Acta Derm Venereol 2014; 94: 583–584

SHORT COMMUNICATION

Increased Risk of Malignant Melanoma in Patients with Systemic Mastocytosis?

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Accepted Oct 24, 2013; Epub ahead of print Jan 28, 2014

Mastocytosis, a group of rare disorders that occur in both children and adults, is characterised by abnormal growth and pathological accumulation of mast cells in one or more organs, most commonly the skin (1). Urticaria pigmentosa (UP) is the most common cutaneous variant. In cases of extracutaneous involvement, systemic mastocytosis (SM) can be diagnosed on the basis of the criteria formulated by the WHO. The course of SM in most patients (90%) is indolent, with more aggressive presentation in only a few.

The incidence of cutaneous melanoma is increasing and although this malignancy and mastocytosis originate from 2 different types of cells (melanocytes from the neural crest and mast cells from haematopoetic stem cells, respectively) they share certain similarities, including expression of the transcription factors MITF and STAT3, and dependence of the growth factor receptor KIT and its ligand stem cell factor for their growth and development (2, 3). We have found 5 published case reports that suggest a relationship between these 2 pathologies. In the first, published in 1979, a patient with nodular mastocytosis developed both melanocytoma and mastocytoma (4). In the second, UP and SM preceded a metastatic melanoma (5) and the third involved combined mastocytoma-junctional naevus (6). In the fourth case, malignant melanoma was diagnosed prior to SM (7). And finally, a patient with telangiectasia macularis eruptive perstans (TEMP), a rare form of cutaneous mastocytosis, was found to have a malignant melanoma (8).

Here, we describe our 4 additional cases and discuss possible associations between these 2 diseases.

MATERIAL AND METHODS

Eighty-one patients with confirmed SM, diagnosed and treated at the Mastocytosis Centre at Karolinska University Hospital and Karolinska Institutet from 2007–2011, 4 were also diagnosed with malignant melanoma.

RESULTS

Among our 81 Swedish patients diagnosed with mastocytosis between 2007 and 2011, 4 (5%) were also diagnosed with malignant melanoma (Table I). Three of these patients (nos 2–4) suffered from both UP and SM and none of these were treated with PUVA. Of those with UP, 2 had indolent SM and cutaneous melanoma and are still alive, while one was diagnosed with a melanoma metastasis that proved fatal. Patient no. 1 did not have UP, but an aggressive form of SM with an associated clonal haematologic non-mast cell lineage disorder instead and died later of leukaemia (9). In this patient a *KIT* D816V mutation was detected in the bone marrow mast cells, but not in the melanoma. Both in the case of our patients and those reported previously, the time point at which the first symptoms of mastocytosis and melanoma appeared is usually not known, making it impossible to determine which of these developed first.

DISCUSSION

Although based on a small number of SM patients, we found that the risk for melanoma among patients with SM appeared higher than in the general population (5% vs

Table I. *Characteristics of 4 patients with systemic mastocytosis (SM) and malignant melanoma (MM)*

Pat. no./ Sex	Diagnosis	Age at SM diagnosis (years)	Age at which symptoms began (years)	$CD2^+/CD25^{+a}$	Serum tryptase[b] (ng/ml)	CM/UP present	MM type, Localisation, Clark level, thickness	Stage	Age at diagnosis of MM	Outcome
1/M[c]	SM-AHNMD-eo/MCL/HCL	63	63	–/+	190	No	Skin, NOS, II, 0.4 mm, not ulcerated	T1a	65	Died from SM
2/F	ISM	38	9	+/+	62	Yes	Skin	nk	20	Alive
3/M[c]	ISM	67	38	–/+	36	Yes	Skin nodular, III, 1.4 mm, not ulcerated	T2a	45	Alive
4/F[c]	ISM	41	14	–/+	70	Yes	Lymph metastasis, no primary MM identified	IV	40	Died from melanoma

[a]All patients showed spindle-shaped morphology and *KIT* D816V mutations of mast cells.

[b]Normal range 11.4 ng/ml.

[c]Major WHO criteria fulfilled.

CM: cutaneous mastocytosis; ISM: indolent systemic mastocytosis; SM-AHNMD/eo/MCL/HCL: SM-associated clonal haematological non-mast cell lineage disorder/eosinophilia/mast cell leukaemia/hairy cell leukaemia: nk.: not known; UP: urticaria pigmentosa; NOS: not otherwised specified.

 doi: 10.2340/00015555-1788
 ISSN 0001-5555

1.2–1.6 % (Cancer incidence in Sweden 2011, Swedish Board of Health and Walfare). This poses the question whether there are any plausible biological explanations for an enhanced incidence of melanoma among patients diagnosed with SM. Both mast cells and melanocytes are dependent on the binding of stem cell factor (SCF) to the KIT receptor. Loss of KIT function results in piebaldism, a disorder of pigmentation characterised by loss of melanocytes which leads to patches of white skin and hair (10). In the case of SM a *KIT* D816V mutation is present in almost all cases (1, 11), whereas in melanoma *KIT* mutations or other gene modifications are less common (<40%). Moreover, even when a *KIT* mutation is present in a patient with melanoma, this mutation is different from that associated with SM (D816V) (2).

On the other hand, melanocytes are highly responsive to proliferative cytokines and it can be speculated that cytokines produced by the large numbers of pathological mast cells observed in mastocytosis contribute to increased risk for melanoma. A plausible hypothesis is that upregulated expression and secretion of the growth factor SCF and other cytokines by mast cells recruit and stimulate the proliferation of melanocytes, which could promote tumourigenesis (12–14) (Fig. 1).

In addition, cutaneous mastocytosis is often treated with PUVA. Since PUVA is known to be a risk-factor for melanoma, such treatment should be used with more caution (15). None of our patients described in this report received PUVA treatment.

We conclude that patients with cutaneous and/or SM should be monitored carefully for possible lesions that precede melanoma such as dysplastic naevi.

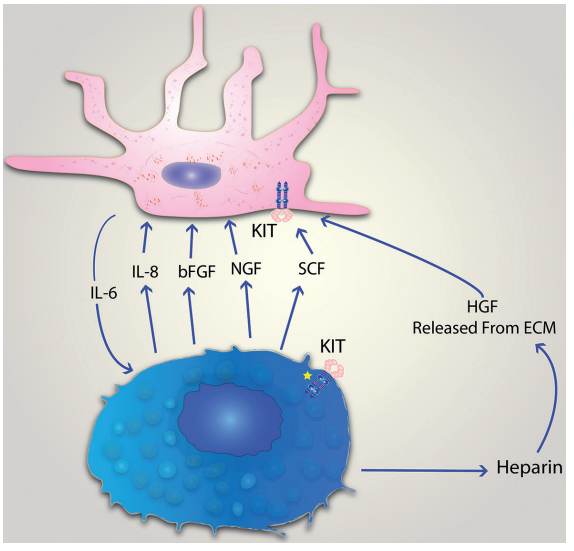

Fig. 1. Melanocytes (top) and mast cells (bottom) can interact and promote the cell growth and other cellular functions through the release of cytokines, e.g., interleukin (IL)-6, IL-8, basic fibroblast growth factor (bFGF), nerve growth factor (NGF) and stem cell factor (SCF). Hepatocyte growth factor (HGF) is bound to the extracellular matrix (ECM) from which it can be released by heparin released from degranulated mast cells. Both mast cells and melanocytes express the SCF receptor KIT. Mast cells in systemic mastocytosis patients exhibit a D816V *KIT* mutation, which leads to a ligand-independent activation of the receptor. Mutations or amplifications of *KIT* are less frequent in melanoma.

ACKNOWLEDGEMENTS

This study was financed by grants from the Swedish Cancer Society; and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet.

The authors declare no conflict of interest.

REFERENCES

1. Todd P, Garioch J, Seywright M, Rademaker M, Thomson J. Malignant melanoma and systemic mastocytosis – a possible association? Clin Exp Dermatol 1991; 16: 455–457.
2. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007; 37: 435–453.
3. Fecher LA, Cummings SD, Keefe MJ, Alani RM. Toward a molecular classification of melanoma. J Clin Oncol 2007; 25: 1606–1620.
4. Sonnenblick A, Levy C, Razin E. Interplay between MITF, PIAS3, and STAT3 in mast cells and melanocytes. Mol Cell Biol 2004; 24: 10584–10592.
5. Okun MR, Bhawan J. Combined melanocytoma-mastocytoma in a case of nodular mastocytosis. J Am Acad Dermatol 1979; 1: 338–347.
6. Northcutt AD, Tschen JA. Combined mastocytoma-junctional nevus. Am J Dermatopathol 2004; 26: 478–481.
7. Lee-Wong M, Laufer M, Karagic M. Mastocytosis, melanoma and sarcoidosis. The Internet Journal of Asthma, Allergy and Immunology 2009; 7.
8. Kowalzic L, Eickenscheidt L, Seidel C, Kribus S, Ziegler H, Komar M. Telangiectasia macularis eruptiva perstans, a form of cutaneous mastocytosis, associated with malignant melanoma. J Dtsch Dermatol Ges 2009; 7: 360–362.
9. Gülen T, Sander B, Nilsson G, Palmblad J, Sotlar K, Horny HP, Hägglund H. Systemic mastocytosis: progressive evolution of an occult disease into fatal mast cell leukemia: unique findings on an unusual hematological neoplasm. Med Oncol 2012; 29: 3540–3546.
10. Alexeev V, Yoon K. Distinctive role of the cKit receptor tyrosine kinase signaling in mammalian melanocytes. J Invest Dermatol 2006; 126: 1102–1110.
11. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, Metcalfe DD. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci USA 1995; 92: 10560–10564.
12. Longley BJ, Morganroth GS, Tyrrell L, Ding TG, Anderson DM, Williams DE, Halaban R. Altered metabolism of mast-cell growth factor (c-kit ligand) in cutaneous mastocytosis. N Engl J Med 1993; 328: 1302–1307.
13. Welker P, Grabbe J, Gibbs B, Zuberbier T, Henz BM. Human mast cells produce and differentially express both soluble and membrane-bound stem cell factor. Scand J Immunol 1999; 49: 495–500.
14. Zhang S, Anderson DF, Bradding P, Coward WR, Baddeley SM, MacLeod JDA, et al. Human mast cells express stem cell factor. J Pathol 1998; 186: 5–66.
15. Lindelöf B. Risk of melanoma with psoralen/ultraviolet A therapy for psoriasis. Do the known risks now outweigh the benefits? Drug Saf 1999; 20: 289–297.