LETTER TO THE EDITOR

Specific blood monocyte distribution in histiocytoses correlates with vascular involvement and disease activity

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Supplementary Table 1: Characteristic of patients with histiocytic disorders.

Case	Age at diagnosis	Age at dosage	Type of histiocytoses	Localization of histiocytoses	Tissue disclosing histiocytic infiltration	Tissue mutational status	VAF on tissue	Myeloid neoplasm	CH	Bone marrow mutational status	VAF on bone marrow	Prior therapy	Therapy at dosage time	Classical monocytes	Intermediate monocytes	Non-classical monocytes	Disease activity
#1	71	71	ECD	mesentery, bone, CNS, peri-renal, heart	mesentery, perinephric fat	*BRAF c.1799T>A*, p.(Val600Glu) *KRAS c.437C>T*, p.(Ala146Val) *TET2 c.3622A>T*, p.(Lys1208*)	14% 10% 45%	CMML	0	*TET2 c.3622A>T*, p.(Lys1208*) *ZRS2 c.896G>A*, p.Cys299Tyr *KRAS c.34G>A*, p.(Gly12Ser) *PPM1D c.1547_1562dup*,p.Met521IIefs*12 *BRAF c.1799T>A*, p.(Val600Glu) *CBL c.1222T>A*, *p.*Trp408Arg	95% 3% 2% 34% 2% 41%	BRAF-inhibitor	IL-1 blockers	96%	3%	1%	Partial metabolic response
#2	68	72	ECD	mesentery, bone, CNS, peri-renal, heart, bone marrow	mesentery, perinephric fat	*BRAF c.1799T>A*, p.(Val600Glu) *CLB c.1243G>A*, p.Gly415Ser *SRSF2 c.283C>A*, p.Pro95Thr *TET2 c.822delC*, p.Asn275IIelfs*18 *TET2 c.763C>T*, p.Gln255* *NRAS c.34G>A*, p.Gly12Ser	10% 6% 2% 5% 41% 4%	CMML	0	*TET2 c.822delC*, p.Asn275IIelfs*18 *TET2 c.763C>T*, p.Gln255* *SRSF2 c.283C>A*, p.Pro95Thr *CLB c.1243G>A*, p.Gly415Ser *NRAS c.34G>A*, p.Gly12Ser	41% 48% 42% 78% 2%	BRAF-inhibitor	None	96%	2%	2%	Partial metabolic response
#3	71	73	ECD	heart, bones, vessels, mesentery, peri-renal	mesentery, perinephric fat	*BRAF c.1799T>A*, p.(Val600Glu)$	10%	ET	0	*JAK2 c.1849G>T*, pVal617Phe *TET2 c.665_666delAT*, p.His222Argfs*2 *TET2 c.1441C>T*,p.Gln481* *TET2 c.4745_4783delinsAGGGC*, p.Thr1585Lysfs*3 *NF1 c.3827G>A*, p.Arg1276Gln	46% 25% 8% 28% 4% 2%	None	MEK-inhibitor	96%	3%	1%	Partial metabolic response
#4	24	25	ECD	vessels, bone, sinus	vessels	No mutation		0	0	None		None	IL-1 blockers	92%	7%	1%	Progressive metabolic disease
#5	72	77	ECD	bone, lung , skin, vessels	skin/bone	*BRAF c.1799T>A*, p.(Val600Glu)$	30%	0	1	*KRAS c.34G>A*, p.(Gly12Ser) *SH2B3 c.1426C>T*, p.(Leu476Phe) *SRSF2 c.52G>T*, p(Val118Leu) *TET2 c.1843delC* *TET2 c.2596C>T*, p.(Gln866*)	3% 46% 45% 43% 40%	BRAF-inhibitor	BRAF inhibitor	94%	5%	1%	Partial metabolic response
#6	64	66	ECD	bone, peri-renal, mesentery	mesentery	No mutation		0	1	*TET2 c.5541G>A*, p.Trp1847	2%	MEK-inhibitor	MEK-inhibitor	81%	8%	11%	Stable metabolic disease
#7	81	81	ECD	bone, heart, vessel, CNS, peri-renal	perinephric fat	*BRAF c.1799T>A*, p.(Val600Glu**) $**	8%	0	1	*ASXL1 c.1934dup*, p.Gly646Trpfs*12 *NF1c.4288A>G*, p.Asn1430Asp *TET2 c.3662G>A*, p.Cys1221Tyr *U2AF1c.470A>C*, p.Gln157Pro	35% 2% 14% 2%	Interferon	Interferon	92%	4%	4%	Progressive metabolic disease
#8	58	63	ECD	bone, mesentery, peri-renal	mesentery	*DNMT3A c.2644C>T*, p.Arg882Cys NF1 *c.7486C>T*, p.Arg2496*	1.3% 53%	0	1	*DNMT3A c.2644C>T*, p.Arg882Cys NF1 *c.7486C>T*, p.Arg2496*	3% 41%	Interferon, IL-1 blockers, TNF-alpha inhibitor, MEK-inhibitor	MEK-inhibitor	71%	24%	4%	Stable metabolic disease
#9	69	71	RDD	perirenal	perinephric fat	*MAP2K1 c.395C>T*, p.(Ala132Val)	2%	0	1	*ERBB4 c.84T>C, p.Tyr283His*	51%	Rituximab	steroids	83%	5%	11%	Complete metabolic response
#10	39	41	RDD	skin, bone, eyes, vessel	skin	*MAP2K1 c.361T>A, p(Cys121Ser)*	4.8%	0	0	None		steroids	None	97%	2%	1%	Complete metabolic response
#11	67	67	RDD	bone	bone	No mutation		0	0	None		steroids	None	92%	4%	4%	Partial metabolic response
#12	62	65	RDD	skin, lymph node	lymph node	No mutation		0	0	None		None	None	87%	5%	8%	Complete metabolic response
#13	61	64	LCH	liver, endocrine, bone, skin	liver, skin	*BRAFc.1457_1471del*,p.(486_490del) *DNMT3A c.1742G>C*, p.(Trp581Ser)	10% 9,6%	0	0	None		vinblastine/steroids	Vinblastine	85%	13%	2%	Progressive metabolic disease
#14	12	22	LCH	bone, skin, endocrine, lung	bone, skin	No mutation		0	0	None		vinblastine/steroids	None	98%	1.5%	0.5%	Partial metabolic response
#15	68	68	LCH	lung, bones	lung	No mutation		0	0	None		None	None	92%	4%	4%	Progressive metabolic disease
#16	18	44	LCH	lung, hypophysis, bones	bone	No mutation		0	0	None		None	None	83%	8%	9%	Complete metabolic response
#17	59	63	LCH	lung, bones, pituitary gland	bone	*BRAF c.1799T>A*, p.(Val600Glu)**$**	9%	0	1	*ASXL1 c.1934dup*, p.Gly646Trpfs*12	3%	None	None	90%	4%	6%	Progressive metabolic disease

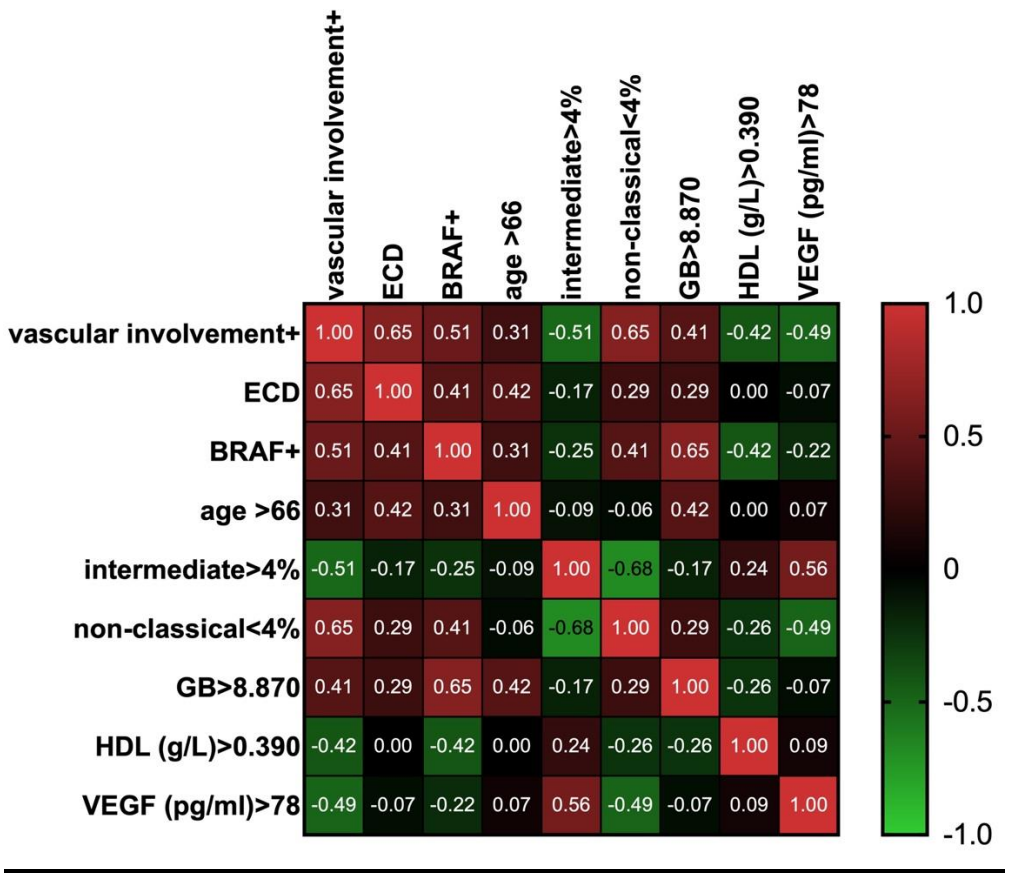
ECD: Erdheim-Chester disease. LCH: Langerhans cell histiocytosis, RDD: Rosai-Dorfman disease. CNS: Central nervous system. CMML: Chronic myelomonocytic leukemia. CH: clonal hematopoiesis. ET: Essential thrombocythemia. VAF: variant allele frequency. $: patient with low-DNA quantity for NGS analysis. VAF>2% on tissue biopsy y was considered significant.

Supplementary Table 2: Main characteristics of patients with histiocytoses, chronic myelomonocytic leukemias, essential thrombocythemias and heathy donors.

	Histiocytoses (n=17)	**Chronic myelomonocytic leukemias (n=7)**	**Essential thrombocytopenias (n=7)**	**Healthy donors (n=21)**	**P value**
Age at blood sampling (years), median [IQR]	66 [53-71]*‘	80 [76-84]	82 [77-87]	73[57-82]	**0.0027**
Sex M/F	10/7	4/3	2/5	9/12	0.5186
Hb (g/dL), median	13.0 [11.5-14.70] ‘	10.4 [9.0-12.1]	9.2 [9.0-14.30]	13.6 [12.65-14.45]	**0.0020**
White count cell (/mm^3)	8100 [5800-9020]	6800 [5000-9900]	9500 [7700-14400]	5600 [4700-6800]	**0.0092**
Neutrophils (/mm^3)	4720 [3700-6305]	2990 [2100-4030]	7040 [5240-9900]	3240 [2735-4180]	**0.0017**
Lymphocytes (/mm^3)	1610 [1150-2230]	1800 [850-2270]	1780 [1060-2860]	1620 [1090-2175]	0.9825
Total monocytes (/mm^3)	620 [505-815]‘	1840 [1190-2653]	940 [550-1040]	490 [365-620]	**<0.0001**
Classical monocytes %	92%[84-96]*	97%[96-98]	76%[71-84]	85.9%[77.6-89.8]	**<0.0001**
Intermediate monocytes %	4%[3-7.5]*	2.5%[1.3-2.8]	13%[9-18]	6.6%[4.4-13.3]	**0.0002**
Non-classical monocytes	4%[1-7]°	0.5%[0.5-1.5]	9% [3-13]	6.1%[4.4-10]	**<0.0001**
Platelet count (G/L)	224 [175-362] *	88 [37-150]	478 [423-1206]	NA	***0.0003***
CRP (mg/L)	4.0 [2.150-13.10] *	NA	49.1 [12.7-130]	2.9 [2.9-2.9]	**<0.0001**
Triglycerides (g/L)	1.505 [0.76-2.14]*	NA	0.51[0.365-0.995]	NA	**0.0147**

P-value is the result of Kruskal Wallis tests. *p<0.05 *vs.* essential thrombocytopenia, ‘ p<0.05 *vs.* chronic myelomonocytic leukemia, °p<0.05 *vs.* healthy donors. All quantitative data are expressed by median with interquartile range [IQR]

Supplementary Figure 1: Heat map for variables correlated with vascular involvement in histiocytoses using Pearson regression model



For the Pearson regression model, we have divided the group using the median of each variable. The variables correlated with vascular involvement were:
- "non-classical" monocytes below 4%: Pearson r: 0.648, 95%CI [0.2430-0.8606]. P=0.005
- ECD: Pearson r: 0,648, 95%CI [0,045 to 0,79]; P=0.005
- *BRAF*^{V600E} mutation: Pearson r: 0.514, 95%CI [0,044 to 0,79]; P=0.035