SHORT REPORTS

Treatment of rheumatoid arthritis with desferrioxamine: relation between stores of iron before treatment and side effects

The generation of free radicals catalysed by iron resulting in peroxidation of synovial membranes has been proposed as the first event in the inflammation of rheumatoid arthritis.[1] Treatment with desferrioxamine to chelate free iron within the joint may reduce this inflammation and thus prevent the progression of damage to the joint. In this study desferrioxamine was used to treat six patients with active rheumatoid disease, which was refractory to conventional drugs that modify the disease.

Patients, methods, and results

Four men and two women, aged 42-76, were treated with desferrioxamine 2·0 g infused subcutaneously into the lower anterior abdominal wall over 20 hours with a syringe pump. Initially, treatment was given daily for five days each week for four weeks or until side effects occurred and then continued on a once weekly basis. Non-steroidal anti-inflammatory drugs and analgesics were given, but no drugs that modified disease such as gold, penicillamine, or azathioprine were used. Haematological variables of peripheral blood were determined by standard laboratory techniques.

In five of the six patients onset of nausea and vomiting after four to 12 days of treatment with desferrioxamine led to temporary withdrawal of the drug. No associated abdominal pain, bowel disturbance, or appreciable loss of weight was noted, and all symptoms resolved within 72 hours. The sixth patient (case 2, table) developed reversible blurring of his vision after five days of treatment but had no abdominal symptoms.

A noticeable difference was observed in the length of the initial period of treatment (four to 12 days) and hence in the total dose of desferrioxamine given before the onset of side effects (7·5-24·0 g). This related closely to differences in the measurements of stores of iron before treatment with a strong correlation between the dose of desferrioxamine and the concentrations before treatment of both haemoglobin ($r = 0·97$, $p < 0·01$, Spearman rank coefficient) and serum iron ($r = 0·91$, $p < 0·02$). A linear relation ($r = 0·90$, $p < 0·05$) between the total dose of desferrioxamine administered before the onset of symptoms and the haemoglobin concentration before treatment was also shown.

The five patients with nausea and vomiting all restarted maintenance treatment within seven days with desferrioxamine 2·0 g once weekly without recurrence of their symptoms. The patient with visual disturbance did not receive further treatment.

Comment

The close correlation found between the dose of desferrioxamine administered before the onset of symptoms and the haemoglobin and serum iron concentrations before treatment suggests that chelation of iron from a pool of limited size may have led to these symptoms. A clinical similarity was noted between the gastrointestinal symptoms reported by our patients and the emesis induced by cytotoxic agents, which act centrally on the chemoreceptor trigger zone to stimulate the vomiting centre.[2] Chelation of iron from the central nervous system might have led to these symptoms; evidence for the removal of iron from the central nervous system by desferrioxamine has been provided experimentally.[3] This would also account for the visual impairment found in one of our patients and in others in previous reports, including a preliminary account in which four of seven patients with rheumatoid arthritis treated with desferrioxamine developed ocular abnormalities.[4] Alternatively, chelation of iron may have an inhibitory effect on the gastrointestinal mucosa and thus mimic sickness induced by radiation.

Measurements of haemoglobin and serum iron concentrations before treatment should provide a means of determining the dose of desferrioxamine that can be given to patients in whom stores of iron are suboptimal.

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Scleroderma presenting with multiple keloids

Scleroderma and keloids have many common features. Their aetiologies are unknown, and both diseases cause proliferation of collagen, its deposition in the dermis, and progressive fibrosis. Both lesions also produce hyperpigmentation. This is the first report of a generalised morphoea type of scleroderma presenting with multiple hyperpigmented pruritic keloidal lesions.

Case report

A 17 year old Nigerian woman presented with generalised pruritic and tender hyperpigmented keloids, hardening of the skin, especially on the fore-

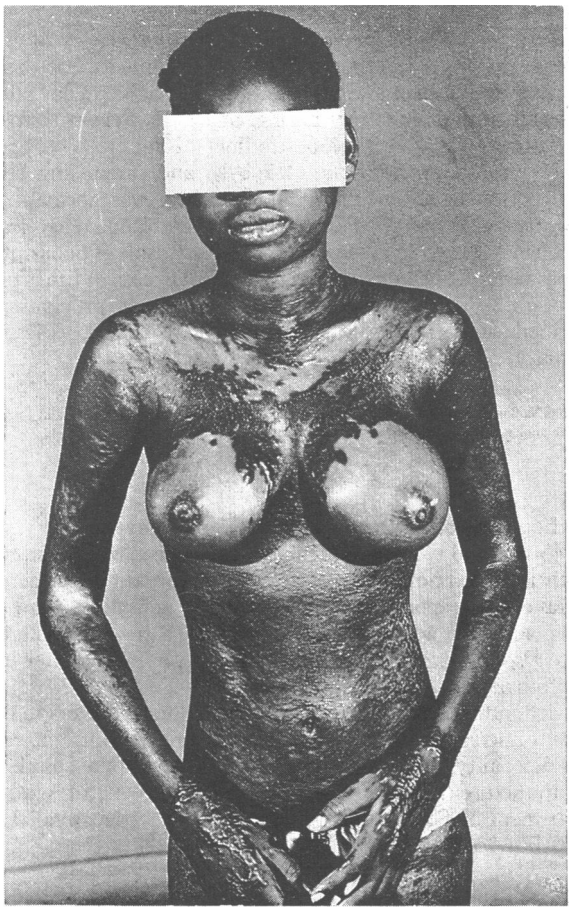
Details of patients' haematological and iron states before treatment, total excretion of iron, and dose of desferrioxamine infused before onset of symptoms

Case No	Age (years)	Sex	Previous treatment	Haemoglobin* (g/l)	Serum iron/total iron binding capacity† (μmol/l)	Serum ferritin‡ (μg/l)	Total urinary excretion (mg)	Dose of desferrioxamine (g)
1	42	F	Gold, azathioprine, penicillamine	96	3/65	12	3·6	7·5
2	76	M	Gold	100	4/75	12	8·5	10·0
3	64	M	Penicillamine	109	4/83	4	8·5	10·0
4	63	M	Gold, azathioprine, penicillamine	110	4/60	11	9·0	18·0
5	66	F	Gold, azathioprine, penicillamine	116	6/45	241§	36·6	18·0
6	65	M	Gold	146	19/65	9	24·3	24·0

*Five of the six patients were anaemic according to World Health Organisation criteria. Normal range for men = 130-160 g/l and for women = 120-150 g/l.
†Normal range = 13-32/45-70 μmol/l.
‡Normal range = 13-250 μg/l. Serum ferritin concentration of ≤12 ng/ml suggests reduced iron stores in patients with rheumatoid arthritis.[5]
§Serum ferritin concentration at upper limit of normal range despite low serum iron probably related to acute inflammation with an erythrocyte sedimentation rate of 129 mm/l in the first hour.
Conversion: SI to traditional units—Iron and total iron binding capacity: 1 μmol/l ≈ 5·6 μg/100 ml.

arms, generalised weakness, weight loss, bilateral contracture of the elbows, and polyarthralgia. The illness had lasted 22 months and had been preceded by recurrent febrile episodes and ache. She had not previously shown any tendency to formation of keloids.

On examination she weighed 38 kg (ideal weight 55 kg) and had widespread hyperpigmented keloidal lesions on the trunk, arms, and neck. The skin of the forearm was thickened and tight. Her lungs were clear. Blood pressure was 110/80 mm Hg and pulse 104 beats/minute. Polyarthralgia was evident, and she had fixed flexion deformities of both elbows.



Patient with generalised morphoea, showing tight and shiny skin, fixed flexion deformity of both elbows, hyperpigmentation, and keloids.

Investigation showed a packed cell volume of 0·39; white cell count $10{\cdot}2 \times 10^9$/l with 34% neutrophils, 8% eosinophils, 56% lymphocytes, and 2% monocytes; erythrocyte sedimentation rate 18 mm in the first hour; genotype AA; random blood glucose concentration 3·5 mmol/l (63 mg/100 ml); normal blood electrolyte concentrations; urea 2·2 mmol/l (13·2 mg/100 ml); and a normal chest radiograph. Barium studies showed a dilated oesophagus without a delay in the transit time; an intravenous pyelogram, an *x* ray film of the hands, serum immunoglobulin concentrations, and results of liver function tests were normal; and a lupus erythematosus cell test was negative. Skin biopsy showed sclerotic features consistent with scleroderma.

Treatment, which was mainly symptomatic, included prednisolone 5 mg twice daily. Her condition remained satisfactory, and joint pain and movement improved.

Comment

This patient presented with fever, weight loss, polyarthralgia, and diffuse hyperpigmentation and appeared to have systemic scleroderma of sclerotic type. In the absence of sclerodactyly, Raynaud's phenomenon, and definite disease of the internal organs, however, generalised morphoea is more likely.

We had no hesitation in associating the development of keloids with the onset of morphoea. Previous scars had not shown any tendency to form keloids. Although keloids usually succeed injury, often a preceding injury cannot be identified.[1] The injury in this case might have been the inflammatory reaction in the dermis found in morphoea. Keloids consist mainly of overabundant deposition of dermal collagen.[2] The fibrosis of scleroderma also results from increased deposition of collagen by dermal fibroblasts.[3] Thus in both conditions the problem is quantitative; the collagen itself is normal.

This patient was very distressed by the extensive hyperpigmentation associated with her disease. Increased pigmentation, which has been described in generalised morphoea, was one of the first changes noted. Two possible mechanisms link generalised morphoea with keloids. The dermal inflammatory reaction may trigger the keloidal process. Also, this patient may have had a sort of "fibrotic diathesis,"[4] manifesting as morphoea and keloids.

Management of the patient was difficult. The pruritus and hyperaesthesia attributed to the keloids responded partially to antihistamines, chlorpheniramine maleate, and promethazine hydrochloride. She improved with regular physiotherapy. Antifibrotic drugs like colchicine and penicillamine were not tried, partly because they were not available and partly because evidence for their sustained benefit in scleroderma is small. Oral prednisolone in small doses was used. The keloidal lesions were too extensive for intralesional triamcinolone, and so we thought that systemic steroids might help. More importantly, it has been suggested that prednisolone in small doses benefits some patients with scleroderma with joint symptoms, chronic disability, and weight loss.[5]

Because of this association of keloid and scleroderma we wonder whether patients with scleroderma are at greater risk of developing keloids.

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OF NURSING CHILDREN

Oh! what a racket do Authors make about this! What thwarting and contradicting, not of others only, but of themselves! What reasons do they bring, why a woman must needs nurse her own Child? Some extorted from Divinity; Sarah nursed Isaac, therefore every Woman must nurse her own child. Why is it not as good an Argument, that because David was a King and a Prophet, therefore every man must be a King, and every King a Prophet? Some have haled it from reason by head and shoulders. The Mother's milk is most convenient for the child, because the child participates of her Nature; as though every cholerick Woman had cholerick Children, and every melancholy woman, melancholy children. Or else, because the Woman cannot love her Child, except she give it such her own self; which if she do not, the more inhumane beast she.

On the other side: It would make a dying man laugh, or a Horse break his halter to hear how they thwart all this again.

Nicholas Culpeper (1616-54)
Directory for Midwives, 1671