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Leucocytoclastic vasculitis induced by prolonged exercise

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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 diascopy 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 C1q, 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

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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

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

necrosis; exocytosis of erythrocytes; depth of infiltrate; vessel wall invasion by neutrophils; amount of leucocytoclasis and amount of fibrinoid necrosis.[7] 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 painless. Some were palpable. The purpura were significantly 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 leucocytoclasis, granulocytes 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 fibrin thrombus formation were not found. On immunofluorescence, 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 capillary loop and once mid-dermal. One biopsy was negative 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, leucocytoclastic angiitis) is characterized by palpable purpura due to deposition of immune complexes in postcapillary venules, primarily of the legs.[8] 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 the physical characteristics of the antibodies which form the complexes. In many cases the disease is self-limiting, and only confined to the skin.[9] 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 2. Histological and immunofluorescence results, in combination with the clinical appearance of the lesion

Biopsy number	Histological LCV	Immunoglobulins	C3c	C1q	Purpura	Erythema
1	+	IgM+	++	−	−	+
2	+	−	+	−	+	+
3	+	−	++	−	+	+
4	+	−	−	−	−	+
5	+	IgM+	++	−	+	+
6	+	IgM++	+	++	+	+
7	+	−	+	−	+	+
8	+	IgM+	+	++	−	+
9	+	−	++	−	+	−
10	+	−	++	−	+	−
11	+	−	++	−	+	−

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.

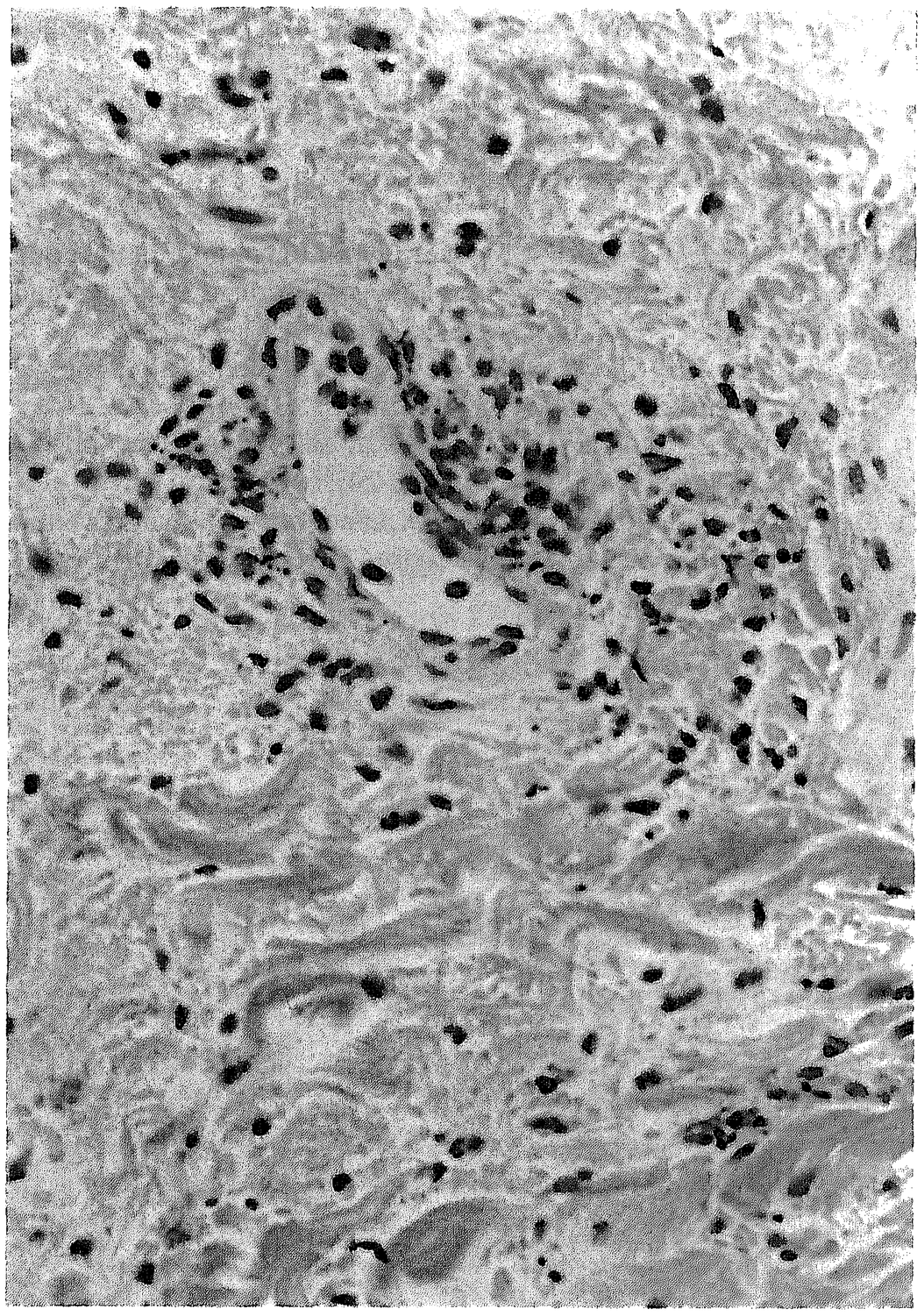

Figure 1. Specimen of a purpura lesion showing neutrophils and mononuclear cells in and around a capillary, and nuclear fragments (haematoxylin and eosin, ×250).

In leucocytoclastic vasculitis, a granular deposition of IgG, IgM, or C3 can be found in the vessel walls on direct immunofluorescence. The lesions should ideally be less than 4 h old.[10] The most sensitive indicator is C3. The leucocytoclastic infiltrate varies depending on the stage of development. The signs of erythrocyte extravasation and fibrin thrombi are only seen in the final stage. This explains our results, and confirms our opinion that we have observed a leucocytoclastic vasculitis in its very early state.[11]

Different explanations can explain our findings. Alterations in immunological or biochemical parameters after endurance exercise have been described by several investigators.[12–15] Most of these returned to normal after 15 min to 21 h. An increase of circulating immune complexes after prolonged exercise in healthy subjects has been shown to contain IgG1, IgG2, IgG3, or IgM antibodies and antigen–antibody complexes.[15] 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 of complement during exercise is not known,[16] but may represent a non-specific immune response to muscle cell inflammation caused by physical activity.[17] C3a and C4a elevation means that the alternative pathway of complement cascade system is activated, possibly by circulating immune complexes, or by non-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.[18,19] During exercise, the cutaneous microcirculation is regulated to establish a stable temperature and systemic haemodynamics.[20] When, however, the core temperature rises, a 10-fold increase in cutaneous blood flow and subsequent vasodilatation occurs. The volume of blood in the relaxed cutaneous veins will increase. This venous dilatation is counteracted by the sympatho-adrenergic innervation of the cutaneous microvasculature, which induces vasoconstriction.[21] 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.

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