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Non Hepatosplenic Extramedullary Manifestations of Chronic Myelomonocytic Leukemia: Clinical, Molecular and Prognostic Correlates

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To the Editor

Chronic myelomonocytic leukemia (CMML) is an aggressive hematological malignancy with overlapping myeloproliferative and myelodysplastic features and an inherent risk for leukemic transformation. [1] Non hepatosplenic extramedullary manifestations (EMM) in CMML have previously been described in small case series and include both, extramedullary hematopoiesis and extramedullary monocytic infiltration [2–4]. While the occurrence of non hepatosplenic EMM in other myeloid neoplasms such as acute myeloid leukemia and chronic myelogenous leukemia have been associated with adverse outcomes and shorter survivals, in CMML the exact prevalence and prognostic impact remain to be documented [5,6]. We carried out this study in a large informative cohort of World Health Organization (WHO) defined CMML patients to i) describe clinical and laboratory correlates of non hepatosplenic EMM in CMML, ii) to assess the prognostic impact of non hepatosplenic EMM, and iii) to document survival outcomes.

Four hundred and fifty-two patients with 2016 WHO-defined CMML were identified from the institutional database [7]. All patients had bone marrow (BM) biopsies and cytogenetic studies performed at diagnosis. Non hepatosplenic EMM for the purpose of this study were

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Author contributions

K. Hoversten, R. Vallapureddy, T. Lasho, C. Finke, R. Ketterling, C. Hanson, N. Gangat, A. Tefferi, and M. Patnaik performed the research. M. Patnaik designed the study. R. Vallapureddy analyzed the data. K. Hoversten, R. Vallapureddy, and M. Patnaik wrote the manuscript.

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defined as: palpable lymphadenopathy, clinical/radiological or biopsy proven leukemia cutis, gingival infiltrates, testicular involvement, central nervous system (CNS) involvement, and myeloid sarcomas. The presence of palpable hepatosplenomegaly was also recorded. EMM were included if present either at the time of CMML diagnosis or within six months of stable disease following diagnosis.

A 29 gene panel next generation sequencing (NGS) assay was carried out on BM DNA specimens on patients obtained at diagnosis for the following genes: *TET2*, *DNMT3A*, *IDH1*, *IDH2*, *ASXL1*, *EZH2*, *SUZ12*, *SRSF2*, *SF3B1*, *ZRSR2*, *U2AF1*, *PTPN11*, *Tp53*, *SH2B3*, *RUNX1*, *CBL*, *NRAS*, *KRAS*, *JAK2*, *CSF3R*, *FLT3*, *KIT*, *CALR*, *MPL*, *NPM1*, *CEBPA*, *IKZF1*, *ETNK1*, and *SETBP1*, by previously described methods [8,9]. All statistical analyses considered parameters obtained at time of CMML diagnosis. Differences in the distribution of continuous variables between categories were analyzed by either Mann-Whitney or Kruskal-Wallis tests. Patient groups with nominal variables were compared by chi-square test. Overall survival (OS) was calculated from the date of first referral to date of death or last contact. Leukemia-free survival (LFS) was calculated from the date of first referral to date of leukemic transformation or death/last contact. Overall and LFS curves were prepared by the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazard regression model was used for multivariable analysis.

Three hundred seventy-three (82%) of the 452 patients had an examination documented at the time of diagnosis, or within six months of diagnosis, and were included in the final analysis (Table 1). The median age was 71 years (range, 20–95), 66% were male. Forty seven% had a “proliferative” CMML phenotype. Twenty two (6%) patients had at least one non hepatosplenic EMM at diagnosis, with 5 (23%) of these patients also having palpable hepatosplenomegaly. The non hepatosplenic EMM included palpable lymphadenopathy 10 (3%), leukemia cutis 7 (2%), gingival infiltrates 4 (1%), myeloid sarcomas 2 (1%), and 1 each with testicular and CNS involvement (0.5%). One hundred and two patients (27%) had palpable hepato and/or splenomegaly, whereas 54 (14%) and 11 (3%) had isolated palpable splenomegaly and hepatomegaly, respectively. Fifteen (71%) patients with non hepatosplenic EMM had a normal karyotype. NGS data was available in 231 (62%) patients and encountered gene mutations included; *TET2* 51%, *ASXL1* 49%, *SRSF2* 44%, *CBL* and *NRAS* 13% each, *SETBP1* 12%, *RUNX1* 9%, *JAK2* V617F and *U2AF1* 8% each, and *DNMT3A*, *IDH1* and *KRAS* 6% each. Risk stratification by the Mayo Molecular Model (MMM) included; 9% low, 28% intermediate-1, 32% intermediate-2 and 55% high risk, respectively.

In comparison to patients without non hepatosplenic EMM or isolated palpable hepatosplenomegaly, those with non hepatosplenic EMM were more likely to have a “proliferative” CMML phenotype ($p=0.0007$) and more likely to be classified as CMML-2 ($p=0.001$) (table 1). On the other hand, patients with isolated palpable hepatosplenomegaly were more likely to have leukocytosis ($p < 0.0001$), monocytosis ($p=0.001$), neutrophilia ($p < 0.0001$), and more likely to have mutations involving *CSF3R* ($p=0.04$), and *c-KIT* ($p=0.0001$). Patients with both, non hepatosplenic EMM and palpable hepatosplenomegaly, in comparison to those without, were less likely to have *Tp53* mutations ($p=0.02$). There was no statistical difference identified in age, gender, hemoglobin, platelet counts, BM blast %, and

or lactate dehydrogenase (LDH) levels between the three groups. Treatment data was available on all 119 (100%) patients with EMM and included; hydroxyurea in 34 (29%), hypomethylating agent therapy in 24 (20%; 5-azacitidine-6, decitabine-18), acute myeloid leukemia (AML) like induction chemotherapy in 19 (16%), interferon alpha in 3 (3%), cladribine in 2 (2%) and best supportive care (including erythropoiesis stimulating agents) options in 37 (31%) patients. Five (4%) patients also underwent allogeneic stem cell transplantation. The one patient with CNS involvement received intrathecal chemotherapy followed by craniospinal radiation. The patient with testicular involvement was treated with involved field radiation therapy (920 cGy), followed by hypomethylating agent therapy. Both patients with myeloid sarcomas had systemic disease and were treated with AML like induction chemotherapy followed by involved field radiation therapy.

At last follow up (median 14 months), 249 (67%) deaths and 69 (18%) leukemic transformations were documented. Median survival was 13.5 months for patients with non hepatosplenic EMM, 13 months for those with palpable hepatosplenomegaly, and 25 months for those without EMM (Figure 1). On univariate analysis, survival was adversely affected by male sex ($p=0.03$), low hemoglobin ($p<0.0001$), high white blood cell count (WBC) ($p=0.0005$), high absolute monocyte count (AMC) ($p<0.0001$), presence of circulating immature myeloid cells ($p=0.002$), circulating blast % ($p<0.0001$), higher LDH levels ($p=0.0004$), palpable hepatosplenomegaly ($p=0.0008$), leukemia cutis ($p=0.02$), “proliferative” CMML phenotype ($p<0.0001$), abnormal cytogenetics ($p=0.003$), absence of *TET2* ($p=0.0004$) and the presence of *DNMT3A* ($p=0.002$), *IDH1* ($p=0.013$), *ASXL1* ($p=0.03$), and *Tp53* ($p=0.014$) mutations. Non hepatosplenic EMM including palpable lymphadenopathy, CNS, testicular involvement and the presence of myeloid sarcomas did not impact OS. On multivariate analysis, only male sex ($p=0.009$, HR 1.6, 95% CI 1.1–2.3), low hemoglobin ($p<0.0001$, HR 1.74, 95% CI 1.3–2.3), palpable hepatosplenomegaly ($p=0.0005$, HR 1.8, 95% CI 1.04–2.2), absence of *TET2* mutations ($p=0.023$, HR 0.7, 95% CI 0.5–0.95), and the presence of *DNMT3A* mutations ($p=0.013$, HR 2.3, 95% CI 1.2–4.3) retained an independent negative prognostic impact. Non hepatosplenic EMM or palpable hepatosplenomegaly did not impact LFS.

The current study is the first to describe the spectrum and frequency of non hepatosplenic EMM present at the time of CMML diagnosis in a large molecularly annotated patient cohort. Non hepatosplenic EMM were seen in 6 % of patients at diagnosis, infrequently involved sanctuary sites such as the CNS and testes (<1%) and were associated with a “proliferative” CMML phenotype and a higher prevalence of CMML-2 morphological subtypes. Palpable hepatosplenomegaly was present in 27% of patients at CMML diagnosis, was associated with leukocytosis, neutrophilia and monocytosis and independently and adversely impacted survival; serving as an important physical exam finding at diagnosis to help with prognostication. Given the limitations of a single institutional retrospective cohort study, these findings do need to be validated prospectively in a larger number of patients.

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Figure 1:
Overall survival of 373 patients with chronic myelomonocytic leukemia stratified by the presence and type of extramedullary manifestations

Table 1:

Baseline patient characteristics for patients with chronic myelomonocytic leukemia (CMML) with a documented physical examination, at time of CMML diagnosis

Variable	Patients with baseline exam at time of CMML diagnosis (n=373)	Patients with non hepatosplenic EMM (n=17)	Patients with palpable hepato splenomegaly (n=97)	Patients without EMM (n=254)	P value comparing columns 3,4 and 5
Age in years; median (range)	71 (20–95)	68 (36–88)	69 (20–92)	72 (27–95)	0.1
Males; n (%)	246 (66)	14 (82)	59 (61)	168 (66)	0.1
Hemoglobin g/dL; median (range)	10.6 (1.4–16.9)	10.4 (7.5–14.6)	10.5 (6.4–17)	10.7 (1.4–16.8)	0.4
MCV femtoliter; median (range)	91 (59–124)	90.5 (77–108)	91 (61–124)	91.6 (59–120)	0.5
WBC x 10 ⁹ /L; median (range)	12.2 (1.3–265)	7.8 (1.8–69)	21 (2–186)	10.8 (1.3–265)	<0.0001
ANC x 10 ⁹ /L; median (range)	5.8 (0–151)	3.3 (0.2–43)	11 (0.5–151)	5 (0–143)	<0.0001
AMC x 10 ⁹ /L; median (range)	2.5 (1.0–84)	2.5 (1.0–9.5)	3 (1.0–40)	2.3 (1.0–84)	0.001
ALC x 10 ⁹ /L; median (range)	1.8 (0–22)	1.4 (0.6–11)	2.3 (0–11)	1.6 (0.3–22)	0.08
Platelets x 10 ⁹ /L; median (range)	96 (7–1184)	89 (27–407)	85 (7–1184)	99 (7–742)	0.4
Presence of circulating immature myeloid cells; n (%)	155 (42)	7 (41)	25 (26)	123 (48)	0.0004
PB blast %; median (range)	0 (0–18)	0 (0–13)	0 (0–15)	0 (0–16)	0.009
BM blast %; median (range)	2 (0–19)	4 (0–19)	3 (0–19)	2 (0–18)	0.4
Lactate dehydrogenase level IU/ml; median (range)	225 (84–1824)	230 (123–1824)	226 (84–701)	223 (98–1227)	0.7
Karyotype; n (%) Abnormal	(n=344) 105 (31)	2 (12)	(n=84) 27 (32)	(n=238) 73 (31)	0.2
FAB CMML Classification; n (%) Dysplastic Proliferative	197 (53) 176 (47)	12 (71) 5 (29)	36 (37) 61 (63)	148 (58) 106 (42)	0.0007

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Next generation sequencing analysis; n (%)	(n=231) 118 (51)	(n=10) 5 (50)	(n=61) 22 (36)	(n=158) 90 (57)	0.05 0.8
1. Epigenetic regulators	15 (6)	1 (10)	5 (8)	9 (6)	0.5
<i>TET2</i>	3 (1)	0	2 (3)	1 (1)	0.2
<i>DNMT3A</i>	13 (6)	2 (20)	4 (7)	7 (4)	0.1
<i>IDH1</i>	113 (49)	7 (70)	36 (59)	69 (44)	0.4
<i>IDH2</i>	6 (3)	0	0	6 (4)	0.9
2. Chromatin regulation	21 (9)	1 (10)	5 (8)	15 (9)	0.4
<i>ASXL1</i>	1 (0.5)	0	1 (2)	0	0.8
<i>EZH2</i>	2 (1)	0	0	2 (1)	0.4
3. Transcription factors	11 (5)	0	1 (2)	10 (6)	0.4
<i>RUNX1</i>	101 (44)	5 (50)	24 (39)	70 (44)	0.8
<i>CALR</i>	18 (8)	1 (10)	3 (5)	14 (9)	0.6
<i>BCOR</i>	4 (2)	0	0	4 (3)	0.6
4. Spliceosome components	18 (8)	0	7 (11)	11 (7)	0.9
<i>SF3B1</i>	2 (1)	0	1 (2)	1 (1)	0.6
<i>SRSF2</i>	30 (13)	1 (10)	11 (18)	18 (11)	0.02
<i>U2AF1</i>	11 (5)	1 (10)	2 (3)	7 (4)	0.3
<i>ZRSR2</i>	31 (13)	0	9 (15)	21 (13)	0.6
5. Cell signaling	6 (3)	0	3 (5)	3 (2)	0.037
<i>JAK2 V617F</i>	3 (1)	0	3 (5)	0	0.0001
<i>MPL</i>	10 (4)	0	9 (15)	1 (1)	0.9
<i>CBL</i>	5 (2)	0	2 (3)	3 (2)	0.09
<i>KRAS</i>	3 (1)	1 (10)	1 (2)	1 (1)	0.0002
<i>NRAS</i>	6 (3)	0	0	5 (3)	0.1
<i>PTPN11</i>	28 (12)	3 (30)	10 (16)	15 (9)	0.4
<i>CSF3R</i>	1 (0.5)	0	1 (2)	0	
<i>C-KIT</i>					
<i>FLT3TKD</i>					
<i>NPM1</i>					
6. Tumor suppressor genes					
<i>Tp53</i>					
7. Others					
<i>SETBP1</i>					
<i>ETNK1</i>					
2008 WHO morphological subtypes; n (%)	306 (82) 67 (18)	12 (71) 5 (29)	78 (80) 19 (20)	215 (85) 39 (15)	0.001
2016 WHO morphological subtypes; n (%)	221 (59) 85 (23) 67 (18)	10 (59) 2 (12) 5 (29)	47 (48) 31 (32) 19 (20)	163 (64) 52 (21) 39 (15)	0.0006
Spanish Cytogenetic risk stratification; n (%)	(n=343) 243 (71) 69 (20) 31 (9)	15 (88) 1 (6) 1 (6)	(n=84) 59 (70) 17 (20) 8 (10)	(n=237) 167 (71) 48 (20) 22 (9)	0.3
Mayo-French cytogenetic risk stratification; n (%)	(n=343) 242 (71) 80 (23) 21 (6)	15 (88) 2 (12) 0	(n=84) 59 (70) 23 (28) 2 (2)	(n=237) 167 (71) 51 (21) 19 (8)	0.1
Mayo prognostic model; n (%)	(n=372) 91 (24) 136 (37) 145 (39)	4 (24) 8 (47) 5 (29)	(n=96) 14 (15) 30 (31) 52 (54)	73 (29) 96 (38) 85 (33)	0.009
Molecular Mayo model; n (%)	(n=230) 20 (9) 65 (28)	(n=10) 0 4 (40)	(n=60) 3 (5) 8 (13)	(n=158) 17 (11) 53 (34)	0.02

Variable	Patients with baseline exam at time of CMML diagnosis (n=373)	Patients with non hepatosplenic EMM (n=17)	Patients with palpable hepato splenomegaly (n=97)	Patients without EMM (n=254)	P value comparing columns 3,4 and 5
Intermediate-1 Intermediate-2 High	73 (32) 72 (55)	3 (30) 3 (30)	22 (37) 27 (45)	48 (30) 40 (25)	
GFM CMML prognostic model; n (%)	(n=230)	(n=10)	(n=60)	(n=158)	0.06
Low	102 (44)	6 (60)	17 (28)	78 (49)	
Intermediate	85 (37)	4 (40)	28 (47)	53 (34)	
High	43 (19)	0	15 (25)	27 (17)	
Leukemic transformations; n (%)	69 (18)	4 (24)	18 (19)	47 (19)	0.7
Deaths; n (%)	249 (67)	13 (76)	69 (71)	163 (64)	0.4
Median follow up in months (range)	13.6 (0–169)	10 (0.1–100)	9 (0.03–120)	16.4 (0–169)	0.017

Key: EMM, Extramedullary manifestations; WBC, white blood cell count; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; PB, peripheral blood; BM, bone marrow; WHO-World Health Organization GFM-Groupe Francophone des Myélodysplasies; FAB, French–American–British

* 5 patients had extramedullary manifestations involving liver, spleen and other organs and were not included in the table.