

POLYARTERITIS NODOSA

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XXIII.

Ueber eine bisher nicht beschriebene eigenthümliche Arterien-
erkrankung (Periarteritis nodosa), die mit Morbus Brightii
und rapid fortschreitender allgemeiner Muskellähmung
einhergeht.

Von

Prof. A. Kussmaul und R. Maier

in Freiburg i. Br.

***DEFINITION
AND CLASSIFICATION***

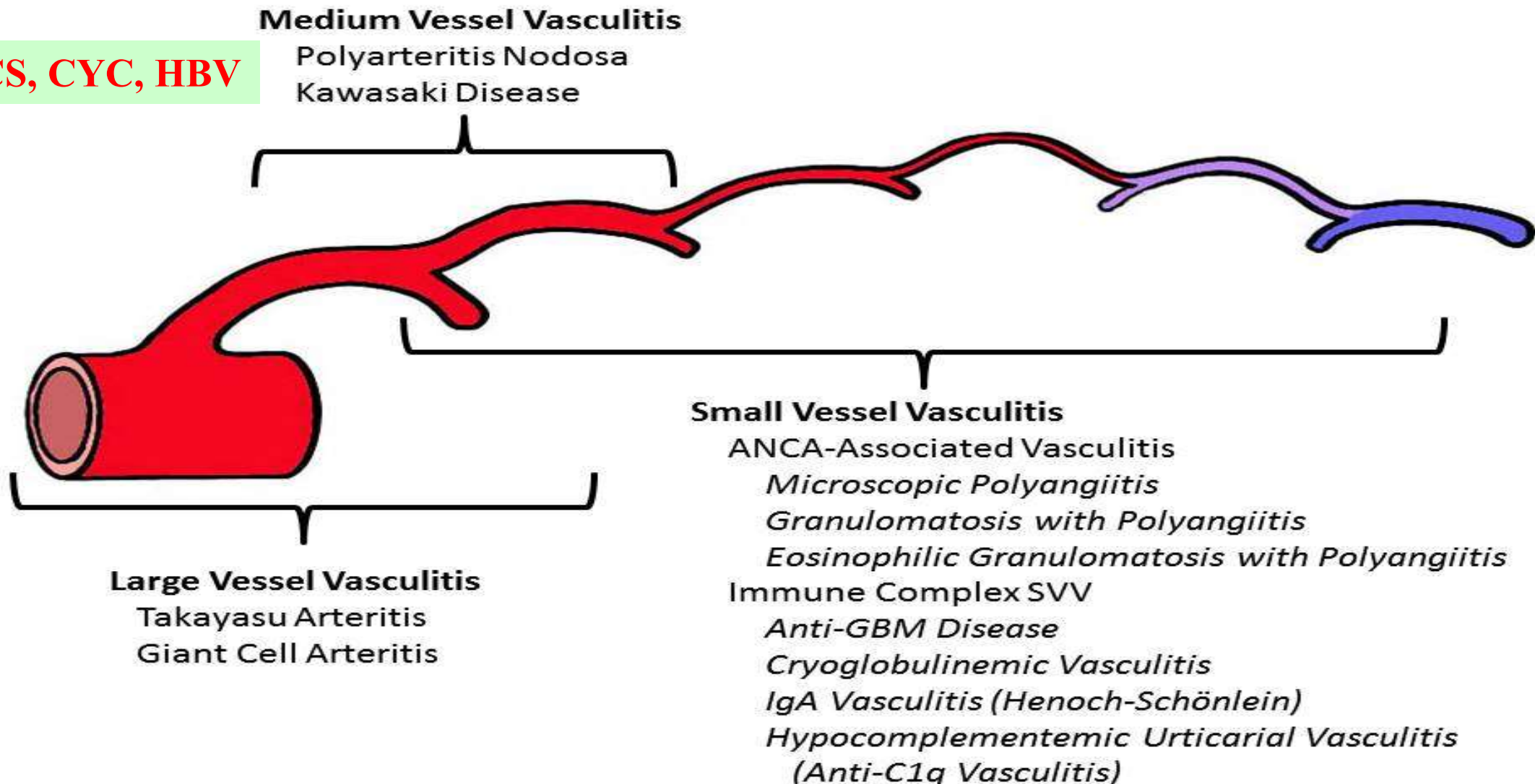
PAN : 1990 ACR CRITERIA

- ✓ Weight loss < 4kg
- ✓ Livedo reticularis
- ✓ Testicular pain or tenderness
- ✓ Mono- or polyneuropathy
- ✓ Diastolic BP > 90 mm Hg
- ✓ Elevated BUN or creatininemia
- ✓ Hepatitis B virus
- ✓ Biopsy of small or medium-sized artery containing PMN

3 of 10 criteria should be present to classify as PAN

THE CHAPEL HILL NOMENCLATURE

CS, CYC, HBV



PAN : DIAGNOSTIC CRITERIA

POSITIVE CRITERIA	
	HBV (viral DNA)
	Mononeuritis multiplex
	Microaneurysms (angiography)
NEGATIVE CRITERIA	
	ANCA positivity
	Asthma
	Glomerulonephritis
	ENT symptoms
	Cryoglobulinemia

Henegar, Arthritis Rheum. 2008: 58, 1528

EPIDEMIOLOGY

ETIOLOGIES

EPIDEMIOLOGY

- ✓ Incidence: 0.7/100 000 h
- ✓ Prevalence : 6.3/100 000 h

(Scott and Bacon, 1982)

□ **Prevalence in France 34,8/1 000 000/h**
(Mahr, 2002)

✓ Incidence decreased concomittently with HBV vaccination and hygienic measures but recently, PAN without HBV infection, is increasing again

OTHER VIRAL INFECTION IN PAN

- ✓ HBV +++
- ✓ HCV (exceptionnal if it exists) ???
- ✓ HIV (rare < 1%)
- ✓ Co-infections HIV/HCV/HBV
- ✓ Parvovirus B19
- ✓ EBV

ORIGINAL ARTICLE

Mutant Adenosine Deaminase 2
in a Polyarteritis Nodosa Vasculopathy

CECR1 gene mutation

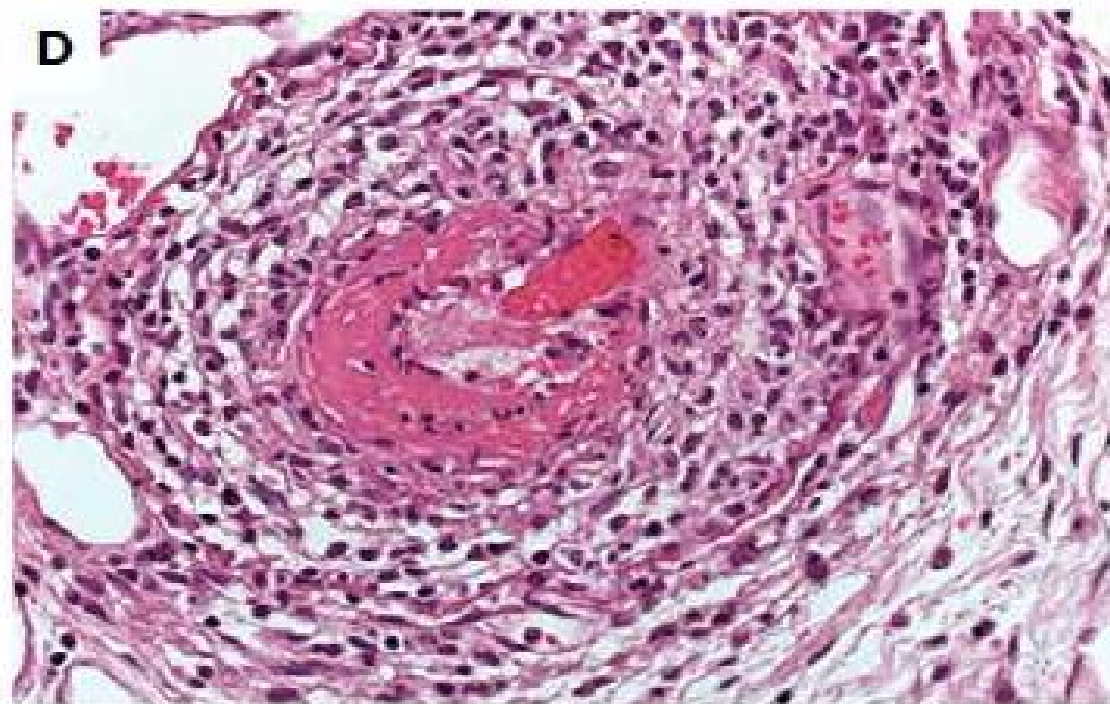
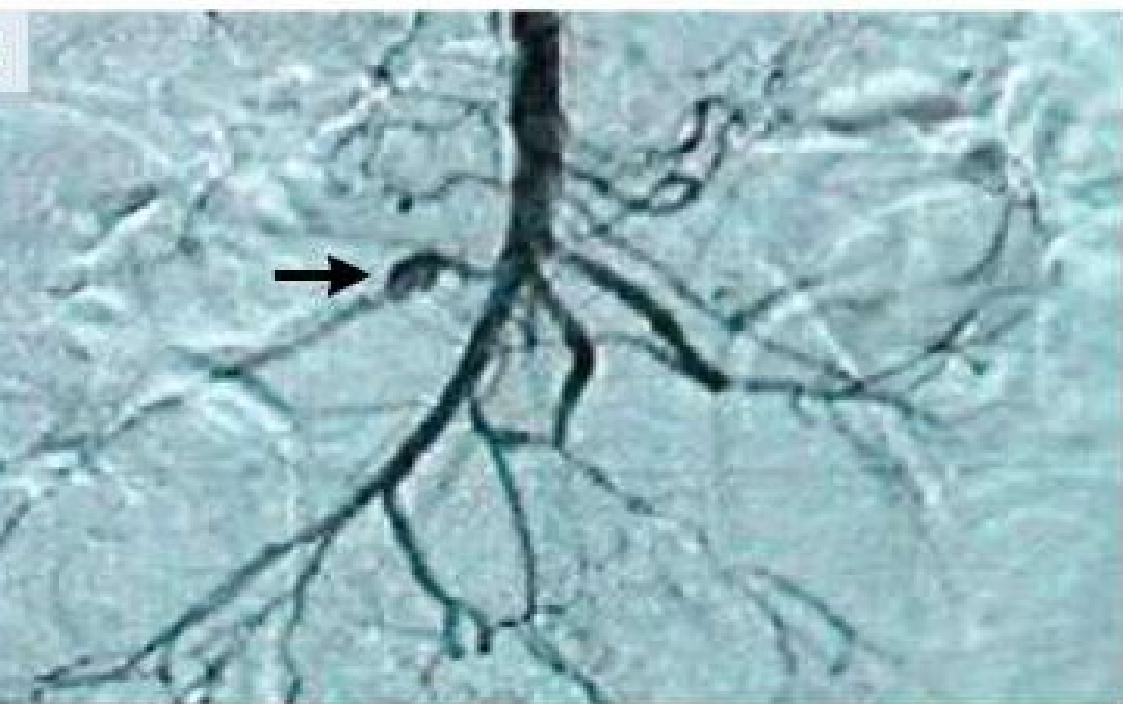
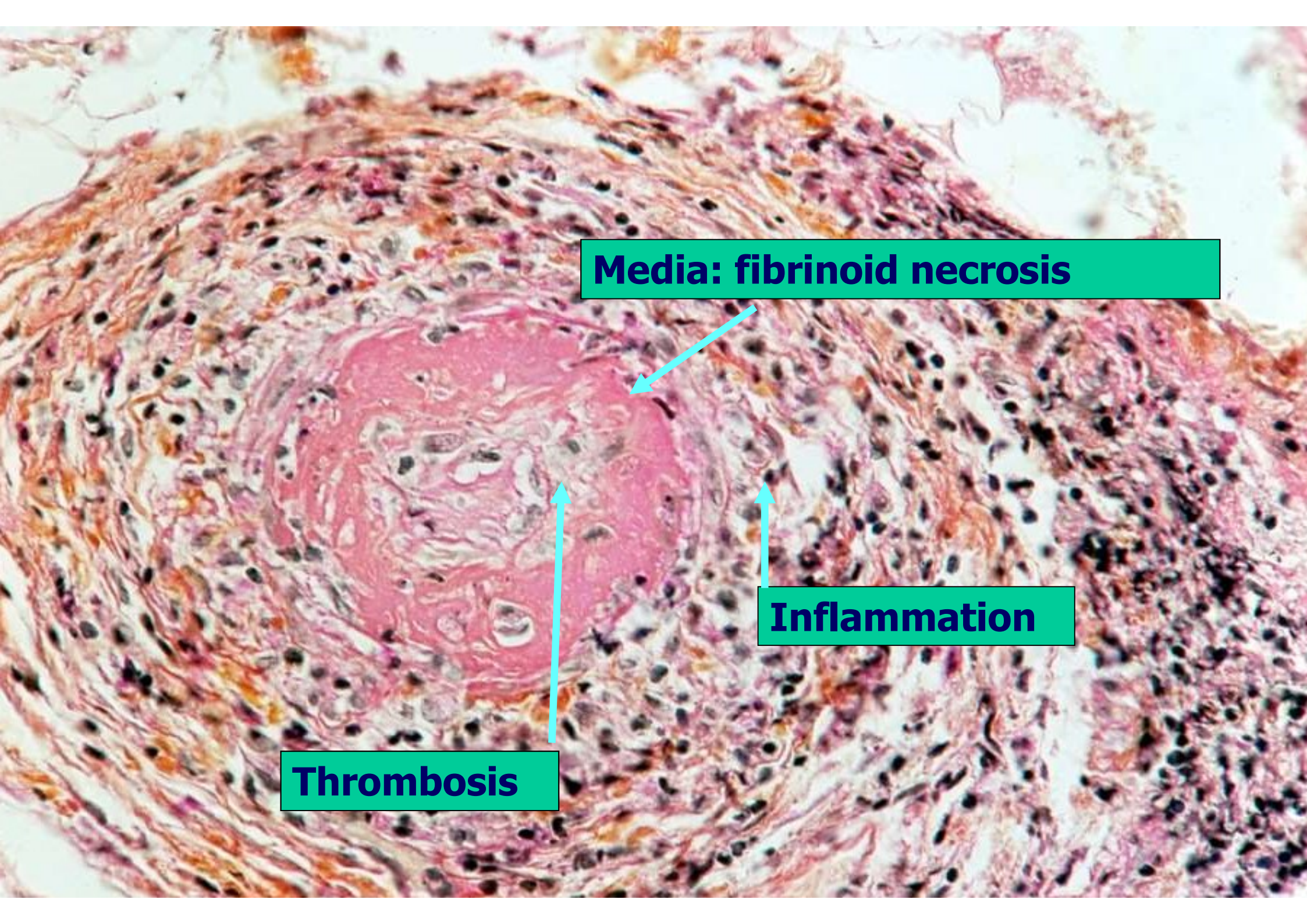


Figure 1. Clinical Features of Polyarteritis Nodosa Associated with Adenosine Deaminase 2 (ADA2) Mutations.

PATHOLOGY

PATHOLOGY

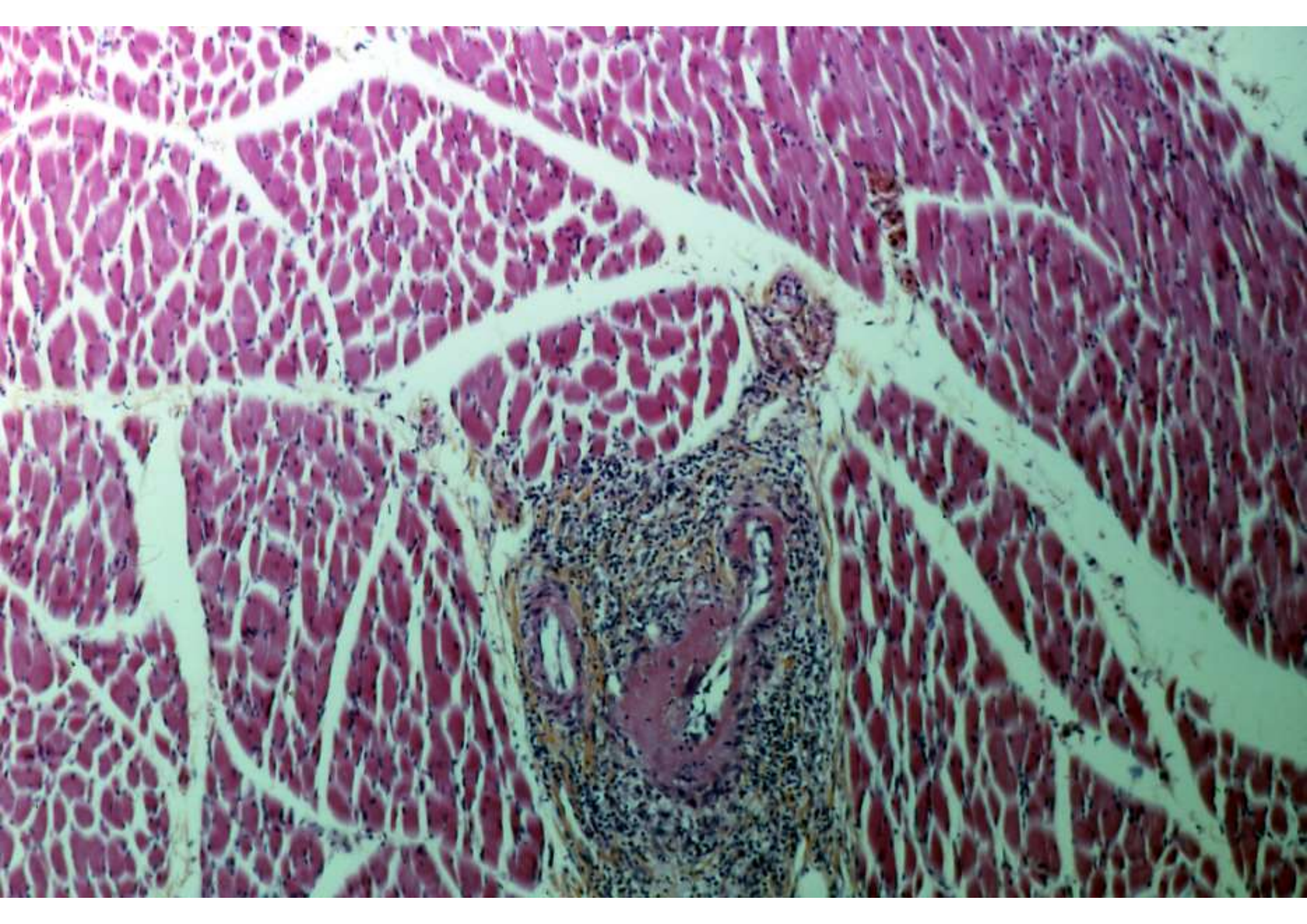
- ✓ Panarteritis
 - ✓ fibrinoid necrosis of the media
 - ✓ cells (inflammation in the adventitia)
 - ✓ intimal proliferation
- ✓ Lesions at different stages of inflammation
- ✓ Evolution : vessels fibrosis

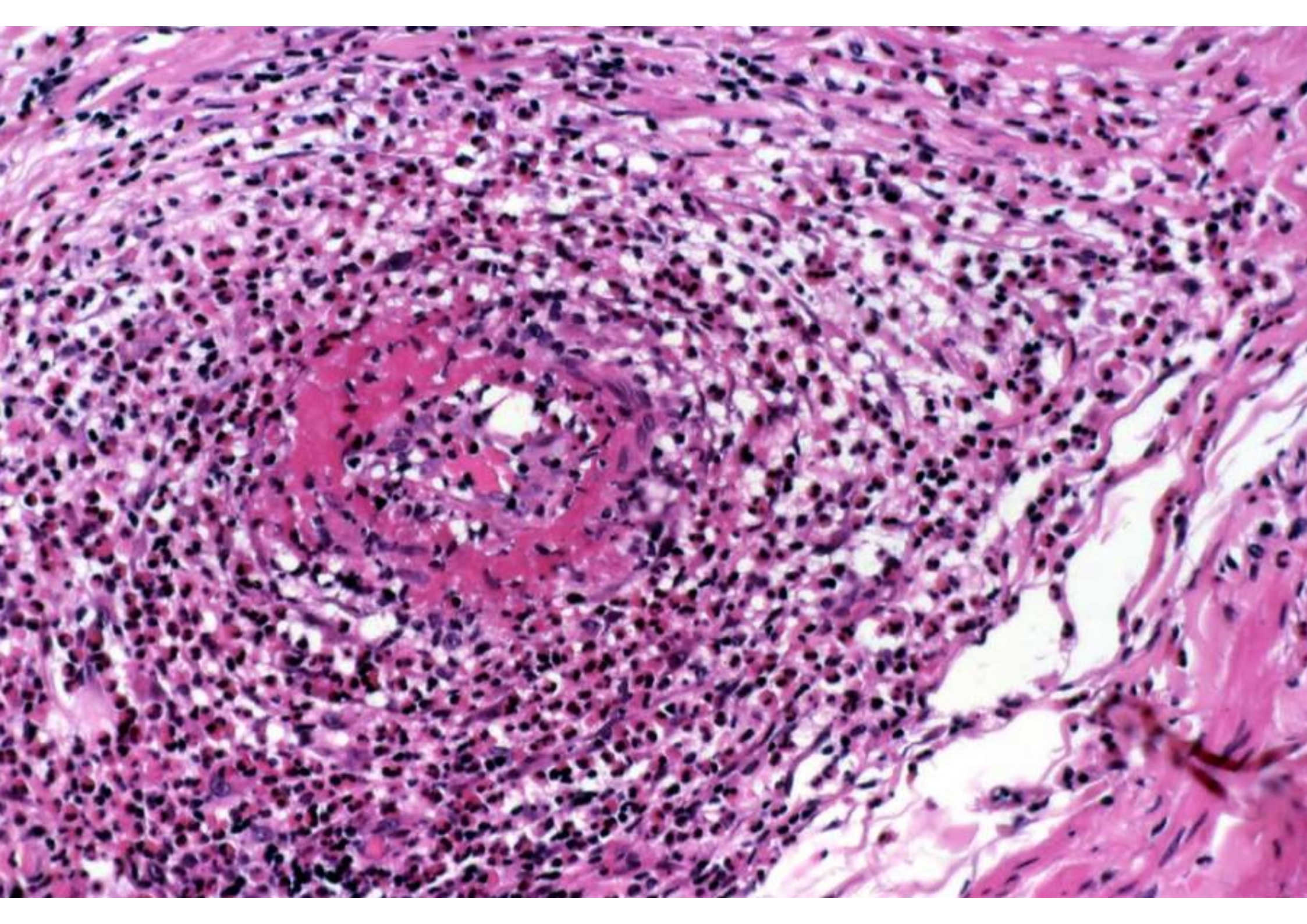


Media: fibrinoid necrosis

Inflammation

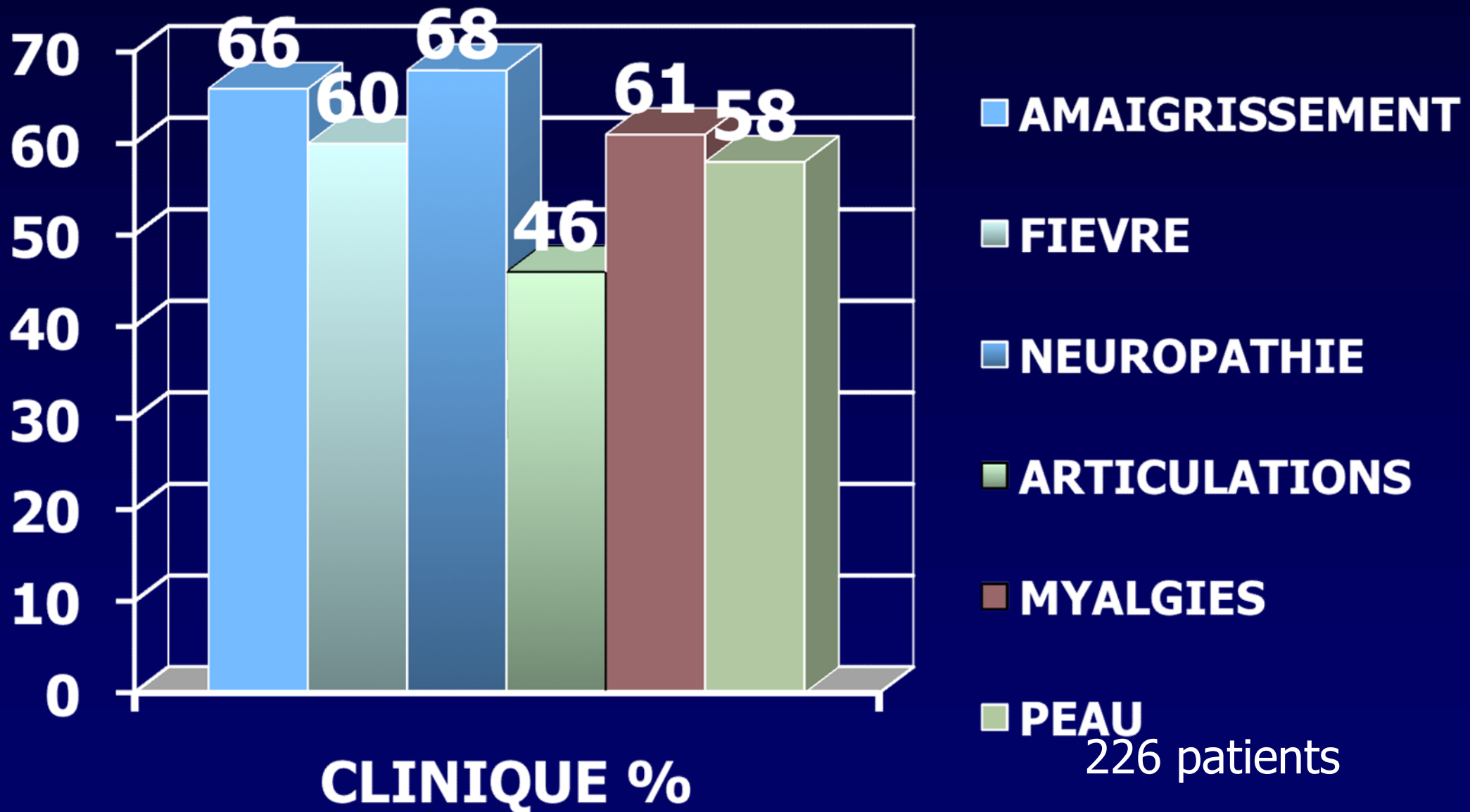
Thrombosis



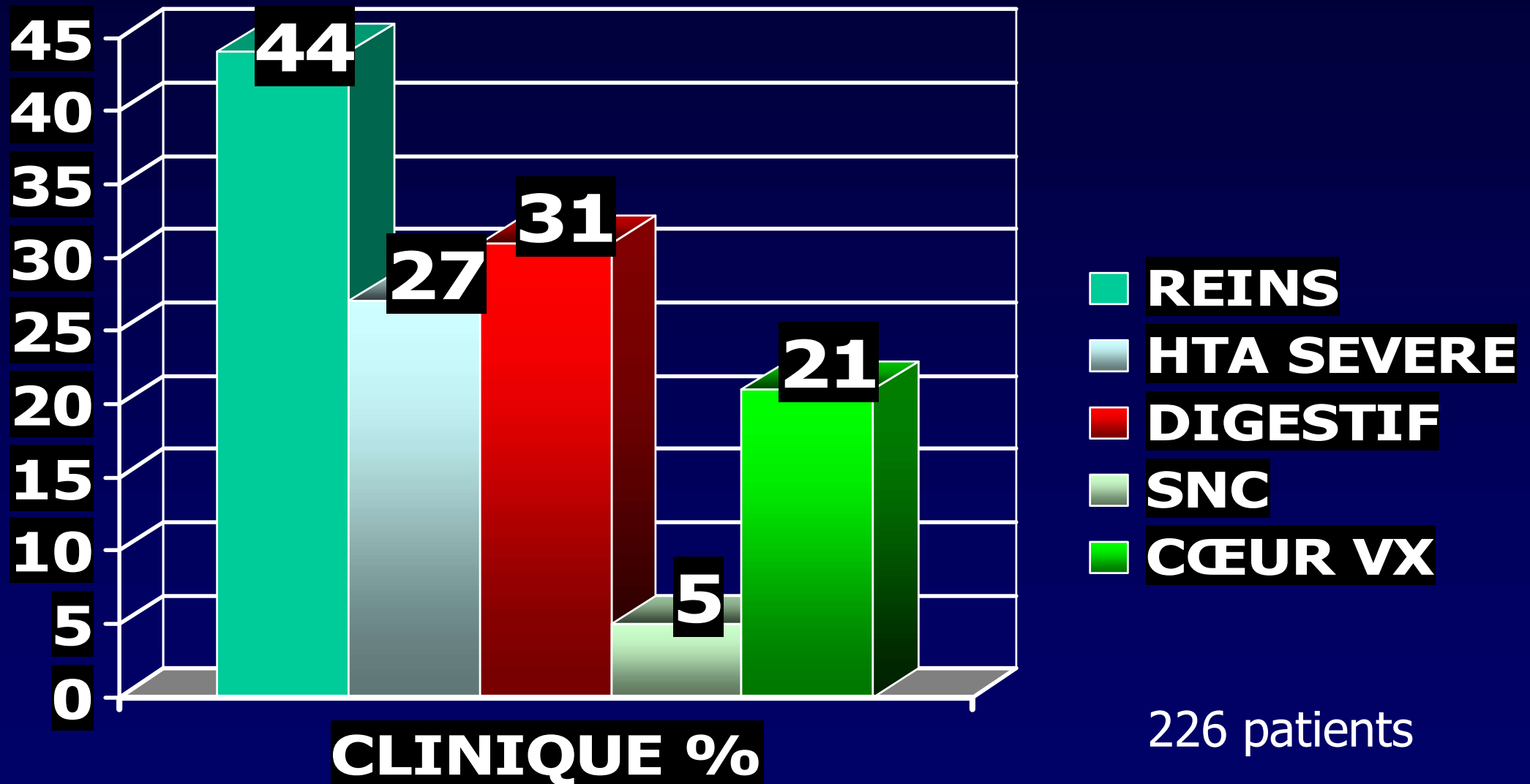


CLINICAL SYMPTOMS

PAN WITHOUT HBV INFECTION



PAN WITHOUT HBV INFECTION



CLINICAL MANIFESTATIONS

Skin

- ✓ Subcutaneous nodules
- ✓ Vascular purpura
- ✓ Ulcers
- ✓ Gangrene
- ✓ Livedo

CLINICAL MANIFESTATIONS



CLINICAL MANIFESTATIONS

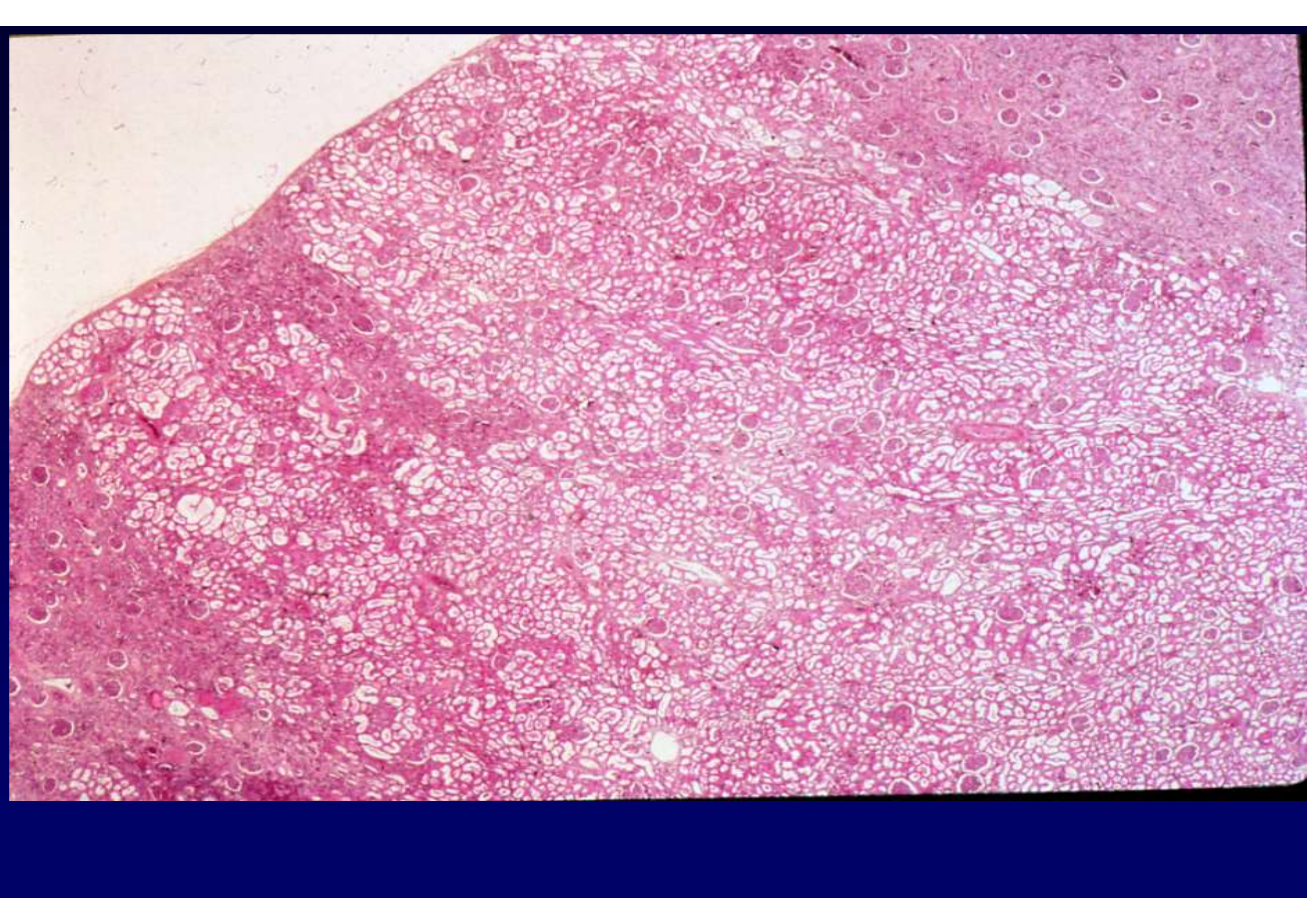
Peripheral neuropathy

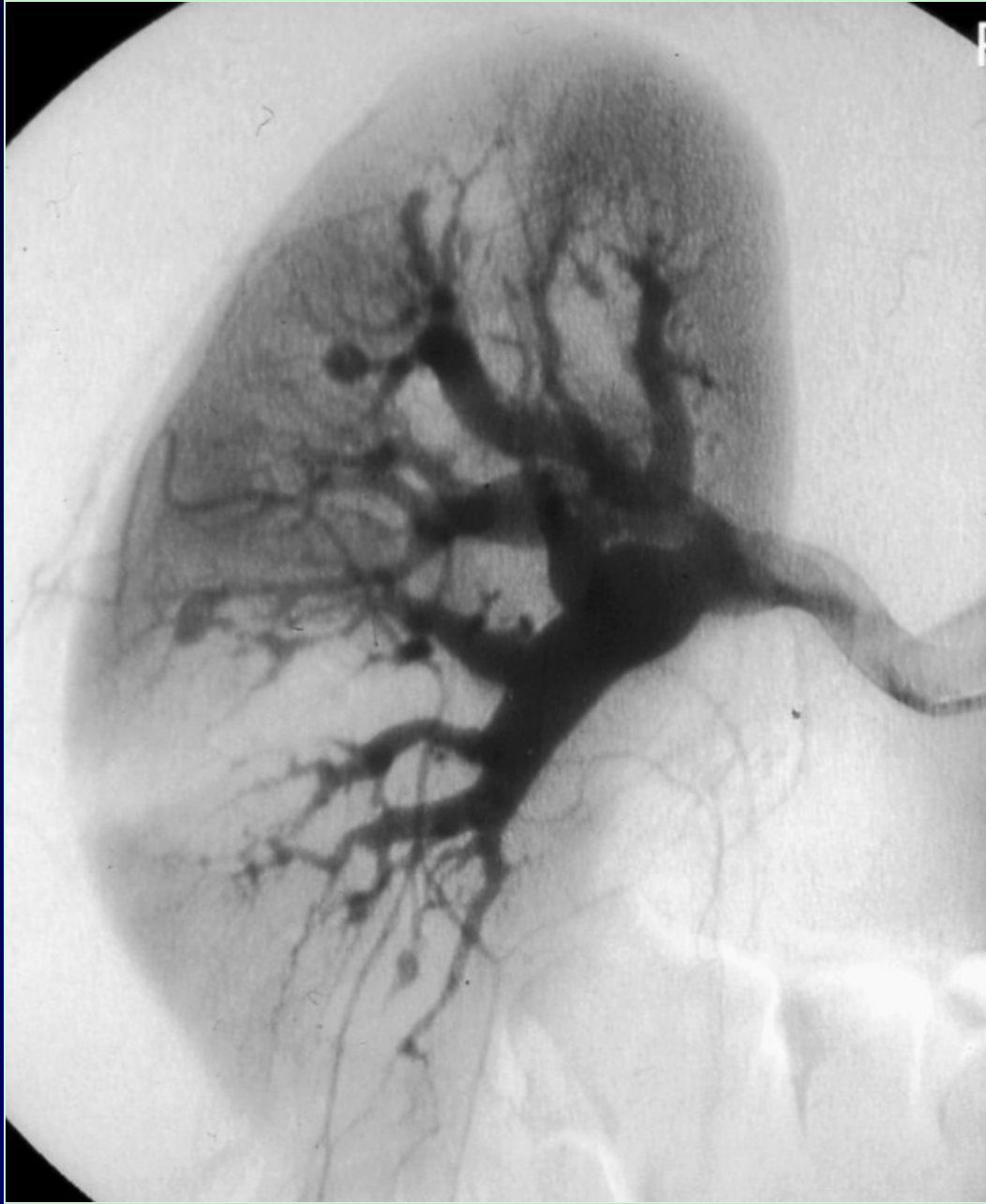
- ✓ Mononeuritis multiplex
 - ✓ SPE et SPI
 - ✓ Sensory motor
 - ✓ rarely: cubital, radial, median
 - ✓ more rare: VII, VIII, III, VI,
- Plexic involvement, neurological bladder

CLINICAL MANIFESTATIONS

Kidneys

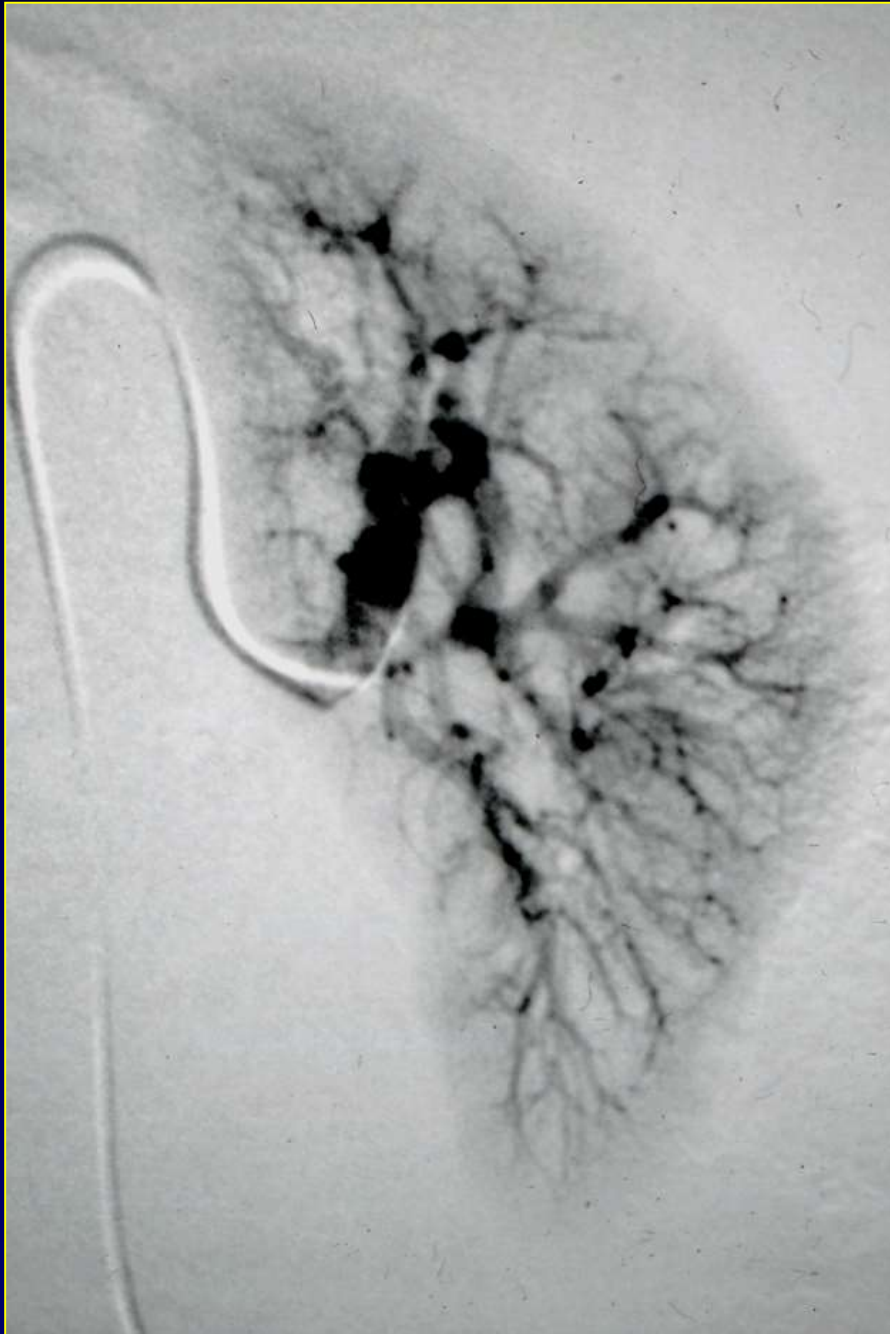
- ✓ Vascular nephropathy
- ✓ Renal infarcts
- ✓ HBP, renin-dependant
- ✓ NO glomerulonephritis







Renal infarcts



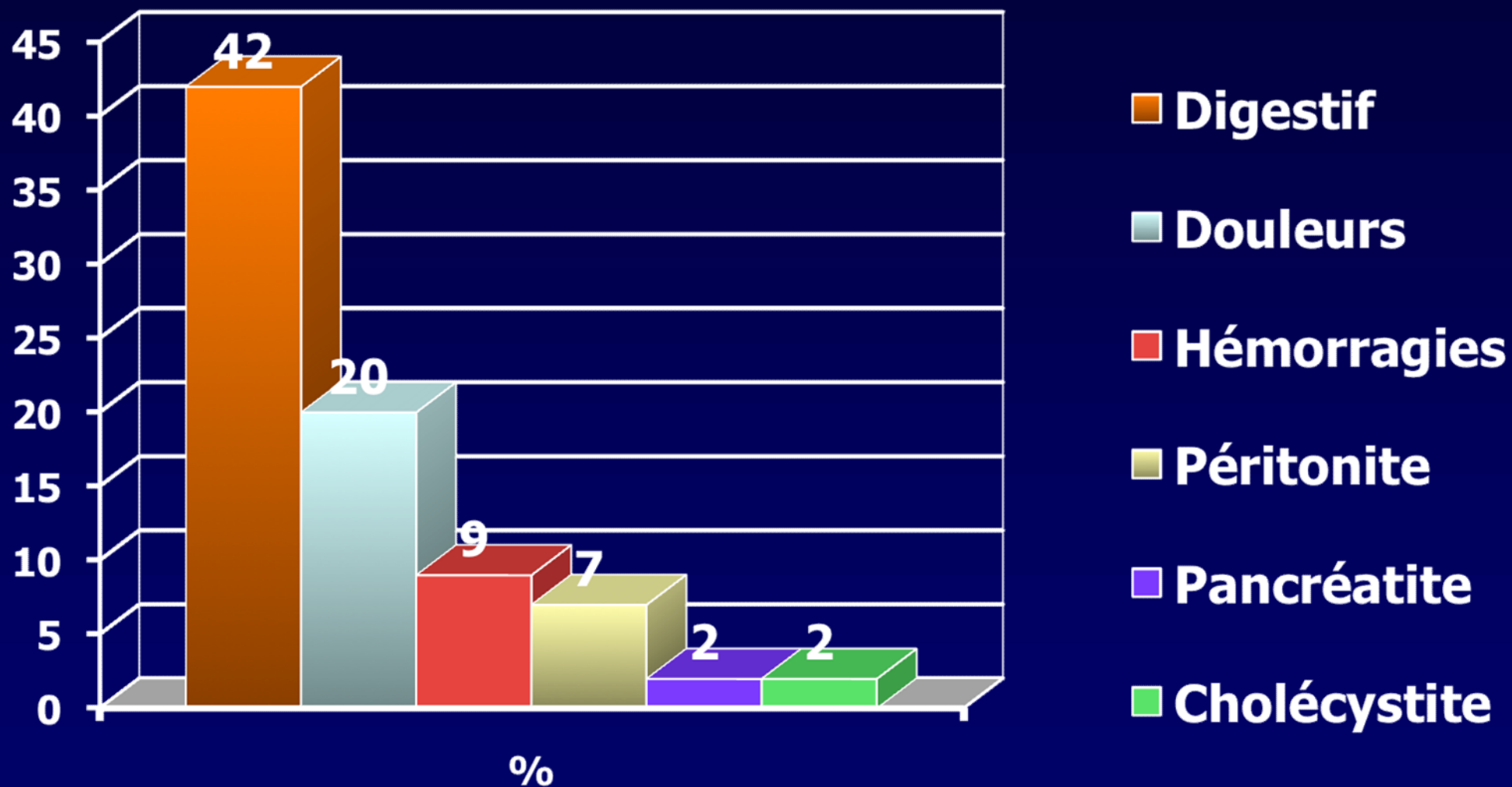
Aneurysms can be
Seen easily during
the washout period
of arterial angiogram

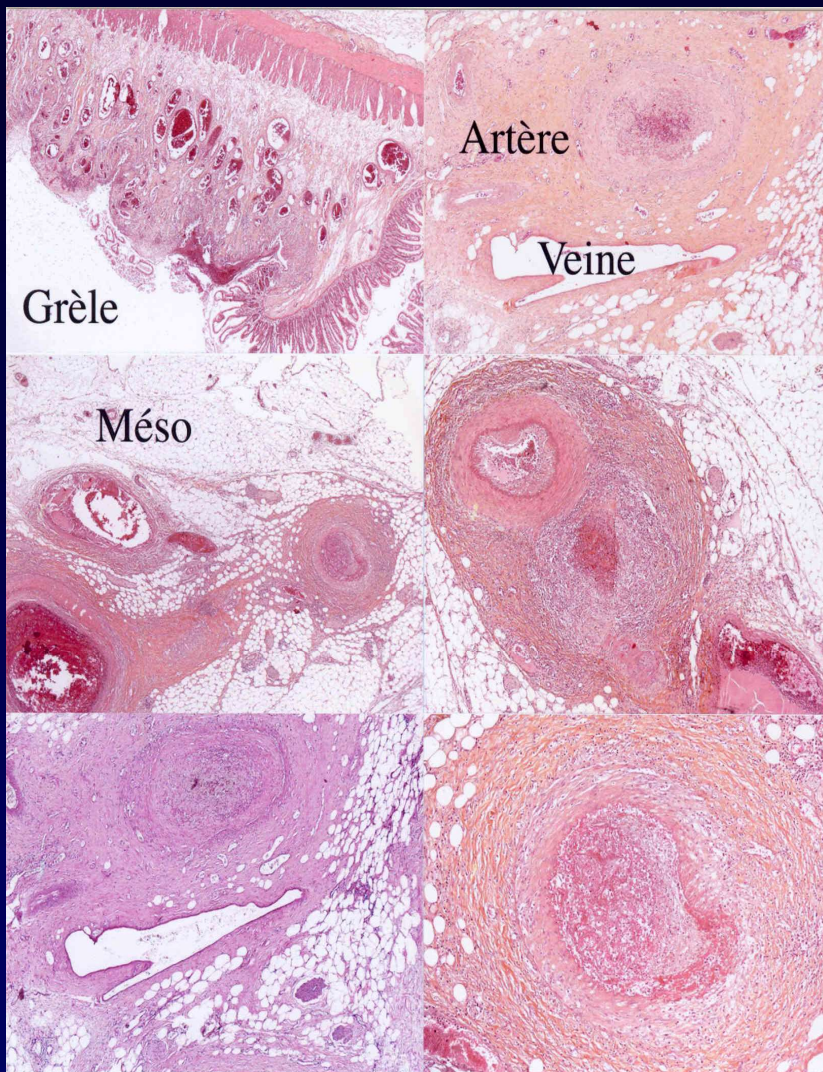
CLINICAL MANIFESTATIONS

Orchitis

- ✓ Testicle or epididymal ischemia
- ✓ No infection
- ✓ More frequent when HBV is present

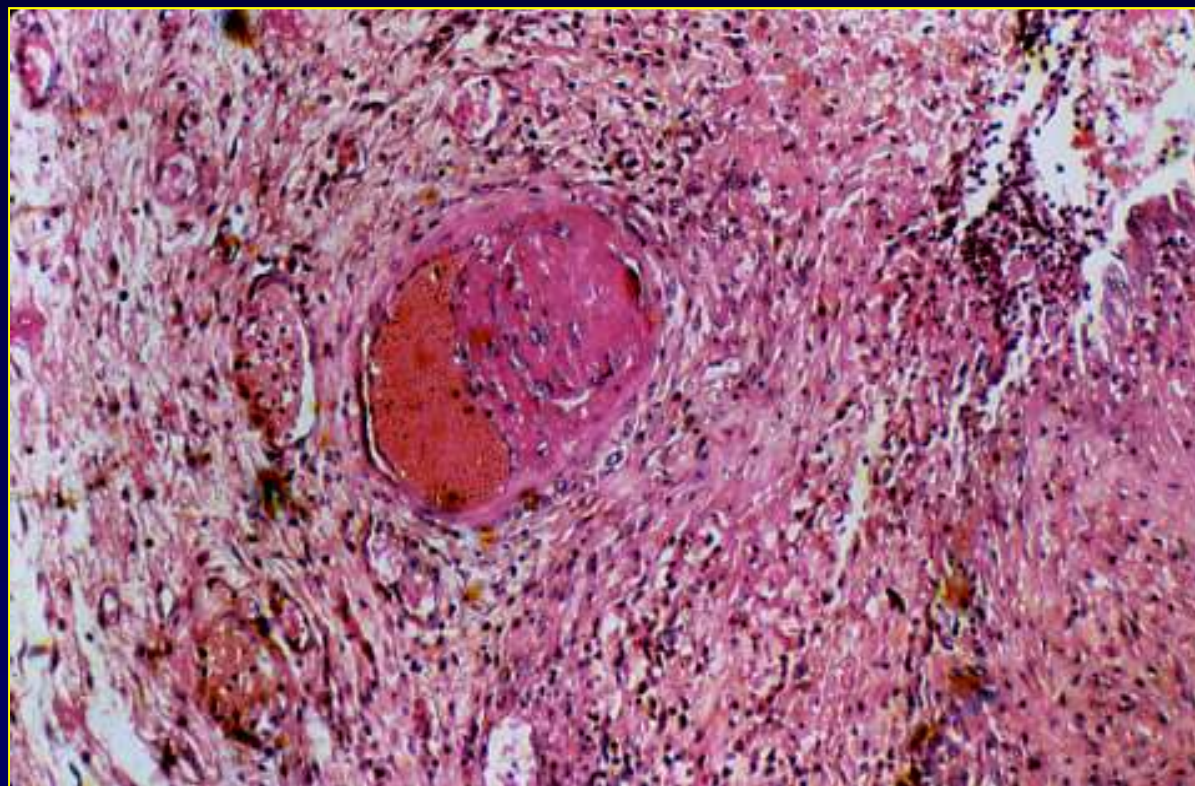
GI VASCULITIS





Anapath Mme Z... Sophie
Grêle + mésos

Centre Hospitalier Châlons en Champagne
Réanimation Dr J-M Korach/ Laboratoire d'Anapath Dr A. Roth

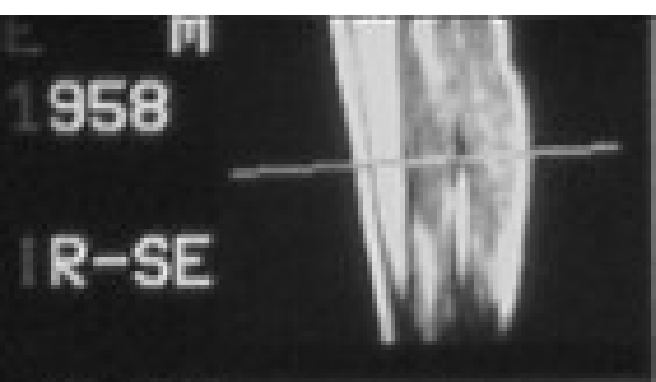


INVESTIGATIONS

- ✓ Endoscopy
- ✓ Abdominal CT scan
- ✓ Angiography
- ✓ Immunology: negative
- ✓ Surgery
- ✓ Biopsies

RARE MANIFESTATIONS

- ✓ Muscle
- ✓ Periosteum



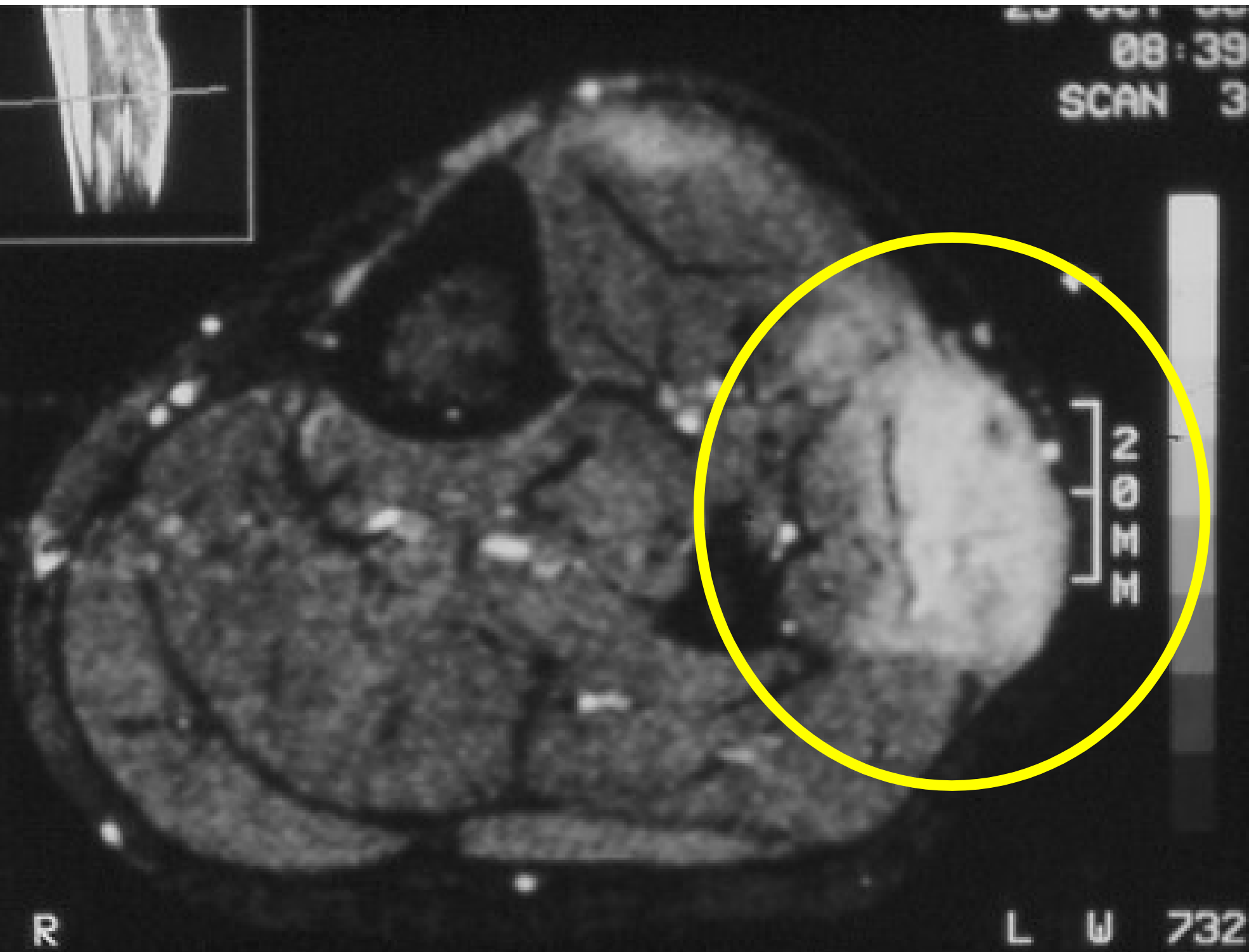
08:39
SCAN 3

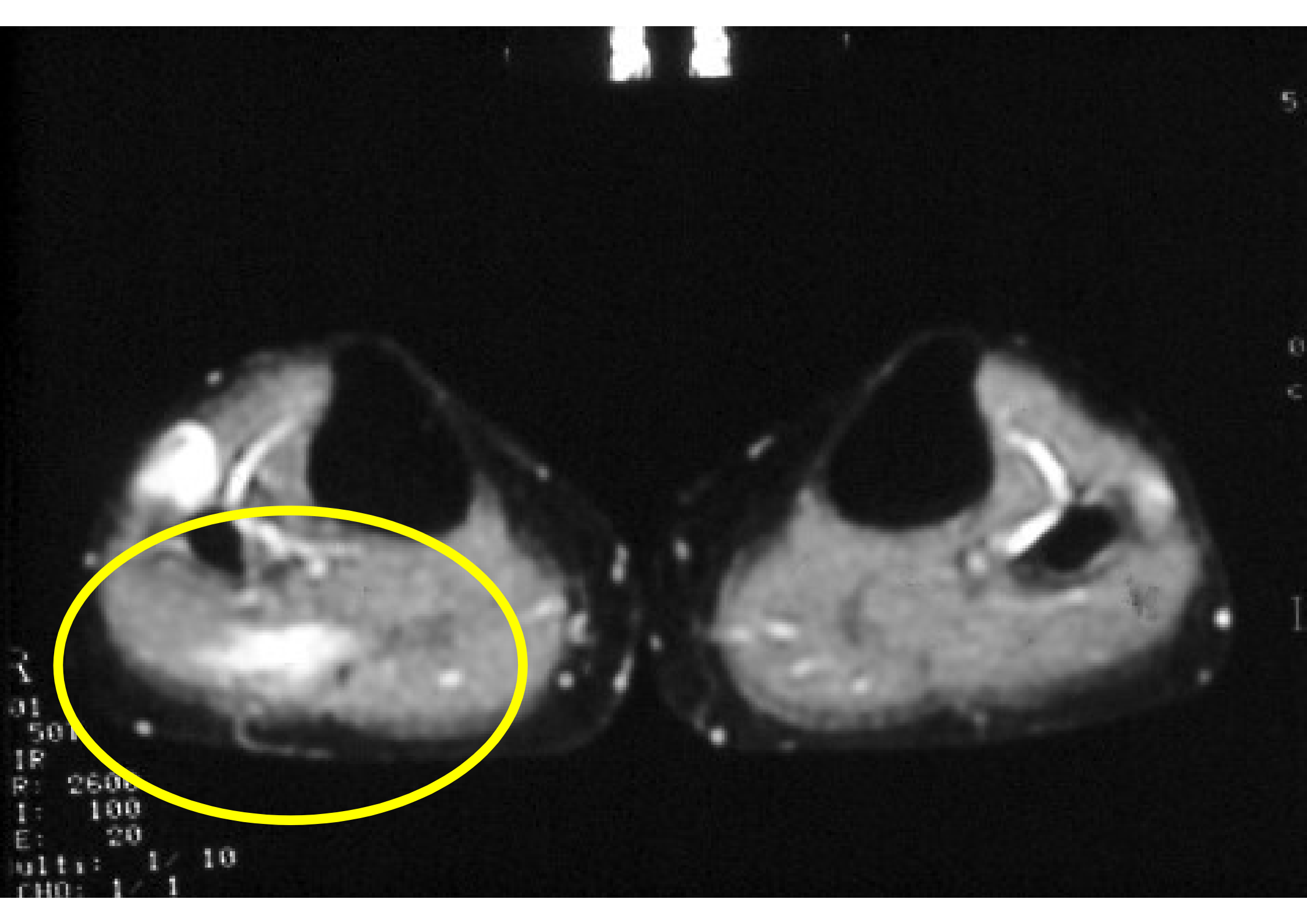
3:57

M
790
30

120

30/1.4
0/ 1.0
8/ 15
-28.5
-4.9





3
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R: 2600
I: 100
E: 20
ult: 1/ 10
CHO: 1/ 1

LABORATORY INVESTIGATIONS

- ✓ Non specific inflammation
- ✓ No inflammation in 20% of patients
- ✓ NO ANCA
- ✓ Eosinophilia (sometimes)
- ✓ Hematuria and proteinuria in some patients with renal infarcts

ANGIOGRAPHY

- ✓ Celiac, mesenteric and renal
- ✓ In patients with abdominal pain
- ✓ In patients with GI bleeding
- ✓ For a diagnostic purpose in case of unexplained weight loss
 - ✓ microaneurisms
 - ✓ Arterial stenoses

MICROANEURYSMS AND STENOSES

- ✓ Microaneurysms are the consequence of fibrinoid necrosis of a segment of arterial wall
- ✓ Stenoses and dilations are the consequence of segmental involvement of the vascular process



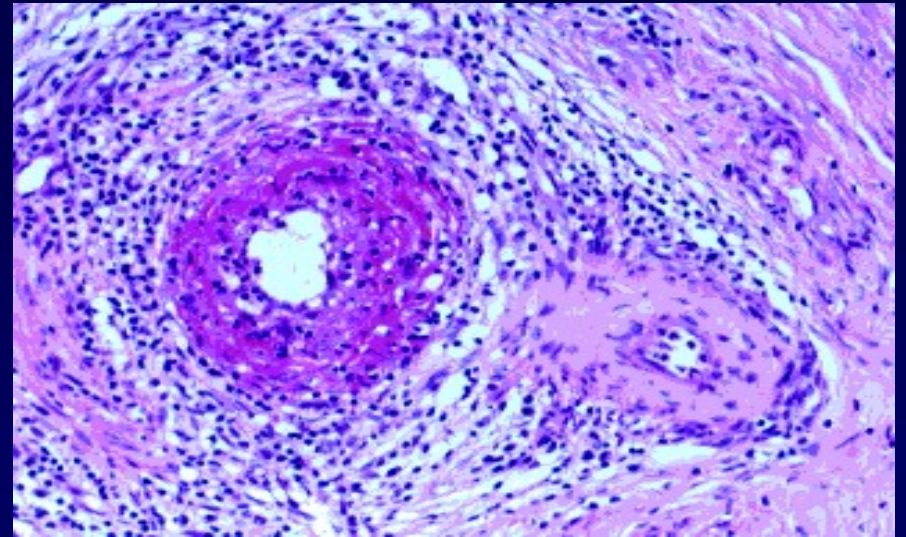
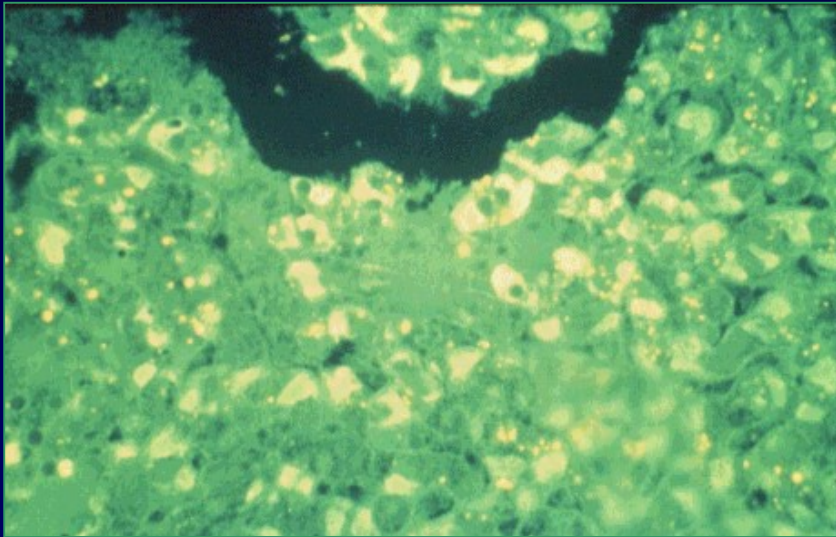


HBV-ASSOCIATED PAN

Hepatitis

HBV

PAN



HBV-RELATED POLYARTERITIS NODOSA

THE VIRUS

- ✓ DNA virus, Dane particle, 42 nm
- ✓ proteins and lipids envelope with HBS Ag (protein S, pre-S2 protein, pre S1 protein)
- ✓ the core: 27 nm, HBc and Hbe, comprising a double-strand DNA and DNA polymerase (reverse transcriptase activity)

HBV-RELATED POLYARTERITIS NODOSA

THE VIRUS

- ✓ responsible for viral hepatitis
- ✓ cirrhosis, liver carcinoma
- ✓ transmitted by blood, sexual contacts, saliva
- ✓ 0.1 - 0.2% in the US and in Northern-Europe
- ✓ 1 - 3% in Southern Europe, Japan, South-America, Russia
- ✓ 15% in Africa (tropical part), Asia

HBV-RELATED POLYARTERITIS NODOSA

HEPATITIS B VIRUS IN PAN

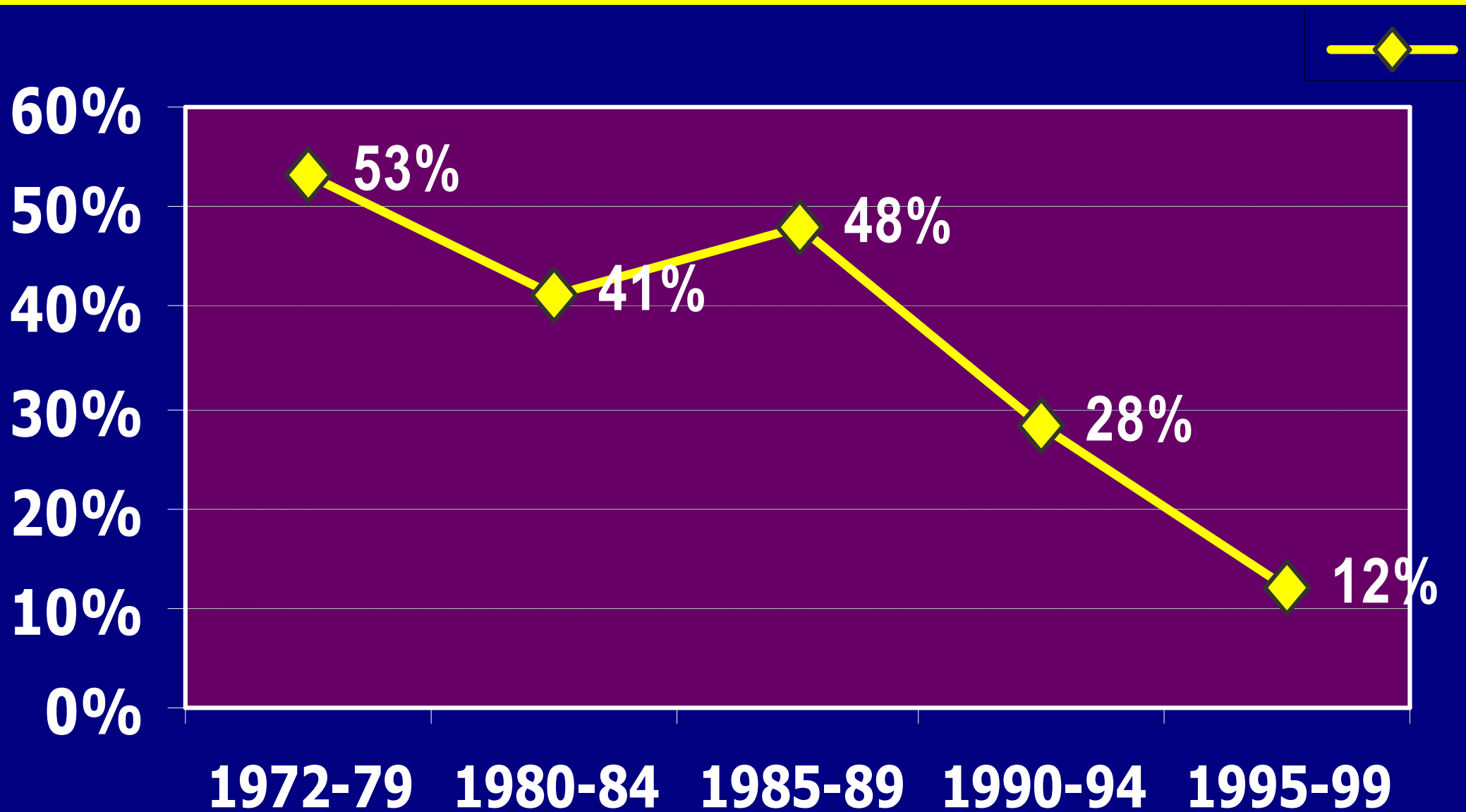
- ✓ A high mutation rate
- ✓ A higher replication level than in chronic hepatitis
- ✓ No universal mutation
- ✓ Generates more immune complex

HBV-RELATED POLYARTERITIS NODOSA

DEMOGRAPHY

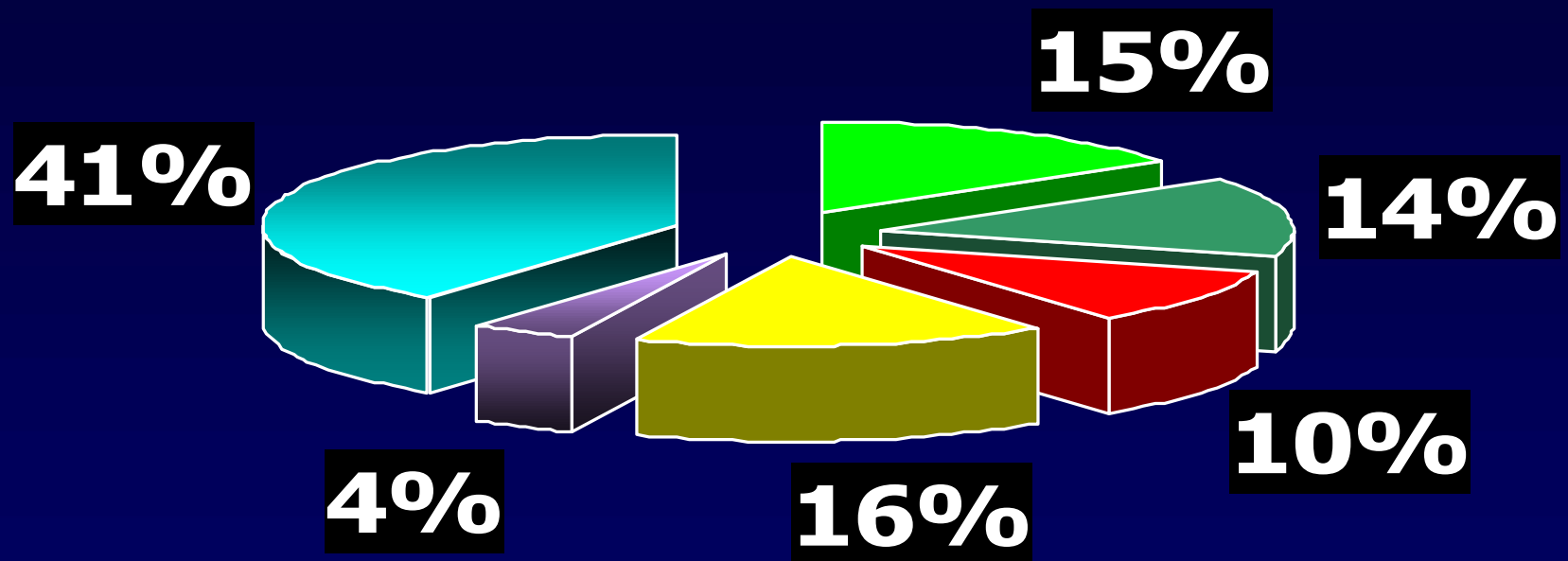
- ✓ 123 patients
- ✓ 83 men, 40 women
- ✓ mean age: 51.7 +/- 16 yr

FREQUENCY OF HBV-RELATED PAN: 1972 - 1999



HBV-RELATED POLYARTERITIS NODOSA

95 patients



 SEXUAL	 IV DRUGS	 TRANSFUSION
 SURGERY ?	 OTHERS ?	 UNKNOWN

HBV-RELATED POLYARTERITIS NODOSA

CONTAMINATION

- ✓ *Identified in 37/95 patients*
- ✓ sexual contamination: 14
 - ✓ heterosexual: 9
 - ✓ homosexual: 5
- ✓ IV drug abuse: 13
- ✓ transfusion: 10
- ✓ *Suspected in 19*
 - ✓ surgery: 15
 - ✓ miscellaneous: 4

HBV-RELATED POLYARTERITIS NODOSA

INCUBATION

- ✓ *Time between infection and PAN*
 - ✓ 405 +/- 519 days
 - ✓ in 7/10 patients, the interval was less than 1 year
- ✓ *Hepatitis was identified in 37 patients*
 - ✓ in 5 patients PAN occurred at the time or immediately after hepatitis

HBV-RELATED POLYARTERITIS NODOSA

CO INFECTION

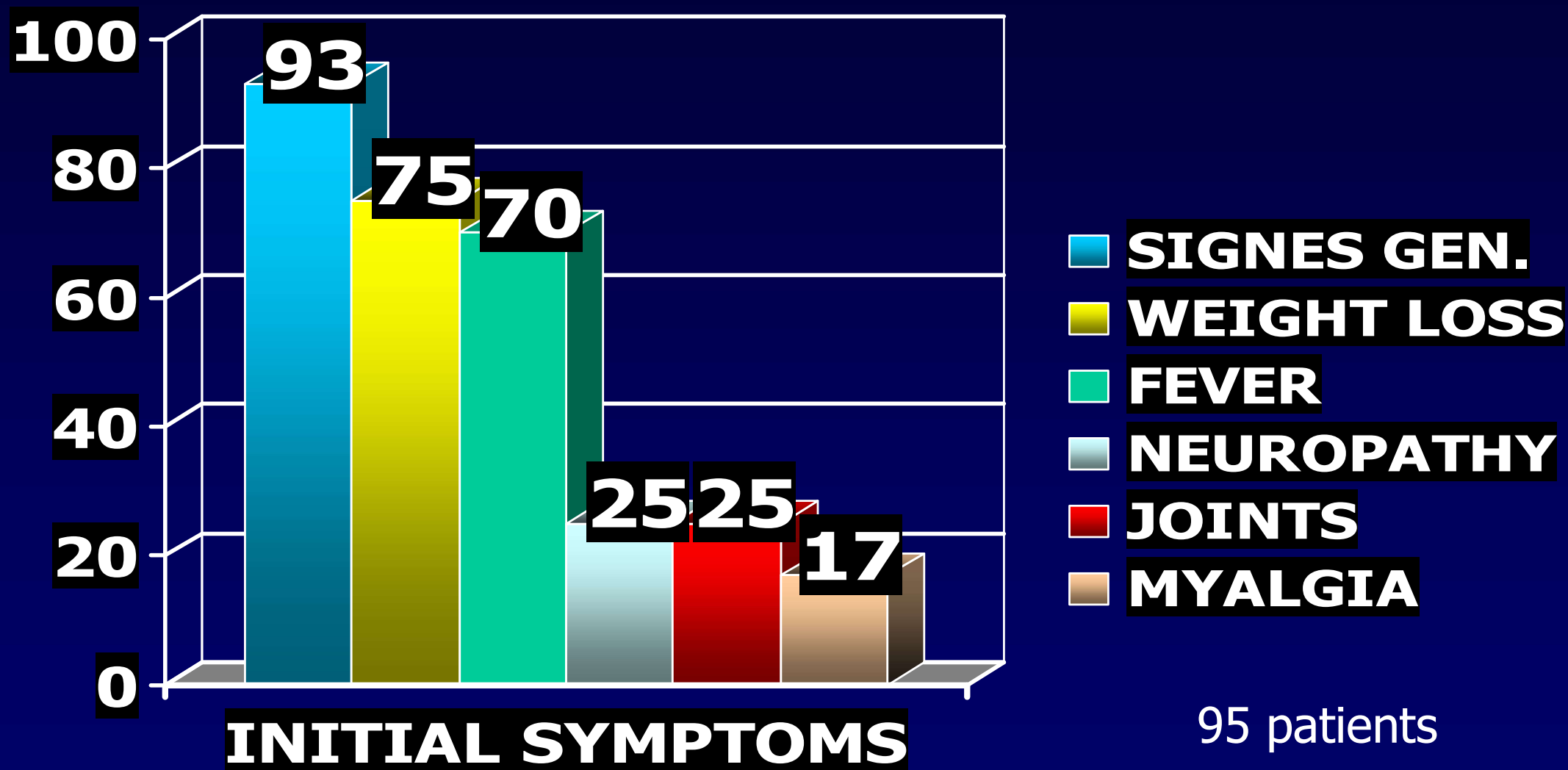
✓ *HCV*

- ✓ 4 patients

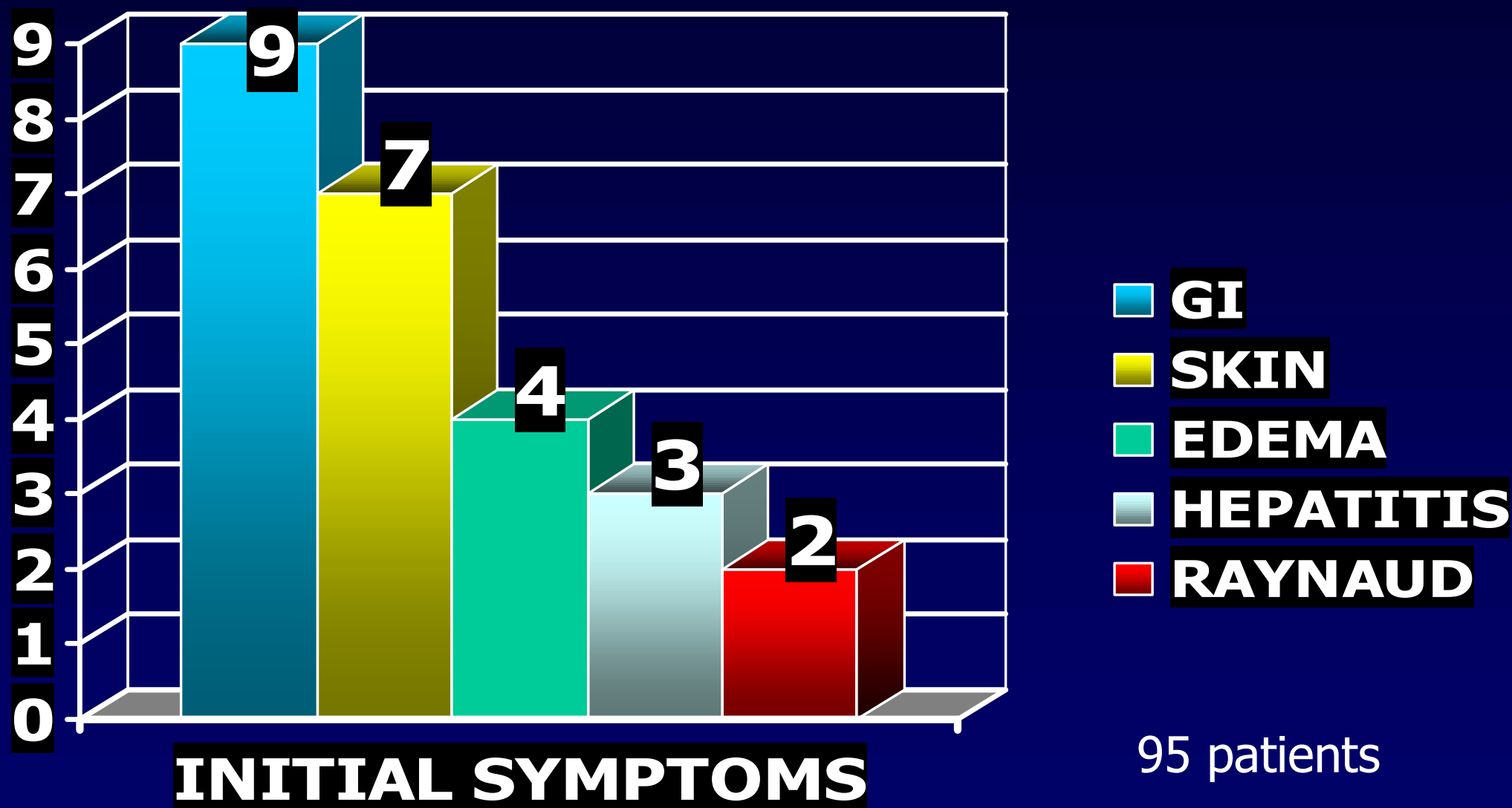
✓ *HIV*

- ✓ no patient at the time of PAN.
- ✓ Two patients were infected later

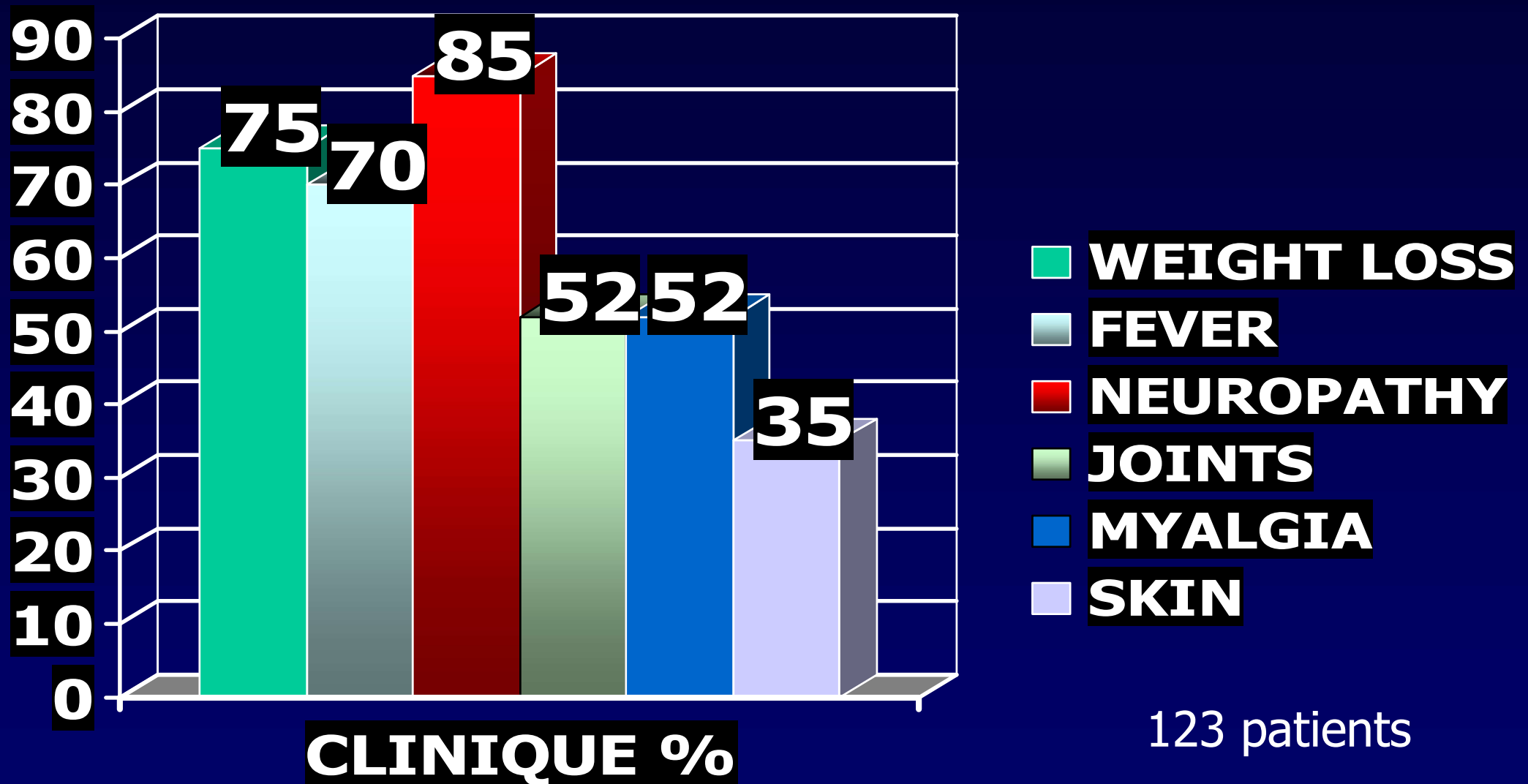
HBV-RELATED POLYARTERITIS NODOSA



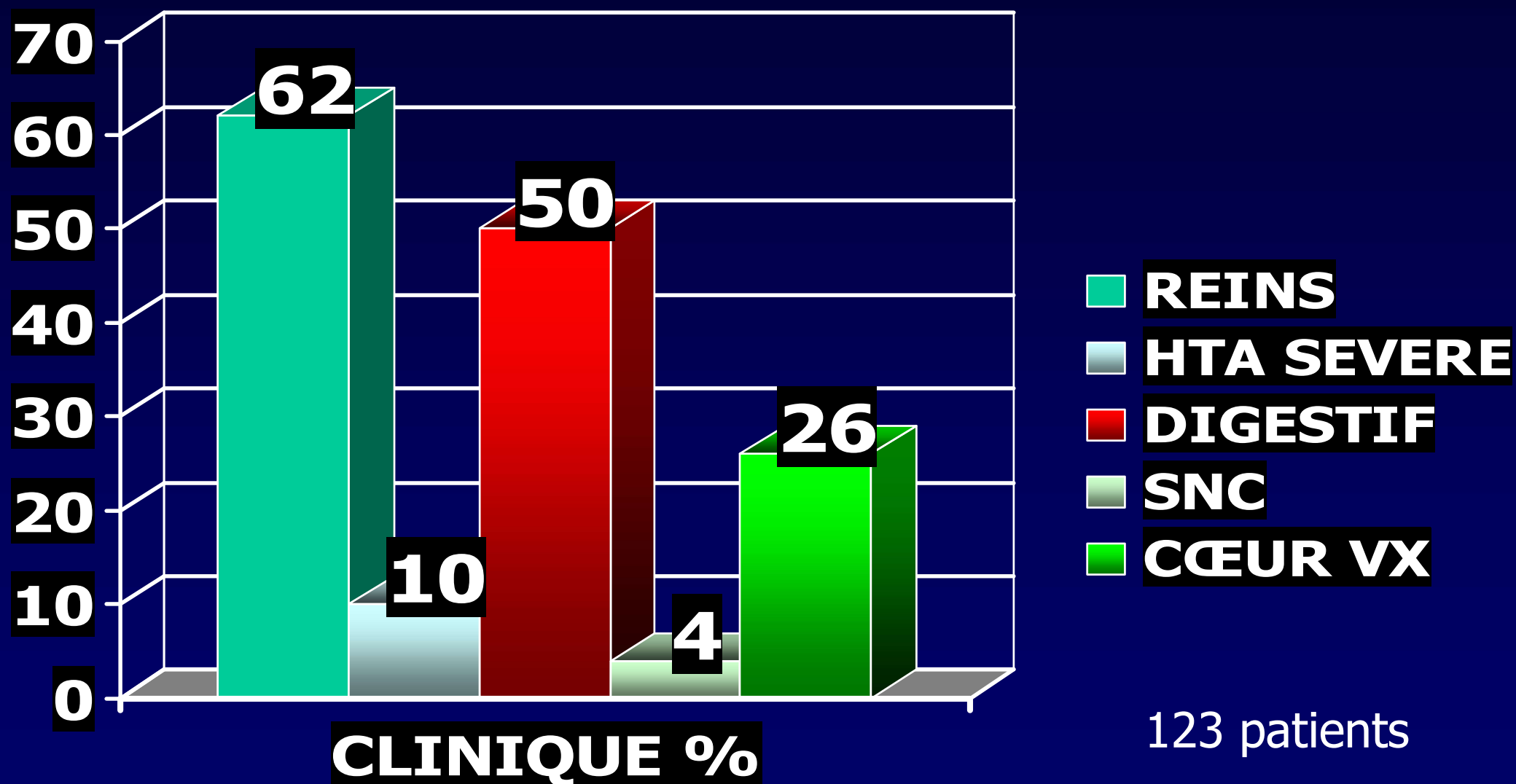
HBV-RELATED POLYARTERITIS NODOSA



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HBV-RELATED POLYARTERITIS NODOSA

LABORATORY INVESTIGATIONS 95 patients

- ✓ ***Transaminases***
 - ✓ normal in 39 patients
 - ✓ x 1 - 5, in 49 patients
 - ✓ x 6 - 20, in 6 patients
- ✓ ***Cryoglobulinemia*** in 4: it disappeared under treatment in 1, persisted in 2 pts who died, monoclonal gammopathy in 2 (associated with HCV-related cryo?)

HBV-RELATED POLYARTERITIS NODOSA

- ✓ *Liver biopsy at the time of diagnosis*
- ✓ performed in 41 patients (missing data 3)
- ✓ normal: 2
- ✓ moderate inflammation 3
- ✓ vasculitis: 2
- ✓ acute hepatitis: 6
- ✓ chronic hepatitis: 19
- ✓ steatosis: 2
- ✓ cirrhosis: 4

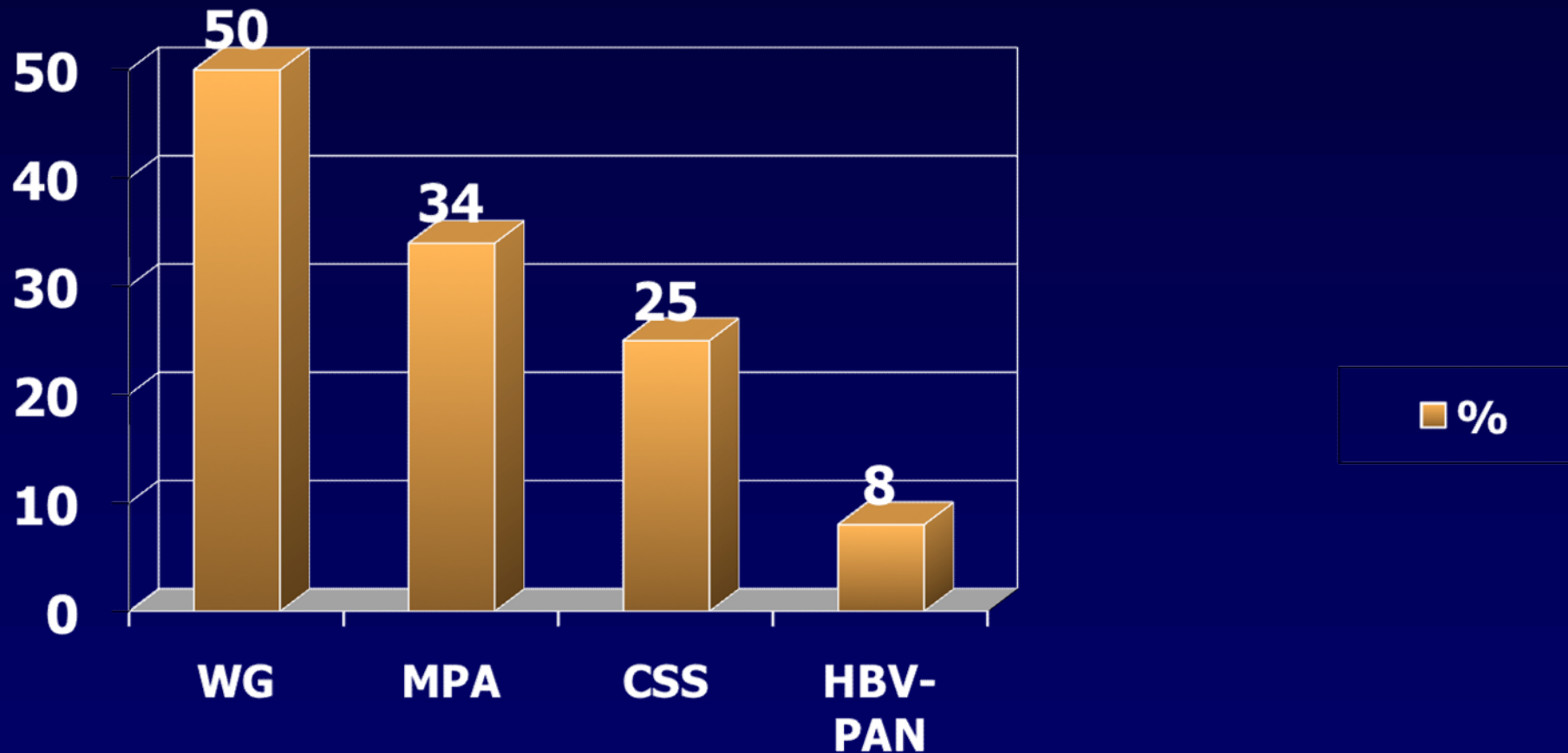
HBV-RELATED POLYARTERITIS NODOSA

INVESTIGATIONS

- ✓ *Angiography*
 - ✓ performed in 61 patients
 - ✓ microaneurysms in 41 (67.2%)

PROGNOSIS AND OUTCOMES

RELAPSE OF SYSTEMIC VASCULITIS

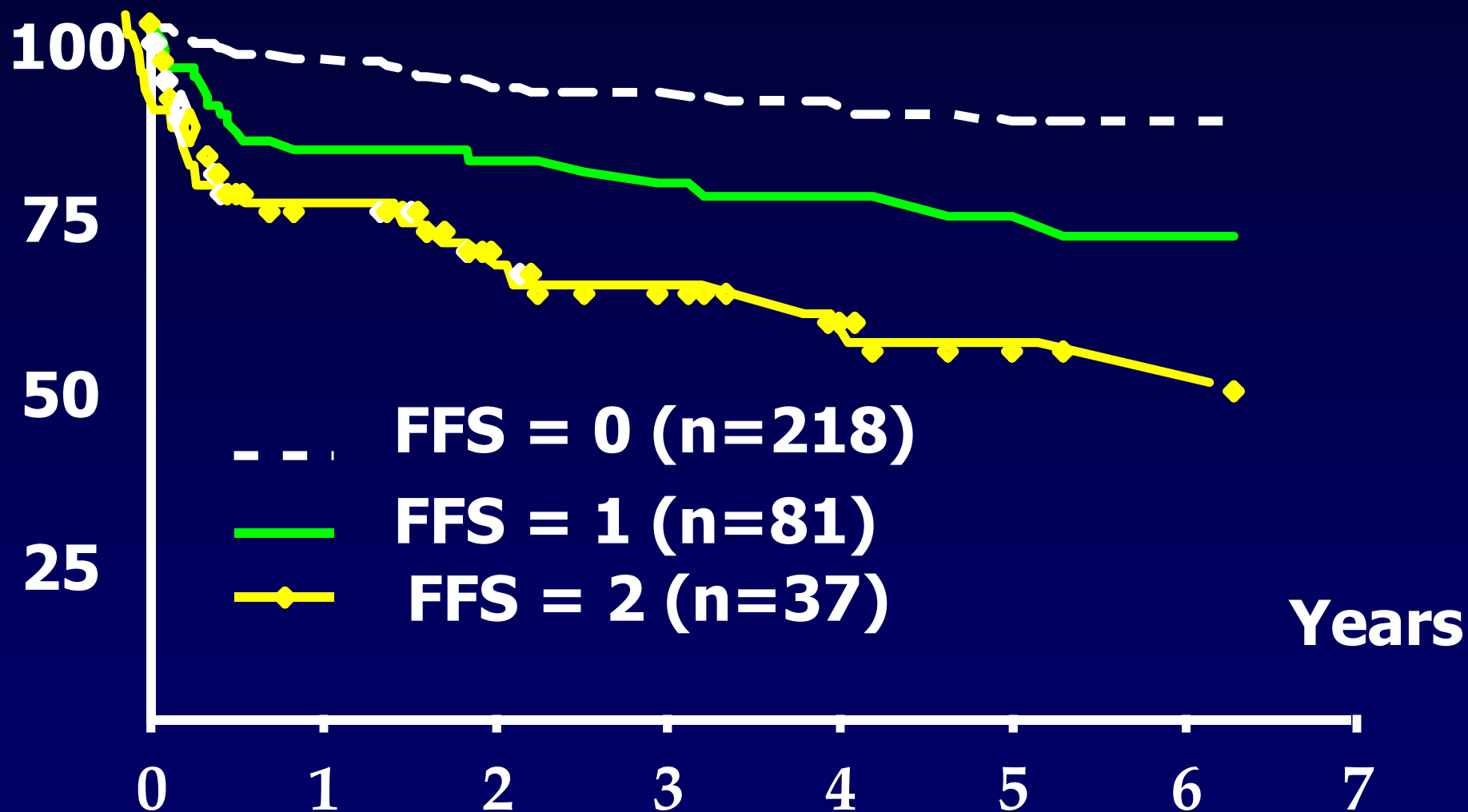


From prospective trials of the French Vasculitis Group

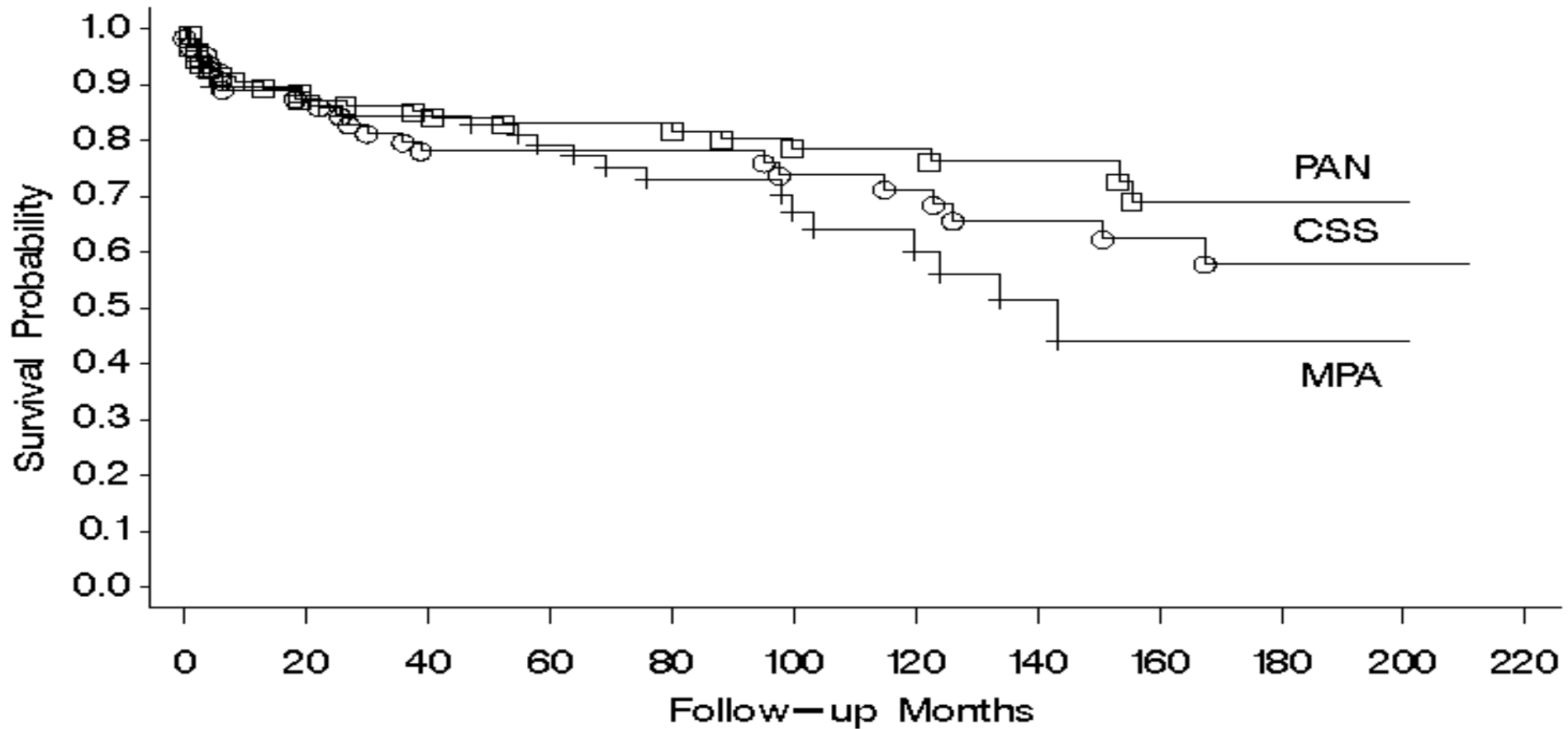
FIVE FACTOR SCORE (1996)

- ✓ Proteinuria > 1 gr/day
- ✓ Creatininemia > 140 μ /L
- ✓ GI tract involvement
- ✓ Specific cardiomyopathy
- ✓ CNS involvement

PROGNOSTIC SCORES IN PAN, MPA AND CSS



SURVIVAL CURVE FOR 215 PATIENTS ACCORDING THE TYPE OF VASCULITIS



OUTCOMES AND PROGNOSIS

- ✓ ***SEQUELLAE***

- ✓ **Renal insufficiency**

- ✓ sequelae of vascular nephropathy
- ✓ arterial hypertension
- ✓ may occur > 10 years after flare

OUTCOMES AND PROGNOSIS

✓ ***SEQUELLAE***

✓ **peripheral neuropathy**

- ✓ recovery can be delayed > 1 year after first flare
- ✓ bedridden...

✓ **In case of HBV infection**

- ✓ chronic hepatitis, liver cirrhosis

TREATMENT

PAN WITHOUT HBV

✓ ***FFS = 0***

✓ *Corticosteroids*

✓ ***FFS > 0***

✓ **CS**

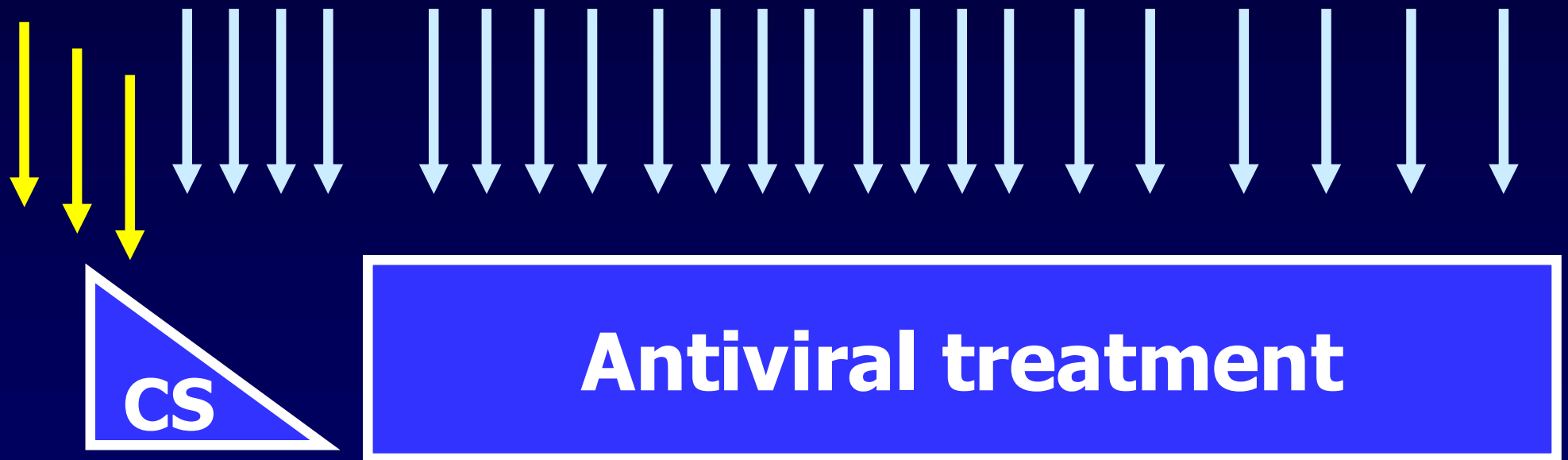
✓ **+ immunosuppressants (CYC)**

HBV-RELATED POLYARTERITIS NODOSA

RATIONALE

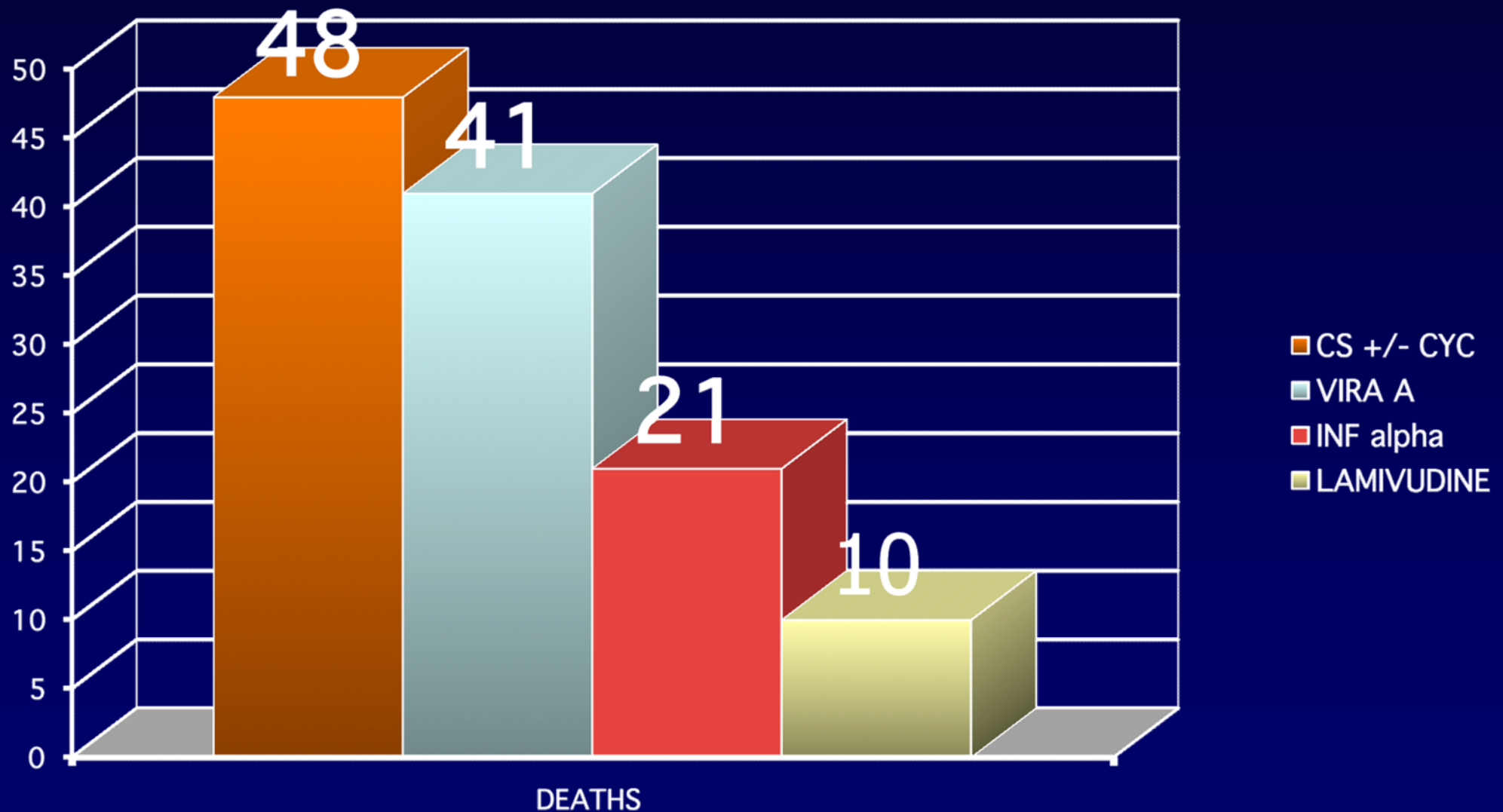
- ✓ PAN is an immune complex disease
- ✓ steroids and immunosuppressants stimulate virus replication
- ✓ antiviral drugs lower or suppress virus replication
- ✓ plasma exchanges clear immune complexes

TREATMENT OF HBV-RELATED PAN

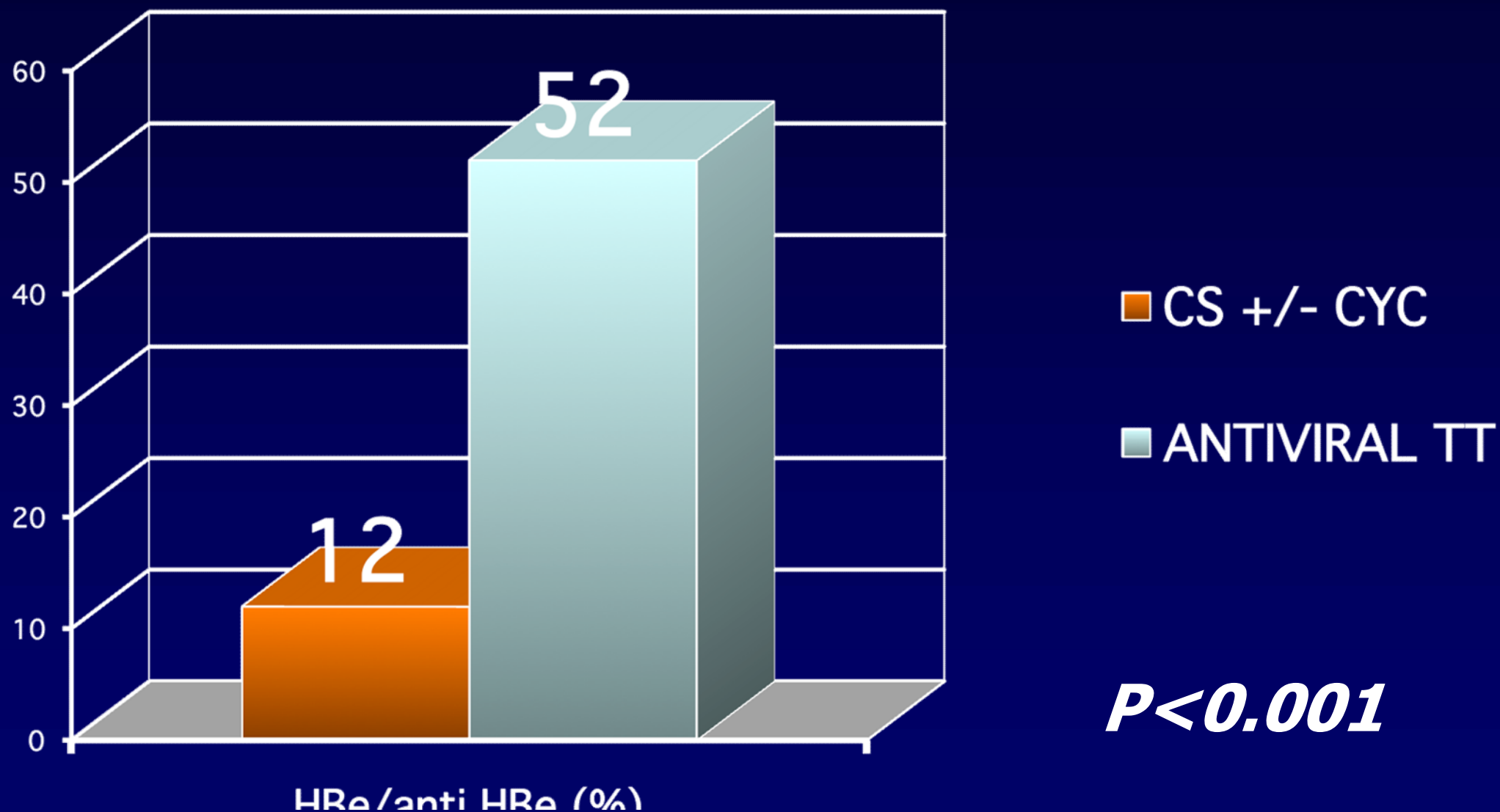


7 - 14 days

HBV-RELATED POLYARTERITIS NODOSA



HBV-RELATED POLYARTERITIS NODOSA



POLYARTERITIS NODOSA

CONCLUSIONS (1)

- ✓ PAN is a rare, severe, acute vasculitis, affecting medium-sized arteries
- ✓ It is often the consequence of HBV infection

HBV-RELATED POLYARTERITIS NODOSA

CONCLUSIONS (2)

- ✓ HBV-PAN shares the same characteristics than PAN without HBV
- ✓ Its frequency decreased in parallel to improved blood safety and vaccination campaigns
- ✓ The major cause of death is GI involvement

HBV-RELATED POLYARTERITIS NODOSA

CONCLUSIONS (3)

- ✓ ANCA are never detected
- ✓ Relapses are rare and never occur when viral replication has stopped
- ✓ Antiviral treatment combined with PE facilitates seroconversion and prevents the development of long-term hepatic complications of HBV infection



Hôpital Cochin
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Rare Systemic and
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