculitis, leu­
cocytoclastic angitis) is characterized by palpable
purpura due to deposition of immune complexes in
postcapillary venules, primarily of the legs. Any
other organ, apart from the skin, can be involved.
Several factors influence the disease activity, including
the concentration of circulating immune complexes, the
half-life of the complex and
of the antibodies which form the complexes. In many
cases the disease is self-limiting, and only confined to
the skin. Leucocytoclastic vasculitis can be triggered
by many factors including bacterial infection, drugs,
immune complexes, blood stasis and systemic disease.
Prolonged exercise can now be added to this list.

Table 1. Distribution of oedema, varicose veins, skin changes as sign of
chronic venous insufficiency (CVI), erythema and purpura after
walking 80 km in 58 volunteers

<table>
<thead>
<tr>
<th></th>
<th>Absent</th>
<th>Present</th>
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</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>24</td>
<td>Moderate in 22 Distinct in 12</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>30</td>
<td>Minor in 19 Stem in 9</td>
</tr>
<tr>
<td>Skin changes as sign of CVI</td>
<td>45</td>
<td>Mild in 9 Severe in 4</td>
</tr>
<tr>
<td>Erythema</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>Purpura</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>Purpura and erythema</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>Urticaria</td>
<td>50</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2. Histological and immunofluorescence results, in combination with
the clinical appearance of the lesion

<table>
<thead>
<tr>
<th>Biopsy number</th>
<th>Histological LCV</th>
<th>Immunoglobulins</th>
<th>C3c</th>
<th>C1q</th>
<th>Purpura</th>
<th>Erythema</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>IgM+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td></td>
<td>+</td>
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<td>-</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
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<td></td>
<td>++</td>
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<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>IgM+</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>IgM+</td>
<td>+</td>
<td>++</td>
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<td>7</td>
<td>+</td>
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</tr>
<tr>
<td>8</td>
<td>+</td>
<td>IgM+</td>
<td>+</td>
<td>++</td>
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<td>+</td>
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<tr>
<td>9</td>
<td>+</td>
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<td>++</td>
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<td>++</td>
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<tr>
<td>11</td>
<td>+</td>
<td></td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

LCV, leucocytoclastic vasculitis; purpura and erythema: - = absent, + = present; immunoglobulins, C3c and C1q: - = absent, + = marginal, ++ = distinct. Biopsies 5 and 6 came from
different purpuric lesions on different legs of the same long-distance walker.
The complement cascade system is activated. C3a and C4a in the blood increase during and directly after short as well as prolonged exercise. The mechanism of activation may represent a non-specific immune response to muscle cell inflammation caused by physical activity. However, the direct activation of specific substances such as C-reactive protein and trypsin. We did not correlate our skin findings with complement activity, but it would be interesting to do this in the future.

Vasculitis may be initiated by an altered cutaneous microcirculation. During exercise, the cutaneous temperature rises, a 10-fold increase in cutaneous blood flow and subsequent vasodilation occurs. The volume of blood in the relaxed cutaneous veins will increase. This venous dilatation is counteracted by the sympathetic-vasoconstrictor, which induces vasoconstriction. This reflex mechanism might fail to work under some circumstances, leading to an overfilled venous system. The consequent rise in capillary volume and pressure can induce extravasation of blood and the appearance of purpura. An elevated capillary pressure will also give rise to more turbulence of blood flow and damage to the vascular wall.

### References
