



(CASE REPORT)



Place of cytology in the diagnosis of systemic mastocytosis: A case report

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GSC Advanced Research and Reviews, 2021, 07(02), 001-005

Publication history: Received on 23 March 2021; revised on 29 April 2021; accepted on 03 May 2021

Article DOI: <https://doi.org/10.30574/gscarr.2021.7.2.0096>

Abstract

Mastocytosis is a heterogeneous group of rare diseases related to the clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells, that accumulate in one or more organ systems. Their pathophysiology is dominated by activating mutations in C-Kit (Stem Cell Factor receptor). Several pathological forms have been described ranging from isolated cutaneous mastocytosis affecting mainly children, to aggressive systemic mastocytosis described mainly in adults with bone marrow involvement. According to the WHO 2016 classification of hematological malignancies, systemic mastocytosis appear as a new entity of "myeloid neoplasms and acute leukemias" that combines cytology (abnormal mast cells) with other genetic and molecular criteria. We describe through this observation the practical side of hematological cytology in the diagnostic orientation of this serious, rare and underestimated pathology.

Keywords: Systemic mastocytosis; WHO; Myeloid neoplasms; Acute leukemias; C-Kit mutation

1. Introduction

Systemic mastocytosis is defined by the involvement of one or more extracutaneous organs (mainly bone marrow, gastrointestinal tract, bone, liver, spleen, lymph nodes, etc.) [1]. they constitute about 10% of mastocytosis (all forms combined) and are more frequent in adults than in children. Clinically, systemic mastocytosis can be revealed by allergic skin manifestations (pruritus, urticaria, angioedema), cardiovascular manifestations (vascular collapse, anaphylactic shock, etc.) [2], mainly due to the pro-inflammatory mediators released by mast cells [3], gastrointestinal disorders (abdominal pain, diarrhea, nausea, etc.) [4], hematological disorders (hepatosplenomegaly, lymph node and bone marrow involvement) [2], and more rarely, bone and neuropsychiatric disorders.

The biological tests required for the diagnosis of mastocytosis are based on the diagnostic criteria of the pathology described by the WHO in 2016 [5]. In our current practice and through this clinical case, cytology based on the demonstration of a mast cell infiltrate with at least 25% of dystrophic forms guides the diagnosis and proves to be of crucial help.

2. Case presentation

We report the case of a 2-year-old girl from a non-consanguineous marriage and a monitored pregnancy, born at term by vaginal delivery, who presented a few weeks after birth with a maculopapular lesion on the trunk, whose gentle stroking caused turgor (positive Darier sign). This lesion was suggestive of cutaneous mastocytosis, which was confirmed by histological study. Other similar lesions, on the trunk and limbs, appeared after several months. During the course of the disease, the patient presented an elevated tryptase concentration of 73.2 mmol/l (normal value <6).

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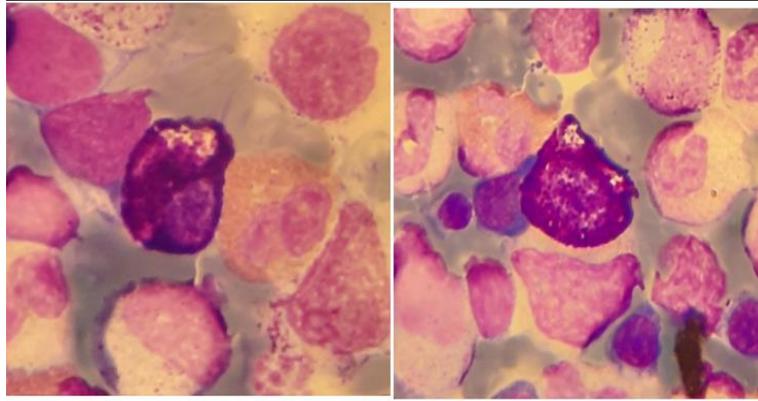


Figure 1 Normal mast cells on BM smear (MGG stain $\times 1000$)

The BM smears was performed in our department and revealed the presence of 13% of mast cells (figure 1 and 2) among all the medullary cells in both MGG (May Grunwald Giemsa) and toluidine blue (figure 3), almost half of which were atypical (spindle-shaped, hypogranulated, metachromatic mast cells) (figure 2), which led to the suggestion of a systemic mast cell disorder.

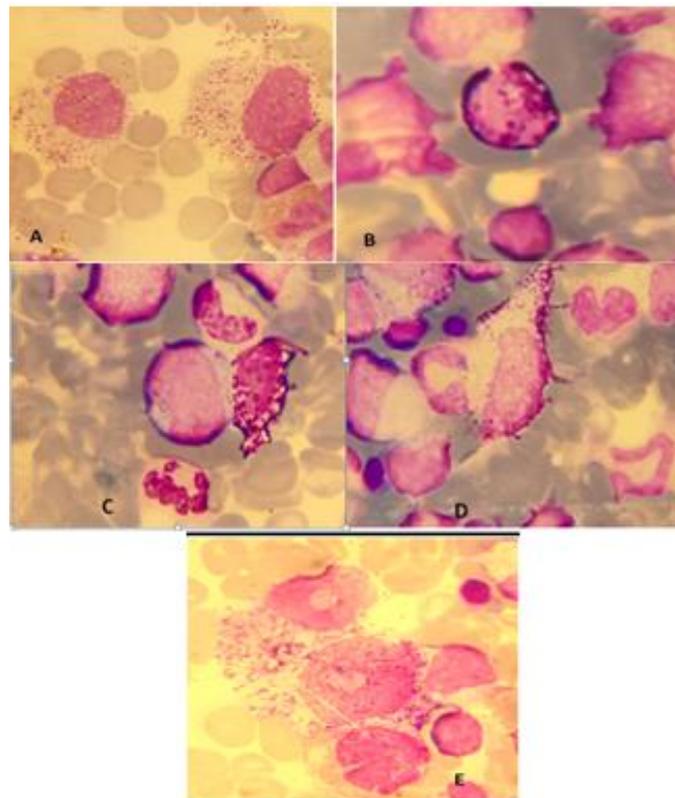


Figure 2 Main cytological aspects of atypical mast cells on BM smear (MGG $\times 1000$)

A. Cytoplasmic hypogranulation: B. Metachromatic mast cell: C. Fusiform mast cell: D. Fusiform mast cell:
E. Promastocyte

The BM biopsies revealed a few days later the presence of an infiltrate of mast cells grouped in clusters on all the cores collected. Due to lack of resources, flow cytometry for mast cell antigenic markers and molecular analysis for c-kit mutation were not performed. However, the diagnosis of systemic mastocytosis was retained according to the WHO 2016 criteria and the girl was put on antihistamine treatment with very favorable evolution.

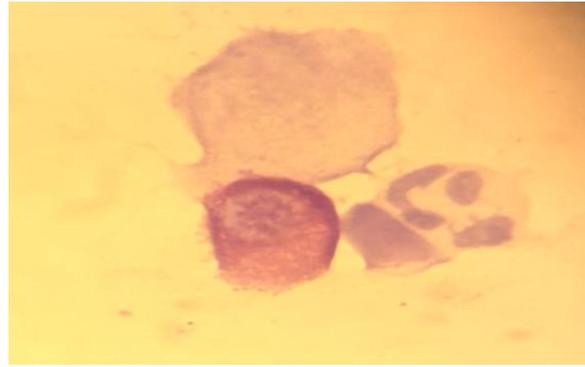


Figure 3 Normal mast cell (toluidine blue ×1000)

3. Results and discussion

Mast cells are cells of innate immunity that appear early in the phylogeny (common ancestor of mast cells and basophiles), characterized by the ability to secrete tryptase [3]. Unlike basophiles, mast cells are located in tissues, with a preference for barriers to the environment; skin, airways, intestinal mucosa. Mast cells derive from hematopoietic precursors of the myeloid lineage [4] and are involved in innate and adaptive immunity through their effector and regulatory actions, with multitude of their function; defense against infectious agents and venoms, antigen presentation, induction and regulation of T cell receptors and reduction of inflammation. [7-9]

Table 1 Updated WHO Classification of Mastocytosis 2016

- Cutaneous mastocytosis (CM)
- Systemic Mastocytosis (SM)
Indolent SM (including BMM)
<ul style="list-style-type: none"> • Smouldering SM • Aggressive SM • SM with an associated hematological neoplasm (SM-AHN or SM-AHNMD) • Mast cell leukemia (MCL)
- Mast Cell Sarcoma (MCS)(MCS)

In the WHO 2016 classification, mastocytosis is one of the entities in the myeloid neoplasia group (Table 1). In WHO 2008, mastocytosis represented one of the 8 subcategories of myeloproliferative neoplasia (MPN) [5]. The diagnosis of mastocytosis is based on a set of clinical, cytological, histological, molecular and phenotypic criteria. Thus according to the WHO 2016 diagnostic criteria for systemic mastocytosis, the diagnosis is confirmed by the combination of the major criterion with a minor criterion or the presence of 3 minor criteria [5]. Cytologically, normal mast cells are medium-sized and highly chromophilic, which allows them to be identified microscopically on a BM smears at low magnification even if they do not exceed 1% of the medullary cells.

On MGG staining, preferably with toluidine blue, the mast cell is a 15 to 25µm cell with a round or spherical mononuclear cell, small nucleocytoplasmic ratio <0.5, central nucleus covered with dense metachromatic granulations stained purple by Giemsa and orange-red by toluidine blue (Figure 3) [10, 11]. In systemic mastocytosis, the most common appearance is the spindle-shaped mast cell, which when found in more than 25% of mast cells, is pathognomonic of the disease. It has an eccentric, oval nucleus and heterogeneous granulations that no longer cover the nucleus (Figure 5). [12]

Table 2 Diagnostic criteria for systemic mastocytosis (WHO 2016)

Major criterion
Multifocal dense mast cell infiltrates (containing ≥ 15 mast cells) in bone marrow or other tissues/organs except the skin
Minor criterion
<p>a. $>25\%$ of mast cells in compact and/or diffuse infiltrates are spindle-shaped and/or immature.</p> <p>b. KIT-D816V or other activating point mutations of KIT.</p> <p>c. Aberrant expression of CD25 (or CD2) by mast cells</p> <p>d. Serum tryptase $>20 \mu\text{g/L}$.</p>

Other cellular atypia can be observed less frequently, especially during aggressive forms such as promastocytes, metachromatic mast cells (Figure 5) or hypogranular mast cells (Figure 6) reminiscent of immature forms of mast cell development. [13] These atypia can be divided into cytoplasmic and nuclear abnormalities. In the cytoplasm ones, they can be the presence of focal hypogranular patches (lacunae) or cytoplasmic vacuoles. In the nucleus, the presence of a prominent nucleolus (promastocyte) or a thin pseudoblastic chromatin can be noticed.

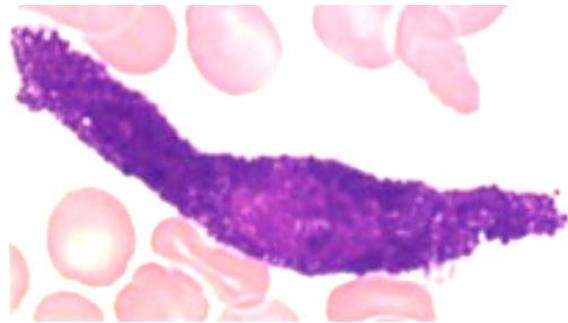


Figure 4 spindle mast cell. [13]

In addition to the qualitative and quantitative analysis of the mast cells, a careful cytological study gives an idea of the cellular abnormalities that may affect the other hematopoietic lineages, thus revealing a possible Hematological Neoplasia Associated with Systemic Mastocytosis (SM-AHN). It will then look for Dyserythropoiesis, dysmegakaryopoiesis, dysgranulopoiesis, eosinophilia or associated lymphoid infiltration. [13]

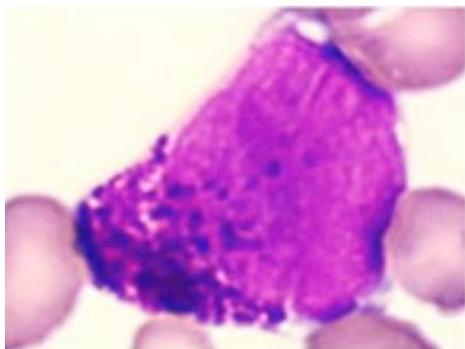


Figure 5 metachromatic blasts [13]

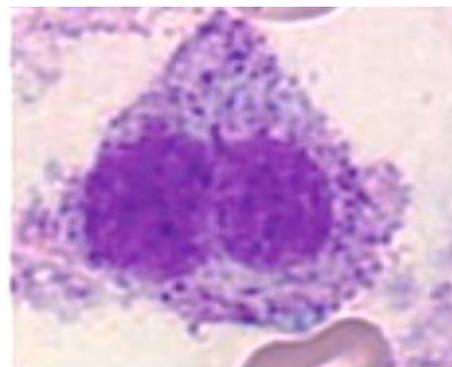


Figure 6 hypogranular mast cell [13]

4. Conclusion

Systemic mastocytosis represents a rare situation. Their clinical suspicion is often difficult. Medullary cytology is a key step in the diagnosis since it highlights mast cell infiltration and the various atypia that may occur in this case. The eye of the cytologist can indeed guide the realization of the various other biological examinations in order to gather the biological criteria established by the WHO to make the diagnosis.

Compliance with ethical standards

Acknowledgments

We thank all the staff of hematology department of Military Hospital Avicenne for excellent support through this investigation.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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