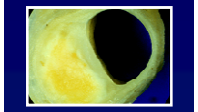
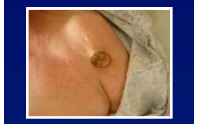
Manifestations extra-articulaires de la PR

Pr Alain Saraux

CHU de la Cavale Blanche
29609 Brest Cedex

Face Face
RÉUNIONS DIGITALES EN DIRECT
Polyarthrite Rhumatoïde
Roche





Extra-articular manifestations of rheumatoid arthritis: An update

Marcella Prete, Vito Racanelli, Liboria Digiglio, Angelo Vacca, Franco Dammacco, Federico Perosa

Les manifestations extra-articulaires doivent être distinguées
- **des comorbidités**
- **et des pathologies associées**

Table 1
Extra-articular manifestations (EAM) in rheumatoid arthritis (RA), according to the Malmö criteria [2] with some modifications, and comparison to common co-morbidities.

Affected tissue or organ	EAM		Co-morbidities
	Not severe	Severe	
Skin	Nodules Raynaud's phenomenon	Petechiae, purpura, ulcers, gangrene	Cancer
Pulmonary system	Bronchiolitis obliterans Organizing pneumonia	Pleuritis Interstitial lung disease	Lung carcinoma
Heart	Valvular heart disease Myocarditis Arrhythmias	Pericarditis Coronary vasculitis and aortitis	Hypertension Heart failure Ischemic heart disease
Nervous system	None identified	Mono/polyneuritis multiplex Central nervous system vasculitis	Depressive syndrome Cervical myelopathy[a]
Eyes	Secondary Sjögren syndrome Sicca syndrome	Episcleritis or scleritis Retinal vasculitides	None identified
Hematological system	None identified	Felty's syndrome	Non-Hodgkin lymphoma Lymphadenopathy Splenomegaly
Kidneys	None identified	Glomerulonephritis Interstitial nephritis Amyloid deposition	None identified
Bone	None identified	None identified	Osteoporosis

[a] Caused by anterior atlanto-axial and subaxial subluxation.

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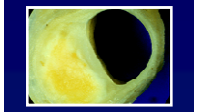

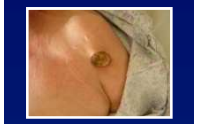

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On les sépare en non sévères (souvent non traitées) et sévères (presque toujours traitées)

Incidence of extra-articular manifestations (EAM) in 8024 patients identified from all the studies cited in Table 2 between 1999 and 2011.

EAM		Patients, n (%)
Subgroup	Type	
Not severe EAM	All	1586 (19.7)
	Nodules	950 (11.8)
	Sicca syndrome	298 (3.7)
	Sjögren syndrome	285 (3.5)
	Raynaud's phenomenon	53 (0.6)
Severe EAM	All	663 (8.3)
	Interstitial lung disease	174 (2.2)
	Serositis (pleuritis and pericarditis)	169 (2.1)
	Vasculitides (cutaneous and systemic)	148 (1.8)
	Peripheral neuropathy	67 (0.8)
	Scleritis and episcleritis	35 (0.4)
	Felty's syndrome	30 (0.3)
	Secondary amyloidosis	27 (0.3)
	Glomerulonephritis	13 (0.2)

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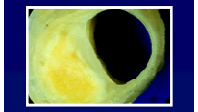
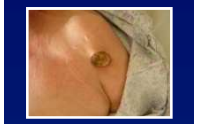
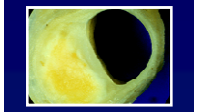


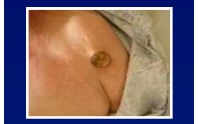


Studies reporting EAM in large cohorts of RA patients.

Type of study	Period of patient inclusion	Median follow-up (years)	Patients, n	EAM incidence		Predictor factors of EAM	Mortality	Ref.
				Subgroups, %	Individual types, %			
Retrospective (Swedish cohort)	1990–1994	4	489	Severe, 7.5	Serositis, [a](3.5); cutaneous vasculitides, (3.0); neuropathy, (0.6); glomerulonephritis, (0.6); Felty's syndrome, (0.2)	NR	Increased	[2]
Retrospective (Italian cohort)	1991	NR	587	All, 40.9; Severe, 15.0	Sicca syndrome, (17.5); nodules, (16.7); Raynaud's phenomena, (6.3%); serositis, (4.4); interstitial lung disease, (4.2); cutaneous vasculitides, (3.7); neuropathy, (1.7); Felty's syndrome, (0.7); amyloidosis, (0.7)	ANA positivity, RF positivity, male gender	NR	[15]
Prospective (English cohort)	Before 1994	5	732	All, 36.8; Severe, 8.4	Nodules, (28.5); Sjögren syndrome, (7.3), interstitial lung disease, (2.2); neuropathy, (2.2), vasculitides, (3.5); Felty's syndrome, (0.5)	NR	NR	[16]
Prospective (Swedish cohort)	1985–1989	10	183	All, 39.9; Severe, 9.8	Nodules, (38.2); interstitial lung disease, (2.2); pleuritis, (1.6); cutaneous vasculitides, (2.2); neuropathy, (1.6); amyloidosis, (1.6); glomerulonephritis, (1.1)	NR	NR	[17]
Retrospective (Rochester, USA cohort)	1955–1985	14.8	424	Severe,15.5	Serositis, (4.9); cutaneous vasculitides, (3.3); vasculitides, (4.7), neuropathy, (1.9); Felty's syndrome, (0.7)	NR	Increased	[18]
Retrospective (Spanish cohort)	1989–1999	10	788	All, 36.2; Severe, 10.6	Nodules, (24.5); Sjögren syndrome, (17.1); interstitial lung disease, (3.7); serositis, (2.4); scleritis and episcleritis, (2.5); vasculitides, (1.3); amyloidosis, (0.6); Felty's syndrome, (0.3)	NR	NR	[19]
Retrospective (Rochester, USA cohort)	1955–1994	11.8	609	All, 40.6; Severe, 21.5	Nodules, (28.2); Sjögren syndrome and sicca syndrome, (19.6); serositis, 6.9; interstitial lung disease, (5.6); cutaneous vasculitis, (3.1); neuropathy, (1.8); scleritis and episcleritis, (1.5); Felty's syndrome (1.5); amyloidosis, (0.4)	Smoking and early disability, ANA positivity, RF positivity	NR	[20]
Retrospective (Turkish cohort)	1988–2003	NR	526	All, 38.4; Severe, 7.4	Nodules, (18.1); sicca syndrome, (11.4); interstitial lung disease, (4.8); Raynaud's phenomena, (3.0); vasculitides, (1.3), Felty's syndrome, (0.3)	RF positivity,	NR	[21]
Retrospective (Swedish cohort)	1985–1989	15.4	183	Severe, 17.5	Serositis, (4.9); interstitial lung disease, (2.8); neuropathy, (2.8); vasculitides, (2.2); scleritis and episcleritis, (2.1); glomerulonephritis, (1.7); Felty's syndrome, (1.1)	Lower C4, RF positivity	NR	[7]
Retrospective (Swedish cohort)	1996–2000	7.6	2900	Severe, 1.5	Serositis, (1.4); interstitial lung disease, (0.6), neuropathy, (0.2); cutaneous vasculitides, (0.13); scleritis and episcleritis, (0.1); Felty's syndrome, (0.03)	High CRP, high DAS-28, smoking, RF positivity (during first 2 years of follow-up)	NR	[8]
Retrospective (Turkish cohort)	2004–2007	4	140	All, 17.8; Severe, 14.2	Interstitial lung disease, (7.1); serositis, (5.7); amyloidosis, (4.3); vasculitides, (1.4); nodules, (2.1); Sjogren syndrome, (1.4); Felty's syndrome, (0.7)	RF	Increased	[5]
Retrospective (Olmsted country cohort)	1995–2007	8.4	463	All, 39.7; Severe, 9.1	Nodules, (23.7); sicca syndrome, (15.9); Sjögren syndrome, (8.2); interstitial lung disease, (4.1); serositis, (3.1); neuropathy, (1.3); episcleritis, (0.6); vasculitides, (0.4), Felty's syndrome, (0.4); amyloidosis (0)	RF positivity and joint erosions	Increased	[22]

NR: not reported; ANA: antinuclear antibodies; Anti-CCP: antibodies to cyclic citrullinated peptide; CRP: C-reactive protein; DAS-28: disease activity score; RF: rheumatoid factor.
[a] They include pleuritis and pericarditis.





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Les principaux traitements sont les suivants

Currently used therapies for EAM in RA patients.

Affected tissue or organ	EAM	Therapy	References
Skin	Subcutaneous nodules; Accelerated rheumatoid nodulosis; Cutaneous vasculitides	Steroids alone or with methotrexate or azathioprine; Anti-TNF-α; Anti-CD20	[44,45,48,49,51,55]
	Raynaud's phenomenon	Symptomatic treatment; calcium antagonists (*dihydropyridine*); vasoactive drugs (*analogue of prostacyclin* PGI_2)	[59–61]
Pulmonary system	Pulmonary nodules; Interstitial lung disease; Pulmonary fibrosis; Pleuritis	Steroids and cyclophosphamide; rituximab	[36,72]
Heart	Pericarditis Myocarditis or endocarditis	Pericardiocentesis; steroids	[36,85,87,88]
Nervous system	Mononeuritis multiplex; Sensory peripheral neuropathy; Central nervous system vasculitis	Steroids and cyclophosphamide; anti-CD20; anti-TNF-α	[4,93,97–99]
Eyes	Scleritis or episcleritis; Retinal vasculitis	Local steroids; cyclosporine; anti-TNF-α; anti-CD20	[101–105]
Hematological system	Felty's syndrome	Methotrexate; anti-CD20; splenectomy	[106,107,111]
Kidneys	Glomerulonephritis; Interstitial nephritis; Secondary amyloidosis	Steroids and cyclophosphamide; chlorambucil; colchicine; anti-TNFα; anti-IL-6; hemodialysis	[124–127]

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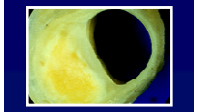
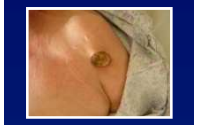
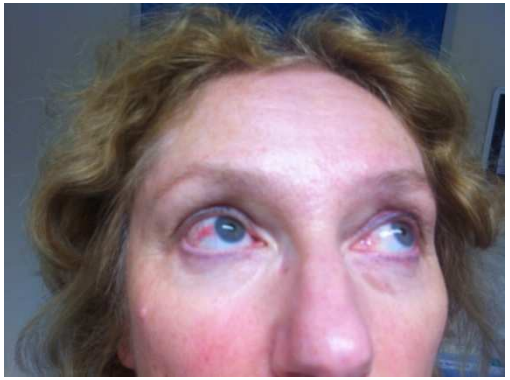


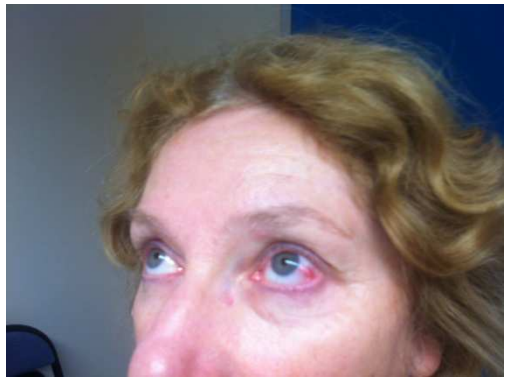


Cas clinique 1

Madame A a une PR séropositive érosive et nodulaire traitée par méthotrexate depuis 5 ans

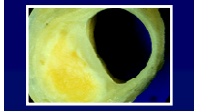
Elle a depuis 5 jours une rougeur des deux yeux

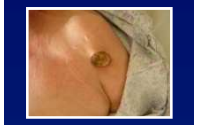


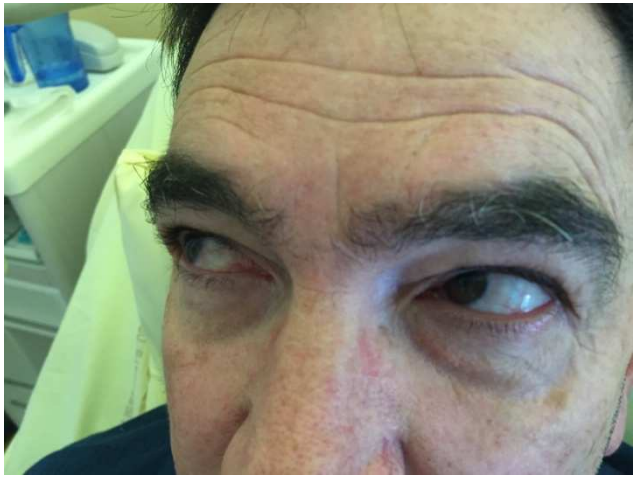


Quel diagnostic évoquez-vous?

Quel traitement proposez vous?







Bilan paraclinique minimum d'une sclérite (ou épisclérite si indication).

Biologie sanguine
- NFS, VS, CRP, fibrinogène
- Électrophorèse des protéines sériques, créatininémie
- AAN, Ac anti-ECT, Ac anti-CCP, FR, ANCA
- Sérologies HSV-1 et -2

Biologie urinaire
- Recherche d'hématurie, leucocyturie et protéinurie

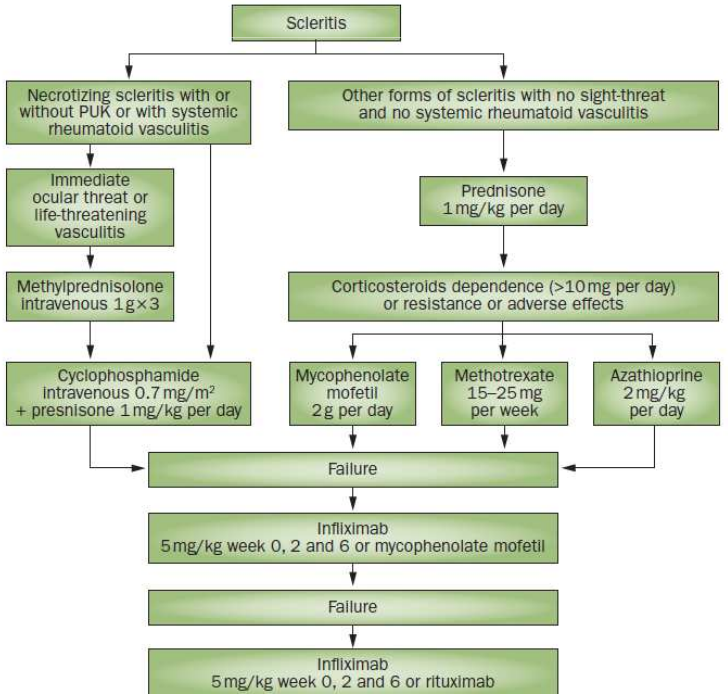
Imagerie
- Radiographie thoracique
- Test cutané tuberculinique

NFS : numération formule sanguine ; VS : vitesse de sédimentation ; CRP, protéine C-réactive ; AAN : anticorps antinucléaires ; Ac : anticorps ; ECT : antigènes solubles du noyau ; CCP : peptides cycliques citrullinés ; FR : facteur rhumatoïde ; ANCA : anticorps anti-cytoplasme des polynucléaires neutrophiles.

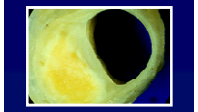
On peut discuter une kératite sur syndrome sec ou une sclérite

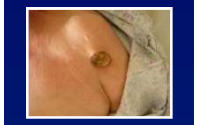
En l'occurrence c'est une sclérite comme ce patient

Une proposition d'arbre décisionnel a été proposé par l'équipe de Cochin en cas de sclérite



Artifoni, M. *et al. Nat. Rev. Rheumatol.* **10**, 108–116 (2014);





Cas clinique 2

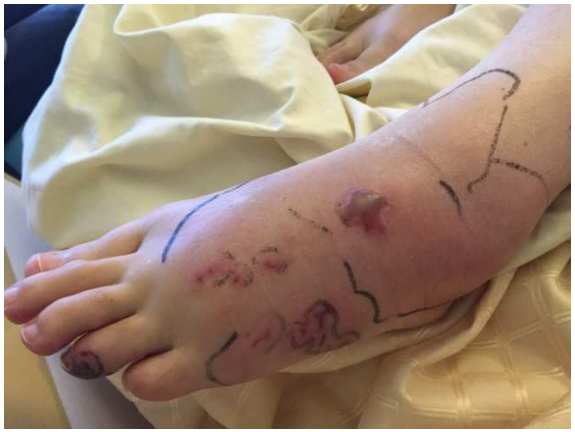
Madame B a une PR séropositive non érosive depuis 5 ans associée à un syndrome de Raynaud

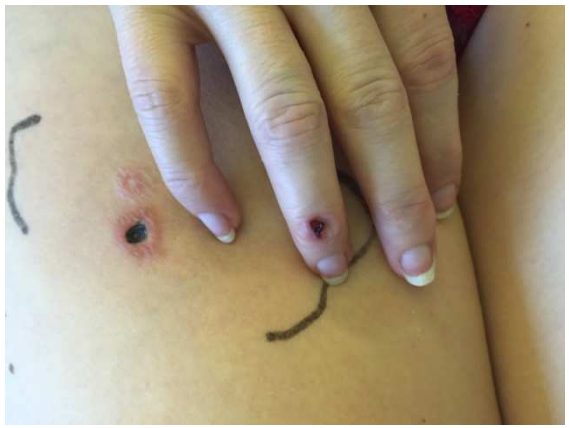
Elle est traitée par Rituximab et 10 mg de methotrexate depuis 2 ans

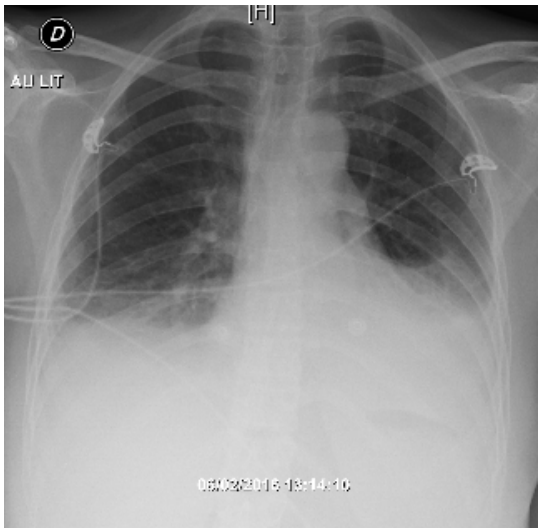
Elle présente depuis 48h une poussée polyarticulaire, une éruption cutanée (annulaire gauche puis pied) fébrile et un essoufflement

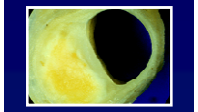
Quel diagnostic évoquez-vous?

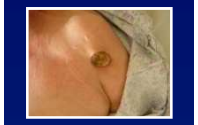
Quels examens complémentaires souhaitez-vous?







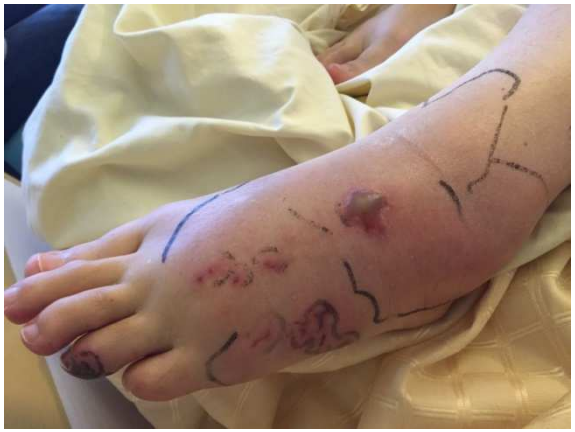
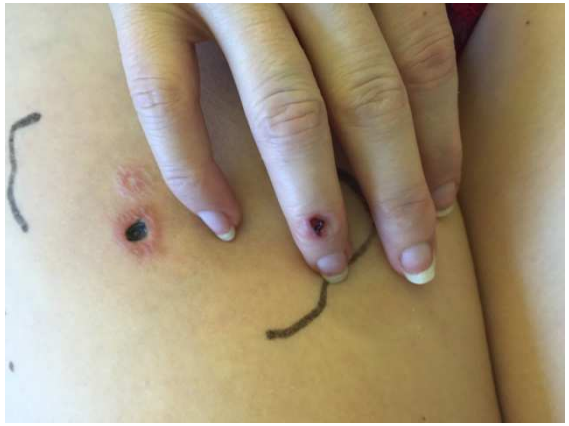
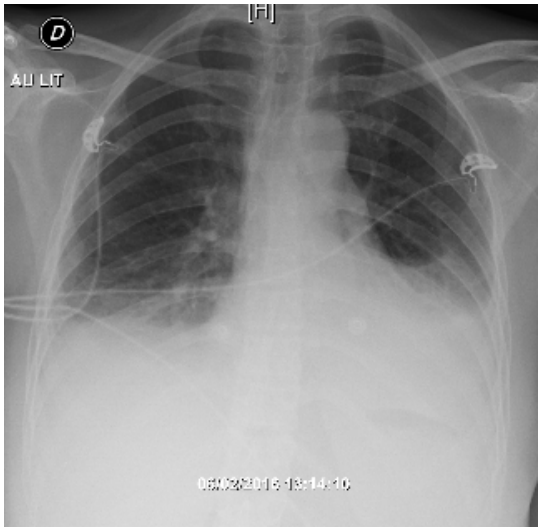


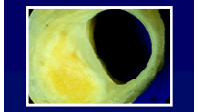


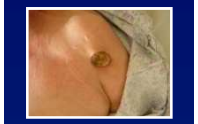
Il s'agit d'un toxic shock Syndrome à streptocoque de type A compliqué d'une CIVD, d'une embolie pulmonaire, et d'un épanchement pleural

Le but est de rappeler que beaucoup de manifestations extra articulaires ne sont pas liées à la PR

Traitée par Rocephine puis corticoïdes, les symptômes s'amendent





Pleuropéricardite

Le diagnostic est surtout clinique et confirmé par

- **RP**
- **ECG et echo cœur**
- **Dosage du C4 dans le sang et le liquide**

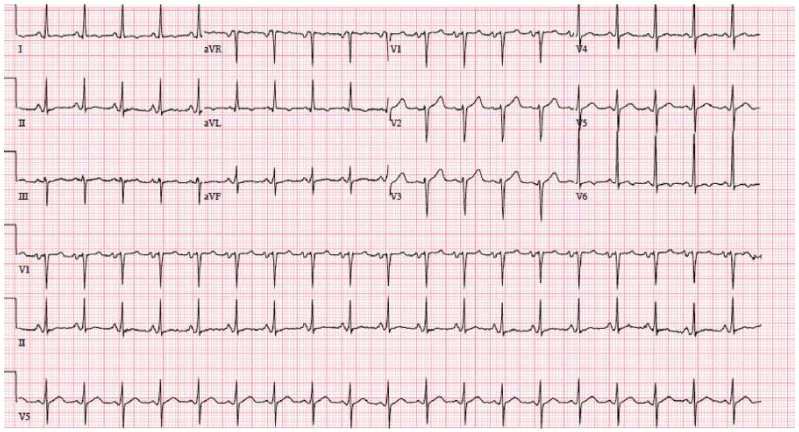
La difficulté est d'éliminer les diagnostics différentiels

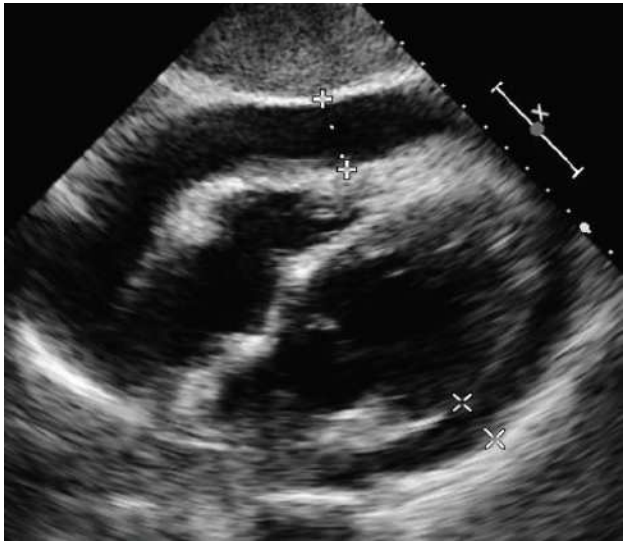
Les complications sont exceptionnelles

Le traitement repose sur la corticothérapie et les traitements de fond

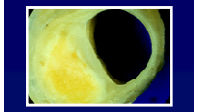
A Rare Case of Cardiac Tamponade Induced by Chronic Rheumatoid Arthritis

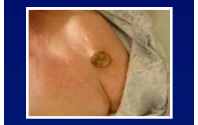
Tariq Yousuf[a, d], Jason Kramer[b], Adam Kopiec[b], Zachary Bulwa[b], Shuvani Sanyal[c], Jeffrey Ziffra[a]





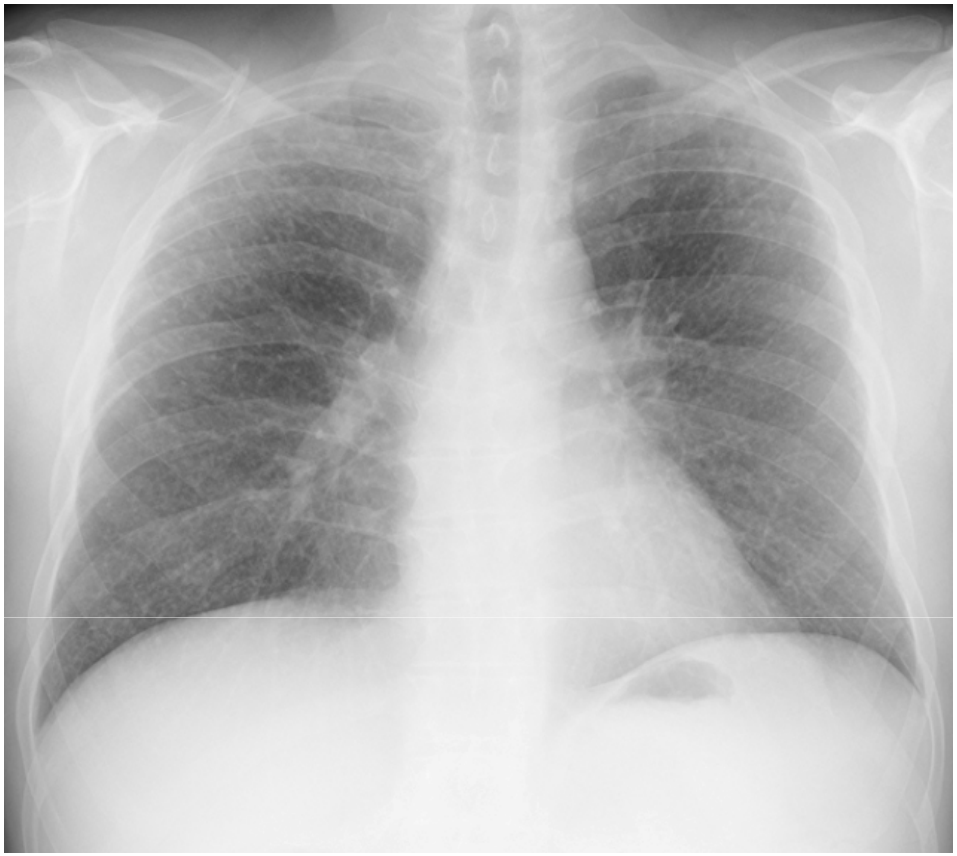
J Clin Med Res. 2015;7(9):720-723

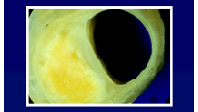


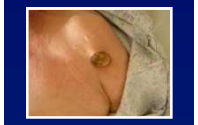


Cas clinique 3

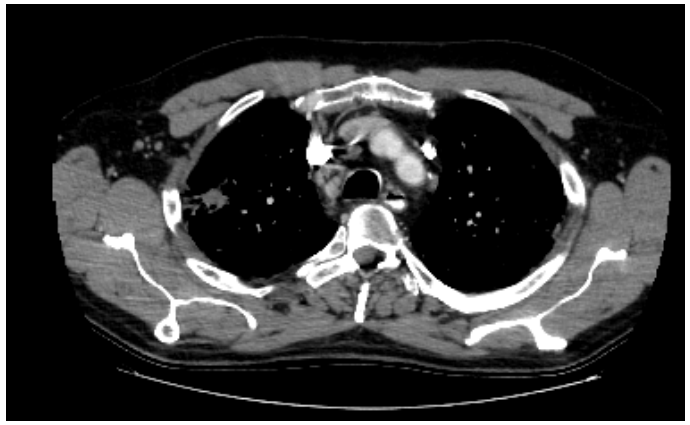
- Monsieur B, né en 1968
- Vous voulez débuter un anti TNF pour une PR séropositive érosive
- Vous faites une radiographie pré thérapeutique qui est la suivante
- Qu'évoquez-vous?
- Que faites vous?

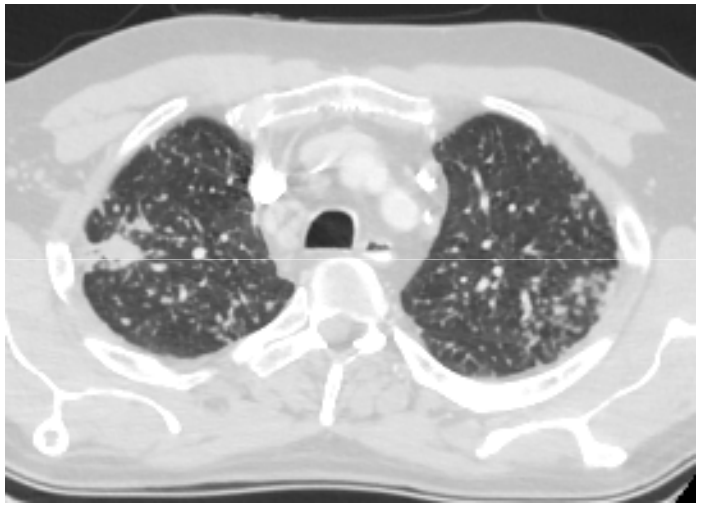






- **Voilà son scanner et son PET scan**
- **Le quantiféron est négatif**
- **Que faites vous?**





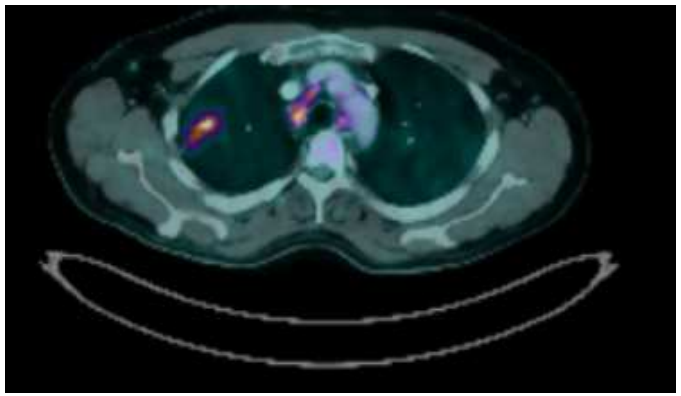


TABLE 1 Pulmonary manifestations of rheumatoid arthritis

Parenchymal
- Interstitial lung disease (*i.e.* usual interstitial pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage and organising pneumonia)

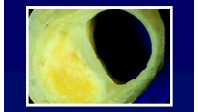
Pleural disease
- Pleural effusion
- Pneumothorax
- Bronchopleural fistula
- Trapped lung syndrome

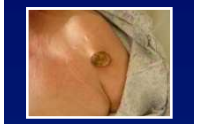
Airway obstruction
- Cricoarytenoid arthritis
- Bronchiectasis
- Follicular bronchiolitis
- Obliterative (constrictive) bronchiolitis

Nodules
- Rheumatoid nodules
- Caplan syndrome

Vascular disease
- Rheumatoid vasculitis
- Pulmonary hypertension

Other
- Drug toxicity
- Infection
- Malignancy
- Thoracic cage restriction
- Thromboembolic disease





LBA normal.

Décision de biopsie chirurgicale

Examen histologique

-du nodule

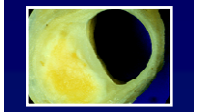
- Plages de fibrose confluentes ou disséminées comportant des nodules fibrohyalins constitués d'épais trousseaux collagènes à disposition nodulaire.
- Importante réaction histiocytaire ponctuée de dépôts anthracosiques et de cristaux visibles en lumière polarisée.
- Il s'agit de petits fragments filiformes réfringents en lumière polarisée.
- L'examen histologique confirme le diagnostic de silicose.

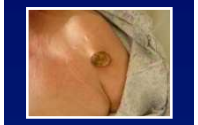
-D'un Ganglion:

- ganglion lymphoïde dont l'architecture est globalement conservée
- importante histiocytose sinusale ponctuée de petits dépôts anthracosiques et dissocié par quelques nodules fibro hyalins parsemés de cristaux compatibles avec de la silice visible en lumière polarisée.

Syndrome de Caplan Colinet

Début d'un anti TNF





Rheumatoid arthritis-associated lung disease

Megan Shaw[1], Bridget F. Collins[2], Lawrence A. Ho[2] and Ganesh Raghu[2]

Les atteintes pulmonaires sont fréquentes et surtout

- ILD
- Bronchiolite
- Nodules pulmonaires

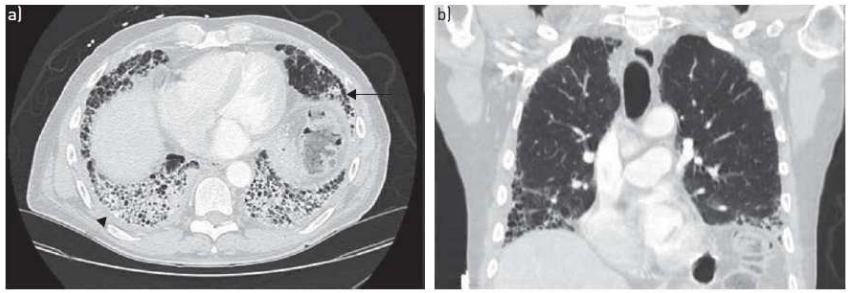


FIGURE 2 a) Axial and b) coronal computed tomography scans of usual interstitial pneumonia pattern in a patient with rheumatoid arthritis. Subpleural and basilar predominant reticulations, minimal ground-glass opacities, honeycombing (arrow) and pleural thickening (arrowhead) are visible, as well as traction bronchiectasis.

TABLE 1 Pulmonary manifestations of rheumatoid arthritis

Parenchymal
Interstitial lung disease (*i.e.* usual interstitial pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage and organising pneumonia)
Pleural disease
Pleural effusion
Pneumothorax
Bronchopleural fistula
Trapped lung syndrome
Airway obstruction
Cricoarytenoid arthritis
Bronchiectasis
Follicular bronchiolitis
Obliterative (constrictive) bronchiolitis
Nodules
Rheumatoid nodules
Caplan syndrome
Vascular disease
Rheumatoid vasculitis
Pulmonary hypertension
Other
Drug toxicity
Infection
Malignancy
Thoracic cage restriction
Thromboembolic disease

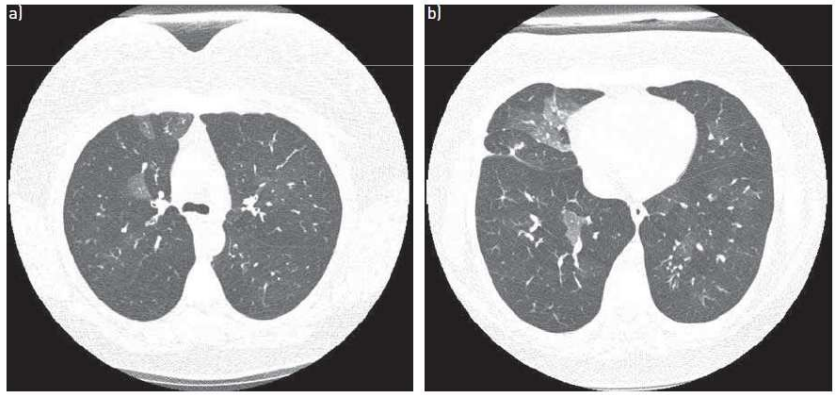
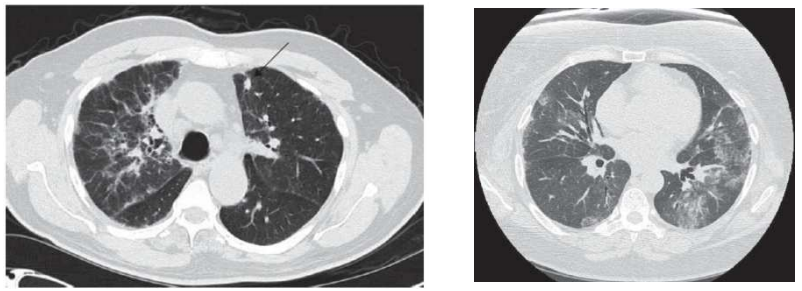
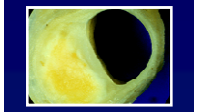
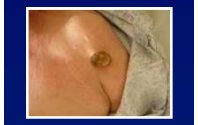


FIGURE 5 a, b) Expiratory computed tomography scans of constrictive bronchiolitis with areas of mosaic attenuation consistent with air trapping in a patient with rheumatoid arthritis.



Eur Respir Rev 2015; 24: 1–16



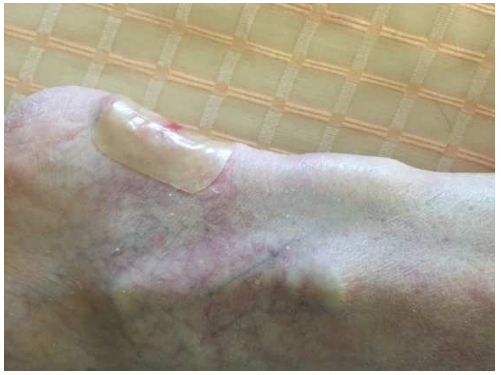
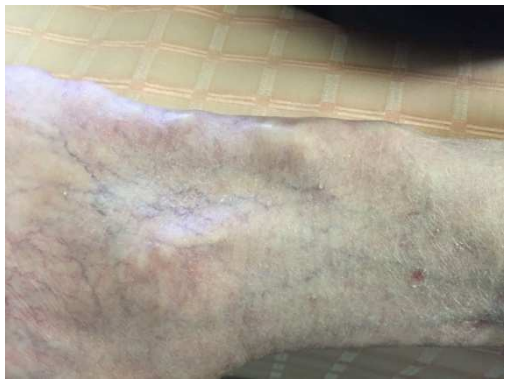
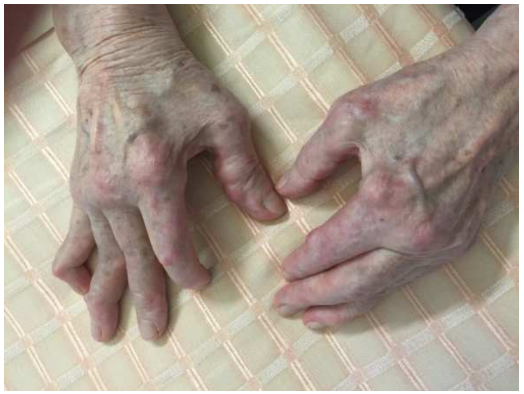


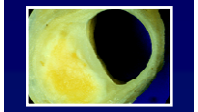
Cas clinique 4

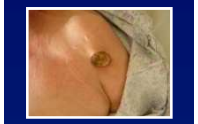
Madame D, 72 ans a une PR qui va bien sous méthotrexate

Elle développe des nodules dont certains très gênant aux talons et à la main droite….

Que peut on proposer?



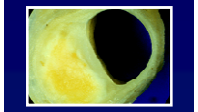


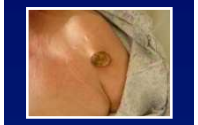
On ne connait ni la cause ni de traitement potentiellement efficace des nodules….

On peut essayer des injections intra nodulaires de corticoïdes et opéré un ou quelques nodules très mal placés…..

Il y a parfois efflorescence sous méthotrexate

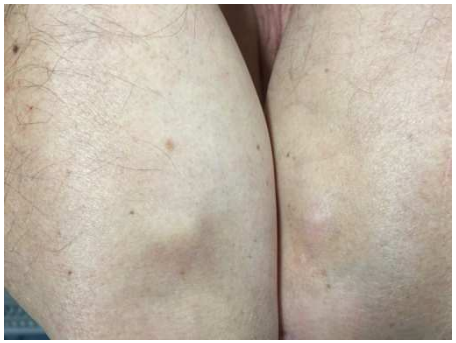
Les anti TNF ne les diminuent pas (Sany et al, non publié)
Certains essaient le plaquenil, le rituximab

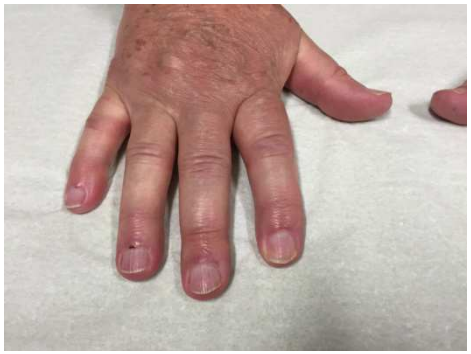


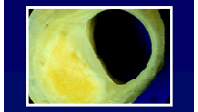


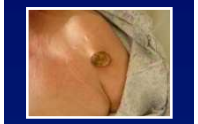
Cas clinique 5

- Monsieur T a 57 ans et a une PR bien équilibrée sous methotrexate
- Il développe après une cure incluant des jets d'eaux chaudes sur les mains des lésions cutanées multiples. Il a cru pour la première avoir une épine dans un doigt
- Quel diagnostic évoquez vous et quelles solutions proposez vous?





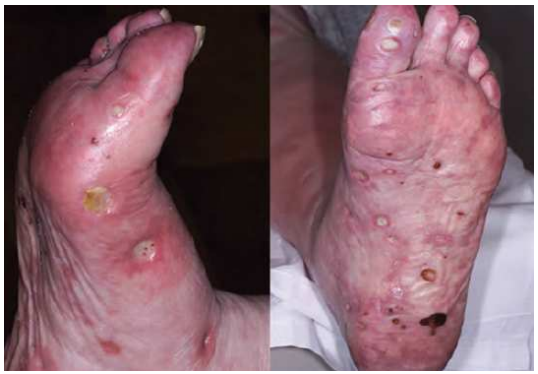




Rheumatoid vasculitis: an update

Ashima Makol[a], Eric L. Matteson[a,b], and Kenneth J. Warrington[a]

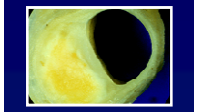
- **L'infarctus unguéal n'est pas significatif**
- **Les autres atteintes sont potentiellement graves**
- **Un schéma thérapeutique simple a été proposé par Makol**
- **MTX plus corticoïdes puis Rituximab restent les traitements les plus utilisés**

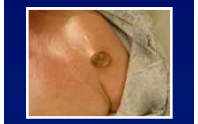


KEY POINTS

- Incidence of rheumatoid vasculitis has declined in the past several decades, but clinical presentation has remained unchanged (cutaneous vasculitis and vasculitic neuropathy remaining the most common).
- Hydroxychloroquine and low-dose aspirin are associated with lower odds of developing rheumatoid vasculitis among RA patients, thus conferring a possible protective effect.
- Despite aggressive use of CYC and biologics, rheumatoid vasculitis remains a difficult EAM to treat, with high relapse rates and mortality that have not changed in over 40 years.

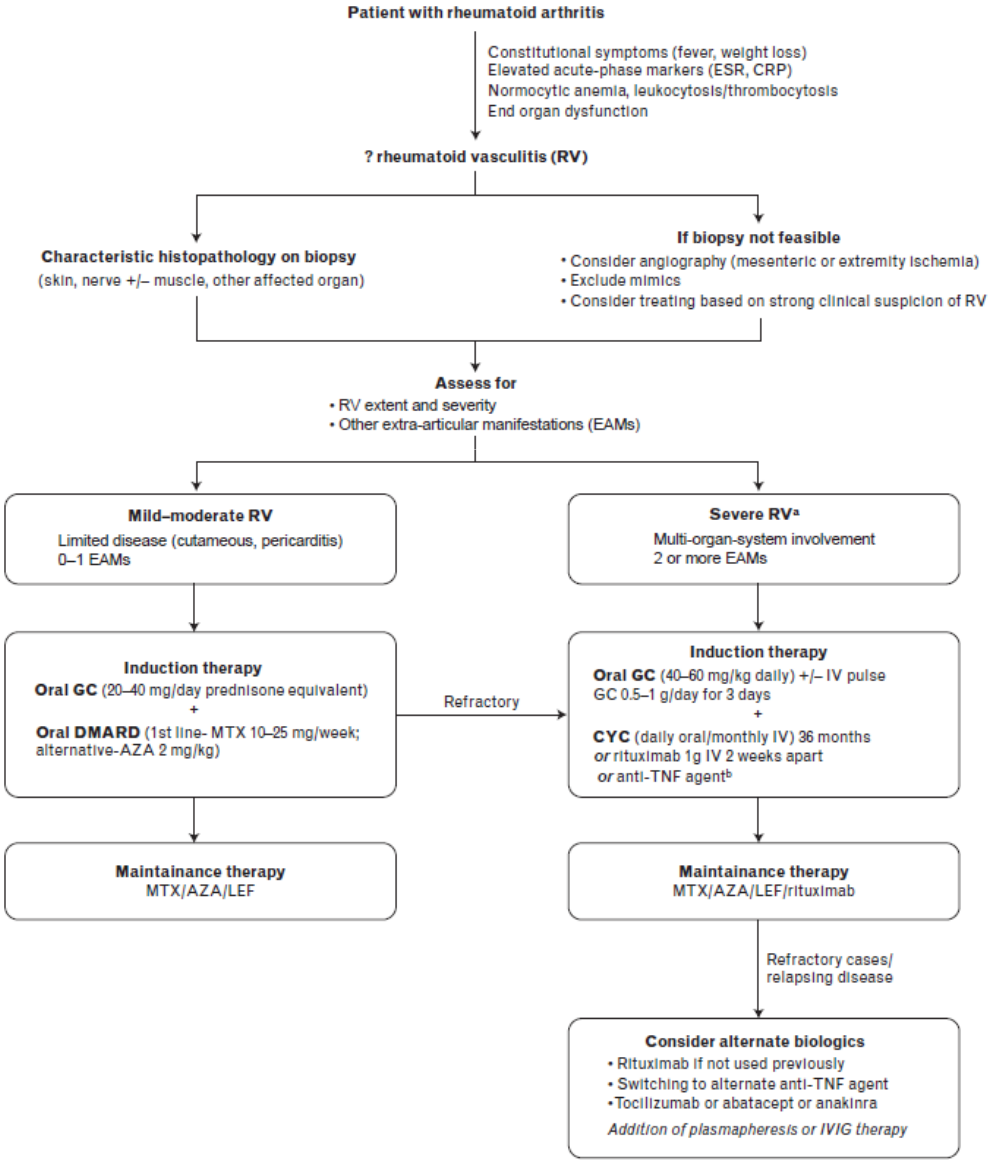
Organ system	Clinical presentation
Skin (most common)	Purpura
	Nail fold infarcts
	Digital ischemia/gangrene
	Cutaneous ulcers (upper or lower extremity)
Peripheral nervous system	Mononeuritis multiplex
	Distal asymmetric/symmetric sensory and/or mixed polyneuropathy
Eye	Episcleritis
	Scleritis (anterior/posterior, nodular/diffuse, nonnecrotizing/necrotizing scleromalacia perforans)
	Peripheral ulcerative keratitis (with or without corneal melt)
	Retinal vasculitis
Heart	Pericarditis
	Myocarditis (presenting as arrhythmias – atrial fibrillation, ventricular arrhythmias and complete heart block)
	Coronary vasculitis (presenting as myocardial infarction)
Lung	Pulmonary angiitis/capillaritis (presenting as alveolar hemorrhage)
Kidney	Pauci-immune glomerulonephritis
	Medium vessel vasculitis (without microaneurysms)
Gastrointestinal tract	Mesenteric vasculitis
	Bowel (commonly ileal or sigmoid) ischemia and/or perforation
Central nervous system	Hypertrophic pachymeningitis
	Central nervous system vasculitis (presentations include seizures, cranial nerve palsies, strokes and myelopathy)

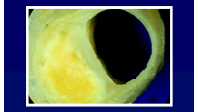


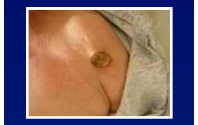


Rheumatoid vasculitis: an update

Ashima Makol[a], Eric L. Matteson[a,b], and Kenneth J. Warrington[a]

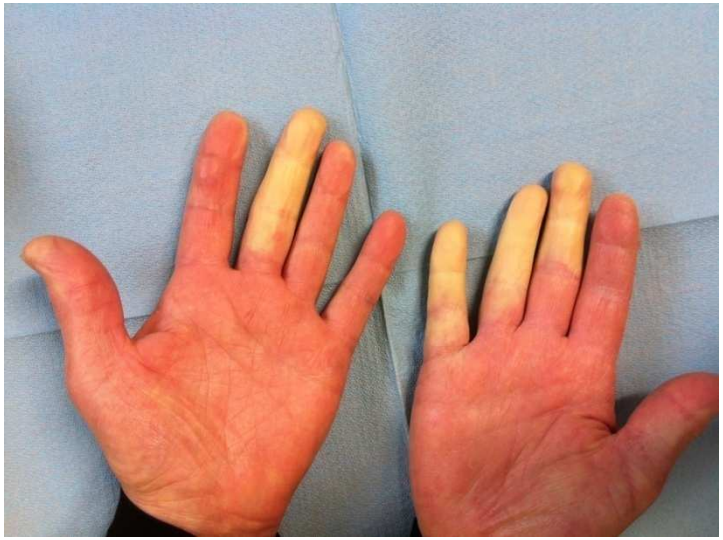


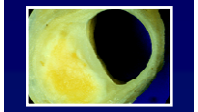


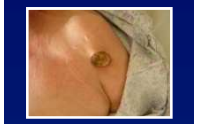


Cas clinique 6

- **Madame S, 32 ans, a une PR bien équilibrée sous methotrexate et anti TNF**
- **Elle a un franc syndrome de Raynaud en arrivant à la consultation!**
- **Qu'en pensez-vous?**







RAYNAUD'S PHENOMENON IN RHEUMATOID ARTHRITIS

A. SARAUX, J. ALLAIN, C. GUEDES, D. BARON, P. YOUINOU* and P. LE GOFF

*Unit of Rheumatology and *Laboratory of Immunology, Brest University Medical School Hospital, Brest, 5 avenue Foch, 29200 Brest, France*

Un syndrome de Raynaud sévère doit faire évoquer une autre connectivite associée mais il n'est pas rare dans la PR, volontiers dans des formes a CRP moins élevée et C4 plus bas, un peu plus de vascularite

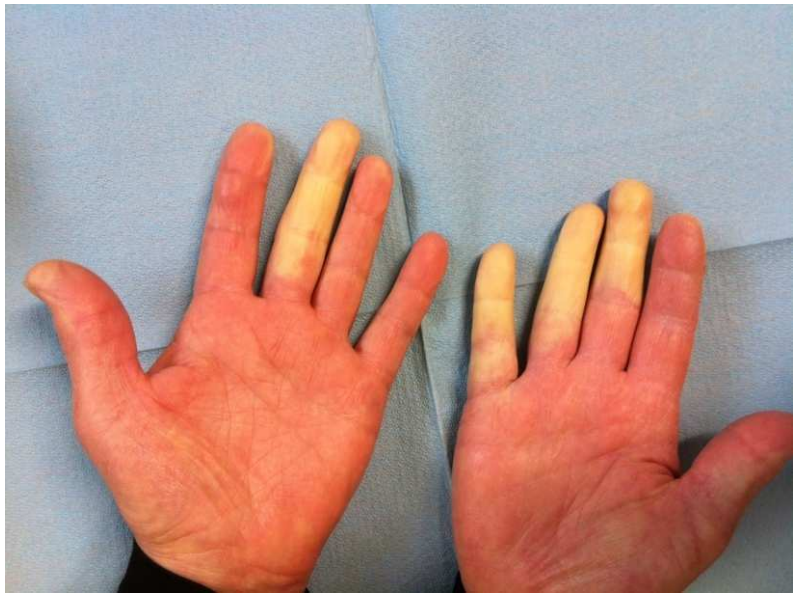
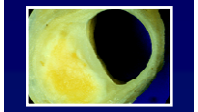


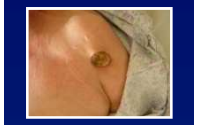
TABLE I

Demographic characteristics, clinical and biological features of 322 RA patients with and without Raynaud's phenomenon

	RA patients with Raynaud's phenomenon	RA patients without Raynaud's phenomenon	*P*
Total number	55	267	
Sex ratio	45:10	209:58	NS
Age	57.9 ± 13.4	58.4 ± 14.2	NS
Nodules	10/55	45/267	NS
Vasculitis	3/55	3/267	0.06
Ritchie's score	8.1 ± 8	10.7 ± 7.7	NS
Lee's score	11.3 ± 7.3	12 ± 7.7	NS
ESR	43.6 ± 30.2	50.9 ± 34.8	NS
CRP	32.02 ± 33	50.5 ± 56	0.005
Latex +	37/54 (69%)	185/264 (70%)	NS
Antinuclear antibodies +	18/53 (34%)	83/258 (32%)	NS
C4	24.8 ± 9.3	28 ± 10.2	0.037
CH50	73.5 ± 16.7	76.75 ± 16.37	NS

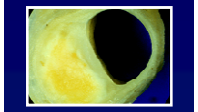
Brit J Rheumatol, 1996, 35, 752-4

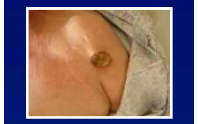




Cas clinique 7

- **Madame W, 62 ans, développe une polyarthrite très évocatrice de PR**
- **Mais elle a une éosinophilie à 750 éléments et une lymphopénie à 950 éléments ….!**
- **Qu’en pensez-vous?**





RMD Open
Rheumatic & Musculoskeletal Diseases

EXTENDED REPORT

Eosinophilia predicts poor clinical outcomes in recent-onset arthritis: results from the ESPOIR cohort

Dewi Guellec,[1] Morgane Milin,[1] Divi Cornec,[1,2] Gabriel J Tobon,[3] Thierry Marhadour,[1] Sandrine Jousse-Joulin,[1,2] Gilles Chiocchia,[4] Olivier Vittecocq,[5] Valérie Devauchelle-Pensec,[1,2] Alain Saraux[1,2]

L'éosinophilie est rare et souvent transitoire
Il n'y a pas de traitement spécifique à envisager sauf si les chiffres sont supérieurs à 2000 et alors le traitement reste celui de la PR

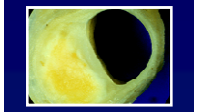
Table 3 Comparison of features after 3 years in the groups with and without baseline eosinophilia

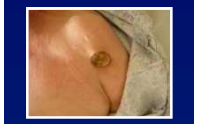
Features	Eosinophils ≥500/mm³ N=26	Eosinophils <500/mm³ N=778	p Value
DAS28, mean (SD)	3.2 (1.2)	2.9 (1.4)	0.17
Patient VAS activity score, mean (SD)	43.6 (32.6)	28.4 (25.9)	**0.05**
Physician VAS activity score, mean (SD)	24.0 (23.0)	19.2 (19.8)	0.32
Morning stiffness intensity, mean (SD)	36.0 (29.7)	21.7 (23.3)	**0.05**
HAQ score, mean (SD)	0.9 (0.7)	0.5 (0.6)	**0.004**
CRP (mg/L), mean (SD)	12.3 (19.5)	6.6 (11.0)	0.95
Rate of erosion progression during year 1, mean (SD)	3.6 (4.0)	3.0 (4.6)	0.83
Rate of erosion progression between year 1 and year 3, mean (SD)	2.5 (3.2)	2.6 (4.2)	0.41
Corticosteroids, n (%)	7/18 (38.9)	229/606 (37.8)	0.92
DMARD, n (%)	18/19 (94.7)	476/669 (71.1)	**0.02**
Methotrexate, n (%)	13/19 (68.4)	370/673 (55.0)	0.24
Methotrexate dosage (mg/week), mean (SD)	14.6 (3.5)	13.3 (3.9)	0.22
Biological agent	2/26 (7.7%)	89/778 (11.4%)	0.76

Bold typeface indicates p≤0.05.
CRP, C reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; VAS, visual analogue scale.

Eosinophilia is rare in recent-onset arthritis. Eosinophilia was mild and transient in most patients. Patients with mild baseline eosinophilia might respond worse to the treatment than the remainder, as they had higher patient-assessed disease activity, morning stiffness intensity, health assessment questionnaire (HAQ) scores, and disease-modifying antirheumatic drug (DMARD) use after 3 years.

Guellec D, *et al. RMD Open* 2015;**1**:e000070.





Baseline Laboratory Test Abnormalities are Common in Early Arthritis but Rarely Contraindicate Methotrexate: Study of Three Cohorts (ESPOIR, VErA, and Brittany)

Marion Le Boëdec, MD,* Thierry Marhadour, MD,*
Valérie Devauchelle-Pensec, MD, PhD,* Sandrine Jousse-Joulin, MD,*
Aymeric Binard, MD,* Bruno Fautrel, MD, PhD,† René Marc Flipo, MD,‡
Xavier Le Loët, MD,§ Jean François Ménard, MD,‖ and Alain Saraux, MD, PhD*

Les cytopénie ne sont pas exceptionnelles, mais ce sont surtout l'anémie et la lymphopénie

	ESPOIR *	VErA *	Brittany *	Total
Anémie	240/809 (29.6%)	50/301 (16.6%)	73/256 (28.5%)	363/1366 (26.6%)
Leucopénie	10/809 (1.23%)	6/301 (1.99%)	2/262 (0.76%)	18/1372 (1.31%)
Neutropénie	15/803 (1.87%)	1/299 (0.33%)	-	16/1102 (1.45%)
Lymphopénie	51/804 (6.34%)	22/299 (7.36%)	-	73/1103 (6.62%)
Thrombocytopénie Thrombocytose Normal	7/809 (0.86%) 128/809 (15.8%) 674/809 (83.3%)	2/301 (0.66%) 29/301 (9.63%) 270/301(89.7%))	4/261 (1.53%) 45/261 (17.2%) 212/261 (81.2%)	13/1371 (0.95%) 202/1371 (14.7%) 1156/1371 (84.3%)

 Semin Arthritis Rheum 42:474–481

Lymphopénie

- **Se voit hors PR si infection (HIV), cancer, corticothérapie, maladie auto-immune (lupus, Sjogren), insuffisance rénale, idiopathique**

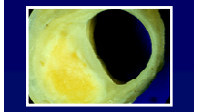
- **Se voit dans la polyarthrite débutante**
  - Au moment du diagnostic
    - lupus érythémateux systémique
    - syndrome de Sjögren primitif
    - parvovirus B19
  - Ultérieurement
    - surtout si traitements (corticothérapie, traitements de fond)

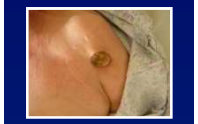
Ng WL et al. Lymphopenia at presentation QJM. 2006 janv;99(1):37-47 ;
Doran MF, et al. Arthritis Rheum. 2002 sept;46(9):2287-93. Lorenzi AR, et al. Arthritis Rheum. 2008 févr;58(2):370-5.

Lymphopénie

- **La lymphopénie est**
  - Facteur de risque d'infection et de néoplasie au cours de l'infection VIH, du lupus, des lymphomes
  - Dans la PR, on observe plus une augmentation du risque infectieux lié à la maladie et aux traitements immunosuppresseurs qu'à la lymphopénie.
  - Elle est souvent transitoire au début de la PR et sans conséquence
  - L'alemtuzumab (qui n'est plus commercialisé), anticorps monoclonal thérapeutique anti CD52, marqueur de membrane des lymphocytes entraîne une lymphopénie profonde dans la PR, sans risque infectieux nettement majoré

Ng WL et al. Lymphopenia at presentation QJM. 2006 janv;99(1):37-47 ; Duquenne C. JBS 2015;82:417-22
Doran MF, et al. Arthritis Rheum. 2002 sept;46(9):2287-93. Lorenzi AR, et al. Arthritis Rheum. 2008 févr;58(2):370-5.

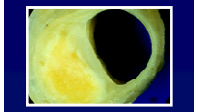


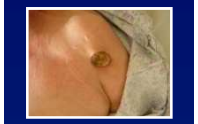


Back up

PLAN

- **Les manifestations extra articulaires (MEA) et leur classification**
- **Les principales MEA**
  - Nodules, Raynaud, cytopénie
  - Pulmonaires, pleurésie, vascularites, neurologiques, sclérites





Extra-articular manifestations of rheumatoid arthritis: An update

Marcella Prete, Vito Racanelli, Liboria Digiglio, Angelo Vacca, Franco Dammacco, Federico Perosa

Les manifestations extra-articulaires doivent être distinguées
- **des comorbidités**
- **et des pathologies associées**

Table 1
Extra-articular manifestations (EAM) in rheumatoid arthritis (RA), according to the Malmö criteria [2] with some modifications, and comparison to common co-morbidities.

Affected tissue or organ	EAM		Co-morbidities
	Not severe	Severe	
Skin	Nodules Raynaud's phenomenon	Petechiae, purpura, ulcers, gangrene	Cancer
Pulmonary system	Bronchiolitis obliterans Organizing pneumonia	Pleuritis Interstitial lung disease	Lung carcinoma
Heart	Valvular heart disease Myocarditis Arrhythmias	Pericarditis Coronary vasculitis and aortitis	Hypertension Heart failure Ischemic heart disease
Nervous system	None identified	Mono/polyneuritis multiplex Central nervous system vasculitis	Depressive syndrome Cervical myelopathy[a]
Eyes	Secondary Sjögren syndrome Sicca syndrome	Episcleritis or scleritis Retinal vasculitides	None identified
Hematological system	None identified	Felty's syndrome	Non-Hodgkin lymphoma Lymphadenopathy Splenomegaly
Kidneys	None identified	Glomerulonephritis Interstitial nephritis Amyloid deposition	None identified
Bone	None identified	None identified	Osteoporosis

[a] Caused by anterior atlanto-axial and subaxial subluxation.

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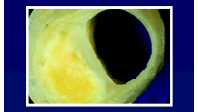

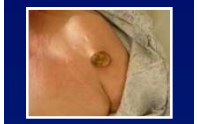

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On les sépare en non sévères (souvent non traitées) et sévères (presque toujours traitées)

Incidence of extra-articular manifestations (EAM) in 8024 patients identified from all the studies cited in Table 2 between 1999 and 2011.

EAM		Patients, n (%)
Subgroup	Type	
Not severe EAM	All	1586 (19.7)
	Nodules	950 (11.8)
	Sicca syndrome	298 (3.7)
	Sjögren syndrome	285 (3.5)
	Raynaud's phenomenon	53 (0.6)
Severe EAM	All	663 (8.3)
	Interstitial lung disease	174 (2.2)
	Serositis (pleuritis and pericarditis)	169 (2.1)
	Vasculitides (cutaneous and systemic)	148 (1.8)
	Peripheral neuropathy	67 (0.8)
	Scleritis and episcleritis	35 (0.4)
	Felty's syndrome	30 (0.3)
	Secondary amyloidosis	27 (0.3)
	Glomerulonephritis	13 (0.2)

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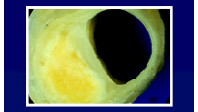
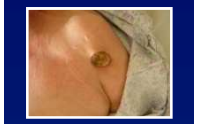
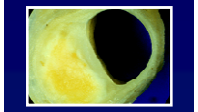


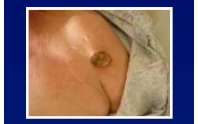


Studies reporting EAM in large cohorts of RA patients.

Type of study	Period of patient inclusion	Median follow-up (years)	Patients, n	EAM incidence		Predictor factors of EAM	Mortality	Ref.
				Subgroups, %	Individual types, %			
Retrospective (Swedish cohort)	1990–1994	4	489	Severe, 7.5	Serositis, [a](3.5); cutaneous vasculitides, (3.0); neuropathy, (0.6); glomerulonephritis, (0.6); Felty's syndrome, (0.2)	NR	Increased	[2]
Retrospective (Italian cohort)	1991	NR	587	All, 40.9; Severe, 15.0	Sicca syndrome, (17.5); nodules, (16.7); Raynaud's phenomena, (6.3%); serositis, (4.4); interstitial lung disease, (4.2); cutaneous vasculitides, (3.7); neuropathy, (1.7); Felty's syndrome, (0.7); amyloidosis, (0.7)	ANA positivity, RF positivity, male gender	NR	[15]
Prospective (English cohort)	Before 1994	5	732	All, 36.8; Severe, 8.4	Nodules, (28.5); Sjögren syndrome, (7.3), interstitial lung disease, (2.2); neuropathy, (2.2), vasculitides, (3.5); Felty's syndrome, (0.5)	NR	NR	[16]
Prospective (Swedish cohort)	1985–1989	10	183	All, 39.9; Severe, 9.8	Nodules, (38.2); interstitial lung disease, (2.2); pleuritis, (1.6); cutaneous vasculitides, (2.2); neuropathy, (1.6); amyloidosis, (1.6); glomerulonephritis, (1.1)	NR	NR	[17]
Retrospective (Rochester, USA cohort)	1955–1985	14.8	424	Severe,15.5	Serositis, (4.9); cutaneous vasculitides, (3.3); vasculitides, (4.7), neuropathy, (1.9); Felty's syndrome, (0.7)	NR	Increased	[18]
Retrospective (Spanish cohort)	1989–1999	10	788	All, 36.2; Severe, 10.6	Nodules, (24.5); Sjögren syndrome, (17.1); interstitial lung disease, (3.7); serositis, (2.4); scleritis and episcleritis, (2.5); vasculitides, (1.3); amyloidosis, (0.6); Felty's syndrome, (0.3)	NR	NR	[19]
Retrospective (Rochester, USA cohort)	1955–1994	11.8	609	All, 40.6; Severe, 21.5	Nodules, (28.2); Sjögren syndrome and sicca syndrome, (19.6); serositis, 6.9; interstitial lung disease, (5.6); cutaneous vasculitis, (3.1); neuropathy, (1.8); scleritis and episcleritis, (1.5); Felty's syndrome (1.5); amyloidosis, (0.4)	Smoking and early disability, ANA positivity, RF positivity	NR	[20]
Retrospective (Turkish cohort)	1988–2003	NR	526	All, 38.4; Severe, 7.4	Nodules, (18.1); sicca syndrome, (11.4); interstitial lung disease, (4.8); Raynaud's phenomena, (3.0); vasculitides, (1.3), Felty's syndrome, (0.3)	RF positivity,	NR	[21]
Retrospective (Swedish cohort)	1985–1989	15.4	183	Severe, 17.5	Serositis, (4.9); interstitial lung disease, (2.8); neuropathy, (2.8); vasculitides, (2.2); scleritis and episcleritis, (2.1); glomerulonephritis, (1.7); Felty's syndrome, (1.1)	Lower C4, RF positivity	NR	[7]
Retrospective (Swedish cohort)	1996–2000	7.6	2900	Severe, 1.5	Serositis, (1.4); interstitial lung disease, (0.6), neuropathy, (0.2); cutaneous vasculitides, (0.13); scleritis and episcleritis, (0.1); Felty's syndrome, (0.03)	High CRP, high DAS-28, smoking, RF positivity (during first 2 years of follow-up)	NR	[8]
Retrospective (Turkish cohort)	2004–2007	4	140	All, 17.8; Severe, 14.2	Interstitial lung disease, (7.1); serositis, (5.7); amyloidosis, (4.3); vasculitides, (1.4); nodules, (2.1); Sjogren syndrome, (1.4); Felty's syndrome, (0.7)	RF	Increased	[5]
Retrospective (Olmsted country cohort)	1995–2007	8.4	463	All, 39.7; Severe, 9.1	Nodules, (23.7); sicca syndrome, (15.9); Sjögren syndrome, (8.2); interstitial lung disease, (4.1); serositis, (3.1); neuropathy, (1.3); episcleritis, (0.6); vasculitides, (0.4), Felty's syndrome, (0.4); amyloidosis (0)	RF positivity and joint erosions	Increased	[22]

NR: not reported; ANA: antinuclear antibodies; Anti-CCP: antibodies to cyclic citrullinated peptide; CRP: C-reactive protein; DAS-28: disease activity score; RF: rheumatoid factor.
[a] They include pleuritis and pericarditis.





Extra-articular manifestations of rheumatoid arthritis: An update

Marcella Prete, Vito Racanelli, Liboria Digiglio, Angelo Vacca, Franco Dammacco, Federico Perosa

Les principaux traitements sont les suivants

Currently used therapies for EAM in RA patients.

Affected tissue or organ	EAM	Therapy	References
Skin	Subcutaneous nodules; Accelerated rheumatoid nodulosis; Cutaneous vasculitides	Steroids alone or with methotrexate or azathioprine; Anti-TNF-α; Anti-CD20	[44,45,48,49,51,55]
	Raynaud's phenomenon	Symptomatic treatment; calcium antagonists (*dihydropyridine*); vasoactive drugs (*analogue of prostacyclin* PGI_2)	[59–61]
Pulmonary system	Pulmonary nodules; Interstitial lung disease; Pulmonary fibrosis; Pleuritis	Steroids and cyclophosphamide; rituximab	[36,72]
Heart	Pericarditis Myocarditis or endocarditis	Pericardiocentesis; steroids	[36,85,87,88]
Nervous system	Mononeuritis multiplex; Sensory peripheral neuropathy; Central nervous system vasculitis	Steroids and cyclophosphamide; anti-CD20; anti-TNF-α	[4,93,97–99]
Eyes	Scleritis or episcleritis; Retinal vasculitis	Local steroids; cyclosporine; anti-TNF-α; anti-CD20	[101–105]
Hematological system	Felty's syndrome	Methotrexate; anti-CD20; splenectomy	[106,107,111]
Kidneys	Glomerulonephritis; Interstitial nephritis; Secondary amyloidosis	Steroids and cyclophosphamide; chlorambucil; colchicine; anti-TNFα; anti-IL-6; hemodialysis	[124–127]

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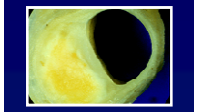
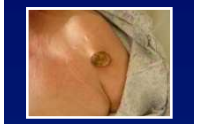




Rheumatoid Nodules

Justin J. Munns, MD, Michael E. Ruff, MD

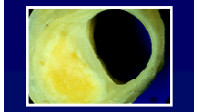
On ne connait ni la cause ni de traitement potentiellement efficace des nodules….
On peut essayer des injections intra nodulaires de corticoïdes et opéré un ou quelques nodules très mal placés…..

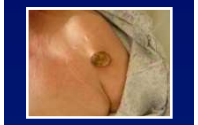
There are no long-term studies clarifying the natural history of rheumatoid nodules, including the rate of spontaneous resolution. Although there are randomized trials examining the role of steroid injections, the long-term results are unclear, as is the value of reducing nodule size. The trials are small, the interpretation of nodule size a bit subjective, and the authors are likely promoters of steroid injection. No randomized controlled trials address the indications for surgery and results of surgery to remove rheumatoid nodules in the upper extremity.

CARACTÉRISTIQUES CLINIQUES, BIOLOGIQUES ET RADIOGRAPHIQUES DES POLYARTHRITES RHUMATOÏDES SELON LA PRÉSENCE OU L'ABSENCE DE NODULES*

Alain SARAUX[1], Jérôme ALLAIN[1], Claudie GUEDES[1], Isabelle VALLS[1], Dominique BARON[1], Pierre YOUINOU[2], Paul LE GOFF[1]

	PR nodulaire (n = 66)	PR non nodulaire (n = 354)	Odds ratio (intervalle de confiance)	P
Age (ans)	57,9 ± 13	57,4 ± 15	-	0,96
Durée d'évolution (ans)	11,39 ± 9,4	7,6 ± 7,3	-	0,0003
Sex ratio F/M	52/14 (3.7)	274/79 (3.5)	1,07 (0,54-2,14)	0,83
Syndrome de Raynaud	13/66 (19,7%)	50/335 (14,9%)	1,40 (0,67-2,88)	0,33
Oeil sec	23/62 (37,1%)	73/335 (21,8%)	2,12 (1,14-3,91)	0,01
Bouche sèche	20/62 (32,2%)	72/334 (21,6%)	1,73 (0,91-3,26)	0,067
Vascularite	4/66 (6,1%)	4/351 (1,1%)	5,6 (1,14-27,47)	0,024
Indice de Lee	14,5±7,8	11,4±7,6	-	0,004
Indice de Ritchie	13,5±11,7	9,8±9,5	-	0,02
C-réactive protéine (mg/l)	52,6±42	45,2±56,1	-	0,022
VS (mm)	55,7±35,4	47,5±33,3	-	0,059
Facteurs rhumatoïdes	55/65 (84,6%)	229/332 (69%)	2,83 (1,33-6,2)	0,003
Anticorps anti-péri-nucléaires	47/63 (74,6%)	206/329 (66,6%)	1,75 (0,91-3,4)	0,068
Anticorps anti-kératine	25/60 (41,7%)	88/317 (27,8%)	1,86 (1,01-3,43)	0,031
Facteurs anti-nucléaires	30/64 (46,9%)	108/343 (31,5%)	1,92 (1,07-3,43)	0,017
Cryoglobuline	8/31	11/192 (0,6%)	5,72 (1,87-17,46)	0,001
DR4	32/50 (64%)	186/341 (54,5%)	1,48 (0,77-2,87)	0,21
C4 (g/l)	24 ± 8,9	28,6 ± 9,7	-	0,00037
CH 50 (µ/ml)	68,3 ± 15,7	77,5 ± 15,6	-	0,00006





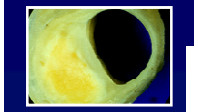
Cas clinique 4

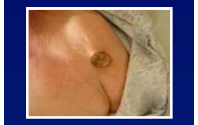
On ne connait ni la cause ni de traitement potentiellement efficace des nodules….
On peut essayer des injections intra nodulaires de corticoïdes et opéré un ou quelques nodules très mal placés…..
Il y a parfois efflorescence sous methotrexate
Les anti TNF ne les diminuent pas (Sany et al, non publié)
Certains essaient le plaquenil, le rituximab

CARACTÉRISTIQUES CLINIQUES, BIOLOGIQUES ET RADIOGRAPHIQUES DES POLYARTHRITES RHUMATOÏDES SELON LA PRÉSENCE OU L'ABSENCE DE NODULES*

Alain SARAUX[1], Jérôme ALLAIN[1], Claudie GUEDES[1], Isabelle VALLS[1], Dominique BARON[1], Pierre YOUINOU[2], Paul LE GOFF[1]

	PR nodulaire (n = 66)	PR non nodulaire (n = 354)	Odds ratio (intervalle de confiance)	P
Age (ans)	57,9 ± 13	57,4 ± 15	-	0,96
Durée d'évolution (ans)	11,39 ± 9,4	7,6 ± 7,3	-	0,0003
Sex ratio F/M	52/14 (3,7)	274/79 (3,5)	1,07 (0,54-2,14)	0,83
Syndrome de Raynaud	13/66 (19,7%)	50/335 (14,9%)	1,40 (0,67-2,88)	0,33
Oeil sec	23/62 (37,1%)	73/335 (21,8%)	2,12 (1,14-3,91)	0,01
Bouche sèche	20/62 (32,2%)	72/334 (21,6%)	1,73 (0,91-3,26)	0,067
Vascularite	4/66 (6,1%)	4/351 (1,1%)	5,6 (1,14-27,47)	0,024
Indice de Lee	14,5±7,8	11,4±7,6	-	0,004
Indice de Ritchie	13,5±11,7	9,8±9,5	-	0,02
C-réactive protéine (mg/l)	52,6±42	45,2±56,1	-	0,022
VS (mm)	55,7±35,4	47,5±33,3	-	0,059
Facteurs rhumatoïdes	55/65 (84,6%)	229/332 (69%)	2,83 (1,33-6,2)	0,003
Anticorps anti-péri-nucléaires	47/63 (74,6%)	206/329 (66,6%)	1,75 (0,91-3,4)	0,068
Anticorps anti-kératine	25/60 (41,7%)	88/317 (27,8%)	1,86 (1,01-3,43)	0,031
Facteurs anti-nucléaires	30/64 (46,9%)	108/343 (31,5%)	1,92 (1,07-3,43)	0,017
Cryoglobuline	8/31	11/192 (0,6%)	5,72 (1,87-17,46)	0,001
DR4	32/50 (64%)	186/341 (54,5%)	1,48 (0,77-2,87)	0,21
C4 (g/l)	24 ± 8,9	28,6 ± 9,7	-	0,00037
CH 50 (µ/ml)	68,3 ± 15,7	77,5 ± 15,6	-	0,00006

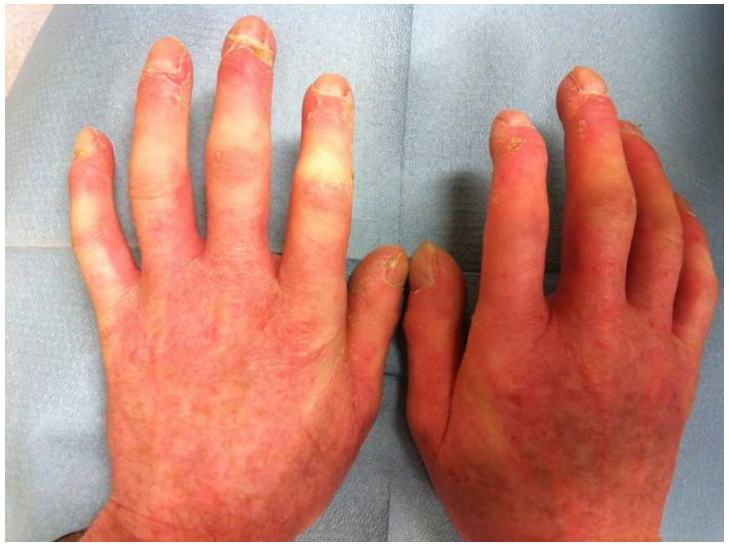




The association of Raynaud's syndrome with rheumatoid arthritis—a meta-analysis

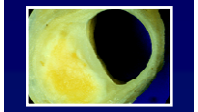
Peter Hartmann · Melvin Mohokum · Peter Schlattmann

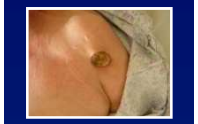
Un syndrome de Raynaud sévère doit faire évoquer une autre connectivite associée



there is a possible indication of an association for RS and patients with RA.

Clin Rheumatol (2011) 30:1013–1019





RAYNAUD'S PHENOMENON IN RHEUMATOID ARTHRITIS

A. SARAUX, J. ALLAIN, C. GUEDES, D. BARON, P. YOUINOU* and P. LE GOFF

*Unit of Rheumatology and *Laboratory of Immunology, Brest University Medical School Hospital, Brest, 5 avenue Foch, 29200 Brest, France*

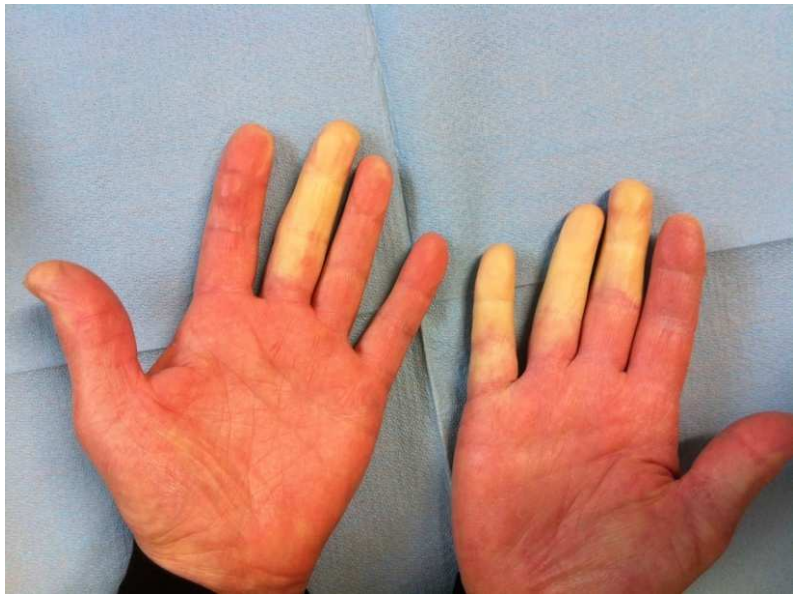
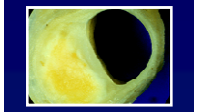


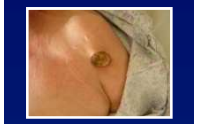
TABLE I

Demographic characteristics, clinical and biological features of 322 RA patients with and without Raynaud's phenomenon

	RA patients with Raynaud's phenomenon	RA patients without Raynaud's phenomenon	*P*
Total number	55	267	
Sex ratio	45:10	209:58	NS
Age	57.9 ± 13.4	58.4 ± 14.2	NS
Nodules	10/55	45/267	NS
Vasculitis	3/55	3/267	0.06
Ritchie's score	8.1 ± 8	10.7 ± 7.7	NS
Lee's score	11.3 ± 7.3	12 ± 7.7	NS
ESR	43.6 ± 30.2	50.9 ± 34.8	NS
CRP	32.02 ± 33	50.5 ± 56	0.005
Latex+	37/54 (69%)	185/264 (70%)	NS
Antinuclear antibodies+	18/53 (34%)	83/258 (32%)	NS
C4	24.8 ± 9.3	28 ± 10.2	0.037
CH50	73.5 ± 16.7	76.75 ± 16.37	NS

Brit J Rheumatol, 1996, 35, 752-4





RMD Open
Rheumatic & Musculoskeletal Diseases

EXTENDED REPORT

Eosinophilia predicts poor clinical outcomes in recent-onset arthritis: results from the ESPOIR cohort

Dewi Guellec,[1] Morgane Milin,[1] Divi Cornec,[1,2] Gabriel J Tobon,[3] Thierry Marhadour,[1] Sandrine Jousse-Joulin,[1,2] Gilles Chiocchia,[4] Olivier Vittecocq,[5] Valérie Devauchelle-Pensec,[1,2] Alain Saraux[1,2]

L'éosinophilie est rare et souvent transitoire
Il n'y a pas de traitement spécifique à envisager sauf si les chiffres sont supérieurs à 2000 et alors le traitement reste celui de la PR

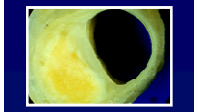
Table 3 Comparison of features after 3 years in the groups with and without baseline eosinophilia

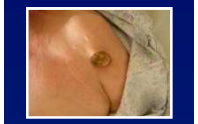
Features	Eosinophils ≥500/mm³ N=26	Eosinophils <500/mm³ N=778	p Value
DAS28, mean (SD)	3.2 (1.2)	2.9 (1.4)	0.17
Patient VAS activity score, mean (SD)	43.6 (32.6)	28.4 (25.9)	**0.05**
Physician VAS activity score, mean (SD)	24.0 (23.0)	19.2 (19.8)	0.32
Morning stiffness intensity, mean (SD)	36.0 (29.7)	21.7 (23.3)	**0.05**
HAQ score, mean (SD)	0.9 (0.7)	0.5 (0.6)	**0.004**
CRP (mg/L), mean (SD)	12.3 (19.5)	6.6 (11.0)	0.95
Rate of erosion progression during year 1, mean (SD)	3.6 (4.0)	3.0 (4.6)	0.83
Rate of erosion progression between year 1 and year 3, mean (SD)	2.5 (3.2)	2.6 (4.2)	0.41
Corticosteroids, n (%)	7/18 (38.9)	229/606 (37.8)	0.92
DMARD, n (%)	18/19 (94.7)	476/669 (71.1)	**0.02**
Methotrexate, n (%)	13/19 (68.4)	370/673 (55.0)	0.24
Methotrexate dosage (mg/week), mean (SD)	14.6 (3.5)	13.3 (3.9)	0.22
Biological agent	2/26 (7.7%)	89/778 (11.4%)	0.76

Bold typeface indicates p≤0.05.
CRP, C reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; VAS, visual analogue scale.

Eosinophilia is rare in recent-onset arthritis. Eosinophilia was mild and transient in most patients. Patients with mild baseline eosinophilia might respond worse to the treatment than the remainder, as they had higher patient-assessed disease activity, morning stiffness intensity, health assessment questionnaire (HAQ) scores, and disease-modifying antirheumatic drug (DMARD) use after 3 years.

Guellec D, *et al. RMD Open* 2015;**1**:e000070.





Baseline Laboratory Test Abnormalities are Common in Early Arthritis but Rarely Contraindicate Methotrexate: Study of Three Cohorts (ESPOIR, VErA, and Brittany)

Marion Le Boëdec, MD,* Thierry Marhadour, MD,*
Valérie Devauchelle-Pensec, MD, PhD,* Sandrine Jousse-Joulin, MD,*
Aymeric Binard, MD,* Bruno Fautrel, MD, PhD,† René Marc Flipo, MD,‡
Xavier Le Loët, MD,§ Jean François Ménard, MD,‖ and Alain Saraux, MD, PhD*

Les cytopénie ne sont pas exceptionnelles, mais ce sont surtout l'anémie et la lymphopénie

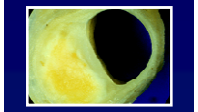
	ESPOIR *	VErA *	Brittany *	Total
Anémie	240/809 (29.6%)	50/301 (16.6%)	73/256 (28.5%)	363/1366 (26.6%)
Leucopénie	10/809 (1.23%)	6/301 (1.99%)	2/262 (0.76%)	18/1372 (1.31%)
Neutropénie	15/803 (1.87%)	1/299 (0.33%)	-	16/1102 (1.45%)
Lymphopénie	51/804 (6.34%)	22/299 (7.36%)	-	73/1103 (6.62%)
Thrombocytopénie Thrombocytose Normal	7/809 (0.86%) 128/809 (15.8%) 674/809 (83.3%)	2/301 (0.66%) 29/301 (9.63%) 270/301(89.7%))	4/261 (1.53%) 45/261 (17.2%) 212/261 (81.2%)	13/1371 (0.95%) 202/1371 (14.7%) 1156/1371 (84.3%)

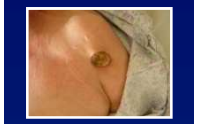
 Semin Arthritis Rheum 42:474–481

Neutropénie

- **Hors PR**
  - Le grand risque est l'infection bactérienne, surtout en dessous de 0,5G/L
  - elle est physiologique chez l'africain (jusqu'à 1G/L), isolée en cas de prise médicamenteuse ou pathologie virale, fluctuante en cas de trouble de margination
  - Elle peut être
    - Centrale (aplasie, envahissement, myélodysplasie)
    - Périphérique (hypersplénisme, trouble de répartition, immunologique en cas de connectivite)

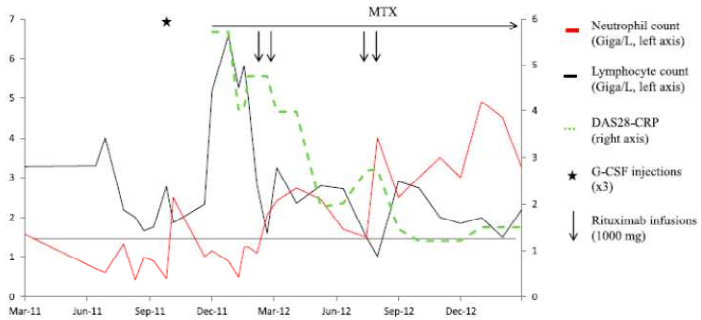
- **Dans la PR**
  - Elle peut être médicamenteuse
  - Elle peut être due à un syndrome de Felty, un clone LGL



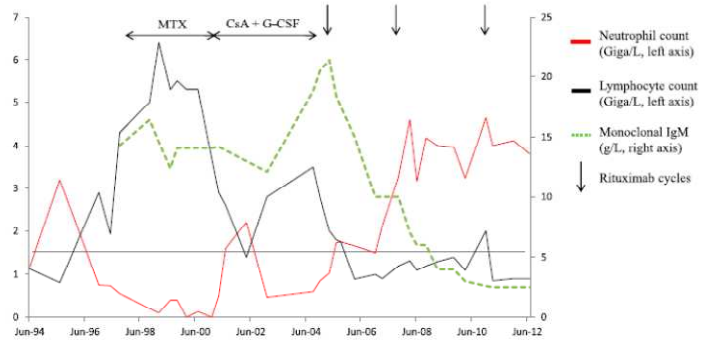


Neutropénie et pseudofelty

- **En cas de pseudo felty (clone LGL), le traitement par rituximab parait efficace sur la PR, sur le clone LGL et sur la neutropénie (n:2)**



- **En cas de syndrome de Felty, le traitement a montré son efficacité dans certains cas (n:5) mais pas dans d'autres**



D Cornec, Blood 2013; A Tomi, Joint Bone Spine 2012

Lymphopénie

- **Se voit hors PR si infection (HIV), cancer, corticothérapie, maladie auto-immune (lupus, Sjogren), insuffisance rénale, idiopathique**

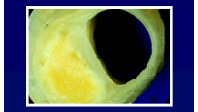
- **Se voit dans la polyarthrite débutante**
  - Au moment du diagnostic
    - lupus érythémateux systémique
    - syndrome de Sjögren primitif
    - parvovirus B19
  - Ultérieurement
    - surtout si traitements (corticothérapie, traitements de fond)

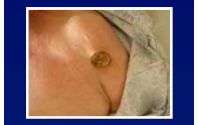
Ng WL et al. Lymphopenia at presentation QJM. 2006 janv;99(1):37-47 ;
Doran MF, et al. Arthritis Rheum. 2002 sept;46(9):2287-93. Lorenzi AR, et al. Arthritis Rheum. 2008 févr;58(2):370-5.

Lymphopénie

- **La lymphopénie est**
  - Facteur de risque d'infection et de néoplasie au cours de l'infection VIH, du lupus, des lymphomes
  - Dans la PR, on observe plus une augmentation du risque infectieux lié à la maladie et aux traitements immunosuppresseurs qu'à la lymphopénie.
  - Elle est souvent transitoire au début de la PR et sans conséquence
  - L'alemtuzumab (qui n'est plus commercialisé), anticorps monoclonal thérapeutique anti CD52, marqueur de membrane des lymphocytes entraîne une lymphopénie profonde dans la PR, sans risque infectieux nettement majoré

Ng WL et al. Lymphopenia at presentation QJM. 2006 janv;99(1):37-47 ; Duquenne C. JBS 2015;82:417-22
Doran MF, et al. Arthritis Rheum. 2002 sept;46(9):2287-93. Lorenzi AR, et al. Arthritis Rheum. 2008 févr;58(2):370-5.

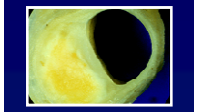


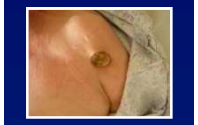


Thrombopénie

Toujours éliminer un artéfact

- **Hors PR**
  - Soit périphérique (Purpura thrombopénique, immunoallergie médicamenteuse, post transfusion)
  - Soit trouble de répartition (hypersplénisme, cirrhose)
  - Soit trouble de l'hémostase (CIVD, microangiopathie thrombotique)
  - Soit centrale (myélodysplasie, myélofibrose, métastases, hémopathies, carence, aplasie)
- **Dans la PR**
  - Association à une pathologie autoimmune (Sjögren, lupus, SAPL*, thyroïdite ou maladie de Basedow)
  - Médicamenteux
- **Connaître les signes de gravité**
    - Purpura ecchymotique
    - Bulles intrabuccales
    - Gingivorragie spontanée
    - Le chiffre à risque: <20 000/mm3,
    - AVK, AINS





Rheumatoid arthritis-associated lung disease

Megan Shaw[1], Bridget F. Collins[2], Lawrence A. Ho[2] and Ganesh Raghu[2]

Les atteintes pulmonaires sont fréquentes et surtout

- ILD
- Bronchiolite
- Nodules pulmonaires

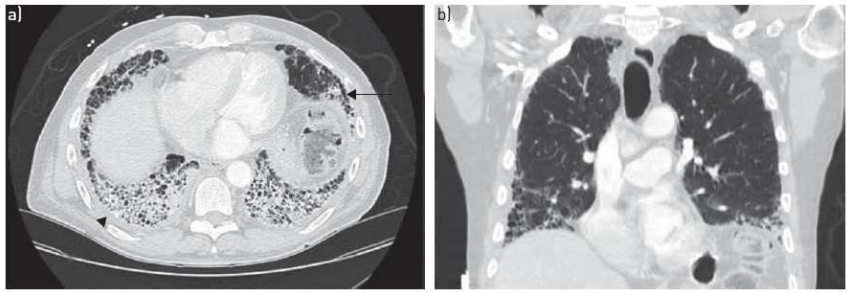


FIGURE 2 a) Axial and b) coronal computed tomography scans of usual interstitial pneumonia pattern in a patient with rheumatoid arthritis. Subpleural and basilar predominant reticulations, minimal ground-glass opacities, honeycombing (arrow) and pleural thickening (arrowhead) are visible, as well as traction bronchiectasis.

TABLE 1 Pulmonary manifestations of rheumatoid arthritis

Parenchymal
Interstitial lung disease (*i.e.* usual interstitial pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage and organising pneumonia)
Pleural disease
Pleural effusion
Pneumothorax
Bronchopleural fistula
Trapped lung syndrome
Airway obstruction
Cricoarytenoid arthritis
Bronchiectasis
Follicular bronchiolitis
Obliterative (constrictive) bronchiolitis
Nodules
Rheumatoid nodules
Caplan syndrome
Vascular disease
Rheumatoid vasculitis
Pulmonary hypertension
Other
Drug toxicity
Infection
Malignancy
Thoracic cage restriction
Thromboembolic disease

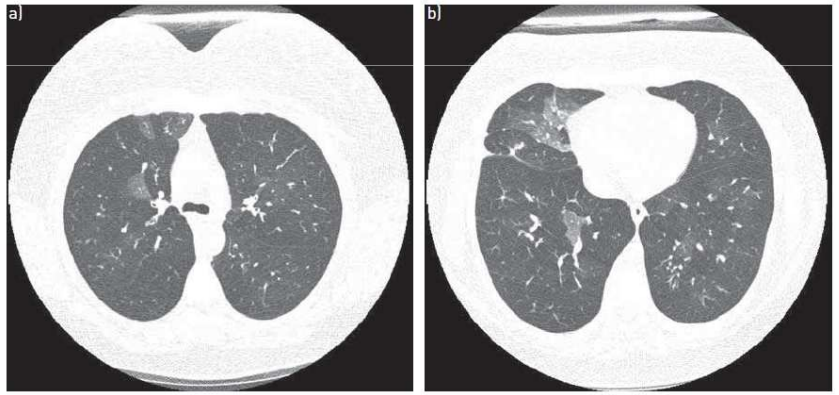
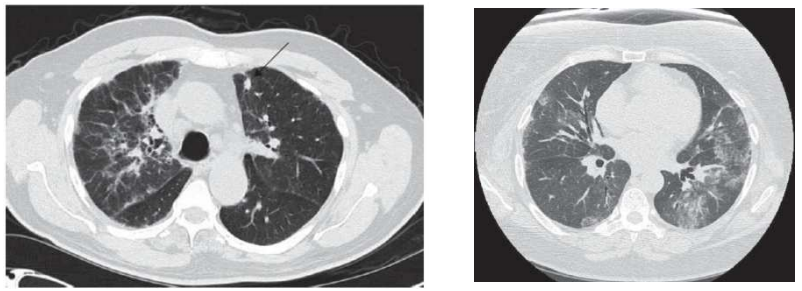
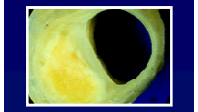
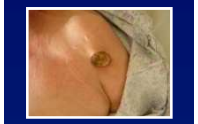


FIGURE 5 a, b) Expiratory computed tomography scans of constrictive bronchiolitis with areas of mosaic attenuation consistent with air trapping in a patient with rheumatoid arthritis.



Eur Respir Rev 2015; 24: 1–16





Pleuropéricardite

Le diagnostic est surtout clinique et confirmé par RP,

- **RP**
- **ECG et echocoeur**

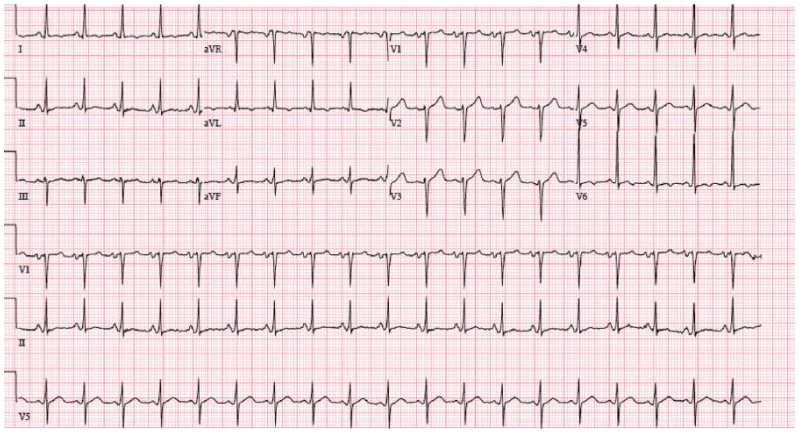
La difficulté est d'éliminer les diagnostics différentiels

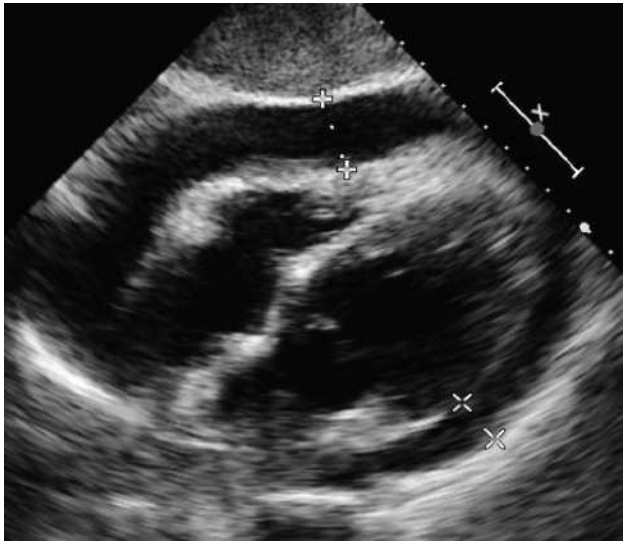
Les complications sont exceptionnelles

Le traitement repose sur la corticothérapie et les traitements de fond

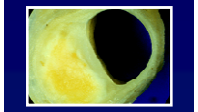
A Rare Case of Cardiac Tamponade Induced by Chronic Rheumatoid Arthritis

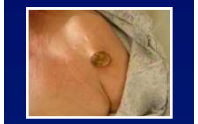
Tariq Yousuf[a, d], Jason Kramer[b], Adam Kopiec[b], Zachary Bulwa[b], Shuvani Sanyal[c], Jeffrey Ziffra[a]





J Clin Med Res. 2015;7(9):720-723

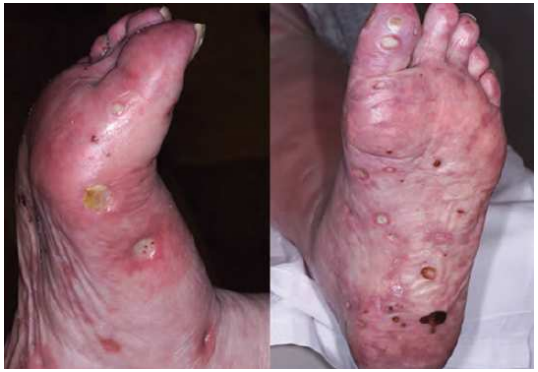




Rheumatoid vasculitis: an update

Ashima Makol[a], Eric L. Matteson[a,b], and Kenneth J. Warrington[a]

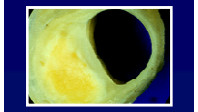
- **L'infarctus ungéal n'est pas significatif**
- **Les autres atteintes sont potentiellement graves**
- **Un schéma thérapeutique simple a été proposé par Makol**
- **MTX plus corticoïdes puis Rituximab restent les traitements les plus utilisés**

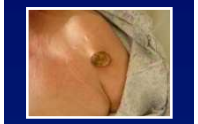


KEY POINTS

- Incidence of rheumatoid vasculitis has declined in the past several decades, but clinical presentation has remained unchanged (cutaneous vasculitis and vasculitic neuropathy remaining the most common).
- Hydroxychloroquine and low-dose aspirin are associated with lower odds of developing rheumatoid vasculitis among RA patients, thus conferring a possible protective effect.
- Despite aggressive use of CYC and biologics, rheumatoid vasculitis remains a difficult EAM to treat, with high relapse rates and mortality that have not changed in over 40 years.

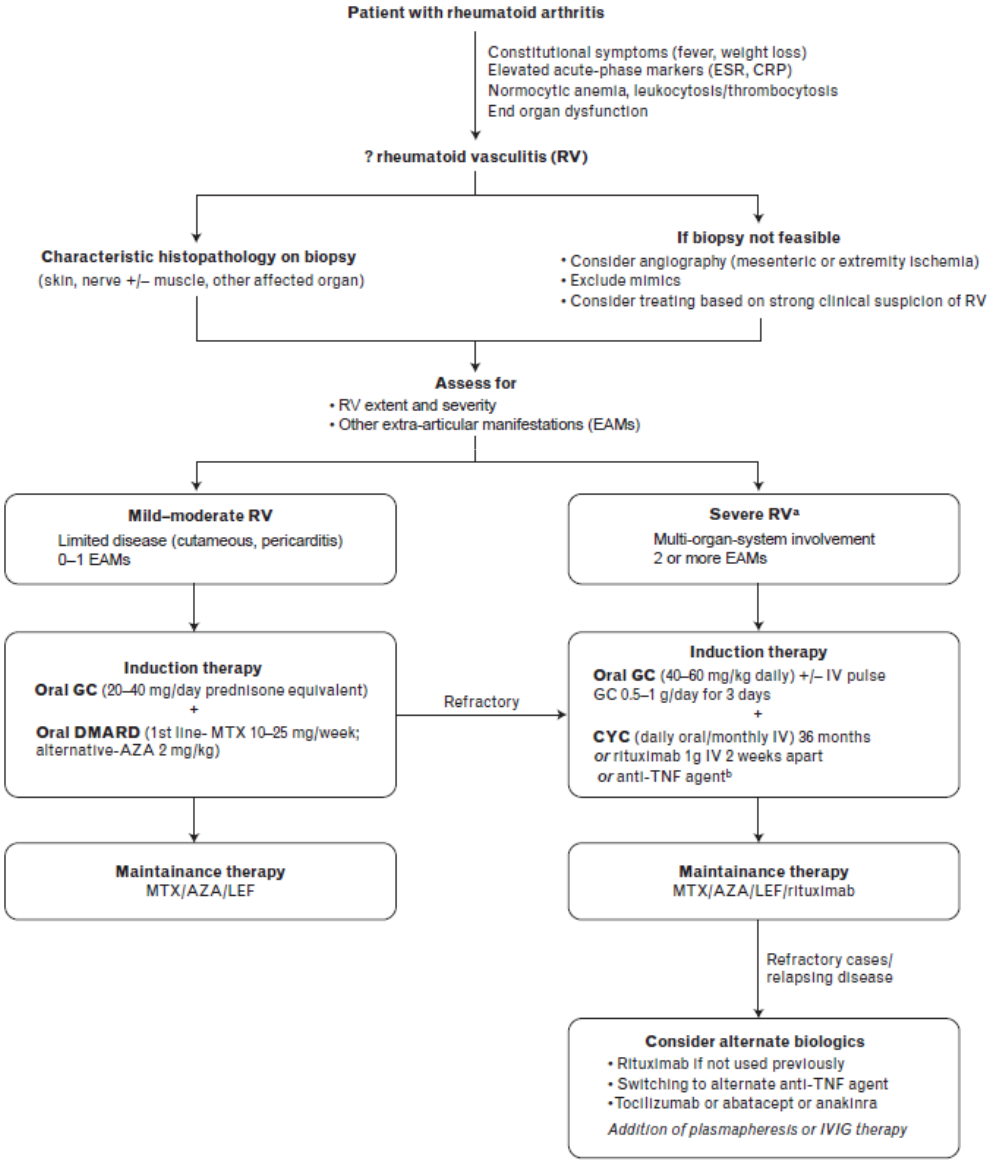
Organ system	Clinical presentation
Skin (most common)	Purpura
	Nail fold infarcts
	Digital ischemia/gangrene
	Cutaneous ulcers (upper or lower extremity)
Peripheral nervous system	Mononeuritis multiplex
	Distal asymmetric/symmetric sensory and/or mixed polyneuropathy
Eye	Episcleritis
	Scleritis (anterior/posterior, nodular/diffuse, nonnecrotizing/necrotizing scleromalacia perforans)
	Peripheral ulcerative keratitis (with or without corneal melt)
	Retinal vasculitis
Heart	Pericarditis
	Myocarditis (presenting as arrhythmias – atrial fibrillation, ventricular arrhythmias and complete heart block)
	Coronary vasculitis (presenting as myocardial infarction)
Lung	Pulmonary angiitis/capillaritis (presenting as alveolar hemorrhage)
Kidney	Pauci-immune glomerulonephritis
	Medium vessel vasculitis (without microaneurysms)
Gastrointestinal tract	Mesenteric vasculitis
	Bowel (commonly ileal or sigmoid) ischemia and/or perforation
Central nervous system	Hypertrophic pachymeningitis
	Central nervous system vasculitis (presentations include seizures, cranial nerve palsies, strokes and myelopathy)

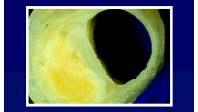


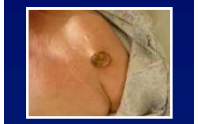


Rheumatoid vasculitis: an update

Ashima Makol[a], Eric L. Matteson[a,b], and Kenneth J. Warrington[a]







Rituximab Therapy for Systemic Vasculitis Associated With Rheumatoid Arthritis: Results From the AutoImmunity and Rituximab Registry

X. PUÉCHAL,[1] J. E. GOTTENBERG,[2] J. M. BERTHELOT,[3] L. GOSSEC,[4] O. MEYER,[5] J. MOREL,[6] D. WENDLING,[7] M. DE BANDT,[8] E. HOUVENAGEL,[9] B. JAMARD,[10] T. LEQUERRÉ,[11] G. MOREL,[12] P. RICHETTE,[13] J. SELLAM,[14] L. GUILLEVIN,[15] AND X. MARIETTE,[16] ON BEHALF OF THE INVESTIGATORS OF THE AUTOIMMUNITY AND RITUXIMAB REGISTRY

- Complete remission of systemic vasculitis associated with rheumatoid arthritis was achieved in nearly three-fourths of the patients receiving rituximab treatment, with a clinically relevant decrease in prednisone doses and an acceptable toxicity profile.
- Rituximab represents a suitable therapeutic approach to induce remission in these patients, although maintenance therapy is likely to be necessary.

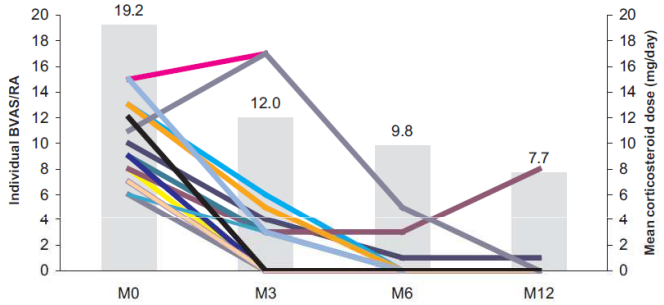


Figure 1. Individual modified Birmingham Vasculitis Activity Score for rheumatoid arthritis (BVAS/RA) and mean corticosteroid dosage before and after rituximab therapy in patients with systemic rheumatoid vasculitis. Each line shows the progression of the individual BVAS/RA. Bars show the mean daily dosage of prednisone at the different end points of the study.

Results. Of the 1,994 patients with RA enrolled in the registry, 17 were treated with rituximab for active SRV. At baseline, the mean Birmingham Vasculitis Activity Score for RA (BVAS/RA) was 9.6, with a mean prednisone dosage of 19.2 mg/day. After 6 months of rituximab therapy, 12 patients (71%) achieved complete remission of their vasculitis, 4 had a partial response, and 1 died with uncontrolled vasculitis. Mean BVAS/RA was reduced to 0.6 and mean prednisone dosage to 9.7 mg/day. At 12 months, 14 patients (82%) were in sustained complete remission. Severe infection occurred in 3 patients, corresponding to a 6.4 per 100 patient-years rate. In the 6 patients who received further rituximab as maintenance therapy between months 6 and 12, no relapse of vasculitis was observed. However, among the 9 patients who did not, a relapse was observed in 3 patients who were treated with methotrexate alone. Remission was reestablished by reintroducing rituximab in 2 cases.

Arthritis Care & Research
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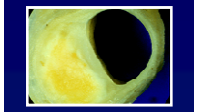
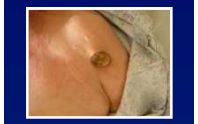




Neuropsychiatric manifestations in rheumatoid arthritis☆

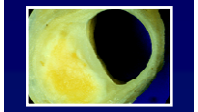
Andrei F. Joaquim [a,*], Simone Appenzeller [b]

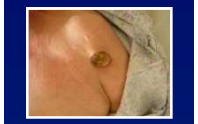
- **Les atteintes neurologiques sont le plus souvent iatrogènes ou intercurrentes (AVC, infection dont zona)**
- **Sont en revanche fréquents**
  - **Les états dépressifs**
  - **Les pathologies compressives (nerfs périphériques, moelle cervicale)**

1) RA disease by itself, with inflammation, autoantibodies, pain, fatigue and disability leading to psychiatric diseases [4,6].
2) The systemic inflammatory processes involving all organs and systems, which can involve the neural tissue (e.g. pachimeningitis or vasculitis) [14].
3) Joint and bone destruction leading to neural compression (e.g. cervical myelopathy symptoms caused by destruction of the atlanto-axial joints and subsequent atlantoaxial subluxation) or the presence of rheumatoid nodules compressing peripheral nerves [3,15–17].
4) Potential side effects of the medication used to obtain disease control, such as corticosteroids, disease modifying drugs (DMARDS) and biological agents (BA) [17].
5) Accelerated atherosclerosis associated with systemic inflammation and autoantibodies [18,19].

- RA can course with neuropsychiatric symptoms caused by neural compression secondary to damage on joints and bones, the diffuse and systemic inflammatory process and also for side effects of the drugs used for disease control.
- Brain involvement can be secondary to vasculitis or inflammatory meningitis, as well as opportunistic infections and side effects of RA medication for disease control. Depression and cognitive dysfunction are quite common, potential related to the disease itself and its chronic and disability condition.
- Spinal involvement is generally consequence of severe inflammation and destructive changes in the cervical spine (such as atlantoaxial subluxation and subaxial subluxation), finally resulting in spinal cord compression.
- Peripheral nervous system involvement is also common and can occur due to compressive (favored by the inflammation of the joints and tendons) and non-compressive neuropathies (secondary to side effects of medication used for treatment, vasculitis, amyloidosis and also specific auto-antibody).

Autoimmunity Reviews 14 (2015) 1116–1122





Cervical spine involvement in rheumatoid arthritis — A systematic review☆,☆☆

Andrei F. Joaquim [a,*], Simone Appenzeller [b]

Main characteristics of the studies involving the prevalence of cervical involvement in patients with RA.

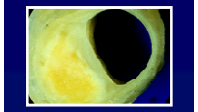
Author/year	N Study type	Follow-up	Frequency of cervical spine involvement Type	Associations	Level of evidence
Blom et al., 2013 [8]	134 Cohort	3–12 yrs	16% at 9 yrs AAS > C2 > SMO > C1	Erosions in peripheral joints Failed more DMARDs	II
Yurube et al., 2012 [9]	140 Cohort	Mean 6 ± 0.5 yrs	43.6% had cervical instabilities. 12.9% had severe cervical instabilities AAS > SMO > SAS.	Corticosteroid administration, destructive changes at baseline and the development of destructive changes during the follow-up ($p < 0.05$)	II
Yorube et al., 2011 [10]	267 patients (140 without cervical involvement) Cohort	>5 yrs	127 (47.5%) at study entry 188 (70.4%) at the end of the study)	Initial cervical involvement, pre-existing destructive changes were related to progression.	II
Ahn et al., 2010 [11]	1120	3 yrs (570 patients) and >3 yrs (137 patients)	320 (28.6%)	Peripheral erosions, age <45 yrs	III
Yan et al., 2008 [12]	71 patients with upper cervical spine involvement	2 month to 46 yrs	AAS > RS > SMO	–	III

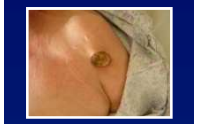
AAS: atlantoaxial subluxation; DMARDs: disease-modifying antirheumatoid drugs; SAS: subaxial subluxation; RA: rheumatoid arthritis; SMO: superior migration of the odontoid; RS: rotational subluxation; VS: vertical subluxation; yrs: years.

Summary of the papers relating radiological modalities and the prevalence of cervical spine disease in RA.

Author	N	Imaging modality	Prevalence of cervical spine involvement	Results	Conclusions	Level of evidence
Magarelli et al. [13]	20 early RA	MRI	25% (enhancement of the periodontoid synovial spaces after gadolinium)	↑ESR, ↑CRP, ↑DAS associated with cervical involvement	MRI was an excellent tool for early detection.	III
Younes et al. [14]	40	Plain radiographs, CT scan and MRI	29	Prevalence varied: 47.5% plain radiographs, 28.2% with CT and 70% with MRI.	↑CRP, ↑DAS associated with cervical involvement MRI > X-rays > CT for diagnosis	III
Narvanes et al. [15]	41	MRI	41	MRI findings correlated with Ranawat's classification and neurological dysfunction.	MRI correlated with clinical myelopathy.	III

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein values; CT: DAS: disease activity score; MRI: magnetic resonance imaging; RA: rheumatoid arthritis.





Cervical spine involvement in rheumatoid arthritis — A systematic review☆,☆☆

Andrei F. Joaquim [a,*], Simone Appenzeller [b]

Summary of the papers relating the clinical effects of DMARD in the Cervical Spine.

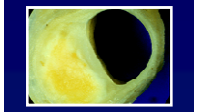
Author	N	Objectives	Results	Conclusions	Level of evidence
Kauppi et al. [16]	149	Compared cervical involvement in patients with single versus combined DMARD	Prevalence of AAS, AAI and SAS were respectively 13 (9%), 6 (4%), and 9 (6%) Poor physical function ($p = 0.024$) and Single treatment strategy ($p = 0.019$) were associated with AAS.	Patients with combined DMARD rarely developed AAS	I

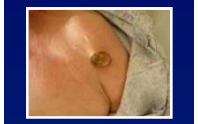
AAS: Atlantoaxial subluxation, DMARDs: disease-modifying antirheumatoid drugs, VS: vertical subluxation

Summary of the papers reporting the progression of cervical spine instabilities after surgical treatment.

Author	N	Objectives	Results	Conclusions	Level of evidence
Ito et al. [17]	43 patients who underwent AA fixation (33 RA and 10 without)	Evaluated the progression of cervical instabilities after surgery for AAS	After mean of 4.2 years of follow-up, patients with RA developed substantial aggravation of the SAS compared with non-RA patients. Risk factor for progression was cervical kyphosis preoperatively.	Long term follow-up was necessary in cervical instabilities in patients with RA treated surgically for detecting the development of SAS.	III
Ishi et al. [18]	58 RA patients who underwent AA fixation	Evaluated the development of postoperative worsening of SAS	After an average of 137 months of follow-up, 19 patients had SAS compared with 39 without SAS. The presence of SAS was associated with a large AA and a small C2–7 angle	Surgeons should avoid extensive correction of AA angles after AA fixation for RA patients.	III
Clarke et al. [19]	51 patients with RA treated with posterior cervical arthrodesis	Evaluate the recurrence of instability after surgery	With a mean follow-up of 8.3 ± 6 years, 13 of 33 (39%) of the patients with AAS developed SAS, seven requiring surgery.	Treatment of AAS prevents SMO but can favor development of SAS. Long term follow-up after AA fixation is necessary.	III

AA: atlantoaxial; AAS: atlantoaxial subluxation; SAS: subaxial subluxation; RA: rheumatoid arthritis.





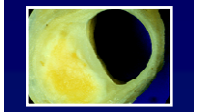
Cervical spine involvement in rheumatoid arthritis — A systematic review☆,☆☆

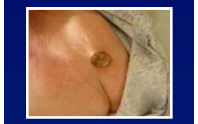
Andrei F. Joaquim [a,*], Simone Appenzeller [b]

Results of the studies that evaluate BA and cervical instabilities in RA.

Author	N	Objective	Results	Conclusions	Level of evidence
Kaito et al. [21]	91	Evaluated patients with RA who received BA for more than 2 years	New cervical spine involvement in 7% patients and worsening of pre-existing involvement in 79% with AAS and 72% with VS.	DMARD prevented de novo cervical lesions but failed to control progression of pre-existing instabilities.	III
Kaito et al. [22]	38	Evaluate the effects of BA on the development and progression of cervical spine lesions	RA activity was controlled with BA therapy (disease activity score — DAS from 4.3 to 2.3) ($p < 0.01$). 12 patients did not have pre-existing cervical instabilities, AAS in 15 cases and VS in 11 cases. Radiological progression: 1 (8%) patients without cervical lesions, 12 (80%) in the AAS group and 9 (80%) in the VS group.	BA prevented the development of de novo cervical spine lesions but failed to inhibit progression of pre-existing RA lesions.	III
Takahashi et al. [23]	220	Evaluate the prevalence of cervical instability in the BA areas	93 (42%) of the patients had cervical instabilities detected with plain radiographs and MRI.	The authors were unable to detect the role of BA in the presence of cervical instabilities.	III

AAS: atlantoaxial subluxation; BA: biological agents; DAS: Disease Activity Score; MRI: magnetic resonance imaging; RA: rheumatoid arthritis.



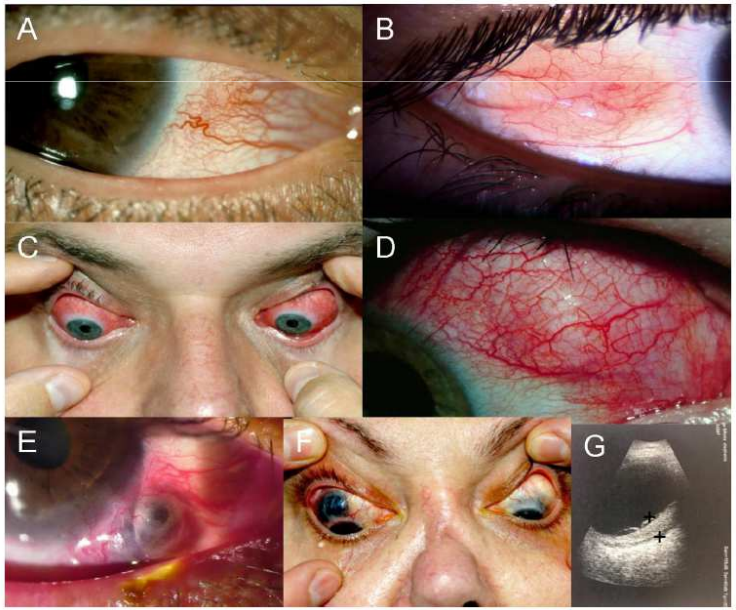


Sclérites et épisclérites : prise en charge diagnostique et thérapeutique

Scleritis and episcleritis: Diagnosis and treatment

E. Héron [a,*], M. Gutzwiller-Fontaine [b], T. Bourcier [b]

- **La PR est classiquement associée aux sclérites, plus que les autres maladies auto immunes**
- **Mais les autres étiologies doivent être recherchées**
- **Le traitement est surtout basé sur les corticoïdes, le méthotrexate ou d'autres immunosuppresseurs, voire les biologiques (surtout anti TNF)**



Bilan paraclinique minimum d'une sclérite (ou épisclérite si indication).

Biologie sanguine
- NFS, VS, CRP, fibrinogène
- Électrophorèse des protéines sériques, créatininémie
- AAN, Ac anti-ECT, Ac anti-CCP, FR, ANCA
- Sérologies HSV-1 et -2

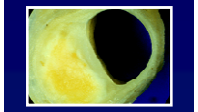
Biologie urinaire
- Recherche d'hématurie, leucocyturie et protéinurie

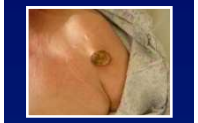
Imagerie
- Radiographie thoracique
- Test cutané tuberculinique

NFS : numération formule sanguine ; VS : vitesse de sédimentation ; CRP, protéine C-réactive ; AAN : anticorps antinucléaires ; Ac : anticorps ; ECT : antigènes solubles du noyau ; CCP : peptides cycliques citrullinés ; FR : facteur rhumatoïde ; ANCA : anticorps anti-cytoplasme des polynucléaires neutrophiles.

Fig. 1. Classification clinique des épisclérites et sclérites. A : épisclérite simple ; B : épisclérite nodulaire ; C : sclérite antérieure diffuse bilatérale ; D : sclérite nodulaire ; E : sclérite nécrosante avec inflammation ; F : *Scleromalacia perforans* bilatérale chez une patiente atteinte de granulomatose avec polyangéite ; G : sclérite postérieure (échographie oculaire).

La Revue de médecine interne 35 (2014) 577–585





Sclérites et épisclérites : prise en charge diagnostique et thérapeutique

Scleritis and episcleritis: Diagnosis and treatment

E. Héron [a,*], M. Gutzwiller-Fontaine [b], T. Bourcier [b]

Détail des principales pathologies associées aux sclérites.

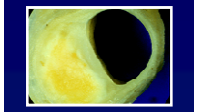
Étude	Watson 1976	McCluskey 1999	Akpek 2004	Lin 2008	Raiji 2009	Sainz de la Maza 2012	Wieringa, 2013	Total
Population, *n*	207	99[e]	243	119	86	500	104	1358
Période de l'étude	1975–1988	1974–1996	1984–2002	1995–2006	2001–2007	2005–2010	1992–2011	
Maladie systémique, n (%)								374 (27,5)
Polyarthrite rhumatoïde	21	5	37	22	10	32	14	141 (10,4)
Spondylarthropathies[a]	5	1	6	2	4	14	1	33 (2,4)
HLA B27 isolé	–	–	–	–	–	24 (4,8 %)	–	–
GPA	1	4	11	8	2	14	7	47 (3,5)
Polychondrite	2	3	4	3	0	11	2	25 (1,8)
Autres vascularites[b]	7	5	10	2	1	8	1	34 (2,5)
MICI	–	–	8	5	–	11	3	27 (2,0)
Lupus systémique	2	1	10	2		10	–	26 (1,9)
Divers[c]	7	8	4	6	9	4	3	41 (3,0)
Infection, n (%)								104 (7,7)
Herpès virus (VZV/HSV)	18 (16/2)	–	15 (11/4)	3 (2/1)	2 (2/0)	35 (HSV)	2 (VZV)	75 (5,5)
Tuberculose	4	–	–	–	–	5	–	9 (0,7)
Syphilis	6	–	1	1	–	–	1	9 (0,7)
Divers[d]	–	–	6	1	2	7	–	11 (0,8)

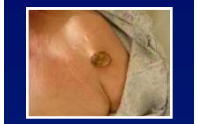
Traitement des sclérites antérieures non infectieuses.

Traitement[a]	Type de sclérite			
	Diffuse	Nodulaire	Nécrosante	Total
	(*n* = 327)	(*n* = 53)	(*n* = 12)	(*n* = 392)
Aucun, *n* (%)	10 (3,1)	4 (7,5)	0	14 (3,6)
AINS	115 (13)	29 (54)	0	144 (36)
Corticostéroïdes	27 (8)	2 (3)	0	29 (7)
Immunosuppresseurs	128 (39)	11 (20)	10 (83,3)	149 (38)
Biothérapie	47 (14)	7 (13)	2 (16,7)	56 (14)

D'après [29].

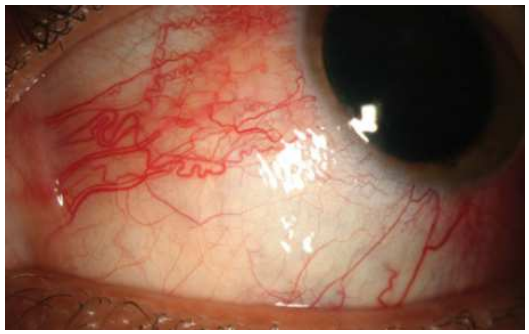
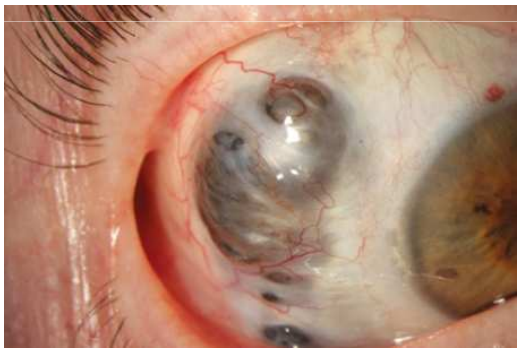
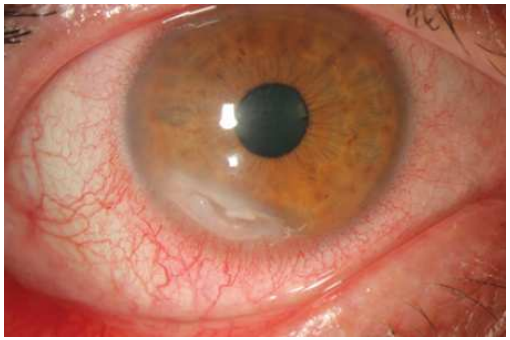
[a]Seule la dernière ligne thérapeutique utilisée, assurant le succès thérapeutique, est prise en compte. AINS : anti-inflammatoire non stéroïdien.

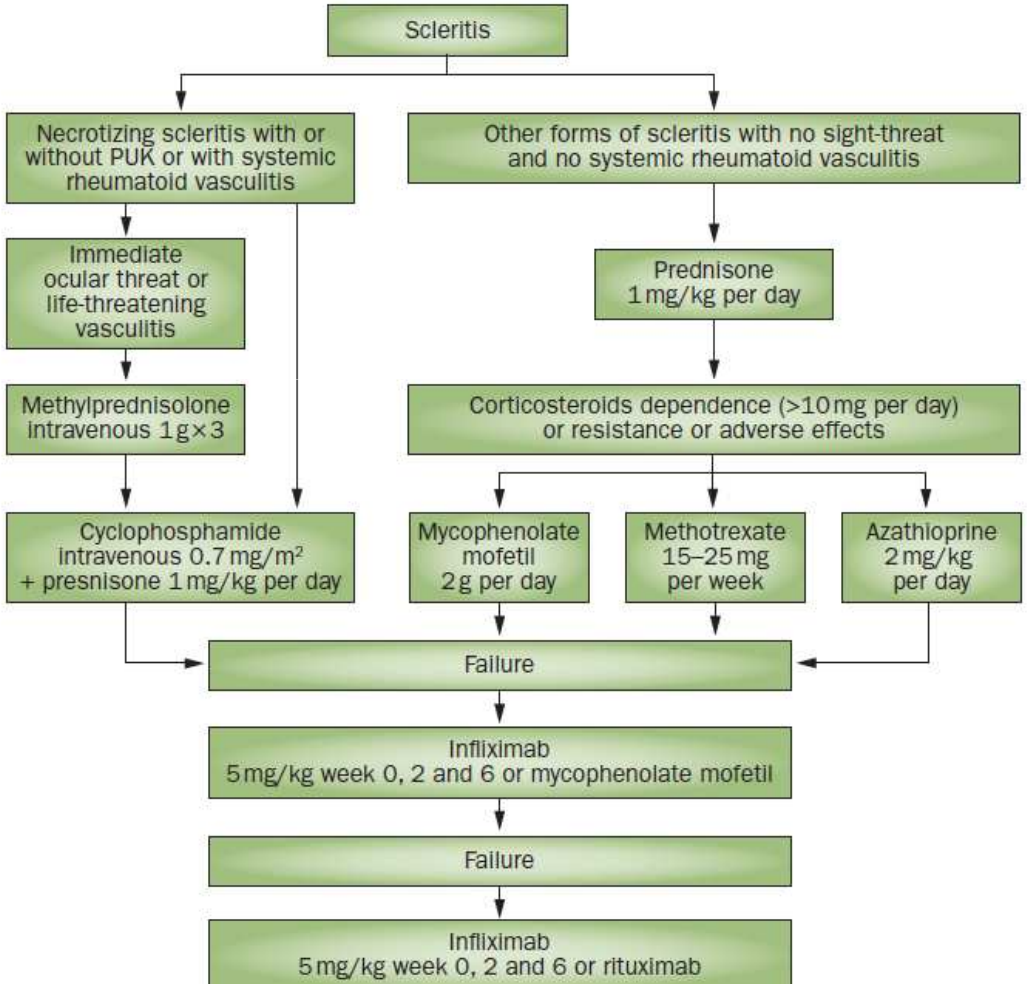




Ocular inflammatory diseases associated with rheumatoid arthritis

Mathieu Artifoni, Pierre-Raphaël Rothschild, Antoine Brézin, Loïc Guillevin and Xavier Puéchal



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