ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN ECD

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Context

Erdheim-Chester Disease: histiocytosis characterized by tissue infiltration of:

- CD68+, CD1a- histiocytes, derived from cells of the mononuclear phagocyte system harboring recurrent mutations in the MAPK-signaling pathway
- inflammatory cells and fibrosis

Haroche J. Blood. 2012.

Context

Vascular endothelial growth factor-A (VEGF):

- regulator of angiogenesis, particularly in cancer and inflammatory processes
- VEGF serum levels ↑ ↑ in POEMS syndrome

  => increase vascular permeability

  => cardiac involvement / myocardial oedema and fibrosis
- Mutant RAS upregulate VEGF expression
- produced by macrophages in Mycobacterial-associated granulomas

  => recruitment of monocytes

Ferrara N. Nature Medicine. 2003
Rak J. Cancer Research. 1995
Harding JS. Cell Reports. 2019

In histiocytic diseases:

- VEGF expressed by histiocytes in LCH
- High serum VEGF in a series of 24 ECD vs healthy controls

Dina A. Journal of Pediatric Hematology/Oncology. 2005.
Arnaud L. La Revue de Médecine Interne. 2009

We hypothesized that VEGF could play a role in ECD pathophysiology

1/ determine if VEGF was expressed by histiocytes in ECD lesions

2/ assess levels of serum VEGF in ECD patients and determine if they are associated with patient's characteristics

Methods

- Retrospective study
- Patients with ECD seen in the French National Reference Center for Histiocytoses of the Pitié-Salpêtrière Hospital
- from 2009 to 2019
- with at least 1 serum VEGF determination

- Biopsies of patients with extreme serum VEGF centrally reviewed and stained for VEGF with 2 IHC antibodies (VG-1 and F-PU483).

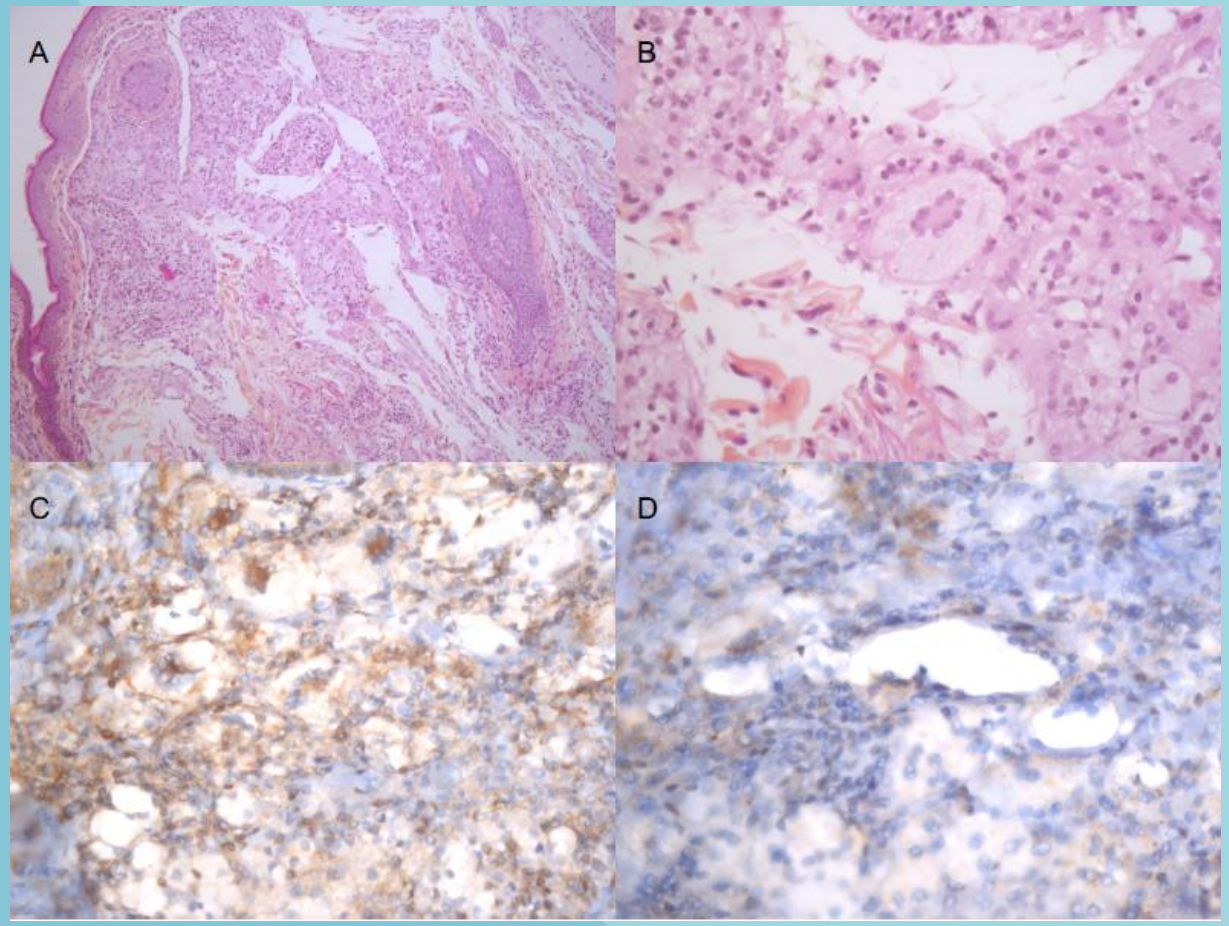
Results: patients

- 248 patients included

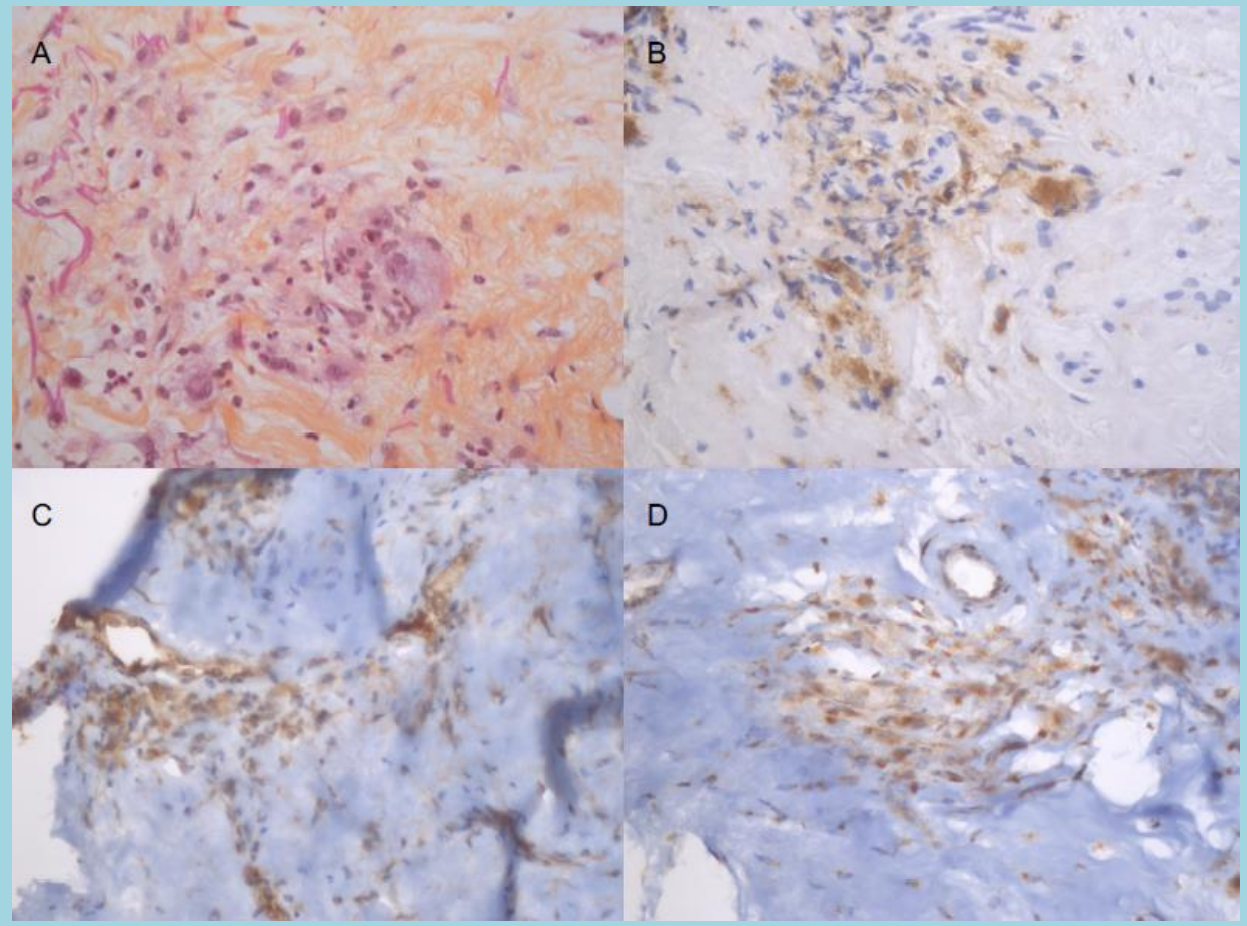
- High serum VEGF (> 500pg/mL): **53.2 %**
- Median sVEGF :
  - 843 pg/mL (IGR 626-1250) in high serum VEGF patients group
  - 288 pg/mL (IQR 194.8- 389.3) in low serum VEGF patients group

Results: pathology

- 26 ECD histological samples: **26/26 had a moderate to high VEGF staining**



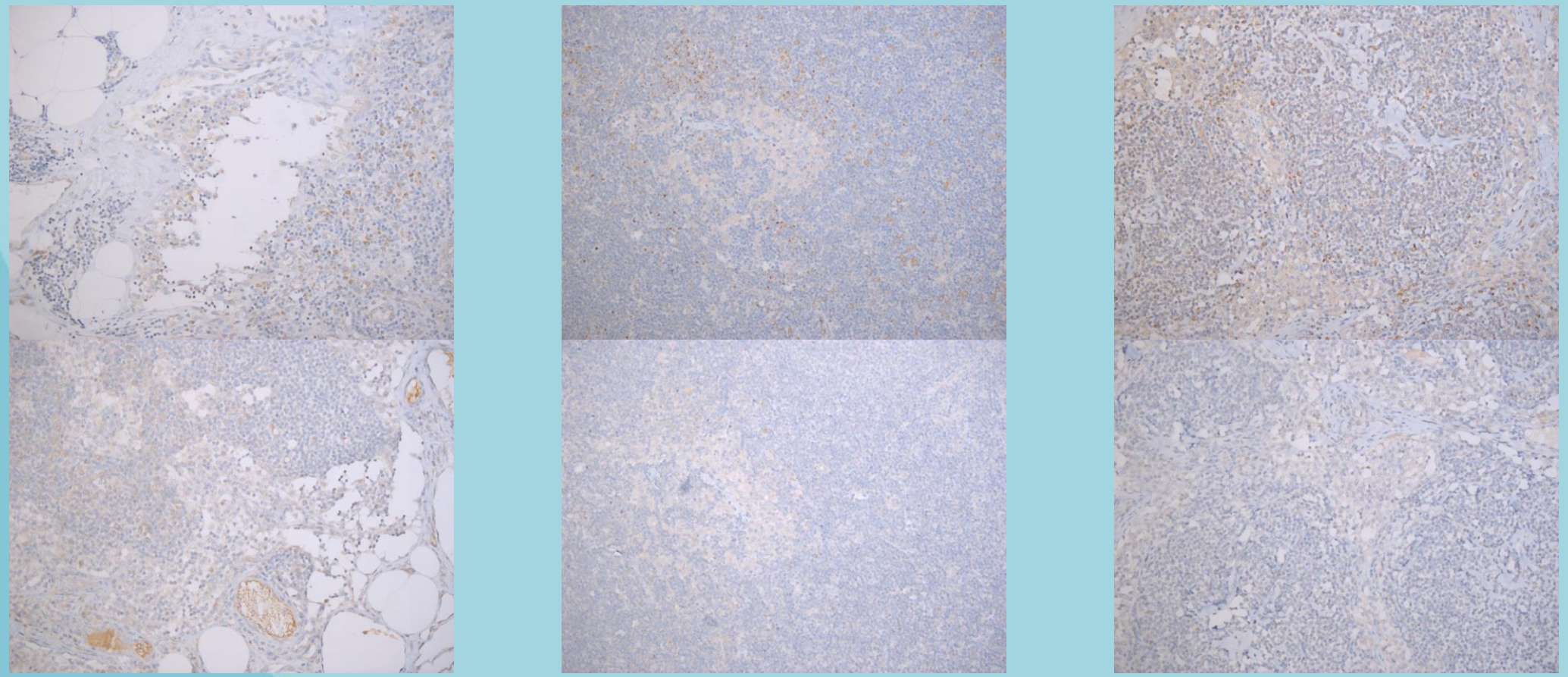
ECD Xanthelasma



ECD Perirenal infiltrate

Results: pathology

- Control: 4 biopsies of reactional sinusal histiocytosis: no VEGF staining on histiocytes



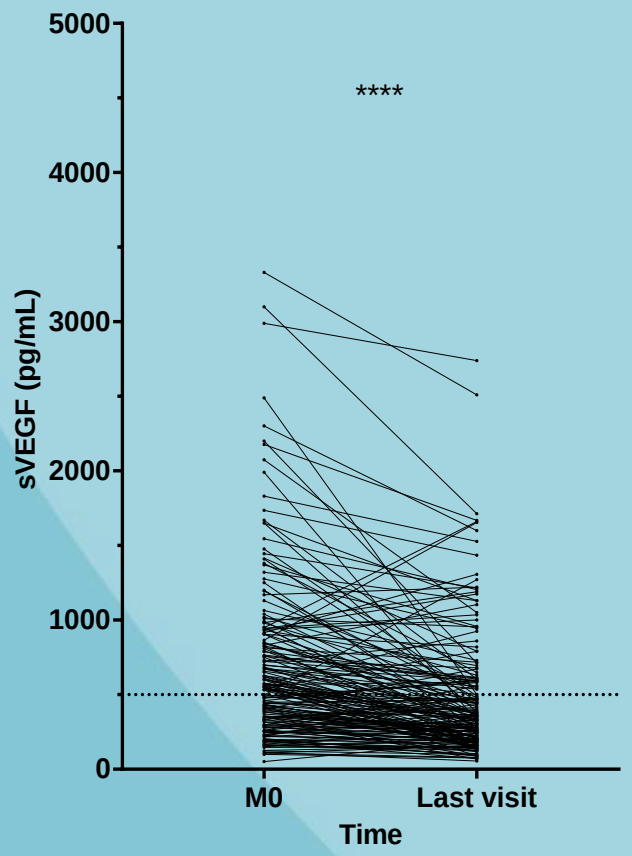
Reactional sinusal histiocytosis

	All (n=248)	High serum VEGF (n=132)	Low serum VEGF (n=116)	p
Sex (M/F)	171/77	95/37	76/40	0.273
Age at diagnosis (mean, SD)	58.3 (14.3)	58.1 (14.3)	58.4 (14.2)	
V600E *BRAF* status, n (%)	142/222 (64.0)	82/122 (67.2)	60/100 (60.0)	0.265
Mixed histiocytosis, n (%)	44 (17.7)	25 (18.9)	19 (16.4)	0.598
Langerhans cell histiocytosis, n (%)	37 (14.9)	21 (15.9)	16 (13.8)	-
Rosaï Dorfman disease, n (%)	6 (2.4)	3 (2.2)	3 (2.6)	-
ECD involvements, n (%)				
Cardiac involvement	125 (50.4)	77 (58.3)	48 (41.4)	0.008
- Pericardia	71 (28.6)	41 (31.1)	30 (25.9)	0.366
- Right atrium pseudotumor	89 (36.8)	55 (41.7)	34 (29.3)	0.043
- Atria-ventricular septum	37 (14.9)	22 (16.7)	15 (12.9)	0.410
- Coronary artery	53 (21.4)	36 (27.2)	17 (14.7)	0.016
- Cardiac dysfunction	25 (10.1)	15 (11.4)	10 (8.6)	0.474
Vascular involvement	149 (60.1)	93 (70.5)	56 (48.3)	0.0004
- Coated aorta	105 (42.3)	66 (50.0)	39 (33.6)	0.009
- Mesenteric artery	40 (16.1)	22 (16.7)	18 (15.5)	0.806
- Renal artery	48 (19.4)	28 (21.2)	20 (17.2)	0.429
Xanthelasma	54 (21.8)	30 (22.7)	24 (20.7)	0.698
Diabetes insipidus	58 (23.4)	28 (21.2)	30 (25.9)	0.388
CNS involvement	88 (35.5)	50 (37.9)	38 (32.8)	0.400
Retro-orbital involvement	45 (18.1)	28 (21.2)	17 (14.7)	0.181
Retroperitoneal involvement	157 (63.3)	93 (70.5)	62 (55.1)	0.006
Deaths, n (%)	66 (26.6)	40 (30.3)	26 (22.4)	0.161

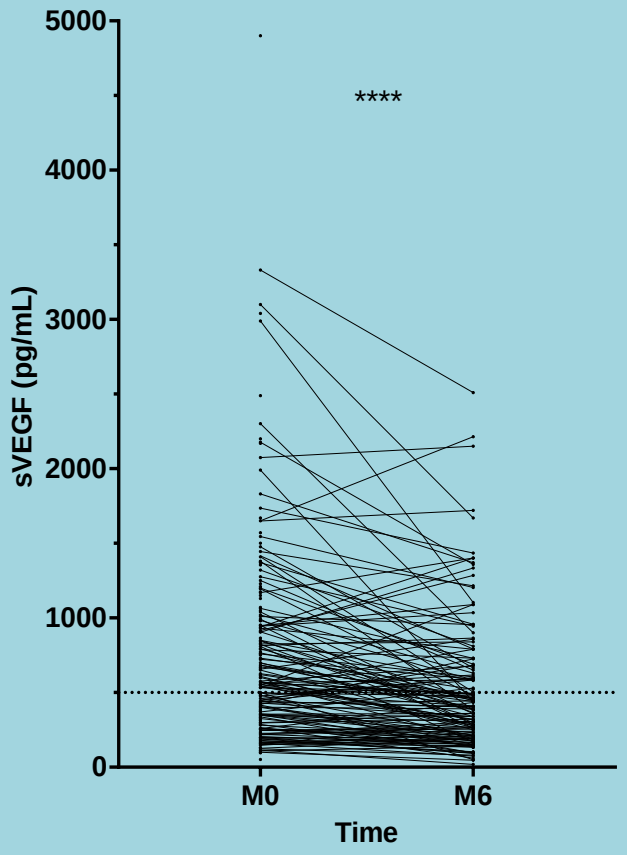
Treatments	All (n=248)	High serum VEGF (n=132)	Low serum VEGF (n=116)	p
Corticosteroids, n (%)	64 (25.8)	31 (23.5)	33 (28.4)	0.372
IFN-α or PEG-IFN-α, n (%)	156 (62.9)	82 (62.1)	74 (63.8)	0.786
Anakinra, n (%)	24 (9.7)	14 (10.6)	10 (8.6)	0.597
Infliximab, n (%)	5 (2.0)	2 (1.5)	3 (2.5)	-
Cladribine, n (%)	6 (2.4)	4 (3.0)	2 (1.7)	-
Imatinib, n (%)	5 (2.0)	2 (1.5)	3 (2.6)	-
Targeted therapy, n (%)	102 (41.1)	66 (50.0)	36 (31.0)	0.002
Vemurafenib, n (%)	84 (33.9)	52 (39.3)	32 (27.6)	0.049
Dabrafenib, n (%)	3 (1.2)	3 (2.2)	0 (0.0)	-
Cobimetinib, n (%)	40 (16.1)	27 (20.5)	13 (11.2)	0.048
Trametinib, n (%)	3 (1.2)	2 (1.5)	1 (0.9)	-

Results: VEGF variation under therapy

Consecutive measurements in 183 patients
Median time between first and last determination:
24 months (SD 31.86)



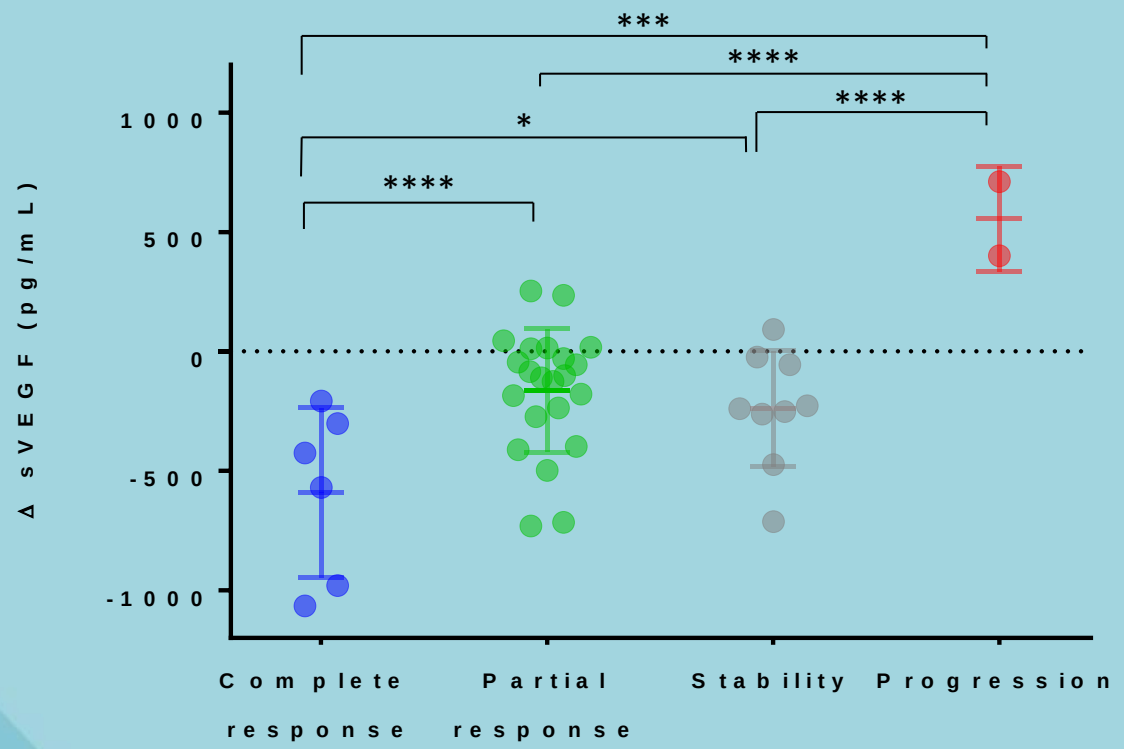
Early variation: 139 patients with a 2nd determination after a 6 months follow-up



Results: VEGF variation and cardiac response under therapy

Consecutive cardiac MRI: 45 patients (median interval: 48 months)

- Thoracic aorta coating in 31 patients (69%): persisted in all cases.
- **Cardiac involvement** in 45/45: 6 complete responses, 25 partial responses, 12 stable, 2 progressions.



Conclusion

- VEGF produced by ECD histiocytes
- Serum VEGF elevation frequent in ECD
- High serum VEGF associated with cardiac and vascular involvement
- Serum VEGF level variation correlates response of cardiac involvement under therapy

⇒ Better insight in the pathogenesis of ECD

⇒ Improvement of cardiovascular involvement detection and follow-up ?

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