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Mastocytosis onset in a patient with treated hairy cell leukemia: just a coincidence?

Running title: Associated mastocytosis and hairy cell leukemia

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Key words: mastocytosis, hairy-cell leukemia, c-kit mutation, BRAF mutation, purin analogs

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Highlights

• Lymphoproliferative disorders associated to systemic mastocytosis are rare
• We report the second case so far of associated mastocytosis and hairy-cell disease
• $BRAF^{V600E}$ mutation was found in hairy cells and not in mast cells
• $KIT^{D816V}$ mutation was found in mastocytes and not in hairy cells
• The physiopathology of this association is not known
Abstract

Mastocytosis is a mast cell disease caused by functionally defective infiltrating mast cells and CD34+ mast cell precursors. The heterogeneous group of mast cell disorders is categorized into five variants in the updated 2017 World Health Organization (WHO) classification among those systemic mastocytosis with an associated neoplasm (SM-AHN). Except for myeloid neoplasia, lymphoproliferative disorders associated to SM-AHN are more scarce.

Here, we report the second case ever described of associated mastocytosis and hairy-cell disease. A 38-year-old female patient without any specific medical history was diagnosed a hairy cell leukemia and \( \text{BRAF}^{V600E} \) mutation was found in hairy cells. Since purine-analogs were avoided to prevent prolonged myelosuppression, she was treated with vemurafenib and rituximab. Despite early discontinuation due to vemurafenib-induced agranulocytosis, a partial response was observed. Strikingly, bone marrow biopsy performed one month after vemurafenib discontinuation revealed a nodular infiltration by 30% tumoral mastocytes. Along with elevated tryptase level, \( \text{KIT}^{D816V} \) mutation on mastocytes and clinical exam, the patient was diagnosed with systemic mastocytosis with an associated hematological neoplasm (SM-AHN). No \( \text{BRAF}^{V600E} \) mutation was found on mastocytes.

The physiopathology of this association is not known and might be only a coincidence or a common genetic driver mutation enhancing mast and hairy cells.

Words: 199 (<200)
To the editor,

Mastocytosis is a mast cell disease caused by functionally defective infiltrating mast cells (or mastocytes) and CD34+ mast cell precursors\(^1\). Cutaneous mastocytosis is characterized by lesions being macules, papules or nodules that are disseminated over most of the body. Systemic mastocytosis is a heterogeneous group of mast cell disorders that is categorized into five variants in the updated 2017 World Health Organization (WHO) classification\(^2\): indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), systemic mastocytosis with an associated neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and finally mast cell leukemia (MCL). SM-AHN encompasses between 5–40% of cases of SM\(^3,4\). Whereas myeloid neoplasia account for the majority of SM-AHN, associated lymphoproliferative disorders have been described but are more scarce\(^5–7\). Here, we report a case of SM associated with hairy cell leukemia.

A 38-year-old female patient without any specific medical history presented to the hospital with severe pancytopenia and splenomegaly. A diagnosis of hairy cell leukemia (HCL) was assessed by bone marrow aspirate massively infiltrated by lymphoid cells (47%) characterized by cytoplasmic projections (Figure 1A). HCL was confirmed by flow cytometry detection of clonal B-cell population (κ light chain–positive, CD11c+, CD25+, CD103+) and a \(BRAF^{V600E}\) mutation. Because of an ongoing severe genital infection, the depth of pancytopenia and the size of the spleen, purine-analogs were avoided to prevent prolonged myelosuppression. A treatment with rituximab (375 mg/m\(^2\) every two weeks) and vemurafenib (960 mg twice daily) for an expected duration of four months was initiated. During her hospitalization, she presented several skin rashes with diffuse maculopapular lesions, without pruritus, resolving into 7-10 days (Figure 2). Vemurafenib was stopped twenty-four days after initiation because of agranulocytosis confirmed on the bone marrow
smear and toxidermia. A full neutrophil recovery was observed ten days after vemurafenib cessation and after two cycles of rituximab, without hematopoietic growth factors support. A bone marrow biopsy performed one month after aplasia ending showed a good partial response with less than 5% of residual hairy cells. Strikingly, the bone marrow biopsy also revealed a nodular infiltration by 30% tumoral mastocytes with CD117 positivity and aberrant expression of CD25 indicating a systemic mastocytosis (Figure 1D-F). Initial bone marrow smears were reconsidered and few dystrophic mastocytes were effectively visualized (Figure 1B-C). Skin biopsies did not show an excess of mast cells in the dermis. The tryptase level was increased at 32 µg/L (Normal < 13 µg/L). A D816V c-kit mutation was found on bone marrow with RNA-sequencing. A retrospective physical exam revealed no neuropsychic symptoms, no fainting or significant loss of consciousness, no digestive or urinary symptoms, no food intolerance. However, the patient complained about chronic rhinitis, daily episodes of pruritus, flushes and dizziness triggered by the shower as well as temperature change and stress. Hence, the patient was diagnosed with systemic mastocytosis with an associated hematological neoplasm (SM-AHN). She had no SM-related C symptoms at the time of diagnosis (inaugural cytopenia were related to HCL since a normalization of blood cells counts was observed after HCL treatment) and physical examination revealed no ascites, telangiectasia, lymphadenopathies, pigmented or dermographic urticaria. Clinically, the splenomegaly decreased from 27 cm to 15 cm one month after vemurafenib cessation as assessed by echographic imaging. The staging work-up did not show hepatomegaly, lymphadenopathy or bone lesions. Six months after vemurafenib treatment, bone marrow aspiration showed normal richness with rare hairy cells and dystrophic mastocytes, blood cells count was normal, whereas splenomegaly was still present. MRD assessment by flow cytometry found residual hairy cells (1.4%) and very
few abnormal mastocytes (0.05%) among total leukocytes. The patient remained under active surveillance without specific treatment.

To the best of our knowledge this is the second case ever described of associated mastocytosis and hairy-cell leukemia, the first being described in 1997 in a 69 old patient in partial remission of both diseases after interferon treatment. Here, the diagnosis of mastocytosis was done in a second time, on a control bone marrow biopsy after HCL treatment. Actually, massive HCL infiltration at diagnosis hampered an easily observation of dystrophic mast cells and no bone marrow biopsy was performed at diagnosis. This finding could retrospectively explain the numerous skin rashes that the patient presented during her hospitalization, not as a cutaneous mastocytosis *per se*, but maybe as a promoting factor through the release of mast cells mediators such as histamine. In our patient an unrevealed mast cell disorder may have contributed to the high level of drug hypersensitivity observed as it has been suggested in the past. The time of onset of either mastocytosis or HCL is not known since the patient had no previous medical history.

Detection of a c-kit point mutation, mostly D816V, in blood, bone marrow, or other lesioned tissue is one minor criteria for mastocytosis diagnosis. *KIT* codon 816 mutations are variably present in SM-AHN patients depending on the subtype of AHN. Sotlar et al. reported the lack of *KIT*\textsuperscript{D816V} mutation in eight patients with lymphoproliferative AHNs. Moreover, the low sensitivity of conventional Sanger sequencing method (variant allele frequency (VAF) around 10%) may result in false-negative cases because of low level mast cell infiltrate and consequently VAF often below 1\%. Interestingly, only RNA-sequencing with a sensibility of 0.1% allowed detection of D816V c-kit mutation in this patient (with negative results in Sanger method and or Next Generation sequencing).
Because the RAF/RAS/ERK/MAPK pathway is a component of downstream signal of c-kit, we tried to assess if *BRAF*<sub>V600E</sub> mutation was also present in mast cells, but couldn’t find once again such a mutation on mast cells but only on hairy cells. This finding is in agreement with a retrospective cohort of 36 subjects with systemic mastocytosis in whom no *BRAF*<sub>V600E</sub> mutations were found<sup>12</sup>.

Mastocytosis treatment results in the combination of symptomatic treatments such as antihistamines block receptors, β-2 agonists or corticosteroids with cytoreductive therapy in cases of aggressive systemic mastocytosis<sup>1</sup>. Cytoreductive drugs that can be used are α-interferon<sup>13</sup>, cladribine<sup>14</sup> or more recently the c-kit tyrosine kinase inhibitors midostaurin<sup>15</sup> or masatinib<sup>16</sup>.

Concerning HCL, cladribine and pentostatin are the two most common first-line treatments both causing prolonged immunosuppression. Around 85% of patients achieve a complete response with either cladribine or pentostatin<sup>17</sup>. A recently proposed second-line treatment for refractory/relapsing HCLs is the combination of an anti-CD20 antibody combined with vemurafenib, an oral BRAF kinase inhibitor<sup>18,19</sup>. In this case, this combination was retained as a first-line treatment to avoid prolonged myelosuppression, considering the severe genital infection at diagnosis. Despite early discontinuation due to vemurafenib-induced agranulocytosis, a partial HCL response was obtained after only two cycles of rituximab and three weeks of vemurafenib. Clinical trials are currently ongoing for first line administration of vemurafenib combined with anti-CD20 immunotherapy. Recently, this combination was also successfully used in three patients presenting severe infections and pancytopenia at diagnosis<sup>20</sup>.

Interestingly, in HCL patients treated with vemurafenib and anti-CD20 antibody, a reversion of symptomatic splenomegaly usually occurs within 2 weeks<sup>18</sup>. Therefore, in our
case, initial splenomegaly was probably due to both mastocytosis and HCL, since only a partial response on the spleen was observed 6 months after HCL treatment completion, whereas in the meantime no hairy cells were cytologically present in the bone marrow.

To conclude, this is the second case ever described to our knowledge of mastocytosis and hairy-cell leukemia in the same patient. The physiopathology of this association is not known and might be only a coincidence or a common genetic driver mutation enhancing mast and hairy cells. Interestingly, purine analog is a feasible treatment in both HCL and SM and can be an attractive therapeutic option if clinical situation finds it necessary for one or both diseases.
References


Figure legends

Figure 1: Bone marrow smear and biopsy of the patient. A: Bone marrow aspiration at diagnosis with lymphoid cells (47%) characterized by cytoplasmic projections (hairy cells). B-C: Increased dystrophic mast cells (spindle-shaped and hypogranulated) on bone marrow aspiration (May-Grünwald-Giemsa staining, original magnification x500). D: Bone marrow biopsy after HCL treatment with multifocal dense mast cell infiltrates (>15 mast cells in aggregates) with CD117 positivity (E) and aberrant expression of CD25 (F). (May-Grünwald-Giemsa staining and immunohistochemical staining, x100).

Figure 2: Maculopapular rash presented by the patient during HCL treatment that was attributed to multiple drugs allergies facilitated by the release of mast cells mediator in this patient with concomitant unrevealed systemic mastocytosis. A: head, B: back, C: torso and neck, D: anterior face of the legs, E: abdomen, F: posterior face of the legs.
Figures

Figure 1.
Figure 2.