

AUTOIMMUNITY IN L GROUP HISTIOCYTOSIS

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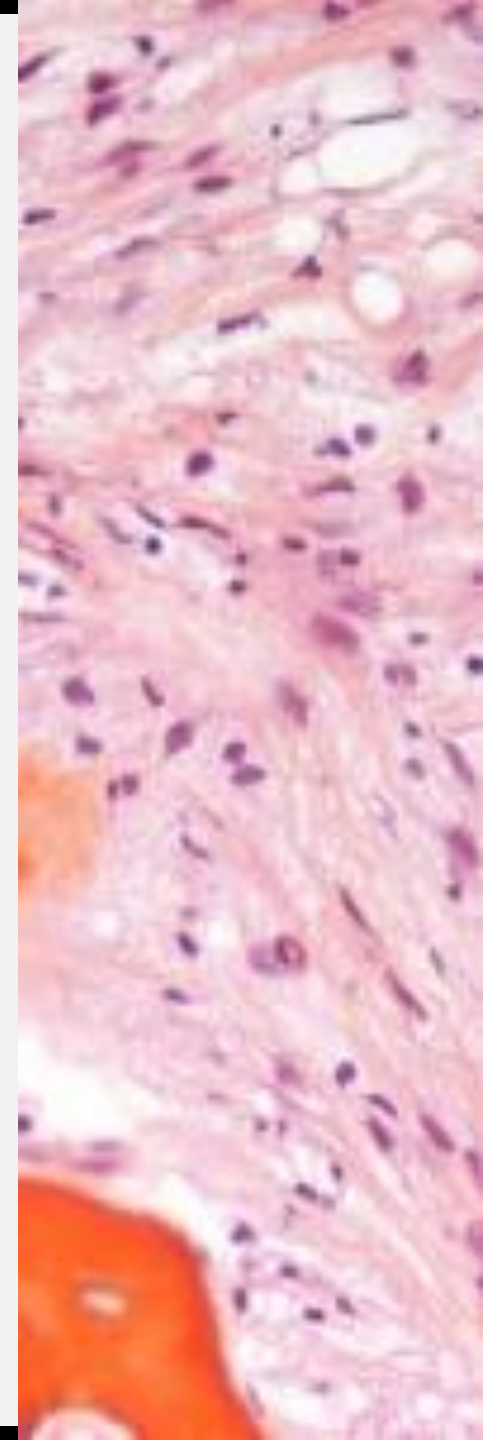
Erdheim Chester disease (ECD) : CD68(+) CD1a(-) histiocytes

Langerhans-cell histiocytoses (LCH) : CD1a (+) histiocytes

Histiocytes such as macrophages and dendritic cells play a role in the regulation of the immune system

Autoimmunity is present in a broad spectrum of diseases in which histiocytes are altered :

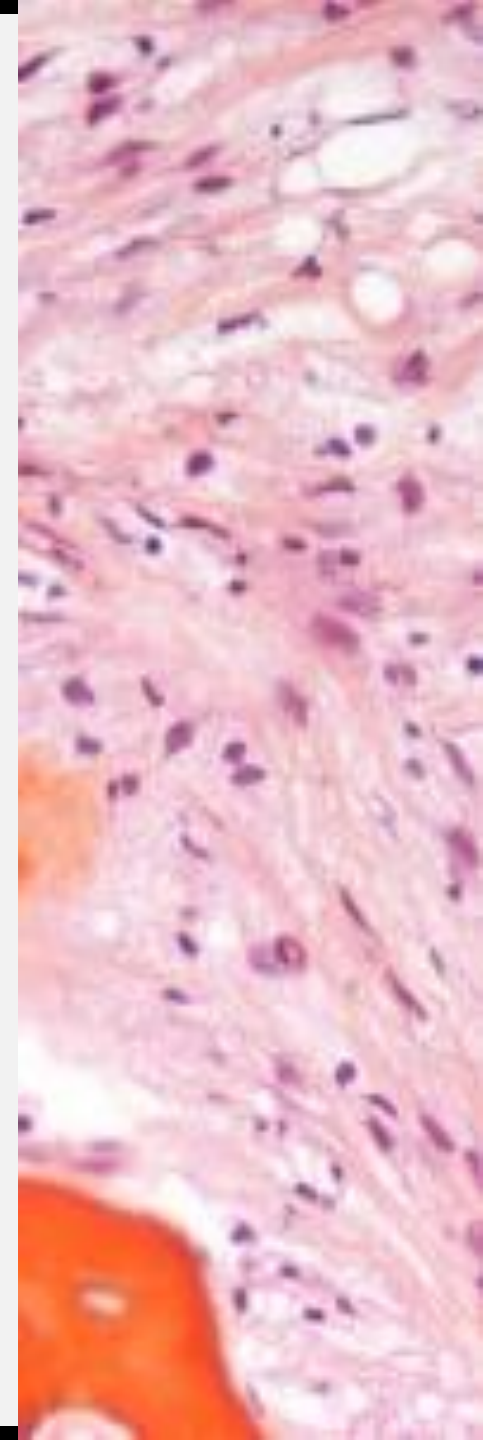
- **Gaucher disease** : antinuclear antibodies in up to 25% of cases
- **Destombes Rosai Dorfman disease** : autoimmunity in up to 20% of cases



Auto-immunity has not been evaluated previously in L-group histiocytoses

BRAF- and *MEK*- inhibitors are widely used

A case of polymyalgia rheumatic was successfully treated with cobimetinib

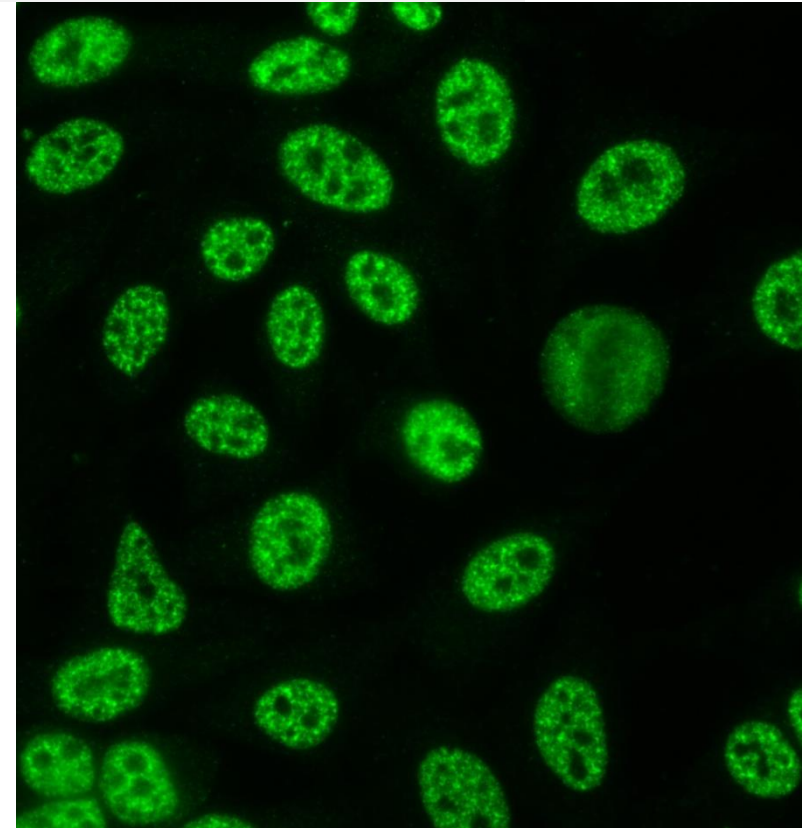


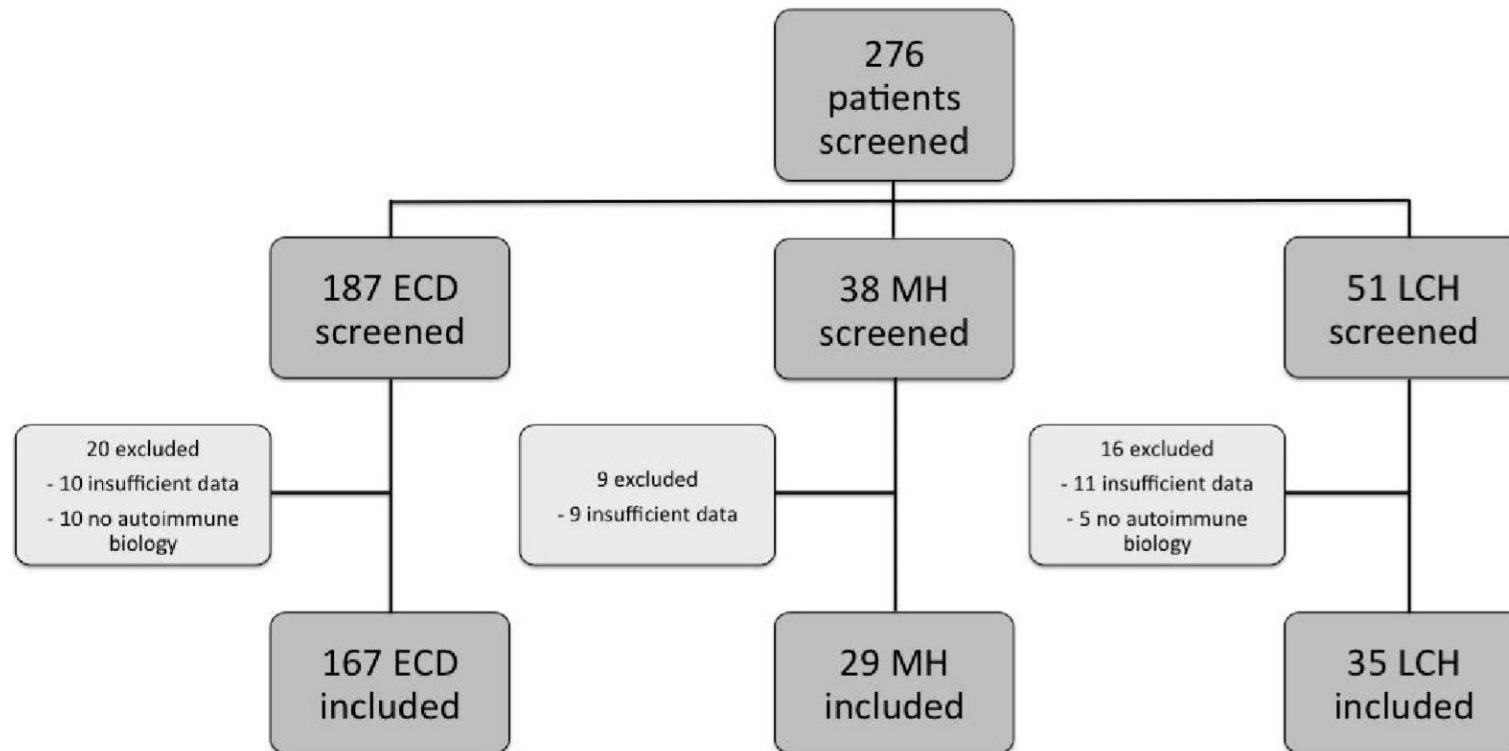
METHODS

Patients with L-group histiocytoses

- supported by histology
- with at least one determination of antinuclear antibodies

seen in the French National Reference Center of Histiocytoses of the Pitié-Salpêtrière Hospital





BIOLOGICAL AUTOIMMUNITY AND AUTOIMMUNE DISEASES IN L GROUP HISTIOCYTOSES

	ECD (n=167)	Mixed histiocytosis (n=29)	LCH (n=35)	p*	p**
Age at histiocytosis diagnosis	57 (15)	58 (12)	36 (15)	<0.0001	<0.0001
Age at ANA determination, mean (SD)	61 (15)	62 (11)	44 (16)	<0.0001	<0.0001
Sex (M/F)	123/44	15/14	16/19	0.006	0.001
AID without ANA/APL (group 1)	16 (10%)	0 (0%)	1 (3%)		
AID with ANA/APL (group 2)	6 (4%)	1 (3%)	0 (0%)	0.091	0.084
ANA/APL/Autoantibodies without defined AID (group 3)	47 (28%)	12 (41%)	6 (17%)		
Total of patients with autoimmunity	69 (41%)	13 (45%)	7 (20%)	0.015	0.047

Table 1. Patients of L-group histiocytosis with autoimmunity

ECD Erdheim Chester disease

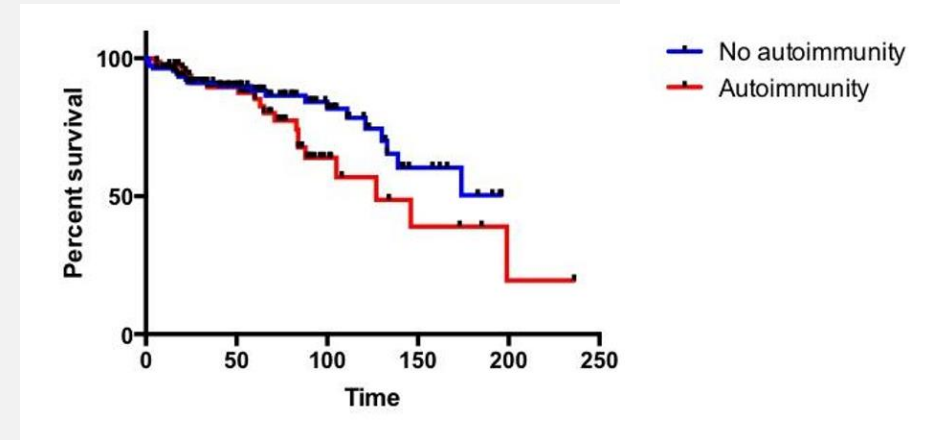
LCH Langerhans-cell histiocytosis

* Comparison between ECD (including mixed histiocytosis) and LCH

** Comparison between 3 groups

AUTOIMMUNITY IN ECD

	All (n=196)	Autoimmunity (n=82)	No autoimmunity (n=114)	p
Sex (M/F)	138/58	53/29	85/29	0.15
Age at diagnosis (mean, SD)	57 (14)	58 (14)	57 (15)	0.36
Age at AAN dosage (mean, SD)	61 (14)	62 (12)	60 (15)	0.30
<i>BRAF</i> status, n (%)				
V600E	108/166 (65%)	43/71 (61%)	65/95 (%)	0.32
Mixed histiocytosis, n (%)	29 (15%)	13 (16%)	16 (14%)	0.84
ECD involvements, n (%)				
Cardiac involvement	96 (49%)	42 (51%)	54 (47%)	0.66
Vascular involvement	116 (59%)	49 (60%)	67 (59%)	1.00
Xanthelasma	45 (23%)	21 (26%)	24 (21%)	0.49
Diabetes insipidus	51 (26%)	22 (27%)	29 (25%)	0.87
CNS involvement	69 (35%)	26 (32%)	43 (38%)	0.45
Retro-orbital involvement	38 (19%)	18 (22%)	20 (18%)	0.47
Retroperitoneal involvement	122 (62%)	47 (57%)	75 (66%)	0.24
Deaths, n (%)	41 (21%)	21 (26%)	20 (18%)	0.21

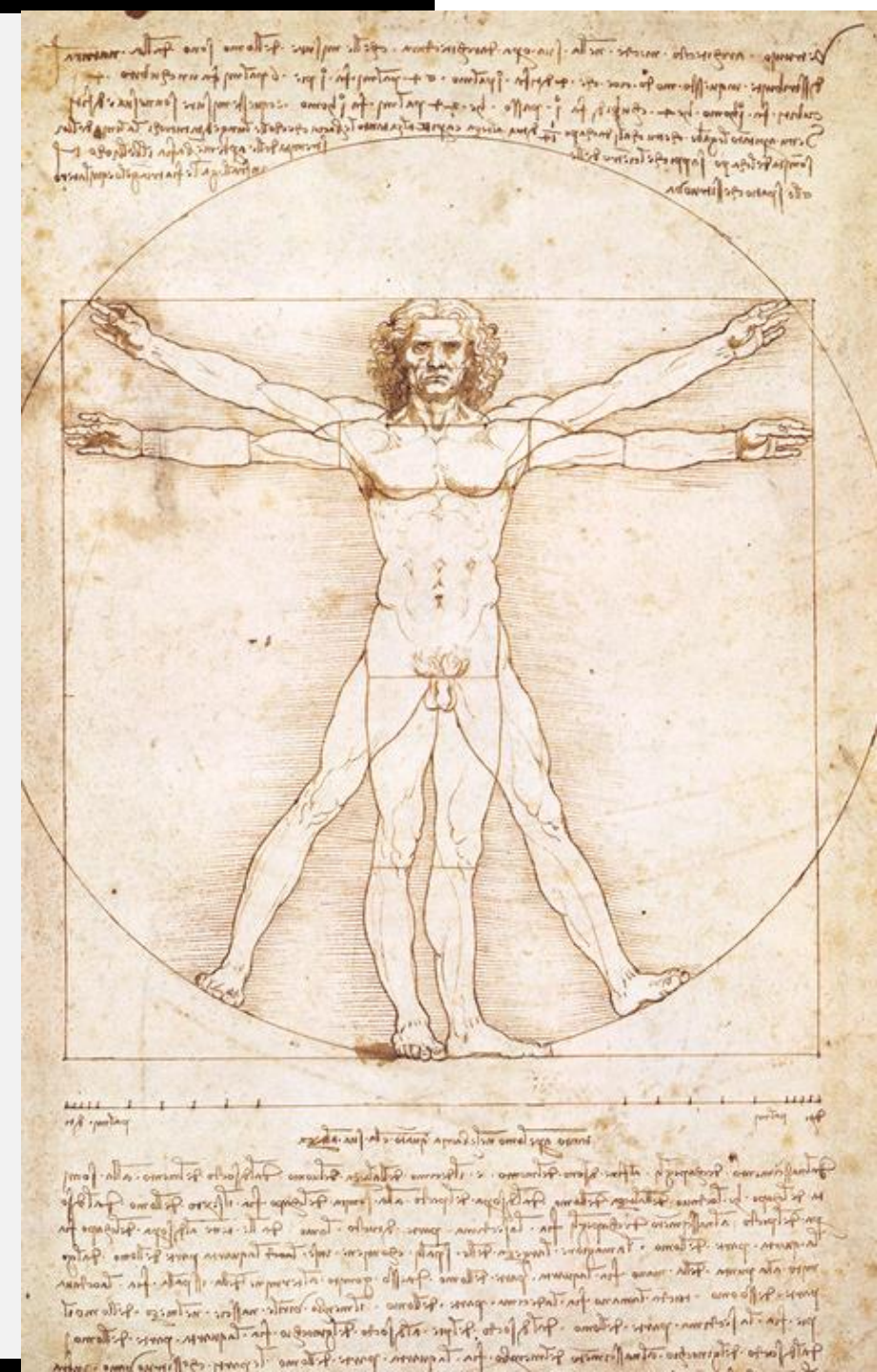


AUTOIMMUNITY IN ECD

12 % of patients had autoimmune diseases :

- autoimmune thyroiditis (n=8)
- primary Sjögren syndrome (n=3)
- systemic lupus erythematosus (n=3)
- Biermer disease (n=2)
- polymyalgia rheumatica (n=2)
- type 1 diabetes (n=2)
- antiphospholipid syndrome (n=1)
- coeliac disease (n=1)
- autoimmune hemolytic anemia (n=1)
- immune thrombopenic purpura (n=1)
- autoimmune alveolitis (n=1)

present before the diagnosis of ECD in 12 cases



TREATMENTS OF PATIENTS WITH ECD

145 patients were treated with interferon-alpha

19 were treated with infliximab

The number of patients with autoimmunity among those who received interferon or infliximab and among those who did not was not significantly different

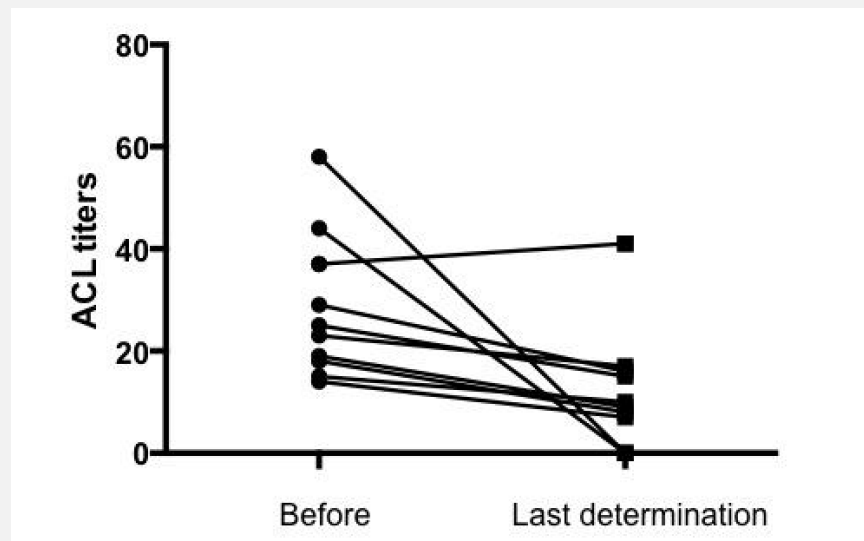
BRAF- AND MEK- INHIBITORS

75 ECD patients were treated with targeted therapy

6 patients had autoimmune disease

18 had positive ANA, 18 had persistent APL antibodies

The anticardiolipid (ACL) antibodies titres significantly decreased during treatment with targeted therapy



CONCLUSIONS

Autoimmunity is frequent in ECD but not in LCH

- Pathological histiocytes could have altered functions of immune homeostasis through modification of their phagocytosis or antigen presentation functions
- In LCH, pathological histiocytes acquire characteristics resembling to those of Langerhans cells
- The microenvironment around pathological histiocytes could participate to the induction of autoimmunity
- An alteration of the destruction of circulating DNA by pathological histiocytes could also lead to increase in ANA occurrence
- Possible Fas Ligand deficit ?

CONCLUSIONS

Autoimmunity improves under *BRAF*- and *MEK*-inhibitors

- The RAS-RAF-MEK-ERK pathway is altered in almost all cases of ECD
- ERK expression is increased in several immune diseases
- ACL titres significantly decreased under BRAF or MEK inhibitor

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ECDGA

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