



Memorial Sloan Kettering
Cancer Center

A MULTINATIONAL SERIES OF 26 PATIENTS WITH MIXED HISTIOCYTIC NEOPLASMS HIGHLIGHTING A DIVERSE MUTATIONAL LANDSCAPE AND SUPERIOR EFFICACY OF TARGETED THERAPIES

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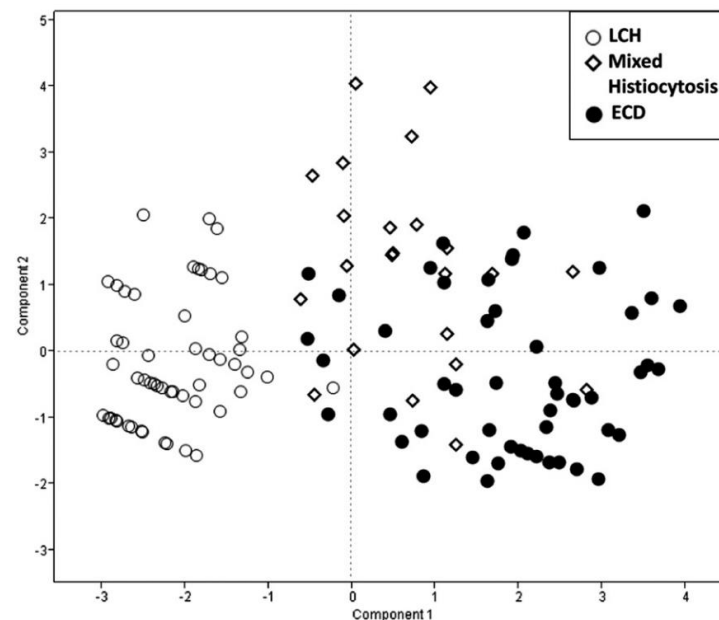
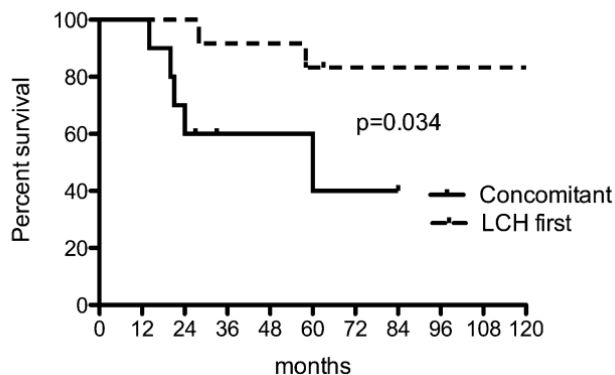
Background

Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the *BRAF*^{V600E} mutation

Baptiste Hervier,¹⁻³ Julien Haroche,¹⁻³ Laurent Arnaud,¹⁻³ Frédéric Charlotte,^{2,4} Jean Donadieu,⁵ Antoine Néel,⁶ François Lifermann,⁷ Carles Villabona,⁸ Bruno Graffin,⁹ Olivier Hermine,¹⁰ Aude Rigolet,^{1,2} Camille Roubille,¹¹ Eric Hachulla,¹² Thierry Carmoi,¹³ Maud Bézier,¹⁴ Véronique Meignin,¹⁴ Marie Conrad,¹⁵ Laurence Marie,¹⁶ Elise Kostrzewa,¹⁷ Jean-Marie Michot,¹⁸ Stéphane Barete,¹⁹ Valerie Taly,²⁰ Karine Cury,¹⁹ Jean-François Emile,^{21,22} and Zahir Amoura,¹⁻³ on behalf of the French Histiocytoses Study Group

Hervier et al, *Blood*, 2014

- LCH prior to or concurrent with ECD
- More ECD-like clinical phenotype
- Poor response (50%) to interferon-alpha
- Associated with *BRAF*^{V600E} mutation
- Worse survival with dyssynchronous diagnoses

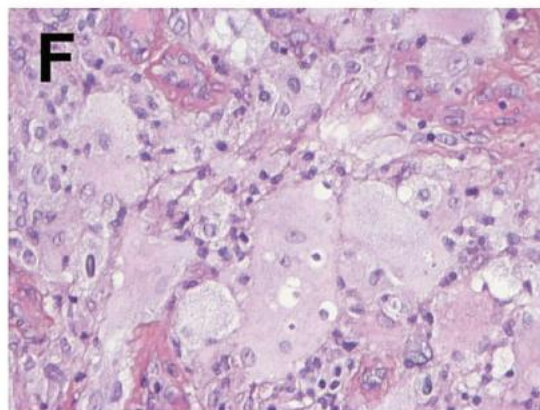
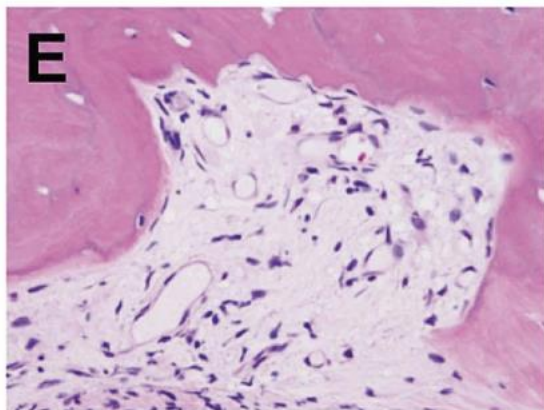
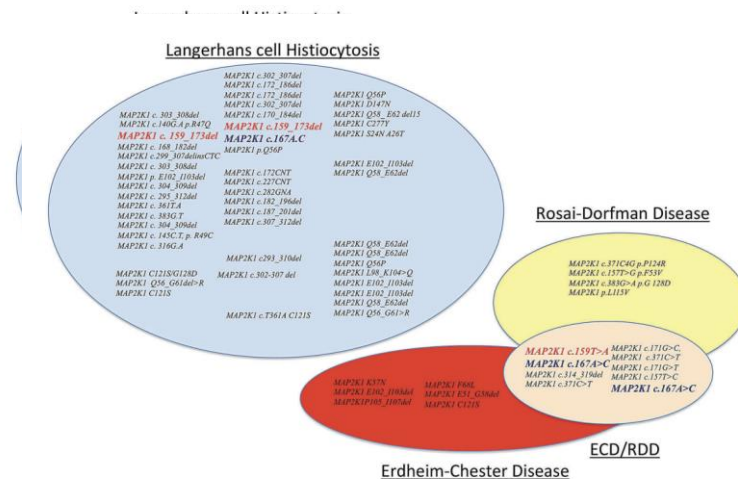


Background

Erdheim-Chester disease with concomitant Rosai-Dorfman like lesions: a distinct entity mainly driven by *MAP2K1*


- ECD phenotype with RDD foci
- 12/13 male
- *MAP2K1* mutations
- Unfavorable responses to conventional therapies, emergence of RDD during ECD therapy

Razanamahery et al, *Haematologica*, 2020



Background

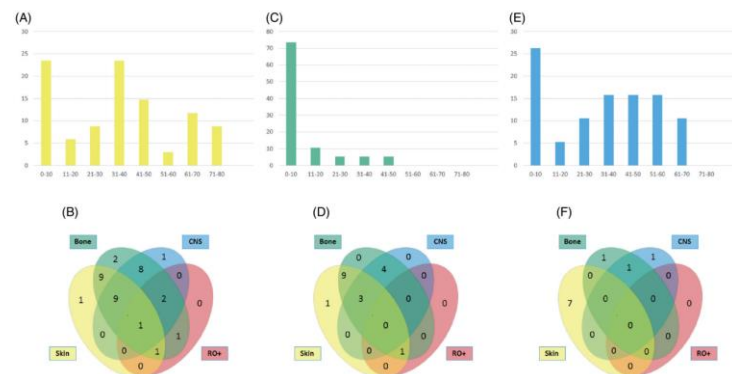
The triptych of mixed histiocytosis: a systematic review of 105 cases and proposed clinical classification

Arturo Bonometti  for Associazione Italiana Ricerca Istiocitosi AIRI ONLUS

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Bonometti et al, *Leukemia and Lymphoma*, 2020

- 105 cases from literature review
- Three types of mixed histiocytosis
 - MS, both diagnosed prior to treatment
 - “Therapy related”
 - Single-system, biphenotypic lesions
- BRAFV600E mutations



Objectives of our study:

- Comprehensive characterization of patient cohort with mixed histiocytosis
- Molecular characterization beyond BRAFV600E and MAP2K1
- Treatment outcomes and implications for management



Methods

- Collaborative retrospective study between MSK, Mayo Clinic, UAB, Assuta Medical Center, Cook County
- Patients with histologically confirmed ECD+LCH, ECD+RDD, RDD+LCH
- Diagnosis confirmed by two or more study pathologists (all reviewed at MSK + collaborator)
- Presenting symptoms, sites of disease, concurrence of diagnoses, mutations summarized
- Conventional and targeted therapies compared for radiologic response and subsequent progression



Results

Characteristic	N (%)	Median
Age at diagnosis	26 (100)	53.6 (18.0-74.1)
Sex		
Male	19 (73)	
Female	7 (27)	
Race		
White	20 (77)	
Black	1 (4)	
Hispanic	1 (4)	
Asian	3 (12)	
Unknown	1 (4)	
Duration of symptom prior to histiocytosis diagnosis, months	--	5.3 (0-166.0)
Diagnosis		
ECD/LCH	19 (73)	
ECD/RDD	5 (19)	
RDD/LCH	1 (4)	
LCH/ECD/RDD	1 (4)	
Concurrence of histiocytosis diagnoses		
Concurrent diagnosis	9 (35)	
Dyssynchronous diagnosis	17 (65)	



Results

Initial Diagnosis				
Mixed Diagnosis	LCH	ECD	RDD	Mixed
LCH/ECD	12 (63%)	2 (11%)	0	5 (26%)
ECD/RDD	0	1 (20%)	1 (20%)	3 (60%)
LCH/RDD	0	0	0	1 (100%)
LCH/ECD/RDD	1 (100%)	0	0	0

Characteristic	N (%)
Sites of disease	
Neurologic	15 (58)
Brain parenchyma	10 (38)
Cardiovascular	7 (27)
Pulmonary	3 (12)
Retroperitoneum	10 (38)
Abdomen	9 (35)
Bone	25 (96)
Skin or subcutaneous	16 (62)
Lymph nodes	5 (19)
Other (reproductive, soft tissues)	6 (23)

Characteristic	N (%)
Histiocytosis mutation	
BRAFV600E	15 (58)
MAP2K1	4 (15)
MAP2K2	1 (4)
MAPK3	1 (4)
RAS isoforms	1 (4)
BRAF non-V600	1 (4)
Kinase fusion	1 (4)
RAF1	1 (4)
No mutation identified	1 (4)



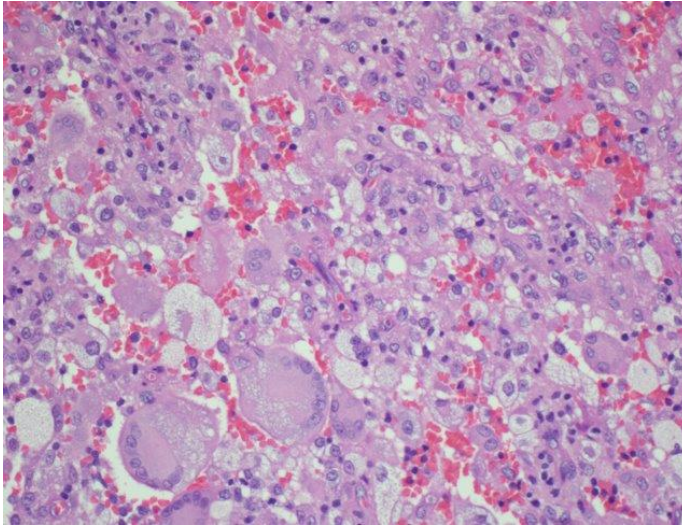
Results

- 82 biopsies in 26 patients
- 68 with one subtype, 14 biphenotypic
 - 8 ECD/LCH
 - 1 RDD/LCH
 - 5 ECD/RDD

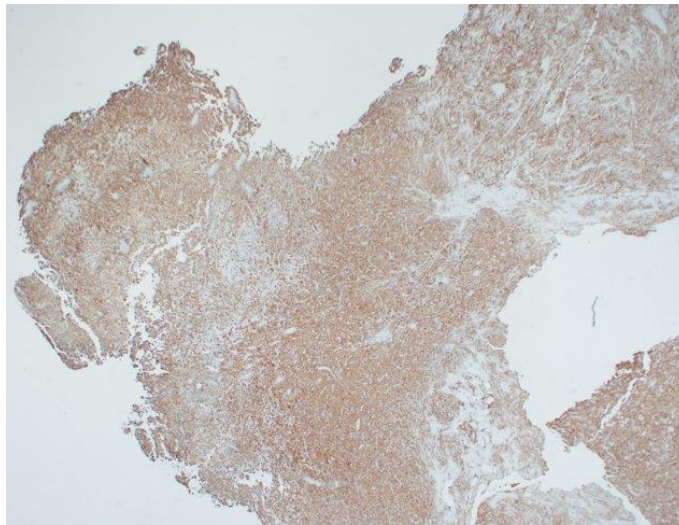
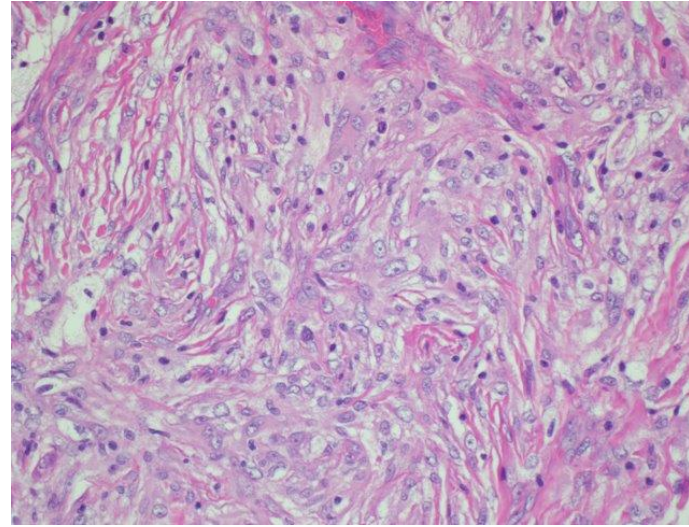
Site	ECD	LCH	RDD	Biphenotypic ECD/LCH	Biphenotypic RDD/LCH	Biphenotypic ECD/RDD	Total
Neurologic		1 (4%)		2 (25%)			3
Brain Parenchyma	1 (3%)		1 (33%)			1 (20%)	3
Cardiovascular							0
Lung/Thoracic/Pleura	1 (3%)						1
Retroperitoneum	4 (11%)		1 (33%)			1 (20%)	6
GI tract/Abdomen	3 (8%)	3 (11%)		1 (13%)			7
Bone	2 (5%)	8 (29%)			1 (100%)	3 (60%)	14
Skin/Subcutaneous	21 (57%)	11 (39%)		5 (63%)			37
Lymph node		4 (14%)					4
Other	5 (14%)	1 (4%)	1 (33%)				7
Total Biopsies	37	28	3	8	1	5	82



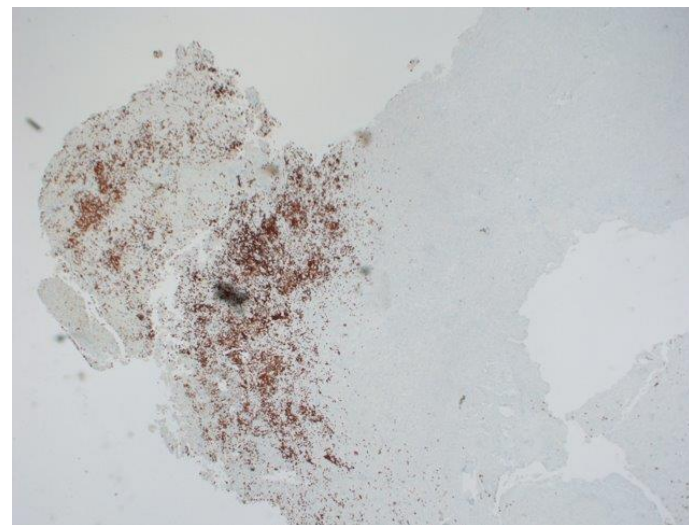
Biphenotypic LCH/ECD (BRAFV600E)



H&E



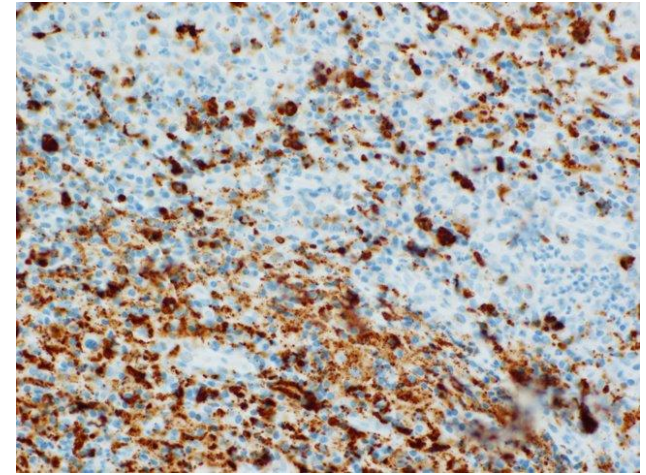
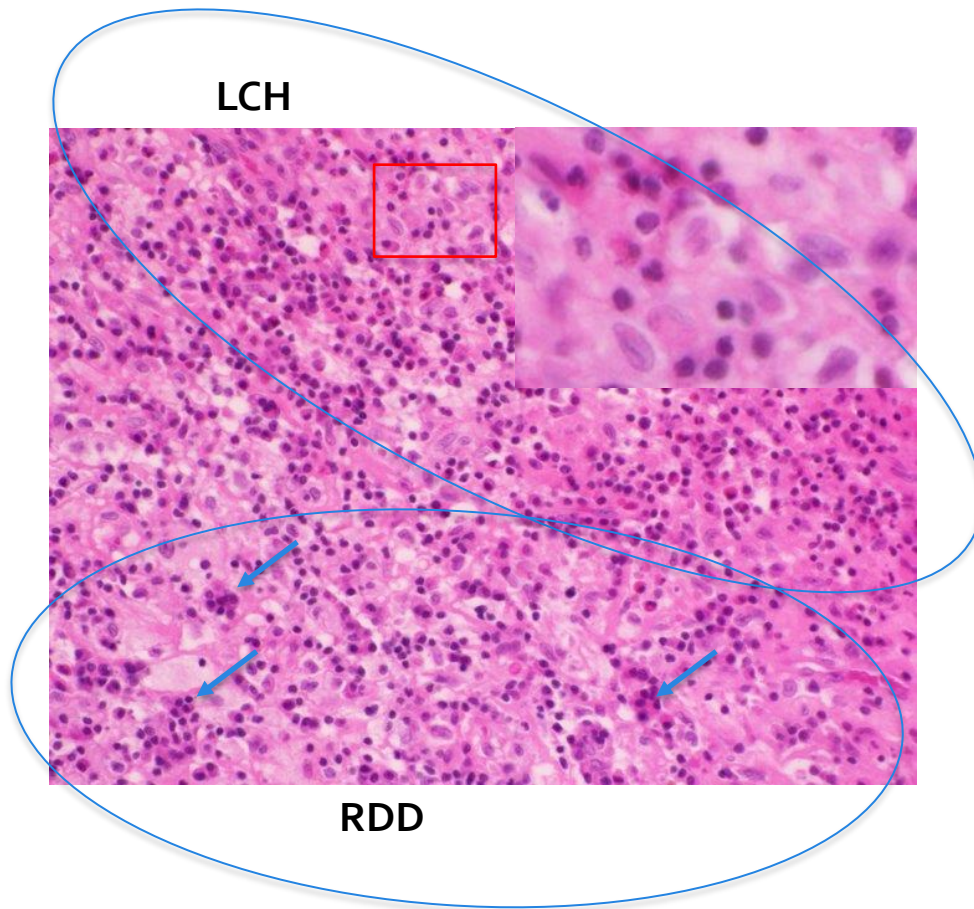
CD68



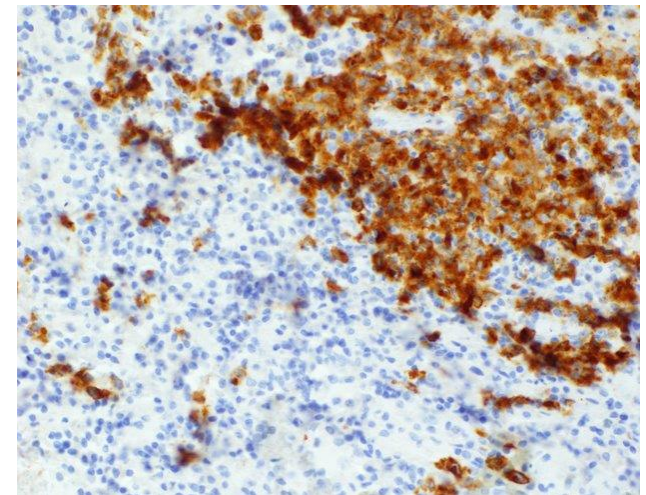
CD1a



Biphenotypic RDD/LCH (MAP2K2 A62P)



CD68



CD1a



Results

Histiocytosis mutation	ECD/LCH	ECD/RDD	RDD/LCH	ECD/LCH/RD D	Total
BRAFV600E	14	0	0	1	15
MAP2K1	<ul style="list-style-type: none"> • MAP2K1 p. C121S • MAP2K1 E102_I103del 	<ul style="list-style-type: none"> • MAP2K1 P105_I107delinsL • MAP2K1 p. G128D 	0	0	4
MAP2K2	0	0	MAP2K2 p. A62P		1
MAPK3	MAPK3 p. V121M	0			1
RAS isoforms	0	KRAS p. G12D	0	0	1
BRAF non-V600	BRAF p. M484_P490 del	0	0	0	1
Kinase fusion	BICD2-BRAF fusion	0	0	0	1
RAF1	0	RAF1 p. K106N	0	0	1
No mutation identified	0	1	0	0	1
Total	19	5	1	1	26



Results

Treatment	N (%) instances	Best Response					Subsequent Progression N (%*)	
		N Complete response	N Partial response	N Stable disease	N Progressive disease	N NE		N Unknown
Corticosteroids	5 (7)	1	1	1	2	0	0	1 (33)
Immunosuppression	7 (10)	1	3	1	2	0	0	5 (100)
Cytotoxic chemotherapy	25 (35)	3	3	5	5	1	8	7 (64)
Targeted therapy	29 (41)	10	15	2	0	1	1	5 (19)
Observation	3 (4)	0	1	1	0	0	1	0 (0)
Imatinib	1 (1)	0	0	0	1	0	0	--
Topical cream	1 (1)	0	0	1	0	0	0	1 (100)

- 71 instances of treatment (66 systemic treatment)
- Conventional therapy: 13/37 CR/PR, 6 SD, 9PD
- Conventional therapy 13/19 with subsequent PD
- BRAF/MEK: 25/29 CR/PR, 2 SD
- BRAF/MEK: 5/27 subsequent PD
- Progression not counted if radiologic response unknown

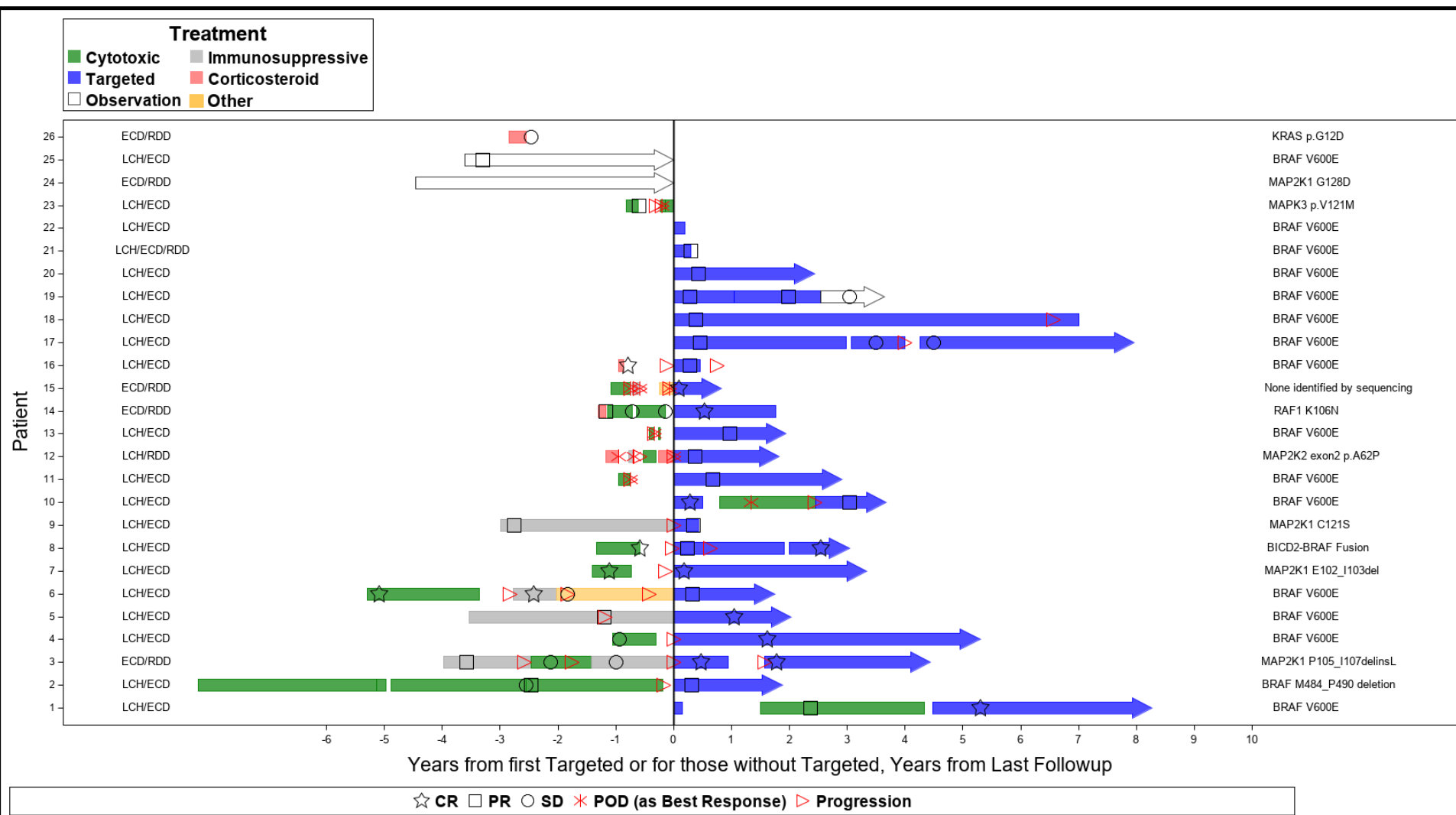


Details of progression on BRAF/MEK

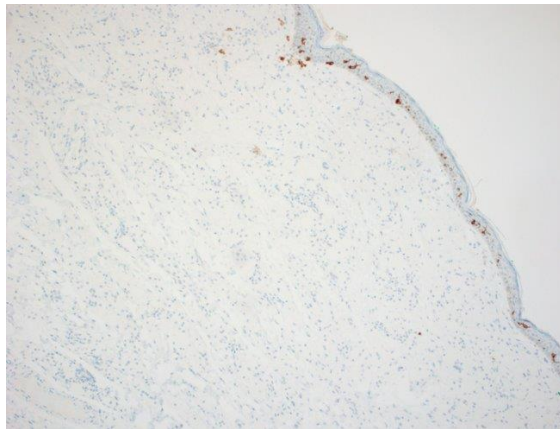
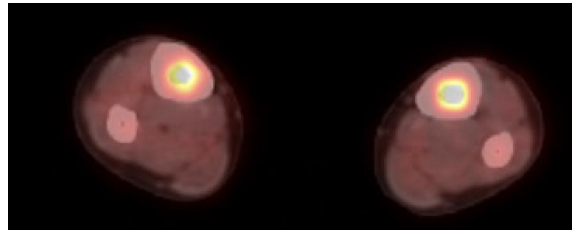
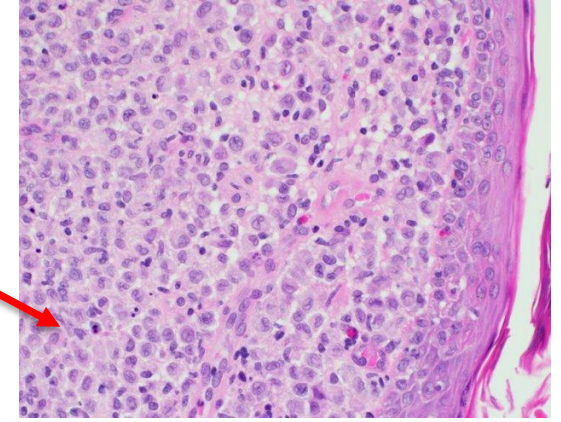
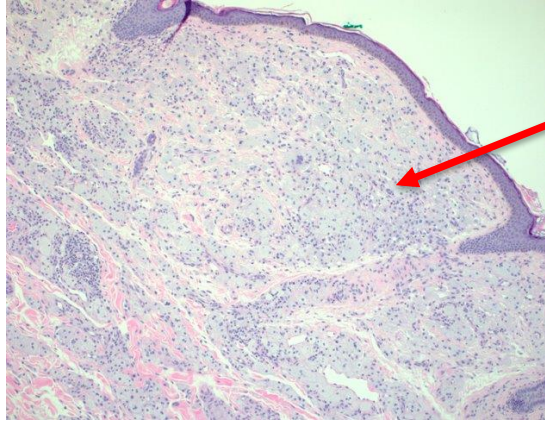
- Progression on or subsequent to targeted therapy
 - Progression on ultra low-dose cobimetinib, response recaptured with dose increase
 - Neurologic progression on low-dose BRAF inhibitor monotherapy (2)
 - Recurrence following discontinuation of BRAF inhibitor
 - Neurologic progression on low dose MEK inhibitor



Treatment

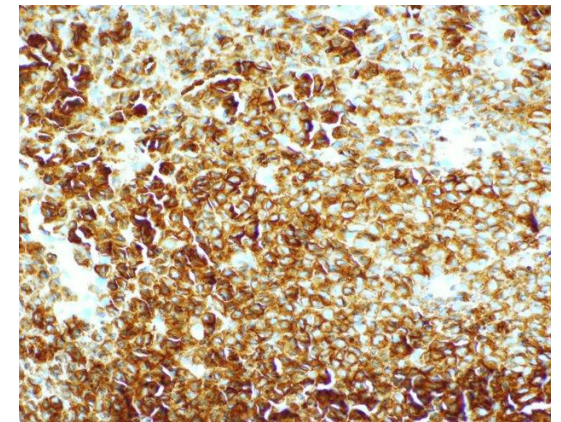


Case examples



CD1a

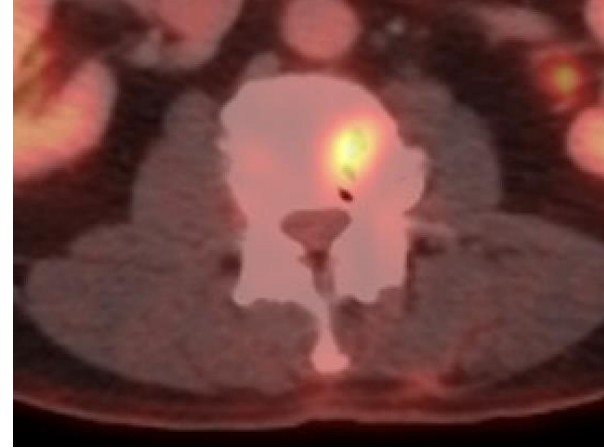
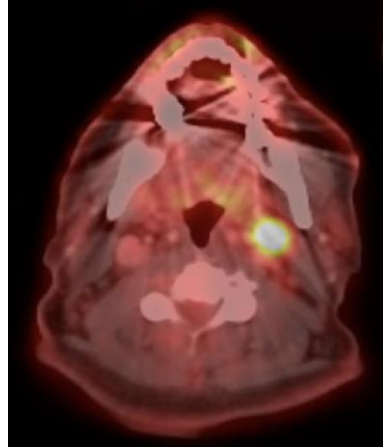
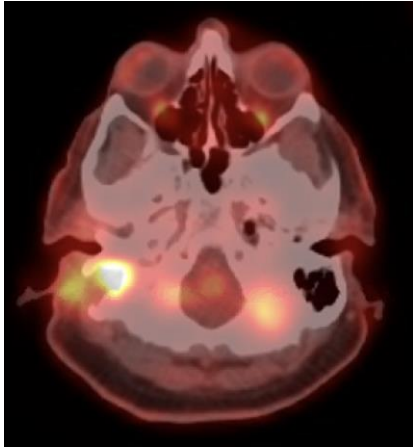
- LCH (skin, nails) refractory to MTX, cytarabine, thalidomide
- Xanthelasma --> non-LCH
- PET/CT with tibial lesions
- BRAF p. M484_P490 del
- Prolonged response to Cobimetinib
- Evolution from LCH to ECD phenotype



CD1a



Case examples



- LCH with of mastoid, lymph nodes, bone
- BICD2-BRAF fusion
- Progression following cytarabine
- Skin assessment demonstrates small papules
- Biopsy → non-LCH
- Lasting response to MEK inhibition



Conclusions

- Mixed histiocytosis represents a diverse clinical and molecular spectrum
- Instances of LCH phenotype with foci of ECD pathology, evolution from LCH to ECD phenotype
- Meticulous attention to elements of non-LCH is needed in LCH patients, clinically and upon biopsy review, especially in the setting of failure of conventional treatment
- Entity is responsive to targeted therapy



Thank you



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