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Original article

Mast cell leukemia (MCL): Clinico-pathologic and molecular features and survival outcome

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ABSTRACT

Mast cell leukemia (MCL) is a very rare subtype of systemic mastocytosis (SM). We have identified 13 such patients (5.9%) among 218 patients with SM seen at our institution between 1994 and 2016. Patients with MCL had poor survival (median 31.6 months); response to various therapies was rare and not durable. Clinical course may be affected by concurrent associated hematologic neoplasm and different genetic profiles. More research is required to decipher this rare and enigmatic SM subtype.

1. Introduction

Systemic mastocytosis (SM) is rare myeloproliferative neoplasm of clonal mast cells. Mast cell leukemia (MCL) [1,2] is a rare subtype of SM and seen in < 1% of SM patients [3]. Other subtypes of SM include indolent (ISM), smoldering (SSM), aggressive (ASM) and SM with associated hematologic neoplasm (SM-AHN) [4]. The diagnosis of MCL is based on the presence of ≥20% mast cells in the bone marrow smears, but most MCL cases are aleukemic type (aMCL), characterized by < 10% peripheral blood mast cells. Till date, only two reports from European colleagues have systematically characterized MCL. One report reviewed 51 cases of MCL collected from various centers in France [1] and another report [5] reviewed 28 cases of MCL from Germany. The outcome of MCL was significantly inferior as compared to other subtypes of SM, with median survival of < 2 years. As reported by other colleagues, none of the currently available therapies have shown durable long term response in MCL. Infrequently, durable partial remissions were observed with single agent cladribine and more recently with midostaurin (a multi tyrosine kinase inhibitor, including abnormal KITD816V kinase, present in SM), now approved new therapy in the US for patients with ASM, SM-AHD, and MCL [5,6]. Survival outcomes do not appear to improve after allogeneic stem cell transplantation [7]. Recently, the mutation profiles of ASM and MCL patients were reported [8–10]. The majority of patients exhibited *KIT* D816V mutation but frequently showed concurrent mutations in additional genes. Commonly observed concurrent mutations genes were *SRSF2, TET2, ASXL2, and K/N-RAS*. It is possible that the clinical course of ASM and the mutation profile is dependent upon the molecular characteristics of the AHN. In addition, presence of *SRSF2/ASXL2/RUNX1* mutations (S/A/R) in patients with MCL was proposed to be an independent predictor for poor survival [5].

2. Patients and methods

In this study, we present our single center experience with MCL. We reviewed 218 patients with SM who presented to our institution between 1994 and 2016. This study was approved by the institutional review board. The survival of patients was calculated from the date of initial presentation to the date of last follow up/death. Kaplan-Meier survival analysis was conducted with GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla, CA). In a subset of 8 patients with available bone marrow samples, we performed an amplicon-based targeted next generation sequencing (NGS) using a panel of 49 cancer-related genes (Thunderbold Myeloid Panel, Rain Dance Technologies) using MiSeq system (Illumina, Inc., San Diego, CA). The median coverage for most genes was between 3000X–4000X, facilitating confident variant calling at 1% sensitivity. A minimum of 250X coverage was required for variant calling.

3. Results

We identified 13 patients with MCL (5.9%). All 13 patients presented with aMCL; none had circulating mast cells. In 4 of 13 patients, associated hematologic neoplasm (AHN) was present: 2 with

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Table 1
Description of patient characteristics and outcomes in patients with aleukemic mast cell leukemia (aMCL).

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Age at diagnosis	73	47	62	59	24	42	74	59	47	69	73	75	72
Ethnicity	Caucasian	Caucasian	African-American	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Sex	Male	Male	Female	Female	Female	Male	Female	Male	Male	Female	Male	Female	Male
Associated clonal hemato-logic non-mast cell lineage disease (AHNMD)	MDS	None	Myeloma	None	None	None	CMML	None	None	None	None	MDS	None
B findings (If yes then which type)	MC > 30%, Dysmyelopoiesis	> 30% MC in bone marrow, Dysmyelopoies-is	MC > 20%, Tryptase > 200	MC > 20%, Tryptase > 200	Splenomegaly, MC > 20%	MC > 30%, Hepatosplenom-egaly	Dysmyelopoiesi-s, Tryptase > 200	Hepatosple-nomegaly; MC > 30%, Tryptase > 200	MC > 30%; Hepatosplenomegaly		MC > 30%, Tryptase > 200	NA	> 30%
C Findings (Y/N)	N	Y	N	N	Y	Y	Y	Y	N	NA	Y	Y	Y
C Findings (If yes then which type)	NA	Anemia (Hb < 9.0); Hepatomegaly with ascites	NA	NA	Anemia (Hb < 10gm/dL)	Skeletal lesions	Anemia/ Thrombocytope-nia	Anemia/ Thrombocy-topenia	NA	NA	Hepatomeg-aly with ascites	Anemia/ thrombocy-topenia	Skeletal lesions
Initial Clinical Presentat-ion (0 = Bone Marrow Alone, 1 = Extra-medul-lary, 2 = Both)	0	2	2	2	2	2	2	2	2	NA	2	0	2
Cutaneous signs and symptoms (Y/N)	N	N	Y-Erythematous rash	Y-Mast cells	Y-Erythematous lesions	Y-Maculopapular rash	Y- Macular rash	Y-Pruritic rash	Y- Macular rash	NA	N	N	N
Constitutional symptoms – Type	Y – Fatigue and weight loss	Y-Weight loss	Y- Weight loss	N	Y-Fatigue	Y-Fatigue, weight loss	Y-Fatigue	Y-Fatigue and Night sweats	Y- Weight loss	NA	Y-Fatigue	Y-Fatigue	Y-Irritability and Fatigue
Allergic/ Anaphyla-ctic symptoms (Y/N)	N	N	Y	N	Y	y	Y	N	N	NA	N	N	N
GI Symptoms (Y/N)	N	N	N	N	Y	Y	Y	Y	N	NA	N	N	N
Skeletal symptoms (Y/N)	N	N	N	N	N	Y	Y	N	N	NA	N	N	Y
Neurological (Y/N)	Y-Neurogenic bladder	Y-Flashes of light	Y	N	N	N	N	Y	Y	NA	Y	N	Y
Other systemic	None	None	None	None	None	None	None	None	None	None	None	None	None

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