Syndrome catastrophique des anticorps anti-phospholipides

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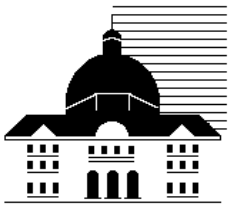
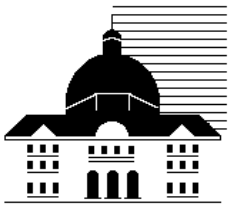


Syndrome des anticorps anti-phospholipides



SAPL défini: Consensus International sur les critères préliminaires de classement.

Arthritis Rheum 1999, 42: 1309-11 updated: J Thromb haemost 2006, 4:295-306

CRITERES CLINIQUES

1. **THROMBOSE(S)** (artérielle, veineuse, ou microvasculaire)

> 1 épisode clinique dans tout tissu ou organe, confirmé par imagerie, Doppler, histologie (sans inflammation pariétale significative). Les AIT et TV superficielles sont exclus.

2. **MORBIDITE GRAVIDIQUE**

- **> 1 mort foetale dès 10 SA** inexpliquée par ailleurs, sans anomalies morphologiques foetales décelables par échographie ou examen direct
- Ou **: > 3 avortements spontanés consécutifs** inexpliqués < 10 SA non liés à une anomalie maternelle anatomique ou hormonale, ou chromosomique parentale
- Ou : **1 naissance prématurée (< 34 SA)** d'un nouveau-né normal morphologiquement, liée à une (pré)éclampsie ou une insuffisance placentaire sévère(s)

aPL: Comment les rechercher ?
Critères biologiques

Lupus Anticoagulant

= Anti coagulant circulant HEMOSTASE

--> 3 Etapes

- Utiliser 2 tests de coag. PL-dépendant: TCA (ind. de Rosner), TCK, dRVVT, TTD…
- suspecté sur l'allongement d'un temps de coagulation
- Inhibiteur démontré par le mélange de plasmas (malade + témoin).
- confirmé par tests de neutralisation (tps de coag. normalisé par PL)
- *Recherche possible sous AVK, mais pas sous héparine ++*

Ac anti-cardiolipine:

test IMMUNOLOGIQUE ELISA sur sérum

- Multiples kits commerciaux + "maison«
- Absence de standardisation/pb du seuil
- Résultats en unités GPL / MPL (> 40 UGPL ou UGPM, 99ème percentile)

Ac anti- β 2 GP I:

idem

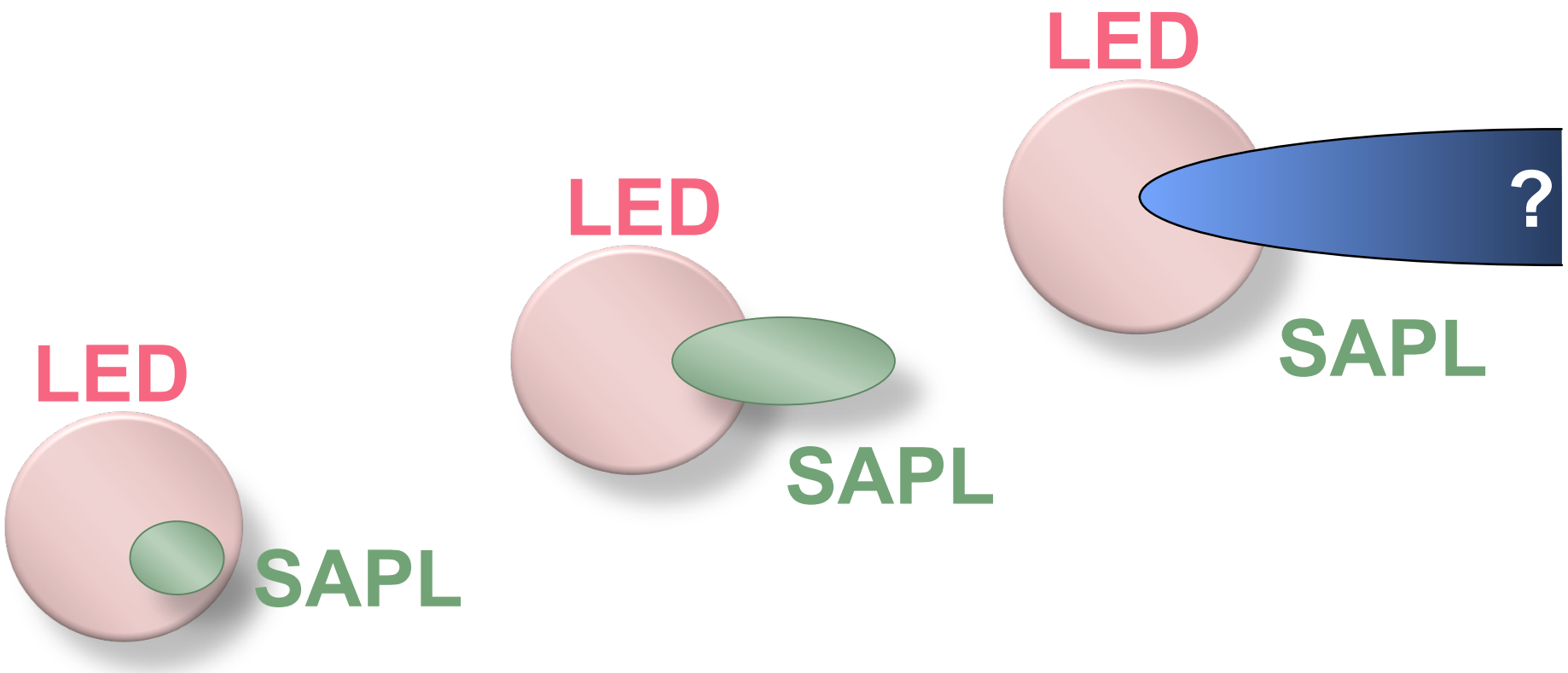
- Mêmes problèmes

DANS TOUS LES CAS CONFIRMER LA POSITIVITE APRES 12 SEMAINES

SAPL défini

1 critère clinique et 1 critère biologique

SAPL: évolution du concept



CIRCONSTANCES ASSOCIEES A LA PRESENCE D' APL

LA isolé "fortuit"

Syndrome APL

- PRIMAIRE
- Associé à:
  - Lupus
  - Autres connectivites

aPL "épiphénomènes"

- Néoplasie
- Hémopathie, PTA
- Infection
- Médicament
- Insuffisance rénale
- BBS, MICI, Hépatopathies,
- Horton
- ? Sujets âgés
- ...

Surtout aCL

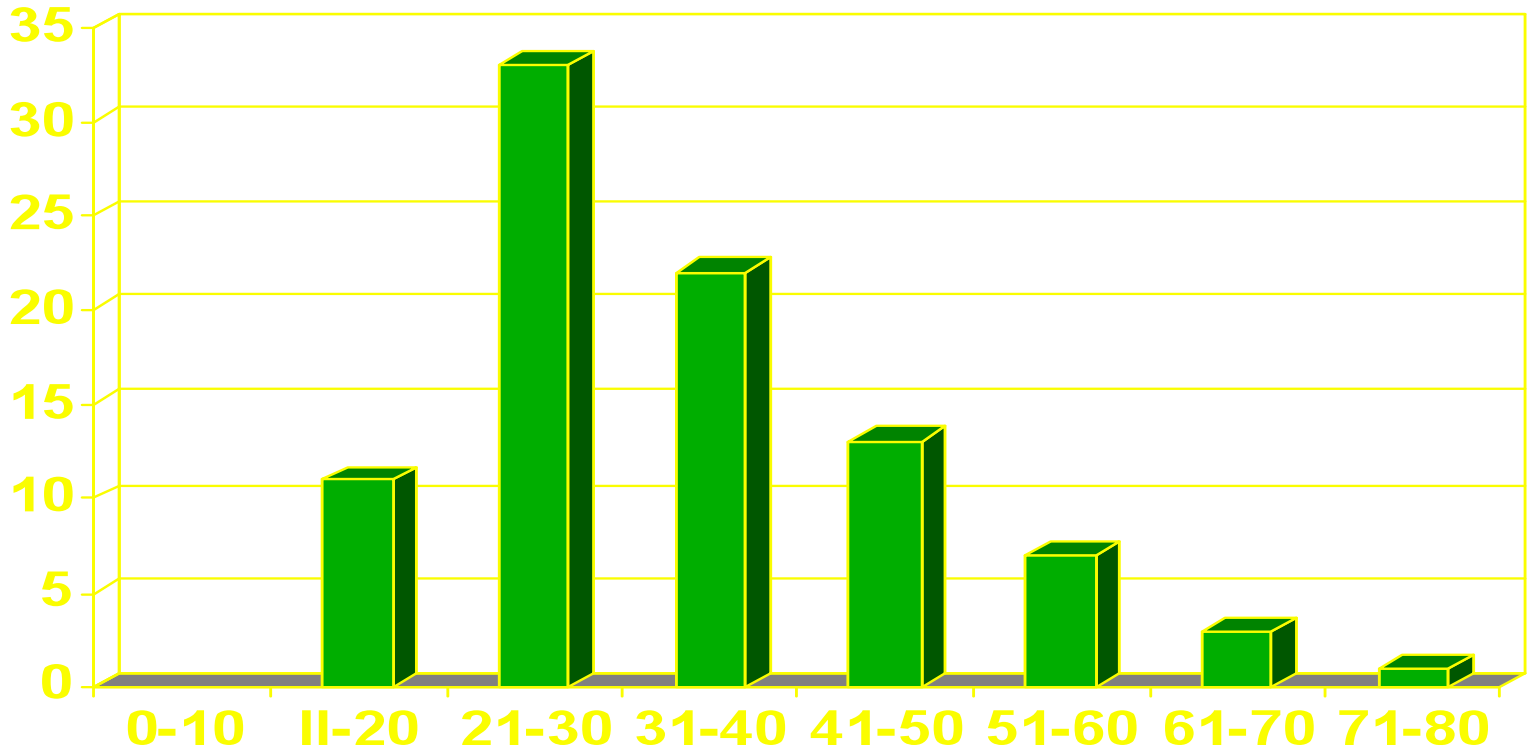
Rareté des: - Thromboses (sauf néoplasie)

- LA, anti b2GP I

Drugs associated with aPL

- Phenytoin
- Quinidine, Quinine
- Éthosuximide
- Chlorothiazide
- Hydralazine
- Procainamide
- Phenothiazines
- α interferon
- β blockers
- Anti-TNF α
- Oestrogen-containing pill ?
- Fansidar® ?
- Cocaine

EURO-PHOSPHOLIPID PROJECT
Age at onset (1,000 pts)



Sex ratio F / M = 5 (7 for SLE, 3.5 for PAPS)

SAPL ET THROMBOSES

- **TOUS SIEGES**
  - veines: souvent territoires atypiques
  - artères: cerveau ++
  - micro-circulation

- **RISQUE SPONTANE ++ DE RECIDIVES**
  - veines → veines
  - artères → artères

52-69% de récidive à 5-6 ans

MANIFESTATIONS « NON » THROMBOTIQUES…

SYNDROME DES ANTIPHOSPHOLIPIDES

THROMBOSES VEINEUSES

THROMBOSES PROFONDES

- membres inferieurs
- membres superieurs
- gros troncs
  - veine cave inferieure
  - veines renales
  - veine porte
  - veines sus-hepatiques
  - veines pulmonaires
  - veine jugulaire
  - sinus veineux cerebraux
- veines surrenaliennes
- veines retiniennes

THROMBOSES SUPERFICIELLES

EMBOLIES PULMONAIRES

Facteurs favorisants associés

THROMBOSES ARTERIELLES

- carotide et ses branches
- systeme vertebro-basilaire

- arteres coronaires
- artere hepatique
- arteres mesenteriques
- arteres renales
- artere splenique
- arteres retiniennes

- arteres des membres
- syndrome de l'arc aortique

- *infarctus placentaires*

THROMBOSES CAPILLAIRES

THROMBOSES INTRACARDIAQUES

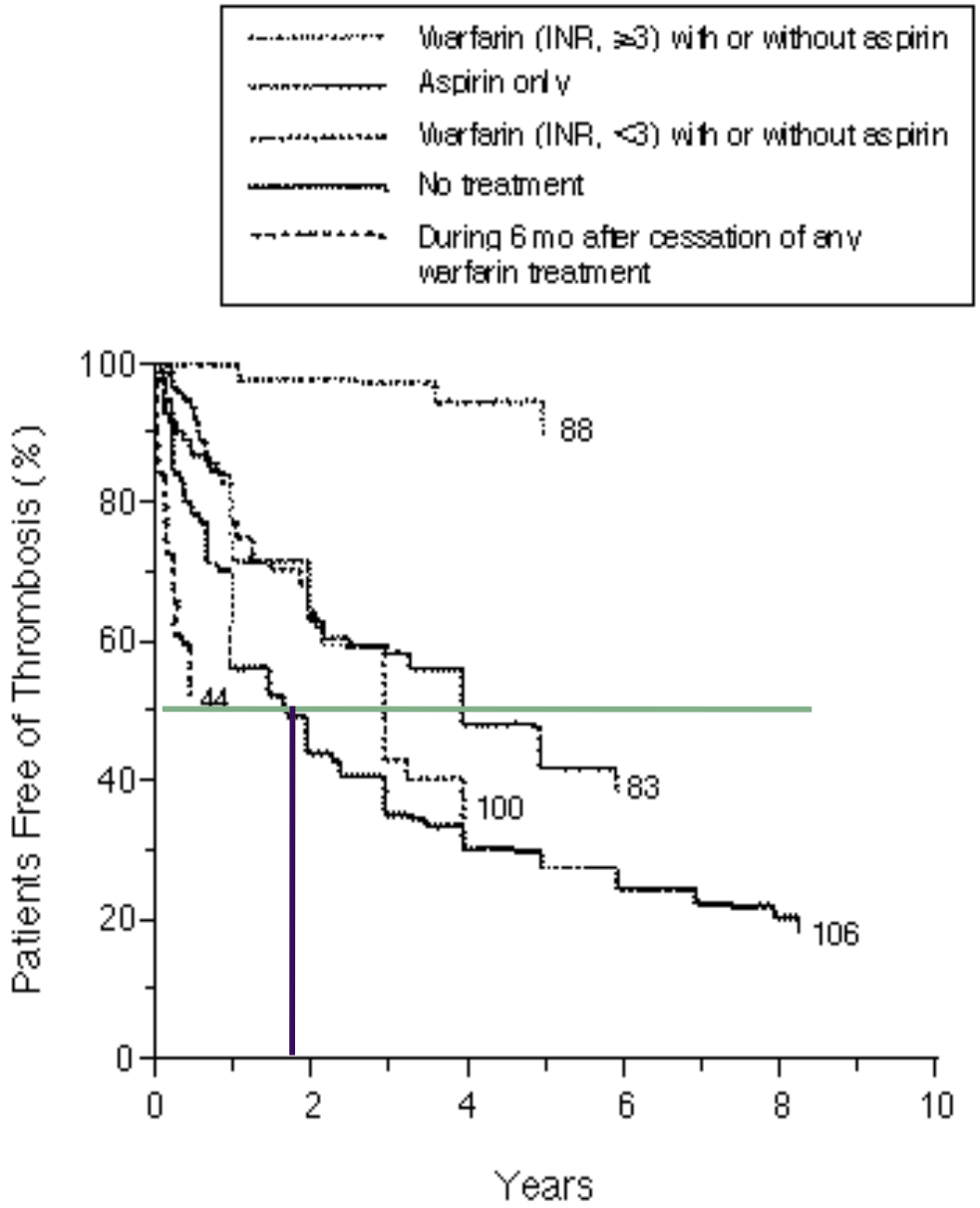
Sous-types cliniques selon le type de vaisseaux thrombosés

OBSTETRICAL

VEINEUX
- TVP (sites inhabituels)
- EP

ARTERIEL - ARTERIOLAIRE
- AVC, AIT, comitialité
- valvulopathie
- livedo
- HTA
- thromboses intra-rénales
- Bone avascular necrosis ?

Sd CATASTROPHIQUE des APL



The Management of Thrombosis
in the Antiphospholipid-Syndrome.
Khamashta MA et al
N Engl J Med 1995, 332:993

Kaplan–Meier Analysis of the Interval from Each Episode of Thrombosis or Change in Treatment to the Next Episode of Thrombosis or Censoring Event in the Same Patient, Throughout the Follow-up Period, According to Antithrombotic Treatment.

SAPL: PREVENTION SECONDAIRE DES THROMBOSES

Contraception adaptée
Pas de tabac

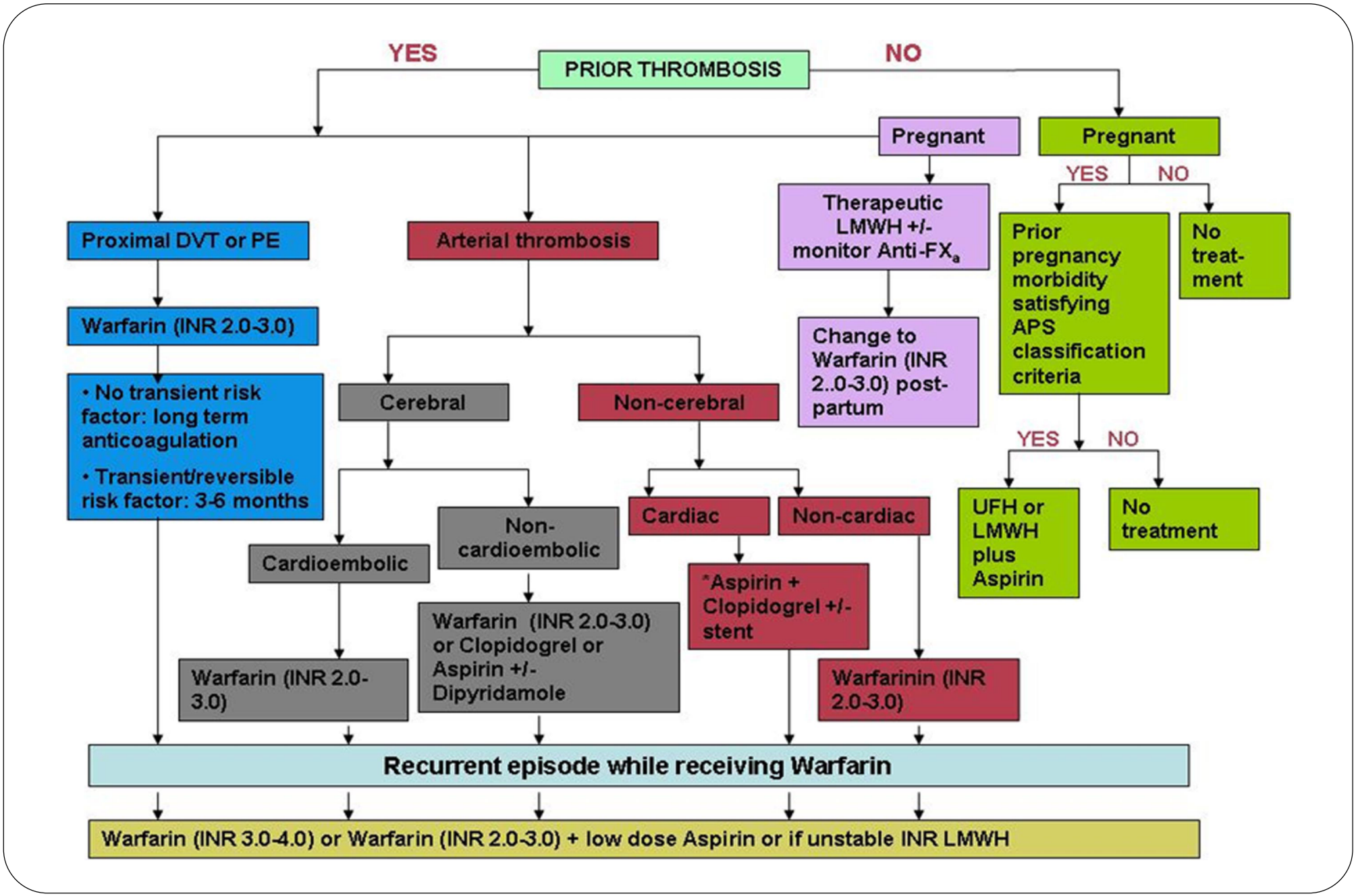
SAPL VEINEUX

INR 2,5
durée: à vie ?

SAPL ARTERIEL NON CARDIOEMBOLIQUE

INR 3 à 3,5
durée: à vie ?
discuté +++: AAP?, 2AAP?, AVK INR 2-3 + AAP?
redux: + aspirine

Fréquences des TIH?


YES
PRIOR THROMBOSIS
NO
Pregnant
Pregnant
YES
NO
Proximal DVT or PE
Arterial thrombosis
Therapeutic LMWH +/- monitor Anti-FXa
Prior pregnancy morbidity satisfying APS classification criteria
No treat-ment
Warfarin (INR 2.0-3.0)
Change to Warfarin (INR 2..0-3.0) post-partum
• No transient risk factor: long term anticoagulation
• Transient/reversible risk factor: 3-6 months
Cerebral
Non-cerebral
YES
NO
Cardiac
Non-cardiac
UFH or LMWH plus Aspirin
No treatment
Cardioembolic
Non-cardioembolic
*Aspirin + Clopidogrel +/- stent
Warfarin (INR 2.0-3.0) or Clopidogrel or Aspirin +/- Dipyridamole
Warfarin (INR 2.0-3.0)
Warfarinin (INR 2.0-3.0)
Recurrent episode while receiving Warfarin
Warfarin (INR 3.0-4.0) or Warfarin (INR 2.0-3.0) + low dose Aspirin or if unstable INR LMWH

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Ronald ASHERSON

J Rheumatol 1992, 19: 508-512

« Asherson's Syndrome »

SAPL « CATASTROPHIQUE »

C’est une MICROANGIOPATHIE

micro >> macrovasculaires

thromboses simultanées

DÉFAILLANCE MULTIVISCERALE

rein, cœur, poumon, cerveau… surrénale

30-50% MORTALITE

SAPL connu ou INCONNU avant l’épisode catastrophique

CATASTROPHIC APS

- 1992 : < 10 cases
- 1998 : 50
- 2001 : 130
- 2008 : > 300 cases

Less than 1% of APS cases

Table 1. Demographic, clinical, and laboratory features of 250 patients with CAPS*

Demographics	
Sex, no. female/no. male	177/73
Age at the time of CAPS, mean ± SD years	37 ± 14
Diagnosis, no. (%) of patients	
Primary APS	116 (46.4)
SLE	100 (40)
SLE-like	12 (4.8)
Other	22 (8.8)
No. (%) with precipitating factors†	143 (58)
No. (%) with CAPS as the first manifestation of APS	116 (46.4)

Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients.

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Présentation clinique

- Manifestations thrombotiques
- Manifestations de mécanisme incertain

Chacune de ces manifestations peuvent se rencontrer dans le SAPL non catastrophique

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Autopsy

Histopathologic features (n = 58)	
Microthrombosis	49 (84.5)
Kidney	32 (65.3)
Heart	27 (55.1)
Lung	24 (48.9)
Brain	24 (48.9)
Spleen	12 (24.5)
Skin	11 (22.4)
Gut	10 (20.4)
Liver	10 (20.4)
Adrenal gland	8 (16.3)
Infarction	31 (53.4)
Brain	19 (61.3)
Heart	9 (29)
Spleen	6 (19.4)
Kidney	5 (16.1)
Lung	5 (16.1)
Adrenal gland	3 (9.7)
Thrombosis of large vessels	11 (18.9)
Pulmonary embolism	7 (12.1)
Nonbacterial thrombotic endocarditis	16 (27.6)
Acute respiratory distress syndrome	4 (6.8)
Alveolar hemorrhage	3 (5.2)
Budd-Chlari syndrome	1 (1.7)
Adrenal hemorrhage	1 (1.7)

Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
Peripheral veins (thrombosis)	59 (23.1)
Spleen	48 (18.8)
Adrenal gland	33 (12.9)
Peripheral arteries (thrombosis)	27 (10.6)
Pancreas	19 (7.5)
Retina	17 (6.7)
Peripheral nerve	12 (4.7)
Bone marrow	10 (3.9)

→ Défaillance d'organe
+ atteinte systémique (nécrose tissulaire)

Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients.

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APS and the KIDNEY

RENAL VEIN THROMBOSIS
RENAL INFARCTION
RENAL ARTERY "STENOSIS"

"APS NEPHROPATHY"

TMA, FIH, organized thrombi, fibrous arterial occlusion, FCA

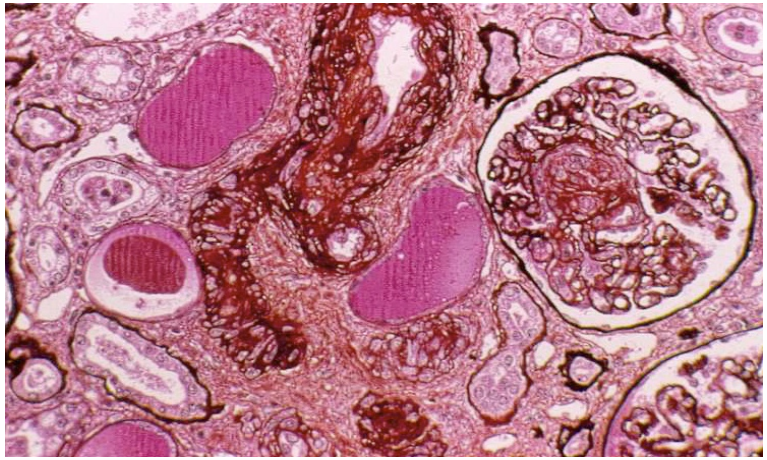
→

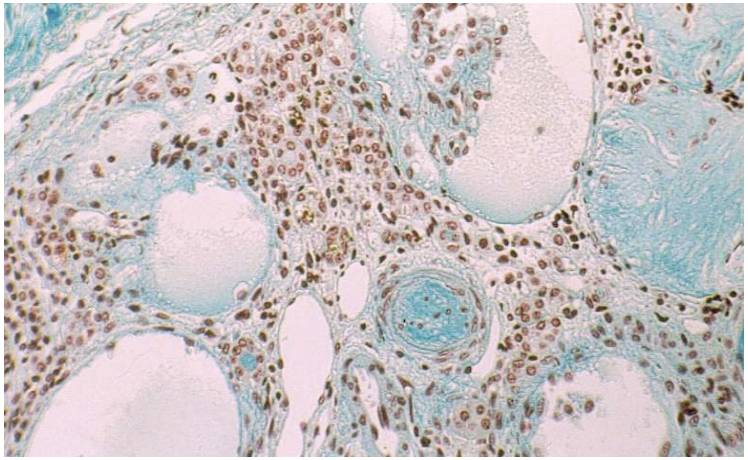
HYPERTENSION
Moderate to Malignant
PROTEINURIA
LOSS OF RENAL FUNCTION

→ Transjugular kidney biopsy
→ May miss cortical kidney lesions

APS nephropathy

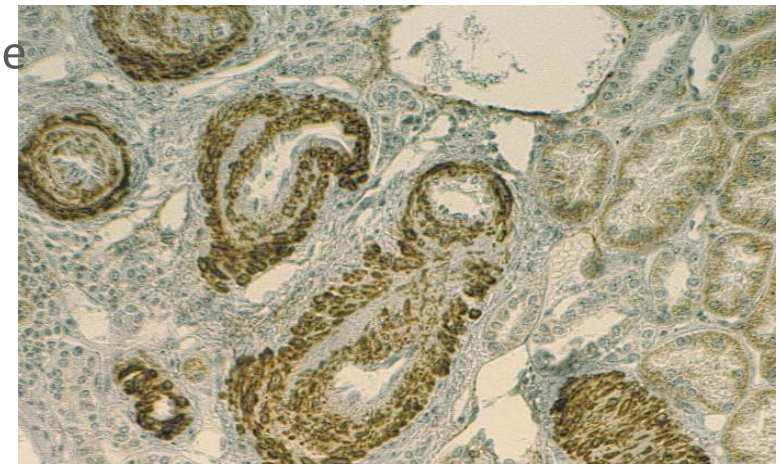
MAT

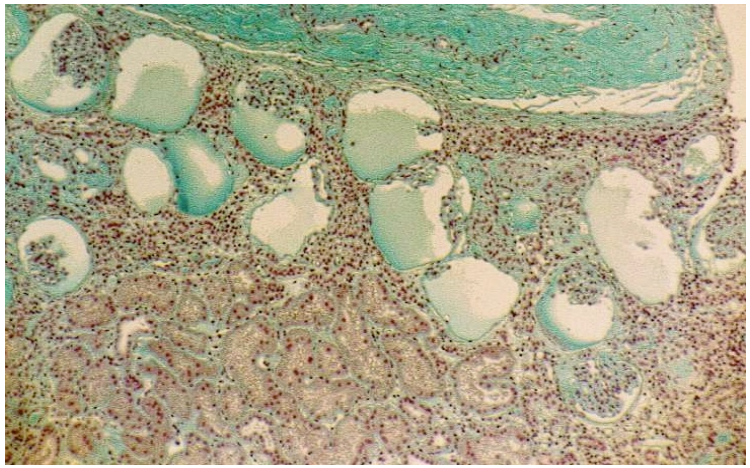




Occlusion Fibreuse

Hyperplasie Fibreuse Intimale





Atrophie corticale focale

Manifestations pulmonaires

Pulmonary involvement in CAPS (68%)?

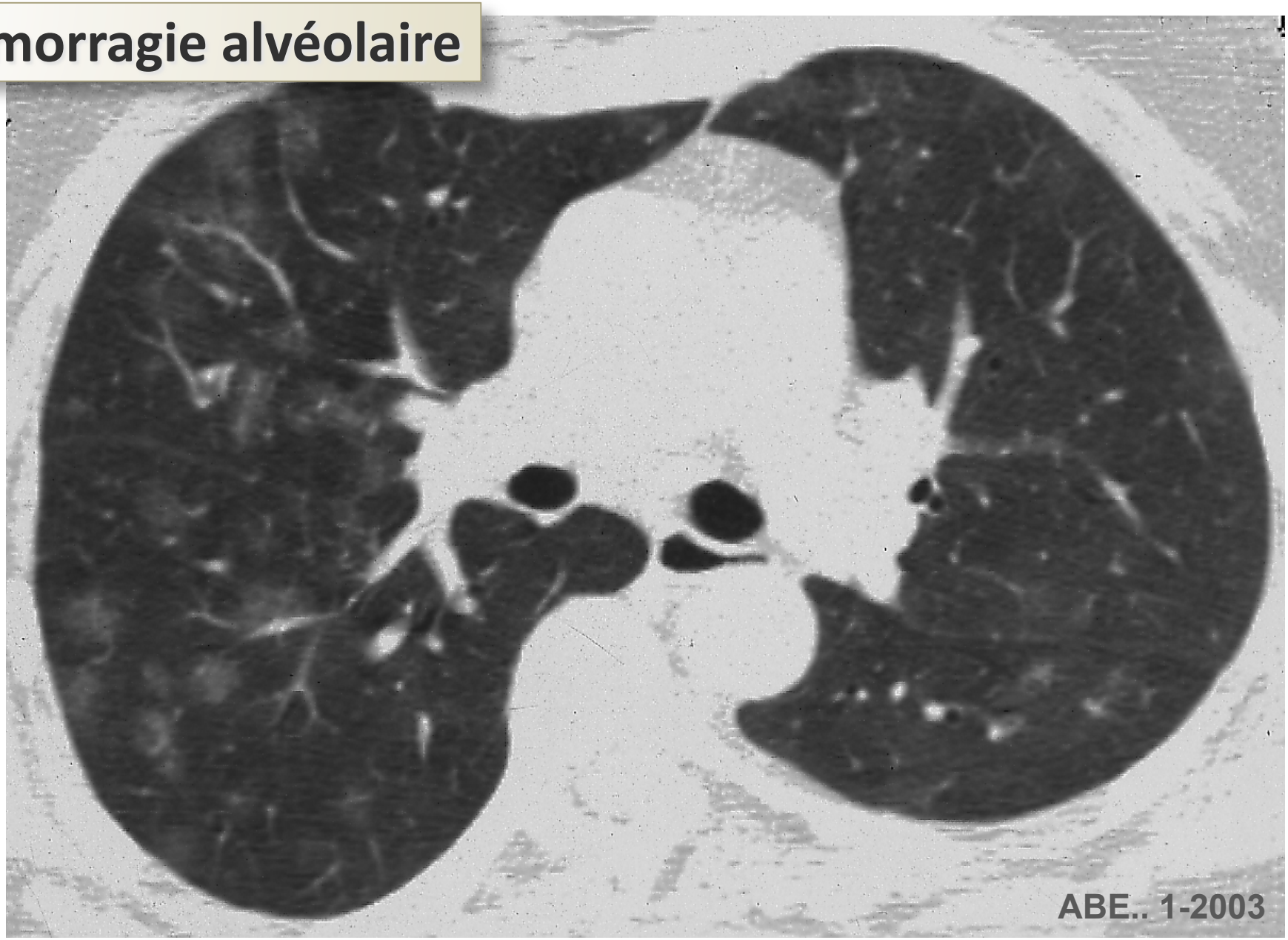
ARDS

→ 150 / 220 patients with pulmonary involement
→ 47 patients (21%) were diagnosed as having ARDS.
→ 19 (40%) died.
→ Pathological studies (n= 10):
- thrombotic microangiopathy : n = 7.
- hyaline membrane formation + IA haemorrhage: n = 2

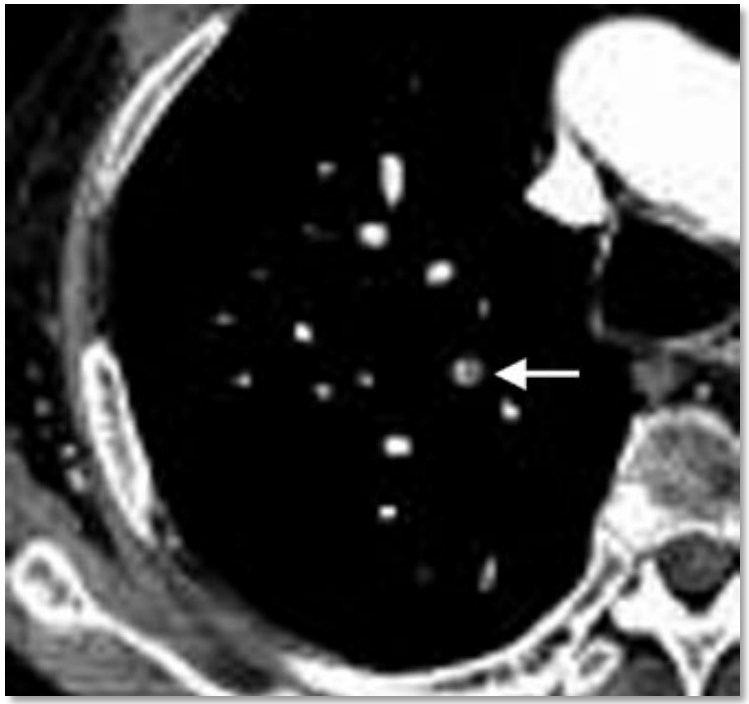
There were no differences in age, sex, precipitating factors, clinical manifestations, or mortality between catastrophic APS patients with and without ARDS.

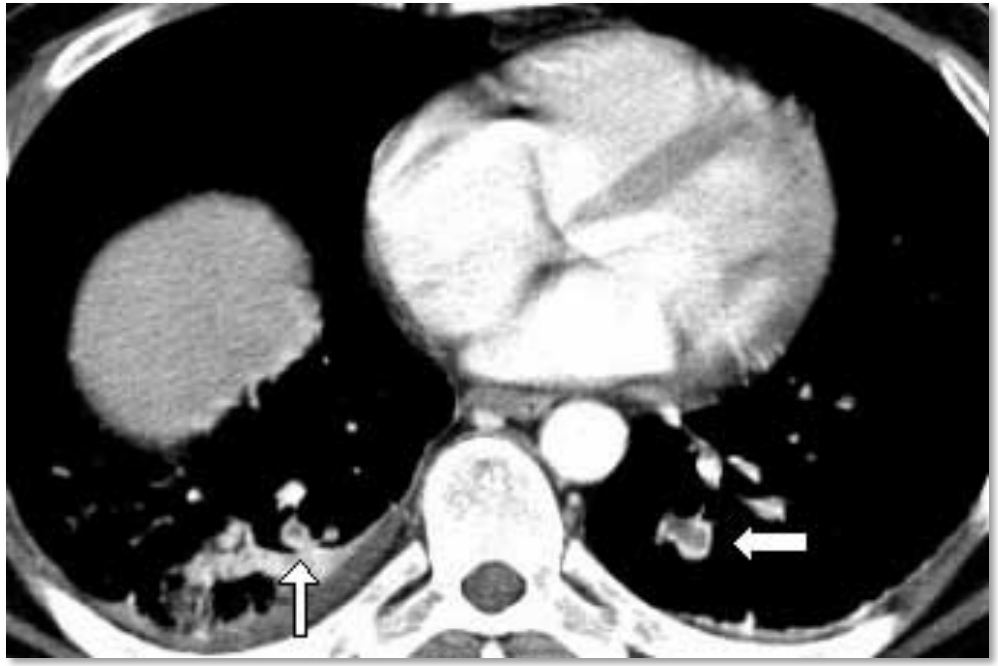
Bucciarelli S et al. ARD 2006;65:413

Hémorragie alvéolaire



Embolie pulmonaire



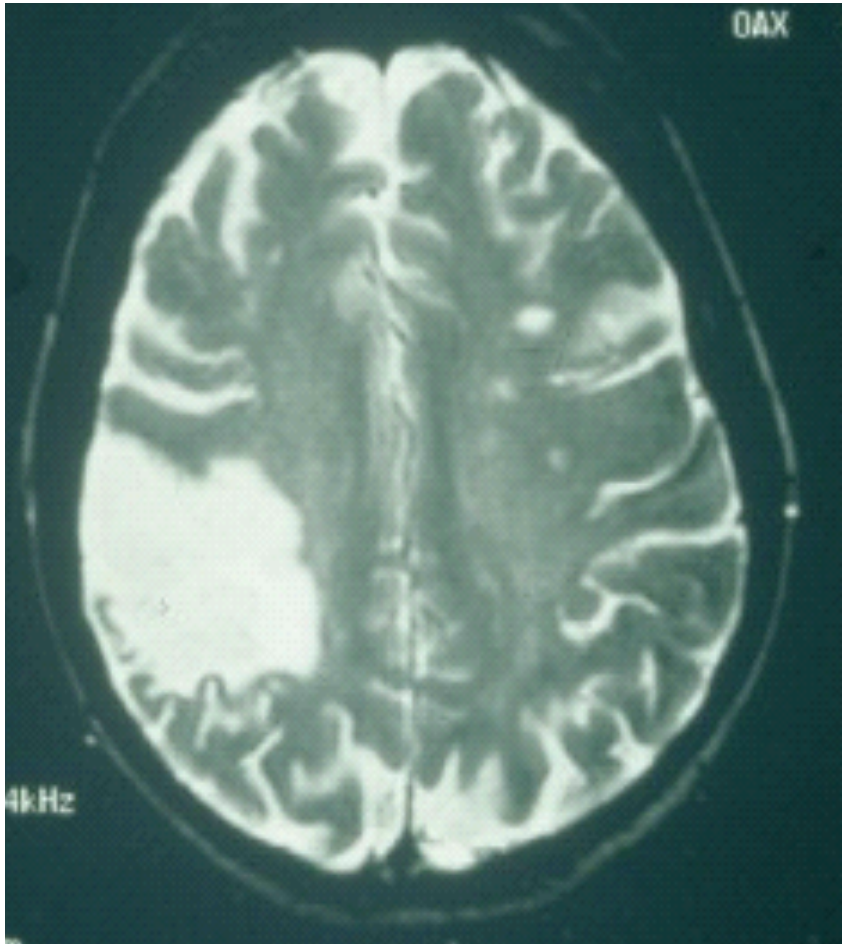


Manifestations neurologiques

Thromboses Cérébrales:
- AIT, AIC
- TV cérébrale
- Encéphalopathie

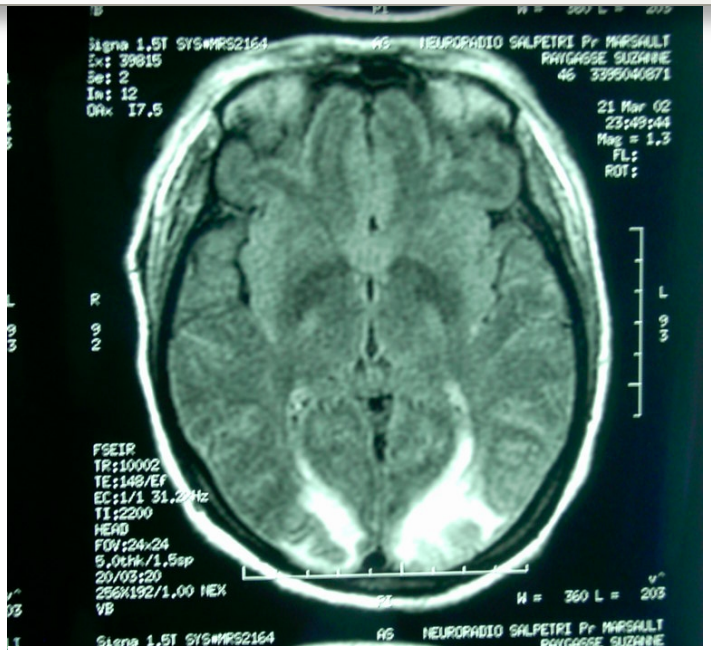
images de démyélinisation type « SEP »

Troubles fonctions cognitives
Démence…
Épilepsie, chorée,
Myélite transverse

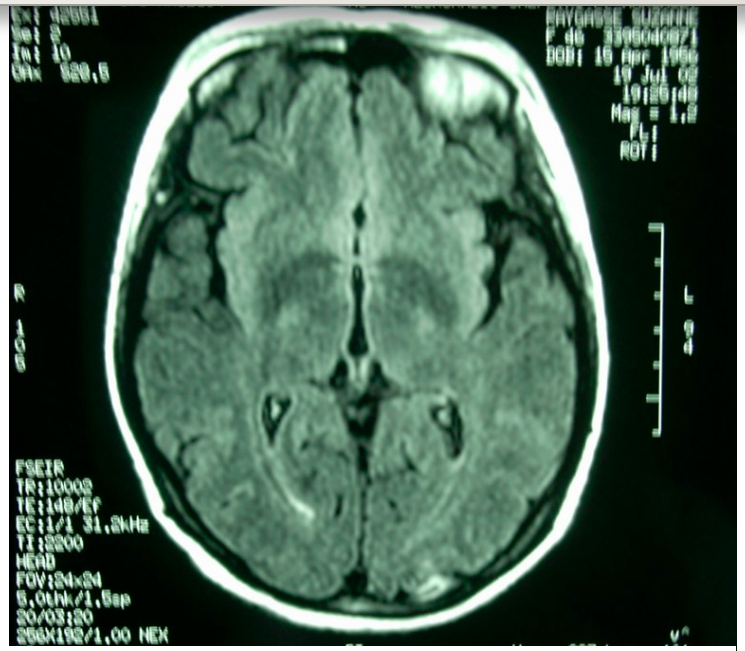


Atteinte neurologique centrale au cours du Syndrome Catastrophique des APL

Posterior Reversible Encephalopathy Syndrome
Tout n'est pas thrombotique !!!



RAYG. S.



March 2002 Renal failure, Hypertension

March 2002 **July 2002**

Cœur et SAPL

- LESIONS VALVULAIRES
  - Mitrale > Aortique > Tricuspide
  - Epaississement diffus >> localisé (végétation)
  - Régurgitation >> Sténose ou mixte
  - Risques: embolie (cérébrale ++) > dysfonction > Osler

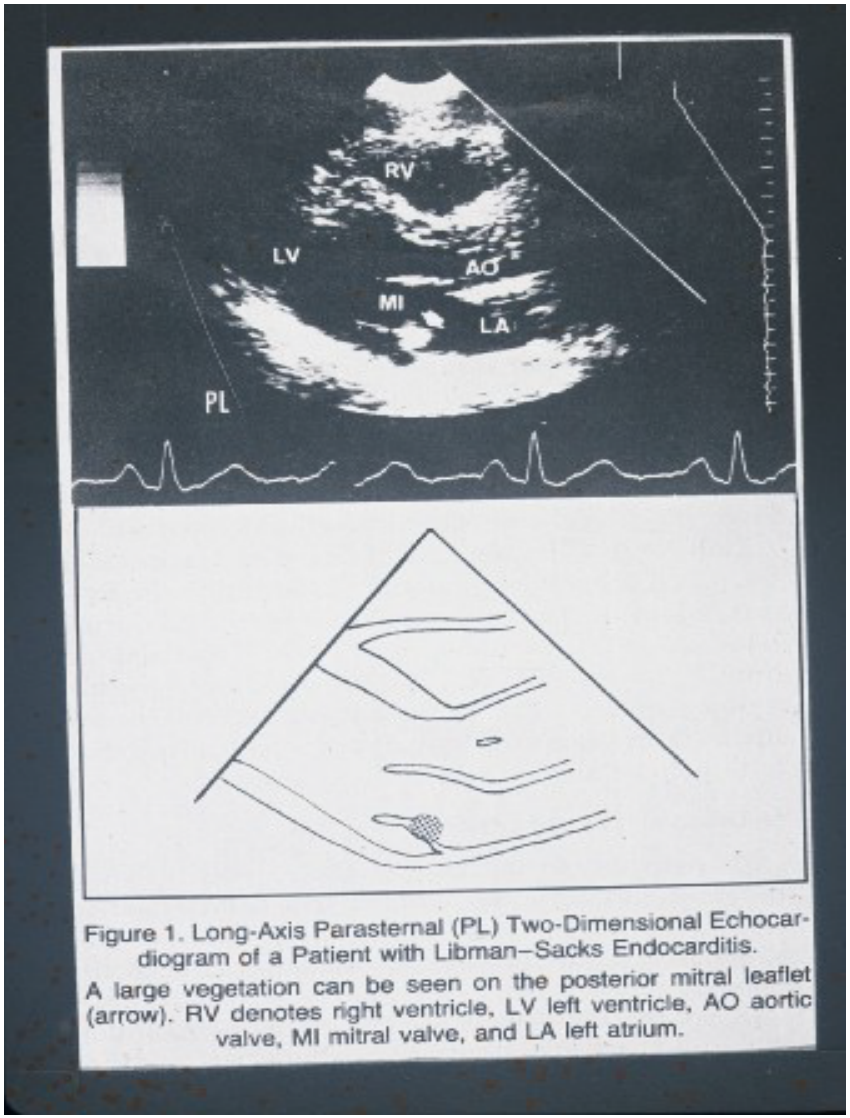


Figure 1. Long-Axis Parasternal (PL) Two-Dimensional Echocardiogram of a Patient with Libman–Sacks Endocarditis.

A large vegetation can be seen on the posterior mitral leaflet (arrow). RV denotes right ventricle, LV left ventricle, AO aortic valve, MI mitral valve, and LA left atrium.

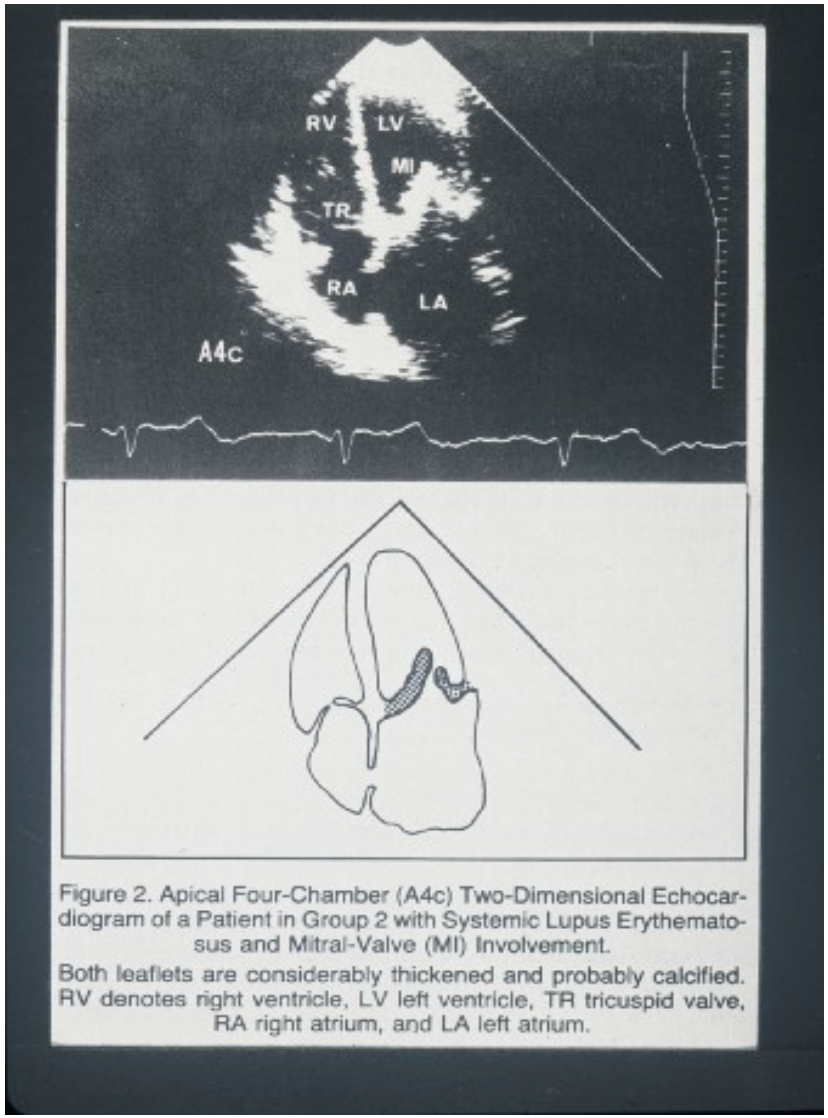
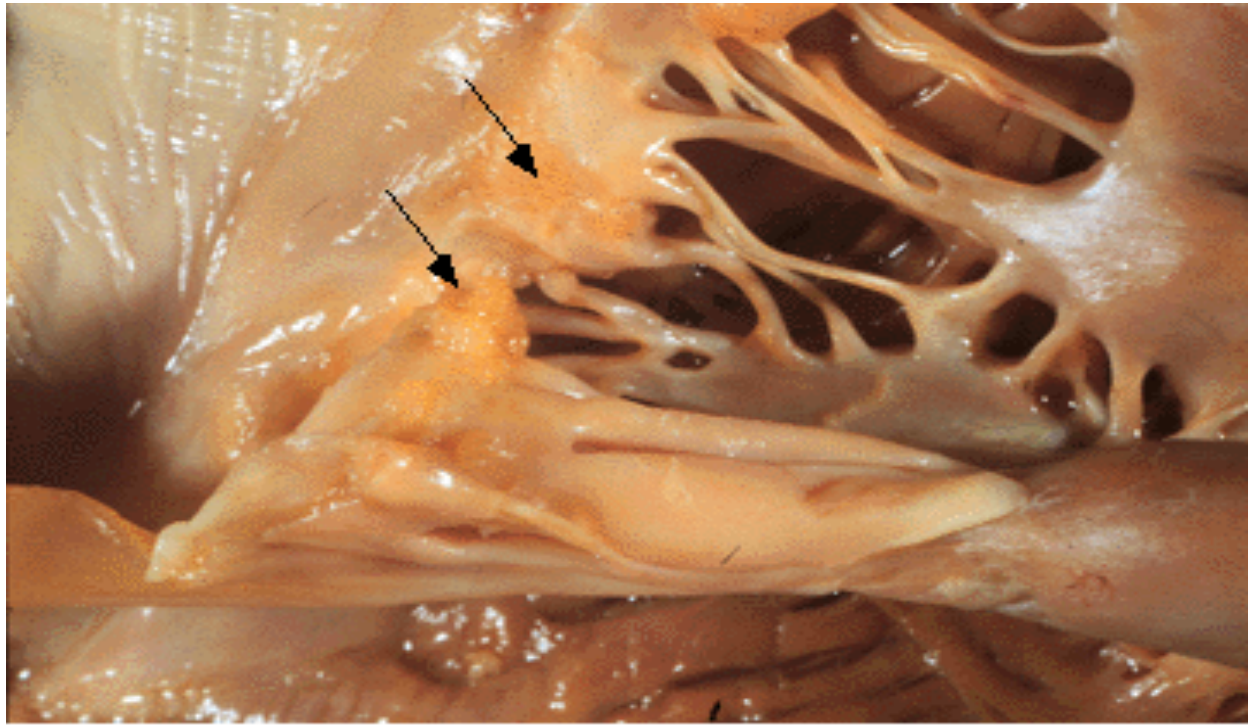


Figure 2. Apical Four-Chamber (A4c) Two-Dimensional Echocardiogram of a Patient in Group 2 with Systemic Lupus Erythematosus and Mitral-Valve (MI) Involvement.

Both leaflets are considerably thickened and probably calcified. RV denotes right ventricle, LV left ventricle, TR tricuspid valve, RA right atrium, and LA left atrium.



Libman Sacks verrucous endocarditis Verrucous endocarditis with valvular vegetations (arrows) in a 52 year-old woman with systemic lupus erythematosus who died of pneumonia and chronic interstitial pneumonitis. The vegetations had not been observed by echocardiography, although a cardiac murmur had been heard by auscultation. A cerebrovascular accident was also found at autopsy. Courtesy of Peter H Schur, MD.

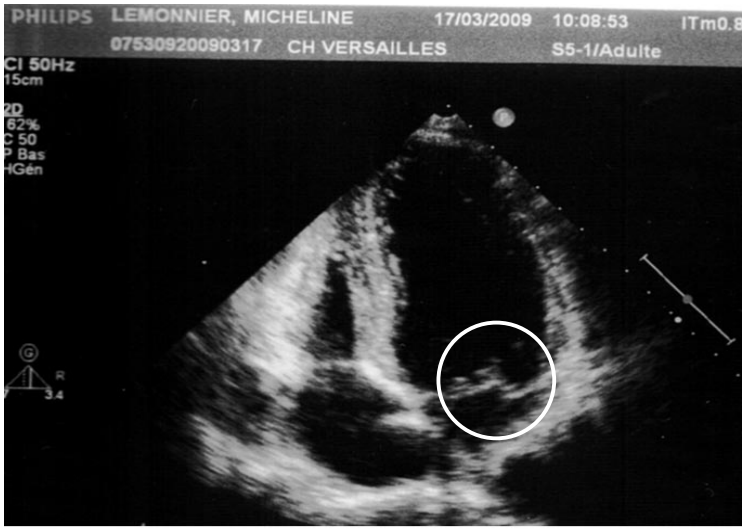
Echographie cardiaque

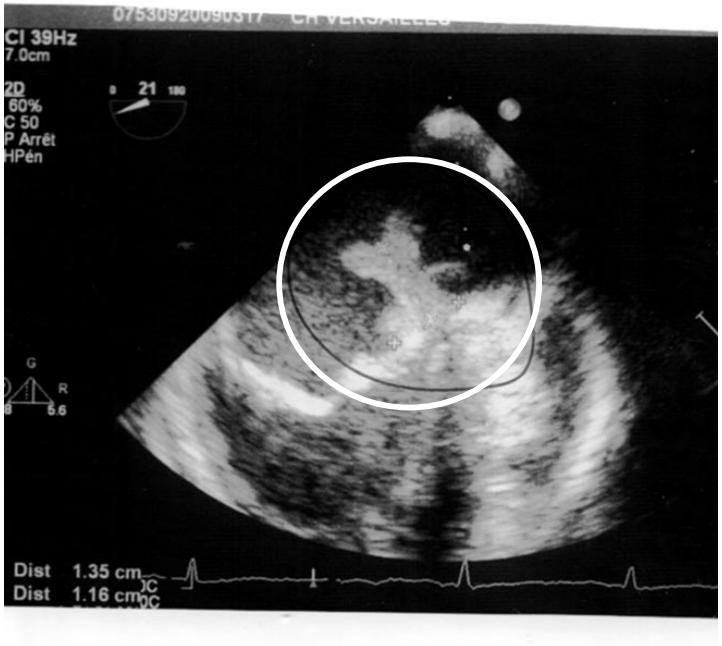
ETT:

- Insuffisance mitrale à 2/4
- ballonisation
- épaississement du feuillet postérieur

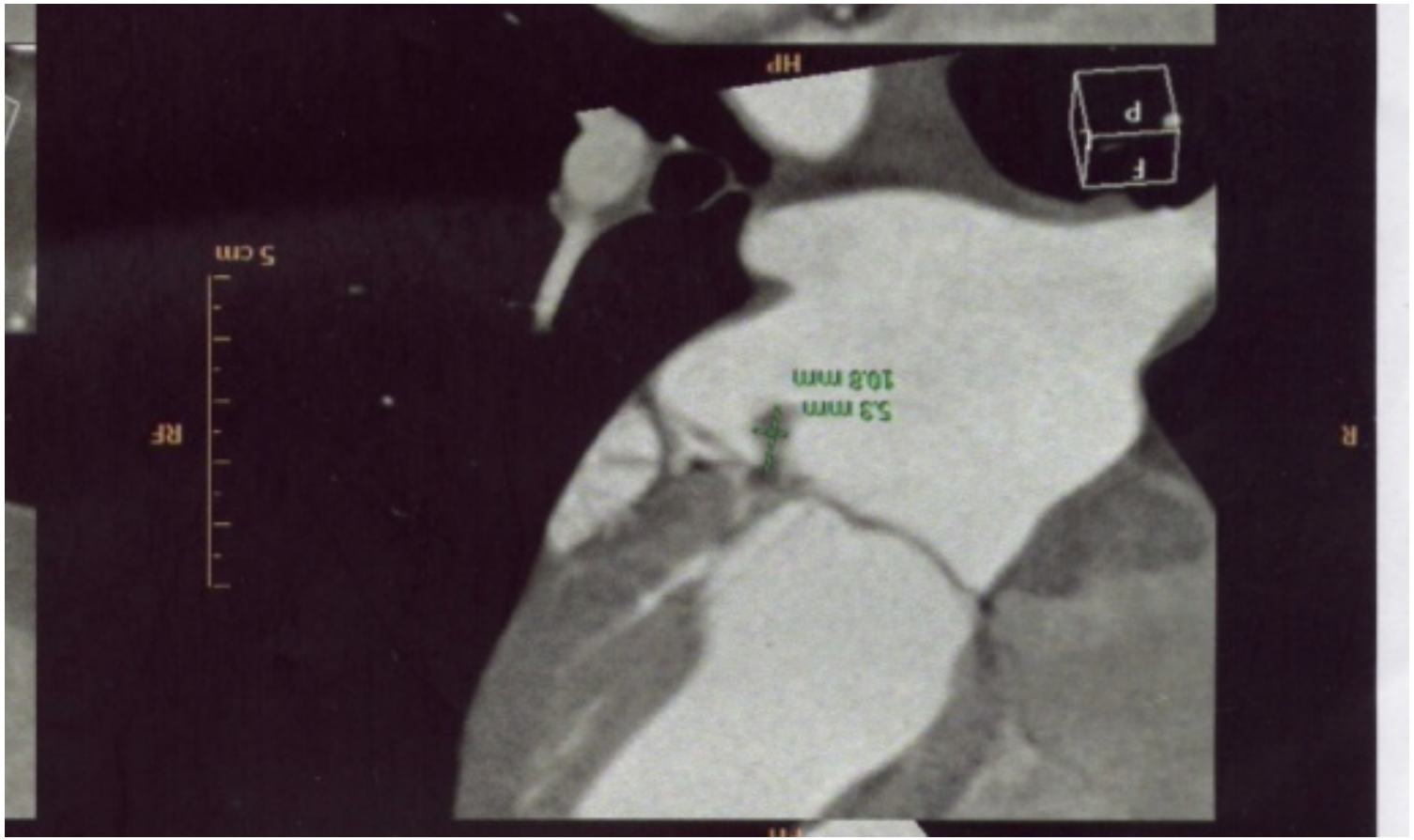
ETO:

- masse polylobée mitrale (14mm de large;20mm de long)
- très mobile





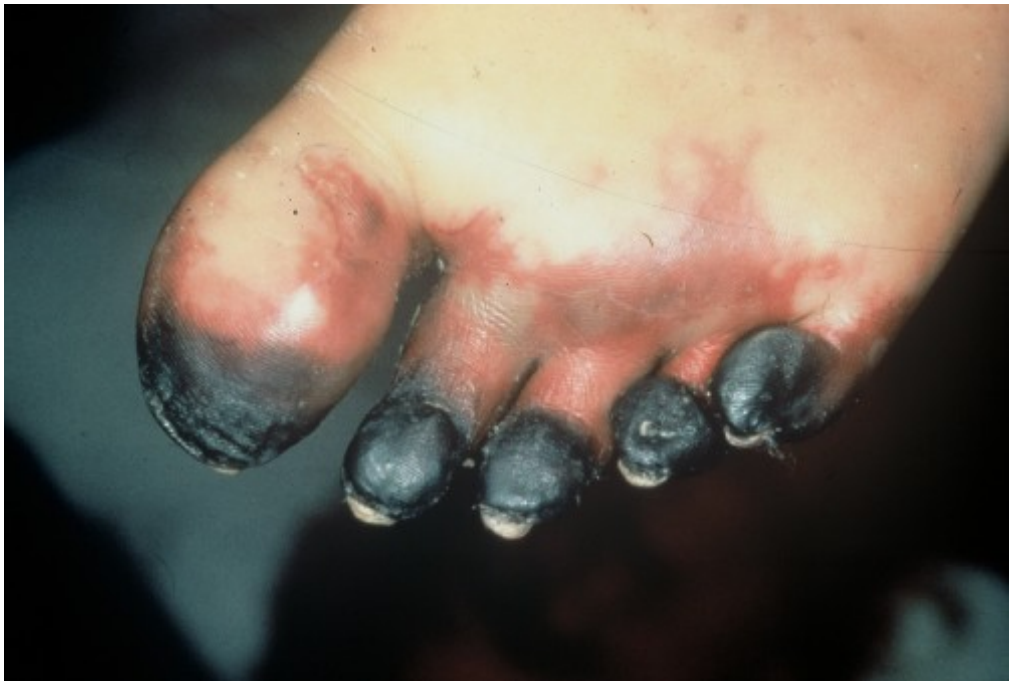
TDM cardiaque (low résolution)

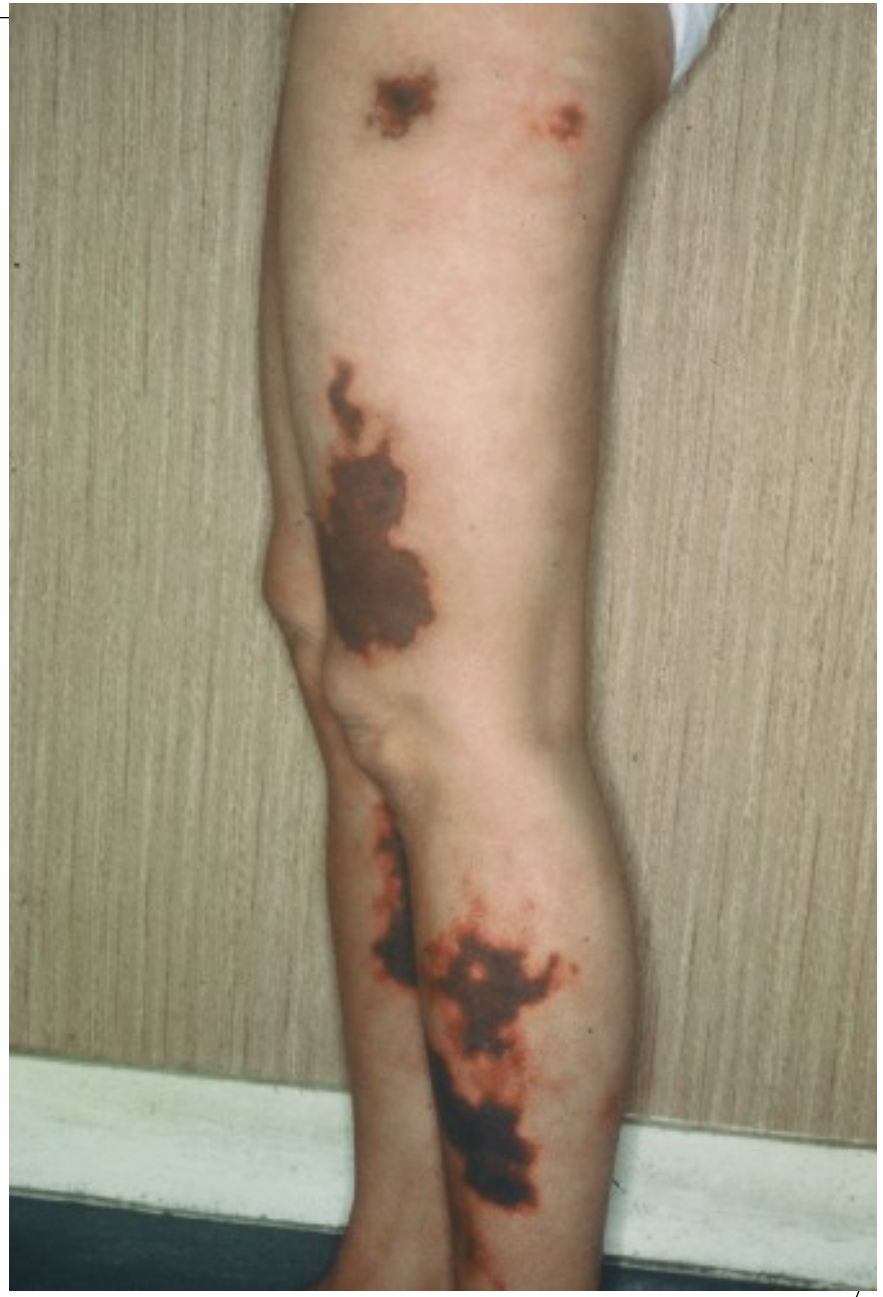


Cœur et SAPL

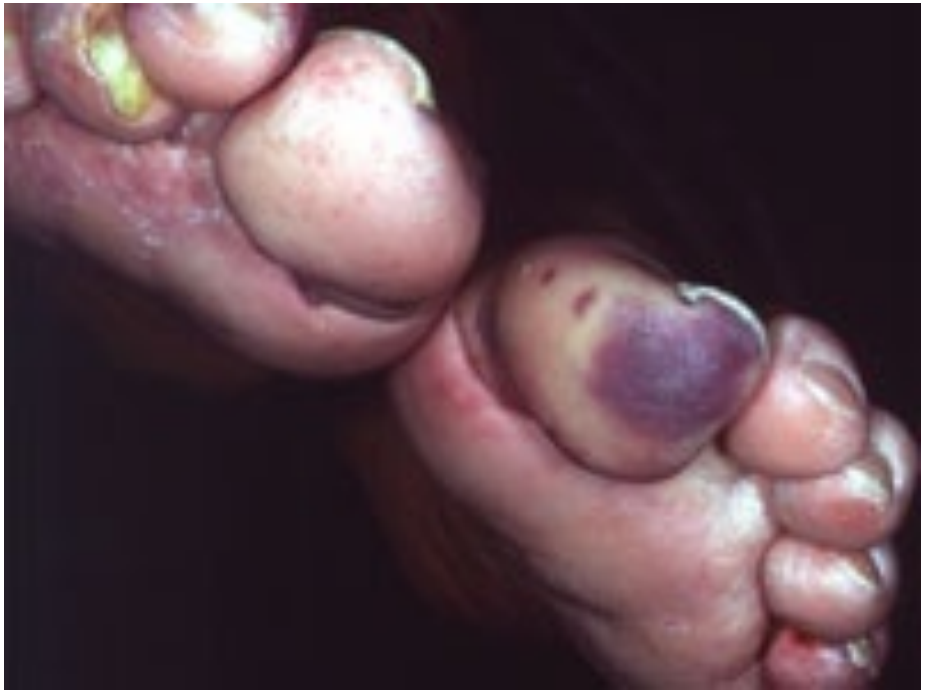
- EMBOLIE PULMONAIRE
- MYOCARDIOPATHIE (segmentaire / diffuse)
- THROMBOSE CORONAIRE (sujet jeune ++)
- MASSE INTRA-CARDIAQUE: thrombose intra-cavitaire (diag dif.)
- HTAP
- ANOMALIES DE LA FONCTION DIASTOLIQUE

Purpura nécrotique
Nécrose cutanée extensive
Nécroses distales

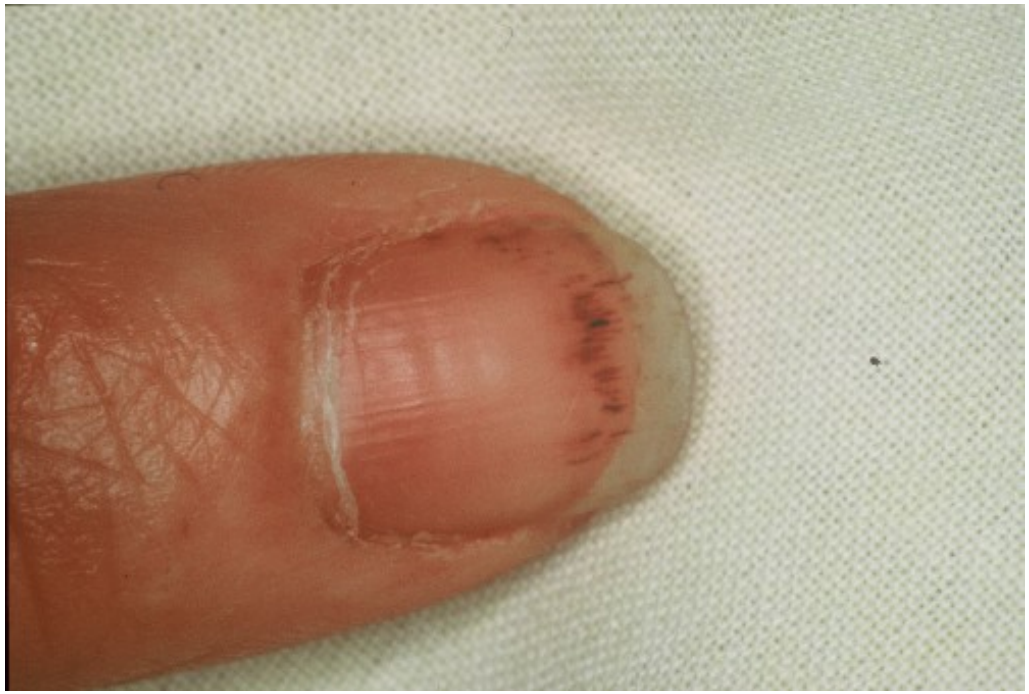


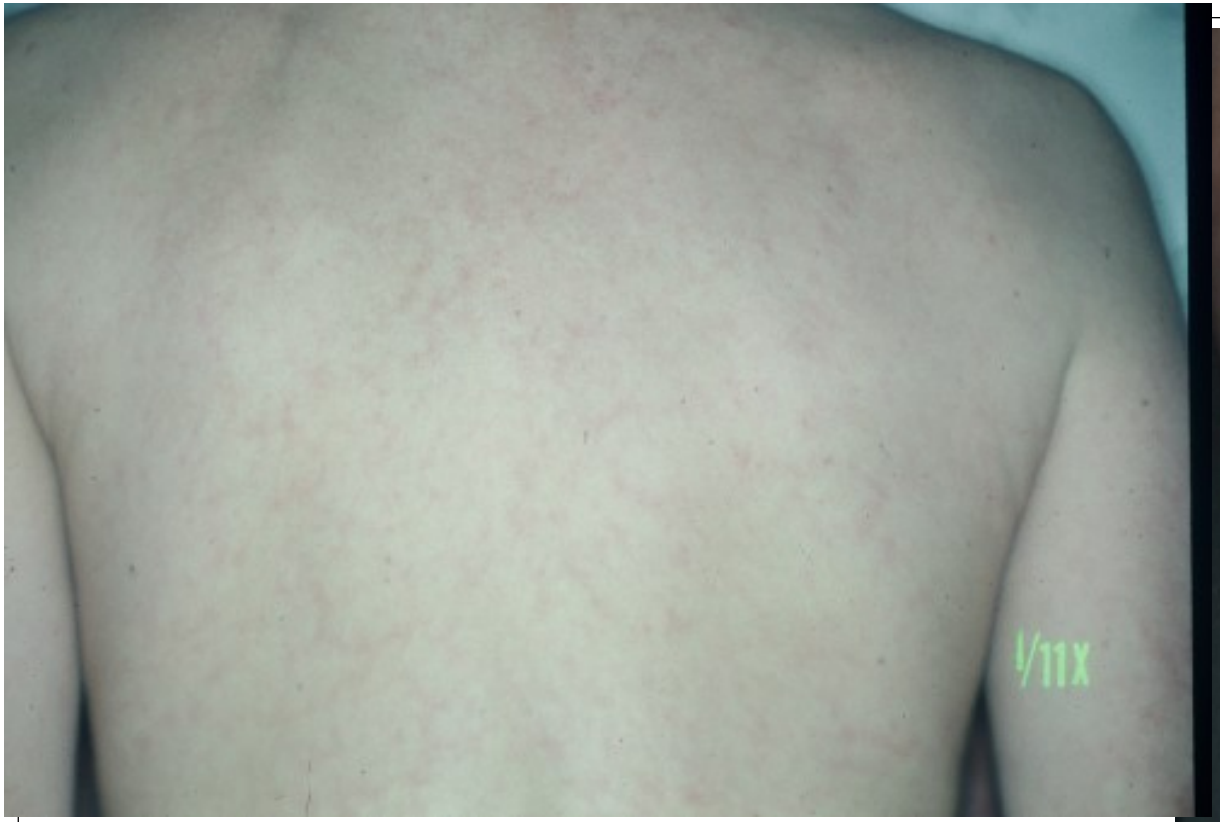


Thrombophlébite superficielle
Ulcère cutané
Gangrène, nodules



Hémorragies sous-unguéales

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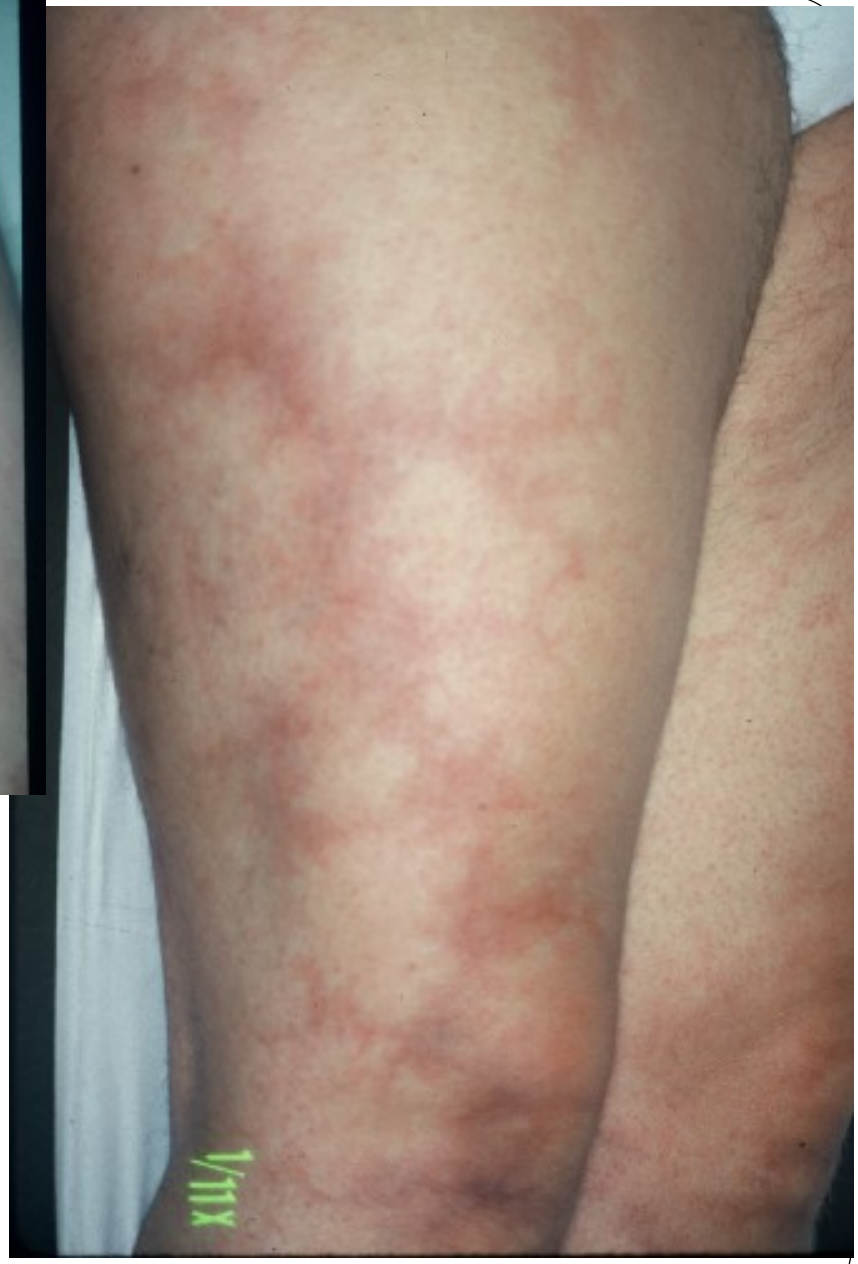
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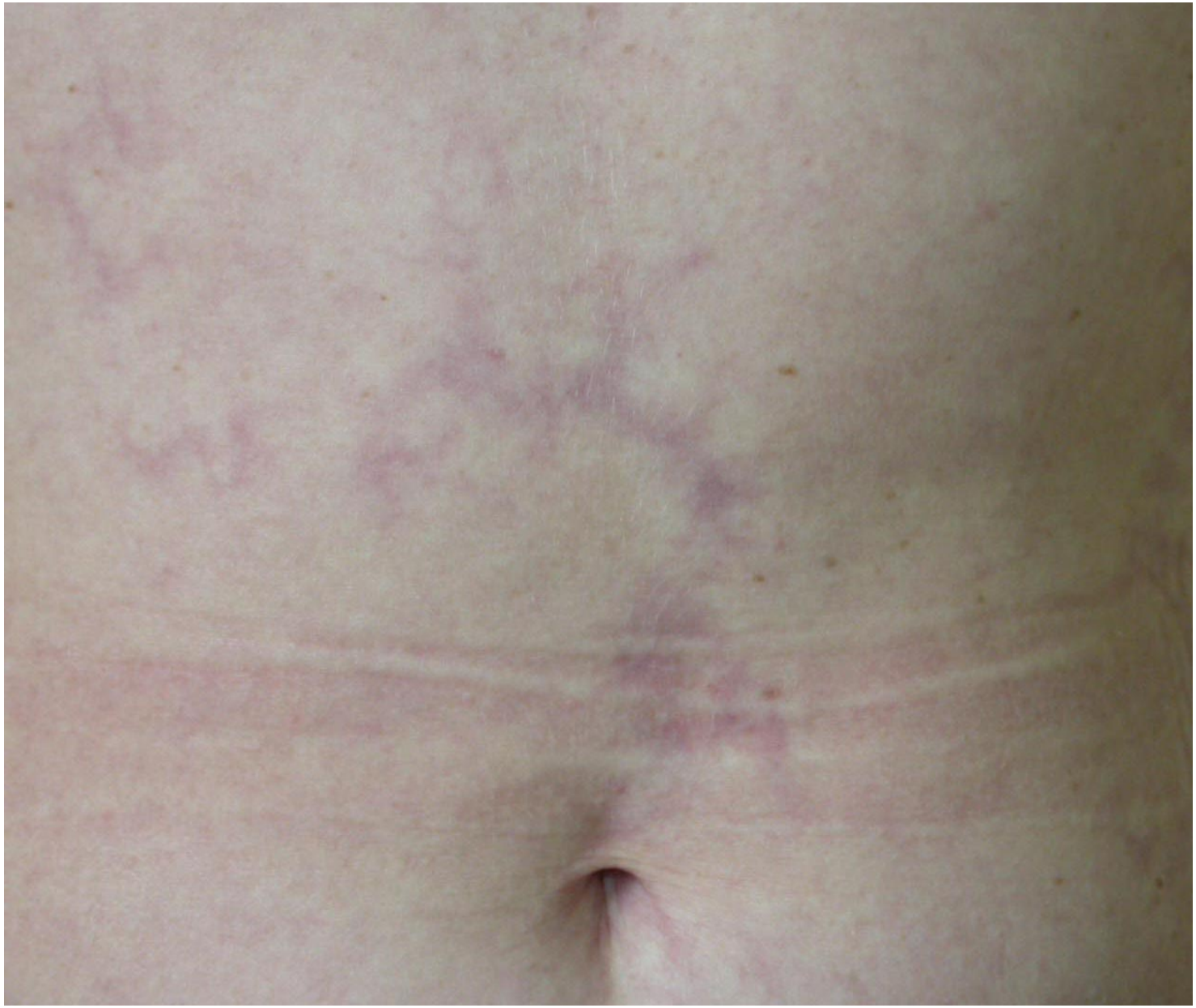
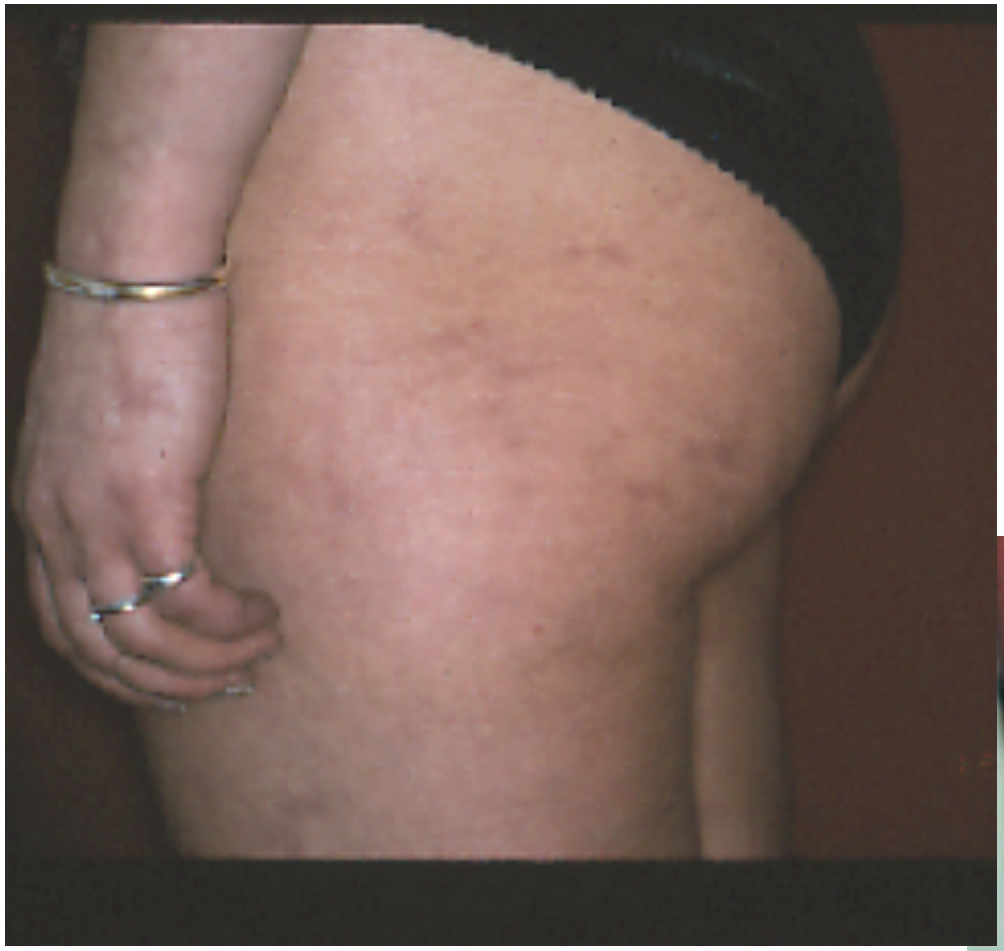
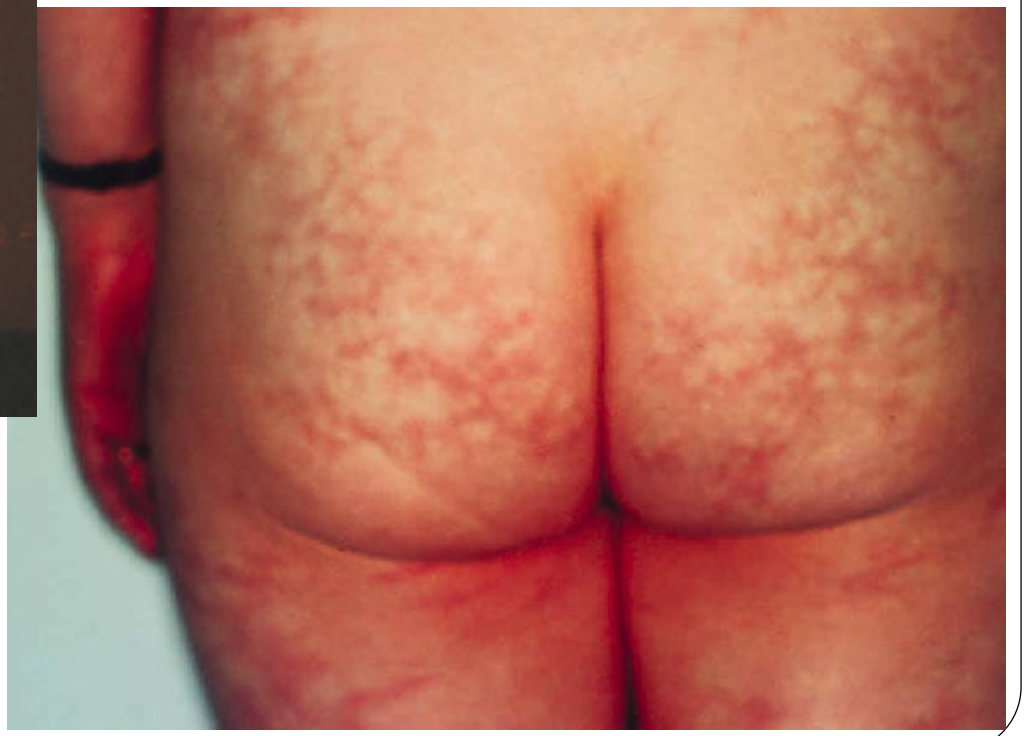
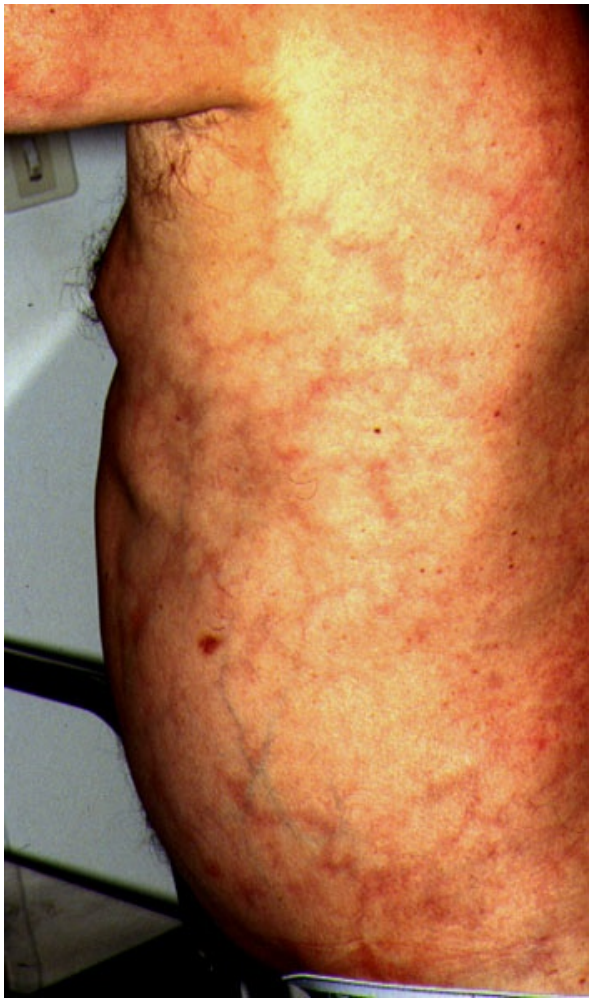
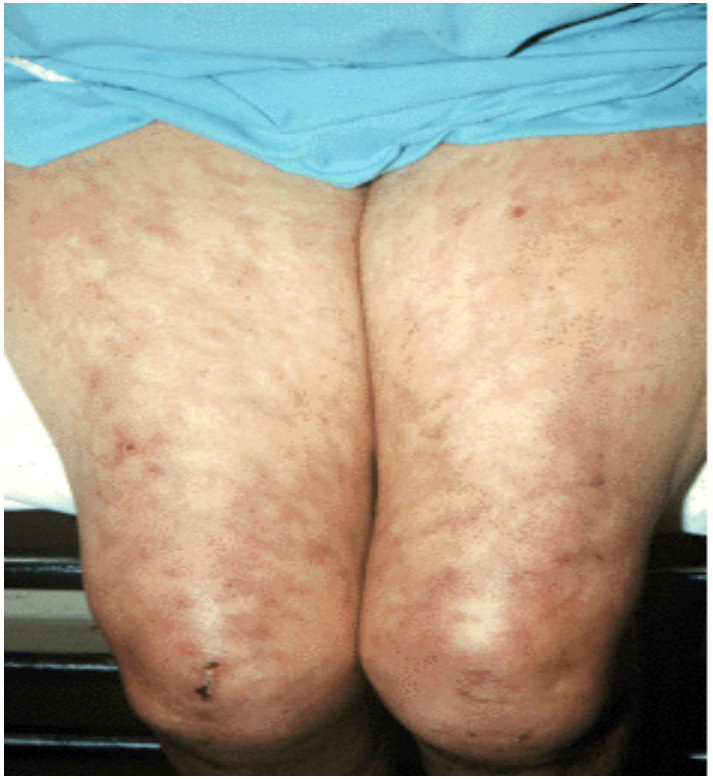




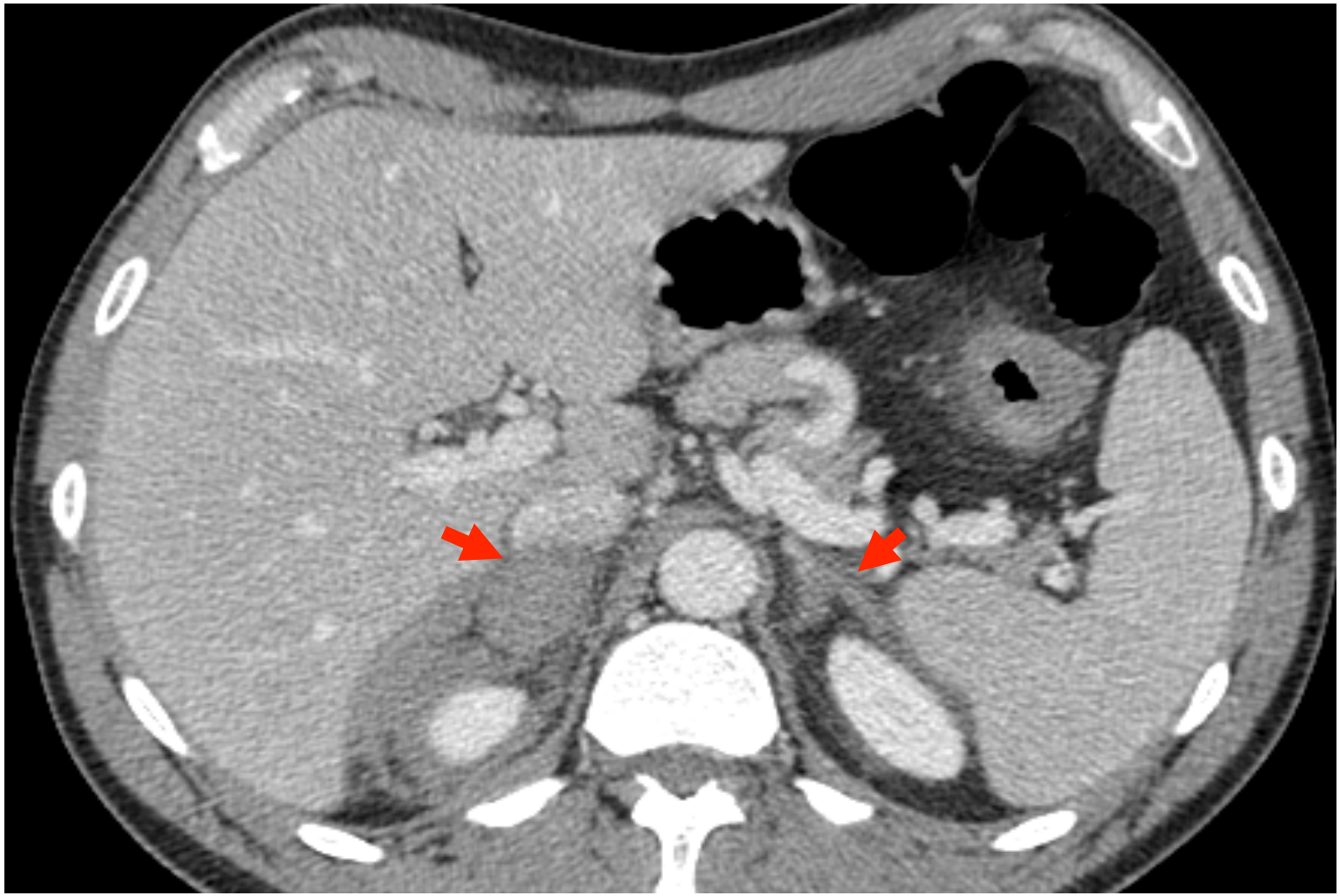


Livedo réticularis





Insuffisance Surrénalienne:
Nécrose Hémorragique des Surrénales



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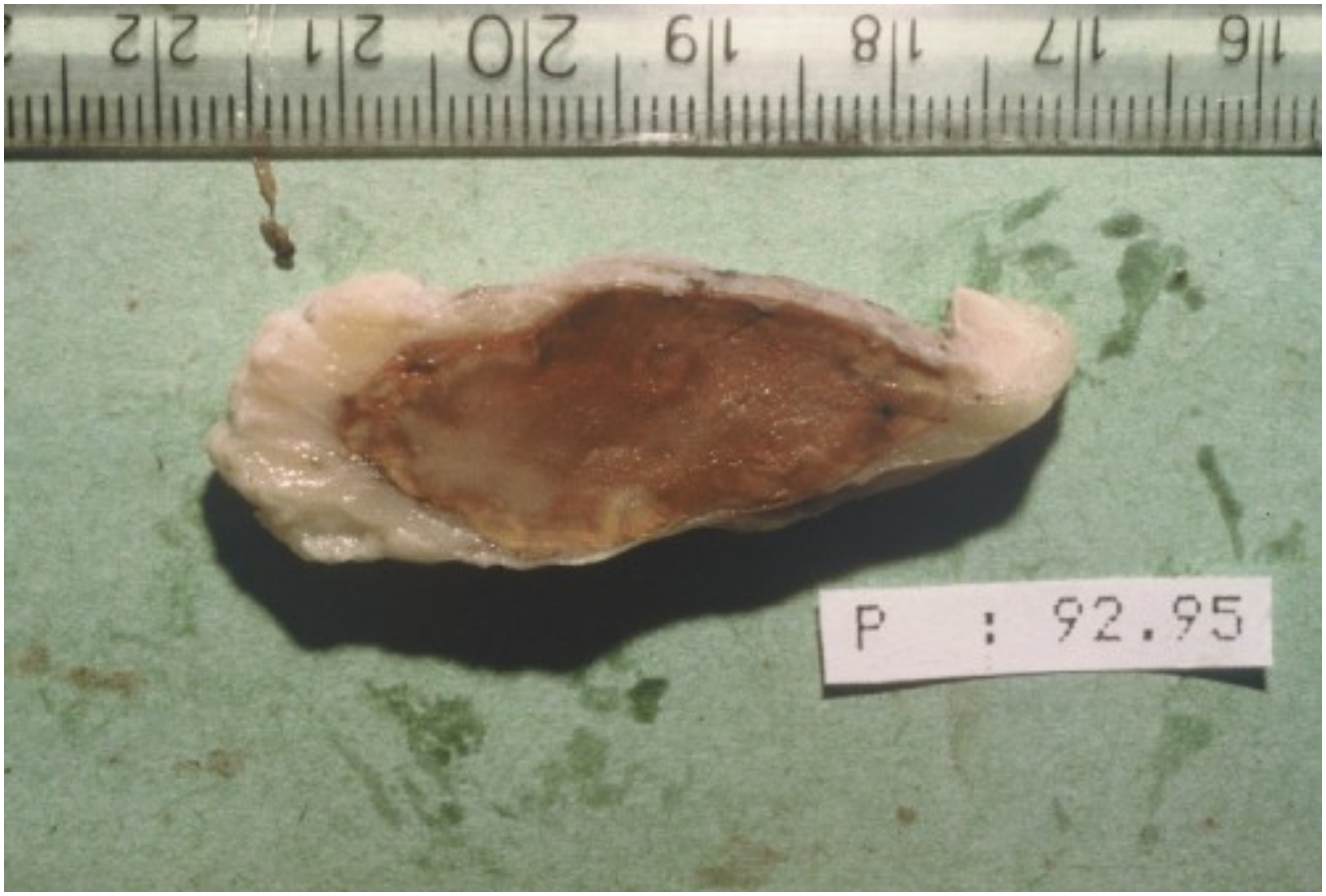


Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients.

Espinosa G et al. Medicine (Baltimore) 2003;82:106-18

Males: 55%

Mean age at presentation : 43 +/- 16 years.

Primary APS: 71%

Within "catastrophic APS " : 33 %

Presenting clinical manifestation of APS: 36%

Symptomatology highly *variable* according to prior steroid treatment

- Abdominal pain
- Adrenal failure: mainly acute (post-operative) / subacute / rarely chronic
- Latency (discovery on CT scan)

Diagnosis : Hormonal status (cortisol, ACTH, stimulation test)

Imaging: CT scan – MRI

LA: 97 % - aCL 93 % (mainly IgG)

Death: 36% of patients with outcome data available

Secondary adrenal atrophy

Mecanism (s)

- Adrenal vein thrombosis --> Adrenal infarction
- Adrenal hemorrhage secondary to thrombocytopenia and /or heparin (?)

Examens biologiques

Plaquettes ≤ 100 000 /mm3: 47 %

Laboratory features, no./no. tested (%)‡	
IgG aCL	197/236 (83.5)
IgM aCL	92/221 (41.6)
IgA aCL	3/71 (4.2)
Lupus anticoagulant	173/223 (77.6)
Disseminated intravascular coagulation	33/221 (14.9)
Thrombotic microangiopathic hemolytic anemia	19/221 (8.6)

+ facteur précipitant: Infections

CAPS - Prognosis

Mortalité

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

44 %

Evolution: 2001-5: 33 %

Mortalité: Causes

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Table 2. Major cause of death and findings of histopathologic studies in patients with CAPS*

	No. (%) of patients with CAPS
Major cause of death (n = 81)	
Cerebral involvement	22 (27.2)
Stroke	15 (18.5)
Cerebral hemorrhage	4 (4.9)
Encephalopathy	3 (3.7)
Cardiac involvement	16 (19.8)
Cardiac failure	14 (17.3)
Arrhythmias	2 (2.5)
Infection	16 (19.8)
Bacterial sepsis	10 (12.3)
Fungal sepsis	3 (3.7)
Pneumocystis carinii pneumonia	2 (2.5)
Suppurative peritonitis	1 (1.2)
Multiple organ failure	14 (17.3)
Pulmonary involvement	8 (9.9)
Acute respiratory distress syndrome	6 (7.4)
Pulmonary embolism	1 (1.2)
Pulmonary hemorrhage	1 (1.2)
Abdominal involvement	4 (4.9)
Liver failure	3 (3.7)
Acute abdomen	1 (1.2)

Mortalité : Facteurs Pronostiques

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

- Higher death rate :

SLE 59 vs 38 % (p = 0.003)

No anticoagulant…78 vs 37 % (p < .0001)

Long term outcome of catastrophic antiphospholipid syndrome survivors.

Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, Lockshin MD. Ann Rheum Dis. 2003;62(6):530-3

63/136 (46%) patients died at the initial event.

Of the remaining 73 patients, information was available for 58 (79%).

66% did not develop further APS related events (follow up of 6 yrs)

19% developed further APS related events but were still alive

16% patients died: multiple organ failure (3), myelofibrosis (1), pneumonia (1) and APS related events (4)

No patients developed further catastrophic APS

+ Residual damage…

One-shot event (recurrence: 1.6%)

CAPS - DIAGNOSIS

Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines.

Asherson RA et al. Lupus 2003;12:530-534

1) Evidence of involvement of three or more organs, systems and/or tissues*
2) Development of manifestations simultaneously or in less than a week.
3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue**
4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)***

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50 % rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 hours).

** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

*** If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Definite catastrophic APS:

- All 4 criteria

Probable catastrophic APS:

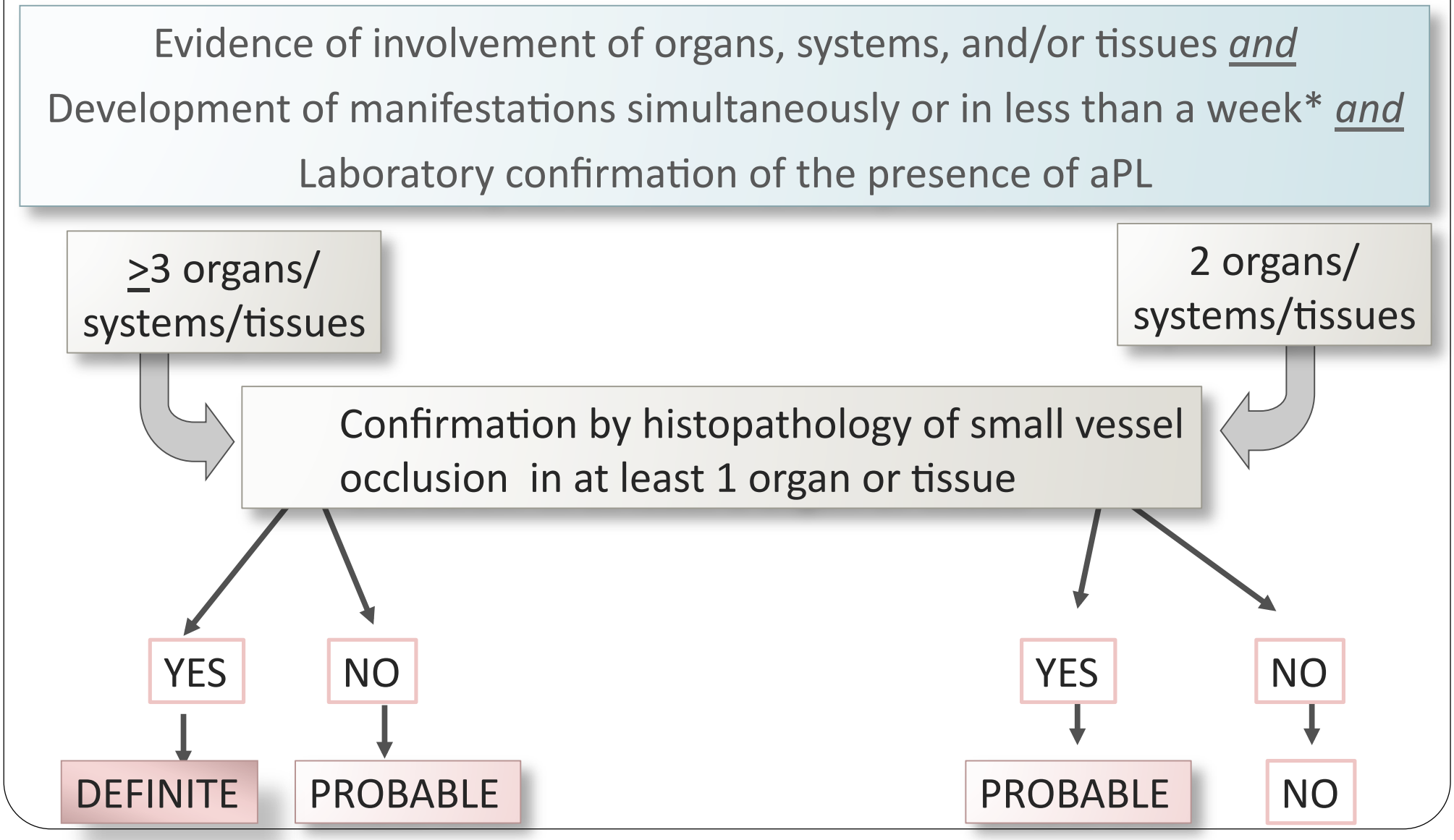
- All 4 criteria, except for only two organs, systems and/or tissues involvement.
- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS.
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

Validation of the preliminary criteria for the classification of catastrophic APS.

Cervera R, et al. Ann Rheum Dis 2005;64:1205-9

It should be emphasized that these criteria are mostly empirical and have been accepted for classification purposes and *are not intented to be used as strict diagnostic criteria in a given patient.*

Classification algorithm of catastrophic APS



Sd Catastrophique APS: Diagnostic différentiel

- Autres MTA
- Thrombopénie induite par Héparine
- CIVD
- Endocardite bactérienne ou marastique (cancer)
- HELLP
- Maladie des emboles de cholestérol
- Myxome
- Cryoglobulinemie
- ...

Amoura Z, Costedoat-Chalumeau N, Veyradier A, Wolf M, Ghillani-Dalbin P, Cacoub P, Meyer D, Piette JC.

Thrombotic thrombocytopenic purpura with severe ADAMTS-13 deficiency in two patients with primary antiphospholipid syndrome.

Arthritis Rheum 2004;50:3260-3264

CAPS - TREATMENT

Treatment in 242 episodes

Bucciarelli S, et al. Arthritis Rheum 2006 Aug;54:2568-76

Treatment used

Anticoagulation *85 % ….*
Steroids 79 %
Cyclophosphamide 31 %
Plasmapheresis 30 %
Ig IV 21 %
AAP 11 %

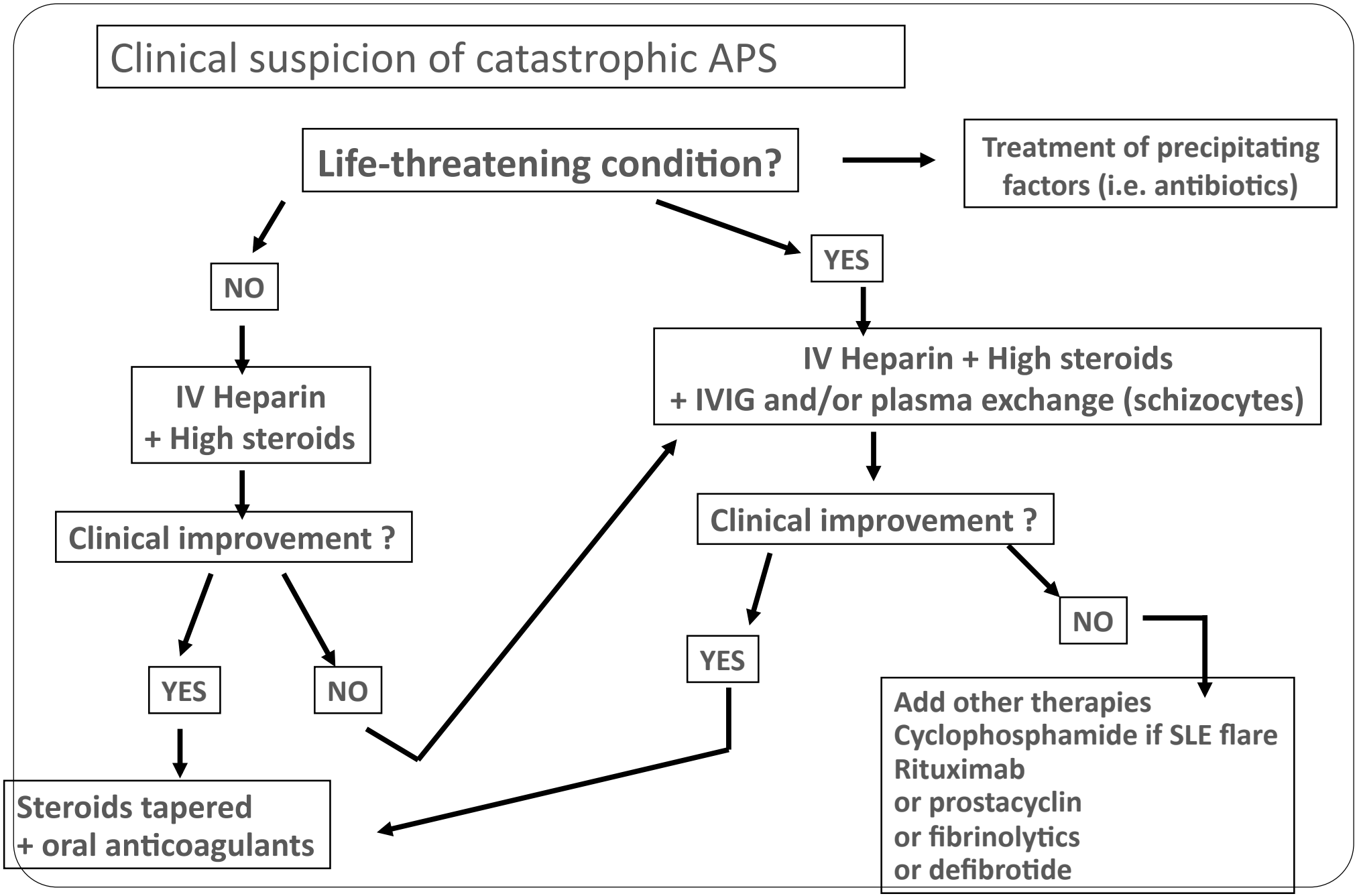
Recovery according to treatment (% de survie)

anticoagulation 63 % vs 22 % ($p < 0.0001$)
anticoagulation + steroids + PE: 78% (NS; 0.08)
anticoagulation + steroids + PE and/or IgIV: 69% (NS; 0.09)
Anticoagulation + steroids + Ig IV: 60%

ANTI-PHOSPHOLIPID SYNDROME

GOAL: TRY TO

	ELIMINATE CIRCULATING AP ANTIBODIES	PREVENT THEIR "DELETERIOUS" EFFECTS
SHORT TERM	***Sometimes***	**+++**
LONG TERM	**Utopian and/or Hazardous ***	**++**


Clinical suspicion of catastrophic APS
Life-threatening condition?
Treatment of precipitating factors (i.e. antibiotics)
NO
YES
IV Heparin + High steroids + IVIG and/or plasma exchange (schizocytes)
IV Heparin + High steroids
Clinical improvement ?
Clinical improvement ?
YES
NO
YES
NO
Steroids tapered + oral anticoagulants
Add other therapies
Cyclophosphamide if SLE flare
Rituximab
or prostacyclin
or fibrinolytics
or defibrotide

CAPS – Prevention?

Most common precipitating factors in 80 patients with catastrophic APS

Infections 35%
- Respiratory tract 15 %
- Cutaneous 8 %
- Urinary tract 6 %

Surgery, trauma & invasive procedures 13%
Neoplasia 8%
Anticoagulation withdrawal*/low INR 8%
Obstetric complications** 6%
Lupus flares 5%
Oral contraceptives 3%

No factor identified 35%

* 2 days…

** Ovulation induction therapie

Not in this series

Perioperative medical management of aPL syndrome: Hospital for Special Surgery experience, review of the literature and recommendations.

Erkan D, Leibowitz E, Berman J, Lockshin MD. *J Rheumatol* 2002; 29: 843-9.

Preoperative assessment

- Surgical and interventional procedures should be the last option in the management of APS patients
- Platelet >100,000/μl due to APS requires no specific therapy; thrombocytopenia does not protect against thrombosis

Perioperative considerations

- Minimize intravascular manipulation for access and monitoring
- Prevent infective endocarditis
- Set pneumatic blood pressure cuffs to inflate infrequently to minimize stasis in the distal vascular bed
- Avoid tourniquets (garrop)
- Maintain high suspicion that any deviation from a normal course may reflect arterial or venous thrombosis
- Collapse may result from adrenal involvement

Perioperative anticoagulation

- Keep periods without anticoagulation to an absolute minimum
- Employ pharmacologic and physical antithrombosis interventions vigorously and start immediately before the operation, continuing until the patient is fully ambulating
- Be aware that APS patients can develop recurrent thrombosis despite appropriate prophylaxis
- Be aware that current conventional doses of antithrombotic agents can result in underanticoagulation: APS patients may benefit from an aggressive approach with higher-than-standard doses

remerciements

Pr JC Piette

Pr Z Amoura

Dr B Wechsler