CUTANEOUS MASTOCYTOSIS IN SINGAPORE

Y K Tay, Y C Giam

ABSTRACT

Mastocytosis is the collective name for a group of clinical syndromes whose signs and symptoms are due to the infiltration of various tissues by mast cells and to the release of chemical mediators by these cells. The skin is the most frequently affected organ. Skin manifestations include urticaria pigmentosa, mastocytoma, diffuse cutaneous mastocytosis and telangiectasia macularis eruptiva perstans.

Seven cases of mastocytosis were seen over a 3-year period at the National Skin Centre from 1989 to 1992. All our patients were in the paediatric age group. There were four boys and three girls ranging in age from one year to five years. The mean age of onset of the disease was 2.3 months. Six patients presented with cutaneous signs and symptoms of urticaria pigmentosa and one patient had diffuse cutaneous mastocytosis. Itch was the most prominent symptom seen in all the patients. All the patients had a positive Darier's sign, pathognomonic for mastocytosis. None of the patients had a positive family history.

Treatment was conservative and symptomatic, with the use of H_1 antihistamines to control itching. A particularly important aspect of management is the avoidance of triggering factors. All our patients have remained well with only skin involvement. The prognosis for children with mast cell disease is good, with at least half of the children with urticaria pigmentosa experiencing reduction of symptoms and lesions by adolescence.

Keywords : mast cell, mastocytosis, urticaria pigmentosa

SINGAPORE MED J 1993; Vol 34: 425-429

INTRODUCTION

Mastocytosis is a disease of fascinating historical interest. In 1869, Nettleship and Tay described the cutaneous manifestations of mastocytosis in a report of an unusual form of urticaria in a two-year-old girl[1]. Sangster suggested the term 'urticaria pigmentosa' in 1878[2] and in 1887, Unna noted the presence of mast cells in the skin lesions[3]. Nearly 50 years later, Sezary designated urticaria pigmentosa as 'mastocytosis'[3]. Finally, in 1949, Ellis[4] clearly established that mastocytosis is a disease that can be systemic and involve internal organs in a report of the autopsy findings in a one-year-old infant with documentation of mast cells in the skin, liver, spleen, thymus, bone marrow, pancreas and lymph nodes.

The skin is the most frequently affected organ (cutaneous mastocytosis). However, mastocytosis may involve the lymphoreticular (liver, spleen, lymph nodes), gastrointestinal, bone marrow and skeletal systems (systemic mastocytosis)[5]. Mastocytosis may also be broadly classified into paediatric onset and adult onset varieties which differ in their age of onset, clinical course and prognosis. Although uncommon, it is important to recognise the signs and symptoms, particularly the cutaneous manifestations as the disease can occasionally lead to systemic involvement and also to avoid the triggering factors which, if unrecognised, may lead to massive degranulation of mast cells and death.

METHODS

We reviewed the records of all the patients with a diagnosis of cutaneous mastocytosis who were seen in the Paediatric Clinic at the National Skin Centre during a three-year period from March 1989 to March 1992. These patients were previously examined and are on follow-up by the senior author.

Diagnosis of the cases was made on clinical grounds and by histopathologic study of skin section. All patients had a full blood count and all were examined clinically for the presence of enlarged lymph nodes and hepatosplenomegaly.

RESULTS

The 7 patients included 4 males and 3 females, aged one to 5 years (mean 2.9 years). The reported age at onset of initial symptoms ranged from birth to 6 months of age with a mean of 2.3 months. None of our patients had a positive family history. All our patients presented with cutaneous signs and symptoms of which 6 patients had urticaria pigmentosa and one patient had diffuse cutaneous mastocytosis. The principal symptom present in all our patients was itch which was aggravated by rubbing and scratching. None of our patients had systemic manifestations such as flushing, breathlessness, wheezing, diarrhoea and syncope. The typical lesions of urticaria pigmentosa consisting of brownish macules and papules were seen (Fig 1). Darier's sign was positive in all our patients. Patient #4 with urticaria pigmentosa had multiple blisters on his trunk and limbs. Patient #5 had diffuse cutaneous mastocytosis (Fig 2). Her skin had a yellowish, thickened appearance with erythematous patches and blisters were noted at the groins. Patient #6 had lesions on the scalp. Differential diagnoses of urticaria pigmentosa include insect bite reactions, post-inflammatory hyperpigmentation and scabies. Patient #7 initially was thought to have post-inflammatory hyperpigmentation secondary to eczema. However, the presence of a positive Darier's sign suggested the diagnosis. Extensive bullae may be the first presentation in an infant who later develops urticaria pigmentosa or diffuse cutaneous mastocytosis. The importance of recognising bullous mastocytosis is exemplified by the fact that blisters can occur at birth, thus resembling other bullous skin diseases of infancy such as bullous erythema multiforme or scalded skin syndrome[6]. Thus, biopsy of bullous lesions is essential for diagnosis.

Skin biopsies were done in 5 patients and this showed dense collections of mast cells in the upper dermis (Fig 3). Special stains for mast cells were performed in patients #1 and #2, using toluidine blue and leder stains respectively. The mast cells stain metachromatically with toluidine blue taking on a deep red-blue hue. The leder stain[7] which is an enzyme histochemical stain using chloroacetate esterase stain the mast cell granules red. Biopsies were not done in two patients as permission was not granted by the parents. None of our pa-

National Skin Centre
1 Mandalay Road
Singapore 1130

Y K Tay, MBBS, M Med (Int Med). MRCP (UK). MRCP (Ire)
Registrar

Y C Giam, MBBS, M Med (Paed), FAMS, FAAD
Senior Consultant Dermatologist

Correspondence to: Dr Y K Tay

Table I - details the clinical data of the patients

No	Age (yrs)	Age of onset	Sex	Symptoms at presentation	Signs	Biopsy	FBC	Clinical Diagnosis
1.	1	6 mths old	F	itchy rashes over back especially after bathing	Hyperpigmented lesions over trunk. Darier's sign positive	Dense perivascular infiltrate of mast cells in upper dermis.	Normal	Urticaria pigmentosa
2.	1	2 mths old	M	itchy, persistent 'mosquito bite' like lesions all over body	pigmented urticarial lesions all over the body. Darier's sign positive	Dermal papillae and upper dermis filled with mast cells.	Normal	Urticaria pigmentosa
3.	3	since birth	M	itchy, brown spots on trunk and limbs	symmetrical, brown macules on trunk. Darier's sign positive	Not done	Normal	Urticaria pigmentosa
4.	3	since birth	M	pigmentation on whole body since birth. 3 mths of age developed blisters after scratching which subsided after a few days.	pigmentation (brown) and multiple blisters. Darier's sign positive	Dense collections of mast cell in upper dermis	Normal	Urticaria pigmentosa
5.	3	2 mths old	F	thickening of skin with itchy red patches on the whole body. 1-2 vesicles on groins.	whole skin is infiltrated with erythematous patches. Papules on neck. 2 vesicles noticed at groins. Darier's sign positive	lichenoid infiltrate of predominantly mast cells and some lymphocytes	Normal	Diffuse cutaneous mastocytosis
6.	3	3 mths old	F	pigmentation (itchy) over body, arms, head.	Brown macules on scalp and trunk. Darier's sign positive	not done	Normal	Urticaria pigmentosa
7.	5	3 mths old	M	itchy, dark brown stains on trunk, arms, increasing in number.	Hyperpigmented macules on trunk and limbs. Darier's sign positive	Dense infiltrate of mast cells in dermal papillae and upper dermis	Normal	Urticaria pigmentosa

tients had palpable liver, spleen or lymph nodes. The full blood count and peripheral blood film were normal in all our patients.

Six of our patients had been seen for the most recent follow-up within the past year. Patient #5 with diffuse cutaneous mastocytosis had defaulted follow-up since February 1990. When last seen in February 1990, several vesicles were present on the back, chest and face. The 6 patients with urticaria pigmentosa have remained well, with the disease well controlled by antihistamines and mild topical steroids. Patient #4 had resolution of his blisters at the age of one. There has been no systemic involvement and no mortality.

DISCUSSION

In Sondergaard's study, the onset of mastocytosis occurred in approximately 55% of patients between birth and 2 years of age. Another 10% develop symptoms between the ages of 2 years and 15 years (paediatric onset)[8]. The remaining 35% of patients developed symptoms after 15 years of age (adult onset)[8]. In the paediatric population in Kettelhut's study evaluated at the National Institute of Health, 16 of the 17 children had onset of their disease before 2 years of age, with 14 manifesting the disease by 6 months of age[9]. In our series of 7 patients, all developed the disease by 6 months of age with two manifesting it since birth. The disease occurs equally in both sexes and all races are affected. Three of our patients were females and 4 were males.

Although mastocytosis is generally an isolated occurrence, rare familial cases have been reported. Recent reports show 47 families with more than one member affected[10], with dominance in 14 families[11]. None of our patients had a positive family history.

Fig 1 - Deeply staining brown macules and papules of urticaria pigmentosa over the trunk.

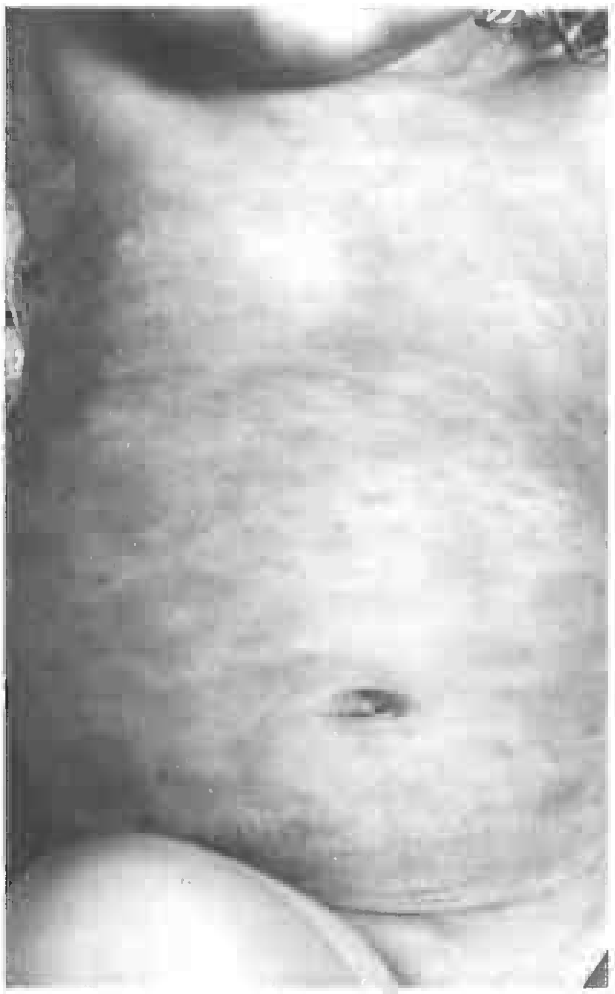
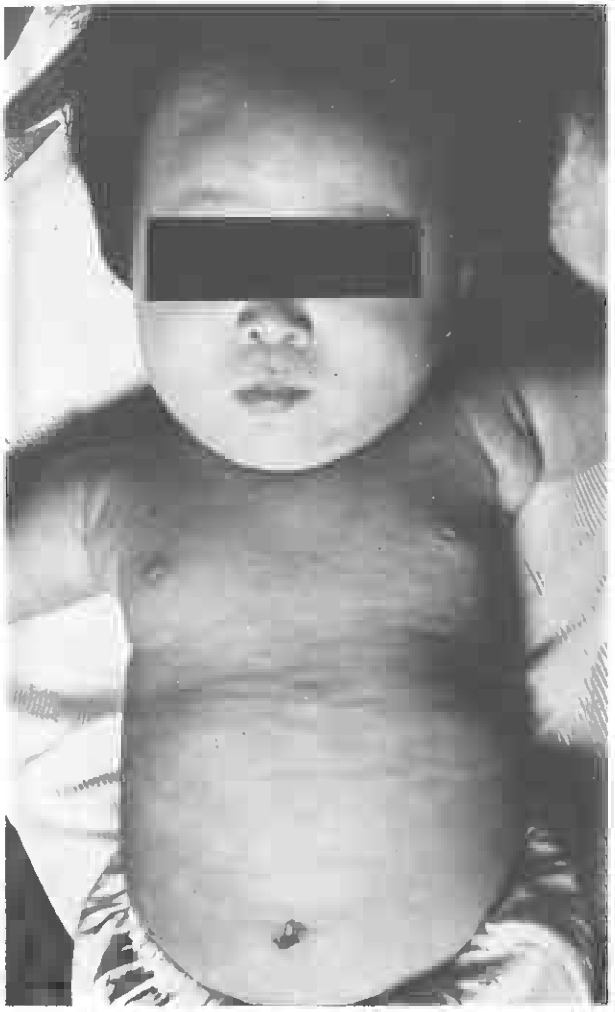


Fig 2 - Diffuse cutaneous mastocytosis showing yellowish thickened skin with papules and plaques.



The most common cutaneous lesions in patients with mastocytosis is urticaria pigmentosa[3]. Six of our patients presented with urticaria pigmentosa. The diagnosis is established by rubbing of the lesional skin, causing local itching, redness and whealing, Darier's sign, pathognomonic for mastocytosis[12]. The principal symptom of urticaria pigmentosa is intense itching experienced by all our patients.

Erythema, oedema and blister formation with subsequent crusting of the lesions have been reported by Orkin in urticaria pigmentosa especially when the disease is of early onset[13]. One patient with urticaria pigmentosa had blisters. Blistering usually subsides spontaneously after 2 or 3 years.

About 15% of patients with cutaneous mastocytosis present with the localised lesion of mastocytoma usually on the extremities. These are red, pink or yellow nodules usually solitary which appear within the first three months of life[14]. In many cases, the lesions spontaneously involute.

Telangiectasia macularis eruptiva perstans[15] is a rare form of mastocytosis seen mainly in adults. The eruption consists of red telangiectatic macules which become oedematous when rubbed. In isolated cases[15], splenomegaly, bone marrow involvement and abnormal skeletal radiographs suggest systemic involvement.

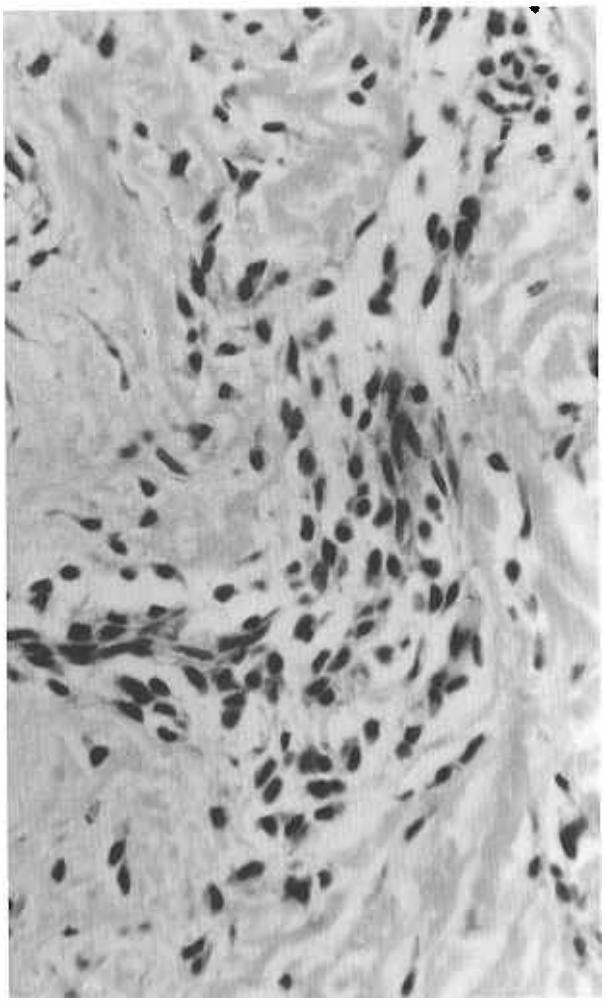
Diffuse cutaneous mastocytosis is a rare variety that usually presents before the age of 3 years[3]. The skin has a red-yellow-brown colour or a peau d'orange appearance with a doughy consistency. Dermographism with the formation of haemorrhagic blisters is common. Extensive bullae, which may rupture leaving erosions and crusts may be the first presentation in an infant who later develops diffuse cutaneous mastocytosis. One of our patients presented with diffuse cutaneous mastocytosis with vesicle formation. These children have complications such as flushing, hypotension, tachycardia, bronchospasm, shock and death due to the massive release of vasodepressor mast cell products. Systemic complications may occur resulting in hepatosplenomegaly, diarrhoea and gastrointestinal bleeding due to a heparin effect[16].

Large numbers of mast cells can infiltrate and produce clinical manifestation in organs other than the skin, especially in older children and adults[17]. Bone is most commonly affected by systemic mast cell disease. Widespread osteosclerosis or osteoporosis or circumscribed areas of lysis or sclerosis may be evident on X-ray examination[10]. Skeletal scintingrams are more sensitive and helpful. Bone pain and pathologic fracture[18] may occur.

Diarrhoea is the most common gastrointestinal symptom and is due to increased production of histamine, prostaglandin D_2[19] and calcitonin. Nausea, vomiting, abdominal pain, malabsorption, duodenal ulcer and gastrointestinal bleeding occur less frequently. Hepatosplenomegaly and lymphadenopathy due to infiltration by mast cells, eosinophilia and fibrosis are sometimes present.

Anaemia, usually mild, normochromic and nomocytic can

Fig 3 - H & E stain showing ovoid and spindle-shaped mast cells with large nucleus in the dermis.



be associated with mastocytosis[20]. Persistent leukocytosis, especially when accompanied by circulating mast cells forbodes the possible development of refractory monocytic leukaemia[21].

Where there is clinical evidence of systemic involvement, especially in patients whose disease onset is in adulthood or in those with long-standing disease, complete blood count and examination of the peripheral smear will exclude anaemia and the presence of circulating mast cells. Further diagnostic evaluations, such as gastrointestinal radiography/endoscopy, skeletal surveys/bone scans, and bone marrow examinations should be reserved for those children who exhibit evidence of organ-system involvement eg anaemia, leukopenia, thrombocytopenia, melaena or severe bone pain[22].

TREATMENT

There is no cure for cutaneous mastocytosis, and treatment is symptomatic. An important aspect of therapy is the avoidance of triggering factors such as temperature changes, friction (eg when bathing, the skin should be pat dry and not to be scratched or rubbed with a rough towel), physical exertion, ingestion of alcohol, use of NSAIDS, morphine, codeine and other narcotics. Patients should be taught the signs of circulatory collapse and be instructed in the appropriate measures to take should shock develop. Epinephrine inhibits histamine release and is the drug of choice in acute circulating collapse.

Chronic symptoms such as itching or mild flushing can be blocked by antihistamines and the treatment of choice is a classical H_1 antihistamine such as hydroxyzine or chlorpheniramine. All our patients were treated with chlorpheniramine with good symptomatic relief. In the child who has peptic ulceration, the addition of an H_2 antihistamine such as cimetidine appears to be beneficial[23].

Ketotifen is a benzocycloheptathiopene that inhibits mast cells degranulation, blocks H_1 receptors and inhibits the release of slow-reacting substance (SRS-A) from leukocytes. It shows promise for the treatment of mast cell disease at a dose of 1 to 2 mg in children. It has been reported to be of benefit in relieving the pruritus and whealing in urticaria pigmentosa[24]. It is well absorbed after oral administration. Two of our patients, #2 and #4, were treated with ketotifen for five months and eleven months respectively with effective relief of pruritus and whealing. The drug however is expensive.

The oral administration of disodium cromoglycate which blocks mast cell degranulation has been shown to reduce pruritus and whealing and is especially useful for diarrhoea[25]. Doses up to 400 mg per day have been suggested for children and as much as 800 mg a day has been proposed for adults. Full benefit should not be expected for at least two to three weeks.

Because mast cell degranulation is a calcium-dependent process, nifedipine or other calcium channel-blocking agents are of potential benefit[26]. It is not recommended for use in children. The starting dose in adults is 10 mg tid.

The application of potent topical corticosteroids under occlusion (eg 0.05% betamethasone diproprionate) has been shown to be beneficial in some patients with urticaria pigmentosa[27]. Improvement of symptoms and partial regression of visible lesions occur as well as a reduction in the number of mast cells in the skin. All our patients were treated with 0.025% to 0.05% betamethasone 17-valerate cream to the lesions with symptomatic improvement.

The use of photochemotherapy (PUVA) in adult patients with urticaria pigmentosa has been associated with a decrease in pruritus and whealing and considerable fading of pigmentary changes[28]. Relapses occurred within 3 to 6 months after the cessation of therapy. The mechanisms of the beneficial effects of PUVA are unknown. The use of PUVA should be reserved for extensive cutaneous disease unresponsive to other forms of treatment. Its long term risks such as an increased probability of developing squamous cell carcinoma and the transient nature of its therapeutic effects mandate that this form of therapy be used cautiously in young patients.

Systemic corticosteroids are used in more severe cases of mastocytosis, for example, when there is malabsorption or ascites. Finally, a solitary mastocytoma that causes systemic symptoms can be surgically excised if other treatments have failed. Premedication with steroids, antihistamines plus careful management during surgery is essential.

PROGNOSIS

Childhood onset of mastocytosis carries a favourable prognosis, with improvement in cutaneous manifestations and abatement of symptoms occurring in at least three-quarters of patients whose disease begins in the first decade of life[29]. Areas of involvement that remain tend to be asymptomatic.

Systemic mastocytosis can occur at any age but the risk of extracutaneous involvement appears to increase with advancing age of onset and is minimal in those whose disease begins in the first two years of life. Mast cell leukaemia has a particularly poor prognosis, usually resulting in death[10].

CONCLUSION

All our patients with urticaria pigmentosa have remained well with only skin involvement. Management consists of educating the parents about the more common systemic effects of

mast cell disease and the avoidance of triggering factors. The patients were treated symptomatically with antihistamines, namely chlorpheniramine and topical application of corticosteroids on involved areas. In addition, two of our patients received ketotifen for varying periods. All our patients achieved good control with decreased pruritus, whealing and flattening of the lesions.

References

1. Nettleship E, Tay W. Rare forms of urticaria. Br Med J 1869;2:323-4.
2. Sangster A. An anomalous mottled rash, accompanied by pruritus, facitious urticaria and pigmentation, "urticaria pigmentosa(?)". Trans Clin Soc Lond 1878;11:161-3.
3. Soter NA. The skin in mastocytosis. J Invest Dermatol 1991;96:32S-39S.
4. Ellis JM. Urticaria pigmentosa . A report of a case with autopsy. Arch Pathol 1949;48:426-35.
5. Demis DJ The mastocytosis syndrome : Clinical and biological studies. Ann Intern Med 1963;59:194-206.
6. Golitz LE, Weston WL, Lane AT. Bullous mastocytosis : diffuse cutaneous mastocytosis with extensive blisters mimicking scalded skin syndrome or erythema multiforme. Pediatr Dermatol 1984;1:288-94.
7. Leder LD. The Chloroacetate esterase reaction. Am J Dermatopathol 1979;1:39-42.
8. Sondergaard J, Asboe-Hansen G. Mastocytosis in childhood. In : Happle R, Grosshans E. eds. Pediatric Dermatology. Berlin, Heidelberg Springer-Verlag 1987:148-54.
9. Kettelhut BV, Parker RI, Travis WD, Metcalfe DD. Hematopathology of the bone marrow in pediatric cutaneous mastocytosis. A study of 17 patients. J Clin Pathol 1989,91:558-62.
10. Stein DH. Mastocytosis : A review. Pediatr Dermatol 1986;3:365-75.
11. Shaw JM. Genetic aspects of urticaria pigmentosa Arch Dermatol 1968;97:137-8.
12. Greaves MW, Sondergaard J. Urticaria pigmentosa and factitious urticaria : direct evidence for release of histamine and other smooth muscle - contracting agents in dermographic skin. Arch Dermatol 1970;101:418-25.
13. Orkin M, Good RA, Clawson CC, Fisher I, Windhorst DB. Bullous mastocytosis. Arch Dermatol 1970,101:547-64.
14. Chagrin I, Sachs P. Urticaria pigmentosa appearing as a solitary nodular lesion. Arch Dermatol Syphilol 1954;69:345-55.
15. Allen BR. Telangiectasia macularis perstans. Br J Dermatol 1978;99(suppl 16):28-9.
16. Smith TF, Welch TR, Allen JB, Sondheimer JM. Cutaneous mastocytosis with bleeding : probable heparin effect, Cutis 1987;39:241-4.
17. Brunning RD, McKenna RW, Rosai J, Parkin JL, Risdall R. Systemic mastocytosis : extracutaneous manifestations. Am J Surg Pathol 1983;7:425-38.
18. Rafii M, Firooznia H, Golimbu C. Pathologic fracture in systemic mastocytosis. Clin Orthop 1983;180:260-7.
19. Poynard T, Natarf C, Messing B. Secretory diarrhoea and prostagladin D_2 overproduction in systemic mastocytosis. N Engl J Med 1982;307:184.
20. Cryer PE, Kissane JM. Systemic mastocytosis. Am J Med 1976;61:671-80.
21. Webb TA, Li CY, Yam LT. Systemic mast cell disease : a clinical and hematopathologic study of 26 cases. Cancer 1982;49:927-38.
22. Kettlehut BV, Metcalfe DD. Pediatric mastocytosis. J Invest Dermatol 1991;96:15s-18s.
23. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhoea in systemic mastocytosis. Ann Intern Med 1979;90:769-71.
24. Czarnetzki BM. A double-blind cross over study of the effect of ketotifen in urticaria pigmentosa. Dermatologica 1983;166:44-7.
25. Czarnetzki BM, Behrendt H. Urticaria pigmentosa : Clinical picture and response to oral disodium cromoglycate. Br J Dermatol 1981;105:563-7.
26. Fairley J, Pentland A, Voorhees J. Urticaria pigmentosa responsive to nifedipine.J Am Acad Dermatol 1984;11:740-3,
27. Barton J, Larker RM, Schechter NM, Lazarus GS. Treatment of urticaria pigmentosa with corticosteroids. Arch Dermatol 1985;121:1516-23.
28. Vella Briffa D, Eady Raj, James MP, Gatti S, Bleehen SS. Photochemotherapy (PUVA) in the treatment of urticaria pigmentosa. Br J Dermatol 1983;109:67-75.
29. Caplan RM. The natural course of urticaria pigmentosa. Arch Dermatol 1963;87:56-67.