The therapeutic effect of cigarette smoking on oral/genital aphthosis and other manifestations of Behcet's disease

Sirs,

An ameliorative action of cigarette smoking on oral aphthosis has been described (1) and because nicotine gum was similarly remedial, a local action was implicated (2). We treated two patients in whom cigarette smoking brought resolution not only to oral but to genital ulcers. In the second patient, cigarette smoking also attenuated extramucosal features of possible Behçet's disease. Based on its effects in these patients, it would appear first, that the action of cigarette smoking on aphthosis is not only local, but systemic; second, that cigarette smoking may be therapeutic for more than aphthosis, and third, because nicotine patches were ineffective in the one patient in whom they were tried, that ingredients in addition to nicotine in cigarette smoke may be contributing to its therapeutic action.

Patient 1. A 43-year-old woman with a 16-year history of Behçet's disease characterized by recurrent oral and vaginal aphthous ulcers was treated initially for 6 months with an undetermined dose of prednisone and subsequently without medication for 5 years, until her admission to Charity Hospital ten years ago. At that time she suffered a right hemiparesis with severe memory impairment. Computerized tomography of the brain revealed a lesion consistent with a left internal capsular infarct. Laboratory investigation showed the white blood cell count to be 7.9 K per mm^3, hemoglobin 13.8 mg/dl, hematocrit 41%, platelets 41%, platelet count 419 K per mm^3, erythrocyte sedimentation rate 33 mm and a C-reactive protein that was within normal range. The cerebrospinal fluid had 514 white cells per mm^3 with 86% polymorphonuclear cells, 4% lymphocytes, 9% monocytes and 1% eosinophil; there were two red blood cells per mm^3, 87 mg/dl of protein, 50 mg/dl of glucose and a negative culture and cytology. Because of the history consistent with Behçet's disease, the patient was treated with 60 mg of prednisone and 8 mg of chlorambucil a day during her 2 week hospitalization. After being discharged the prednisone and chlorambucil were gradually tapered off from her daily prescribed regimen and after 18 months discontinued. The oral and genital aphthosis responded in part to this regimen of drugs,increasing again following its discontinuation, but then abating completely after the patient began smoking one pack of cigarettes a day two and a half years later (she had discontinued smoking 19 years earlier, 3 years prior to her disease onset). The aphthosis recurred each time she stopped smoking for more than a week but would abate again in 1 to 2 days each time she began to smoke a pack of cigarettes a day. When she tried substituting a 22 mg transdermal nicotine patch for the cigarettes, the oral and genital ulcers recurred. She presently smokes one to two packs of cigarettes a day and for the past 5 years has experienced no aphthosis and suffered no further progression of her dementia.

Patient 2. A 43-year-old man has a 16-year history of established Behçet's disease which was characterized initially by oral and genital aphthous ulcers, erythema nodosum, lower extremity inflammatory polyarthritis, pathergy, and neuropsychiatric manifestations. At the initiation of his disease, treatment with 100 mg of prednisone a day brought partial relief to his aphthosis, erythema nodosum, polyarthritis and pathergy, but gradual tapering of the prednisone to 10 mg a day led to a recurrence of these disease manifestations. An increase of prednisone to 20 mg a day brought about their partial resolution.

During the ensuing 4 to 5 years, courses of chlorambucil, azathioprine, and methotrexate each resulted in only marginal improvement. Ten years ago, while still on 20 mg of prednisone a day, the patient started smoking cigarettes and experienced immediate elimination of his aphthosis and erythema nodosum, a marked attenuation of his inflammatory polyarthritis, subsidence of his pathergy, and a decrease in his neuropsychiatric symptoms. Each time he stopped smoking, the aphthosis would recur within 1 or 2 days but would subside again within two days after he began once more to smoke a pack of cigarettes a day. He has been almost free of all disease manifestations other than occasional psychological complaints for the past 10 years while continuing to smoke one to two packs of cigarettes a day.

The first patient had possible and the second definite Behçet's disease as defined by the 1990 International Study Group for Behçet's disease (3). Cigarette smoking eliminated oral and genital aphthous in both patients, and in the second, brought complete or partial resolution of erythema nodosum, inflammatory polyarthritis, pathergy, and subjective neuropsychiatric symptoms. Although nicotine has been reported to heal oral aphthous ulcers, it has never been reported to affect genital ulcers nor attenuate the extramucosal features of Behçet's disease. Moreover, the healing action of cigarettes, smokeless tobacco, and nicotine gum on oral ulcers has been considered to be local in action (3) and has been attributed solely to nicotine, in contrast to its apparent action in the present cases, in which the ingredients in cigarette smoking exerted a systemic effect.

Histopathological evidence suggests that the underlying pathogenesis of both idiopathic aphthosis and the aphthosis and erythema nodosum of Behçet's disease is a small-vessel vasculitis,secondary to intense inflammation engendered by infiltrates of both polymorphonuclear (PMN) and mononuclear cells (4). These effects of Behçet's disease on PMN and mononuclear cells appear to intersect with the inhibitory effects that the constituents of cigarette smoking have on these cells,offering a possible basis for the salutary action of cigarette smoking (Table I). Importantly, the alpha and beta unsaturated aldehydes in cigarette smoke are even more potent than nicotine in their effect on PMN chemotaxis (5).

In summary, smoking cigarettes, which increases levels of both nicotine and aldehydes, suppressors of PMN and mononuclear cell function, resulted in a healing action both on oral and genital aphthosis in two patients and ameliorated erythema nodosum, inflammatory polyarthritis, pathergy, and subjective neuropsychiatric symptoms in the patient with established Behçet's disease. This is the first report describing a systemic action of cigarette smoking on aphthosis or an ameliorative action on other manifestations of Behçet's disease. The dangers of cigarette smoking are well recognized but its use may be justified in selected patients with Behçet's disease since the alternative agents, *i.e.*, corticosteroids, cytotoxics, and thalidomide have an

Table I. Contrasting effects of Behçet's disease and the components of smoke on inflammatory cell function.

Behçet's disease	Cigarette smoke
Overall neutrophil function is enhanced (6)	Overall neutrophil function is inhibited (5)
Level of PMN-generated oxygen free radicals is increased (7)	Level of PMN-generated oxygen free radicals is decreased (11)
Migration of PMN increases (6)	Spontaneous migration of PMN is inhibited (12)
PMN production of superoxide anion is enhanced (7)	PMN production of superoxide anion is inhibited (10)
PMN chemotactic activity is increased (8)	PMN chemotactic activity is decreased (5)
Increased monocyte production of IL-2, IL-10 and TNF (9)	Production of IL-2 and TNF is inhibited (13)
PMN antibody-dependent cytotoxicity is promoted (10)	PMN microbicidal funtion is inhibited (14).

even greater long-term toxicity. A large well controlled prospective trial is needed.

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A case of familial Mediterranean fever, Behçet's disease and polyarteritis nodosa complicated by perirenal haematoma

Sirs,

Familial Mediterranean fever (FMF) is characterized by attacks of fever, accompanied by abdominal, chest or joint pain (1).

The most serious complication is the development of amyloidosis, causing chronic renal failure. There are also a number of reports of individuals who have vasculitis associated with FMF (2, 3).

We describe a case of FMF associated with the features of Behçet's disease (BD) and probable polyarteritis nodosa complicated by spontaneous perirenal and retroperitoneal haematoma.

A 37-year old man was admitted to our hospital with a two-week history of malaise, high fever, severe myalgia and severe abdominal and right flank pain in the last four days. He had a history of recurrent abdominal attacks and fever since the age of 8. He also reported periodic arthritis independent of the abdominal attacks. He had been diagnosed as having FMF at the age of 20 and colchicine was administered, which he admitted not to take it regularly. In addition, he also reported recurrent oral and genital ulcerations, and papulo-pustular skin lesions in the last two years.

On admission, he had a temperature of 39°C, blood pressure 160/100 mm/Hg, and the heart rate 98/min. Physical examination revealed abdominal tenderness, rebound and a mass in the right flank. Two ulcerations on the tongue and six genital ulcerations scars were also found. On funduscopic examination, grade II hypertensive retinopathy was found. Pathergy test was positive.

Laboratory findings were as follows: haemoglobin 7 gr/dl, white blood cell count 24,700 mm^3 and platelet count 645,000 mm^3, the erythrocyte sedimentation rate (ESR) was 129 mm/h, C-reactive protein 5.35 mg/dl, antistreptolysin O titre 583 IU/ml (normal = 0-200), urea 45 mg/dl (n = 5-20), creatinine 1.9 mg/dl (n=0.5-1.4). Urine analysis revealed proteinuria (0.9 g/day) and microscopic haematuria (5-8 red blood cell/ per high-power field). ANA, anti-DNA, c-ANCA, p-ANCA, C3, C4, ACA IgG and M, HBs Ag, anti-HBs, anti-HCV were negative or within normal limits. Abdominal computed tomography (CT) revealed right perirenal and retroperitoneal haematoma (Fig. 1). Renal angiography revealed microaneurysms and a cortical infarct. Rectal biopsy for amyloidosis was negative. The patient refused renal biopsy. Screening for mutations of the MEFV gene showed that he was heterozygote for the M694V mutation.

He was commenced on i.v. cyclophosphamide (1 gr/month) and colchicine (2 mg/day). He was discharged fit, but failed to visit for the next 4 months. In July 2000 the patient was readmitted to hospital for recurrent oral ulcerations and uncontrolled hypertension (200/120 mm/Hg). Abdominal CT showed significant regression of the right perirenal haematoma. His blood pressure stabilised with antihypertensive drugs and, in addition to colchicine 1.5 mg/day, cyclophosphamide 2 mg/kg/day was administered orally this time. No further attack has been observed during the follow-up period since he was discharged from hospital.

The presented patient fullfils the described criteria for FMF by Livneh *et al.* (4). BD was diagnosed on the basis of diagnostic criteria proposed by the International Study Group of Behçet's disease (5).

Reports exist showing the association between FMF and PAN (3), FMF and Henoch-Schönlein purpura (2). FMF and

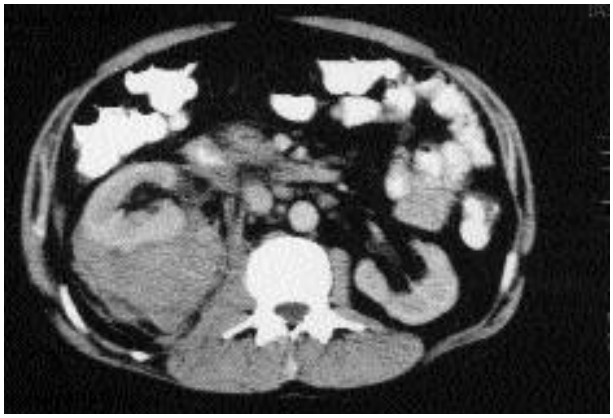

Fig. 1. Abdominal computed tomography revealing a right perirenal and retroperitoneal haematoma.