Letters to the Editor

Pseudo-dermatomyositis as a complication of hydroxyurea therapy

Sirs,

Hydroxyurea is one of the most widely used chemotherapeutic agents. Adverse cutaneous effects are increasingly recognized complications of hydroxyurea therapy, including mainly xerosis, hyperpigmentation of both skin and nails (1-5). Acral erythema, both oral and leg ulcerations, or allergic vasculitis complicating hydroxyurea therapy have more rarely been described (5-7). Previous authors have therefore found cutaneous side effects in 10% to 35% of patients treated with hydroxyurea (3, 5); there was furthermore a correlation between both the cumulative drug regimen and the time of onset of the cutaneous complications (5). We observed a case of particular interest, a patient with chronic myelogenous leukemia who developed a dermatomyositis-like eruption related to hydroxyurea therapy.

A 68-year-old woman had a diagnosis of chronic myelogenous leukemia in 1992. She was given oral hydroxyurea therapy at a daily dose of 0.5 gram to 2 grams. She presented in June 1999 with a one-month history of cutaneous lesions involving both the hands and face. The patient received treatment with a combination of diltiazem and omeprazole and 2 g daily hydroxyurea. On admission the patient had no fever. Cutaneous examination showed a dermatomyositis-like eruption, i.e.: (i) a band-like, scaling erythema along the dorsa of the metacarpo-phalangeal and inter-phalangeal joints of her hands; and (ii) a marked periorbital erythema with telangiectatic heliotrope rash on her face (Fig. 1). There was also a painful ulcer along the pretibial area of the lower right leg. The general physical examination was otherwise normal, and notably both myalgias and muscle weakness were absent. Laboratory findings were as follows: erythrocyte sedimentation rate 30 mm/hr (N < 20), C-reactive protein 15 mg/l (N < 5), hemoglobin 7.4 mmol/l, white cell count 56 x 10^9/l (N: 4-10) (7.1% polymorphonuclear cells, 3% lymphocytes, 22% monocytes, 3.6% promyelocytes), platelets 822 x 10^9/l (N: 150-400). Liver and renal tests, blood protein electrophoresis, creatine kinase and aldolase were within normal limits. Autoantibody screening tests, including rheumatoid factors, antinuclear antibodies, antiphosholipid and anticardiolipin antibodies, lupus-like anticoagulant, antineutrophil cytoplasmic antibodies and cryoglobulin were negative. Blood cultures, urinalysis, bacterial (*Borrelia burgdorferi*) and viral serologies (cytomegalovirus, Epstein-Barr virus, parvovirus B19, coxsackie, hepatitis and human immunodeficiency virus) were all negative. Other exams, including chest radiographs, abdominal ultrasound and echocardiography, were normal. Because of the painful ulcer of the right lower leg, both a venogram and arterial ultrasound examination of the lower limbs were carried out, which were normal.

Skin biopsy of the lesion involving the dorsal area of the second right metacarpophalangeal joint was performed, and histological examination demonstrated hyperkeratotic epidermis and vacuolar changes of the basal keratinocytes, associated with moderate pericapillary inflammatory infiltrates composed of lymphocytes throughout the dermis. There was no evidence of either granulomas or vasculitis. Direct immunofluorescence was negative.

The diagnosis of pseudo-dermatomyositis and a painful ulcer of the right lower leg related to hydroxyurea therapy was made, resulting in discontinuation of hydroxyurea treatment. The dermatomyositis-like lesions gradually faded, and completely healed within 6 weeks. The ulcer on the right lower leg disappeared within 4.5 months. Chemotherapy for the chronic myelogenous leukemia was initiated with aracytin subcutaneously (100 mg twice a week). At the 5-month follow-up, the patient remains free of all cutaneous features.

Hydroxyurea chemotherapy is associated with cutaneous impairment and notably, diffuse cutaneous dryness, acquired ichtyosis of the lower limbs, hyperpigmentation of both the skin and nails, palmo-plantar keratoderma, or painful and necrotic ulcerations (1-8). However, only a few authors have previously reported a dermatomyositis-like eruption in patients receiving hydroxyurea therapy (1, 3, 5, 7-9). Our patient also developed a characteristic dermatomyositis-like eruption, associating erythema of both the dorsa on the metacarpo-phalangeal and inter-phalangeal joints of her hands and her face. Both clinical and biochemical muscle impairment were absent in our patient, also confirming previous authors' data (1, 5). In the present case, a diagnosis of pseudo-dermatomyositis related to hydroxyurea therapy could reasonably be made for several reasons: 1) hydroxyurea was the sole drug possibly responsible for the skin manifestations; 2) the occurrence of the pseudo-dermatomyositis eruption and the painful ulceration along the right lower leg was concomitant; 3) the search for both infectious and connective-tissue disorders was negative; 4) pseudo-dermatomyositis was documented 7 year after the initiation of hydroxyurea therapy (i.e., a total dose of 3,100 gm hydroxyurea over a 7-year period), which is in accordance with previous data showing that dermatomyositis-like cutaneous lesions developed 2 to 10 years after initiating hydroxyurea (1, 5); and 5) the rapid and complete resolution of all cutaneous manifestations was obtained after stopping hydroxyurea treatment. Dermatomyositis related to a paraneoplastic syndrome (i.e., secondary to the associated myeloproliferative disorder) could therefore be excluded.

The pathological mechanisms of dermatomyositis-like cutaneous lesions due to hydroxyurea therapy are still not clearly understood, but may be related to a direct toxic effect of hydroxyurea (i.e, inhibition of DNA synthesis) rather than to an immunologic process (1, 5, 9, 10). Our patient developed pseudo-dermatomyositis 7 years after the initiation of hydroxyurea therapy, which also supports the hypothesis of cutaneous damage induced by the long-term accumulation of the drug in both the epidermis and dermis. Finally, our findings highlight the importance of recog-

(a) **(b)**

Fig. 1. (a) Band-like, scaling erythema along the dorsa of the metacarpo-phalangeal and inter-phalangeal joints of the patient's hands. **(b)** Periorbital erythema with telangiectatic heliotrope rash on the patient's face.

nizing such pseudo-dermatomyostis cutaneous lesions as a complication of hydroxyurea therapy, leading to a correct diagnosis and thereby avoiding aggressive and unnecessary investigations. Physicians, particularly rheumatologists, should therefore be aware of the existence of such pseudo-dermatomyositis cutaneous lesions in patients receiving hydroxyurea therapy.

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Antinucleolar antibodies and parvovirus B19 arthritis

Sirs,

We read with great interest the article by Ferri *et al.* (1) in which they describe parvovirus B19 bone marrow infection in a significant percentage of systemic sclerosis (SSc) patients. The authors suggest the inclusion of B19 among the different viral agents which have been proposed to be responsible for the autoimmune alterations observed in SSc. One of the characteristics of the autoimmune findings in SSc is the presence of ANA with an antinucleolar pattern (AnoA) in the IIF in 8-43% of patients (2). Although they have been occasionally described in other processes, AnoA are almost exclusive linked with SSc and related processes (3). Recently we treated a patient with acute polyarthritis caused by B19, in whom we detected serum antinucleolar antibodies. This finding has not been described previously.

The patient is a 26-year-old female employed at a geriatric residence; she is also a part-time baby-sitter. Five days before admission, she complained of fever (38°C) and erythematous exantema with a mild itch which began at the forearms and extended to the thorax; these symptoms lasted for one day. Later, she presented odynophagia and myalgia, and the next day arthralgia at the shoulders and cervical and lumbar raquis, and symmetrical arthritis in the MCP and PIP of the hands, knees and ankles. The rest of the anamnesis was negative.

The patients came into the hospital using a wheelchair. Her general status was good and her physical examination was normal except for the synovitis and limited mobility in the shoulders, elbows, wrists and lumbar and cervical vertebral column. Radiographies of the thorax, hands, knees and pelvis were normal. A hemogram was normal. ESR was 28 mm and CRP 32 mg/l (NV < 8). Coagulation tests, serum parameters, Igs, C4, rheumatoid factor and serologies for *Salmonella, Brucella, Yersinia*, lues, rubeola IgM, HBV, HCV, CMV, EBV and *Borrelia burgdorferii* were normal or negative. The C3 level was 63 mg/dl (NV: 85-195) and ANA were positive at a 1/160 titer with a nucleolar pattern.

ENA and anti-dsDNA were negative. IgM antibody for parvovirus B19 was positive. Clinical symptoms disappeared completely after 3 weeks of antiinflammatory treatment with indomethacin. Three months later, ANA were negative, C3 had become normal, she presented Ig G antibody for HPV B19, and Ig M was undetectable.

In patients with B19 infections, laboratory alterations suggesting an autoimmune phenomenon are often found: diminished complement levels, circulating immunocomplexes and the transient presence of different autoantibodies including RF, ANA, anti-ssDNA, anti-dsDNA, anticardiolipins, anti-lymphocytes, anti-SSA, anti-SSB, anti-RNP and anti-Scl 70 (4-6), often associated to SSc (2) as well. The presence of antinucleolar antibodies has not been described in B19-induced arthritis, although they have been described in patients infected by other viruses such as infectious mononucleosis and hepatitis A (3).

AnoA include several kinds of autoantibodies targeted at antigens mainly located in the nucleoli. They are usually detected by IIF in Hep-2 cells and several patterns of IF have been described. They are primarily found in patients with SSc or related processes such as Raynaud's phenomenon or overlap syndromes. Nevertheless they have sometimes been described in diseases such as SLE, RA, DM-PM, GVHD and some neoplasic diseases (3).

In our patient, AnoA was transient. One year later she presented neither Raynaud's phenomenon nor any other symptom suggestive of SSc. However, after the findings of Ferri *et al.*, we believe that our patient should be followed for a longer time in order to exclude a possible evolution to SSc.

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