Bullous Urticaria Pigmentosa (Cutaneous Mastocytosis) and Sodium Cromoglycate Therapy

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Abstract. Two cases of cutaneous mastocytosis in infancy are reported in which the clinical response to therapy with oral sodium cromoglycate was satisfactory. A review of the current literature is presented, with comments on the possible mode of action of sodium cromoglycate in mastocytosis.

Key words: Bullous; Urticaria; Pigmentosa; Sodium cromoglycate

Willemze et al. (11) recently reported a 27-year-old male with cutaneous mastocytosis who had been followed up since the age of 2½ years. They reviewed the literature on urticaria pigmentosa, stressing the facts of early onset and variable clinical course, many progressing to systemic involvement with mast cell deposits in liver, spleen, lymph nodes and bone. Burgoon et al. (1) reported on 3 cases of urticaria pigmentosa in infancy who progressed to systemic involvement and they quoted another 5 similar cases previously reported (one each) by Ellis (4), Dewar & Milne (3), Warin & Hughes (9), Waters & Lacson (10) and Rider et al. (5). Even with this progression the prognosis as regards skin involvement is not uniformly bad. Robinson et al. (6) described a spontaneous remission of bullous lesions. All their 5 patients ceased to have bullae between the ages of 9 months and 3 years after onset, although other abnormalities of the skin such as discolouration, a 'pig-skin' texture and urtication, persisted. Burgoon et al. (1) scrutinised the literature and discussed the cases of Dewar & Milne (3), Rider et al. (5) and Warin & Hughes (9). They categorized these cases with one of their own as having polysystemic mast cell involvement and stressed that diffuse skin involvement is rarely present without multisystemic involvement.

Until recently, treatment of mast cell disease has been largely disappointing, antihistamines being of some value in controlling the pruritus, but not in influencing the disease process.

Soter (8) reported on 6 patients with mastocytosis who were given disodium cromoglycate in a double-blind trial involving a placebo. All patients had diarrhoea, abdominal pain and extensive skin lesions giving rise to frequent wheals and pruritus. Three had psychological abnormalities manifested as irritability, inability to walk normally and difficulty in concentrating. Two experienced pain after drinking alcoholic beverages and the third had malabsorption.

With disodium cromoglycate therapy the pruritus, diarrhoea and abdominal pain disappeared after 4–6 weeks. Alcohol was tolerated without incident and those with psychological difficulties reported an improvement in their symptoms. The serum albumin was noted to rise in the patient with malabsorption. Disodium cromoglycate certainly ameliorated the varying clinical manifestations of mastocytosis in these patients and the authors thought the site of its action may extend beyond the mast cell.

Sauder et al. (7) also reported on the use of oral disodium cromoglycate in a 5½-year-old boy with mastocytosis. They found a definite and gratifying regression of the pruritus in their patient and a decrease in urinary histamine following treatment, with a corresponding increase in this and recurrence of symptoms when the drug was stopped.

The following two cases illustrate a similar effect of sodium cromoglycate in alleviating signs and symptoms of cutaneous mastocytosis.

CASE REPORTS

Patient 1

A boy, born 4.12.77. At birth he had blisters on hands and feet and some areas of erosion. In addition there were erythematous patches involving most of the skin.

An initial diagnosis of epidermolysis bullosa or bullous ichthyosiform erythrodermia was made. He was given penicillin and cloxacillin to prevent secondary infection. One week after birth he was transferred to Alder Hey Children's Hospital. He was a healthy baby, but with extensive skin lesions consisting of erythematous plaques of varying shape, scattered over limbs and trunk. Many plaques had blisters superimposed on their surface, varying from 1 mm to 1 cm in diameter. The anterior abdominal wall showed several areas of thickened skin with a lichenified (leather-grain) pattern (Fig. 1). Liver, spleen and kidneys were not palpable. It was noted that when he cried the unaffected skin became deeply cyanosed and then scarlet before returning to a pre-crying condition. A clinical diagnosis of urticaria pigmentosa was made and a biopsy confirmed this.

Laboratory investigations

Hb. 14.1 g/dl; white cell count, 14000; neutrophils, 34%; lymphocytes, 60%; monocytes, 6%. Mast cells were not present in the peripheral blood. Liver function, urea, and electrolytes were all normal. Bone marrow, normal aspirate and a skeletal survey revealed no bony infiltrations.

Transmission electron microscopy showed large numbers of mast cells, some of which were degranulating. The high-power view showed some typical mast cell granules and many atypical ones.

In January 1978, anti-histamine therapy was started, with promethazine hydrochloride, 5 mg t.d.s. and chlorpheniramine maleate, 0.5 mg t.d.s. Local application of fusidic acid tulle and ointment gave some improvement. When aged 8 weeks he was discharged home on this regime but he continued to develop new blisters and in March was re-admitted and azatadine maleate 0.25 mg bid. substituted. After initial improvement he was re-admitted in April with haemorrhagic blisters which were secondarily infected with *Staphylococcus aureus* and B-haemolytic Streptococcus. He was then treated with gentamicin cream and oral lincomycin: the antihistamine therapy was changed back to promethazine hydrochloride and chlorpheniramine maleate.

By May, blisters were appearing and the promethazine dosage was increased to 15 mg b.d. and 30 mg nocte and azatadine again tried, 0.25 mg t.d.s.

In February 1979, colour changes which had hitherto been controlled, returned when the antihistamines were reduced.

In June 1979, oral sodium cromoglycate, 100 mg t.d.s. was started. In the first 24–48 hours there was worsening of the irritation and appearance of more blisters. The condition then stabilised. After 2 months a dramatic improvement was noted, with only 1 blister from June to October 1979. He was then receiving sodium cromoglycate and promethazine at night.

In February 1980, further urtication was observed and the dose of sodium cromoglycate was increased to 300 mg daily. He has now had no new blisters for 9 months and the skin lesions are all fading.

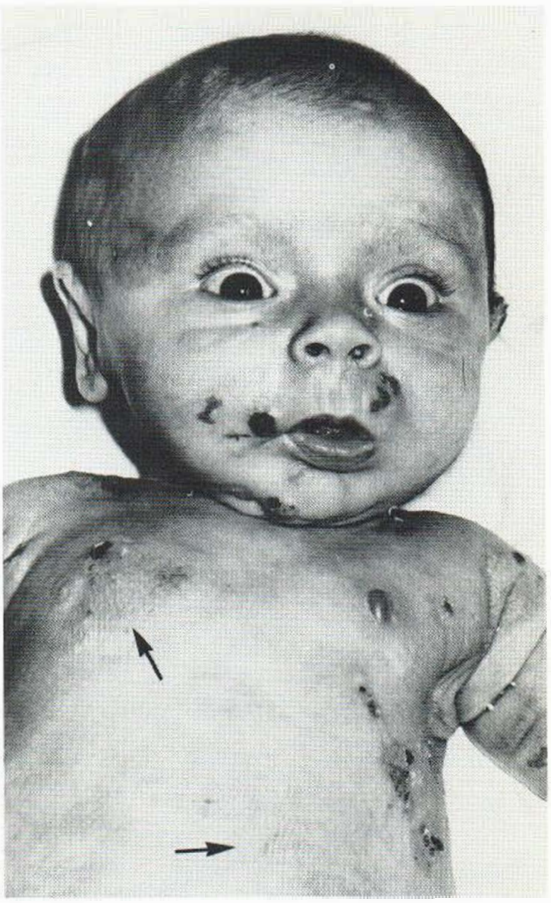

Fig. 1. Case 1. Extensive skin involvement, with bullae and leather-grain patterning of skin (*arrows*).

Patient 2

This infant, born on 20.12.78, was covered at birth with a pigmented papular and bullous eruption (Fig. 2). The lesions urticated on friction and a diagnosis of urticaria pigmentosa was made. A biopsy made at age 2 weeks confirmed this.

No specific treatment was instituted initially except for fusidic acid tulle and ointment for bullae which ulcerated. The baby thrived normally but was admitted to hospital on several occasions for upper respiratory tract infections, whooping cough, pneumonitis and tonsillitis. In June 1979, sodium cromoglycate 20 mg t.d.s. was started because of constant blister formation.

In July 1979 there were no new blisters and the lsesions had started to fade. The father thought his child was a different baby; he had become happy, contented and active, 3 days after commencing treatment; Trimeprazine tartrate was being given for night sedation. In October 1979 there had been no new blisters and because of difficulty in administering the sodium cromoglycate, this was stopped.

By November 1979 he had deteriorated, blistering had returned and sodium cromoglycate was restarted, with improvement by December. In January 1980 he was admitted with a chest infection and one day after admission, passed blood rectally.

Numerous investigations revealed him to be anaemic and to have reduced xylose absorption.

7.1.80: Hb, 9.5 g/dl; wcc, 18000; neutrophils, 14008; lymphocytes, 3240; monocytes, 720. Occult blood, positive.

9.1.80: Hb, 9.8 g/dl; wcc 14000; neutrophils, 6160; lymphocytes, 6580; monocytes, 1120. Red blood cells showed anisocytosis, anochromia with some schistocytes and slight polychromasia. Serum iron, <3; TIBC, 78; serum ferritin, $<5\ \mu g h^{-1}$. Blood xylose level, 14.5 $\mu g\%$ (normal >20).

25.1.80: Jejunal biopsy, normal villous pattern.

Up to April 1980 the cause of the iron deficiency had not been determined but it was thought he could be develop-

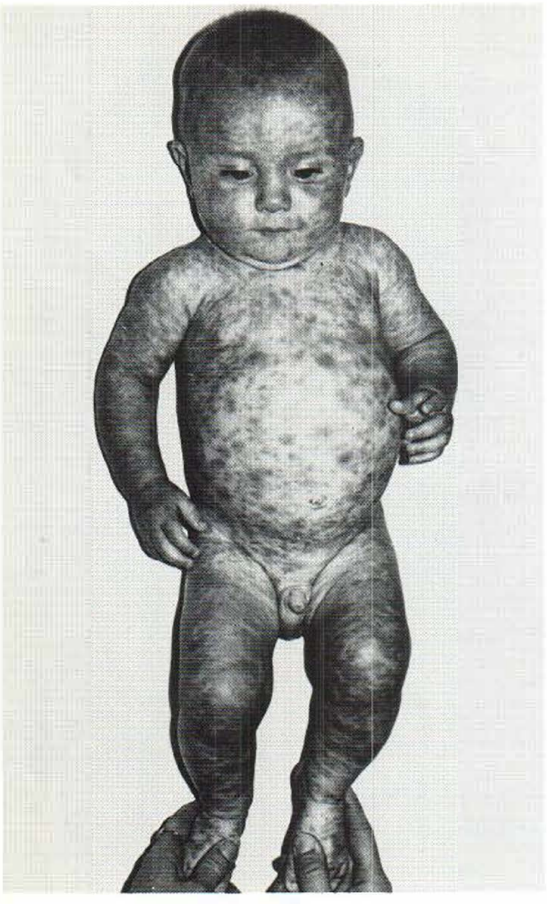

Fig. 2. Case 2. Widespread skin involvement.

ing systemic mastocytosis or have a solitary mastocytoma in the gastro-intestinal tract.

DISCUSSION

Our two cases illustrate typical features of bullous urticaria pigmentosa or diffuse cutaneous mastocytosis.

The cyanotic attacks in case 1 were similar to the cases described by Dewar (3) and by Waring (9). Dewar's case was a 4-month-old boy with cyanosis on crying and physical stimulation. Warin described cyanosis and flushing in his case. This phenomenon is presumably caused by histamine release from the mast cells. In our first case we have described the appearance of parts of the skin as leather-grained (Fig. 1). This corresponds to various descriptions by other authors, Degos in 1951 (2) referred to a 'peau d'orange' appearance in his case. Robinson et al. (6) referred to the skin in Cases 1 and 4 of his series of 5 as having a 'pigskin-like' or 'pebble-grain' appearance. Burgoon et al. (1) mentioned the term 'scotch-grain' or 'pebble-grain' when describing the skin of his 3 patients, one of whom was an adult. This is by no means the rule in urticaria pigmentosa, however, and our second case certainly had no such 'leather-graining' of his skin (Fig. 2).

Rider et al. (5) reported on a little girl with symptoms similar to our second case, namely gastro-intestinal disturbance with blood in the stools and a hypochromic anaemia. This case was categorized as polysystemic mast cell involvement, as were those reported by Warin, Dewar and Burgoon.

Despite the undoubted spontaneous regression in most cases reported, sodium cromoglycate would seem to offer substantial and worthwhile relief with hastening of this regression in mastocytosis.

As regards the mode of action of sodium cromoglycate, this is still unclear. It is thought to prevent the release of chemical mediators, such as histamine, from the mast cell. It also has a stabilizing effect on the mast cells in the gastro-intestinal tract. The local protective effect on the gastro-intestinal muccosa after ingestion of sodium cromoglycate could be due to inhibition of the function of eosinophils, thus preventing cytotoxity. A proportion of oral sodium cromoglycate is absorbed from the buccal mucosa and can be detected in the urine 6 hours after its administration. The buccal absorption may account for some of the general action of sodium cromoglycate as well as local gastro-intestinal effects (12).

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A Double-Blind Study of the Effects of Benzoyl Peroxide 20% and Eusol and Liquid Paraffin on the Microbial Flora of Leg Ulcers

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Abstract. Leg ulcers in 30 patients were treated for 6 weeks with either benzoyl peroxide 20% (Benoxyl 20) or Eusol and liquid paraffin. The types and numbers of micro-organisms/cm² leg ulcer surface were assessed initially and after 2 and 6 weeks of treatment. There was no significant difference between the preparations as regards their ability to reduce the surface count of aerobic micro-organisms. The only significant result was a reduction in the number of lesions colonized by *Staphylococcus aureus* when treated with benzoyl peroxide.

Key words: Leg ulcer; Microbiology; Therapy; Eusol; Benzoyl peroxide

Benzoyl peroxide is known to have an antibacterial effect *in vitro* (1), and has been used to treat cutaneous ulcers (3, 7). Our aim was to examine and compare any changes in the bacterial flora of leg ulcers during treatment with either benzoyl peroxide, or Eusol and liquid paraffin. The latter was employed as a comparative treatment since it is widely used in dermatological practice.

METHOD

Subjects

Thirty patients with ulcers on the lower legs entered the study; 17 received treatment with 20% benzoyl peroxide and 13 with Eusol and liquid paraffin (equal parts); the latter preparation is extensively used in the United Kingdom for the treatment of leg ulcers. This study was part of a larger clinical investigation. Full clinical and therapeutic details will be reported elsewhere. The 30 patients in this study were the only group to have detailed microbiological investigations carried out. In all but 3 subjects the ulcers were predominantly venous in origin but the clinical status of the patients did not influence either the pretreatment microbiological data or the response to therapy.

Bacteriology

Samples were taken from the centre of each lesion immediately after removal of the dressing at time 0, 2 and 6 weeks. Samples were always taken by the same person (D. D.). One cm² of the ulcer surface was sampled through a sterile metal template using an alginate swab moistened in saline, followed by a dry alginate swab. (If the ulcer was smaller than the template, the whole ulcer was swabbed and the area measured by planimetry.) Both swabs were aseptically broken off into 20 cm³ nutrient broth + 1% sodium hexametaphosphate and the swabs were dissolved by vigorous vortexing. Serial tenfold dilutions of the swab solution in nutrient broth were made immediately. Counts were performed by the method of Miles and Misra (6) on blood agar and MacConkey agar aerobically, and on vitamin K_1 blood agar (K_1BA) and neomycin vitamin K_1 blood agar (NeoK_1 BA) anaerobically (9). Since the count procedure involved much aeration, and it was not possible to perform a second strictly anaerobic count procedure, a plain cotton swab was used to sample the area around the template for strictly anaerobic bacteria. This swab was inoculated immediately onto prereduced K_1BA and NeoK_1BA plates. All anaerobic plates were incubated in GasPak jars (90% H_2 + 10% CO_2) at 37°C and inspected after 48 hours and 1 week. Aerobic plates were incubated at 37°C and inspected after 24 hours and 48 hours.

The count of aerobic and facultatively anaerobic bacteria/cm² was determined and the presence or absence of strict anaerobes was noted. Aerobic isolates were fully identified, anaerobic Gram-negative rods were presumptively identified using antibiograms (9): other anaerobic isolates were loosely grouped as anaerobic and microaerophilic cocci, or Gram-positive rods.

RESULTS

The range of organisms isolated and the changes in flora during treatment are shown in Table I. Each type of organism was found with similar frequency