Vascularites associées aux hémopathies (SMD/LMMC/Lymphomes) et cancers

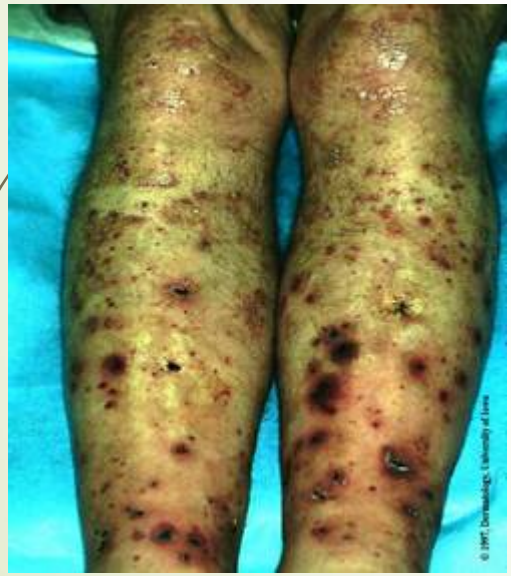
Arsene Mekinian
Service de médecine interne
Hôpital Saint Antoine
arsene.mekinian@aphp.fr
0615456720

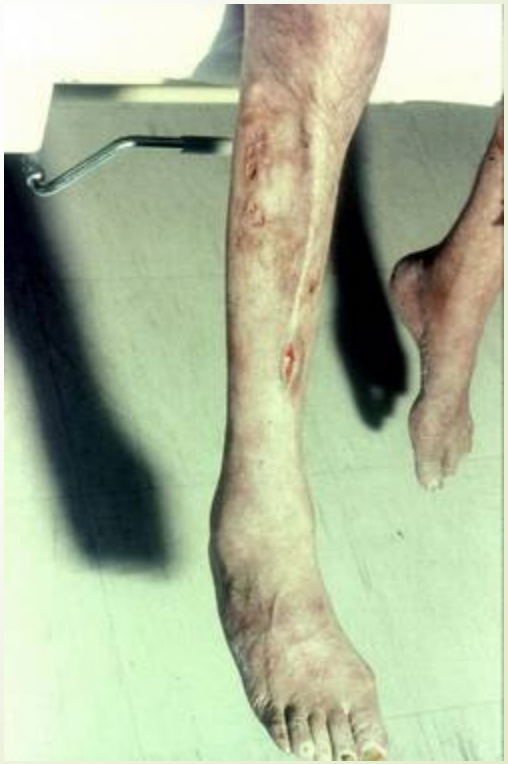
Vascularites :
Évoquer différentes étiologies avant la forme paranéoplasique

- Infections: virales, bactériennes, fungiques
- Médicaments:
  - antibiotiques: pénicilline, sulfamides, quinolones,….
  - chimiothérapie : bléomycine, methotrexate, gemcitabine, CYC
  - cytokines: IFN, IL2, GCSF, GMCSF
  - Ac monoclonaux: rituximab, alemtuzumab
- Cryoglobulinémie

Vascularites « paranéoplasiques » associées aux hémopathies et cancers

- Type de vascularites / type de pathologie sous jacente
- Phénotype : +++ peau, articulaire et neurologique périphérique
- Impact sur la survie ?
- Traitement MAI ou hématologique ?





Etude GFEV n=65

Table 1. Vasculitides associated with malignancy, the 65 malignancies associated with vasculitis, and demographic data*

Parameter	Value
Sex, no. (%) male/female	43 (71.7)/17 (28.3)
Age, mean ± SD (range)	62.4 ± 12.9 (22–89)
Type of vasculitis associated with malignancy (n = 60)	
Leukocytoclastic vasculitis	27 (45)
With digital necrosis	4 (6.7)
With Sweet's syndrome	2 (3.3)
With nerve microvasculitis	1 (1.7)
Polyarteritis nodosa	22 (36.7)
Wegener's granulomatosis	4 (6.7)
Microscopic polyangiitis	3 (5)
Henoch-Schönlein purpura	3 (5)
Granulomatous cutaneous vasculitis	1 (1.7)
Malignancies associated with vasculitis (n = 65)	
Hematologic	41 (63.1)
Myelodysplastic syndrome	21 (32.3)
Refractory anemia with excess blasts	11 (16.9)
Refractory anemia	3 (4.6)
Chronic myelomonocytic leukemia	7 (10.8)
Lymphoid malignancy	19 (29.2)
Non-Hodgkin's lymphoma	6 (9.2)
Diffuse large B cell	3 (4.6)
Mantle zone	1 (1.5)
T cell lymphoma†	2 (3.1)
Hodgkin's disease	4 (6.2)
Chronic lymphocytic leukemia	4 (6.2)
Hairy cell leukemia	1 (1.5)
Multiple myeloma	4 (6.2)
IgGκ	3 (4.6)
IgAκ	1 (1.5)
Myelofibrosis	1 (1.5)
Solid tumors	24 (36.9)
Lung cancer	5 (7.7)
Adenocarcinoma	3 (4.6)
Small-cell carcinoma	1 (1.5)
Squamous-cell carcinoma	1 (1.5)
Genitourinary plus gynecologic	9 (13.8)
Renal cancer	3 (4.6)
Bladder	1 (1.5)
Ovarian	2 (3.1)
Endometrial	1 (1.5)
Breast cancer	2 (3.1)
Gastrointestinal cancer	7 (10.8)
Colon	2 (3.1)
Stomach	2 (3.1)
Small intestine	2 (3.1)
Hepatocellular carcinoma	1 (1.5)
Nasopharyngeal	1 (1.5)
Mesothelioma	1 (1.5)
Adenocarcinoma, origin unknown	1 (1.5)

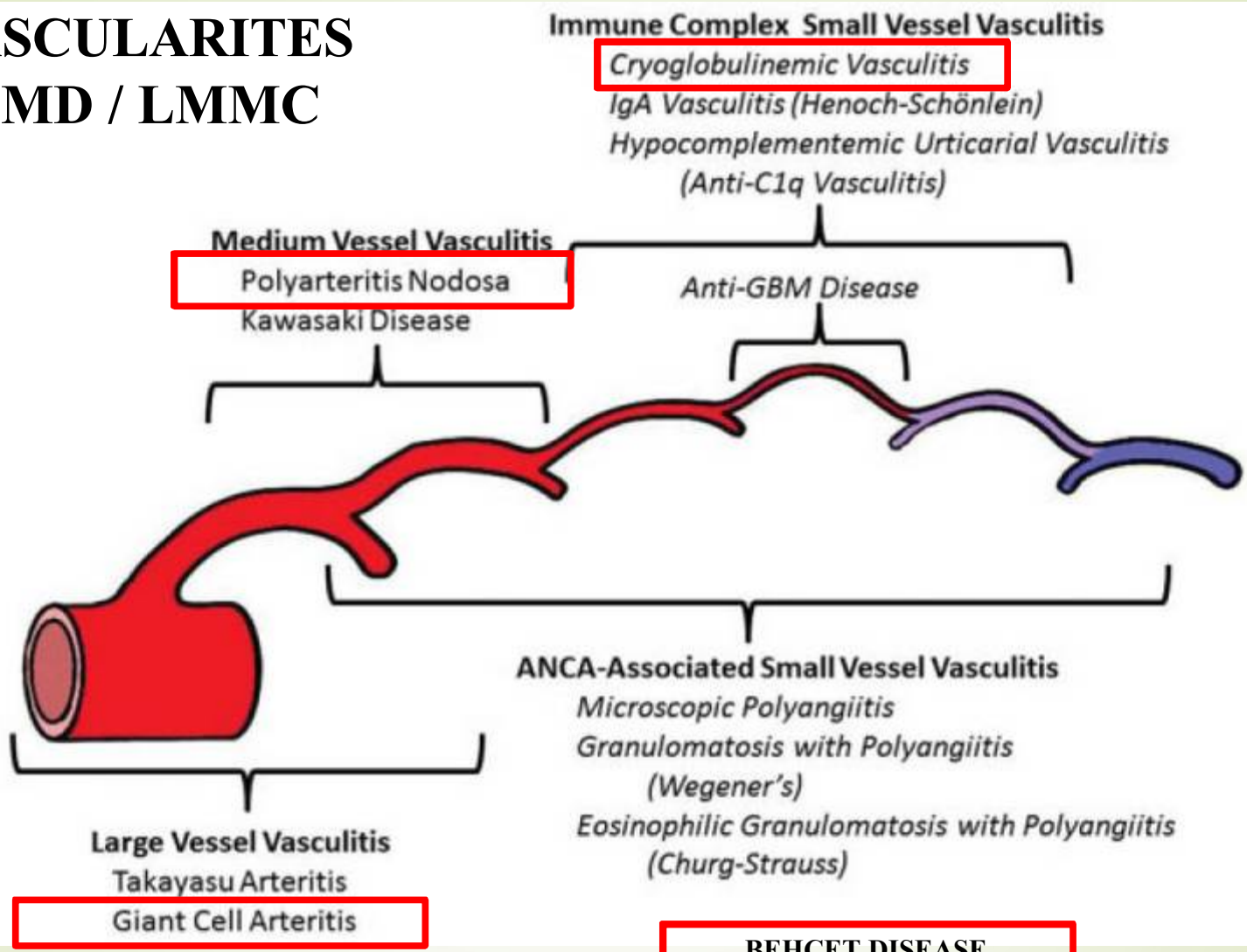
		Vasculitis				
Malignancy	n	PAN (n = 22)	LV (n = 27)	WG (n = 4)	MPA (n = 3)	HSP (n = 3)
Myelodysplastic syndrome	21	9	9	1	1	0
Lymphoid malignancies	19	6	9	1	2	0
Solid tumors	24	7	9	2	1	3

Fain Arthritis & Rheumatism 2007

Table 6. Comparisons of vasculitis characteristics according to the type of malignancy*

Vasculitis characteristic	Type of malignancy			P
	Solid tumor	Lymphoid	MDS	
Necrotizing vasculitides†	47.6	47.1	52.4	NS
Cutaneous manifestations	76.3	76.5	81	NS
Arthralgias	57.1	17.6	61.9	0.01
Peripheral neuropathy	47.6	35.3	14.3	0.05
Renal involvement	19	5.9	42.9	0.02
Lung involvement	4.8	5.9	19	NS
Gastrointestinal involvement	14.3	0	23.8	NS
Inflammatory syndrome	76.2	52.9	81	NS
Monoclonal gammopathy	9.5	42.9	10	0.02
ANCA positivity	25	18.2	20	NS
Steroid dependence	27.8	25	63.2	0.04
Vasculitis complete remission	66.7	87.5	47.6	0.04
Cancer complete remission	42.9	35.3	4.8	0.01
Death	47.6	47.1	76.2	NS

VASCULARITES SMD / LMMC



Manifestations auto-immunes associées SMD : types

First author [Ref.], year	Subjects, n (rate, %)	Age, years[a] (median)	Context of study	Most frequent AICs[b]		Factors associated with AICs
Komrokji [12], 2016	391/1,408 (28%)	75% were >60 years	Bi-institutional retrospective study	Hypothyroidism ITP RA	44% 12% 10%	Female gender WHO refractory anemia or RAMD subtypes RBC transfusion independence
Mekinian [8], 2016	123	74	Multicenter survey for a wide spectrum of AICs	Systemic vasculitis CTDs Inflammatory arthritis Neutrophilic dermatosis	32% 25% 23% 10%	Younger age, male gender Higher-risk MDS *Specific associations:* CMML and vasculitis Behçet's disease and trisomy 8 Low-risk MDS and CTD High-risk MDS and ND
Mekinian [9], 2014	68	72 (31–89)	Case series (n = 22) added to 46 previously published cases with inflammatory arthritis	RA PMR RS3PE	62% 26% 12%	NA
Al Ustwani [10], 2013	44	59 (16–82)	Case series (n = 10) added to 34 previously published cases	Vasculitis Seronegative arthritis Skin lesions[c]	27% 18% 13%	NA
De Hollanda [20], 2011	46/235 (19.5%)	78 (68–93)	Multicenter retrospective analysis	Cutaneous lesions Noninfectious fever Arthralgia/arthritis Peripheral neuropathy	24% 13% 13% 10%	Higher-risk MDS (per WPSS)
Dalamaga [19], 2008	21/84 (25%)	74.61 ± 8.08[d]	Single-center survey of cutaneous manifestations	Photosensitivity Leukocytoclastic vasculitis Prurigo nodularis Neutrophilic dermatosis Ecchymosis/purpura	28% 24% 14% 10% 10%	Higher-risk MDS Hypergammaglobulinemia
Marisavljevic [21], 2006	20/284 (7%)	NA	Single-center retrospective study.	Skin vasculitis RA Neutrophilic dermatosis Sjögren's syndrome AIHA	25% 20% 10% 10% 10%	Female gender
Giannouli [18], 2004	13/70 (18.6%)	67	4-year prospective study of 70 patients with MDS	Isolated AICs CTDs Systemic vasculitis	38% 38% 24%	Younger age
Hamidou [73], 2000	20	68 (36–96)[e]	Part of a prospective study of 200 patients (n = 60 with MDS)	Systemic vasculitis Neutrophilic dermatosis Fasciitis	45% 10% 10%	NA
Enright [5], 1995	30/221 (7.4%)	63 (7.5–87)	Single-center retrospective analysis	Vasculitis CTD Other	60% 17% 37%	NA
Billström [17], 1995	10/82 (12%)	66 (53–77)	Retrospective single-center report	Leukocytoclastic vasculitis	50%	Younger age Complex karyotype

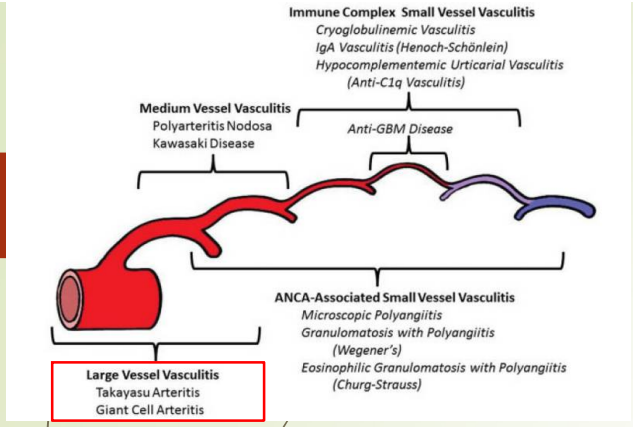
Manifestations associées SMD : Etude française

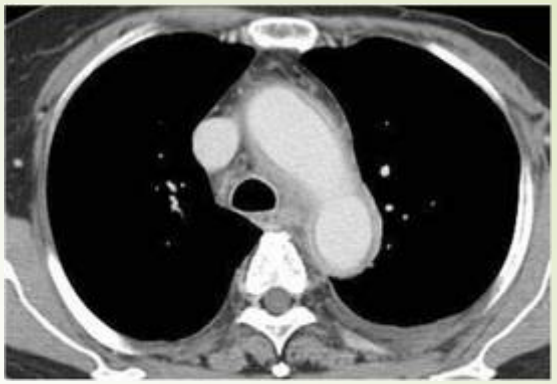
		Type	Inclassés n=29 (24%)
Vascularites	**39 (32%)**	PAN (12) Horton (9) Behcet (6) Cryo (3) GPA (1) Inclassée (8)	6 (15%)
Connectivites	**31 (25%)**	PCA (18) Lupus (8) SAPL primaire (4) Myosite (3) Sjogren (2)	0
Pathologies neutrophiliques	**12 (10%)**	Abcès aseptique Sweet (9) Pyoderma (2)	0
Rhumatismes inflammatoire	**28 (23%)**	PPR (10) PR (4) RS3PE (4) Indéterminés (10)	10 (36%)
Inclassés	**13 (11%)**	-	13

MAI variées / incomplètes ou inclassées
Absence d'association avec certaines MAI

Vascularites et SMD

Auteur	VASC /MAI	AGC/Taka	PAN	ANCA +	Cryo	VASCU leucocyt	Behcet
Berthier 2001	6/14	4	1	0	0	1	0
Hamidou 2001	8/8	-	8	-	-	-	-
Giannouli 2004	4/13	1	0	1	0	2	0
Bouali 2005	0/40	0	0	0	0	0	0
De Hollanda 2011	5/46	0	-	3	2	-	0
Mekinian 2016	39/123	9	12	1	3	8	6
Total	62/244 (25%)	14 (23%)	21 (34%)	5 (8%)	5 (8%)	11 (18%)	6 (10%)





Case	Gender	Age	MDS Type	IPSS	Karyo-type	Type of vasculitis	Treatment	Time relation of vasculitis to MDS	Outcome
1[12]	F	52	RAEB-t*		normal	TA	GC Bone marrow transplantation	0	Dead for infection
2[13]	M	67	RAEB-1	0.5	normal	TA	GC	0	Stable
3[13]	M	60	RARS	0.5	normal	TA	GC	+2 year	AML (4 months later)
4[14]	M	62	RCMD	0.0	normal	TA	GC MTX	+2 months	AML (12 months later) Dead for infection
5[15]	F	75	RAEB-2	1.5		GCA	GC	0	Dead for infection
6[16]	F	67				GCA	GC	-3 year	Stable
7[11]	F	68	RAEB-t*			GCA	GC	-4 months	Dead for AML
8	F	71	RCMD	1.0	t(6:11) (q27:q23)	TA s/o	GC	0	AML (4 months later) Dead for AML

- **GCA n=7 / 123 SMD/MAI**
- **GCA évolution similaire sans SMD**
- **PPR rémission dans 44% et corticodependance 30%**

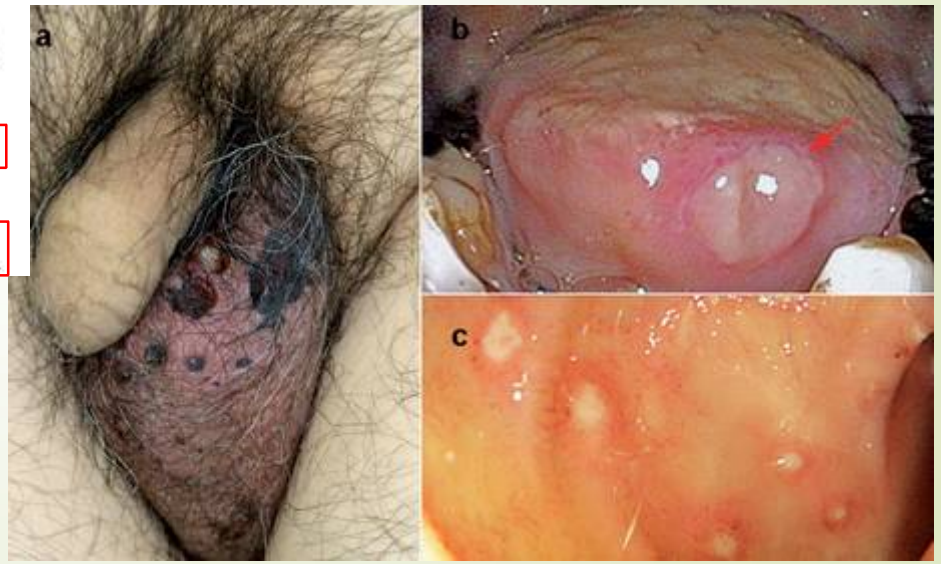
- **Etude cas contrôles AGC MSD/ SMD**

Maladie de BEHCET associée aux SMD

N=31

	n (%)
Sex	
Male	12 (39)
Female	19 (61)
Symptoms[a]	
Recurrent oral aphthae	27 (87)
Recurrent genital aphthae	23 (74)
Eye lesions	3 (10)
Skin lesions	17 (55)
Erythema nodosum	11 (35)
Papulopustular lesions or acneform nodules	6 (19)
Positive pathergy test	8/15 (53)
Other symptoms	
High fever	17 (55)
Gastrointestinal ulcerations	22 (71)
Arthritis	2 (7)
Vascular disease	3 (10)
HLA-B51, positive	2/13 (15)

- Atteinte digestive
- Peu d'atteinte neurologique ou ophtalmologique
- Association avec trisomie 8
- Risque SMD et Behcet augmente dans trisomie 8 constitutionnelle



Koguchi-Yoshioka, Acta Derm 2014

Maladie de BEHCET associée aux SMD

- 41 avec hémopathies /651 Maladie de Behcet

	BD with malignancies (n = 41)	BD without malignancies (n = 610)
Age (years)	44.4 ± 13.3	37.5 ± 13.7**
Age at time of BD diagnosis (years)	37.2 ± 13.8	35.4 ± 11.2
Female (n)	25 (61.0%)	224 (36.7%)**
Oral ulcer	41 (100%)	605 (99.2%)
Genital ulcer	31 (75.6%)	441 (72.3%)
Ocular lesions	10 (24.4%)	102 (16.7%)
Pathergy reaction	12 (29.3%)	189 (31.3%)
Gastrointestinal involvement	16 (39.0%)	96 (15.7%)**
Skin lesions	29 (70.7%)	386 (63.3%)
Arthritis	9 (22.0%)	149 (24.4%)
Vascular involvement	4 (9.8%)	136 (22.3%)
CNS involvement	0	29 (4.8%)

	With solid malignancies (n = 13)	With hematologic malignancies (n = 29)
Age at the time of malignancy diagnosis (years)	53.3 ± 9.3	40.7 ± 12.9**
Age at time of BD diagnosis (years)	41.6 ± 14.6	34.9 ± 12.9
Time interval (years)†	12.5 ± 9.2	6.9 ± 7.4*
Female (n)	10 (76.9%)	16 (55.2%)
Having active BD during emergence of malignancies	3 (23.1%)	24 (82.8%)***
BD disease activity during emergence of malignancies‡	1.3 ± 2.5	4.0 ± 2.3**
Oral ulcer	13 (100%)	29 (100%)
Genital ulcer	11 (84.6%)	21 (72.4%)
Pathergy reaction	3 (23.1%)	9 (31.0%)
Ocular lesions	4 (30.8%)	6 (20.7%)
Gastrointestinal involvement	3 (23.1%)	13 (44.8%)
Skin lesions	10 (76.92%)	20 (69.0%)
Arthritis	4 (30.8%)	5 (17.2%)
Vascular involvement	0	4 (9.8%)

Yi LIN International Journal of Rheumatic Diseases 2014

Maladie de BEHCET associée aux SMD : série française

Characteristics	Behçet's disease MDS/CMML N=11	Behçet's disease N=63
Age, years	75 (65 – 87)	48 (39 – 57)
Erythema nodosa	1/9 (11%)	8/63 (13%)
Pseudofolliculitis	1/9 (11%)	39/63 (62%)
Arthralgia	5/10 (50%)	46/63 (73%)
Central neurological impairment	0	16/63 (25%)
Uveitis	0	33/63 (52%)
Deep venous thrombosis	1/10 (10%)	9/63 (14%)
Oral aphtosis	9/10 (90%)	62/63 (98%)
Genital aphtosis	3/10 (30%)	45/63 (71%)
Endoscopic abnormalities	6/10 (60%)	8/63 (13%)

Characteristics	Behçet's disease MDS/CMML N=11	Crohn's disease N=100
Endoscopic abnormalities	6/10 (60%)	100/100 (100%)
Jejunal lesions	0	4/100 (4%)
Ileal lesions	5/10 (50%)	67/100 (67%)
Colon lesions	4/10 (40%)	55/100 (55%)
Sigmoid/rectum lesions	3/10 (30%)	32/100 (32%)
Anus lesions	5/10 (50%)	17/100 (17%)
Granuloma	1/8 (10%)	19/100 (19%)

Wesner N et al under submission

Périartérite noueuse non-virales

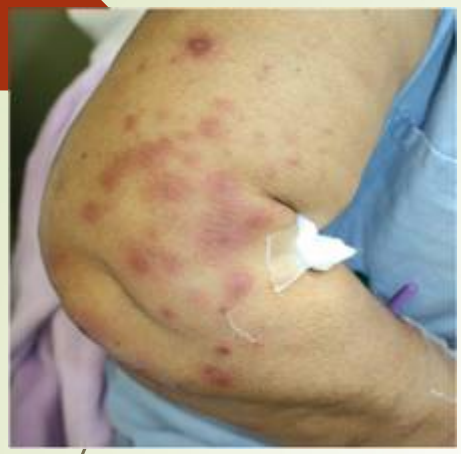
Patient	Age	Sex	Symptoms	Eosinophilia	Complications	Vasculitis Diagnosis	Treatment	Outcome
1	72	M	C, PMR, A, S, K	No	Myocardial infarction	Skin biopsy	CS	Death (myocardial infarction)
2	61	M	C, L, N, K	Yes		Renal angiogram	CS, CY, HA, VP16	Death (infection)
3	73	M	C, PMR, TA, K	No	Cerebral hemorrhage	TA biopsy (ANCA+)	CS, MTX	Death (CNS vasculitis?)
4	76	M	C, PMR, L, S, K	No		Renal angiogram	CS, CY	Death (nocardia)
5	66	M	C, A, L, E, G, K	Yes		ACR criteria	CS, MTX	Death (pneumocystosis)
6	57	F	C, PMR, G, E, K	Yes	Arterio-biliary fistula	Hepatic angiogram	CS, CY, VP16	Death (CNS vasculitis?)
7	67	F	C, PMR, S, A, G, K	Yes	Gastric arterial rupture	Necropsy	CS	Death (vasculitis)
8	58	M	C, N, K	No	Perirenal hematoma	Renal angiogram	CS, CY	Alive

Abbreviations: C, constitutional symptoms; PMR, polymyalgia rheumatica; A, arthritis; S, skin; K, kidney; CS, corticosteroids; L, lung; N, nerve; CY, cyclophosphamide; HA, hydroxyurea; VP16, etoposide; TA, temporal artery; MTX, methotrexate; E, ear; G, gut.

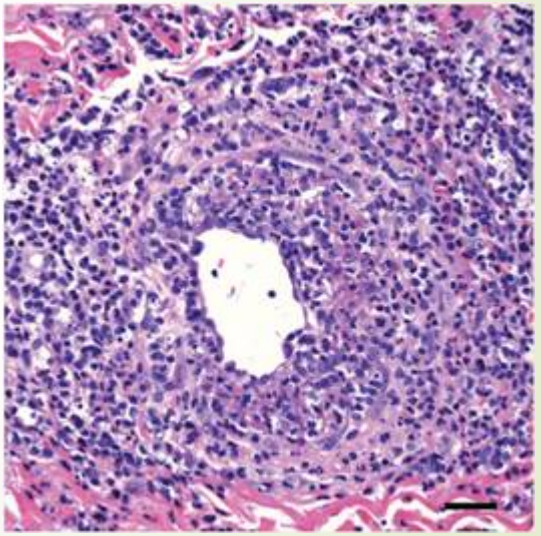
Pronostic sévère +++?
Micro-anévrismes ?

Hamidou Seminars Arhtritis 2001

Vascularites cutanée leucocytoclasique (SOV)



- purpura vasculaire /nodules / lésions urticariennes non migratrices
- ulcérations /nécroses



- nécrose de la paroi des petits vaisseaux et d'un infiltrat constitué de polynucléaires neutrophiles et de fragments nucléaires isolés « nus » (phénomène appelé « leucocytoclasie »)
- IF dépôts d'immunoglobulines et de complément

N=21 SMD + atteinte cutanée:

- vascularite leucocytoclasique 29% cas

Odell Lancet 2015

VASCULARITES CRYO / ANCA positives

Cryoglobulinémie

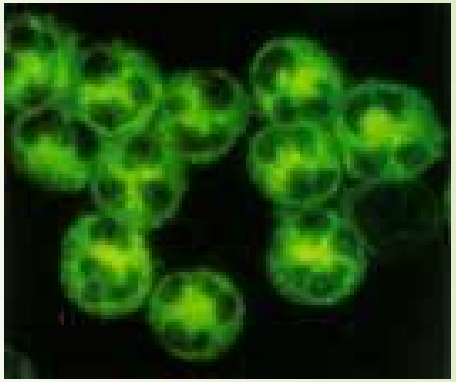
- 2/46 De Hollanda
- 3/123 Mekinian
- Aucune les autres séries
- +++ Pathologies lymphoïdes

ANCA positives (MDS primaire)

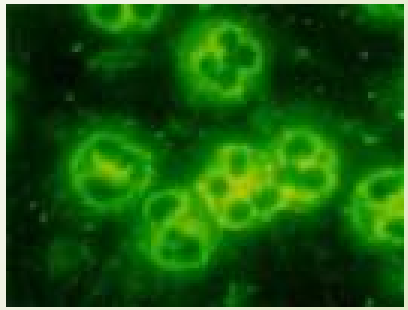
- 3/46 De Hollanda (GPA/ EGPA/ MPA
- 1/123 Mekinian
- Aucune les autres séries

Prévalence ANCA dans SMD/LMMC

AutoAc	SMD non MAI N=155
AAN	20%
Anti ECT	4%
Anti CCP	3%
FR	12%
APL	22%
ANCA	9%
Aspect ANCA	C (n=7), P (n=7)
Spécificité ANCA	Indiff (10), PR3 (0) BPI (2), MPO (1) Lactoferrine (1)



ANCA cytoplasmique



ANCA périnucléaire

M Hamidou Rheumatol 2000.39:417-420

Manifestations auto-immunes et SMD : Association fortuite – paranéoplasique?

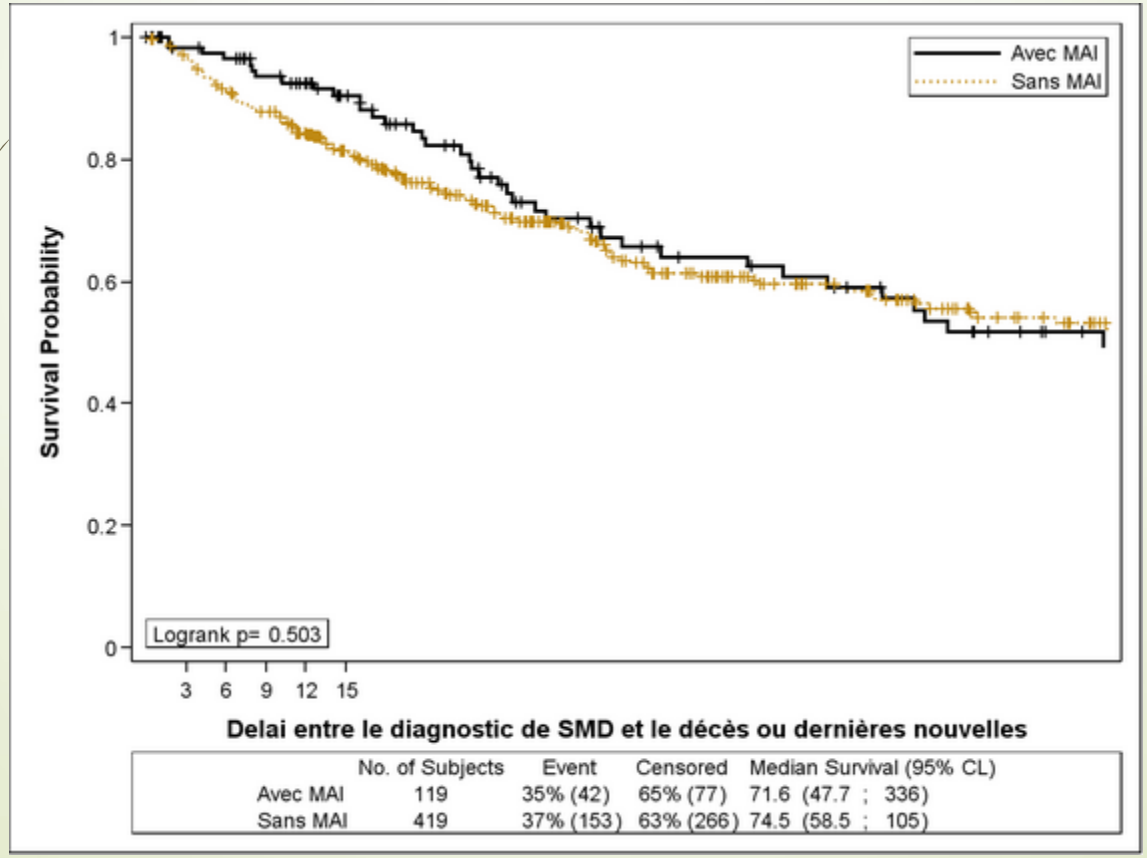
	POUR	CONTRE
Délai SMD - MAI	concomitant	Délai >5 ans ?
Type MAI	PAN Behcet	AGC ? Vascularite ANCA?
Anomalies immunologiques	Peuvent être absents	Présents sans MAI
Type SMD/LMMC	LMMC +++	ASIA
Caryotype	Trisomie 8 - Behcet	-
Réponse ttmt SMD	Agents hypomethylants	-
Evolution MAI	Corticodependance Rechutes	Évolution MAI /SMD pas toujours parallèle

Absence de marqueur pour confirmer le caractère associé MAI avec SMD

Manifestations auto-immunes et SMD : facteur de gravité et impact survie?

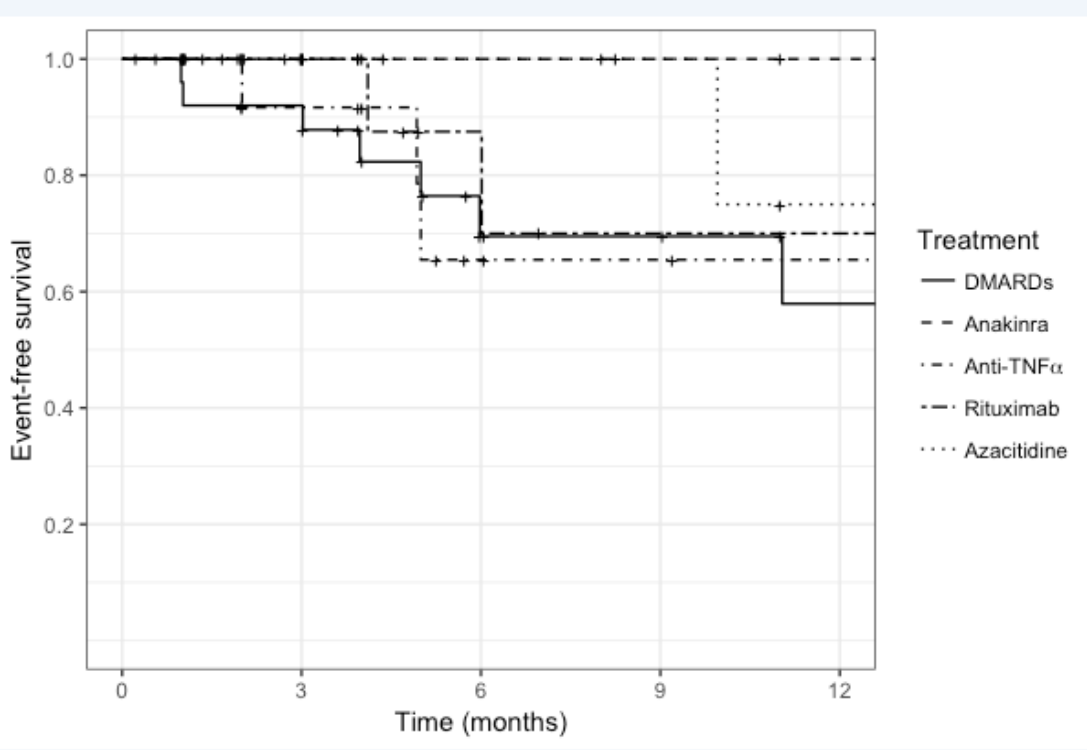
Giannouli compare SMD avec et sans MAI

- ❑ Pas de différence
  - ✓ anomalies cytogénétiques
  - ✓ transformation leucémique
  - ✓ survie
- ❑ Pronostic lié au score pronostic international (IPSS)



Efficacité des biothérapies pour manifestations auto-immunes des SMD

N=120 lines	Steroids N=25	DMARDs N=26	Biologics N=42	Rituximab N=12	Azacytidine N=10
SAID response	20/24 (83%)	8/21 (43%)	13/36(36%)	7/12 (58%)	5/7 (68%)
Duration (months)	2 (1-72)	5 (1-41)	9 (1-125)	5 (1-42)	8 (2-25)
CRP before/at the end	90 (48-117) 15 (4-85)*	53 (40-115) 19 (3-95)	57 (21-89) / 48 (11-87)*	18 (5-50) 12 (5-50)	44 (24-71) 3 (3-20)*



Steroid sparing effect of various treatments in MDS related SAID

Mekinian A Autoimm Rev 2018

Azacytidine pour les manifestations auto-immunes des SMD

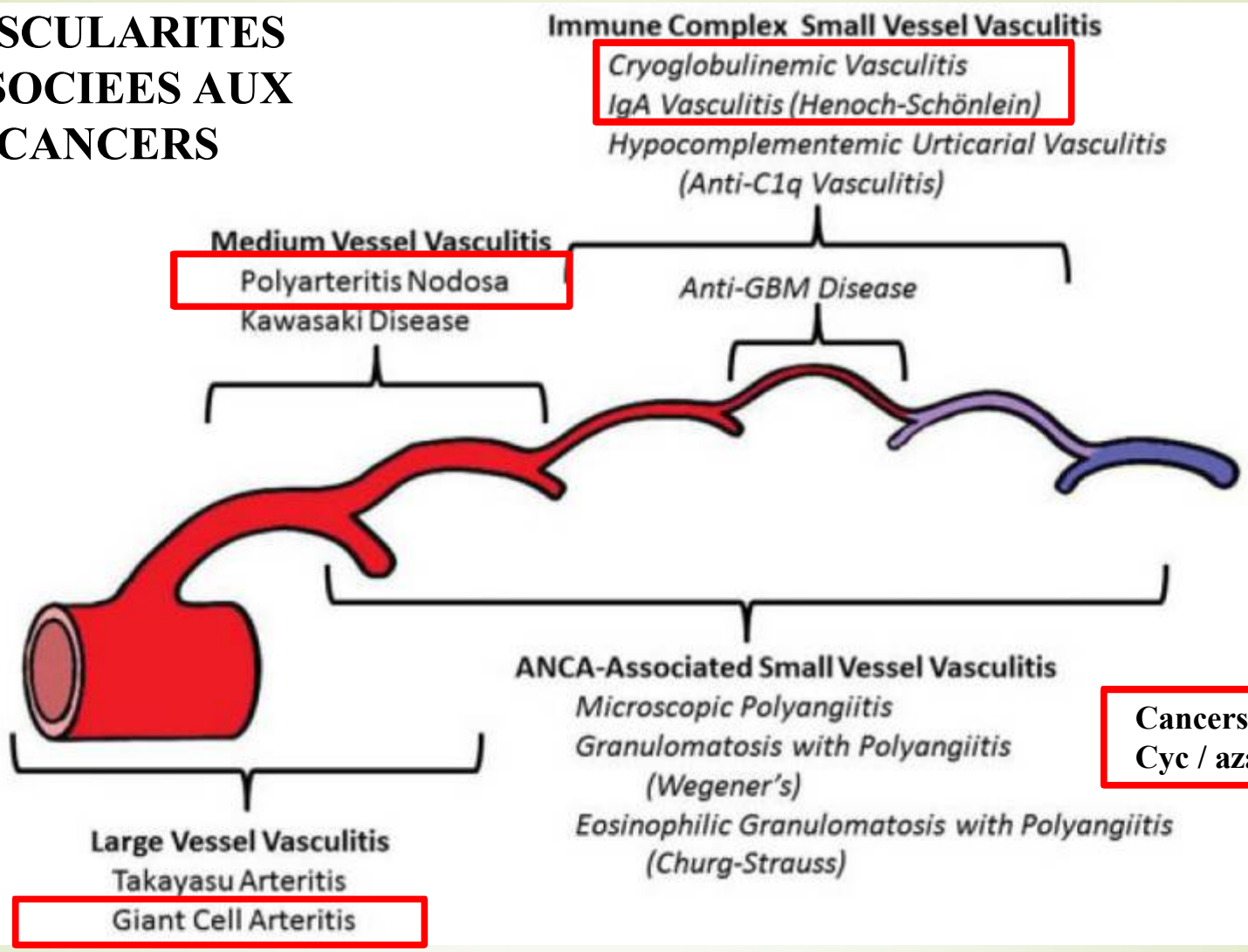
- MAI systémiques réfractaires ou corticodépendantes : N=20
  - Sweet (n=4)
  - Behçet (n=4)
  - PCA (n=3)
  - PPR (n=3; 13%), AGC (n=2) Vascularite (n=2)
  - LED (n=2)
  - Sjögren avec SAPL (n=1)

	Avant AZA	Après AZA	p
Poussée MAI	**50%**	**15%**	**0.04**
Rémission MAI	**15%**	**50%**	**0.04**
Dose Corticoïdes	**17 (10-40)**	**8 (0-13)**	**0.007**
Autre IS	50%	25%	0.2

- Essai AZA dans SMD avec MAI réfractaire / corticodependant (Celgene) en cours

Fraison et al ***Leukemia Res 2016***

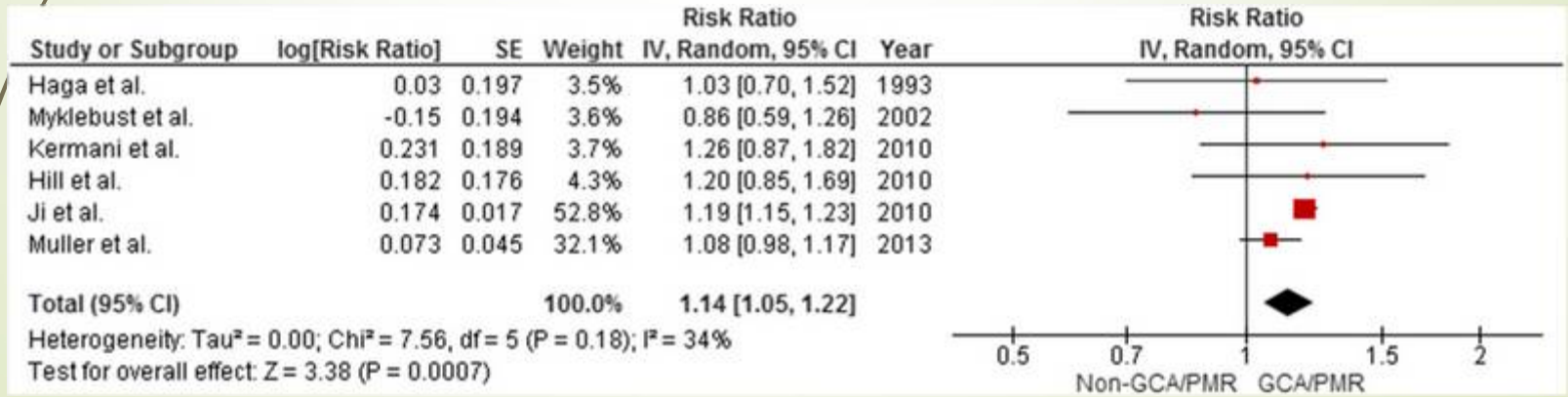
VASCULARITES ASSOCIEES AUX CANCERS



Cancers induits +++
Cyc / aza

ACG/ PPR et CANCER / HEMOPATHIES

Study	Age/Sex	TAB Result	Type of Malignancy (location)	Stage	Delay (mo)†
Hamrin[7]	74 M	GCA (healed)	K (prostate)	Local	After (12)
Östberg[8]	77 M	GCA	K (cecum)	Local (bulky)	After (12)
	73 M	GCA	K (bladder)	Regional	After (6)
	72 F	GCA	K (sigmoid colon)	NR	Synchronous
	82 F	GCA	K (kidney)	Local	Synchronous
von Knorring[35]	62 M	GCA	K (brain)**	Local	After (9)
Larregain-Fournier[36]	73 M	GCA	B cell CLL	Early	Synchronous
Dupuy-Braud[37]	81 F	GCA	Myeloma	Early	Synchronous
Hoag[38]	77 F	GCA	K (kidney)	Local	Synchronous
No author[39]	84 M	GCA	WMG	NA	Synchronous
Bensaïd[40]	76 M	GCA	B cell CLL	Early	After (6)
Lie[41]	45 F	GCA	K (lung)	Local	Synchronous
Billström[17]	67 F	Fibrosis	RAEB-t	NA	Before (4)
Speed[42]	60 M	GCA	K (lung)	Regional	After (18)
	60 M	NA	K (lung)	Local, advanced	Synchronous
Gonzalez-Gay[43]	73 M	GCA	B cell CLL	Early	Synchronous
Estrada[44]	68 F	GCA + amyloidosis	Myeloma	NR	Synchronous
Keung[45]	68 F	GCA*	Myeloma	NA	Synchronous
Solans[46]	61 M	NA	K (kidney)	Local	After (4)
Hutson[13]	72 F	NA	K (breast)	Local	Synchronous
	79 F	NA	Lymphoma	NA	Before (2)
Orbo[47]	68 F	GCA	Uterus	Local	Synchronous
Kohli[48]	68 F	GCA	RA	NA	Synchronous††
Espinosa[49]	75 F	GCA	RAEB	NA	Synchronous
	79 F	Not Done	CMML	NA	Synchronous
Mouadeb[50]	74 F	GCA	K (esophageal)	Local	Synchronous
Steurer[51]	67 M	Large-vessel arteritis	RAEB	NA	Synchronous

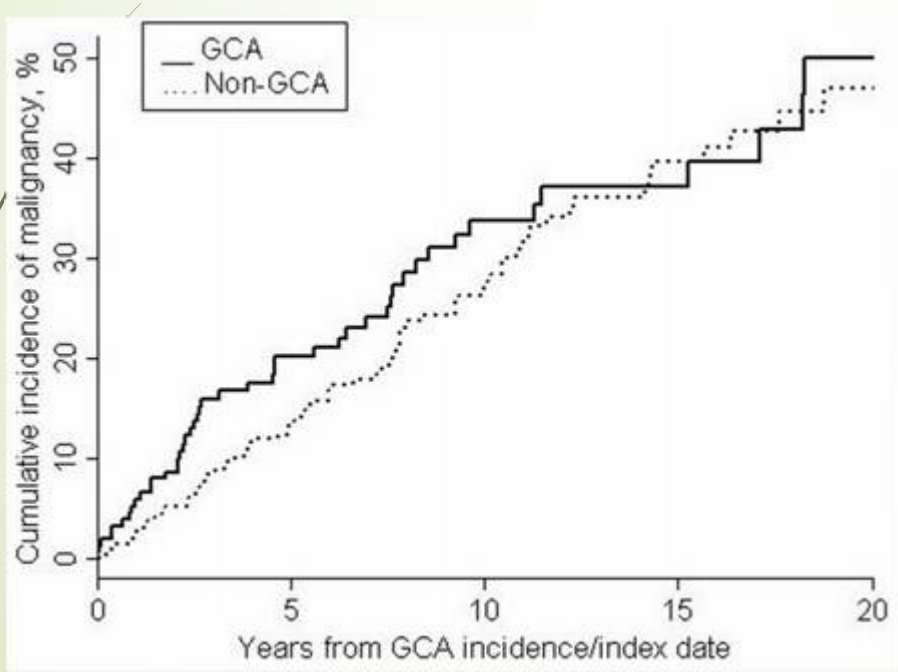


P. Ungprasert et al. / Seminars in Arthritis and Rheumatism 2014

Eric Liozon J Rheumatol 2006

ACG et BAT+

	Males			Females			Total		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancer sites (140–208)	15	0.71	1.4 (0.8, 2.3)	16	14.54	1.1 (0.7, 1.8)	31	25.83	1.2 (0.8, 1.6)
Colorectal (153–4)	3	0.87	1.9 (0.37, 5.41)	2	2.90	0.69 (0.21, 3.04)	5	4.55	1.1 (0.4, 2.5)
Lung (162)	1	1.43	0.7 (0.2, 4.8)	1	1.25	0.8 (0.2, 5.7)	2	3.33	0.6 (0.2, 2.8)
Breast (174)				2	2.5	0.8 (0.2, 3.3)			
Prostate (185)	8	3.33	2.4 (1.01, 4.7)						
Bladder (188)	1	0.5	2.0 (0.03, 11.1)	1	0.36	2.8 (0.04, 15.4)	2	1	2.0 (0.2, 7.3)
Other[a]	3	4.29	0.7 (0.3, 2.3)	11	7.33	1.5 (0.8, 2.7)	14	12.72	1.1 (0.6, 1.9)



Catherine L. Hill Rheumatology 2010

VASCULARITE Ig A (purpura rhumatoide)

PILLEBOUT parmi 250 : cancer 6,8%
Mortalité 28% en cas de cancer

Table SI. *Characteristics of 47 previously reported cases of Henoch-Schönlein purpura associated with solid-organ malignancy*[a]

Case no.	Authors, year (ref.)	Age, years/ Sex	Solid-organ malignancy	Onset of vasculitis in relation to malignancy	Response to treatment	Outcome, follow-up[b]
1	Cairns et al., 1978 (5)	63/M	Lung carcinoma	9 months before	Partial remission[c]	Deceased, 21 months
2	Cairns et al., 1978 (5)	73/M	Lung carcinoma	3 months before	Remission[d]	Deceased, 24 months
3	Maurice, 1978 (6)	59/M	Lung carcinoma	3 months before	Remission[d]	Alive, 25 months
4	Mitchell & Hoffbrand, 1979 (7)	57/M	Lung carcinoma	Synchronous[e]	Remission[d]	Alive, 48 months
5	Pfitzenmeyer et al., 1989 (8)	79/M	Lung carcinoma	6 months before	NR	Deceased, 17 months
6	Gutierrez Macias et al., 1992 (9)	78/M	Lung carcinoma	Synchronous[e]	NR	NR
7	Blanco et al., 1997 (10)	67/M	Lung carcinoma	Synchronous[e]	NR	NR
8	Pankhurst et al., 2004 (11)	NR	Lung carcinoma	Synchronous[e]	NR	NR
9	Curgunlu et al., 2004 (12)	57/M	Lung carcinoma	22 months after	Remission[d]	Alive, 48 months
10	Weiler-Bisig et al., 2005 (13)	64/M	Lung carcinoma	Synchronous[e]	Remission[d]	Deceased, 30 months
11	Ponge et al., 1998 (14)	75/M	Lung carcinoma	Synchronous[e]	Remission[d]	NR
12	Frigui et al., 2009 (15)	50/M	Lung carcinoma	6 months before	Remission[d]	Alive, 6 months
13	Mitsui et al., 2009 (16)	67/F	Lung carcinoma	Unk duration after	NR	Deceased, 17 months
14	Mitsui et al., 2009 (16)	69/M	Lung carcinoma	Unk duration after	NR	NR
			Hypopharyngeal carcinoma	Unk duration after	NR	NR
15	Garcias & Herr, 1982 (17)	60/M	Prostate carcinoma	Synchronous[e]	Partial remission[f]	NR
16	Pertuiset et al., 2000 (3)	77/M	Prostate carcinoma	Synchronous[e]	Remission[d]	Alive, 48 months
17	Couzi et al., 2002 (18)	86/M	Prostate carcinoma	Synchronous[e]	Remission	Alive, 3 months
18	Zurada et al., 2006 (4)	71/M	Prostate carcinoma	Synchronous[e]	NR	NR
			Renal carcinoma	2 months before		
19	Zurada et al., 2006 (4)	86/M	Prostate carcinoma	Synchronous[e]	NR	NR
20	Pertuiset et al., 2000 (3)	46/F	Renal carcinoma	Synchronous[e]	Remission[d]	Alive, 36 months
21	Hong, 2010 (19)	25/M	Renal carcinoma	6 months before	Remission[f]	NR
22	Mitsui et al., 2009 (16)	63/F	Renal carcinoma	Unk duration after	NR	NR
23	Maynard et al., 2010 (20)	34/M	Renal carcinoma	Synchronous[e]	Remission[f]	NR
24	Li Voon Chong & Buckley, 1997 (21)	67/M	Gastric carcinoma	Synchronous[e]	NR	Deceased, 1 month
25	Mitsui et al., 2009 (16)	78/M	Gastric carcinoma	Unk duration after	NR	NR
26	Mitsui et al., 2009 (16)	88/M	Gastric carcinoma	Unk duration after	NR	NR
27	Mitsui et al., 2009 (16)	53/M	Gastric carcinoma	Unk duration after	NR	NR
			Prostate carcinoma	Unk duration after	NR	NR
28	Hughes et al., 1993 (22)	58/F	Breast carcinoma	12 mo before	NR	Deceased, 2 weeks
29	Maestri et al., 1995 (23)	60/F	Breast carcinoma	Synchronous[e]	NR	NR
30	Arias-Santiago et al., 2010 (24)	47/F	Breast carcinoma	Synchronous[e]	Remission[e]	NR
31	Mitsui et al., 2009 (16)	71/F	Thyroid carcinoma	Unk duration before	NR	NR
32	Mitsui et al., 2009 (16)	44/M	Thyroid carcinoma	Unk duration after	NR	NR
33	Mitsui et al., 2009 (16)	73/M	Thyroid carcinoma	Unk duration after	NR	NR
			Cholangiocarcinoma	Unk duration after	NR	NR
34	Fain et al., 2007 (25)	55/M	Carcinoid tumor	3 months before	NR	Deceased, 6 months
			Schwannoma	3 months before	NR	
35	Hayem et al., 1997 (26)	55/M	Carcinoid tumor	6 weeks before	NR	Deceased, 6 weeks
36	Mitsui et al., 2009 (16)	74/F	Maxillary carcinoma	Unk duration after	NR	NR
37	Mitsui et al., 2009 (16)	69/M	Maxillary carcinoma	Unk duration after	NR	NR
38	Mitsui et al., 2009 (16)	71/F	Cervical carcinoma	Unk duration after	NR	NR
39	Mitsui et al., 2009 (16)	18/F	Cervical carcinoma	Unk duration before	NR	NR
40	Mitsui et al., 2009 (16)	69/M	Colon carcinoma	Unk duration after	NR	Deceased, 6 months
41	Mitsui et al., 2009 (16)	73/M	Colon carcinoma	Unk duration before	NR	NR
42	Mitsui et al., 2009 (16)	69/M	Hepatocellular carcinoma	Unk duration after	NR	NR
43	Mitsui et al., 2009 (16)	65/F	Endometrial carcinoma	Unk duration after	NR	Deceased, 9 months
44	Pankhurst et al., 2004 (11)	NR	Epiglottic carcinoma	Synchronous[e]	NR	NR
45	Weiler-Bisig et al., 2005 (13)	59/M	Esophageal carcinoma	Synchronous[e]	NR	Deceased, 6 weeks
46	Zurada et al., 2006 (4)	46/F	Anal carcinoma	Synchronous[e]	NR	NR
47	Mitsui et al., 2009 (16)	47/F	Rectal carcinoma	Unk duration after	NR	Deceased, 6 months
			Ovarian carcinoma	Unk duration after	NR	

VASCULARITE Ig A (purpura rhumatoide)

	HSP With Malignant Disease	HSP Without Malignant Disease	Statistical Comparison
No. of patients (References)	19 (24-36, and Present Report)	158 (6, 21-23)	
Age, yr (range)	59* (29-79)	39-53** (16-86)	ND
M/F ratio	8.5	1.3	$P = .005$
Prior acute infection (%)	5	33	$P = .03$
Cutaneous purpura (%)	100	98	NS
Joint involvement (%)	95	57	$P = .009$
Synovitis (%)	42	14	$P = .005$
Gastrointestinal involvement (%)	58	42	NS
Gastrointestinal bleeding (%)	21	11	NS
Renal involvement (%)	84	60	NS
Renal insufficiency (%)	26	15	NS
Polyclonal IgA increase, n (%)	7/12 (58)	36/55 (55)	NS

Pertuiset 2000 Semin Arthritis

VASCULARITE et LYMPHOMES

N= 2503 lymphomas / 5 ans
N= 108 avec MAI

n, %	CLL (n=46)	B-HNL (n=31)	T-HNL (n=11)	DLBCL n=12)	HL (n=8)	Total (n=108)
Cytopenias **- AIHA** **- ITP** **- Erythroblastopenia**	36 (78,3%) 26 10 0	23 (74,2%) 15 6 2	7 (63,6%) 6 1 0	6 (50%) 4 2 0	5 (62,5%) 4 1 0	77 (71,3%) 55 20 2
Neurological diseases **- Guillain-Barré syndrome** **- Peripheral neuropathy**	2 (4,3%) 1 1	3 (9,7%) 1 2	3 (27,3%) 3 0	1 (8,3%) 1 0	2 (25%) 1 1	11 (10,2%) 7 4
Systemic vasculitis **- GCA** **- Cryoglobulinemic vasculitis**	3 (6,5%) 2 1	2 (6,5%) 0 2	0 0 0	1 (8,3%) 1 0	0 0 0	6 (5,6%) 3 3
Inflammatory arthritis	2 (4,3%)	1 (3,2%)	0	1 (8,3%)	1 (12,5%)	5 (4,6%)
Skin diseases	1 (2,2%)	0	1 (9,1%)	0	0	2 (1,9%)

Jachiet Leukemia 2018

VASCULARITE et LYMPHOMES AI

- Angioimmunoblastic T-cell lymphoma (AITL),
- 18% of T-cell lymphomas cases ; 1.2% of all non-Hodgkin Lymphomas

- Lymphadenopathy, hepatosplenomegaly, fever, anemia, autoimmune features, and polyclonal hypergammaglobulinemia

- Diagnostic difficile +++ maladie AI ou autre lymphome

- TFH CD3/ CD4/ CD10 / CXCL13

- 10/77 LAI= 12% vascularites
- +++ cutanée
- Vascularite leucocytoclasique
- Vascularite avec cryoglobulinémie II

VASCULARITE et LYMPHOMES LGL

- T-LGL leukemia is based on the presence of a
- persistent population of circulating
- T-LGL (0.5 10/L)
- The clonal T-LGL cells = CD3+CD8+CD45RA+CD57+CD62L-
  Clonal rearrangement of the T-cell receptor (TCR)- gene.

- Vascularite cutanée +++ / urticarienne / histologie leucocytoclasique

- 6/229 = 3%

Alexandra Audemard, MD[a], Thierry Lamy, MD, PhD[b], Benoît Bareau, MD[b], Flore Sicre, MD[c]

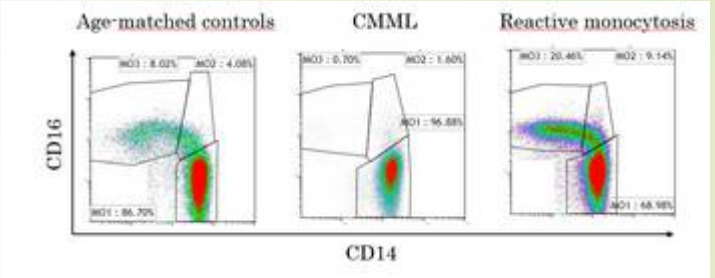
Type of vasculitis	Bio-clinical characteristics	Histopathologic findings
Cryoglobulinemia mixed type 2 with IgM κ	Purpura, arthritis, myalgia, and proteinuria	Membranoproliferative glomerulonephritis
Cryoglobulinemia mixed type 2 with IgM κ	Purpura, polyneuritis, and RI	Membranoproliferative glomerulonephritis
Single organ vasculitis	Purpura, acrosyndrome, and cachexia	Leucocytoclastic vasculitis
ANCA-negative microscopic polyangiitis	Purpura, arthritis, polyneuritis	Leucocytoclastic vasculitis
Giant cell arteritis	Cachexia and headache	Multinucleated giant cells
ANCA-negative microscopic polyangiitis	Purpura and polyneuritis	Necrotizing vasculitis
Single organ vasculitis	Purpura	Lichenoid vasculitis
Cryoglobulinemia	Purpura, arthritis, and RI	Leucocytoclastic vasculitis
Single organ vasculitis	Purpura	Leucocytoclastic vasculitis
Cryoglobulinemia	Purpura, arthritis, and RI	Leucocytoclastic vasculitis and endo-capillary glomerulonephritis
Cryoglobulinemia mixed type 2 with IgM κ	Purpura	Leucocytoclastic vasculitis

Table 1 Summary of the Autoimmune Diseases and Serologic Abnormalities in LGL Leukemia

Autoimmune Disorders	Prevalence	References
Rheumatic Diseases		
Rheumatoid arthritis	17%-36%	6,24
Felty's syndrome	40%	27
Sjögren syndrome	2%-27%	6,42
Systemic lupus erythematosus	Rare	43-45
Behçet disease	Rare	47
Vasculitis	Rare	6
Hematological Disorders		
Pure red cell aplasia	5%-27%	23,24
Autoimmune neutropenia	20%	62
Immune thrombocytopenia	4%	62
Autoimmune hemolytic anemia	5%-9%	24,62,73
Evans syndrome	Rare	79
Endocrinopathies		
Hashimoto thyroiditis	2%-3%	62,73
Graves disease	Rare	62
Cushing syndrome	Rare	62
Autoimmune polyendocrinopathy	Rare	62
Miscellaneous		
Chronic inflammatory bowel disease	2%-5%	6,83
Glomerulonephritis	Rare	6
Polyneuritis	Rare	6
Multiple sclerosis	Rare	27
Isolated Serologic Abnormalities		
Rheumatoid factor	41%-61%	6,24,62
Antinuclear antibody	38%-48%	6,23
Polyclonal hypergammaglobulinemia	35%-45%	6,14
Positive direct Coombs test	14%	27,62
Antiplatelet antibody	25%	27,62
Antineutrophil antibody	20%-41%	14,27,58

VASCULARITE PARANEOPLASIQUE

- Données rares et rétrospectives



- Age / sexe masculin
- Formes corticorésistantes / dépendantes
- Type vascularite / type hémopathie-cancer
- Formes incomplètes / sévères
- Hémopathies lymphomes +++ > SMD-LMMC > Cancers

- NFS ++++ / anémie inflammatoire a distance / monocytose
- Lymphome avec signes B/ syndrome tumoral / +++ LAI – LGL

- Difficulté de diagnostic / nécessité biopsies multiples/ analyse / marqueurs+++

Club SNFMI
Médecine interne , hématologie et oncologie : MINHEMON

Manifestations auto-immunes/inflammatoires des hémopathies et cancers

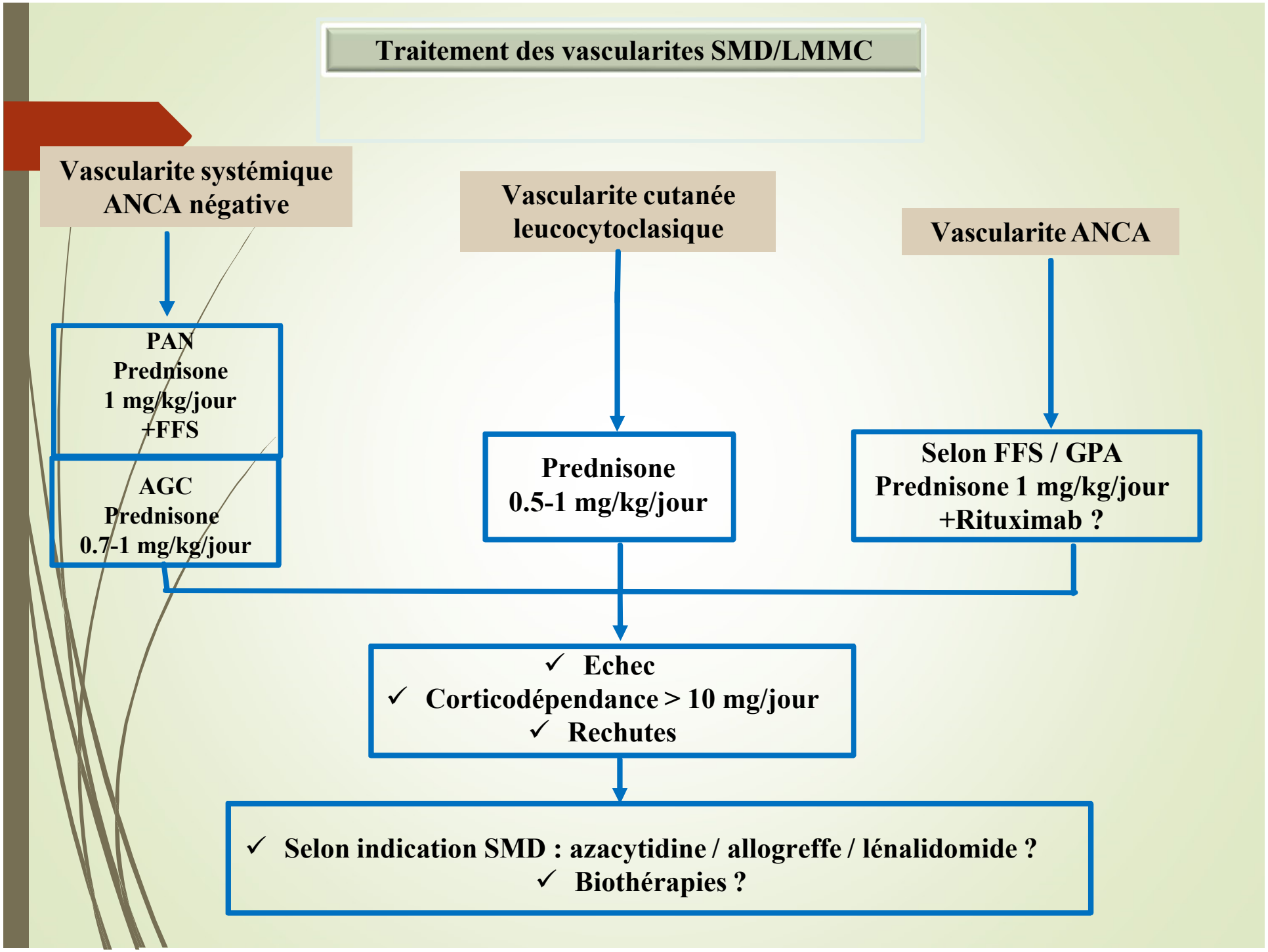
- *Syndrome myélodysplasiques (avec P Fenaux, GFM)*
- *Lymphomes Hodgkin et NH (avec P Coppo)*
- *Manifestations associées MGUS (avec O Decaux , L Garderet)*
- *Manifestations associées aux SMP (avec JJ Kiladjian)*
- *Manifestations associées aux cancers (avec T André)*

- ✓ Etudes collaboratives,
- ✓ Etudes physiopathologiques
- ✓ Information
- ✓ RCP

Président : Dr Arsène Mekinian
Président d'honneur: Pr Olivier Fain
Vice-président : Pr Paul Coppo
Secrétaire : Dr Sophie Georgin Lavialle

Arsene Mekinian / Olivier Fain
Médecine interne, APHP Hôpital Saint Antoine Paris
arsene.mekinian@aphp.fr

Projets en cours	Responsables
Orbitopathies des gammapathies (+AL)	S Abad Sebastien.abad@aphp.fr
Cytopénies associées hémopathies (MDS LMMC LYMPHOMES)	A Mekinian / O Fain Arsene.mekinian@aphp.fr
Myélodysplasies chez des patients ayant une FMF	S Georgin Lavialle Sophie.georgin@aphp.fr
MGUS cliniquement significatifs	A Fayard, L Garderet Laurent.garderet@aphp.fr
Identification moléculaire Willebrand-MGUS	P Aucouturier / Y Chantran Pierre.aucouturier@inserm.fr
Vascularites associées SMD/ LMMC	AL Roupie, A Mekinian, O Fain Arsene.mekinian@aphp.fr
Maladies autoinflammatoires associées à MGUS	S Georgin Lavialle Alexandre Terre Sophie.georgin@aphp.fr
Dermatoses neutrophiliques sous biothérapies Fasciite Shulman avec hémopathie	Jean David Bouaziz Jeandavid.bouaziz@aphp.fr


Traitement des vascularites SMD/LMMC
Vascularite systémique ANCA négative
Vascularite cutanée leucocytoclasique
Vascularite ANCA
PAN
Prednisone
1 mg/kg/jour
+FFS
AGC
Prednisone
0.7-1 mg/kg/jour
Prednisone
0.5-1 mg/kg/jour
Selon FFS / GPA
Prednisone 1 mg/kg/jour
+Rituximab ?
✓ Echec
✓ Corticodépendance > 10 mg/jour
✓ Rechutes
✓ Selon indication SMD : azacytidine / allogreffe / lénalidomide ?
✓ Biothérapies ?

	Malignancies, n	SIR (95% CI)	p
All malignancies*	16	0.96 (0.55–1.57)	1.00
All malignancies excluding NMSC	9	0.70 (0.32–1.34)	0.36
NMSC	7	1.83 (0.73–3.76)	0.19
By malignancy type			
Lung carcinoma	2	3.10 (0.38–11.21)	0.27
Bladder carcinoma	2	3.47 (0.42–12.55)	0.23
Melanoma	1	1.95 (0.05–10.84)	0.80
Gastric carcinoma	1	2.37 (0.06–13.20)	0.69
Rectal carcinoma	1	1.64 (0.04–9.13)	0.91
Renal cell carcinoma	1	2.36 (0.06–13.13)	0.35
Uterine carcinoma	1	4.14 (0.10–23.09)	0.43

	Tatsis, *et al* 1999[12]	Pankhurst, *et al* 2004[13]	Faurschou, *et al* 2009[14]	Van Daalen, *et al*
Study period	1989–1993	1982–2002	1973–1999	1989–2015
Study area	Germany	United Kingdom	Denmark	the Netherlands
Cohort	477 patients with GPA	78 patients with GPA and patients with 122 MPA	293 patients with GPA	203 patients with AAV: 120 patients with GPA and 62 patients with MPA
Controls	479 patients with RA (unmatched)	129 patients with HSP (unmatched), 333 patients with SLE (unmatched), and incidence rates from the general population (matched for sex and age)	2930 controls from the general population (matched for sex and year of birth)	Incidence rates from the general population (matched for sex, age, and time period)
Main results	OR for all malignancies: 1.79 (95% CI: 0.92–3.48). OR for simultaneous occurrence of GPA and malignancy: 18.00 (95% CI: 2.30–140.67). OR for renal cell carcinoma: 8.73 (95% CI: 1.04–73.69)	RR (compared to HSP): 0.85 (95% CI: 0.69–1.05). RR (compared to SLE): 0.31 (95% CI: 0.14–0.7). RR (compared to the general population): 6.02 (95% CI: 3.72–9.74)	OR for all malignancies: 1.4 (95% CI: 0.9–2.2). OR for testicular carcinoma: 6.4 (95% CI: 1.1– 38). OR for NMSC occurring < 2 years before GPA: 4.0 (95% CI: 1.4–12)	SIR for all malignancies: 0.96 (95% CI: 0.55–1.57). SIR for NMSC occurring < 2 years before AAV: 2.1 (95% CI: 0.25–7.60). RR for GPA (compared to MPA): 1.86 (0.55–8.03)
Patients with preceding malignancy, n (%)	23 (4.8)	20 (10.0)	26 (8.9)	18 (8.9)
Specific malignancies (n)	Renal cell carcinoma (7) Bladder carcinoma (1)	Renal cell carcinoma (1) NMSC (1)	Renal cell carcinoma (2) Bladder carcinoma (1) NMSC (7) Testicular carcinoma (2)	Renal cell carcinoma (1) Bladder carcinoma (2) NMSC (7)

Emma E. van Daalen J Rheum 2017