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Therapeutic challenge during the long-term follow-up of a patient with indolent systemic mastocytosis with extensive cutaneous involvement

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Abstract. – From a dermatological aspect, it posed a considerable challenge the skin-limited form of mastocytosis, urticaria pigmentosa and indolent systemic mastocytosis (ISM) with cutaneous lesions. Despite the favourable prognosis, lifelong dermatological control is needed, during which the average symptomatic therapy does not always seem adequate.

We report here the case of a female ISM patient with recurrent cutaneous symptoms that impaired her quality of life, with a follow-up time of 27 years. During this long follow-up period, the cutaneous lesions could be controlled by antihistamines, leukotriene antagonists, glucocorticoids, local immunosuppressants or local UV radiation for only relatively short periods. Imatinib mesylate was, therefore, introduced in an attempt to control the cutaneous lesions. Tyrosine kinase inhibition is an unusual dermatological therapeutic option.

This case illustrates that imatinib mesylate was a good choice with which to achieve a reduction of the skin lesions in this *KIT* D816V mutation-negative disease: it led to a temporary appreciable improvement of the patient's quality of life.

Key Words:
Myeloproliferative neoplasm, Indolent systemic mastocytosis, *KIT* D816V mutation, Imatinib mesylate, Tyrosine kinase inhibitor.

Introduction

Systemic mastocytosis (SM) is a rare chronic myeloproliferative neoplasm characterized by abnormal mast cell proliferation with accumulation in one or more extracutaneous organs[1,2]. The 2008 World Health Organization classification defines various subtypes of SM, including indolent SM (ISM), SM associated with a clonal non-mast cell lineage disease (SM-AHNMD), aggressive SM (ASM) and mast cell leukaemia[1].

For dermatologists, considerable challenges are posed by cutaneous mastocytosis without bone marrow involvement as a skin-limited disease, and by ISM involving the bone marrow with cutaneous symptoms. Though the mastocytes in ISM involve several organs, including the bone marrow, it frequently presents clinically with cutaneous symptoms alone or in combination with recurrent mediator-related systemic symptoms (e.g. pruritus, flushing, diarrhoea and headache)[2]. The life expectancy in ISM is more favourable than in the other variants of SM: the great majority of the patients have an almost normal life expectancy and a low disease progression rate. Nevertheless, the quality of life of these patients can be severely affected by the mediator-related systemic and/or cutaneous symptoms[3]. The only therapeutic option for the specific cutaneous symptoms is symptomatic therapy: commonly antihistamines, leukotriene antagonists, glucocorticoids, local immunosuppressants or local UV radiation, and in selected special cases tyrosine kinase inhibitors (TKIs)[2,4,5]. The usefulness of TKIs in SM has been actively investigated in recent years, but the role of imatinib mesylate therapy in controlling the cutaneous lesions in ISM has not been well established[6-8].

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This case report describes a female patient with ISM who was followed up for 27 years, during which the recurrent specific cutaneous symptoms frequently greatly impaired her quality of life. Her case illustrates the potential value of imatinib mesylate even in *KIT* D816V mutation-negative ISM, with achievement of a temporary improvement of the skin-related symptoms.

Case Presentation

The patient presented with diffuse brownish papular lesions on the face, the trunk and the upper and lower extremities in 1986. Her lesions regularly became red and elevated, with no obvious cause. The Darier sign was positive. Histopathology of the skin biopsy confirmed the diagnosis of mastocytosis.

The otherwise attractive young female patient was highly disturbed by her skin symptoms, which included itching, and the appearance of her skin greatly influenced her quality of life.

She was treated first with antihistamines and PUVA. However, because of the worsening of the skin symptoms and the result of the bone marrow biopsy, which confirmed ISM, interferon-alfa was administrated in weekly doses of 2x3 million IU for 1 year. This resulted in relief of her symptoms for a period of 2 years, during which she was given only sodium-chromoglycate. Subsequently, in consequence of the progression of her cutaneous symptoms, repeated interferon-alfa therapy was introduced in weekly doses of 3x3 million IU for another year, which again resulted in the temporary relief of her symptoms. However, eosinophilia and cutaneous progression shortly appeared (Figure 1/a). As the recurring cutaneous symptoms, greatly disturbed the patient's quality of life, imatinib mesylate was introduced, even though neither *FIP1L1-PDGFRA* gene rearrangement nor a *KIT* D816V mutation nor any imatinib-sensitive KIT mutation was present. Shortly after the beginning of imatinib mesylate treatment her skin symptoms improved, the lesions become macular and the itching disappeared. She took imatinib mesylate periodically between 2008 and 2010. When the newly introduced imatinib treatment first given a daily dose of 400 mg was commenced for 6 months, which was followed by a daily dose of 100 mg. She has currently been off imatinib for more than 2 years, and although she still has brownish macular lesions all over her body, the lesions do not interfere with her quality of life; she needs antihistamine treatment only occasionally (Figure 1/b).

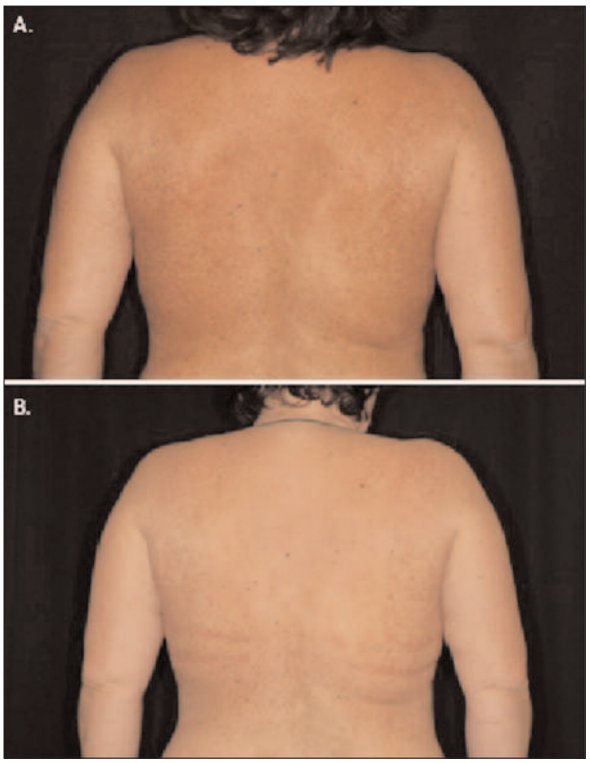

Figure 1. ***A,*** The diffuse brownish papular pruritic lesions of this patient before the introduction of imatinib mesylate treatment. ***B,*** A clear improvement of the skin lesions was seen after imatinib mesylate treatment.

Discussion

In recent years, TKIs, including imatinib, have revolutionized the treatment of patients with chronic myeloid leukaemia and gastrointestinal stromal tumours[9,10]. Increasing evidence has emerged to suggest that a small subset of SM patients who are *KIT* D816V-unmutated or who have a very rare imatinib-sensitive KIT mutation may also benefit from imatinib mesylate therapy, which is presumed to reduce the mast cell mediator levels and results in an improvement in the mediator-related symptoms[6-8,11,12]. In cases of SM with eosinophilia, molecular investigation (*FIP1L1-PDGFRA* rearrangement) is required, as only patients with rearranged *PDGFRA* will respond to imatinib therapy. Interestingly, *KIT* D816V-mutated SM patients with eosinophilia give no response[13]. The published data concerning the effects of imatinib mesylate on the cutaneous lesions in ISM are still a matter of debate. Only a small number of case reports in paediatric diffuse cutaneous mastocytosis and in adult patients with cutaneous mastocytosis associated

with chronic myelomonocytic leukaemia have been found to demonstrate a marked improvement following the administration of imatinib mesylate[7,14,15].

In light of the previously reported rare imatinib-sensitive *KIT* mutations located in exons 9 and 11, we screened our patient for the most frequently reported *KIT* mutations in exons 9, 11 and 17, using Sanger sequencing[13]. Although sequence analysis did not reveal any *KIT* mutations in exon 17, where the most common observed KIT D816V mutation occurs and the other, though rare imatinib-resistant mutations are mostly located, we decided to introduce imatinib mesylate in an effort to control the skin lesions. This case demonstrates that imatinib mesylate therapy may be benefit, even in *KIT* D816V-unmutated cases of ISM, resulting at least temporarily in regression of the cutaneous symptoms.

Conclusions

Our case has revealed that imatinib mesylate can be useful, even if with only a limited role, in a *KIT* D816V-unmutated ISM patient with extensive cutaneous involvement. When the cutaneous lesions in ISM can no longer be controlled by antihistamines, leukotriene antagonists, glucocorticoids, local immunosuppressants or local UV radiation, imatinib mesylate may temporarily reduce the skin lesions and improve the quality of life of the patient.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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