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Mast Cell Disorders, Melanoma and Pancreatic Carcinoma: From a Clinical Observation to a Brief Review of the Literature

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ABSTRACT Mastocytosis can be associated with other clonal or non-clonal hematologic diseases as well as a variety of non-hematologic malignancies. A 75-year-old Caucasian male patient was referred to us with a 5-month history of neutrophilic leukocytosis and mild splenomegaly. He had developed a cutaneous melanoma sixteen years ago. According to the clinical and pathological features, a final diagnosis of systemic mastocytosis was established. The patient started treatment with interferon-α at a dose of 3 MIU/day, combined with low doses of prednisone. We observed a rapid disappearance of symptoms. Unfortunately, after 3 months a diagnosis of pancreatic adenocarcinoma was established. A review of the literature suggests that mastocytes could have a pivotal role in several malignancies. Different chemokines, mitogenic factors, chemical mediators of inflammation, and specific gene mutations could explain the association between mastocytosis and other hematologic and non-hematologic disorders.

KEY WORDS: mastocytosis, melanoma, pancreatic neoplasms, tryptases

INTRODUCTION

Mastocytosis includes a group of disorders affecting both children and adults, characterized by an exponential proliferation and accumulations of mast cells in one or more organs (1). According to the 2008 WHO classification, mastocytosis is categorized under cutaneous mastocytosis that accounts for about 90% of cases (with often only a cutaneous localization), and systemic mastocytosis (2).

Systemic mastocytosis is characterized by an infiltration of clonally derived mast cells in different tissues, including the bone marrow, skin, gastrointestinal tract, liver, bones, lymph nodes, and spleen. The

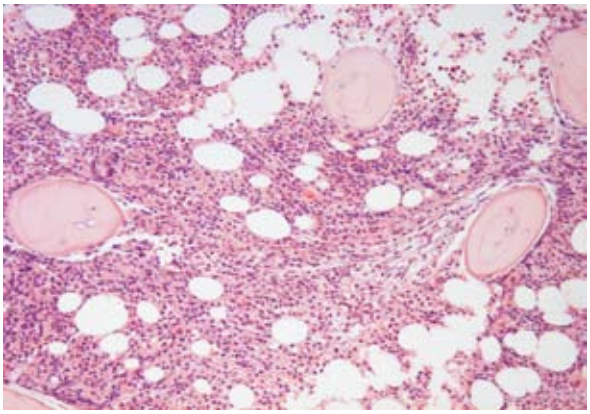

Figure 1. Hyper-cellular bone marrow with granuloblastic hyperplasia and peri-trabecular areas of fibrosis (hematoxylin-eosin, ×40).

diagnosis is based on the identification of neoplastic mast cells and/or genetic mutations (2,3). At the same time, it can be associated with other clonal or non-clonal hematologic diseases as well as a variety of non-hematologic neoplasms, emphasizing shared pathophysiologic mechanisms (1,3). In this regard, different etiopathogenetic factors may be involved: chemokines (as CCL1, CCL2, CXCL8, CCL3, CCl4, CCL5), mitogenic factors (GM-CSF), chemical mediators of the inflammation and specific gene mutations; this could explain the association between mastocytosis and other hematologic and non-hematologic disorders, such as malignant melanoma (MM) and pancreatic cancer.

Starting from a clinical observation, we reviewed the literature focusing on the role of mast cells in several pathogenic processes that can involve different cell lineages.

CASE REPORT

A 75-year-old Caucasian male patient was first admitted to our Hematology Center in April 2012 with a 5-month history of neutrophilic leukocytosis (WBC 15.13 × 10^9/L; neutrophils 9.76 × 10^9/L) and mild splenomegaly (15.4 × 15.5 cm). His familial history was negative for hematologic diseases and/or malignancies. In his personal medical history, a cutaneous MM was removed 16 years earlier (3.5 mm Breslow, ulcerated with IV Clark's level; pT3b N2a M0, Stage IIIB), for which he received treatment with dacarbazine (850 mg/m^2 every 28 days for a total of 6 cycles) and interferon-α (3.000.000 international units [MIU]/day × 3 times/weekly for a total of 36 months). Periodic clinical and instrumental examinations, performed at planned intervals over the years, showed no disease recurrence.

On admission, the clinical examination revealed a splenomegaly combined with a mild hepatomegaly; no lymphadenopathies were found. The laboratory investigations confirmed the neutrophilic leukocytosis (WBC 16.96 × 10^9/L; neutrophils 11.38 × 10^9/L; lymphocytes 2.54 × 10^9/L, and monocytes 1.63 × 10^9/L) and mild thrombocytopenia (platelets 109 × 10^9/L). An increase in polyclonal gammaglobulins and erythrocyte sedimentation rate (ESR) was also observed.

A chronic myeloproliferative disease was suspected and molecular evaluation of JAK-2 mutations and BCR-ABL rearrangement were negative. A cytogenetic analysis was carried out on bone marrow cells, but no karyotype abnormalities were detected. A bone marrow biopsy showed the presence of granuloblastic hyperplasia, with less than 5% of undifferentiated CD34+ progenitor cells and scattered CD20+ and

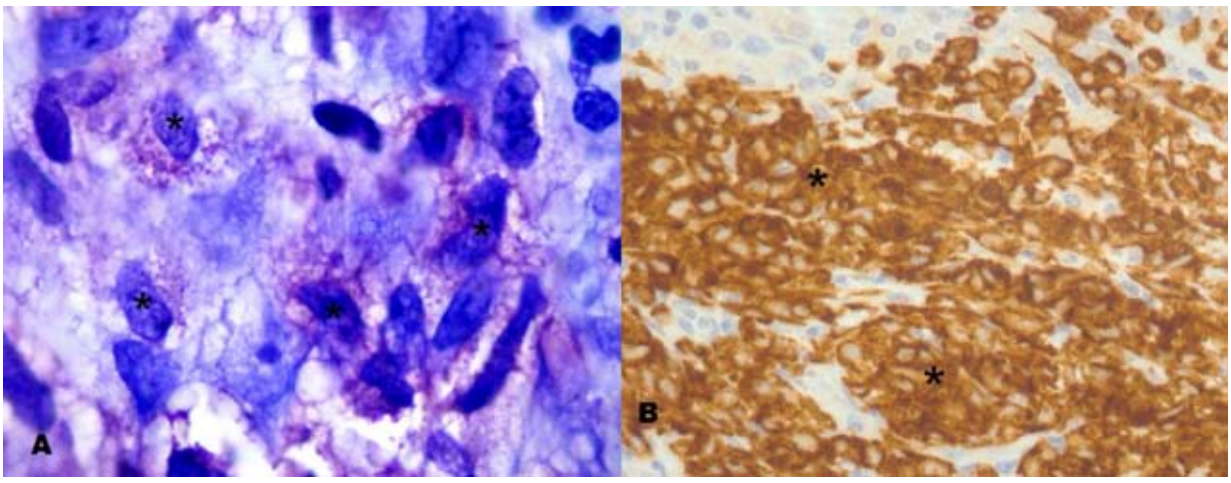

Figure 2. Aggregates of mast cells (asterisks) showing intracytoplasmic metachromatic granules (2a, Giemsa stain, ×100) and strong expression of c-kit (2b, ×40). In panel B, the brown color is the positive c-Kit receptor immunostaining.

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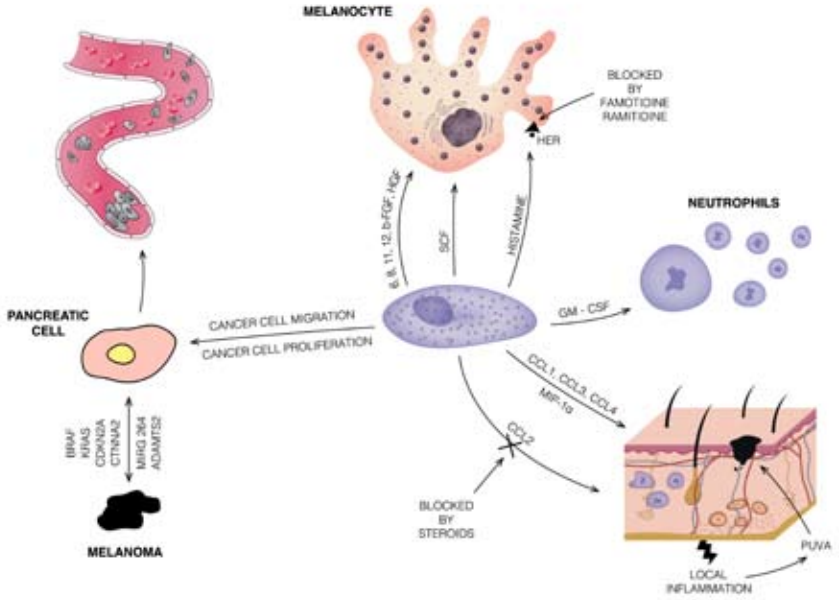

Figure 3. Physiopathologic pathways between mast cells, pancreatic cells, melanocytes, and neutrophils. CCL1, CCL2 (blocked by steroids), CCL3, CCl4, CCL5, and CXCL8 chemokines secreted by mast-cells can induce recruitment of the neutrophils in tissues, while granulocyte-macrophage colony stimulating factor (GM-CSF), secreted by active mast cells, can determine neutrophilia. Accordingly, there is a local inflammation in the skin (cutaneous manifestations of mastocytosis), which can result in a high utilization of therapy with psoralen and ultraviolet A therapy (PUVA therapy), with a relative increased risk of melanoma. Mast-cells via interleukin (IL) 6, 8, 11, 12, basic fibroblast growth factor (b-FGF), hepatocyte growth factor (HGF), nerve growth factor (NGF), stem cell factor (SCF), and histamine can determine morpho-structural changes in melanocytes. In addition, both mast-cells and melanocytes express the KIT receptor. Mast-cells orchestrate cancer cell migration and proliferation in pancreatic cells (also justified by high levels of serum tryptase in patients with pancreatic cancer, as well as a major aggressive course of pancreatic cancers with a high mast cells population in tissue samples). In turn, malignant pancreatic cells and melanoma (bottom left) share specific gene alterations such as CDKN2A, CTNNA2, MIRG264, BRAF, KRAS, and ADAMTS2.

CD3+ lymphocytes. Furthermore, focal areas of fibrosis were observed around the bone trabeculae (Figure 1), along with features of increased bone remodeling. Parathormon, serum calcium levels, alkaline phosphatases, and thyroidal hormone analyses were within the normal ranges; a bone scintigraphy highlighted unspecific osteo-artopathic features. The total body computerized axial tomography confirmed the isolated splenomegaly (17 cm × 15 cm) and a mild hepatomegaly, without other findings.

Six months later, because of progressive asthenia combined with persistent neutrophilic leukocytosis and progressive increase of the spleen (19 × 20 cm) a further bone marrow evaluation was performed. The second bone biopsy showed a granuloblastic hyperplasia with a prevalence of immature MPO+/CD34- progenitor cells mainly within the inter-trabecular space. Multiple peri-trabecular and peri-venous nodular aggregates of predominantly fusiform cells showing metachromatic granules at Giemsa staining (Figure 2, a) and C-kit expression (Figure 2, b) were also observed. An increase of bone remodeling was also present with irregular thinning of the bone trabeculae. The serum tryptase level was ≥80 ng/mL. Based on the clinical and pathologic features, a final diagnosis of systemic mastocytosis was established.

A treatment with interferon-α at a dose of 3MIU/day, combined with low doses of prednisone, was started. We observed a rapid disappearance of symptoms associated with a normalization of the peripheral blood values and a reduction of spleen volume. Unfortunately, 3 months later the patient experienced a worsening abdominal pain. Ultrasonography and computed tomography (CT) revealed a pancreatic lesion, involving the surrounding tissues and the celiac axis, combined with multiple abdominal lymphadenopathies and peritoneal carcinomatosis. A biopsy of the pancreatic lesion was diagnostic for a pancreatic adenocarcinoma. The patient was in stage IV and was treated with the chemotherapy FOLFIRINOX regimen (fluorouracil/irinotecan and oxaliplatin). Unfortunately, the patient died 5 months after the diagnosis of the pancreatic cancer. Because of the absence of melanoma recurrence over 16 years and because of the absence of nodal involvement by melanoma metastases at the diagnosis of systemic mastocytosis, we believe that the patient died due to stage IV pancreatic adenocarcinoma.

Table 1. Benign and malignant melanocytic lesions reported in literature associated with mast cell disorders

Author	Year	Sex	Age	Cases	Serum tryptase	Type MSTO	Symptoms	Other diseases	Onset of MM	Melanocytic lesion	Same sample
Okum	1979	F	30	1	NR	Mastocytoma	-	-	NA	Melanocytoma	+
Silverman	1988	M	1	1	NR	Mastocytoma	-	-	NA	Congenital Nevus	+
Todd	1991	F	45	1	NR	Systemic	Hepato-Splenomegaly, Flushing, Diarrhoea	-	After MSTO (26 years)	Melanoma Breslow: 5.6 mm	-
Northcutt	2004	F	57	1	NR	Mastocytoma	-	-	NA	Junctional nvus	+
Lee-Wong	2009	M	30	1	NR	Systemic	Pruritus, puffy eyes, fatigue, headaches, osteopenia, trombocytopenia	Sarcoidosis	Prior MSTO NR	Melanoma Breslow: NR	-
Kowalzick	2009	F	62	1	↔	Telangiectasia macularis eruptive perstans	-	-	Synchronous	Melanoma Breslow: 0.65 mm	-
Donati	2014	F	38	1	↔	Urticaria pigmentosa	Itching in the lesions	Obesity	After MSTO (36 years)	a) Melanoma Breslow: 0.5mm b) Melanocytic Nevi	+ +
Hägglund	2014	M F M F	63 38 67 41	4	↑ ↑ ↑ ↑	Systemic MSTO Systemic MSTO + CM Systemic MSTO + CM Systemic MSTO + CM	Not reported Not reported Not reported Not reported	CNMLD - - -	After MSTO (2 years) Prior MSTO (18 years) Prior MSTO (22 years) After MSTO (26 years)	Melanoma: 0.4 mm Melanoma: NR Melanoma: 1.4 mm Nodal MUP	- - - -
Current case	2015	M	75	1	↑	Systemic MSTO	None	Neutrophylic Leucocytosis	Prior MSTO (16 years)	Melanoma: 3.5 mm with 2 nodal metastases	-

F: female; M: male; NR: non reported; NA: not applicable; MSTO: mastocytosis; CM: cutaneous mastocytosis; NP: not provided; MUP: melanoma with unknown primary; CNMLD: clonal hematologic non-mast cell lineage disorder; Same sample: the melanocytic lesion and the mast cell disorder were in the same tissue sample;↔: normal range; ↑: means high levels

DISCUSSION

The clinical observation of a patient who developed three different cancers, one of them derived from mastocytes (systemic mastocytosis), stimulated us to review the literature, focusing on the role of mast cells in different hematologic and non-hematologic diseases.

Mast-cell diseases and hematological alterations

In about 40% of cases, systemic mastocytosis is associated with other hematologic non-mast cells-related disorders (2,3). However, sporadic data on neutrophilic leukocytosis as prodromal onset of a systemic mastocytosis have been reported (1). Few reports are available on the pathogenetic role of some chemokines and their receptors, which could be involved in various clinical forms of mastocytosis (4). In 2006, Homey *et al.* analyzed the role of CCL1, CCL2, CCL3, CCl4, CCL5 (RANTES), and CXCL8 (IL-8) obtained from HMC-1 line mast cells (Figure 3) In this study, the authors specifically highlighted how the chemokine CCL2 differs from the others, as its expression can be significantly inhibited with glucocorticoid therapy (5). Other chemokines (belonging to the CCL family and MIP-1α) are responsible for the recruitment of neutrophils in several tissues (including the skin), increasing the inflammatory process without inducing a neutrophil

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proliferation (Figure 3). Moreover, it has been demonstrated that the activated mast cells can release GM-CSF (6), which is the pivotal growth factor required for neutrophil expansion (Figure 3). Based on these data, it can be assumed that a subset of activated mast cells produces GM-CSF (primarily responsible for the neutrophilia) and chemokines of the CCL family in systemic mastocytosis, which are responsible for the recruitment of neutrophils in the skin lesions (in case of cutaneous involvement). Our observations suggest that a neutrophil leukocytosis can in some cases hide an underlying rare disease.

Mast-cell diseases and benign/malignant melanocytic neoplasms

Although MM and mastocytosis arise from two different cell types, the occurrence of mastocytosis and MM in the same patient might suggests a relationship between the two disorders (Figure 3). Indeed, a Swedish paper has reported a higher risk of MM in patients with mastocytosis compared with the general population (5.0% vs 1.2-1.6%) (7).

Since 1979, a total of 13 patients (9 cases of MM and 4 cases of benign melanocytic lesions) with mast cell diseases and melanocytic lesions, both benign and malignant, have been reported in the literature (7-15). With regard to MM (median thickness: 1.02 mm, range: 0.4-5.6 mm) the diagnosis of MM and mastocytosis was synchronous in 1 case, while a diagnosis of mastocytosis preceded the one of MM in 4 cases, and was metachronous in the other 4 cases. Additionally, as reported in the Table 1, in 5 cases (38%) the benign/malignant melanocytic lesions were in the same tissue sample of a mast cell proliferation, presenting as combined tumors, further confirming an underlying interdependence between these two cell lineages. In fact, the release of chemokines, stem cell factors and histamine (*via* the histamine-2 (H2) receptor) by mast cells supports the proliferation of melanocytes (Figure 3). In this regard, it is known that both melanocytes and mastocytes express two transcription factors (MITF and STAT3), and that melanocytes are dependent on KIT and its ligand (stem cell factor (SCF)) for their growth and development (7,8,16). Other important cytokines – such as interleukin (IL)-6, IL-8, basic fibroblast growth factor (bFGF), and nerve growth factor (NGF) – are involved in the common pathway of both of these different cellular lines (13). Finally, it is known that some treatments, e.g. 311 nm ultraviolet B (UVB= and psoralen and ultraviolet A (PUVA), usually used for cutaneous mastocytosis, may increase the relative risk of developing MM (7,13).

Recently, Siiskonen *et al.* reported that the number of tryptase$^+$ and chymase$^+$ mast cells is lower in deeply invasive melanomas compared with in-situ melanomas and dysplastic nevi; moreover, a low number of the tryptase$^+$ mast cells is associated with a poor survival both in deeply invasive melanomas and in superficially invasive melanomas at an advanced stage (17). The authors suggest that the serine proteinases (tryptase and chymase) may inhibit the melanoma growth. However, the authors did not find any significant correlation between the number of the tryptase$^+$ mast cells and the most important clinic-pathologic features (age, sex, Breslow, ulceration, mitoses, microsatellites, tumor-infiltrating lymphocytes, regression, growth phase, cell type, lymphovascular and/or perineural invasion, and horizontal tumor diameter) (17).

In summary, while some papers emphasize that the infiltration of mast cells in the primary melanoma is associated with a better prognosis (17-20), other ones show that the infiltration of mast cells is associated with invasive melanoma and neo-vascularization, favoring the tumor growth (21-23). In this regard, since there are currently conflicting data and considering the versatility of mast cells (17,18), further studies will be needed to better define the pivotal role of the mast cells in the etio-pathogenesis of MM.

Mast-cell diseases and pancreatic cancer

Since Paul Ehrich discovered the important role of mastocytes in the immune system of the vertebrate in the late 1800's, several other functions have been identified for these cells (24), such as their role in the gastrointestinal system where they are involved both in inflammatory diseases and in the development of malignancies.

Regarding pancreatic cancer, it has been shown that a mast cell infiltration in the tumor is associated with a higher tumor grade and cancer cell migration (Figure 3), proliferation, and invasion, with a consequent decrease in the survival of these patients (24-26).

Histologically, mast cells are contained in the tumor stroma, but not connected with the malignant pancreatic cells (26). Comparable findings were also detected in MM, where the mast cell infiltration was peri-tumoral and not in connection with the melanoma cells (13). However, in a recent paper, Giuşcă *et al.* found that (regarding liver metastases from different neoplasms) intra-tumor mast cells were significantly correlated with tumor grade and nodal status, while peri-tumoral mast cells were significantly correlated with overall survival (27). Accordingly, it can be assumed that the mast cells influence the tumor cells

via cytokine signals. This hypothesis could be also confirmed by the presence of elevated serum tryptase activity in patients with a diagnosis of pancreatic cell carcinoma (26). Similarly, serum tryptase levels correlate with the density of tryptase$^+$ mast cells and the microvascular density in breast cancer before radical surgery, corroborating the pro-tumoral effects of mast cells in angiogenesis promotion (28). In this regard, serum tryptase activity could be an important biomarker in the monitoring of patients with pancreatic cancer as well as those with other malignancies (26,27).

Melanoma and pancreatic cancer

The association of MM and pancreatic carcinoma is characterized by an increased frequency of CDKN2A mutations in both malignancies (29). However, Fidalgo *et al.* did not find CDKN2A mutations in three patients (with both MM and pancreatic carcinoma), but rather identified two rare gene mutations (a 616 kb duplication at 2p12 encompassing the CTNNA2 and MIR4264 genes and a 368 kb duplication at 5q35.3 containing the GRM6, ADAMTS2, ZNF879, and ZNF354C genes), widening the spectrum of connections between the two malignancies (24). Finally, in a very recent report, Heestand *et al.* identified BRAF and KRAS mutations in patients with pancreatic carcinoma, suggesting their pivotal role in the pathogenetic mechanism of this malignancy (29) (Figure 3).

The encoded KIT protein is a transmembrane protein belonging to the family of type III receptors, tyrosine kinases, and plays an important role in the development of hematopoietic stem cells, mast cells, melanocytes, germ cells, and interstitial cells of Cajal (30). The role of KIT signaling in melanocyte biology has been extensively studied, and the regulation of the KIT pathway is complex, depending on multiple cellular factors (31,32). Currently, genetic mutations of KIT have been detected in mucosal (39%) and acral (36%) melanomas and in skin with sun-induced damage (28%) (32), but not in the less-investigated pancreatic cancer.

It has been demonstrated that KIT protein is involved in mediating differentiation and proliferation of pancreatic islets during fetal pancreatic development (33); however, no conclusive data on the role of KIT in the development of pancreatic ductal adenocarcinoma are available (34). Amsterdam *et al.* demonstrated that KIT expression is negative in the pancreatic cells of healthy adults, whereas it becomes positive in the cancerous pancreatic cells (35). These results suggest mutational events which lead to the malignant transformation of pancreatic cells.

CONCLUSION

As suggested by the literature data, mast cells can modulate different normal and abnormal cells via cytokine signals. Mastocytes seem to have a pivotal role in several malignancies (such as in melanoma and pancreatic cancer) and serum tryptase levels could be an important prognostic factor. Moreover, different chemokines, mitogenic factors, chemical mediators of the inflammation, and specific gene mutations could explain the association between mastocytosis and other hematologic and non-hematologic disorders.

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