Drug-induced Lupus Erythematosus Aggravated by Oral Zinc Therapy

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Abstract. A woman with hypertension had been treated with hydralazine and propranolol for the past 6 years. Leg ulcers and mild joint involvement had been observed for 3 years. When oral zinc therapy was started, multisystemic manifestations of a lupus erythematosus-like syndrome developed within one week. The possible implication of zinc in drug-induced lupus is discussed.

Key words: Zinc; Lupus erythematosus; Hypertension

Many drugs have been implicated in a lupus erythematosus-like syndrome (5). Hydralazine is one such high-risk drug and about 10% of treated patients develop clinical and laboratory signs of a lupus-like reaction (7). To my knowledge zinc has never previously been incriminated.

CASE REPORT

A 58-year-old woman with atopic eczema as a child, but without any past or family history of autoimmune diseases, had been treated with hydralazine (Apresol®, from 30 to 200 mg per day, and propranolol (Inderal®), from 120 to 640 mg per day, since 1971. When an essential hypertension was diagnosed. Other medications included polythiazide (Renese®), potassium chloride (Kalium bromid®), and propylthiouracil (Thiouracil®) for shorter periods, and thyroxine (Levaxin®) since 1973 after a radioiodine-treated hyperthyroidism.

Three years after initiation of the antihypertensive therapy, recurrent leg ulcers developed on the distal part of the right leg. They healed slowly after topical treatment with effervescence zinc sulphate (Solvezink®), 0.2 g (corresponding to 45 mg Zn++) three times daily, was started in August 1977 without a preceding serum zinc determination. Within one week the patient developed fever (39.5°C) and a violaceous rash. She was in relatively good general condition but complained of abdominal distress and had noticed black stools once. The joint involvement was unchanged.
Physical examination revealed facial butterfly rash and a widespread erythematous maculopapular eruption with elements of purpura on the legs and to a lesser extent on the trunk and arms. Her leg ulcers had enlarged and new ulcers were seen on the distal part of her left leg. Oral ulcers were present. There were no other physical abnormalities. Her blood pressure was 180/140 mmHg.

Routine laboratory tests in blood disclosed an erythrocyte sedimentation rate (ESR) of 110 mm/hr, anemia with hemoglobin concentration 90 g/l and a decreased albumin/globulin ratio, but other findings were normal, including urea nitrogen and serum creatinine. In urine a microscopic hematuria with 50–150 red blood cells per high-power field and a slight proteinuria (0.3 g/l) were observed. The first fecal examination for occult blood was positive, the subsequent controls were negative. Other investigations gave normal results and included sigmoidoscopy, roentgenogram of colon, chest X-ray and electrocardiogram. An intravenous pyelography was not performed 'due to prior history of anaphylactic reaction to intravenous contrast medium.

Clinical improvement followed withdrawal of zinc. Within a few days fever and abdominal distress disappeared and the oral ulcers healed. However, skin, joint and laboratory signs of renal involvement persisted. Relapsing skin eruptions and recurrent leg ulcers constituted the major complaints. Skin graft was tried but rejected. The patient was transferred to the Department of Internal Medicine in December 1977.

Laboratory investigations included persistence of elevated ESR, anemia, decreased albumin/globulin ratio and signs of mild renal involvement. In addition, further laboratory studies disclosed presence of antinuclear antibodies in a titre of 1/400 with a diffuse staining pattern, cold agglutinins in a titre of 1/512, several positive L.E-cell preparations, elevated IgM level (5 g/l), a high titre against cytomegalovirus (CMV) which remained unaltered and a decreased 24 hr endogenous creatinine clearance (75 ml/min). Other laboratory data were normal, including serum zinc, complement levels (C3 and C4), CI esterase inhibitor, Coombs' test, cryoglobulins, rheumatoid factor, WR, urea nitrogen, serum creatinine and various coagulation values. Tests for anti-DNA antibodies were negative. No circulating immune-complexes were detected with platelet aggregation test and CI\(_4\)-binding activity was normal. Intradermal tests gave positive skin reactions to mumps skin test antigen, candida and streptokinase-streptodornase, a negative reaction to trichophytin, a normal response to histamine and no response to autologous serum. The skin response to PPD 2 TU was strongly positive. The patient was a slow acetylator.

Several biopsy specimens from leg ulcers and skin rash revealed fibrinoid necrosis of small blood vessels of the upper dermis, perivascular cellular infiltrate consisting of polymorphonuclear leukocytes, extravascular erythrocytes and nuclear dust consistent with necrotizing leukocytoclastic vasculitis (Fig. 1).

A diagnosis of drug-induced lupus erythematosus was made, the antihypertensive drugs were withdrawn and only the treatment with thyroxine was continued. The skin eruption disappeared in a few days, the leg ulcers healed completely in 3 months and the joint involvement declined gradually. Half a year after drug withdrawal the patient was asymptomatic and after a further half-year the blood pressure was still normal in the absence of any treatment. Routine laboratory studies in blood and urinalysis gave normal results and the glomerular filtration rate was within normal limits 2 months after drug therapy was stopped. The antinuclear factor titre had declined to 1/100 and remained unaltered during the following year.
Provocation test with zinc tablets (Solvezink®), 0.2 g three times a day for one week, did not provoke a lupus reaction.

**DISCUSSION**

Side effects from oral zinc sulphate therapy are rare (2). An autoimmune-like reaction has not been reported. In the present patient, who had been treated with hydralazine and propranolol for 6 years, multisystemic manifestations of a lupus erythematosus-like syndrome with renal involvement developed within one week after initiation of oral zinc therapy. Leg ulcers and arthralgia/arthritis preceded zinc administration. Elimination of zinc was followed by clinical improvement but complete remission of clinical symptoms was seen only after withdrawal of the anti-hypertensive drugs. Thus, the observed lupus-like syndrome seemed to be hydralazine-induced, but oral zinc therapy appeared to severely aggravate the reaction. Hydralazine has frequently been implicated in drug-induced lupus (5). Propranolol might be considered but has been suspected in only one report (4). Thyroxine and the agents administered for shorter periods did not influence the clinical course.

The diagnosis of drug-induced lupus was based upon the same criteria as those for spontaneous lupus erythematosus laid down by the American Rheumatism Association (3). Laboratory and histological findings were consistent with the diagnosis. Controversy exists regarding renal manifestations in drug-induced lupus, but Alarcon-Segovia for instance (1) observed renal involvement in 20% of his patients. The strong PPD reaction and the high but unaltered CMV titre may represent an altered immunologic state.

The clinical course following drug elimination was benign. The patient was asymptomatic in half a year after elimination of the antihypertensive drugs. One year after drug withdrawal only a positive antinuclear factor test persisted. The blood pressure remained normal without treatment. This is a recognised but rare phenomenon (7).

The pathogenetic mechanisms involved are unclear. A slow acetylator phenotype predisposes to hydralazine-induced lupus (8) but to my knowledge zinc does not interfere with drug acetylation. However, immunologic factors appear to play a major role in drug-induced lupus (9). Clinical and laboratory studies have suggested that zinc is involved in immunologic functions (6). Thus, one possibility is that zinc interacts with hydralazine by altering the immunologic response.

To conclude—oral zinc sulphate may be an aggravating factor in drug-induced lupus. A provocation test with oral zinc after elimination of the antihypertensive drugs proved negative. The ultimate test would have been to rechallenge the patient with hydralazine alone and in combination with zinc but this was not done for ethical reasons.

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**REFERENCES**