## Case Report Systemic mastocytosis in association with chronic lymphocytic leukemia and plasma cell myeloma

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**Abstract:** Systemic mastocytosis with associated clonal haematological non-mast cell lineage disease (SM-AHNMD) is a heterogeous group of mast cell disorders with different clinical, pathologic and underlying molecular characteristics. While myelomonocytic/myeloid neoplasia overwhelmingly predominates the AHNMD component, lymphoproliferative disorders rarely occur as an AHNMD component of SM-AHNMD. Here we report two cases of SM-AHNMD, in which the AHNMD component is chronic lymphocytic leukemia in one case, and concurrent chronic lymphocytic leukemia as well as plasma cell myeloma in another case. To the best of our knowledge, this is the first case report of SM-AHNMD with chronic lymphocytic leukemia and plasma cell dyscrasia simultaneously.

Keywords: Chronic lymphocytic leukemia, systemic mastocytosis, systemic mastocytosis with associated clonal haematological non-mast cell lineage disease

#### Introduction

Mastocytosis is a clonal mast cell disease derived from bone marrow hematopoietic progenitor cells (HPC) that manifest with an unusually broad spectrum of clinical and morphologic appearance [1]. Systemic mastocytosis (SM), a major subtype of mastocytosis according to the current WHO classification [2], is a heterogeneous group of mast cell disorders involving at least one extracutaneous organ, with or without evidence of skin infiltration. Due to its bone marrow origin, it is not surprising that bone marrow is the most commonly involved extracutaneous site; therefore, bone marrow aspiration and biopsy are commonly employed to establish the diagnosis of mast cell disorders.

SM with <u>a</u>ssociated clonal <u>h</u>ematological <u>n</u>on-<u>m</u>ast cell lineage <u>d</u>isease (SM-AHNMD) is the second most common subtype of SM after indolent SM (ISM) [3, 4]. While associated myeloid/ myelomonocytic neoplasia in SM-AHNMD accounts for 82%-90% of SM-AHNMD [3-5], associated lymphoproliferative disorders (LPD) in SM -AHNMD are rare. For example, lymphoid neoplasia only consists of 11% of SM-AHNMD in the largest cohort of SM-AHNMD studied so far [5]. In their study of 138 SM-AHNMD, Pardanani et al found 7 patients (5.1%), 5 patients (3.6%) and 2 patients (1.5%) had lymphoma, plasma cell myeloma (PCM), and chronic lymphocytic leukemia (CLL) as a component of SM-AHNMD, respectively [5]; however, SM in association with simultaneous CLL and PCM, to the best of our knowledge, has not been reported in the literature. In the present study, we report two patients with SM-AHNMD, one SM-AHNMD patient has an associated CLL, and the other patient has associated concurrent CLL and PCM.

#### Cases report

#### Clinical history

Case #1 is a 56-year-old female with a history of

CLL diagnosed in June 2001. However, she was not treated until progression with bulky lymphadenopathy in November 2004. Since then she had undergone extensive treatment with no complete and sustainable remission ever achieved. Her treatment regimens included fludarabine monophosphate (Fludara), rituximab, methylprednisolone, alumtuzuman (Campath), and multiple other agents such as anti-CD40 antibody, the BCL-2 antagonist AT-101, and adenovirus ISF35 intra-nodal therapy.

A marrow biopsy in 2006 revealed she had SM with CLL cells comprising 20% of total cellularity; therefore, a SM-AHNMD was diagnosed in this patient. Subsequently, the patient received three cycles of bendamustine and rituximab. which ended in May 2009, and achieved a partial response with residual disease as demonstrated in a follow-up (see below for more details). Two and half months after the diagnosis of SM-AHNMD, she underwent matched unrelated donor (MUD) allogeneic hematopoietic stem cell transplantation using a conditioning regimen containing fludarabine, cyclophosphamide, and rituximab (FCR). Two follow-up marrow biopsies showed no morphologic or immunophenotypic evidence of residual CLL. However, SM persisted. Her total serum mast cell tryptase is 10.3 ng/ml (normal range: 0.4-10.9 ng/ml). The patient has not come to the clinic since November 2009.

Case #2 is a 57-year-old white female, who had a monoclonal gammopathy of undetermined significance (MGUS) prior to her CLL diagnosed at an outside institution in February 2003. She had an IgG kappa paraprotein with no urinary light chain and normal renal function. She was seen at our institution in October 2008 and was assessed as having stage I CLL. Her CLL progressed to stage II disease in August 2009. Her marrow biopsy at that time revealed CLL and PCM in addition to SM (see below); hence a SM with concurrent CLL and PCM was diagnosed. Approximately 3 months after the above diagnosis, she was treated with lenaidomide and rituximab on a clinical trial. The patient's significant past medical history includes multiple skin rashes over the extremities. Her relevant laboratory findings include a total serum mast cell tryptase of 21.4 ng/ml (normal range: 0.4-10.9 ng/ml). Review of the outside slides obtained in February 2010 revealed persistent SM, residual CLL and PCM.

#### Histocytomorphology

Marrow aspirate smears were stained with Wright-Giemsa according to the standard operating procedures. Marrow biopsies are stained with Hematoxylin and Eosin (H&E) after fixation in acid zinc formalin and decalcification. A marrow clot section was stained with H&E after fixation with 10% neutral formalin.

#### Flow cytometry

Single cell suspension from marrow aspirates was stained with the following fluorochromeconjugated surface and intracellular antibodies: CD5, CD10, CD13, CD14, CD19, CD20, CD23, CD33, CD38, CD45, CD138, FMC-7, surface kappa, surface lambda, intracellular kappa, and intracellular lambda. A tube containing CD25-FITC/ CD2-PE/CD45-PerCP/CD117-APC was added for both patients. After staining, the cells were analyzed by FACSCaliber (Becton Dickinson, San Jose, CA). Data were acquired using CELL-Quest software (Becton Dickinson) and analyzed using Paint-A-Gate software (Becton Dickinson).

#### Immunohistochemistry

Immunohistochemistry was performed on either marrow core biopsy or clot section. The following antibodies were used: CD2 (1:40 dilution) (Novocastra through Leica Microsystems, Bannockburn, IL), CD25 (1:20 dilution) (Novocastra through Leica Microsystem), CD117 (1:150) (Dako, Dakoctomation, Carointeria, CA), CD138 (1:60) (abD Serotec, Raleigh, NC), kappa (1:500) (Biocare Medical, Concord, CA), lambda (1:35) (Biocare Medical), or mast cell tryptase (1:600) (Dako). Staining for CD2 and CD25 were performed using a BioTek Solutions Tech-Mate 1000 automated immunostainer (Ventana Medical Systems, Tucson, AZ) using the Dako horseradish Envision + peroxidase/ diaminobenidine detection system (Dako). The remaining stains were performed on Dako Autostainer using Envision (+) Detection Kit (Dako). Microwave antigen retrieval was employed for all antibodies.

# Molecular cytogenetics by fluorescence in situ hybridization (FISH)

FISH on interphase preparation was performed on marrow aspirate using the following probes:



Figure 1. (See Figure Legends in next page)

**Figure 1.** Morphologic and immunohistochemical features of SM-AHNMD (case #1). A & B. Bone marrow biopsy showed one of several nodular lymphoid infiltrate (A) composed of small mature lymphocytes with round nuclear contours, coarse chromatin, absent to small nucleoli (B). Of note, there are no spindle cells present. (A. H&E, original magnification 100x; B. H&E, original magnification 400x). C & D. One of the granulomatous nodules present in the bone marrow core biopsy. At the center of the nodule are numerous haphazardly arranged spindle cells admixed with scattered eosinophils surrounded by small mature benign-appearing lymphoid cells (C). These spindled cells have abundant weak eosinophilic cytoplasm with sparse granules, reminiscent of degranulated abnormal mast cells (C. H&E, original magnification 200x; D. H&E, original magnification 400x). E & F. These spindle cells are strongly positive for CD117 (E) and tryptase (F) (E & F: original magnification 400x). G: Scattered (lower part) and a single (right upper corner) CD25(+) mast cells are present (original magnification 400x).

dual color dual fusion LSI CCND1/IgH (11q13;14q32) probe set, ATM(11q22.3), D12Z3(12 centromere), D13S319(13q14.3), LAMP1(13q34), p53(17p13.1). All probes were purchased from Abbott Molecular (Des Plaines, IL), and each probe set was scored on 200 interphase nuclei.

#### Mutational analysis of C-Kit

Bone marrow aspirates were evaluated for an activating point mutation, resulted from a change of aspartic acid (D) to valine (V) at codon 816 (D816V) in the kinase domain of ckit using polymerase chain reaction (PCR). Briefly stated, DNA was isolated and subjected to allele-specific PCR amplification using an oligonucleotide primer set specific for the exon 17 of c-kit, and an allele-specific primer that specifically initiates amplification from the allele containing the point mutation in codon 816. Each assay included a positive control reaction using DNA from a plasmid that contains the c-kit D816V mutation and a negative control using placental DNA. PCR products were analyzed by electrophoresis and UV transillumination of ethidium bromide stained gel.

## Results

## Morphologic findings

Case #1 has had 11 bone marrow biopsies at our institution since April 2005. Nodular lymphoid infiltrate accounting for approximately 20% of total cellularity was present in the first marrow biopsy (**Figure 1A & B**). The lymphoid infiltrate was composed of small matureappearing lymphocytes with round nuclear contours, coarse chromatin, absent to small nucleoli, consistent with CLL. However, mast cells were not present until the 4<sup>th</sup> marrow biopsy, which was performed in May 2006. As shown in Figure 1 C & D, there was a "granulomatous" infiltrate in the marrow biopsy. These granulomatous infiltrates were composed of clusters of haphazardly arranged spindle-shaped cells in the center admixed with scattered eosinophils surrounded by small benign-looking lymphocytes and rare plasma cells (Figure 1C) at the periphery. At higher magnification, these spindle cells had abundant slightly eosinophilic cytoplasm with sparse small granules (Figure 1D). Targeted immunohistochemistry revealed these spindle cells are strongly positive for CD117 (Figure 1E) and mast cell tryptase (Figure 1F), diagnostic of mast cells. These mast cells are also positive for CD25 (Figure 1G), but negative for CD2 (data not shown). Based on the constellation of spindled cell shape, immunophenotypic aberrancy, number of mast cells in a cluster (>15 cells), and history of CLL, a diagnosis of SM-AHNMD was made. While the subsequent 7 bone marrow biopsies showed fluctuation of CLL, the mast cell disease persisted.

Case #2 has only two marrow biopsies at our institution. Frequent plasma cells and small lymphoid cells were easily appreciated on the first marrow aspirate (Figure 2A). Of note, scattered spindle shaped sparsely granulated mast cells were occasionally spotted (arrow in Figure 1A). While there were no sheets of plasma cells, plasma cells infiltrated the marrow in an interstitial pattern (Figure 2B) and accounted for approximately 20% of the total cellularity by CD138 staining (Figure 2C). These plasma cells were positive for kappa (Figure 2D), but negative for lambda (Figure 2E) light chain expression. In addition, several lymphoid nodules (Figure 2F) composed of small mature lymphocytes with similar morphologic features to those described in case #1 were present, consistent with a marrow involvement with CLL. Due to the presence of scattered atypical mast cells, we opted to perform CD117 and mast cell tryptase



Figure 2. See Figure Legends in next page.

#### CLL and systemic mastocytosis

**Figure 2.** Morphologic and immunohistochemical features of SM-AHNMD (case #2). A. Bone marrow aspirate smear showed scattered plasma cells, small lymphoid cells and rare spindled mast cell (arrow) with sparse granules (Wright-Giemsa, original magnification 500x). B & C. Frequent plasma cells distributed in an interstitial pattern (B) and accounted for ~20% of total cellularity based on CD138(C) (B. H&E, original magnification 400x. C. original magnification 200x). D & E. These plasma cells were positive for kappa- (D) but negative for lambda- (E) light chain immunoglobulin (D & E. original magnification 400x). F. A nodular lymphoid infiltrate composed of small mature lymphocytes with morphologic features consistent with CLL (H&E, original magnification 400x). G & H. CD117- (G) and mast cell tryptase- (H) positive mast cells are located at the periphery of the nodular lymphoid infiltrate (G & H. original magnification 400x). I. Rare spindle cells are positive for CD25 (original magnification 400x).



**Figure 3.** Immunophenotypic features of neoplastic cells by flow cytometry. A. Forward and side scatter properties showed the red cell population is within the lymphoid gate. B-E. Compared to normal small mature B-cells (blue) (B & D) and T-cells (green) (B), the neoplastic cells (red) are positive for CD5 (B), CD19 (B, C, E), CD20(dim) (D), CD23 (D), but negative for CD10 (C) and FMC-7 (E). F. The neoplastic B-cells are surface lambda immunoglobulin restricted compared to small mature polytypic B-cells (blue).

immunostains. As shown in Figure 2G and H, clusters of CD117- (G) and mast cell tryptase-(H) positive mast cells were highlighted at the peripheral of CLL nodules. Scattered spindled mast cells are also positive for CD25 (**Figure 2I**). CD2 immunohistochemistry was performed on the marrow core biopsy, unfortunately, the area containing mast cell infiltrate was cut through, and therefore, the mast cells could not be assessed for CD2 immunopositivity (date not shown).

## Flow cytometry

The CLL cells from both patients exhibited similar immunophenotype as demonstrated in Figure 3. Compared to normal small mature T cells (population in green) (Figure 3B) or B cells (population in blue) (Figure 3B, D, and F), the neoplastic B cells (populations in red) were dim positive for CD5 (B), CD19(B, C, E), and CD20 (D), positive for CD23(D), and dim positive for surface lambda immunoglobulin light chain (F), but negative for CD10 (C), FMC-7 (E), and kappa (F). A tube containing the combination of anti-CD25/CD2/CD45/CD117 antibodies was added to the marrow aspirate from both patients, but no mast cells were detected. Monoclonal plasma cells were not detected by flow cytometry in the second patient's marrow aspirate.

#### Molecular cytogenetics

A monoallelic deletion at 13q14.3 locus was found in 14.9% of the cells examined from the forth marrow aspirate of case #1. Biallelic and monoallelic deletion at this locus was found in 17% and 30% of cells examined, respectively, from the marrow aspirate specimen of case #2.

## D816V activating point mutation by PCR

No D816V was found in either of the patients.

## Discussion

We report two cases of SM-AHNMD, one in association with CLL, the other in association with concurrent CLL and PCM. Together with the reported cases of SM with CLL, it appears that CLL as AHNMD component is a rare but recurrent phenomenon, requiring awareness to make the correct diagnosis. In particular, SM should be within the differential diagnosis when dealing with "granulomatous" infiltration composed of spindled cells in CLL cases. Our second case is the first case report of SM in a patient with concurrent CLL and PCM.

Increased numbers of mast cells have been reported in LPD (6) and reactive conditions; however, SM-AHNMD can only be made if diagnostic criteria are met as outlined by the recent WHO classification [2]. Notably, the MC from our two cases displayed aberrancies at several levels: (1) morphologically, MCs were spindled shape with less granules, and they formed clusters with more than 15 cells; (2) Immunophenotypically, these mast cells exhibited CD25 positivity, which is the hallmark of atypical MCs, and is always absent in normal or reactive mast cells [7].

C-Kit D816V activating point mutation at the kinase domain has been extensively studied in various forms of SM-AHNMD. While almost all (93%) of adult patients with indolent and aggressive forms of SM show the presence of D816V, only 29% of patients with welldifferentiated SM harbor such mutation [8]. Pardanani A and colleagues further pointed out that D816V mutation is significantly associated with advanced age, an aggressive clinical course, increased bone marrow mast cell content, and chronic myelomonocytic leukemia [9]. However, the c-kit D816V mutation was not detected in all 8 patients of SM-AHNMD with LPD as AHNMD component in AHNMD cells including 1 case of SM-B-CLL, 1 case of B-lymphoblastic leukemia, 1 case of hairy cell leukemia, 2 cases of MGUS, and 3 cases of PCM [10].

MCs are derived from CD34+/kit<sup>+</sup> pluripotent HPCs in the marrow [11], and studies have shown that the kit mutation was detected in CD34(+) hematopoietic cells in approximately one-third of patients with mutated MCs [8]. The c-kit mutational status in CD34(+) HPCs from our two cases is not known, since we did not fractionate this population; however, based on the negative c-kit mutation from our unfractionateded whole marrow cells, we postulate a negative c-kit mutation in the CD34(+) HPCs, although a false negative result cannot be completely ruled out due to under amplification of DNA from this minute population.

While the high frequency of c-kit D816V mutation among MCs and leukemic myelomonocytic

No. of	Occurance of CLL	CD25/CD2	D816V in unfracti-	D816V	D816V	D816V in	Ref
case(s)	in relationship	on MC	onated marrow cells	in MC	in CLL	CD34(+)	
	to SM					HPC	
1	SM first, then CLL with long latency	P/N	Р	P*	Ν	Р	18
1	Simultaneous	P/P	Ν	ND	ND	ND	19
1	SM first, then CLL	P/P	ND	Р	Ν	ND	20
1	SM was 10 years earlier than CLL	P/P	ND	ND	ND	ND	17
1	Not known	Not known	ND	Р	Ν	Р	8
1	Not known	P/not known	ND	Р	Ν	ND	10
2	Not known	Not known	Not known	Not known	Not known	Not known	5

Table 1. Summary of reported cases of SM-CLL

\*D816V was not done on sorted MC; however, since this case has a lot of mast cells and the unfractionated population is positive for D816V, it is reasonably to assume D816V is also positive in MC. MC-mast cells; HPC-hematopoietic progenitor cells; Ref-references; P-positive; N-negative; ND-not done.

cells (SM-CMML) may point to a common precursor in these patients [10], studies of D816V in SM-CLL do not support such a conclusion. For example, among 4 cases of SM-CLL in which the D816V is present in the MC component, the CLL AHNMD component lacks such mutation [10].

All LPD associated with SM thus far are of B-cell origin, with SM-PCM being the most common [10, 12-15], followed by SM-MGUS [10, 16]. The association between CLL and SM in SM-AHNMD is rare, accounting for only 1.45% of 138 SM-AHNMD cases studied so far [5]. However, it is becoming increasingly recognized since the first case report in 2001 [17]. English literature review has revealed, up to present, 8 reported cases of SM in association with CLL [5, 8, 10, 17-20] (Table 1). Among these 8 reported SM-CLL cases, 4 cases are described as a single case report [17-20]. Together with our current 2 cases, like its myeloid counterparts [2], CLL can develop before, simultaneously with, or after SM. Retrospectively, the so-called "superficial dermatitis" as alleged by outside institution on our case #2 may have been due to the underlying SM. Like all the previously reported cases of SM-CLL, the SM in our 2 cases showed a stable clinical course without signs of progression during the time period the patients were followed. namely, there are no "C" findings (impaired organ function due to MC infiltration) including hepatomegaly with impaired liver function, osteolytic lesions and/or pathological fractures, hypersplenism, malabsorption and weight loss due to GI MC infiltrates.

It is of interest to point out that our case #2 has both CLL and PCM as AHNMD component of SM -AHNMD, which was not reported in the literature to the best of our knowledge. Although CD5 positivity in the monotypic B-cell population has been reported in portion of lymphoplasmacytic lymphoma (LPL), none of these LPL cases had features of CLL [21]. While detailed molecular studies in order to determine the clonal relationship between CLL and PCM components cannot be performed and beyond the scope of this study, based on the different monotypic immunoglobulin light chain expression between CLL (lambda-restricted) and PCM (kappa-restricted) in our case #2, it is reasonable to believe these two components are two independent and separate events. Mast cell tryptase-positive reactive MCs were found to be increased in marrows involved by LPL and CLL [6]; conversely, reactive lymphocytosis was reported in marrows heavily infiltrated by SM [22]. Our case #2 clearly has three separate components simultaneously, all of which are malignant. MCs in Waldenstrom macroglobulinemia/ LPL are thought to be key players in sustaining the growth of malignant lymphoplasmacytoid cells [6, 23]. It remains unclear at this point how MCs may potentially affect associated plasma cells in PCM or CLL cells, or vice versa.

Treatment options for SM include wait and watch alone, topical therapy, symptomatic noncvtoreductive and cvtoreductive therapies [3]. The current recommendations for treating SM-AHNMD are to treat SM and AHNMD components in patients with SM-AHNMD separately as if the other component is not present [24]. The clinical outcome of SM-AHNMD is mainly determined by the associated AHNMD component [3], and that is why hydroxyurea was frequently used in SM-AHNMD [25]. However, hydroxyurea did not exhibit substantial anti-MC effect, and for this reason. Lim et al recommended 2chlorodeoxyadenosine and interferon-alpha as first line therapy [25]. Since the SM component was not symptomatic in either of our two patients, only the symptomatic CLL was treated with stem cell transplant for case #1, and chemotherapy for case #2. In both cases, CLL component responded to treatment, but the SM was present persistently.

In summary, we report two cases of SM-CLL, one of which also contained PCM as AHNMD component. While rare, SM-CLL and SM-CLL-PCM do occur rarely, therefore, awareness of such an entity will avoid missed diagnosis. In addition, these two cases highlight the importance of using multi-modality approaches to address SM-AHNMD cases.

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