Orogenital ulcers, SLE and hydrallazine

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Summary
The case is reported of a man developing drug-induced systemic lupus erythematosus while taking hydrallazine. The illness was characterized by arthritis and a purpuric rash particularly in the light-sensitive areas as well as orogenital and cutaneous ulceration. Anti-nuclear antibody and DNA binding were positive. All clinical manifestations disappeared on withdrawal of hydrallazine.

Introduction
Hydrallazine-induced systemic lupus erythematosus (SLE) occurs frequently when hydrallazine is used in a dose of >200 mg/day although a few patients have been reported who developed the syndrome while taking smaller doses (Perry, 1973; Ullman et al., 1974; Harland, Facchini and Timbrell, 1980). Orogenital ulceration has not previously been reported in association with hydrallazine- or other drug-induced lupus syndrome.

Case report
A 62-year-old white postmaster was referred for investigation of his multi-system illness. When aged 55 years in 1972 he suffered a transient left hemi-anesthesia and was found to be hypertensive. Metyldopa caused a dry mouth and was replaced by propranolol, clonidine and a thiazide diuretic. In 1976 he had an uncomplicated inferior myocardial infarction and in early 1977 hydrallazine (50 mg thrice/day) was substituted for clonidine as his hypertension was out of control. Satisfactory control was rapidly obtained and he remained well for about 9 months. From January 1978 he began to get intermittent attacks of arthralgia predominantly affecting elbows, knees and wrists which lasted for about one week. In September 1978 he had an influenza-like illness followed by a blepharoconjunctivitis and in October that year he developed peripheral oedema requiring furosemide and a potassium supplement. From mid-1979 his arthralgia became continuous. He also noticed an intermittent rash on his legs and forearms until in October 1979 a severe exacerbation of the arthralgia was associated with superficial skin ulcers over the proximal interphalangeal joints of both hands. These had still not healed one week later when he developed a red painful swelling on the outer aspect of his right leg below the knee, and 3 days later he noticed painful ulcers on the hard palate and tongue as well as several on the inside of his prepuce. He was then treated with indomethacin and talampicillin without improvement until admitted to hospital.

On examination he had the orogenital ulcers described and a non-painful ulcer over the dorsum of the fifth proximal interphalangeal joint of the right hand. He had widespread purpura, especially in the light-sensitive areas, and larger ecchymotic lesions. There was a fluctuant abscess 5 cm in diameter below and lateral to his right knee. There was no joint abnormality. BP was 130/70 mmHg and he had evidence of a small right pleural effusion. On slit lamp examination of his eyes there was no evidence of prior anterior uveitis.

Investigations
Antinuclear antibody positive 1/160. DNA binding positive 1/256. Parietal cell, smooth muscle, thyroid antibodies negative. Rose Waaler test negative. IgG 32-0 g/l (9-5 to 16-5), IgA 3-55 g/l (0-9 to 4-5), IgM 8-25 g/l (0-65 to 2-0). Complement screen normal. Urinary protein 0-1 g/l, 0-2 g/day. Urea 12-9 mmol/l. Creatinine 224 μmol/l, creatinine clearance 33 ml/min. Hb 10-5 g/dl, WBC 4-4 × 10⁹/l, normal differential. Platelets 230 × 10⁹/l, ESR 128 mm/hr. Culture of aspirate from lesion below right knee – *Staphylococcus aureus*. Urethral culture – *Bacteroides fragilis*. Skin biopsy: subepidermal vesicle, the roof of which had undergone coagulative necrosis; no evidence of vasculitis. HLA antigens:
A2, A3, B7, BW44. Acetylator phenotype: slow. Isoniazid half-life 4.28 hr (rapid acetylators 0.8–2.2 hr, slow acetylators >2.2 hr).

Progress

Hydrallazine was withdrawn and his blood pressure was controlled by propranolol alone. Within one week his mucosal ulcers and the skin rash had disappeared leaving the leg abscess and skin ulcer to resolve more slowly. His total intake of hydrallazine was estimated to be 150 g. Eleven months later he remained free from relapse.

Comment

Behçet’s syndrome has been reported in association with SLE but not when drug-induced (Delrieu et al., 1977). Like other auto-antibody associated side effects of hydrallazine, orogenital ulceration was completely reversible in this patient when the drug was withdrawn.

It has been suggested that hydrallazine-associated lupus occurs almost exclusively in slow acetylators (Strandberg et al., 1976). However, its occurrence in patients receiving a lower dose suggests an additional mechanism. A hypothesis to explain the whole syndrome might be that slow acetylation leads to high blood concentration of hydrallazine and that susceptible patients develop a response with formation of antibodies which are similar to antinuclear antibody and anti-DNA. Patients on a low dose of hydrallazine might have a very slow acetylator status. This seems to be borne out in the present patient as his isoniazid half-life is at the upper end of the range for the slow acetylator phenotype.

A second hypothesis proposed by Harland et al. (1980) suggests an alternative toxic pathway for hydrallazine metabolism which is independent of acetylation. This suggestion is based on the demonstration of a disparity between the rate of acetylation of test drug (fast) compared to that of hydrallazine (slow). There is so far no report of the reverse situation that the finding of slow acetylator status is misleading. Slow acetylation underlies most of the reported toxic reactions to hydrallazine.

Acknowledgments

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References

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