Secondary Erythermalgia in an HIV-infected Patient Is there a Pathogenetic Relationship?

Sir,

The syndrome of red, warm, swollen and painful extremities has been divided into three types by Drenth & Michiels: primary erythermalgia, secondary erythermalgia and erythromelalgia (1, 2). Erythermalgia and erythromelalgia are two distinct entities and have to be separated. In all types the pain is relieved by cold, whereas exposure to warmth and physical exercise worsens the condition. Primary erythermalgia is a very rare congenital disorder of unknown pathophysiology, which arises in young children and young adults and has a bilateral symmetrical distribution which is not treatable. An autosomal dominant inheritance pattern has been documented in a large family with 29 affected members over three generations (3). Secondary erythermalgia is related to a variety of clinical conditions such as drug ingestion, cutaneous vasculitis, systemic lupus erythematosus, diabetes mellitus, rheumatoid arthritis and hypertension (4). Treatment consists of stopping a possibly causative medication and/or improvement or healing of the underlying disease.

Erythromelalgia, the third type, is the most common variant and restricted to conditions with essential thrombocythemia or other myeloproliferative disorders associated with abnormal thrombocytic function. In the later patient group, treatment with aspirin leads to marked relief. Erythromelalgia due to thrombocythemia is typically asymmetric. Histopathology of erythromelalgia in thrombocythemia shows arterial thrombosis and swollen endothelial cells with large nuclei, and narrowing of the lumen by proliferation of surrounding smooth muscle cells (5, 6). Erythromelalgia may progress to ischemic acrocyanosis or necrosis of fingers and toes (7). In a previous study, we analyzed retrospectively 273 patients with essential thrombocythemia who were seen at the Mayo Clinic between 1975 and 1989 (8). Of the 273 patients with essential thrombocythemia, 62 had related skin manifestations. Fifteen patients had erythromelalgia, and in 11 it was an initial sign of essential thrombocythemia. As expected, a remarkable relief of symptoms was noticed after treatment with acetyl salicylic acid or after lowering the platelet count with chemotherapy or radiotherapy (^{32}p). Michiels et al. showed that erythromelalgia was the presenting symptom in 26 of 40 patients (65%) with thrombocythemia (7).

To the best of our knowledge no report on secondary erythermalgia and HIV-infection exists. Here we present this association for the first time.

CASE REPORT

A 29-year-old female, who was known to be seropositive for HIV-infection as a result of intravenous drug abuse since 1986, was seen because of increasing pain at the distal arms and hands with redness and swelling which had developed within the last 9 months. The patient had advanced HIV infection and showed a history of recurrent *Candida* stomatitis. She had generalized lymphadenopathy and thrombocytopenia (124×10^9/l). Her dermatological history was remarkable for impetigo contagiosa in 1987, folliculitis, trichomycosis axillaris, mollusca contagiosa, flat warts at the dorsum of the hands and condyloma acuminata in the genito-anal area, tinea pedis and seborrhoeic dermatitis. Antinuclear factors were slightly positive, with 1:80 speckled pattern, but antibodies against DNA were negative. Waaler-Rose and Latex test were negative. The leukocyte count was 3.05×10^9/l, hemoglobin 13.1 g/l and thrombocytes 135×10^9/l. Her T-helper cell count was 140×10^9/l. The patient classified for B3 according to the revised CDC-classification system for HIV-infection (9). Her current medication included didanoside 2×200 mg daily and $3\times$ trimethoprim 160 mg/sulfamethoxazole 800 mg once a week. The patient had documented palmar erythema since 1987, but at the beginning of 1995 increasing redness and swelling occurred on both hands. Pain increased in a warm environment and decreased under cold water rinsing. Physical exercise worsened the signs and symptoms. Clinical examination revealed hyperemic and warm hands (Fig. 1). The fingers were swollen and slightly painful. At the time of examination she showed dry skin, condyloma acuminata in the perianal and vulvar region, numerous mollusca contagiosa on the face and flat warts at the dorsum of the hands. Furthermore, she had marked seborrhoeic dermatitis and tinea pedis.

Fig. 1. Red, swollen hands which differ markedly from a control.

DISCUSSION

The pathogenesis of red, warm, swollen and painful extremities remains unclear. In patients with essential thrombocythemia or polycythemia vera, erythromelalgia is caused by rheological problems. Medication against thrombocytic aggregation leads to marked improvement. In patients with secondary erythermalgia an autoimmune disease may be involved and has been discussed recently by Drenth et al. (10). Itin et al. (11) reported on a series of patients with periungual and acral erythema in those patients with HIV-infection. An autoimmune process was also suggested for this phenomenon. Secondary erythermalgia is known under medication with calcium channel blockers but has not been observed in combination with didanoside or trimethoprim/sulfamethoxazole. In a patient under didanosine Pedailles et al. (12) have observed acral erythema which appeared 9 days after the introduction of the drug. The erythema was painful and accompanied by swelling. However, bullous lesions with following desquamation were observed. The skin changes disappeared within a few days, although the drug was continued. In our patient the appearance of erythermalgia and drug ingestion did not coincide. In addition, the natural course in our patient was persistent over 9 months.

Erythermalgia in HIV-infected patients may represent a major form of periungual erythema. Further studies are necessary to clarify the pathogenetic relationship of erythermalgia and HIV-infection.

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