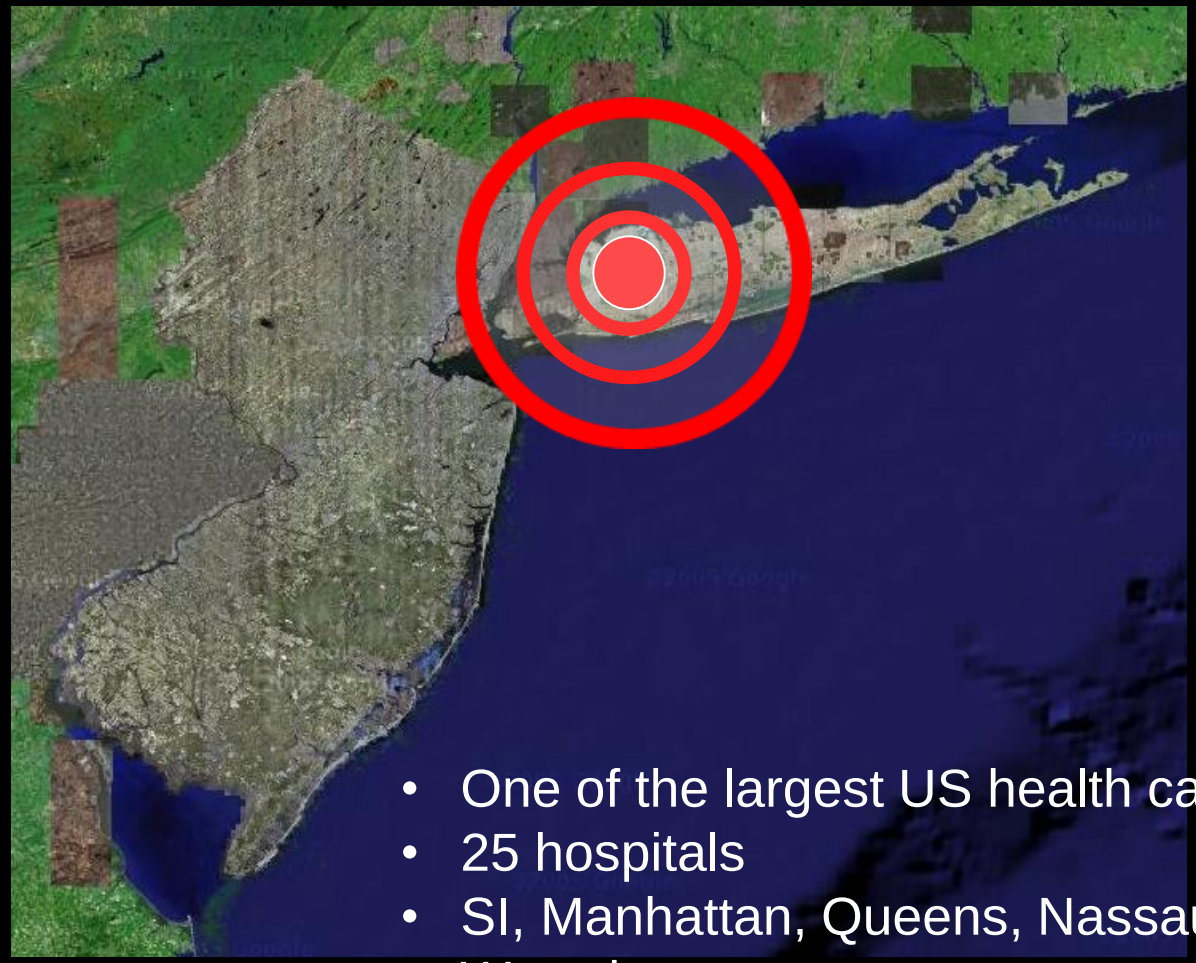
Antiphospholipid Syndrome:
It's Far More Than You Think

Richard Furie, MD
Chief, Division of Rheumatology
Northwell Health
Professor of Medicine
Zucker School of Medicine at Hofstra/Northwell

Richard Furie, MD
Disclosures:

Nothing to disclose



Northwell Health

- One of the largest US health care systems
- 25 hospitals
- SI, Manhattan, Queens, Nassau, Suffolk, Brooklyn, Westchester
- 2400 full-time doctors
- Medical school (Zucker SOM at Hofstra/Northwell)
- 120 training programs (1500 trainees)
- 36 full-time and 24 voluntary rheumatologists

Learning Objectives

- Discuss the pathogenesis of Antiphospholipid Syndrome
- Recognize the full spectrum of APS manifestations
- Describe advances in diagnosis and management of APS

The APS Problem

- Case: 58 y/o female
  - 30 years of SLE, quiet on no medicines until 2009
  - Onset of AHA initially controlled with MMF and rituximab
  - During her first visit in 2009:
    - Beta-2 glycoprotein I IgG Ab: >150 U/ml (<15)
    - Anticardiolipin IgG Ab: 120 GPL (<15)
  - No history of miscarriage or thrombosis

The APS Problem

- Would you advise therapy for thrombosis prevention?
- If so, which medicine?
  - ASA
  - Clopidogrel
  - Warfarin
  - Prednisone
  - Hydroxychloroquine
  - Something else?
- What are the data for primary prevention?

The APS Problem

- Case continued
  - Placed on ASA 81 mg per day in 2009
- Stroke October 2010
  - Treated with heparin and then warfarin
  - She has done well since except for low-grade AHA
    - MMF and intermittent rituximab

- What are the data for secondary prevention?
- What is the appropriate INR target?
- Why does this all happen?

APS Update

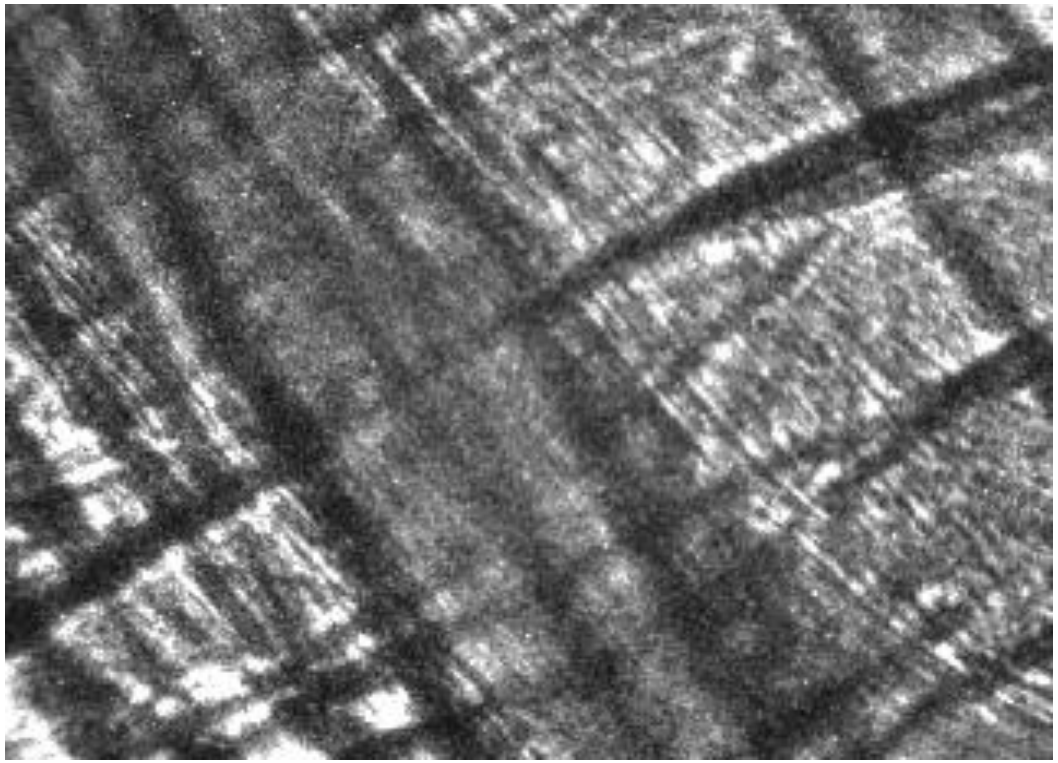
- Pathogenesis
- Diagnosis
- Treatment challenges
- Unusual complications
- Drug development

APS Update[1]

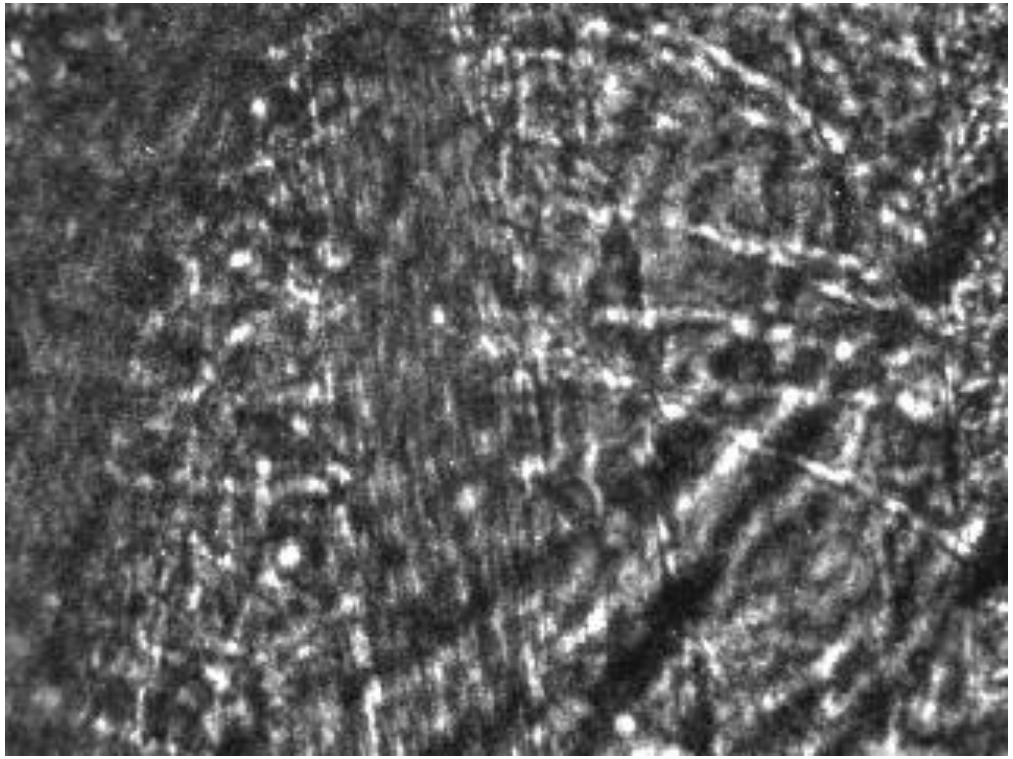
- **Pathogenesis**
- Diagnosis
- Treatment challenges
- Unusual complications
- Drug development

[1]Garcia D, Erkan D NEJM 2018

Collaboration Then and Now



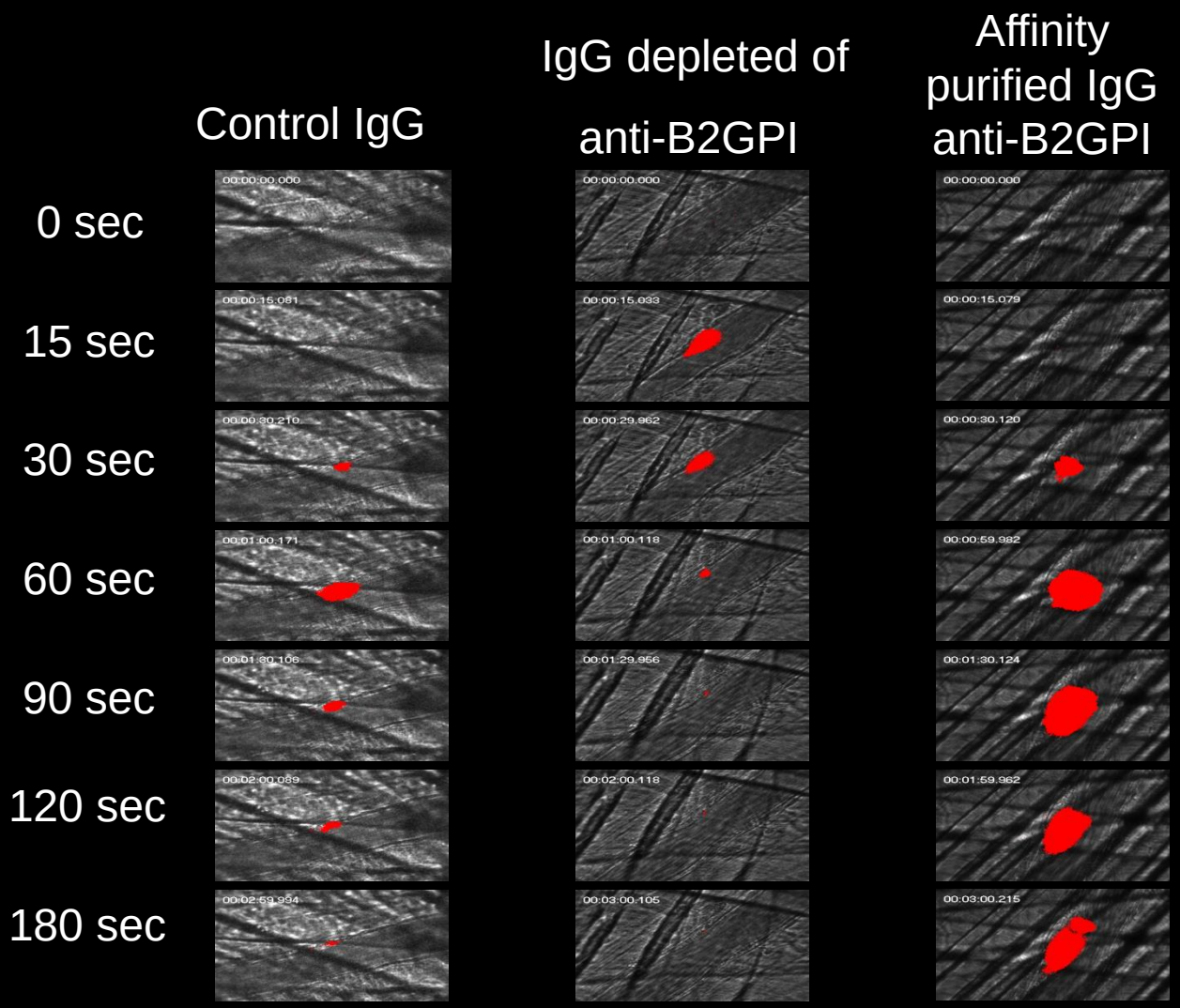
Control serum



Patient: SLE and APS

(high β2GPI and aCL Ab)

Effects of Affinity Purified Anti-β2GPI Ab on Thrombus Formation



Arad A et al. Blood 2011

Pathogenesis

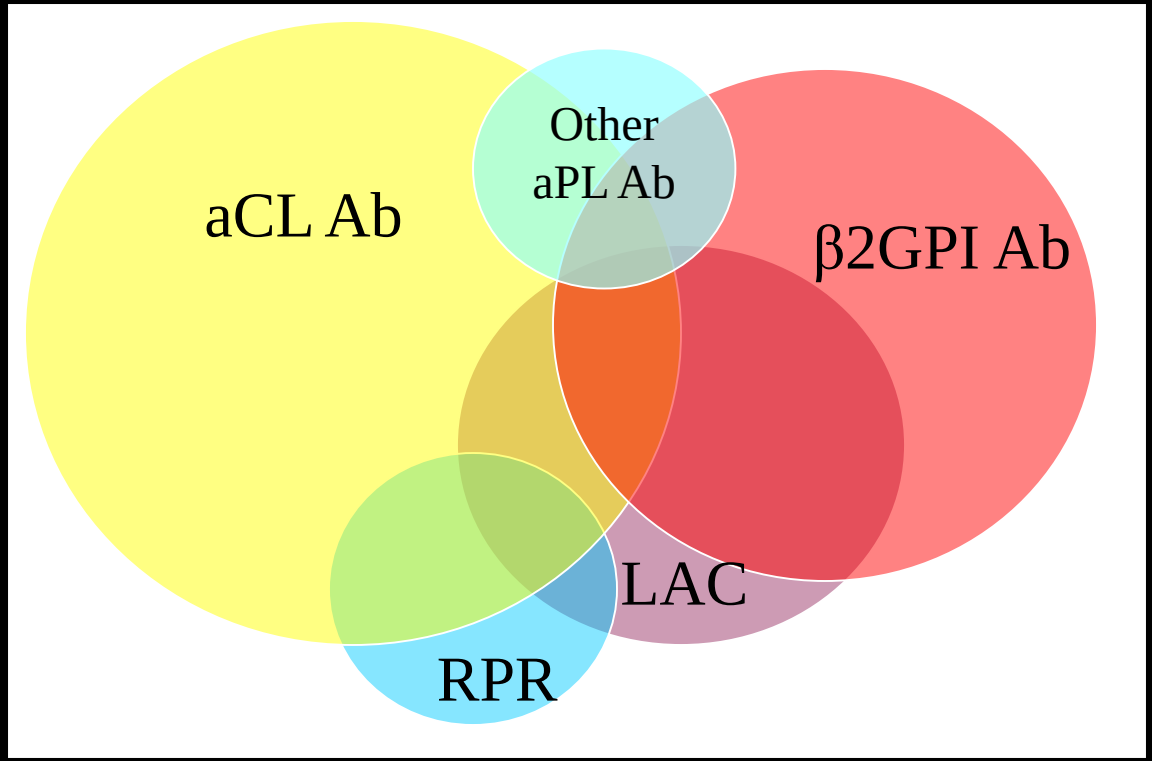
- β2GP1 and anti-β2GP1 autoantibodies co-localized on the platelet thrombus but not the endothelium
- Anti-β2GP1 autoantibodies enhanced both platelet and endothelial activation
- When platelet thrombus formation was blocked, enhanced fibrin generation and endothelial cell activation were eliminated
- The anti-β2GP1 autoantibody/β2GP1 complex binds to the thrombus, enhancing platelet activation, and platelet activation leads to enhanced endothelium activation and fibrin generation

Proulle V et al. Blood 2014

APS Update

- Pathogenesis
- **Diagnosis**
- Treatment challenges
- Unusual complications
- Drug development

The Family of Antiphospholipid Antibodies



The Lupus Anticoagulant at Northwell

Silica Clotting Time
and/or
Dilute Russell Viper Venom Time

Other PL Antibody Tests

- Antibodies to:
  - **Phosphatidyl serine/prothrombin (PS/PT)**
  - **β2 D1**
  - Phosphatidyl serine
  - Phosphatidyl ethanolamine
  - Phosphatidic acid
  - Phosphatidyl inositol
  - Phosphatidyl glycerol
  - Phosphatidyl choline
- What do they add?
- Seronegative APS?

APS Update

- Pathogenesis
- Diagnosis
- **Treatment challenges**
- Unusual complications
- Drug development

Treatment Challenges

- Primary prevention (? ASA[1]; HCQ)
- Safe and convenient secondary prevention
- Warfarin refractory patients
- CAPS
- Obstetrical complications

[1]Erkan D et al. Arthritis Rheum. 2007 Jul;56(7):2382-91.

Predictors of Thrombotic Risk

- Triple positivity (LAC, β2GPI Ab, aCL Ab)[1]
  - 104 asymptomatic patients
  - Mean F/U: 4.5 years
- 25 first thrombotic events
  - 5.3%/y vs. 1.4% in single positivity patients
  - 37% cumulative incidence over 10 y

[1]Pengo V et al. Blood. 2011 Oct 27;118(17):4714-8.

APS: Secondary Prevention

Comparison of High- and Moderate-Intensity Warfarin Groups

Outcome	INR 3.1 - 4.0 (n=56)	INR 2.0 - 3.0 (n=58)	P Value
Recurrent Thrombosis	6	2	0.15
Bleeding Any / Major	14 / 3	11 / 4	0.13 / 0.96

Crowther MA et al. N Engl J Med. 2003; 349:113-8

Treatment of Warfarin-Refractory Disease

- Anti-platelet agents
  - ASA, clopidigrel
- Anticoagulants
  - Heparins
  - Dabigatran: direct thrombin inhibitor
  - Rivaroxaban: Xa inhibitor
  - Apixaban: Xa inhibitor
- Hydroxychloroquine: protects Annexin V
- Steroids
- Cyclophosphamide
- Rituximab
- Eculizumab
- Plasmapheresis
- IVIG

APS Update

- Pathogenesis
- Diagnosis
- Treatment challenges
- **Unusual complications**
- Drug development

Unusual Complications

- Thrombotic microangiopathy
- Catastrophic APS
- Movement disorder
- Livedoid vasculopathy
- APL nephropathy
- Heart disease (valvular disease, intracardiac thrombi, coronary occlusion)
- Adrenal insufficiency
- Pulmonary hypertension
- Osteonecrosis
- Arteriopathy

Thrombotic Microangiopathy

27 year old female with a 5 year history of SLE (and antiphospholipid antibodies) was admitted to the hospital because of confusion and fever.

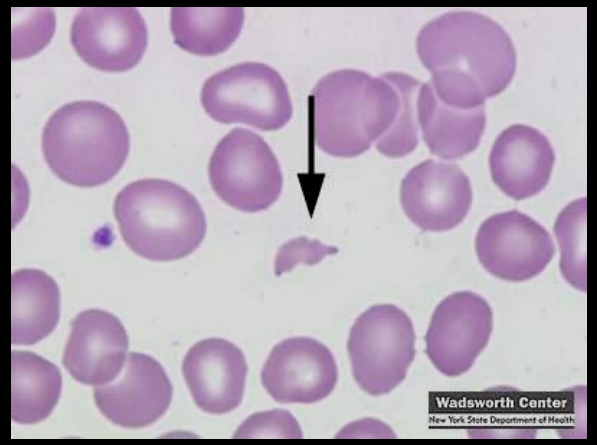
Stupor turned to coma

Thrombotic Microangiopathy

Hb	6.8 g/dL
Plt	12 K/uL
PT / PTT	12 / 66 seconds
DIC screen	normal
LAC	positive
Creatinine	1.9 mg/dL

Thrombotic Microangiopathy

LDH	1200
Haptoglobin	not detectable
Reticulocyte count	15.5 %
Direct Coombs test	negative
Blood smear	



Thrombotic Microangiopathy

Thrombotic Microangiopathy[1]

1. Thrombocytopenia
2. Microangiopathic hemolytic anemia (schistocytes)
3. Organ dysfunction (kidney; brain; heart; GB)

Treatment

Plasmapheresis: complete response within one week

[1]Symmers W St C. Br Med J 1952.

Catastrophic APS

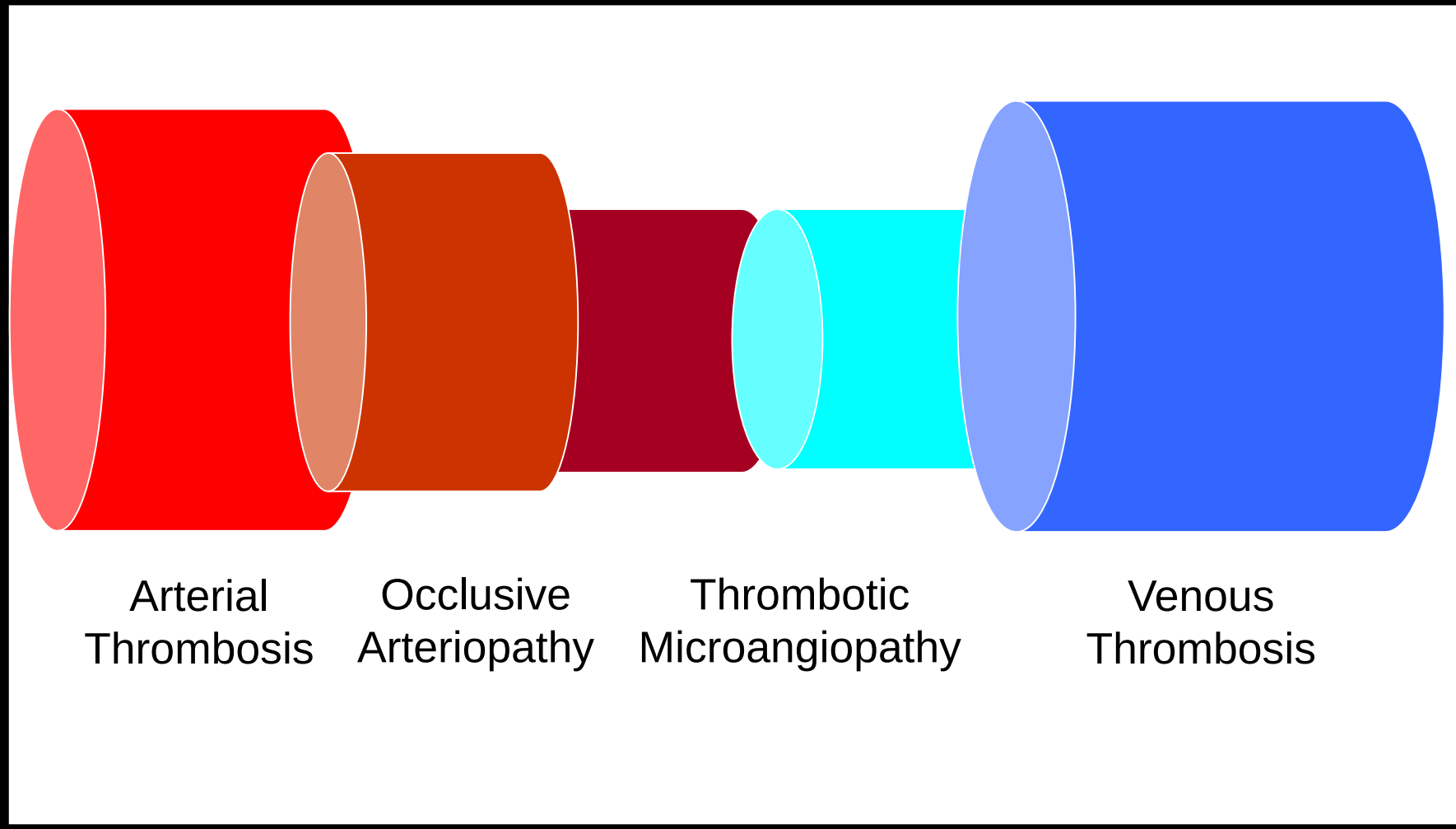
- **1994 Jain R et al: SLE and Thrombotic Microangiopathy[1]**
  6/7 patients with TM were APL Ab positive
  1/7 patients had PAPS

- **1991 Greisman S et al: Occlusive Vasculopathy[2]**
  2 SLE patients with occlusive vasculopathy and APL Ab

- **1992 Asherson RA: Catastrophic APS[3]**

[1]Jain R et al. Semin Arthritis Rheum 1994; [2]Greisman SG et al. Arch Intern Med. 1991 Feb;151(2):389-92.\;
[3] Asherson RA. J Rheumatol. 1992 Apr;19(4):508-12

APS Vasculopathies



Movement Disorders

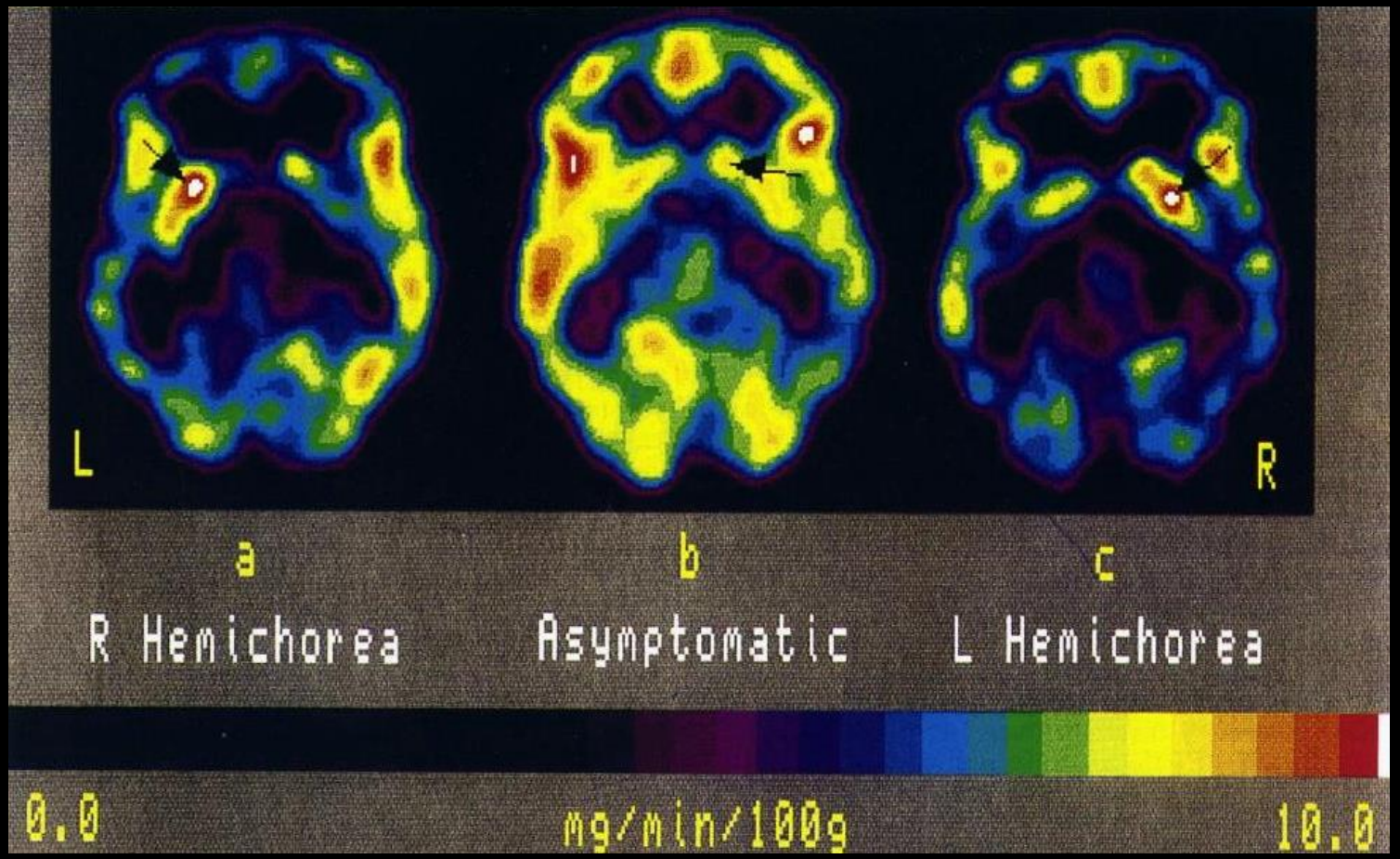
A 24 year old female with recently diagnosed thrombocytopenia was referred for evaluation of possible SLE.

During the interview, she had spontaneous flailing movements of the right upper extremity.

Plts: 70,000; DNA Ab: positive; IgG aCL: 88

Movement Disorders

PET Scan



Furie R et al. Neurology. 1994 Nov;44(11):2197-9

Chorea

- **Associated with SLE and with PAPS**
- **Striatal hypermetabolism**
- **Pathogenesis unknown**
    - Microvascular occlusion
    - aPL binding to striatal tissue

The patient has remained thrombocytopenic. She has been treated with ASA 81 and has not had a thrombotic episodes. Two uncomplicated pregnancies.

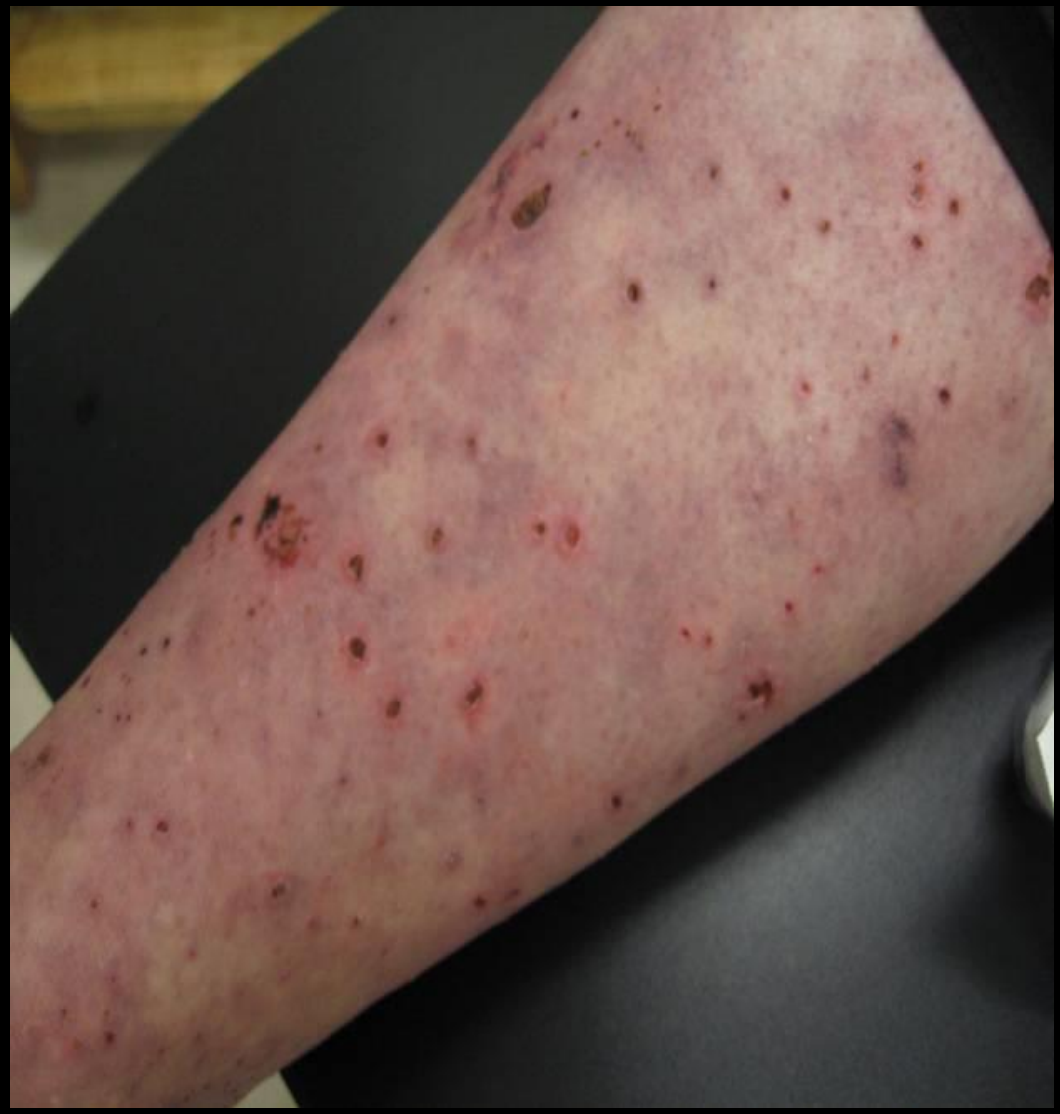
Livedoid Vasculopathy

A 39 year old female with known SLE and APL antibodies presented with painful diffuse skin lesions.

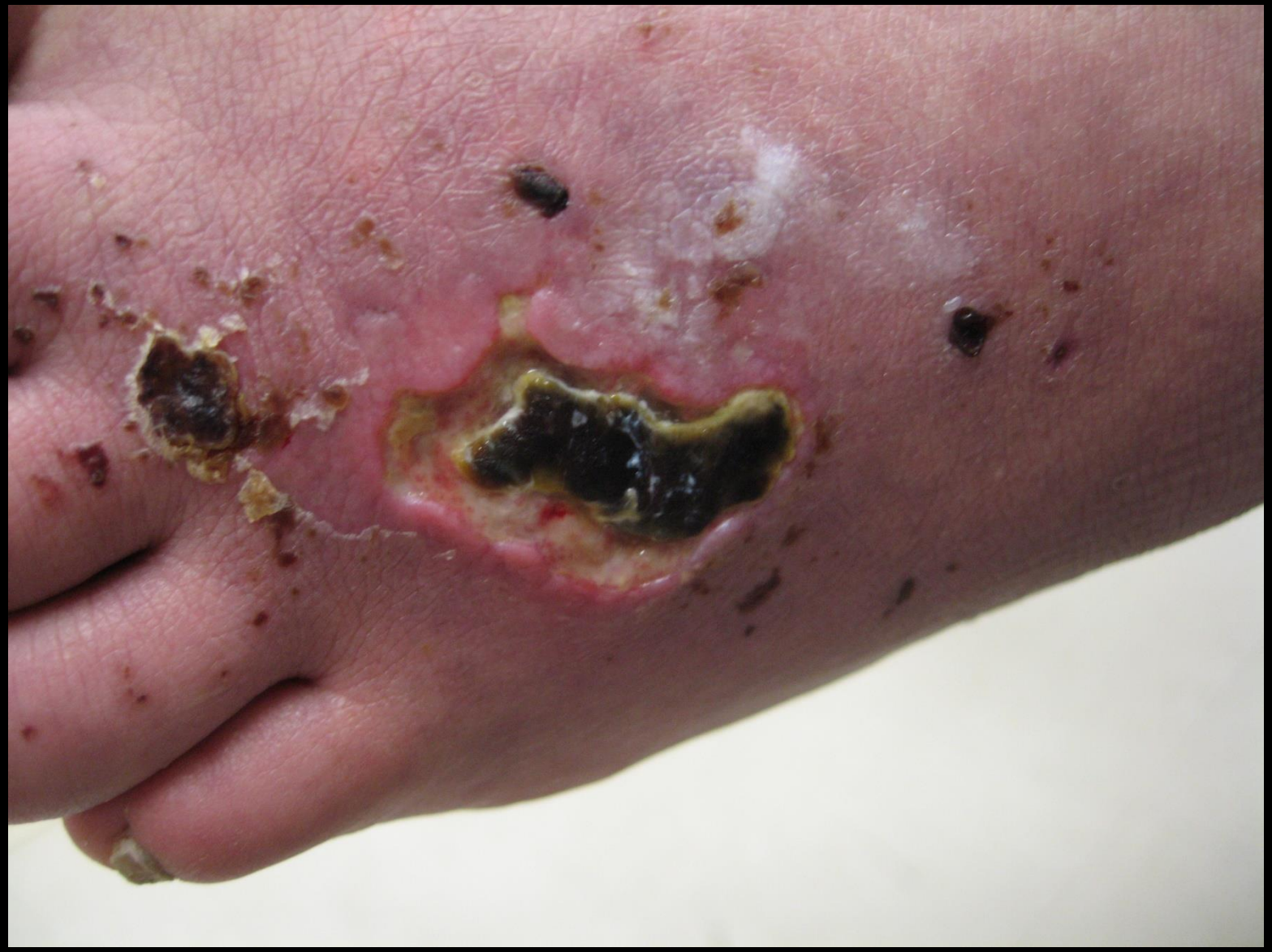
A biopsy demonstrated arteriolar occlusion without vasculitis.

A significant response occurred with warfarin alone.

Livedoid Vasculopathy



Livedoid Vasculopathy



APL Nephropathy

A 51 year old female with known SLE developed worsening renal function in the absence of significant proteinuria.

Laboratory tests were notable for creatinine 2.7 and APL antibodies.

Kidney biopsy: WHO class II (mesangial) and …

APL Nephropathy

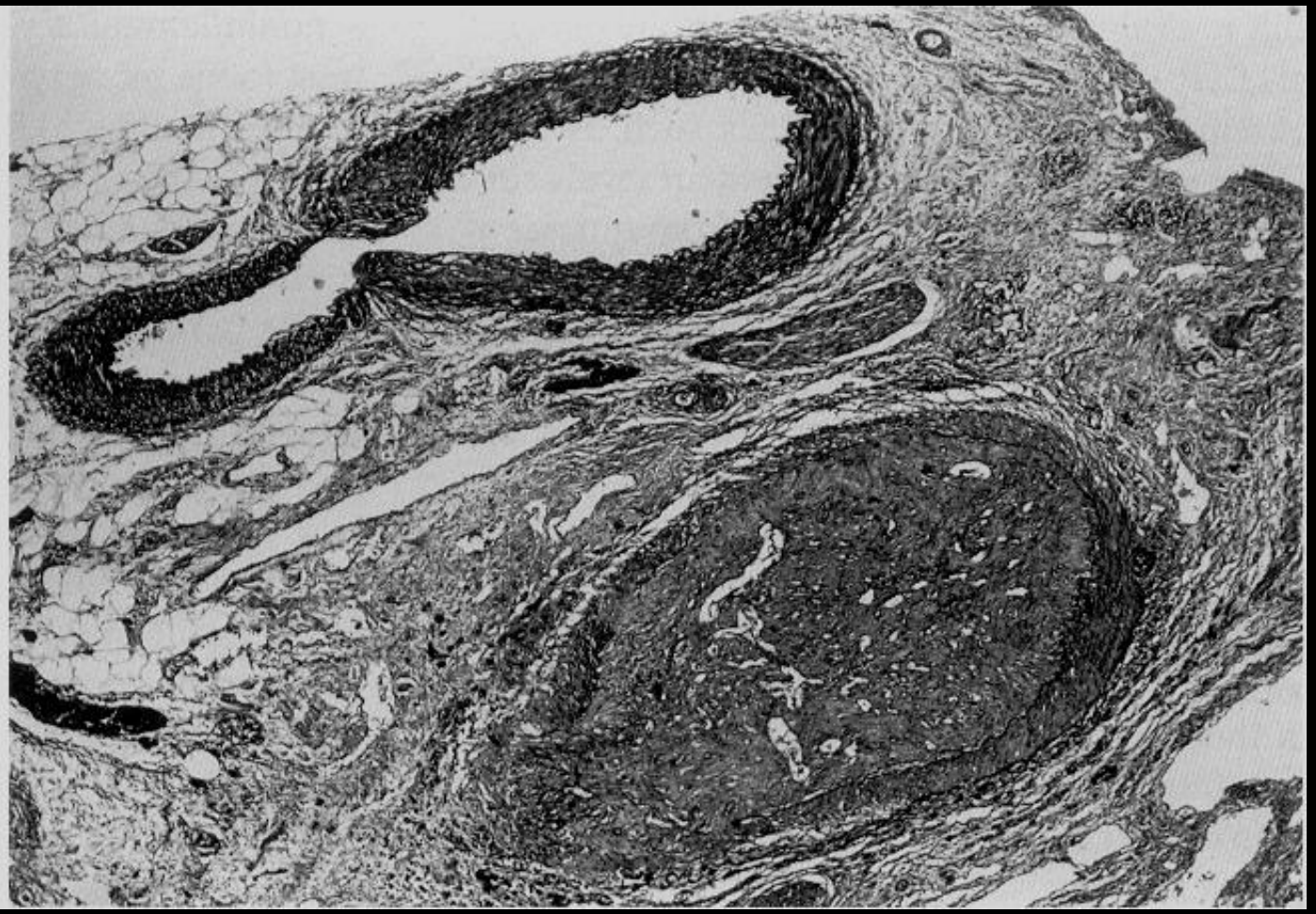


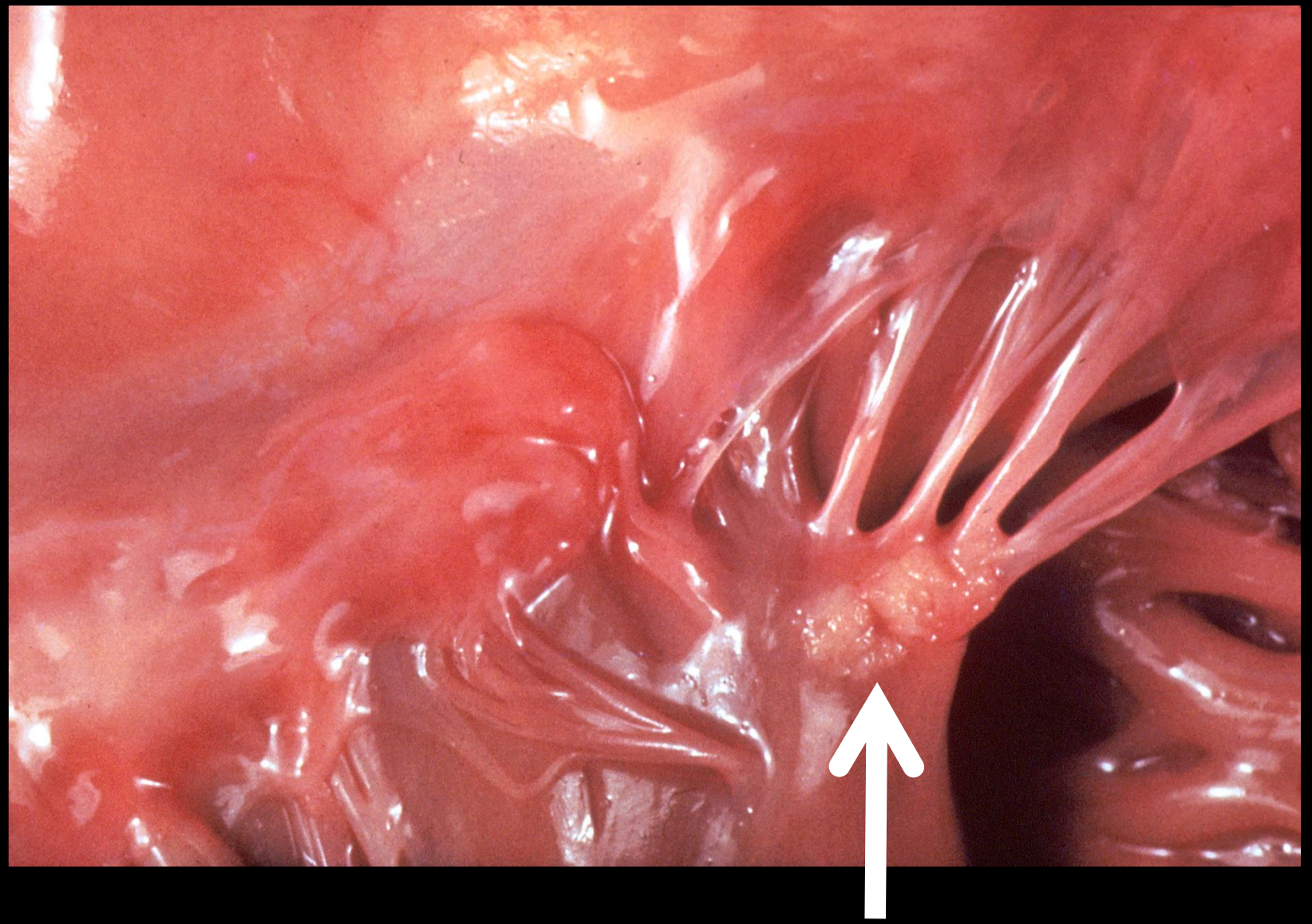
Fig 3: An interlobar artery is occluded by a recanalized thrombus. An adjacent artery has a patent lumen (original magnification 50×).

Cardiopulmonary Disease in APS[1]

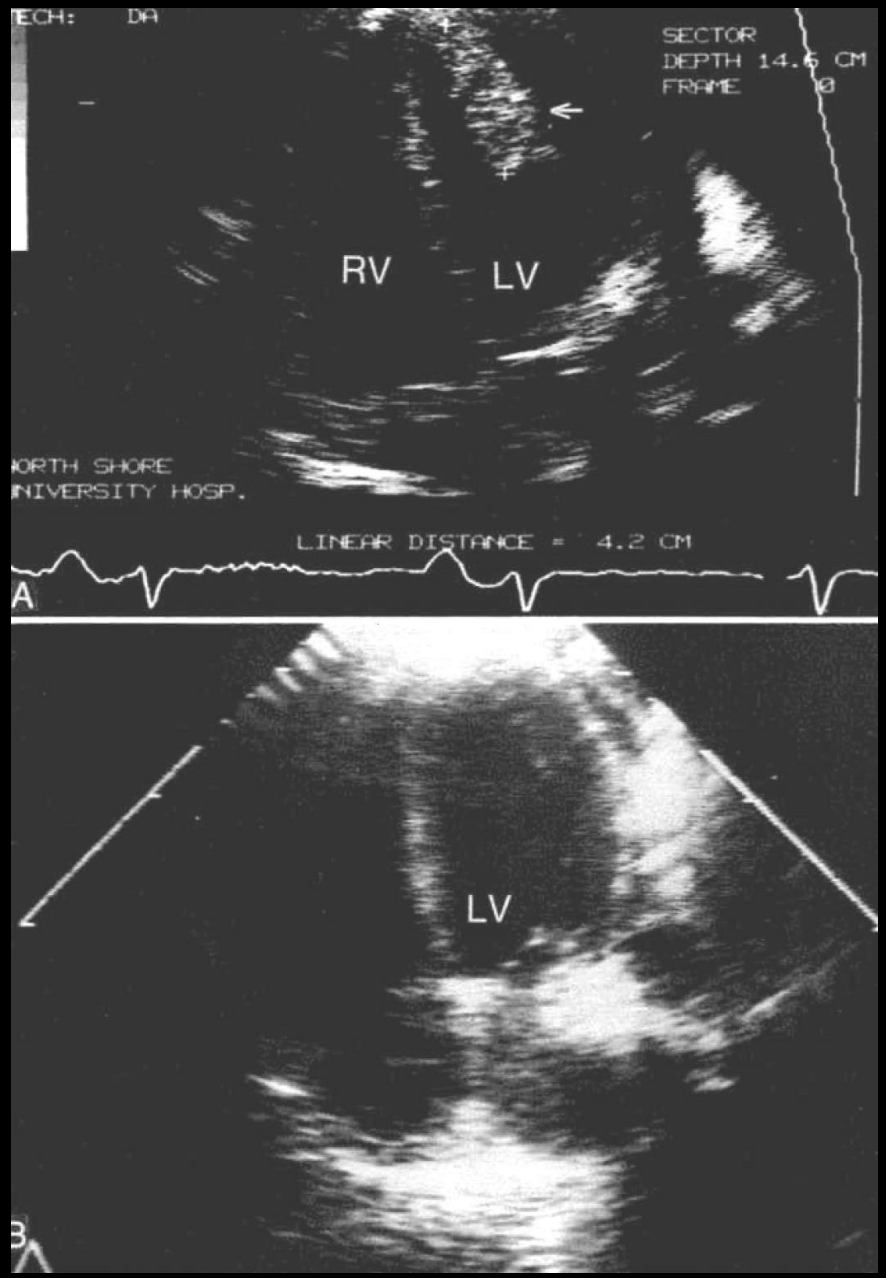
- Valvular heart disease[2]
  - Insufficiency murmurs
  - Vegetations
- Intracardiac thrombosis
- Coronary thrombosis
- Pulmonary hypertension

[1]Kaplan SD et al. Am Heart J 1992; 124:1331-1338; [2]Chartash EK et al. Am J Med 1989; 86 (4): 407–412;

Valvular Disease in APS



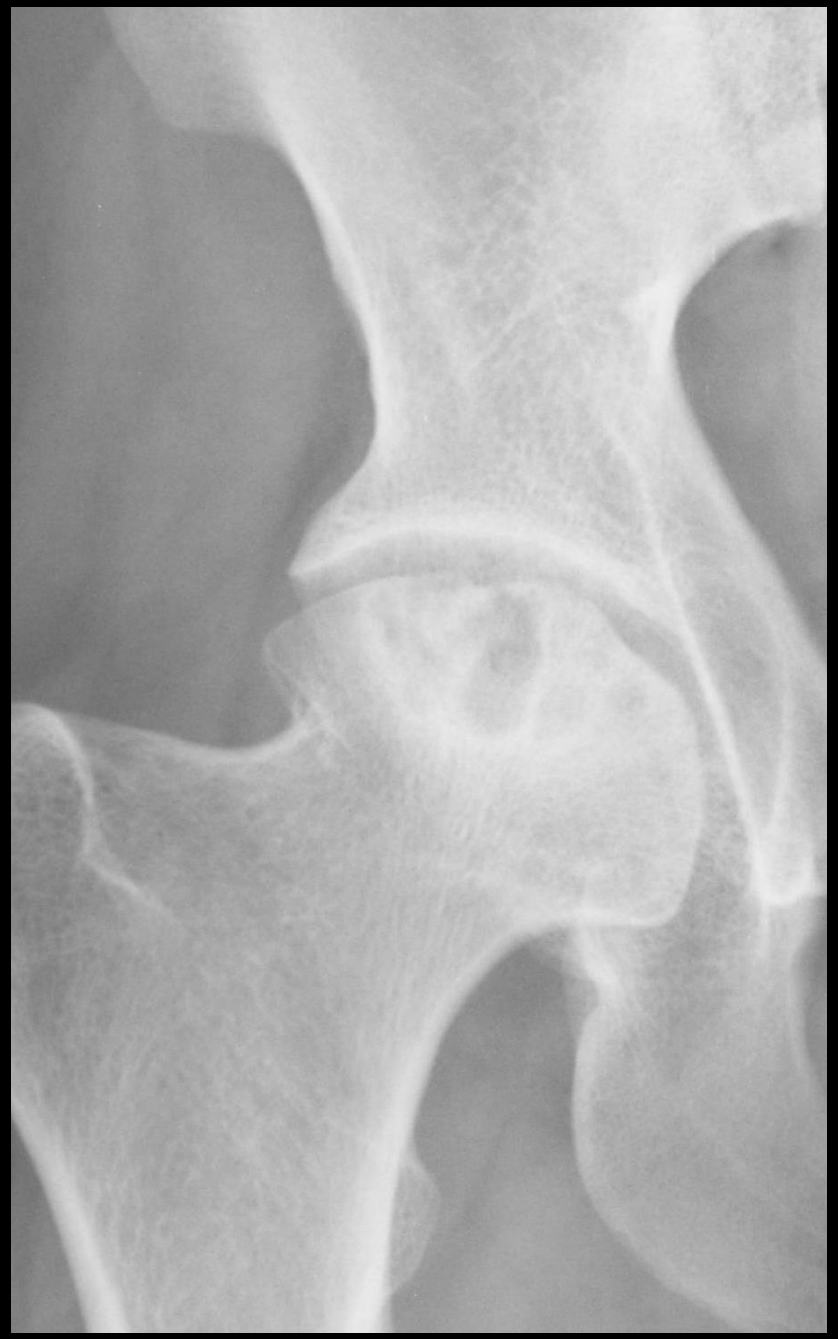
Intracardiac Thrombus

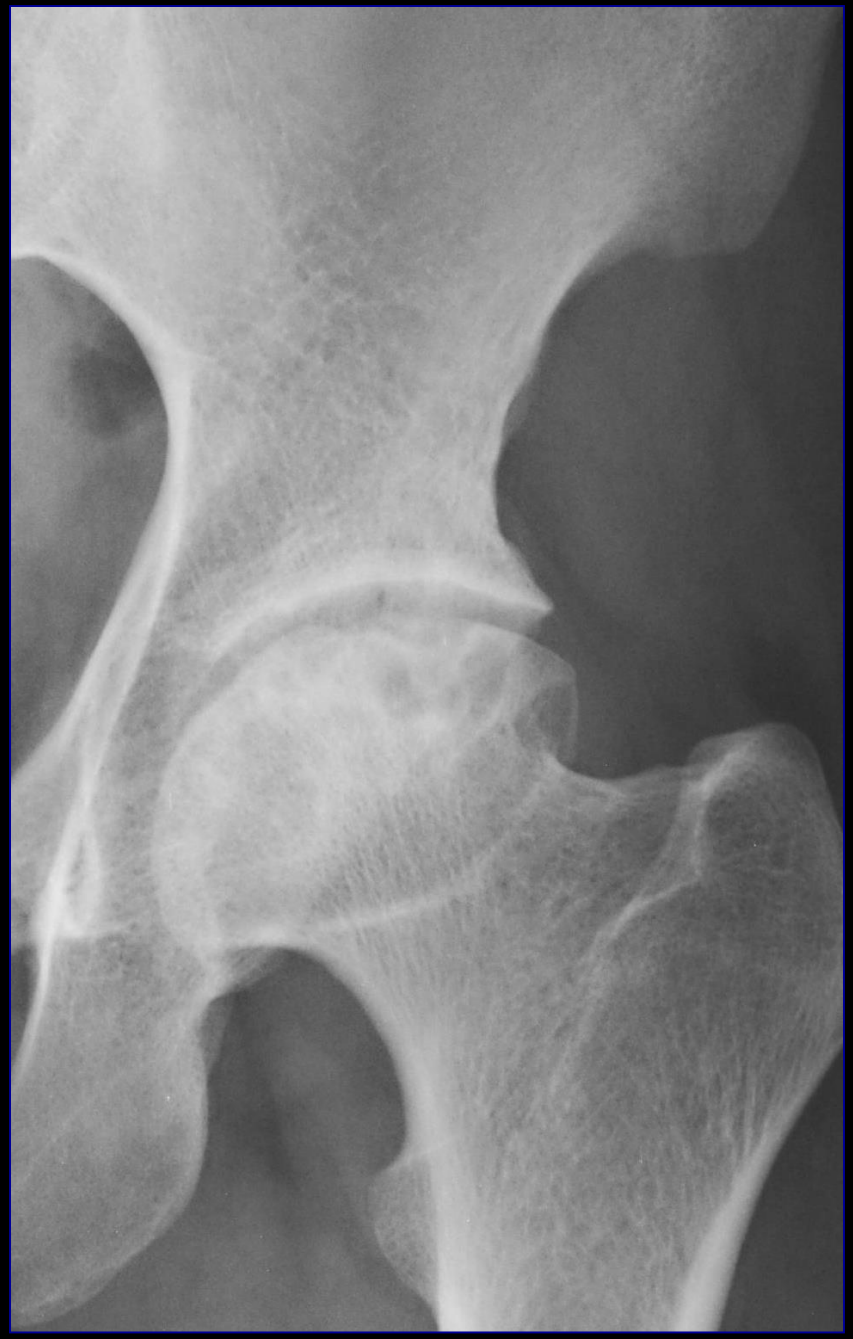


Osteonecrosis

35 year old female with 19 year history of bilateral hip/knee/ankle pain **BUT NO** prior history of osteonecrosis risk factors

High titers of aCL Ab; all other autoAb absent





Adrenal Insufficiency and APS

67 y/o female with SLE and APS (stroke) maintained on warfarin had persistent fever and tachycardia post-op elective urologic surgery.

Abd CT: bilateral adrenal masses (4 x 3 cm)

Low cortisol; improvement on hydrocortisone 15 mg daily

Adrenal Insufficiency and APS

86 case review[1]:

- 71% PAPS; 55% male
- 36% adrenal disease first APS manifestation
- Abdominal pain, hypotension, fever
- Imaging: adrenal hemorrhage; bilateral 77%
- Histology (22 patients):
  - Hemorrhagic infarction with vessel thrombosis (55%)
  - Adrenal hemorrhage (27%)
- Pathogenesis: adrenal vein thrombosis with secondary adrenal hemorrhage

[1]Espinosa G et al. Medicine 2003

Arteriopathy

37 y/o F with SLE (DLE, arthritis, Raynauds) and APS (DVT) chronically treated with steroids, HCQ, MMF, and rivaroxaban. She had been serologically active (Sm Ab) and LAC positive.

She had an acute cerebral infarct resulting in right hemiplegia.

MRI: left MCA and PCA territory infarcts
Angio: severe left carotid stenosis (Moya-Moya[1]-like) and similar involvement of the right carotid

[1]Takeuchi K, Shimizu K. Brain Nerve 1957;9:37-43

Arteriopathy

Treatment:

1. Left superficial temporal artery to MCA microanastomosis
2. Warfarin
3. ? Immunosuppressives (sirolimus)

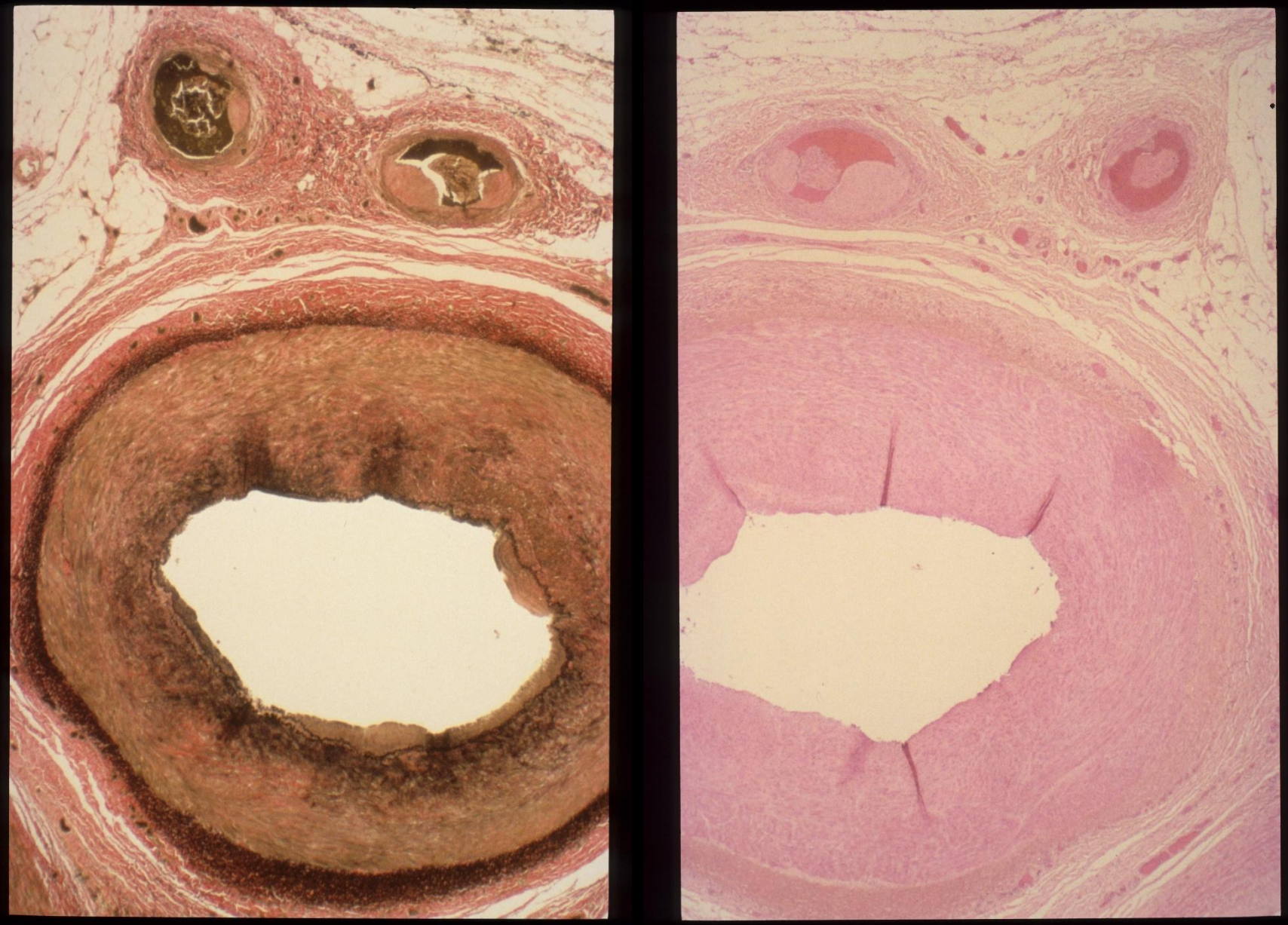
Issues:

1. Should warfarin have been substituted for rivaroxaban?
2. What is the nature of her carotid disease?

Arteriopathy

- Thrombosis is not the only vascular complication
- Vascular cellular infiltrates/fibrosis of the intima and media[1]
- mTORC pathway involved in renal vascular lesions[2]
  - 37 kidney transplant recipients with aPL Ab: 10 on sirolimus
  - Sirolimus: 3 of 10 had loss of functional allografts at mean f/u 7 years
  - No sirolimus: 24 of 27 had loss of functional allografts

[1]Alarcón-Segovia D et al J Rheumatol 1989; [2]Canaud G et al. NEJM 2014



1991: JB (27 y/o male; hx SLE, APS, TMA): Popliteal Artery

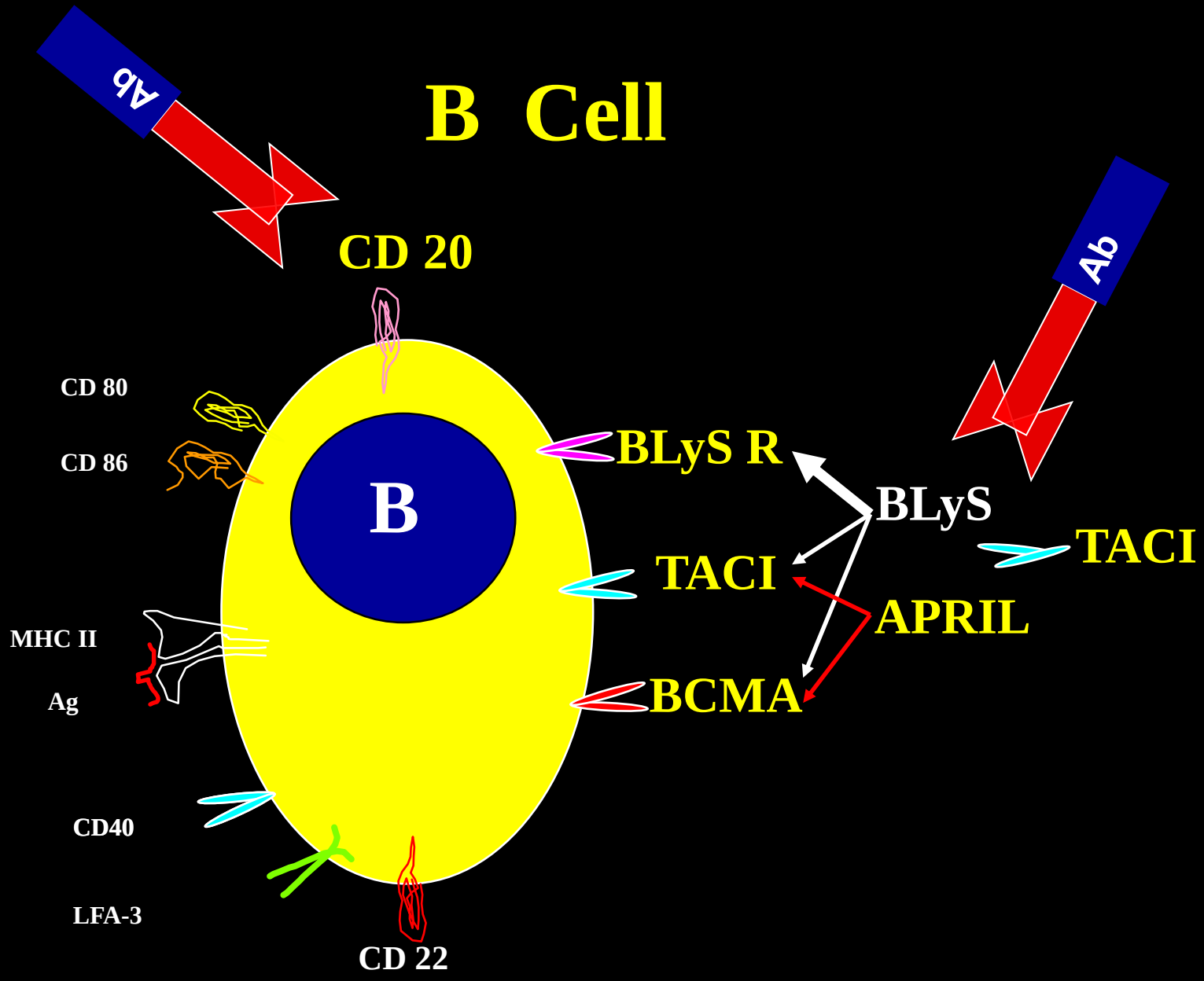
APS Update

- Pathogenesis
- Diagnosis
- Unusual complications
- Treatment challenges
- **Drug development**

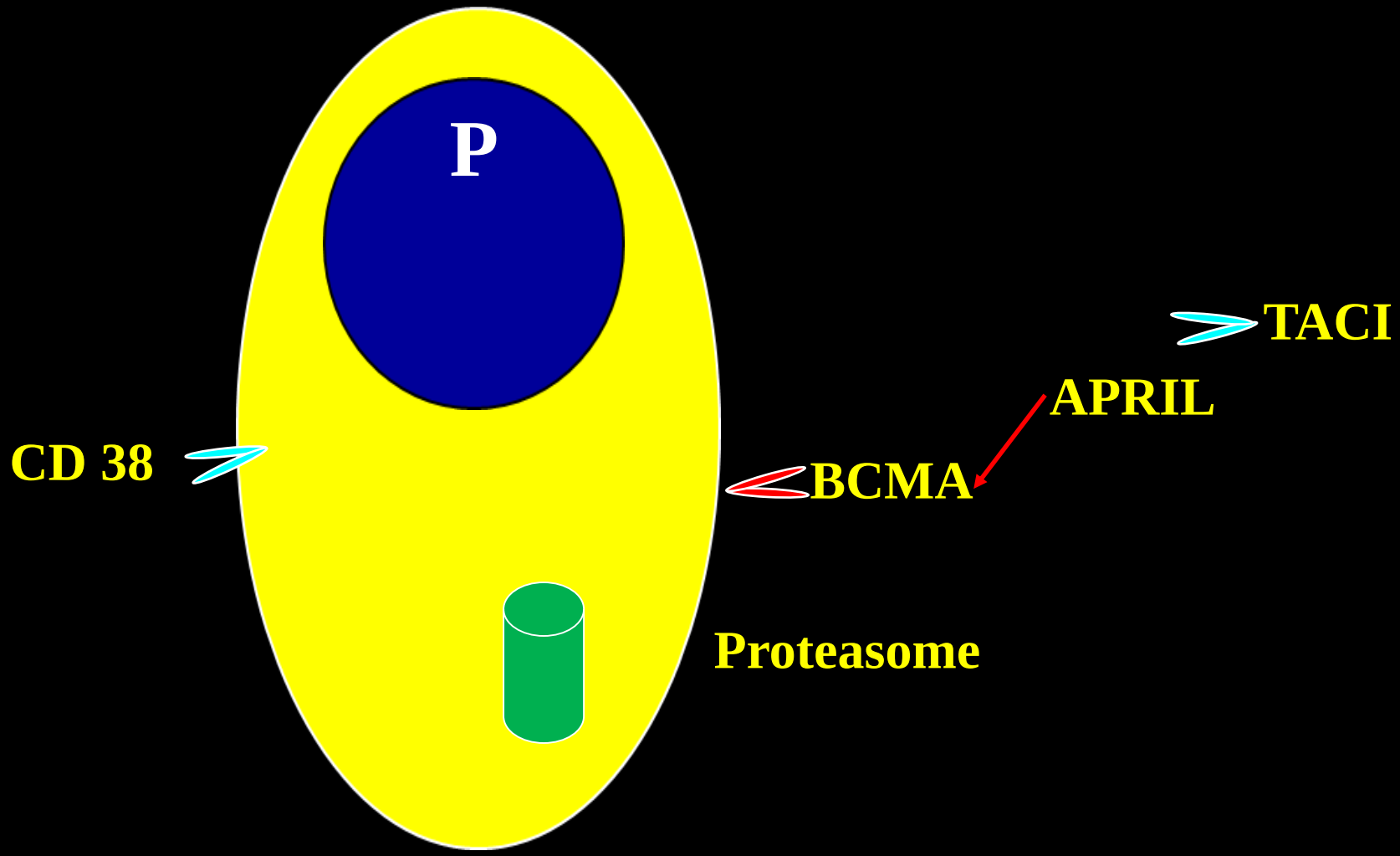
Drug Development Strategies

Treatment strategies:

- Immunologic approaches
- Novel anticoagulants
- Novel anti-platelet agents


B Cell
Ab
CD 20
Ab
CD 80
CD 86
B
BLyS R
BLyS
TACI
TACI
APRIL
MHC II
Ag
BCMA
CD40
LFA-3
CD 22

Plasma Cell-Directed Therapies



B- and Plasma-Cell Targeted Therapy

- LJP 1082 (domain I β2GPI)[1]
  - ~10% reduction in IgG β2GPI Ab
- Rituximab (RITAPS[2])
  - Rare normalization of aPL Ab
- Belimumab
  - ~30% aCL Ab reduction (vs ~20% PL)[3]
  - ~55% GPL pos converted to neg (vs. 40% PL)
- Plasma cell targets
  - Proteasome inhibition
  - Antibodies to CD 38

[1]Horizon A et al. Arthritis Rheum 2003; [2]Erkan D Arthritis Rheum 2013; [3]Stohl W et al. Arthritis Rheum 2012

DOACS

- Direct thrombin inhibitors
- Direct Xa inhibitors
  - 8 APS patients failed rivaroxaban (5 arterial thrombosis)[1]
  - RAPS (Rivaroxaban in AntiPhospholipid Syndrome)[2]
    - PD endpoint: Endogenous Thrombin Potential (ETP)
    - Rivaroxaban did not reach the non-inferiority threshold
    - No thrombotic events among the 110 patients
  - ASTRO-APS: Apixaban for the Secondary Prevention of Thromboembolism Among Patients with the Antiphospholipid Syndrome: arterial thromboses
  - TRAPS[3]

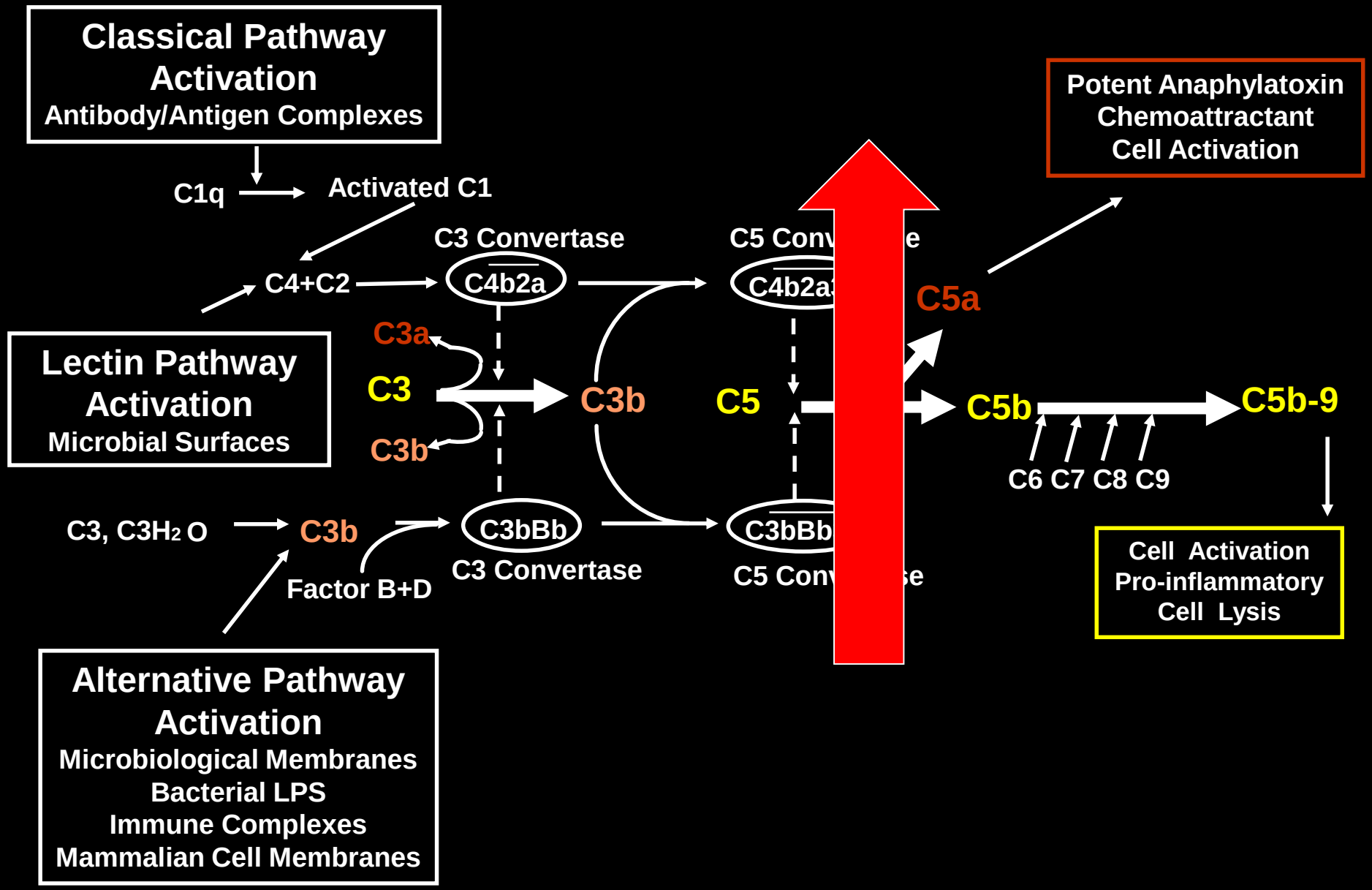
[1]Signorelli F et al. Clin Rheumatol 2015; [2]Cohen H et al. Lancet Haematol 2016; [3]Pengo V et al. Blood 2018

Other Novel Approaches

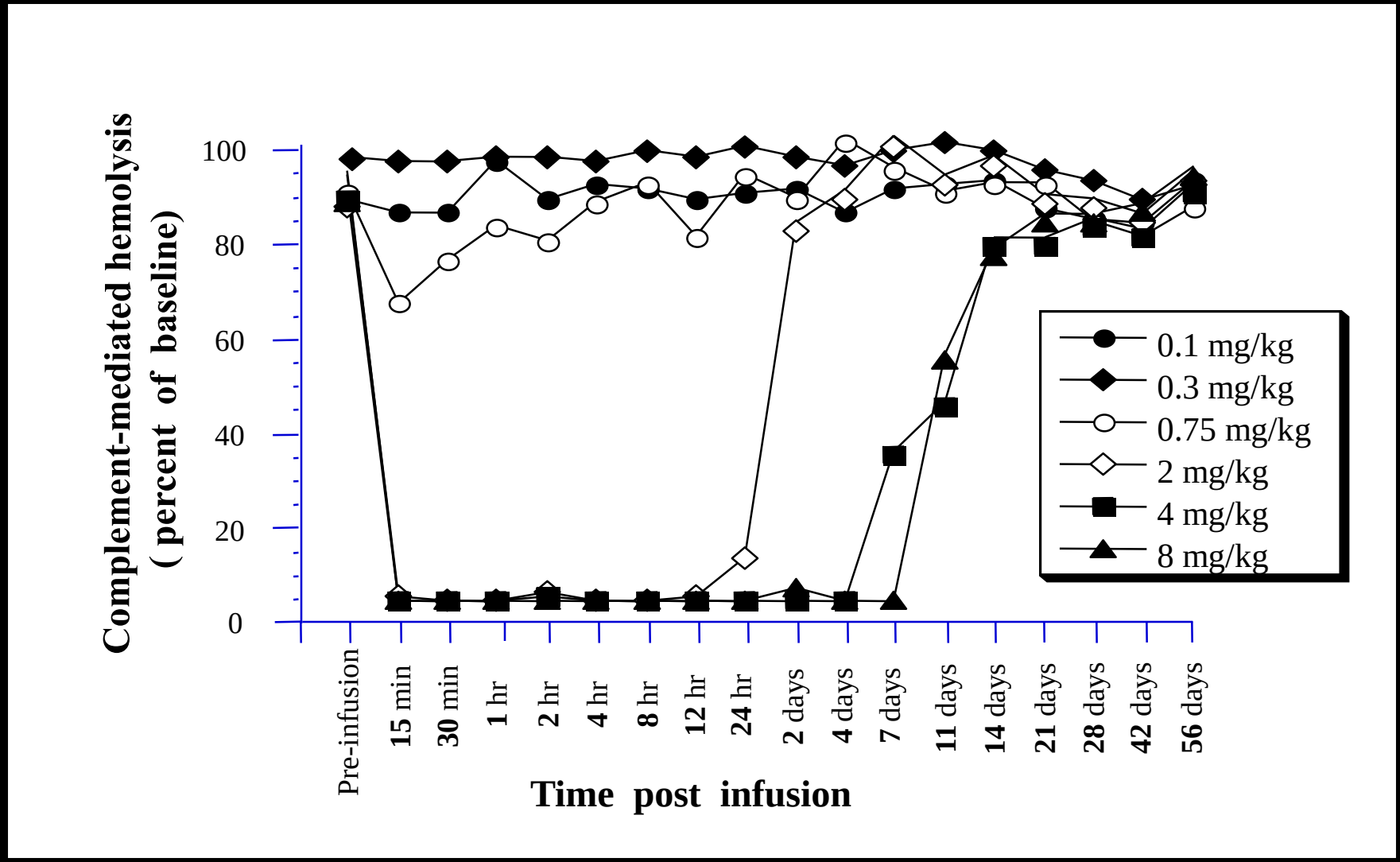
- Hydroxychloroquine[1,2]
- Eculizumab approved for PNH, aHUS, MG
    - Off-label use in APS and/or SLE (10 cases)[3]
        - Thrombosis refractory to anticoagulation
        - TMA

[1]Petri M Curr Rheumatol Rep 2011; [2]Rand JH et al. Blood. 2010;
[3]Kello N, El-Khoury L et al. submitted

Complement Activation



Eculizumab Pharmacodynamics



Furie R et al Innovative Therapies 2001

Challenges to Clinical Research

1. Thrombosis event rate off therapy is low (<5%)
2. Thrombosis event rate on therapy is very low
3. Medicolegal aspects of studying pregnancy
    - Certolizumab in APS
4. Would autoantibody be accepted as a surrogate?
    - What % reduction is protective?
    - Subpart H and E FDA code
5. Is APS an orphan disease?
    - What is the prevalence of APS?

Treatment Needs

- Primary prevention
- Safe and convenient secondary prevention
- Warfarin refractory patients
- CAPS
- Obstetrical complications

Thank you