Pseudoxanthomatous Mastocytosis (xanthelasmoidea) Treated with PUVA Therapy

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We herein report a case of mastocytosis with unusual cutaneous manifestations resembling pseudoxanthoma elasticum or xanthoma which were exaggerated on the intertriginous areas including axillae, groin and neck in a 39-year-old woman. It was characterized by multiple yellowish papules and plaques with a cobblestone appearance. In addition, there were diffuse reddish macules and papules of varying sizes mainly on the trunk and extremities. Histopathologic findings showed a very dense infiltrate of large numbers of round to oval cells in the upper and mid dermis. These cells revealed metachromasia on the toluidine blue stain. She also had hepatosplenomegaly and some evidence of bone marrow involvement. There was significant improvement in the skin lesions with psoralen plus ultraviolet A (PUVA) therapy and potent topical corticosteroid. (Ann Dermatol 7:3(3)253–258, 1995)

Key Words: Mastocytosis, Pseudoxanthoma, PUVA therapy

Mastocytosis is a general term applied to local and systemic accumulations of mast cells1. The most common cutaneous lesions in patients with mastocytosis are the red-brown macules, papules and plaques of urticaria pigmentosa (UP)2. One of the uncommon variant of UP is pseudoxanthomatous mastocytosis or xanthelasmoidea, as a lifelong form, by Griffiths et al3 in 1975.

Treatment of mastocytosis includes the use of H1 and H2 antihistamines, oral disodium cromoglycate, PUVA therapy, and potent topical corticosteroid preparation4.

We present a case of pseudoxanthomatous mastocytosis which showed a good response to PUVA therapy and potent topical corticosteroids.

REPORT OF A CASE

A 39-year-old woman was referred to our clinic with diffuse reddish or yellowish maculopapular eruption on her trunk and extremities. Her past history showed these skin lesions had been present since her age of three and were associated with intermittent episodes of pruritus but no blistering. Rubbing, warm baths and alcohol ingestion caused wheals and flushing. Emotional stress and anxiety further aggravated the symptoms. She had not previously had gastrointestinal symptoms, and she had not suffered from headaches or bone pain. No members of her family had any cutaneous disorders.

On examination, there was a profusion of multiple reddish-yellow macules and papules varying in size mainly on the trunk and extremities (Fig. 1). There were also multiple yellowish, verrucous papules and plaques with a cobblestone appearance on her axillae, groins and neck (Fig. 2). Urticaria with a surrounding erythematous flare (Dariet's sign) usually developed after firm stroking (Fig. 3). Her liver and spleen were enlarged but lymphadenopathy was not present. Examination of all other systems was normal.

Skin biopsy specimens obtained from the papules on her neck, right axilla and groin commonly showed a very dense infiltrate of large num-

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bers of round to oval cells in the upper and mid dermis(Fig. 4). These cells revealed many basophilic granules in their cytoplasm, these granules disclosed metachromasia on the Giemsa and toluidine blue stains and positivity to PAS. On electron microscopy, the nuclei of the mast cells were smooth in outline and round or oval shaped. The cytoplasmic granules were uniform in their size but showed absence of the typical lamellar substructures seen in normal mast cell granules (Fig. 5).

A complete blood cell count showed marked thrombocytopenia(83,000/mm³) as well as mild anemia(Hb;11.5g/dl, Hct;35.6%) and leukopenia (4300/mm³). Neither increase in basophil number nor eosinophilia was found. Other laboratory studies including liver function tests, urinalysis, stool examination, serum protein electrophoresis, LAP score, immunoglobulins, complements and EKG were all negative or within normal limits. Peripher-
Fig. 4. A skin biopsy specimen taken from on the right axilla shows a very dense infiltrate of large numbers of round to oval cells in the upper and mid dermis (Hematoxylin & eosin stain, ×100).

Fig. 5. The mast cell shows its smooth outline and uniform cytoplasmic granules (EM, ×5,000).

Fig. 6. Mast cell on the peripheral blood smear (Wright & Giemsa stain, ×1,000).

Fig. 7. A; Diffuse infiltration of mast cells on the bone marrow biopsy. B; Mast cells showing metachromasia on the bone marrow smear (A; Hematoxylin-eosin stain, ×100, B; toluidine blue stain, ×1,000).

al blood smear revealed a few mast cells (3%) on Wright-Giemsa staining (Fig. 6).

A bone marrow aspiration revealed normal red and white-cell precursors but a marked increase in mast cell count. Evaluation of marrow aspirate and biopsy specimens revealed patchy infiltration of mast cells with basophilic cytoplasmic granules. These cells revealed metachromasia in toluidine blue stain (Fig. 7).

Radiologic findings were as follows; chest X-ray and upper GI series showed no evidence of definite abnormalities. But the flat abdomen X-ray showed mild hepatomegaly and moderate splenomegaly. On the abdominal sonography the echogenecity of the liver was somewhat coarse and
there was marked splenomegaly.

She was initially treated with oral antihista-
mines and steroids together with potent topical
corticosteroid ointment (clobetasol propionate).
However, as her skin lesions and itching showed
some resistance to this therapy, we next used PUVA
therapy. 8-Methoxypsoralen (methoxalen) was
given orally in the dose of 0.6 mg per kg body
weight. Two hours later the patient was exposed
to UVA (320-400 nm, peak at 365 nm) in Ultralite
6809 (H. Waldmann, Germany). The initial dose
of UVA was 1.5 J/cm². The dose was increased at
subsequent visits with the aim of maintaining
minimal erythema in the clinically uninvolved
skin. PUVA treatments were given at least twice
weekly at intervals of not less than 48 hours. After
16 treatments her symptoms were nearly relieved
and the skin lesions were completely faded away. Total
cumulative dose of UVA was 111.8 J/cm² for all 16
treatments.

But 3 months after discontinuation of PUVA
treatment, her skin lesions recurred. We offered to do
further treatment and evaluation but she declined
more extensive investigations.

DISCUSSION

Mastocytosis is a disorder characterized by the
infiltration of mast cells in tissues. The disease
can be classified according to the age of onset into ju-
venile or adult, or it can be classified according to the
clinical presentation. Although the age of onset is
important since it may determine the prognosis,
classification according to clinical presentation is
far more useful. Clinically, the disease may pre-
sent as cutaneous, systemic, or malignant forms.
The cutaneous types include the UP, cutaneous
solitary mastocytoma, diffuse cutaneous mastocy-
tosis, telangiectasia macularis eruptiva perstans,
and erythroderma. The most common cutaneous
lesions in patients with mastocytosis are the yel-
low-tan to red-brown macules, papules, and
plaques of UP.

In our case, there were diffuse reddish macules
and papules, as seen in the typical UP, mainly on the
trunk and extremities. But our case shows not only
multiple yellow-tan papules but also some coalescent
plaques on the intertriginous areas such as axillae,
groins and neck. Clinically these lesions resemble
those of psedoxanthomatous mastocytosis or xan-
thesmoidea, an uncommon variant of UP, de-
scribed as such by Tilbury Fox in 1875 and, in a life-
long form, by Griffiths et al in 1975. It was charac-
terized by pale yellow nodules 1 mm to 2 cm in di-
ameter which have been present in profusion since birth. Erythema, but no urtication, was
elicted by rubbing. The spleen was enlarged. A
dense mast cell infiltrate was found histologically.
The patient had a large upper gastrointestinal hem-
orrhage. Rasmussen used the term xanthelas-
moidea to describe the cutaneous lesions in a young
child with 1 to 2 cm papules, each of which was
studded with 10 to 20 yellow puncta.

Although the present case shares some common
features with Griffiths et al's, it is different in other
respects. First, the skin lesions were composed of
papules and plaques rather than nodules. Second, cut-
naneous folds were exaggerated and the skin
changes were most marked in the axillae and groins.
Third, Darier's sign was positive. Finally, bone
marrow involvement was found in our patient.

The earliest and most practical way of establishing
the diagnosis of mastocytosis is by performing a
skin biopsy of affected site. In UP the number of
mast cells in the papillary dermis, particularly
around blood vessels, is increased. These cells are
characterized by metachromasia as demonstrated
by use of basic dyes, such as Giemsa's reagent or
toluidine blue. The histologic alterations in single,
multiple, and disseminated lesions of UP are indis-
tinguishable. In our case, total three biopsy speci-
mens commonly showed a very dense infiltrate of
large numbers of mast cells in the upper and mid
dermis. These cells disclosed metachromasia on the
Giemsa and toluidine blue stains. Examination of
skin biopsy specimens however does not help to pre-
predict risk of systemic manifestations.

Mast cell proliferation not only may occur in the
skin but may involve such organs as the lymph
nodes, gastrointestinal system, bones, blood, liver,
and spleen. In various studies, 10 to 70% of patients
with UP had systemic disease. The bone mar-
row seems to be the most frequently involved site
and it is best demonstrated by bone marrow biopsy.
A mast cell infiltrate may be present in the bone
marrow, and mast cell leukemia may rarely develop.
In an evaluation of 35 adults patients with UP,
46% had a focal increase in the numbers of mast
cells in the bone marrow. In our case, there is
only a patchy infiltration of mast cells in the marrow
without atypical mast cells or other associated leukemic changes.

Bone involvement occurs in the 70% of patients with systemic mast cell diseases\textsuperscript{13}. It is approximately 10 times more common in adults than in children\textsuperscript{14}. The proximal long bones are most often affected, followed by the pelvis, ribs, and skull. Some patients may complain of bone pain\textsuperscript{15}. The diagnosis of bone involvement is usually established by skeletal survey, which may show diffuse osteosclerosis or osteoporosis\textsuperscript{16,17}. Although a bone survey could not be thoroughly performed in our patient, there was no signs of bone involvement on plain films.

Hepatomegaly may be found in approximately 10% of patients with systemic mast cell disease\textsuperscript{18}. This generally is of no consequence because liver function tests are normal\textsuperscript{19}. However, fibrosis and cirrhosis have been known to occur\textsuperscript{20}. Furthermore, infiltration of mast cells along the portal tracts may produce portal hypertension and ascites\textsuperscript{21}. Splenic involvement is frequently observed in patients with mastocytosis; it was found in 28(48%) of one group of 58 patients\textsuperscript{22}. Although this in itself may not produce functional abnormalities, markedly increased splenic weight generally occurred in patients who fit into unfavorable categories of mastocytosis\textsuperscript{23}. In our patient, organomegaly may be associated with a longer history of mastocytosis and recently Horan\textsuperscript{24} suggested that the duration of the disease is one of the most important factors in determining the incidence of hepatosplenomegaly.

Gastrointestinal symptoms are prominent in systemic mastocytoses and estimated to occur in approximately 23% of patients\textsuperscript{16}. Lesions may occur at all levels of the GI tract and radiographs with the contrast media may show peptic ulcers, abnormal mucosal patterns, and motility disturbances. Peptic ulcers with the potential for bleeding have been estimated to occur in approximately 10% of patients with systemic mastocytosis\textsuperscript{25}. Upper GI series taken in our patient revealed no abnormalities.

The treatment of UP in the past has focused primarily on ameliorating symptoms of intermittent pruritus, whealing, or flushing. These treatments include H1 and H2 antihistamines used concurrently, cromolyn sodium, aspirin used with H1 and H2 antihistamines, and, recently nifedipine\textsuperscript{26}.

The use of PUVA may be of benefit to some patients with mastocytosis\textsuperscript{27-29}. The mechanism by which this modality improves cutaneous mastocytoses is unknown. Whether there is an actual decrease in the number of mast cells in the skin following PUVA therapy is not conclusive\textsuperscript{30,31}, and the levels of histamine appear to be unchanged during therapy. There is a report, however, describing a decrease of histamine's major metabolite in the urine\textsuperscript{32}. Among the beneficial effects reported with PUVA are generalised tanning with fading of the macules and loss of Dariet's sign. The use of local photochemotherapy with trioxsalen has also been shown to be effective\textsuperscript{33}. Exposure to natural sunlight has been associated with a diminution of cutaneous lesions in occasional cases, but no controlled studies with ultraviolet B phototherapy have been reported\textsuperscript{2}. In this case, PUVA treatments were given twice weekly. After 16 treatments her symptoms were nearly relieved and skin lesions were completely faded out. The total cumulative dose of UV\textsubscript{A} was 111.8 J/cm\textsuperscript{2} for all 16 treatments. But 3 months after discontinuation of PUVA treatment, her skin lesions recurred. It is important to note that discontinuation of this therapy usually results in relapse as shown in our case and other reports\textsuperscript{34-36}. PUVA treatment, therefore, seems indicated only in patients who are severely inconvenienced by the disease, particularly if it has failed to respond to conventional therapy.

The prognosis for the patients with mast cell diseases is variable. Children whose mastocytosis persists into adult life typically exhibit a course similar to adult-onset mastocytosis, in which 15–30% of patients develop systemic involvement as in our case\textsuperscript{10} Although systemic mast cell disease is known to be associated with malignancy, the nature of this association is unclear. Complete blood cell count may give some idea of the progress of the disease because leukocytosis, especially with circulating mast cells and eosinophilia may herald the onset of leukemia\textsuperscript{37}. In our patient, a marked thrombocytopenia with mild anemia and leukopenia is found but not eosinophilia. Although the peripheral blood smear exhibit a few circulating mast cells in our case, the observation of circulating mast cells does not always imply an aggressive malignant condition; it has been reported in patients with UP who have been otherwise healthy\textsuperscript{33}. Further close observation will be needed in our case.
REFERENCES