

ORIGINAL ARTICLE

Indolent systemic mastocytosis treated with narrow-band UVB phototherapy: study of five cases

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Abstract

Background Mastocytoses represent a heterogeneous group of stem cell disorders marked by an abnormal hyperplasia and accumulation of mast cells in one or more tissues, including bone marrow, gastrointestinal tract, liver, spleen, lymph nodes and skin. Indolent systemic mastocytosis (ISM) is characterized by red-brownish and pruriginous maculopapular lesions, a bone marrow infiltration without functional impairment and an indolent clinical course with a good prognosis. In particular, the most common cutaneous symptoms are urticarial rash and mild-to-high pruritus.

Objectives This study analyses the clinical outcome of patients affected by ISM with prevalent pruriginous cutaneous symptoms and a scarce response to anti-histamines treated using narrowband ultraviolet B (NB-UVB) phototherapy.

Methods Narrowband ultraviolet B phototherapy was administered in a UV-irradiation cabin equipped with fluorescent UVB lamps with a peak emission at 311–313 nm. The perception of pruritus severity was assessed using the Visual Analogue Scale (VAS) before starting the treatment and at each control.

Results A complete remission of the cutaneous lesions and pruritus was documented in all patients after a median of 40.3 UV treatments and a median cumulative dose of 51.4 J/cm², with a lasting remission over a 6-month follow-up. The median VAS score at the beginning of the treatment was 86.6 (SD = 6.64), whereas it decreased to 6.66 (SD = 3.75) after 3 months of therapy.

Conclusions Our work provides evidence that NB-UVB phototherapy is useful for the treatment of the cutaneous symptoms and pruritus in ISM.

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Conflict of interest

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Introduction

Mastocytoses represent a heterogeneous group of stem cell disorders marked by an abnormal hyperplasia and accumulation of mast cells (MC) in one or more tissues, including bone marrow, gastrointestinal tract, liver, spleen, lymph nodes and skin.^{1,2}

Depending on clinical features and extent of organ involvement, mastocytoses are classified into seven variants, ranging from an isolated cutaneous involvement to more aggressive systemic syndromes.³

Indolent systemic mastocytosis (ISM) is the most frequently variant of systemic mastocytosis; the bone marrow is almost invariably affected and contains multifocal dense infiltrates of mast

cells with a low infiltration grade (<30%) and a typical cellular phenotype c-Kit⁺, tryptase⁺, CD2⁺ and CD25⁺. Serum total tryptase level is >20 ng/mL in almost all cases. Clinically, skin lesions in ISM are characterized by a pruriginous maculopapular urticaria pigmentosa-like eruption. The prognosis appears to be good, with an indolent clinical course and a normal life span.^{1,4}

Cutaneous and systemic symptoms are related to the local burden and release of secretory products from activated and hyperproliferating mast cells, so that the mainstay of treatment are anti-mediator drugs, with the aim to minimize the massive release of histamine and other major secretory products and provide relief of pruritus.³

For this reason, conventional therapies are ‘mediator-targeting’ drugs including H₁-antihistamines and H₂-antihistamines. Furthermore, sodium cromoglicate, proton pump inhibitors, leukotriene antagonists, β_2 agonists and corticosteroids are also differently employed to limit the local mast cell infiltration and obtain adequate symptom relief.⁴

Long-wave ultraviolet radiation [psoralen plus ultraviolet A (PUVA) or UVA1 alone] have been successfully employed as a second-line therapy to treat cutaneous symptoms in patients affected by mastocytosis who were not responsive to first-line therapies with anti-mediator drugs.^{5,6}

We present five cases of ISM with prevalent cutaneous symptomatology unresponsive to H₁-antihistamines and H₂-antihistamines and intolerant or with contraindications to the employment of PUVA-therapy, and treated using narrowband UVB phototherapy (NB-UVB).

Patients and methods

The study concerns five patients, two women and three men (median age: 61.3 years, range 22–77), affected by ISM (Table 1).

For each patient, the diagnosis of ISM was made in agreement with haematologists after a careful clinical evaluation and an exhaustive biohumoral screening.

In particular, each bone marrow biopsy showed the presence of a multifocal infiltrate of mast cells (<30% in all cases), with expression of CD2 and CD25. The assessment of baseline serum tryptase levels showed markedly increased values; in particular, all the patients showed values more than 20 ng/mL. A bioptic tissue sample from a cutaneous lesion was obtained, with a histological diagnosis of cutaneous mastocytosis in all cases.

Clinically, all patients presented widespread erythematous-brownish maculopapular urticaria pigmentosa-like lesions with severe pruritus; four patients suffered from recurrent abdominal pain, nausea or diarrhoea, but no evidence of associated clonal haematologic disorders, significant lymphadenopathy or hepatosplenic involvement was found.⁷

All patients were initially treated with H₁-antihistamines, H₂-antihistamines and proton pump inhibitors, with a poor response to treatment and inadequate control of pruritus.

Furthermore, PUVA-therapy was contraindicated in one patient because of an active hepatitis-B infection with altered liver enzymes. In four patients, the presence of a marked gastrointestinal involvement, characterized by nausea and dyspepsia, made the intake of 8-methoxypsoralen difficult.

Narrowband UVB phototherapy was administered in a UV irradiation cabin (Waldmann-Lichttechnik, Villingen-Schwenningen, Germany), equipped with eight Philips TL-01® (Eindhoven, the Netherlands) fluorescent UVB lamps with a peak emission at 311–313 nm.

The starting dose was 100 mJ/cm², with dose increments of 50 mJ/cm² at every treatment. Therapy was given three times a week on non-consecutive days, and during NB-UVB treatment,

Table 1 Clinical profiles of the five patients with UVB-NB phototherapy parameters, VAS scores and outcomes

	Name, gender/age	Mastocytosis variant	Age of onset of the disease (years old)	No. UVB treatments	Cumulative dose (J/cm ²)	VAS (time zero)	VAS (2 weeks)	VAS (1 month)	VAS (2 months)	VAS (3 months)	Follow-up (6 months)
1	S.G., F/22	ISM	1	35	72	75	60	40	20	0	Complete remission
2	R.F., M/50	ISM	41	89	132	90	70	45	25	10	Complete remission
3	M.F., M/77	ISM	74	33	24.8	85	65	50	35	10	Complete remission
4	T.P., M/75	ISM	68	36	28.6	85	70	55	35	5	Complete remission
5	T.M., F/59	ISM	55	50	53.7	95	75	50	25	5	Complete remission
	Median values			40.3	51.4	86.6	66.6	48.3	28.3	6.66	
	Standard deviation			–	–	6.64	5.13	5.1	6	3.75	

ISM, indolent systemic mastocytosis; VAS, Visual Analogue Scale.

each patient was given protective spectacles. In particular, considering the possibility of mast cell degranulation, a protocol with lower irradiation increments was employed.

Photographs of each patient were taken before, during and after treatment. Informed written consent forms were obtained from the patients, after the nature of the treatment and details on its possible benefits and side-effects had been carefully explained.

The perception of pruritus severity was assessed using the Visual Analogue Scale (VAS), a single-item linear pruritus scale graded from 0 to 100; before starting the treatment (time zero) and at each control every 2 weeks, patients were asked to give a number to quantify the intensity, spread and discomfort caused by itch.

A 6-month follow-up has been executed to evaluate the clinical response.

Results

The response to treatment was assessed by scoring concerning pruritus and a clinical examination of cutaneous involvement, with the help of photographic documentation.

The perception of pruritus assessed by the VAS scale is summarized in Table 1. The median VAS score at the beginning of the treatment was 86.6 (SD = 6.64), whereas it decreased to 6.66 (SD = 3.75) after 3 months of therapy.

A good control of pruritus was documented after 2 months of therapy and a complete remission after a median of 40.3 UVB-NB treatments (range 33–89), corresponding to a median of 3.5 months of therapy (range 2.9–7.4 months). The median cumulative UV dose was 51.4 J/cm² (range 24.8–132 J/cm²).

The tapering of the irradiation was accomplished by decreasing the frequency of treatment to twice and then once a week; when the patients maintained the remission of cutaneous symptoms, treatment had then been discontinued.

Phototherapy was well tolerated and there was no treatment interruption because of side-effects.

In the follow-up period, no sign of relapse was documented, and all patients were still showing a lasting remission of itch and cutaneous lesions (Fig. 1).

Discussion

Indolent systemic mastocytosis is the most common variant of systemic mastocytosis, accounting for about two-thirds of all cases, and generally involving both the skin and bone marrow.^{1,4}

Bone marrow is affected in almost 100% of cases and usually contains multifocal dense mast cell infiltrates, together with compact reactive lymphocytic infiltrates near mast cell aggregates.⁷ Cutaneous urticaria pigmentosa-like lesions are reported in more than 90% of cases.⁸

These mast cell infiltrates do not affect bone marrow function, so that patients with ISM tend to present only symptoms related to the release of mediators and to the local mast cell burden, especially in the skin and gastrointestinal tract, with a prolonged clinical course and a normal life expectancy.^{3,4}

Generally, treatment of mastocytosis is only symptomatic and will not change the course of the disease, aiming at avoiding mast cell degranulation and inhibiting the actions of the constitutive mediators released by mast cells (especially histamine and leukotrienes).⁷

Although a great heterogeneity regarding mast cell-mediator-related symptoms exists, mild-high pruritus is by far the most common clinical presentation, and more importantly, one of the greatest causes of discomfort for the patient.

According to the guidelines for the treatment of mastocytosis, patients with ISM do not require a cytoreductive therapy to limit mast cells proliferation, and first-line therapy involves H₁-antihistamines, which are useful in mitigating cutaneous symptoms and H₂-antihistamines, mainly employed to treat

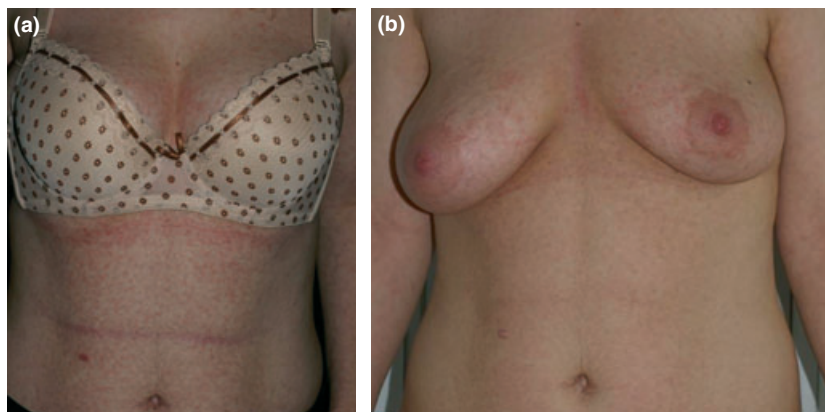


Figure 1 Patient 1, a 22-year-old woman affected by indolent systemic mastocytosis (ISM) and cutaneous involvement characterized by pruriginous red-brownish maculopapules on the trunk and arms, before (a) and after (b) NB-UVB phototherapy.

gastric hypersecretion.^{2–4} An association with a proton pump inhibitor is sometimes requested, especially when gastrointestinal manifestations are particularly intense.⁶

Nonetheless, some patients find these treatments ineffective, and intense pruritus is generally the most recalcitrant symptom. In these cases, sodium cromoglicate, topical corticosteroids, leukotriene antagonists and UVA irradiation (psoralen plus 365 nm UVA or 340–400 nm UVA1 alone) can be used as second-line therapies.^{9–14}

In our cases, PUVA-therapy was contraindicated because of an active hepatitis-B infection in one patient; in the other patients, who already presented gastrointestinal symptoms before starting the treatment, the intense dyspeptic symptomatology related to the intake of the photosensitizing agent made the employment of this therapy unfeasible.

Although itch appears to be one of the most responsive subjective symptoms to UVB-NB phototherapy, as documented in several diseases associated with pruriginous cutaneous involvement such as chronic urticaria,^{15,16} atopic dermatitis,¹⁷ psoriasis,¹⁸ chronic renal insufficiency,¹⁹ polycythemia vera,²⁰ HIV-related pruritus²¹ and symptomatic dermatographism,²² there is a lack of well-designed clinical studies on patients affected by ISM, pruritus and UVB-NB phototherapy, but several *in vitro* studies have proved different UVB mechanisms of action on mast cells.

In particular, some studies analyzed the influence of UVB on survival and histamine release from human mast cells, providing evidence that these cells need to be viewed as additional major targets in the skin involved in immunomodulation by UV light. From this point of view, it has been proved that the high susceptibility of this cell type towards UV light seems to partially depend on the state of cellular activation.^{23–27}

Guhl *et al.* investigated the effects of UV irradiation at therapeutic doses on mast cells purified from human skin, examining baseline and stimulated release of histamine, tryptase, interleukin (IL)-6, IL-8 and tumor necrosis factor- α (TNF- α).²⁸

Histamine is the major biogenic amine of skin mast cells that is stored bound to proteoglycans in cytoplasmic granules ready to release on mast cell activation; UVB irradiation led to striking inhibition of stimulated histamine liberation in a clearly dose-dependent manner, displaying a dual effect on mast cells by triggering slight, but significant histamine release from resting mast cells and suppressing the same release by up to 90% when cells were appropriately stimulated.

Levels of tryptase were also found to be remarkably reduced after UVB irradiation, thus suggesting that UV light has a negative impact on the discharge of mast cells granules into the outer cell environment, especially when mast cells are excessively stimulated.

Immunosuppressive effects induced by UVB irradiation were therefore predominant in activated mast cells, as confirmed by their beneficial effects in inflammatory diseases; theoretically, this could also happen in cutaneous conditions characterized by a slight and constant mast cells activation, as in cutaneous mastocytosis.

Mast cells are also known to be the source of several cytokines and chemokines, which are released on activation in addition to histamine; another significant finding was therefore the suppression of proinflammatory cytokines secretion in human skin mast cells detected after UVB irradiation and irrespective of the activation state of the cell.²⁸

Another important aspect about UV immunomodulation concerns the induction of apoptosis in skin infiltrating cells. In particular, UV light is normally unable to induce apoptosis in healthy skin mast cells, even with high single UVB doses or after repetitive low-dose UVB irradiation. On the contrary, the apoptotic reactivity of mast cells towards UVB proportionally rises with their proliferative activity degree and immaturity.²⁹

In fact, Guhl *et al.* demonstrated that human mast cells can be induced to undergo classical apoptosis changes in response to irradiation with UVB or UVA1, and effects are more pronounced with UVB, in a dose-dependent apoptotic response.²⁹

In our study, all patients presented a pronounced pruriginous symptomatology that we measured using a single-item VAS.

Quantification of pruritus severity is problematic because of its subjective nature and poor localization; the VAS is proved to be an instrument with good validity and excellent reliability when a measurement from the patients' viewpoint is necessary, and its use is highly recommended to assess the intensity of pruritus and global quality of life.^{30,31}

In our patients, as demonstrated by a median VAS score decreasing from 86.6 to 6.66 after 3 months of therapy, the employment of NB-UVB phototherapy allowed a complete remission of pruritus in all patients, and a 6-month follow-up showed good and lasting clinical results.

These clinical data may suggest that UV light can directly affect mast cells, and NB-UVB mechanism of action in mastocytosis could be related to an increased sensitivity to apoptotic signals in immature and highly proliferating mast cells.

A recent study by Prignano *et al.* reported good clinical results with the employment of NB-UVB for the treatment of seven patients affected by urticaria pigmentosa, the commonest form of cutaneous mastocytosis; on the whole, all patients received 36 phototherapy treatments and an excellent reduction in pruritus was documented.³² Nevertheless, to our knowledge, there is no clinical study evaluating the possible beneficial effects of NB-UVB phototherapy in patients affected by ISM.

In summary, our work suggests that NB-UVB phototherapy is useful as a second-line therapeutic modality for the treatment of cutaneous symptomatology in patients affected by systemic mastocytosis, in whom PUVA-therapy has failed or can not be administered and pharmacological therapy provides poor control of symptoms.

The main limitation of our study has to do with the extent to which the findings can be generalized beyond the cases studied. Actually, the number of cases of our study limits the strength of the conclusions that can be drawn from the data, being too small

for broad generalizations. The second limitation concerns the possibility to identify which subgroups of patients could be more likely to benefit from this therapy and a split body treatment may add confirmatory evidence.

For this reason, further studies are required to investigate the long-term effects of this therapy and define, more clearly, how NB-UVB may modulate the functional properties and survival of proliferating immature mast cells in the skin.

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