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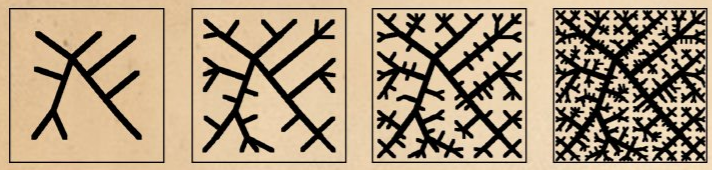

Specializing in the treatment, reconstruction, and management of
Acute and chronic wounds • Diseases and defects of the soft tissues • Injuries, diseases, and defects of the hand and extremities • Defects of the head and trunk

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Hypercoagulability: Prethrombotic and Microthrombotic Disorders

Original presentation February 24, 2000, Maui
at the Boswick Burn and Wound Meeting

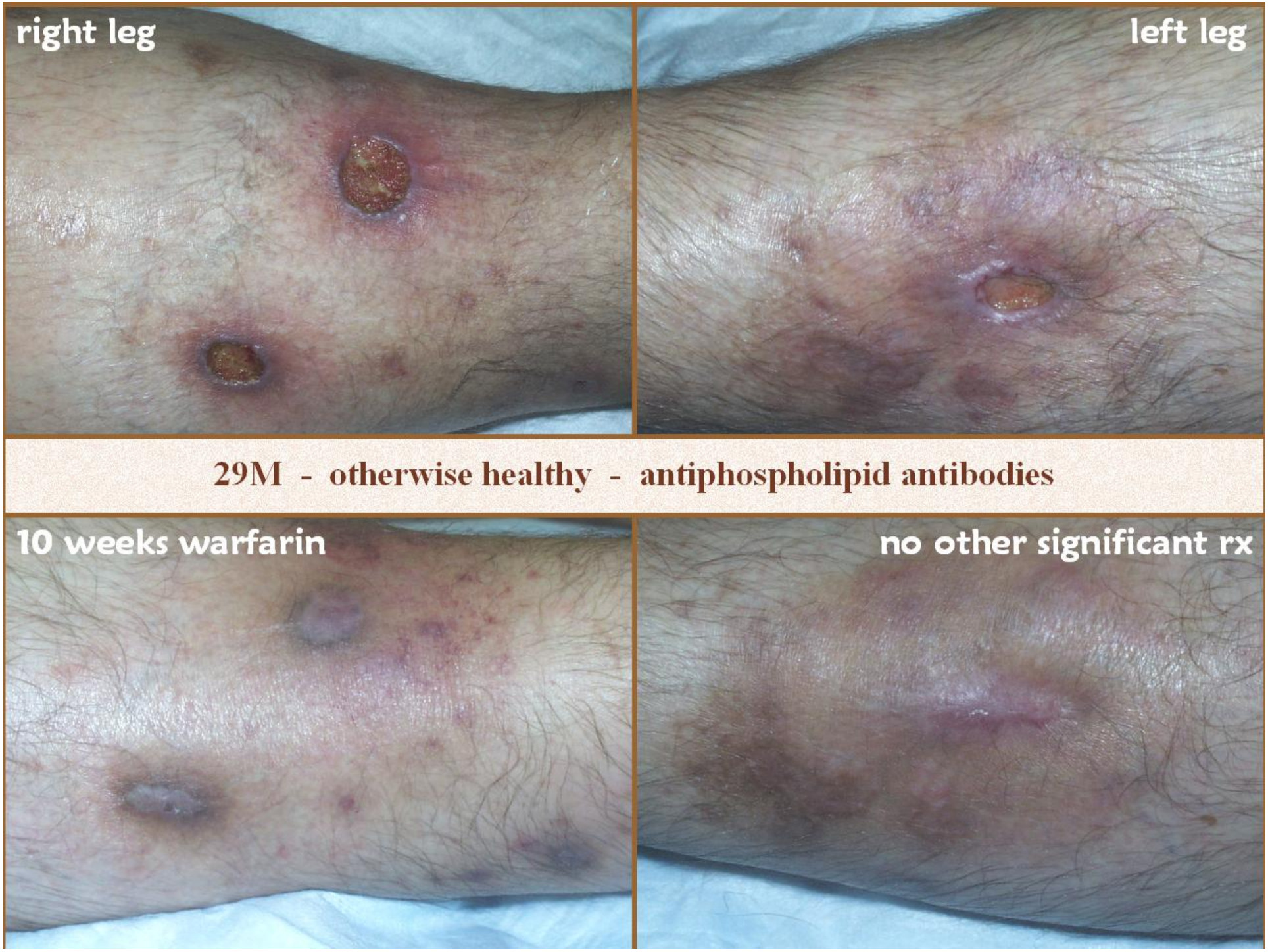
Further presentations & updates, 2001, 2003, 2004, 2005

Most recent presentation, October 27, 2005, Phoenix
at WOCN, Rocky Mountain Chapter, Annual Meeting

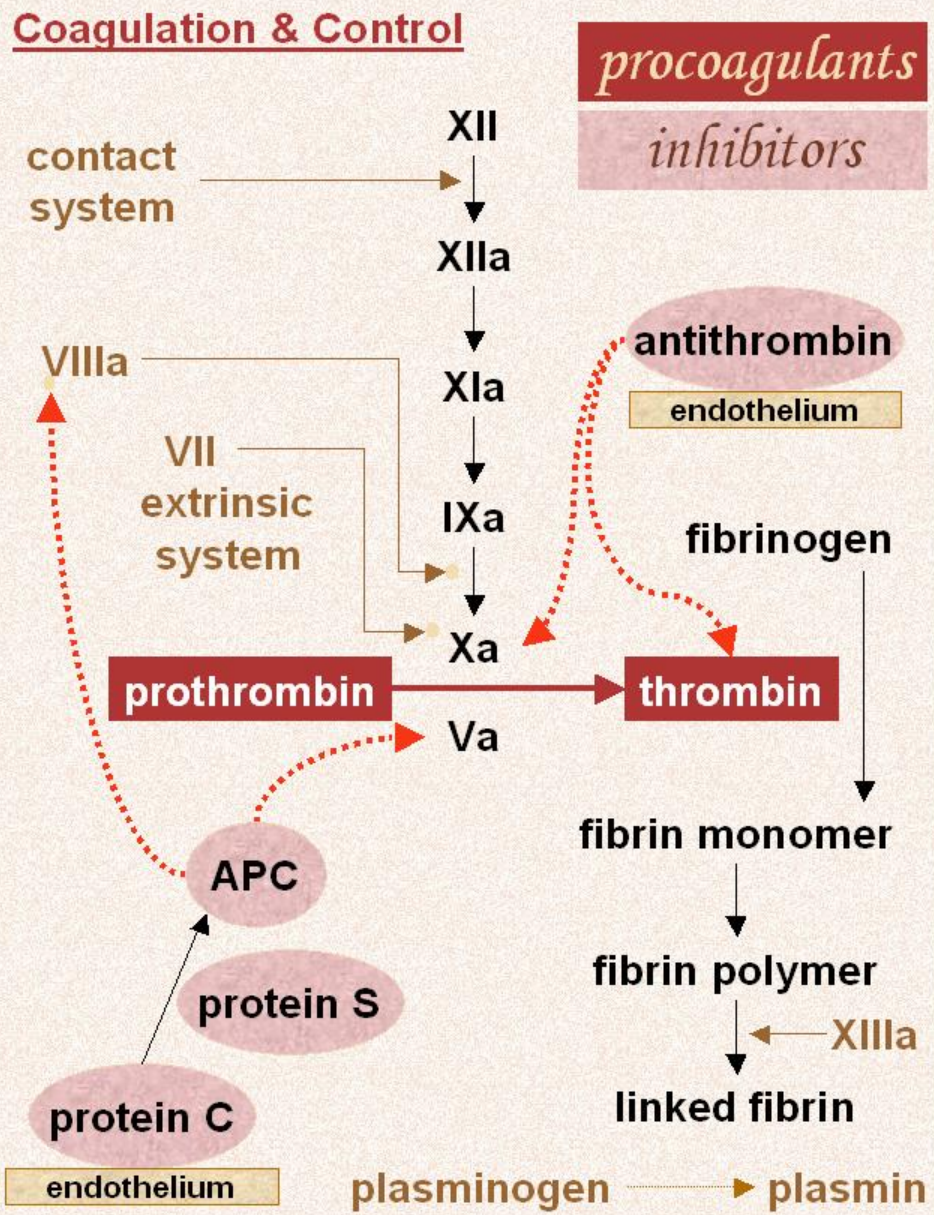
PRE-THROMBOTIC & MICROTHROMBOTIC DISORDERS

HYPERCOAGULABILITY

Marc E. Gottlieb, MD, FACS Phoenix, AZ


right leg
left leg
29M - otherwise healthy - antiphospholipid antibodies
10 weeks warfarin
no other significant rx

THE BIOCHEMISTRY OF COAGULATION AND THROMBOSIS



[1] *nominal function*

a - blood does not clot in blood vessels

b - blood clots instantly on exposure to anything else

[2] *reality*

a - coagulation is a complex chaotic non-linear multicontrol system

b - non- "homeostatic" oscillations, offsets, and saturations occur . . .

c - meaning that hyper- and hypo-coagulability also occur

d - altered coagulation causes clinical disorders: acute and chronic / overt and subtle

THROMBO - OCCLUSIVE DISORDERS

1	hemodynamic disorders	**Examples:** *vascular compression* *arteriovenous malformations* *atrial fibrillation*	vessels normal blood normal coagulation normal
2	endo-vasculopathies	**Examples:** *thromboangiitis* *small vessel atherosclerosis* *alloplastic implants*	***vessels abnormal*** blood normal coagulation normal
3	exo-vasculopathies	**Examples:** *immunopathies* *connective tissue disorders* *calcium-phosphate disorders*	***vessels abnormal*** blood normal coagulation normal
4	non-hypercoagulable hemopathologies	**Examples:** *hemoglobinopathies* *dys- & cryoproteinemias* *red cell & platelet abnormalities*	vessels normal ***blood abnormal*** coagulation normal
5	**hypercoagulability**	disorders of the coagulation system intrinsic: *the prethrombotic disorders* extrinsic: *examples - estrogens, cancer*	vessels normal blood normal ***coagulation abnormal***

macrovascular - microvascular ischemia - infarction

Categories 1 - 2 - 3 - 4

coagulation is intrinsically normal

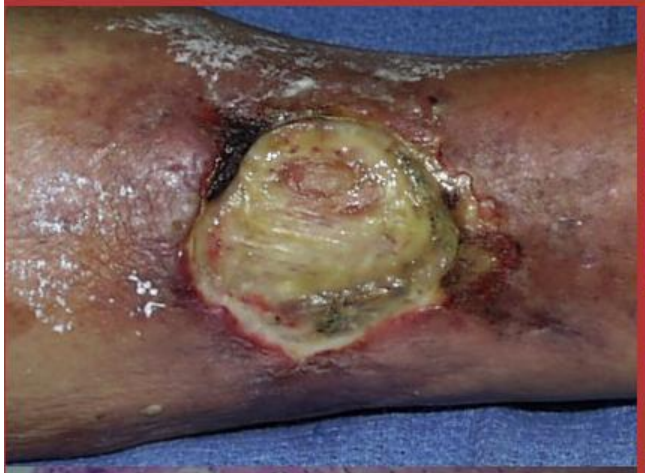
thrombosis is "normal" in response to blood stasis or thrombotic activation

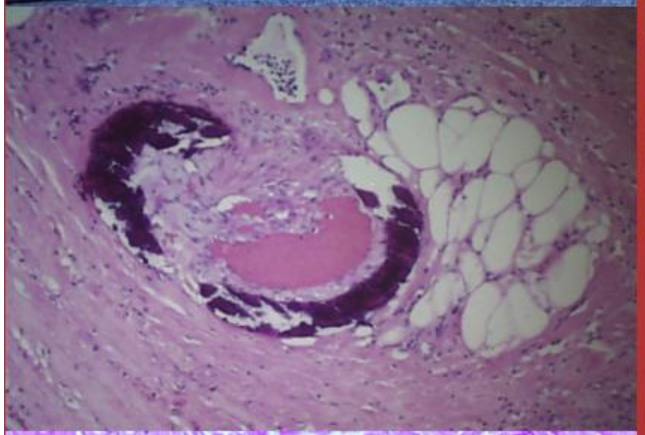
Category 5

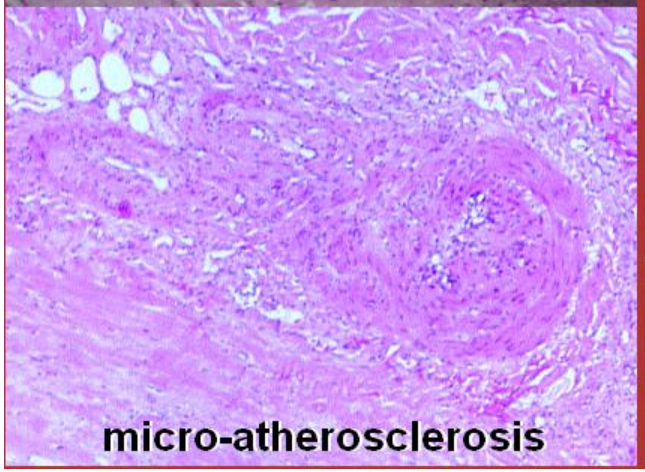
abnormal thrombosis is primary event

blood stasis and vascular occlusion are consequences

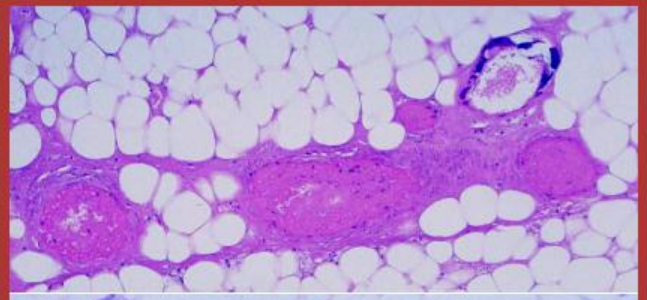
2 & 3 - VASCULOPATHIC MICRO-OCCLUSIVE DISORDERS

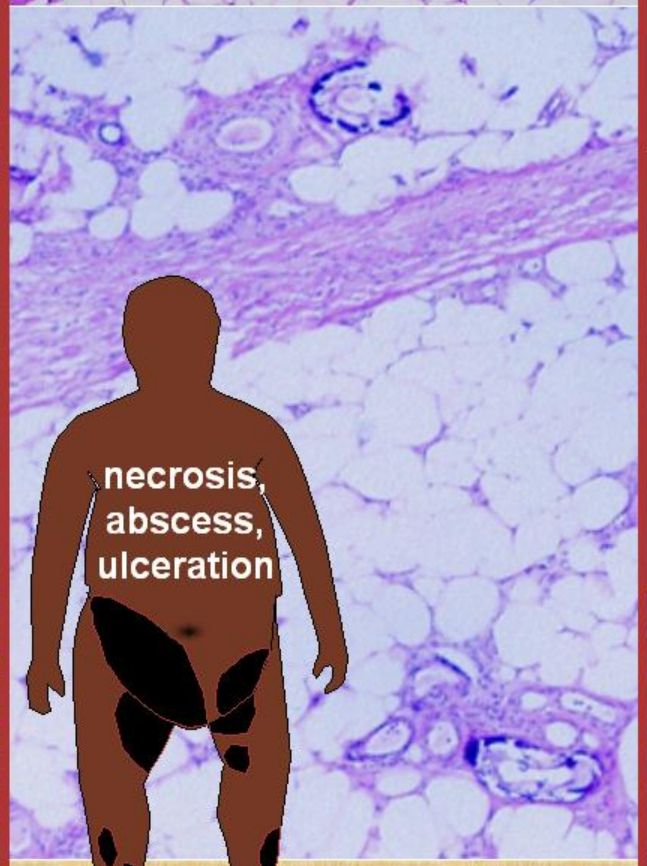






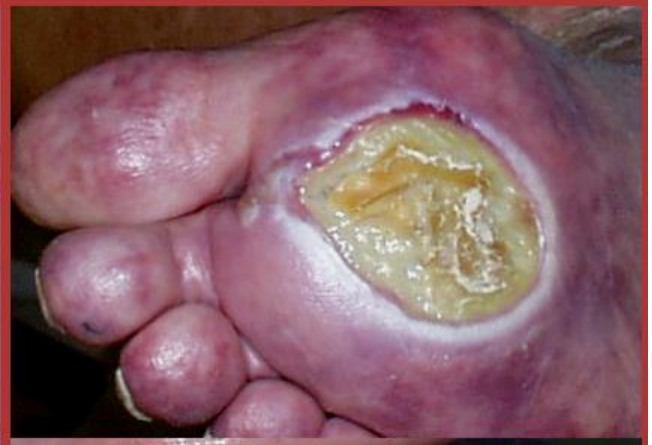
micro-atherosclerosis

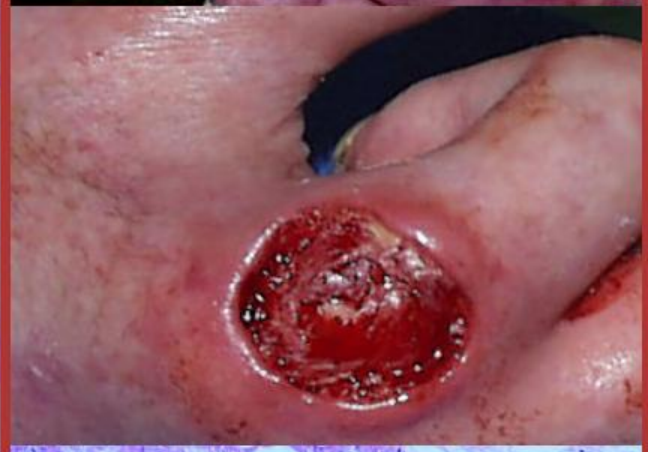


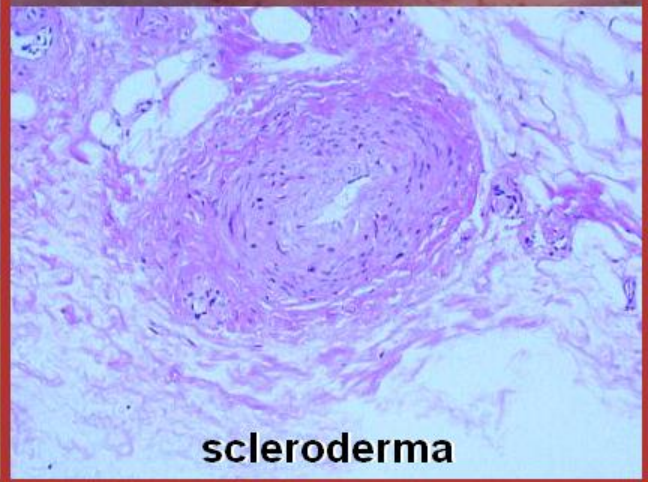


necrosis,
abscess,
ulceration

panarterial
calcinosis
(Mönckeberg's) from
tertiary hyperparathyroidism





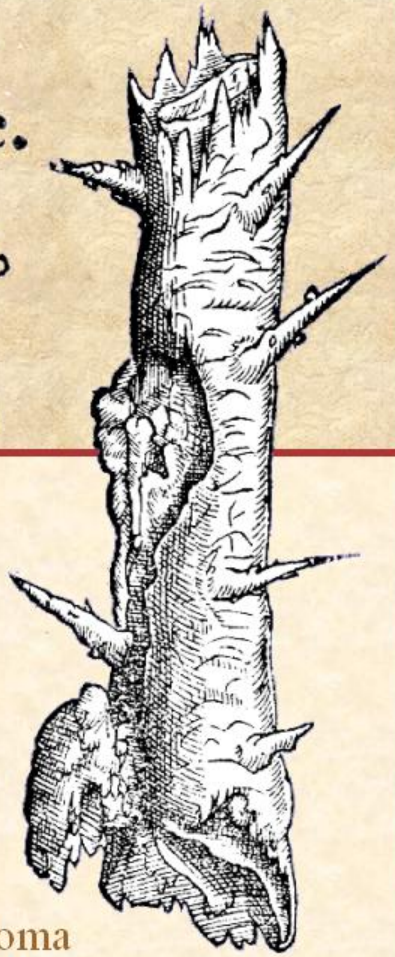


scleroderma

4 - NON-HYPERCOAGULABLE MICROTHROMBOTIC DISORDERS

Arbor Thurifera.
The Frankincenſe tree.
• • •
filleth vp hollow vlcers,
it cloſes raw wounds

John Gerard's *Herbal*,
Thomas Johnson's 1633 2nd edition



[1] ***hemoglobinopathies***

sickle cell disease
thalassemias
other hemolytic anemias

[2] ***dys- & cryoproteinemias***

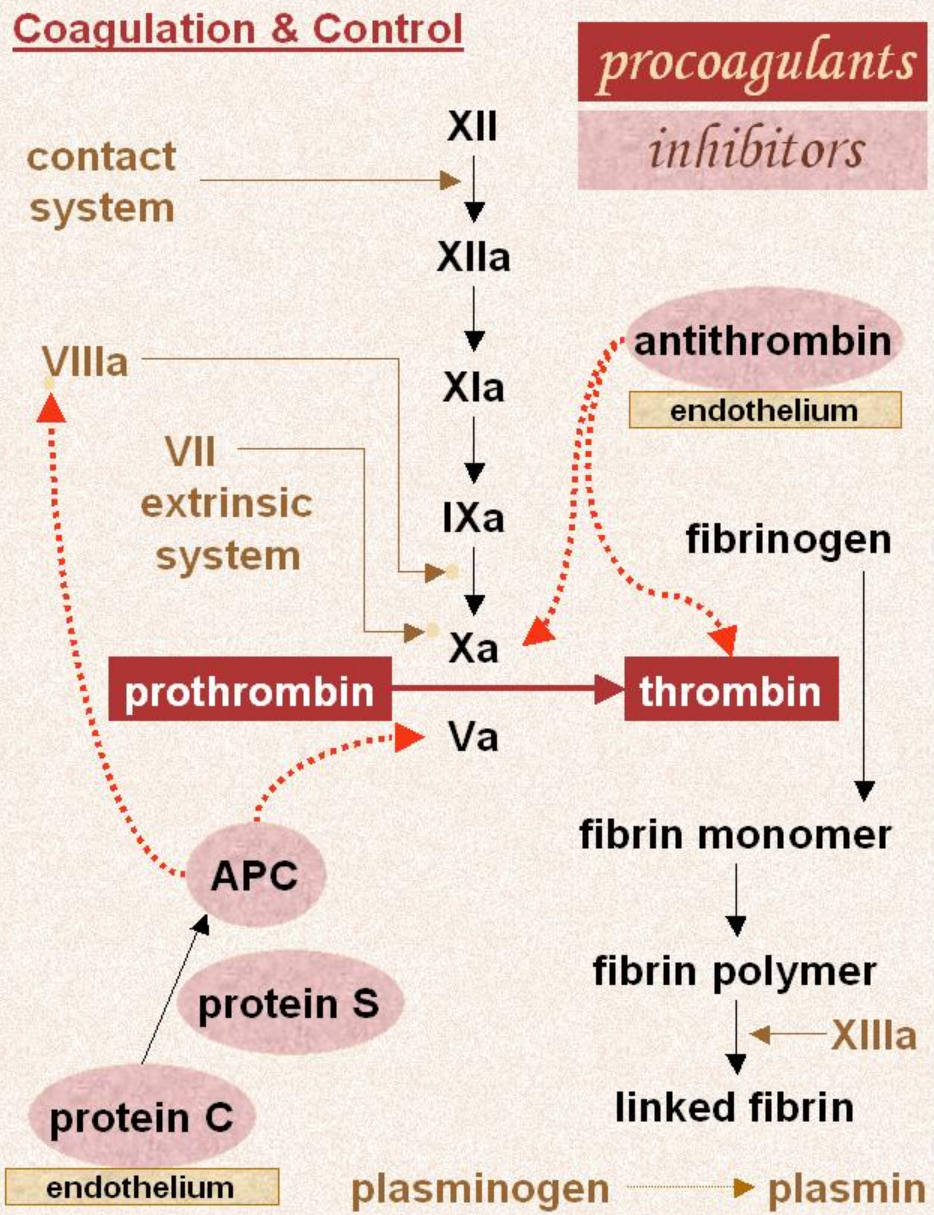
cryoglobulinemia
cryfibrinogenemia
macroglobulinemia & myeloma

[3] ***hematocyte & platelet abnormalities***

polycythemia rubra vera
hereditary spherocytosis
thrombotic thrombocytopenic purpura
myeloproliferative disorders
leukemias

Sts. Cosmas & Damian, by the Schwäbische Master of the Schnaiter Alter

5 - THE HYPERCOAGULABLE "PRE-THROMBOTIC" DISORDERS



[1] ***intrinsic prethrombotic disorders***

factor V
factor V Leiden, other f.V mutations
prothrombin gene mutation
antithrombin III deficiency
protein C and protein S abnormalities
fibrinogen
plasminogen
warfarin

[2] ***related disorders***

antiphospholipid antibodies
anticardiolipin
lupus anticoagulant
homocysteine disorders
estrogens, pregnancy

[3] ***disease associations***

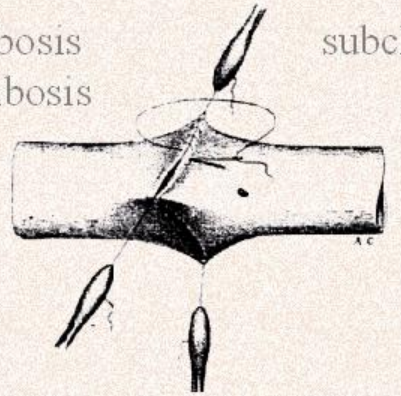
connective tissue disorders, inflammation
acute and chronic venous disease
cancer (Trousseau)
paroxysmal nocturnal hemoglobinuria

1A CLINICAL CONSEQUENCES AND SYNDROMES - GENERAL

1 acute large vessel macrothrombosis (overt life-and-limb threatening events)

These are "old hat" medicine, but practitioners must adjust their perspective to recognize that, in individual patients, they may be due to hypercoagulability.

cava-ilio-femoral-tibial venous thrombosis
aorto-ilio-femoral-tibial arterial thrombosis
other peripheral arterial thrombosis
coronary artery thrombosis
cerebrovascular thrombosis
pulmonary embolism
graft and valve thrombosis



subclavian vein thrombosis (paget-schroeder)
hepatic vein thrombosis (budd-chiari)
pituitary apoplexy (sheehan and others)
retinal artery and vein occlusion
intracranial sinus thrombosis
spinal apoplexy
visceral apoplexy (adrenal, renal, bowel)

2 microthrombosis (subacute, chronic, recurring, perplexing, refractory problems)

Vascular occlusion and ischemia are not overt.

Instead, patients have secondary clinical events, oftentimes chronic, recurring, and refractory to treatment, the underlying causes of which may have eluded diagnosis.

miscarriage
non-healing ulcers
soft tissue complications of trauma and surgery
unrecognized problems and syndromes

3 other features

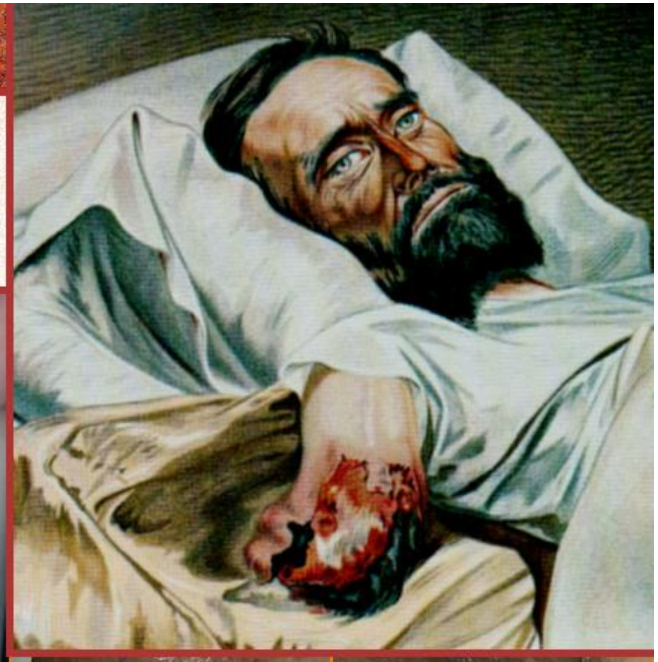
Things that don't add up.
Things that don't respond to treatment.

familial and hereditary risks
quantifiable risks (eg factor V Leiden: 5-10 / 50-100)
warfarin resistance warfarin necrosis
susceptibility to oral contraceptives

1B CLINICAL CONSEQUENCES - WOUNDS

microthrombosis - effects on wounds and tissues

(acute, subacute, chronic, recurring, perplexing, refractory problems)

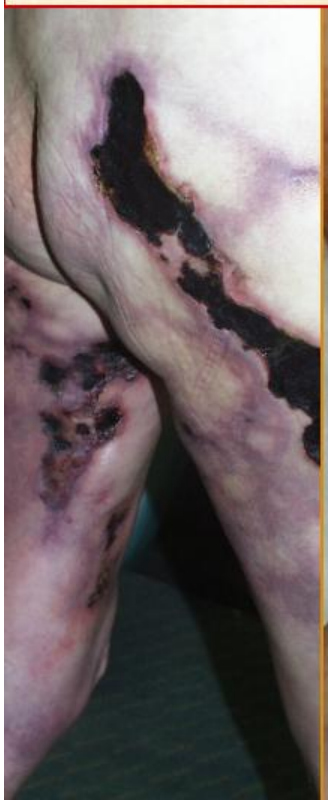


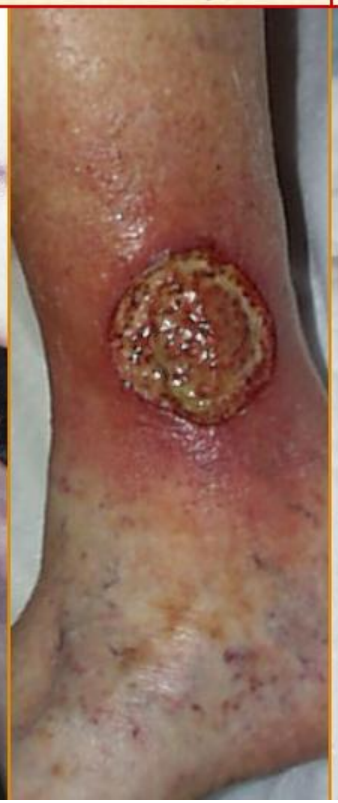
acute active necrosis and ulceration

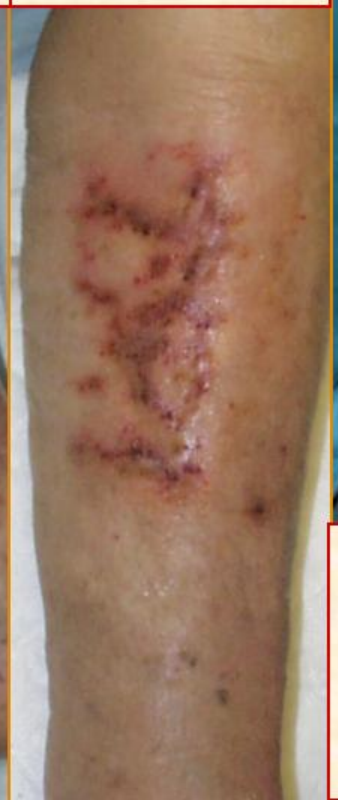
chronic and persistently active necrosis and ulceration

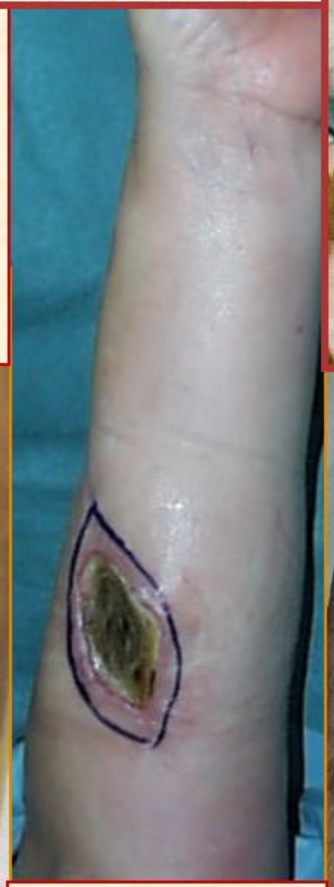
(most commonly lower extremities, but not solely)

failure to respond to otherwise appropriate treatment

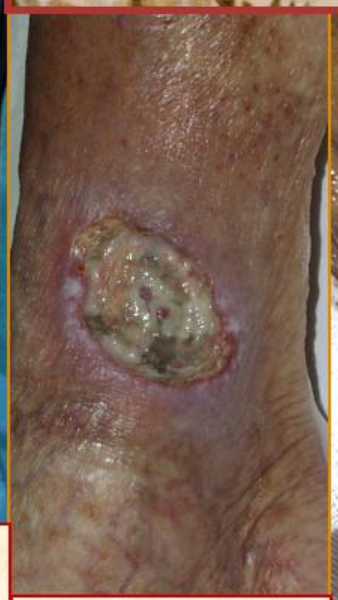




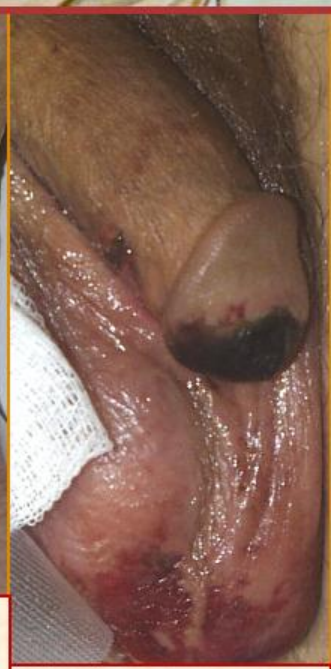




post-traumatic pathergy and complications



post-operative dehiscence and infarction



warfarin necrosis

2A DIAGNOSIS OF HYPERCOAGULABLE DISORDERS - GENERAL

Suspicion and inclusion in the differential diagnosis are based on:

[1]
awareness that these disorders exist

[2]
these criteria (active clinical events, or by history)

any recurrent thromboembolism

inexplicable arterial thromboembolism

recurrent or unexpected deep vein thrombosis

recurrent or unexpected pulmonary embolism

peculiar or rare thromboembolic events

thromboembolism in young healthy people

thromboembolism triggered by illness or injury

recurrent thromboembolism in spite of treatment

absence of common risks or identifiable injury

(e.g. retinal artery occlusion in a young healthy person)

miscarriages

familial history

trauma-induced soft tissue pathergy
(infarction, dehiscence, etc.)

multiple complicated or failed operations

warfarin resistance

presence of associated disorders
(eg venous or rheumatoid disease)

things that just don't add up

Hypercoagulable ulcers have no pathognomonic features, but they can have a relatively distinctive appearance.

Suspicion and inclusion in the differential diagnosis are based on:

[1] *awareness that these disorders exist*

[2] *these criteria (active clinical events - or - by history):*

distinctive or consistent physical findings

recalcitrant, continuously pathological wound behavior (inflammation, necrosis, pathergy, progressive ulceration)

impaired wound behavior characteristic of severe ischemia

pathergy, necrosis, dehiscence after treatment

failure to respond to customary wound care

failure to respond to interventions specific for other diagnoses

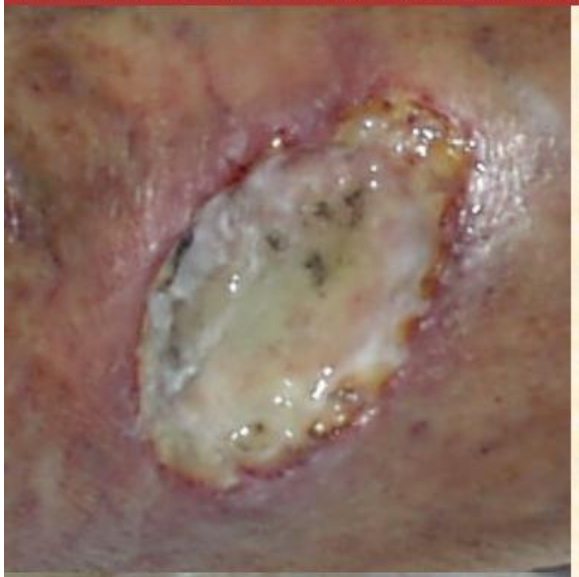
absence of other risks (eg venous or rheumatoid disease)

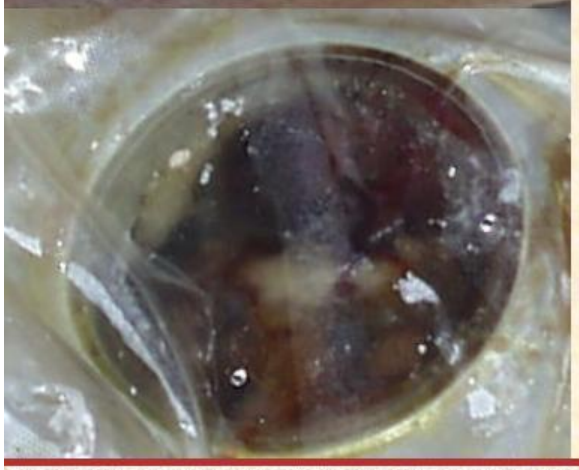
presence of other risks (eg venous or rheumatoid disease)

❊ any of the general criteria ❊

things that just don't add up

DIAGNOSIS - PHYSICAL EXAM



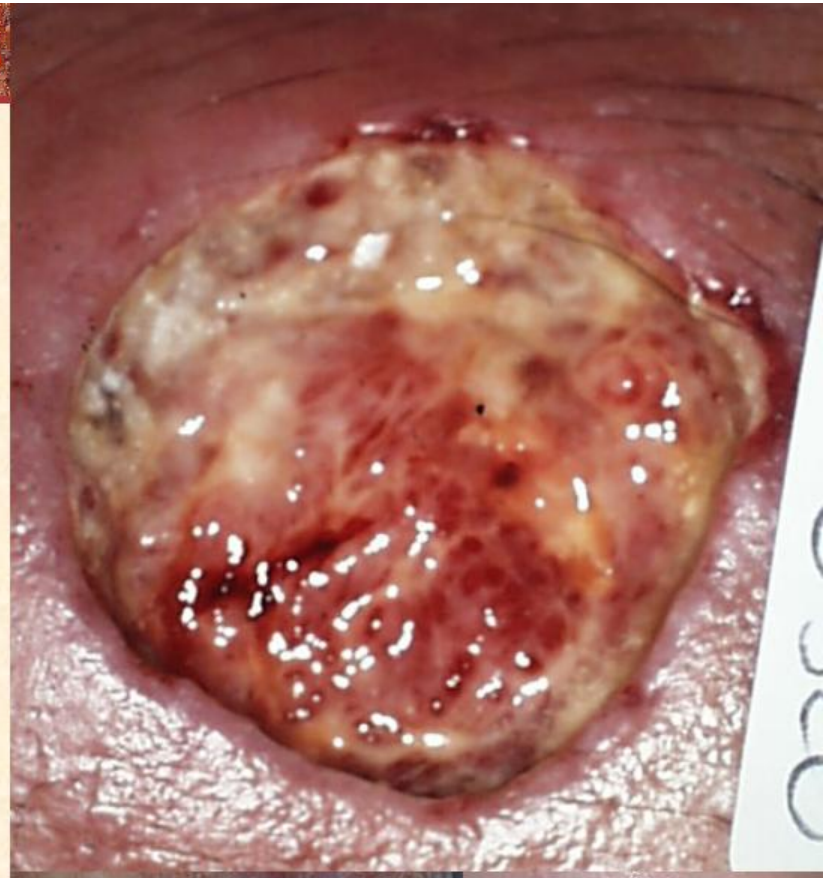


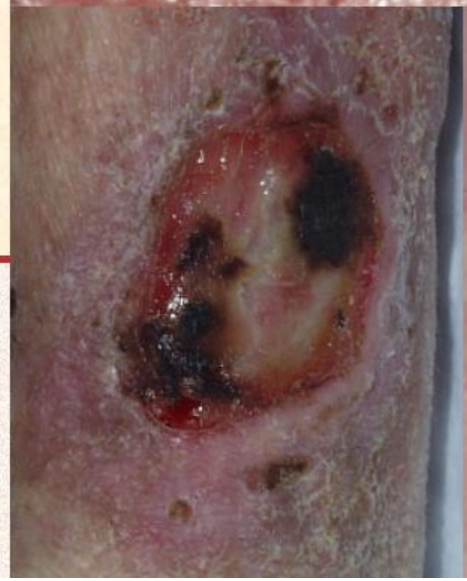
inflammation
absence of inflammation
necrosis
active ulceration
infarction
dehiscence
pathergy

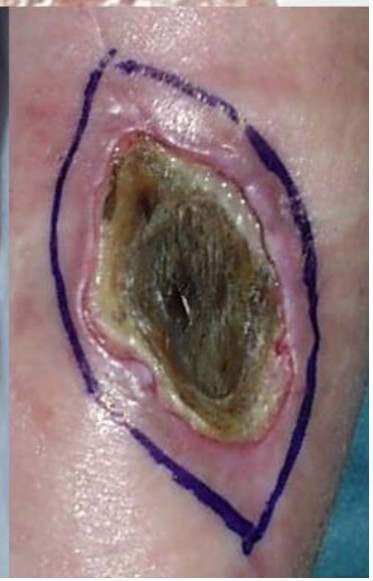
mixed wound module
periwound stasis

absence of other stigmata

misbehavior over time
failed expectations







DO NOT confuse hypercoagulability with

pyoderma gangrenosum
immunopathic disorders
other vascular and thrombotic disorders

and vice versa

2C DIAGNOSIS: EVALUATION AND EXACT DIAGNOSIS

Confirmation and exact diagnosis are made by laboratory evaluation.

Prethrombotic and microthrombotic screen

[1] *ordinary blood counts & clotting studies*

CBC PT, PTT

[2] *screen for connective tissue disorders*

sedimentation rate CRP anti-DNA
rheumatoid factor ANA

[3] *hypercoagulable studies:*

Factor V Leiden prothrombin mutation
protein C protein S
fibrinogen plasminogen
antithrombin III homocysteine
lupus anticoagulant anticardiolipin
cryoglobulins cryofibrinogen

Hypercoagulable ulcers are NOT diagnoses of exclusion.

Other disorders must be excluded, reconciled, or accounted for, but these diagnoses can be made on specific criteria.

Other studies may include:

TcPO2

laser doppler
(arterial ultrasound, doppler, PVR not useful)

biopsy and histology
microthrombi & aggregates
vascular thickening & luminal narrowing
vasculitis
other microvasculopathies

Hyper-fibrinogenemia seems to be a common denominator ; high values are meaningful

Some tests may be confusing.

Retest after acute phase.

Some hypercoagulable patients do not fit standard profiles.

Presumptive diagnosis and treatment may be based on strong suspicion and absence of other confirmed diagnoses.

3A HYPERCOAGULABLE DISORDERS - TREATMENT - GENERAL

Acute treatment

[1]
treat clinical syndromes, causes, and sequelae

[2]
thrombolysis
in select cases
(thrombolysis is under-utilized)

[3]
anticoagulation

<u>serious situations</u>: heparins acutely, transition to warfarin

<u>less serious situations</u>: warfarin only, but consider heparin pretreatment to avoid necrosis

<u>ancillary treatments</u>:
antiplatelet drugs, thromboembolectomy, caval filters, venous ligation, etc., hyperbaric oxygen

Long-term therapy or prophylaxis

Warfarin or not; if so, for how long?

how serious was the acute event?

how serious were the sequelae?

is this a recurrent event?

what are the calculable risks?

can the patient afford another acute event?

can the patient afford the required care?

episodic or continuous?

are there substitutes?

will antiplatelet drugs help?

genetic counseling / family workup?

3B TREATMENT - WOUNDS AND SOFT TISSUES

Mandatory treatments to control wound (as for all wounds and ulcers)

[1] *control acute conditions (all wounds)*
- hygiene
- silver - sulfa
- edema control
- elastics, elevation
- debridement
- drainage

[2] *control conditions (diagnosis specific)*
- corticosteroids
- anticoagulants
- revascularize
- pressure offloading

[3] *treat associated disorders*
- rheumatoid
- venous
- arterial
- hematological

[4] *general*
- establish correct diagnosis
- symptomatic relief
- attention to details of care

Discretionary treatments to heal wound (specific for diagnosis and patient)

[1] *interim closure*
- biologicals
- alloplastics

[2] *hyperbaric oxygen*

[3] *antithrombotic therapy*
- thrombolytics
- anticoagulants

*** *essential* ***

(warfarin alone can rapidly resolve some ulcers of long duration)

[4] *definitive closure*
- topical care
- contract & epithelialize
- surgery-grafts
- surgery-flaps

*** *do not attempt closure until patient is anticoagulated* ***

Open wound control can be confounded by continuing microthrombosis and pathergy.

Control of these factors is crucial.

maintain anticoagulation

until healed wounds are mature

(risk of recurrent ulceration)

3 - 12 months

CLINICAL PROFILES

Young or healthy people

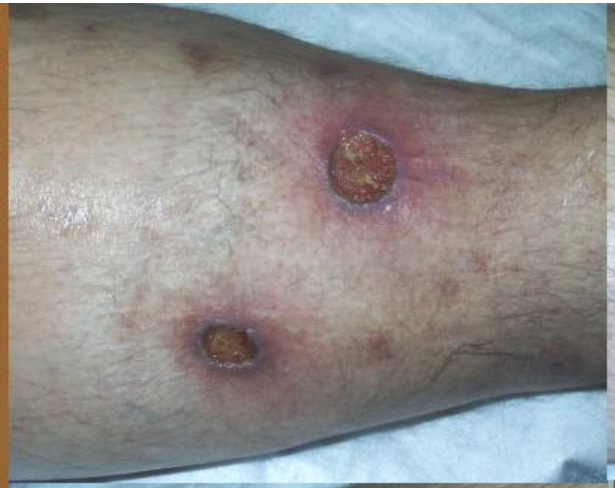
Association with connective tissue disorders

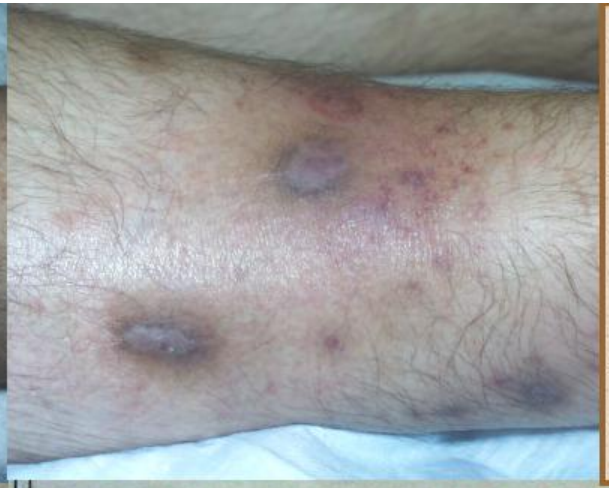
Fatal complications

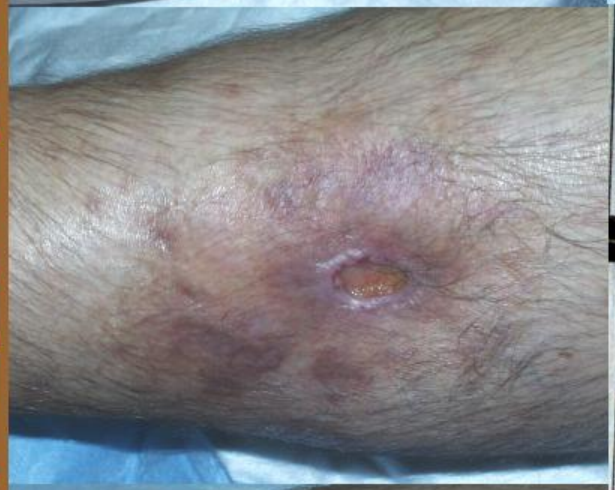
Patients with other risks or diagnostic confusion

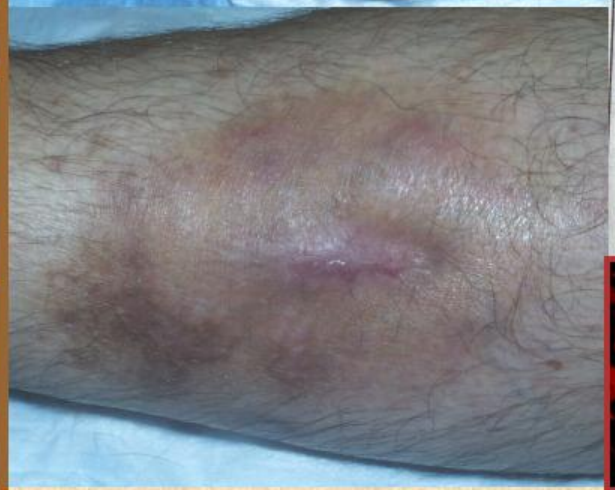
Patients who do not or who may have these disorders

Re-evaluating old patients









29M, healthy

leg ulcers:
no response
to other care

antiphospholipid
antibodies

healed by warfarin

CARDIOLIPIN Ab IgG, IgM, IgA
CARDIOLIPIN IgA 15 H

Reference Range for Cardiolipin IgA

IgA Result:	Interpretation:
<12	Negative
12-15	Borderline
>15	Positive

CARDIOLIPIN IgG 24 H

Reference Range for Cardiolipin IgG

IgG Result:	Interpretation:
<15	Negative
15-20	Low Positive
20-80	Moderate Positive
>80	High Positive

CARDIOLIPIN IgM <15

Reference Range for Cardiolipin IgM

IgM Result:	Interpretation:
<15	Negative
15-20	Low Positive
20-80	Moderate Positive
>80	High Positive

history and exam zero in on these diagnoses
no other risks for ulceration
no response to other treatment
expected response to anticoagulation

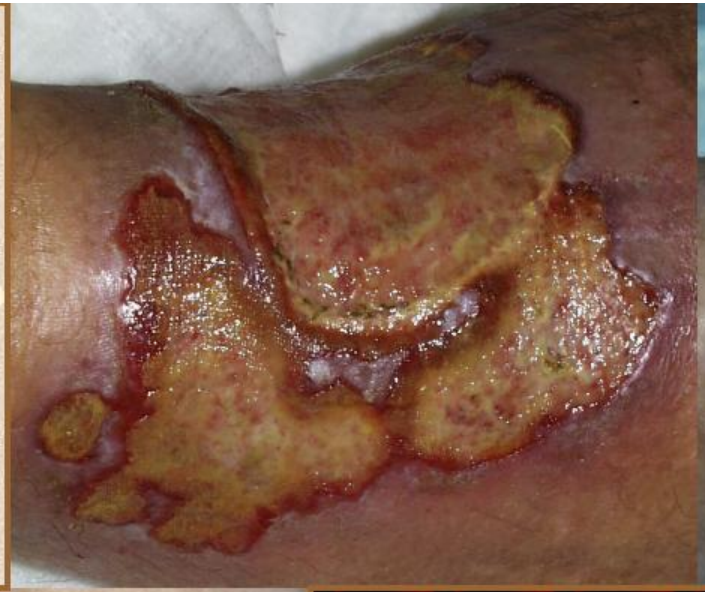
43F, otherwise healthy

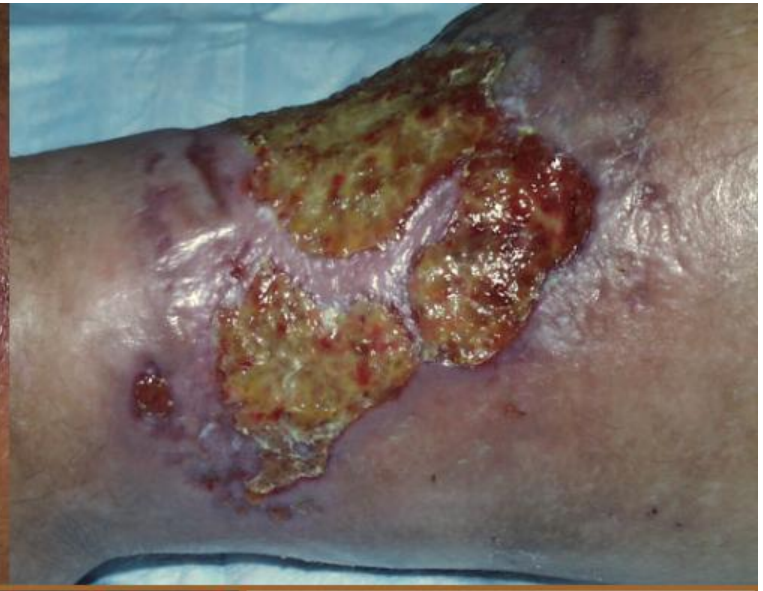
leg ulcers many years; multiple DVT & PE

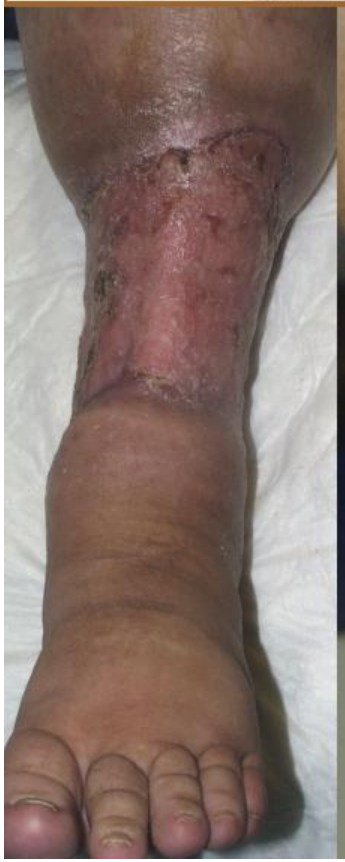
proteins C & S deficient

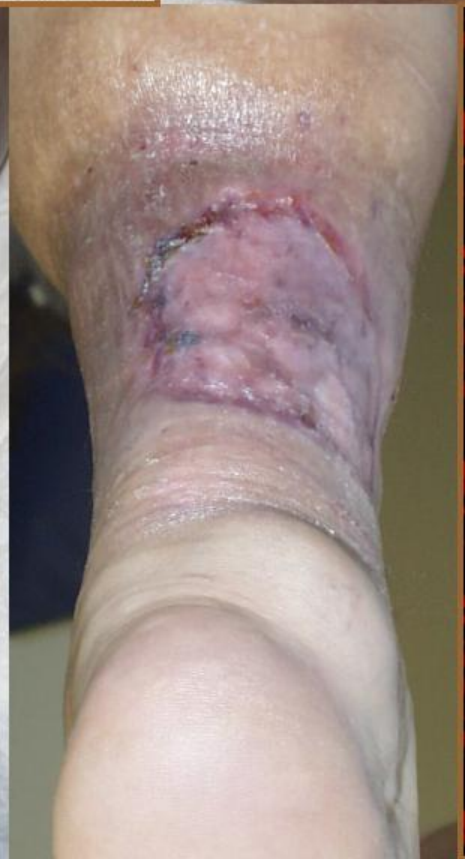
TcPO2s confirm periwound ischemia

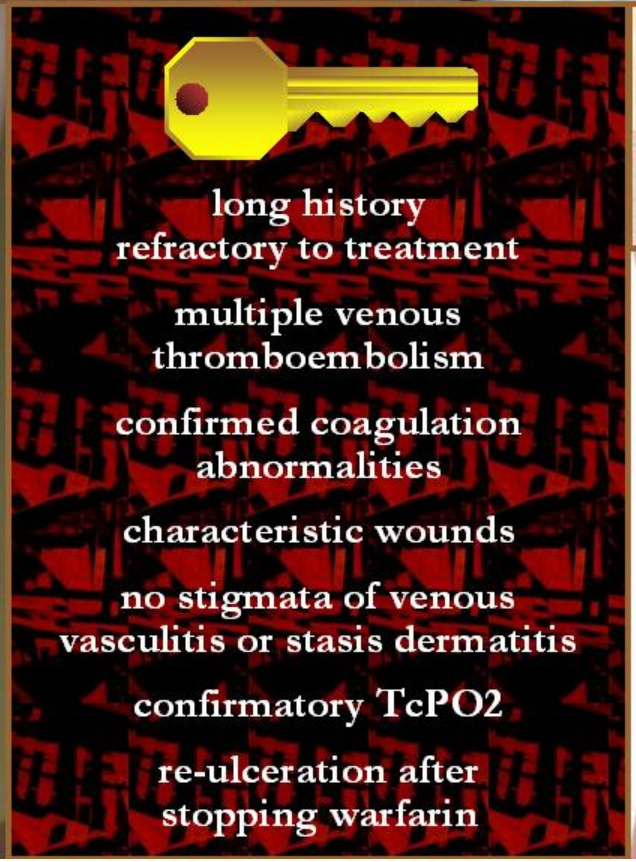
healed by warfarin and integra











long history refractory to treatment

multiple venous thromboembolism

confirmed coagulation abnormalities

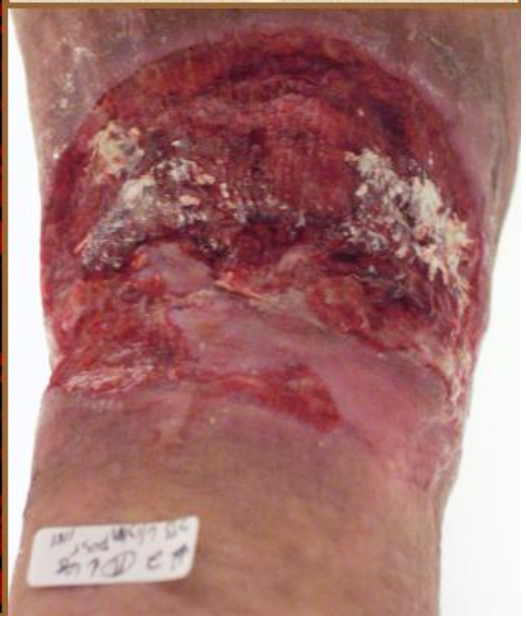
characteristic wounds

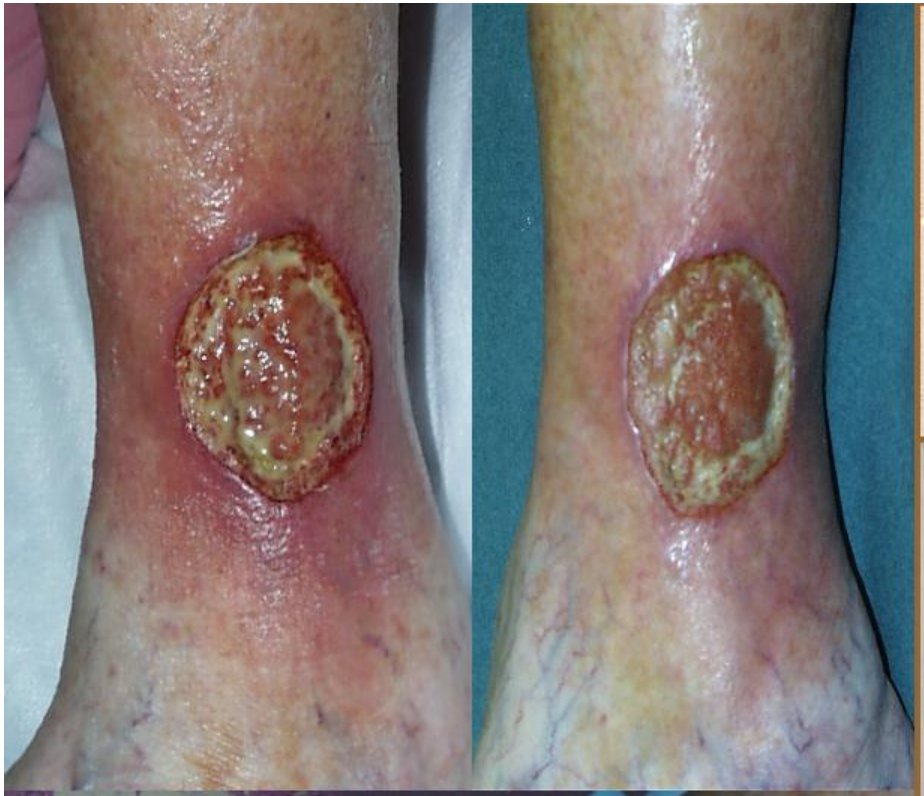
no stigmata of venous vasculitis or stasis dermatitis

confirmatory TcPO2

re-ulceration after stopping warfarin

re-ulceration after stopping warfarin





61F, healthy

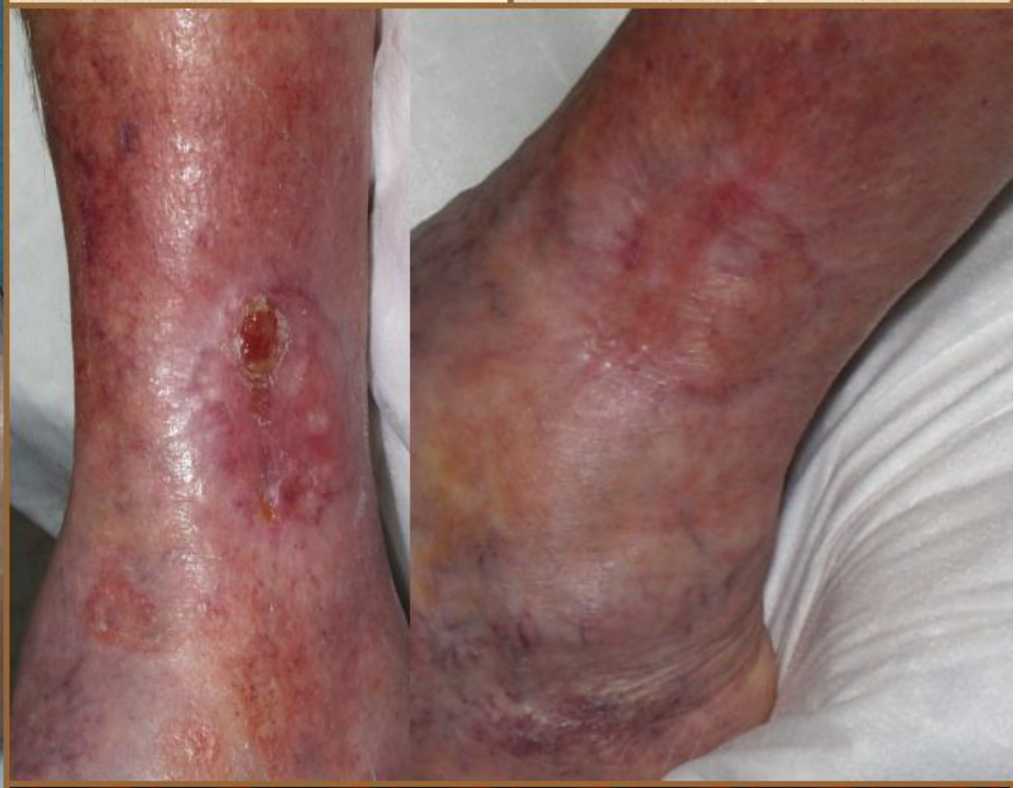
1. hx multiple DVT / PE

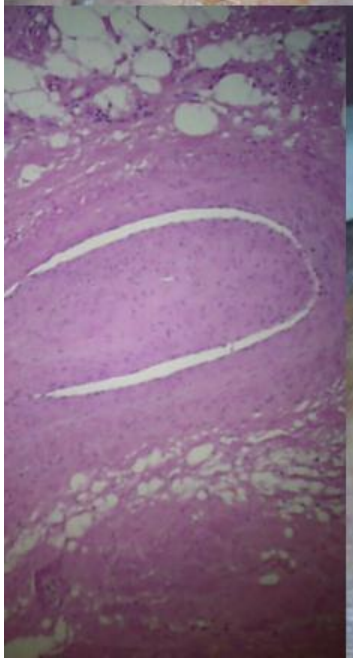
protein S deficient

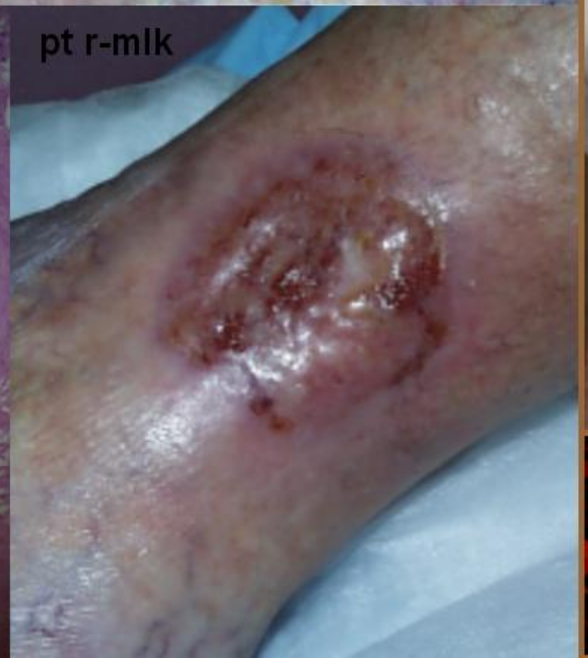
healed with Integra and warfarin

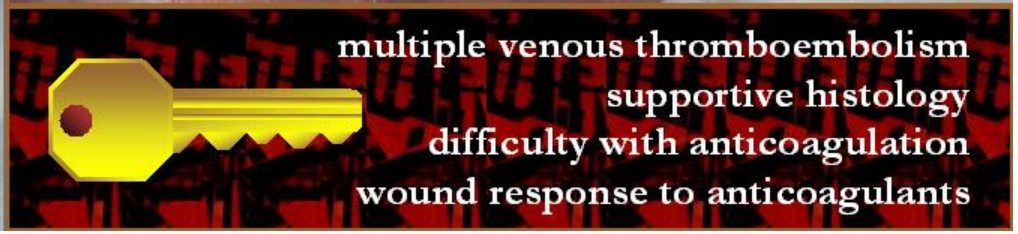
2. recurrent DVT with INR 2.5 - 3.0

rehealed with INR 3.5 - 4.0







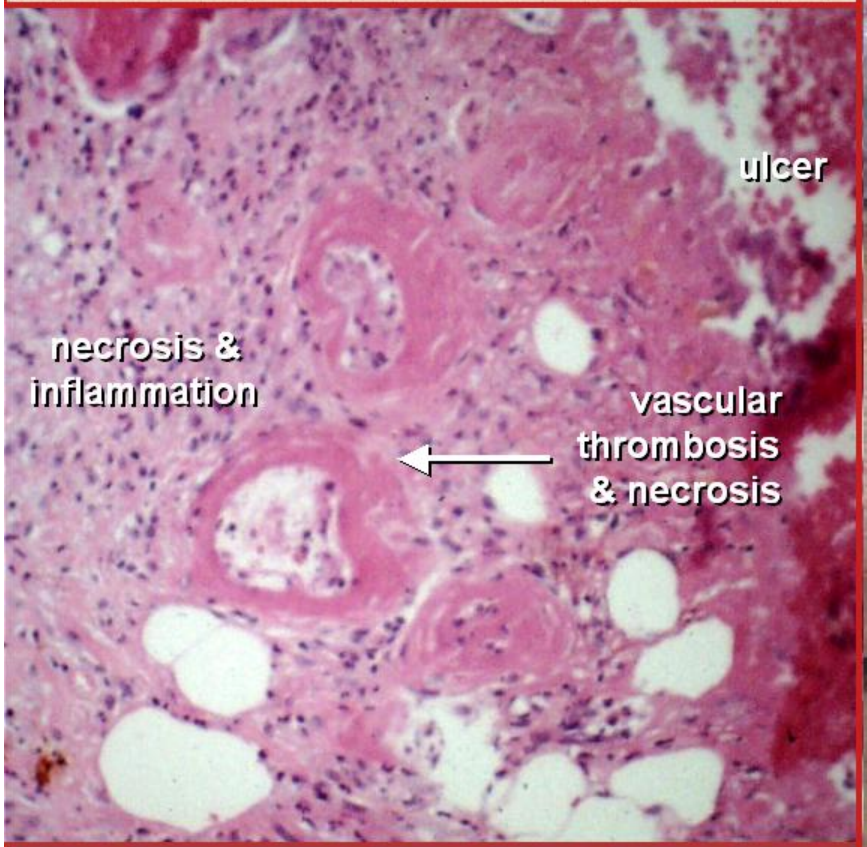


69F, no relevant risks or history

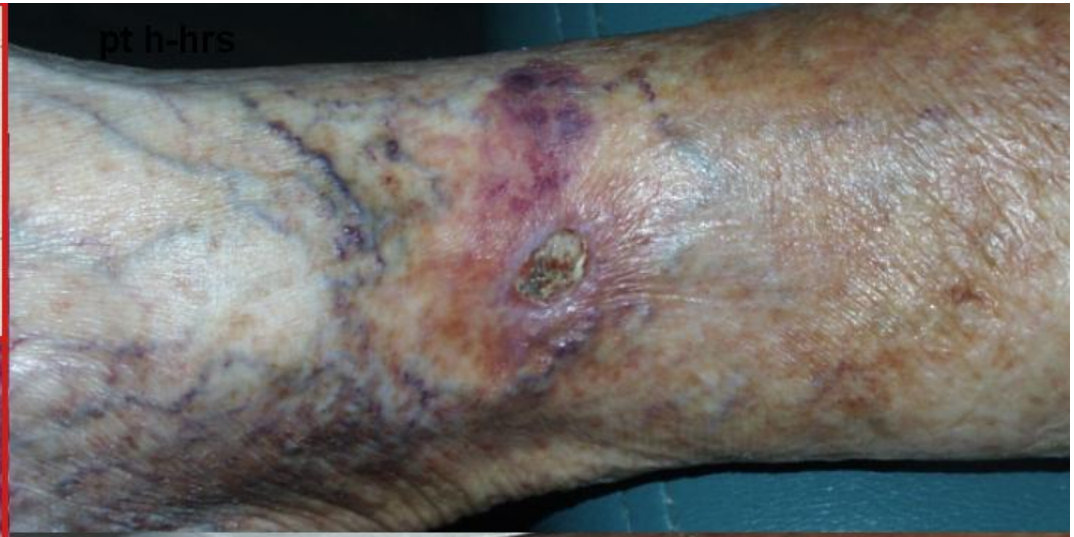
acute ulcer over varicose veins;
necrosis and dehiscence after surgery

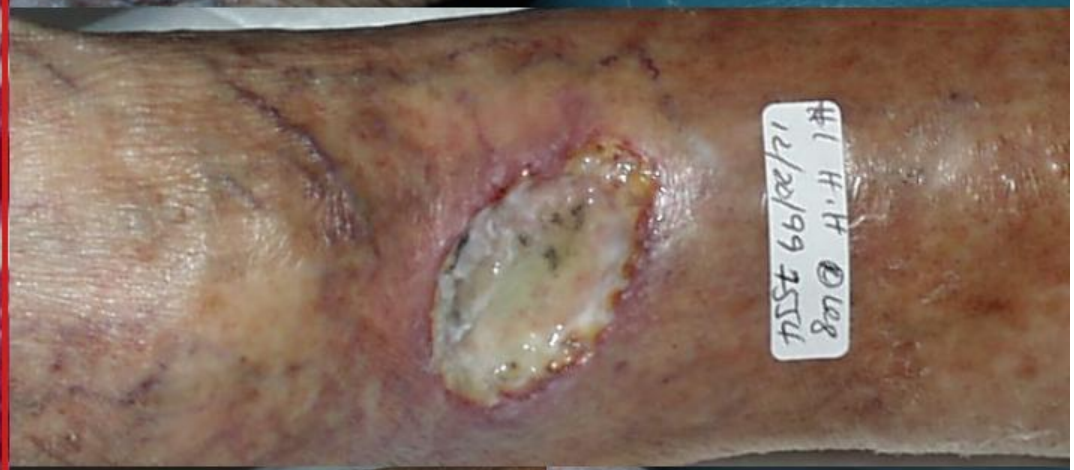
protein C deficient; cryoglobulins

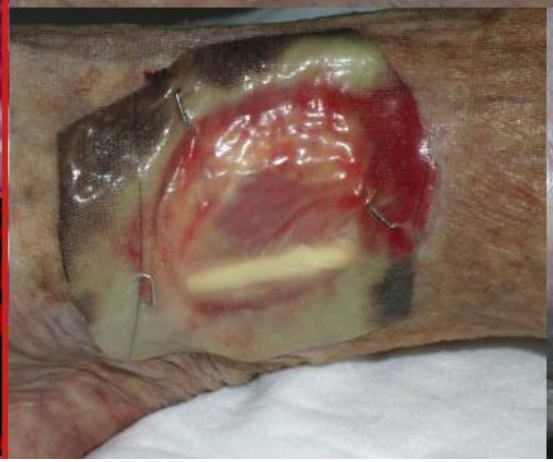
healed by warfarin and integra

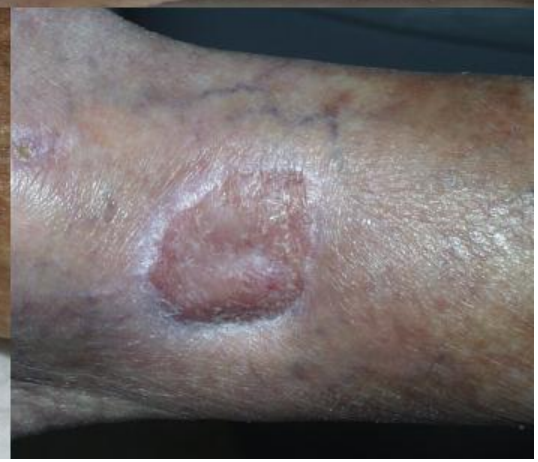


association with venous disease
failure to heal with basic care
pathergy
failed surgery
success after anticoagulation









45F, no relevant risks or history

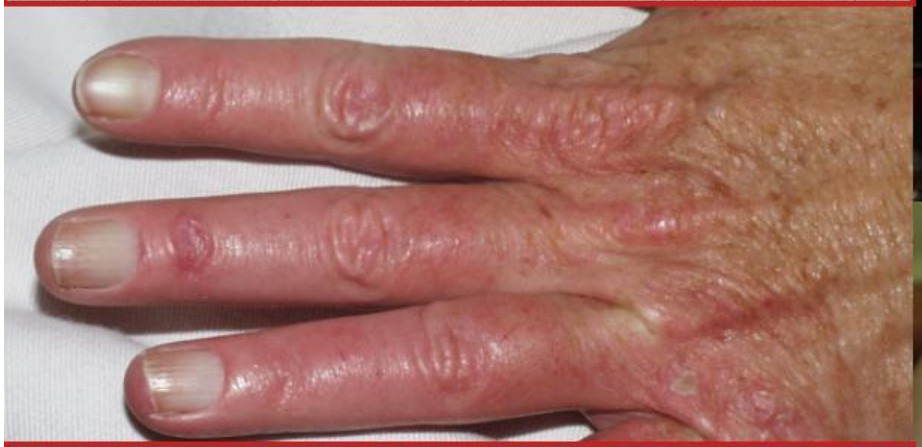
2 years soft tissue necrosis, amputations, multiple surgical complications, inanition, suicidal

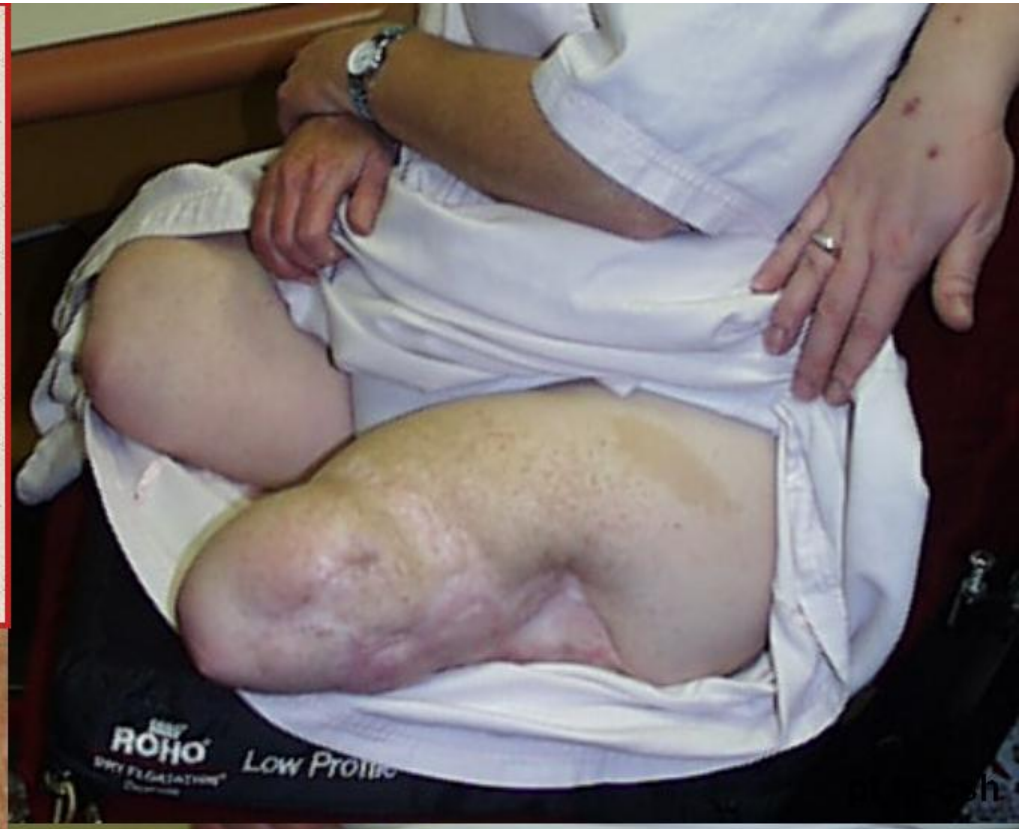
homocysteine elevated

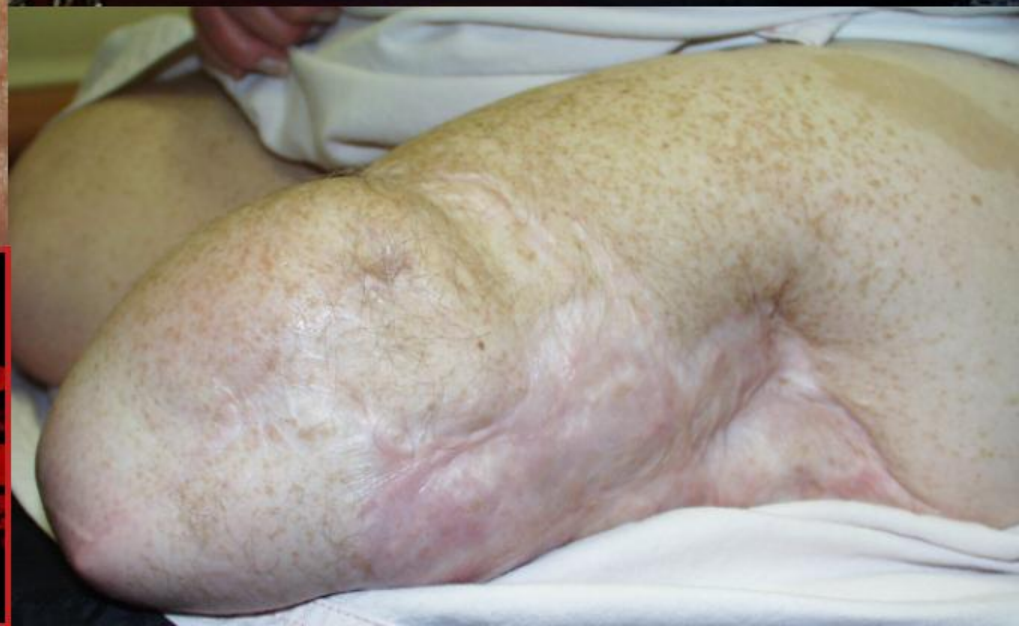
TcPO2s - periwound ischemia

healed by warfarin, hyperbaric oxygen, and integra

healed and loving life







unusual profile for ischemic necrosis
progressive necrosis and amputations
multiple complicated operations
confirmatory TcPO2
response to anticoagulation
response to hyperbaric oxygen
failure to make diagnosis

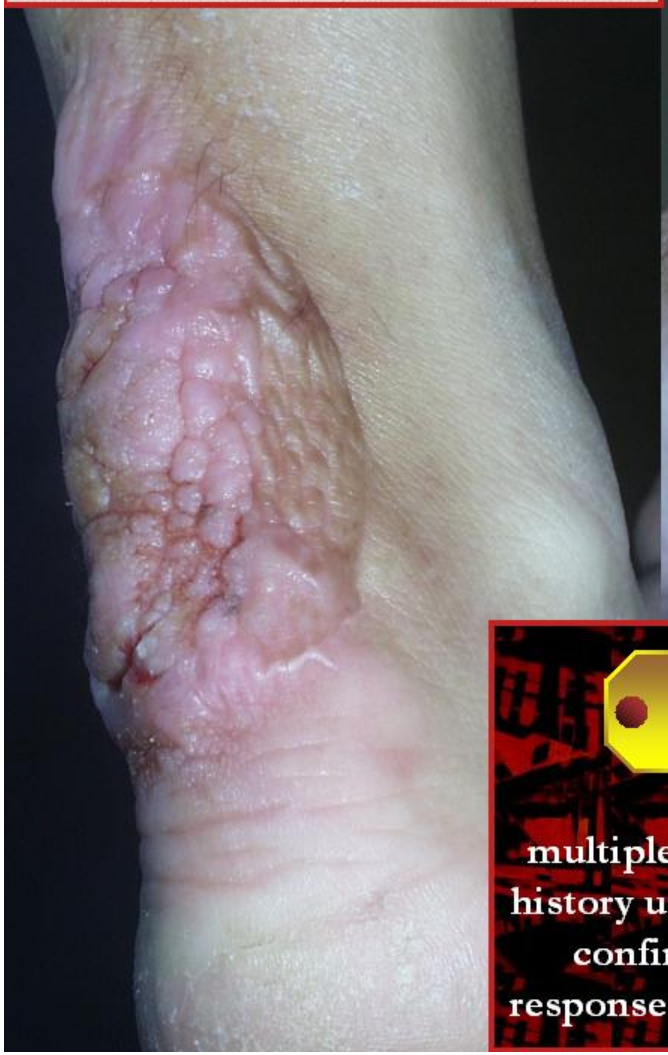
44F, achilles rupture

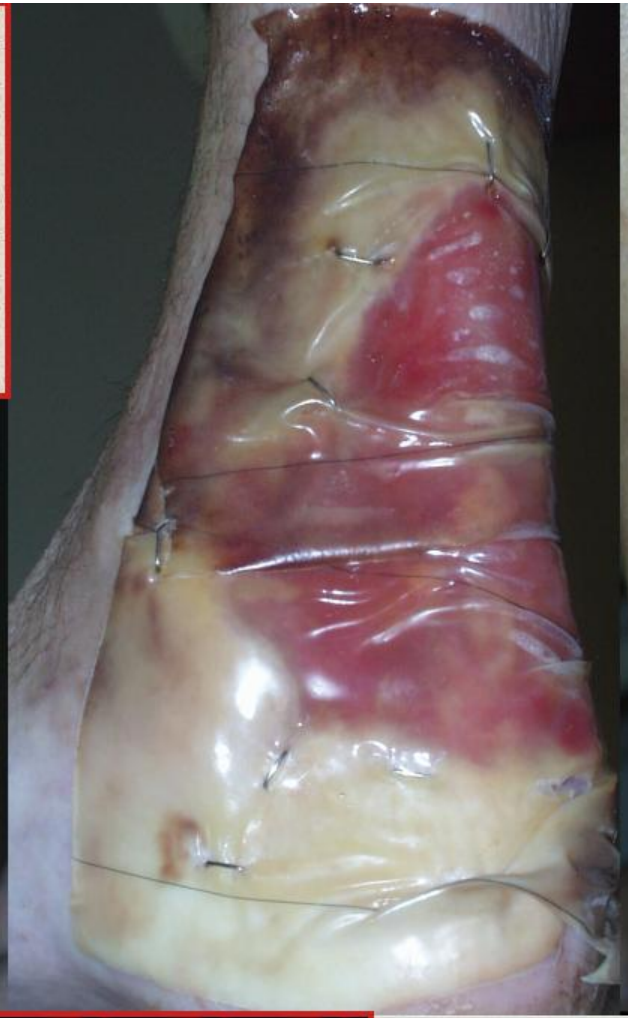
multiple failed surgery
blind from retinal artery occlusion

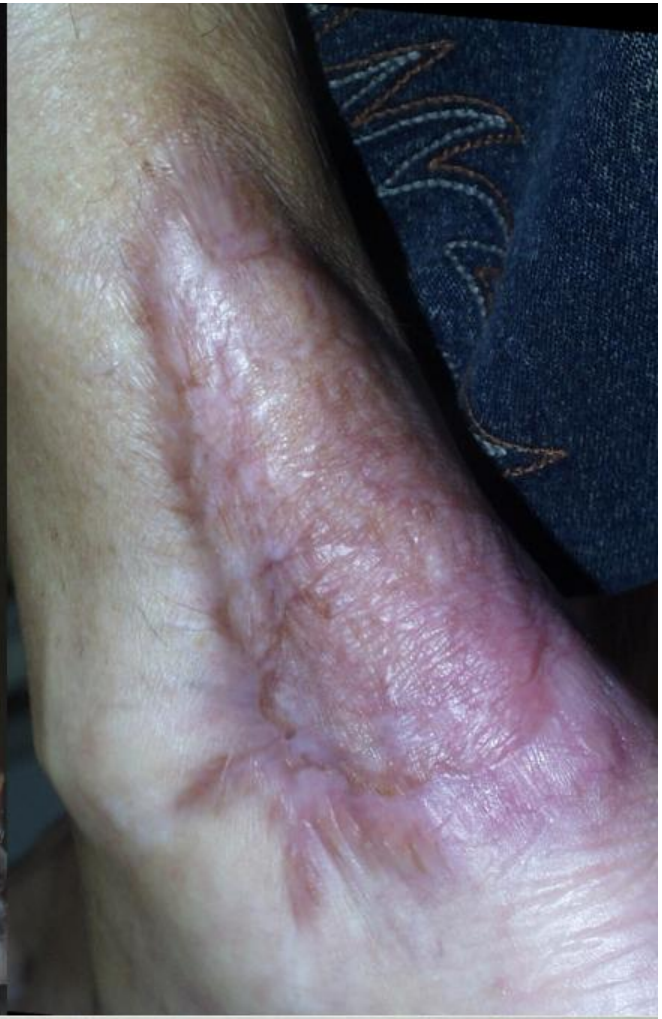
anticardiolipins elevated

TcPO2s - periwound ischemia

healed by warfarin,
hyperbaric oxygen, and integra







pathergy
multiple failed operations
history unusual thrombosis
confirmatory TcPO2
response to anticoagulation

ANTICARDIOLIP AB, IGA/IGG/IGM:			
Cardiolipin ABS, IGG	12	HI	0-10
Cardiolipin ABS, IGA 11			0-12
Cardiolipin ABS, IGM	41	HI	0-9
Fibrinogen, Quantitative:			
Fibrinogen, Quant	596	HI	170-460

Fibrinogen levels can be increased in acute phase response, pregnancy, use of estrogens and oral contraceptives.

retested and confirmed after acute phase

CLINICAL PROFILES

Young or healthy people

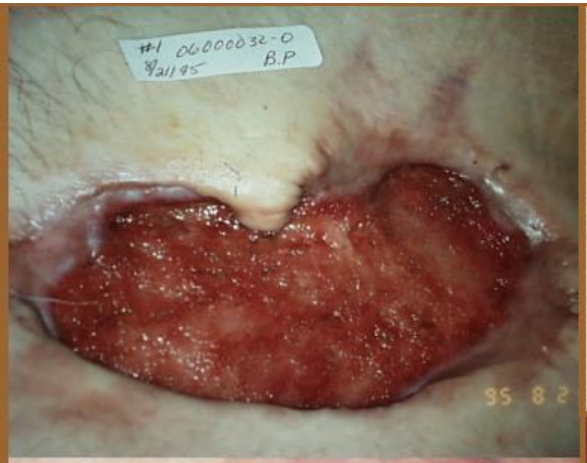
Association with connective tissue disorders

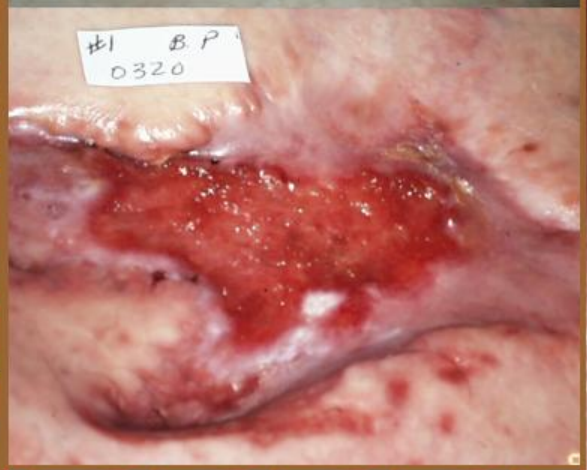
Fatal complications

Patients with other risks or diagnostic confusion

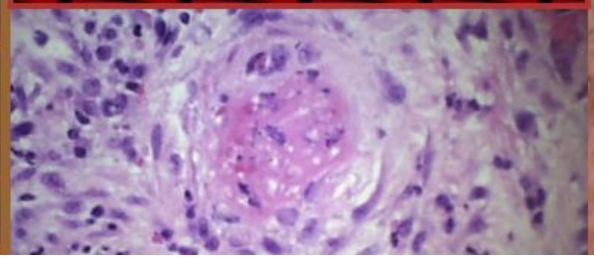
Patients who do not or who may have these disorders

Re-evaluating old patients





trauma pathergy
multiple failed operations
failed response to other care
response to anticoagulants
supportive histology



34M, lupus
rx: corticosteroids

1. problem wounds, hand and groin, following trauma

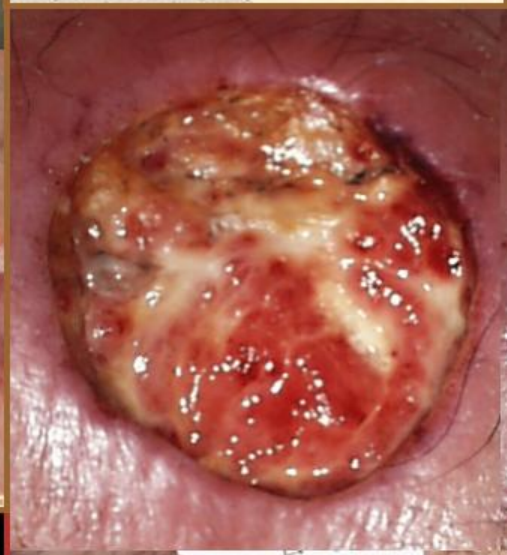
healed with difficulty with misc. care

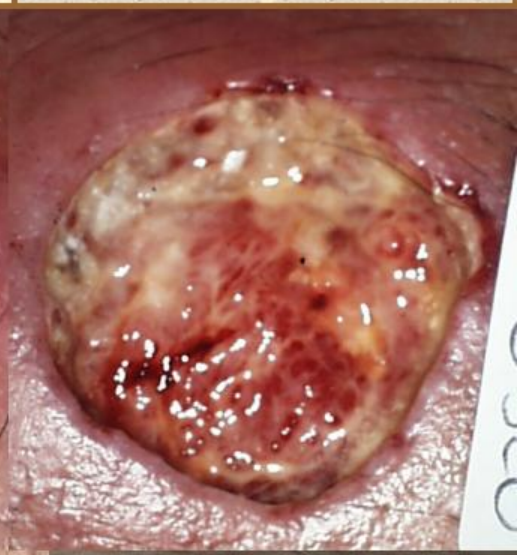
2. leg ulcer after trauma

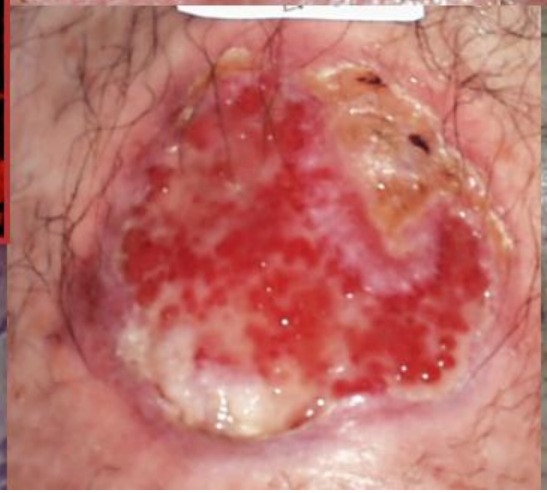
refractory to care

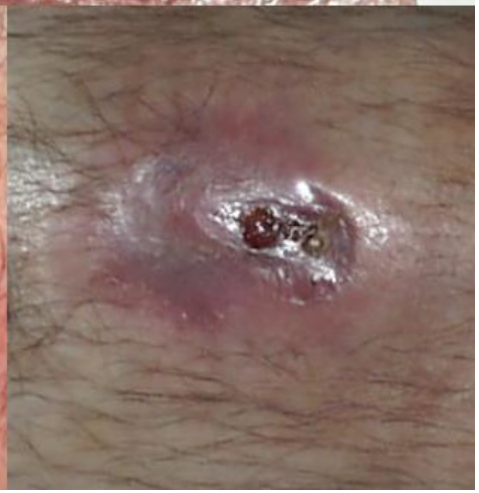
antiphospholipid antibodies

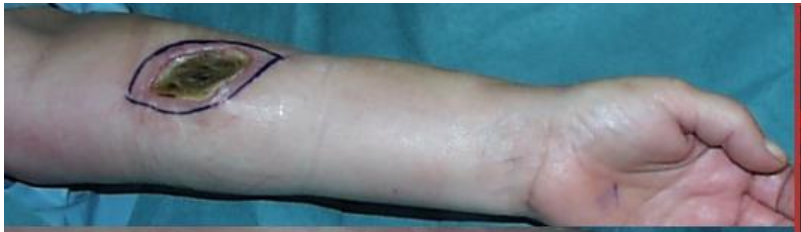
healed with warfarin

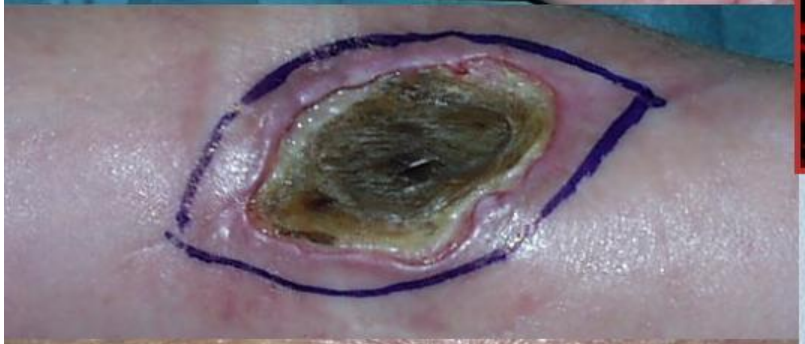


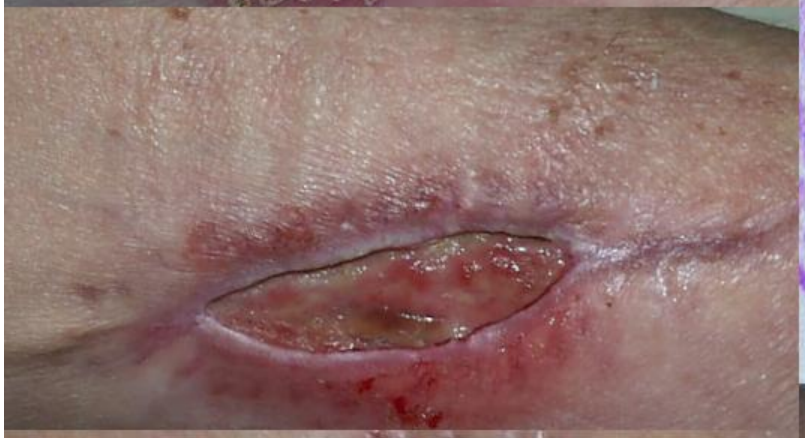


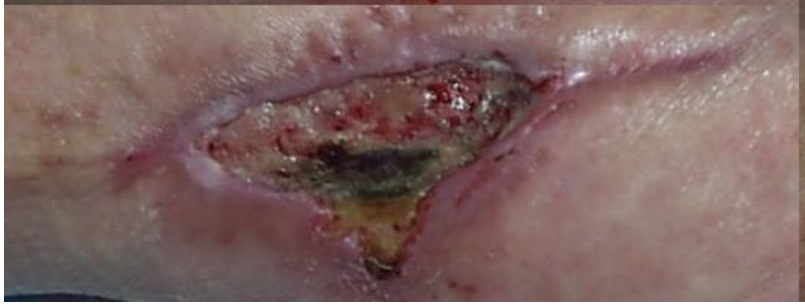












upper extremity

pathergy

repetitive necrosis

confirmatory histology

refractory to treatment

multiple failed operations

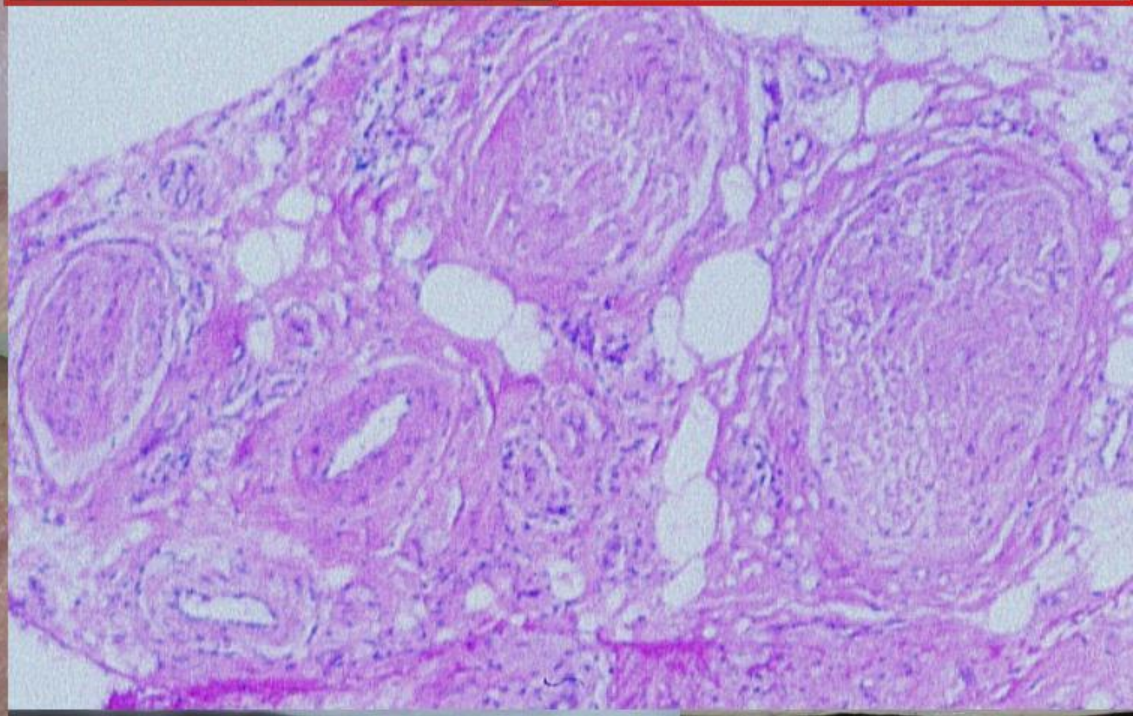
response to anticoagulation

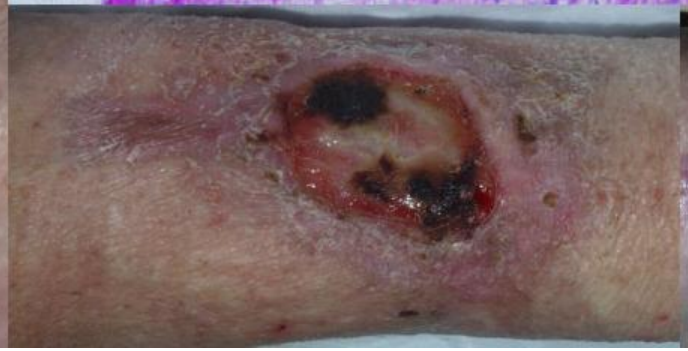
53F, dogbite forearm, rheumatoid arthritis

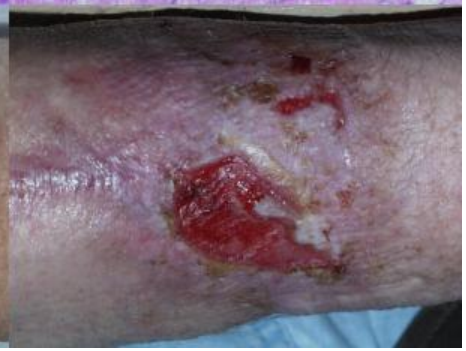
necrosis and ulceration; multiple failed procedures

proteins C & S abnormalities

healed by warfarin, but recurrent ulceration





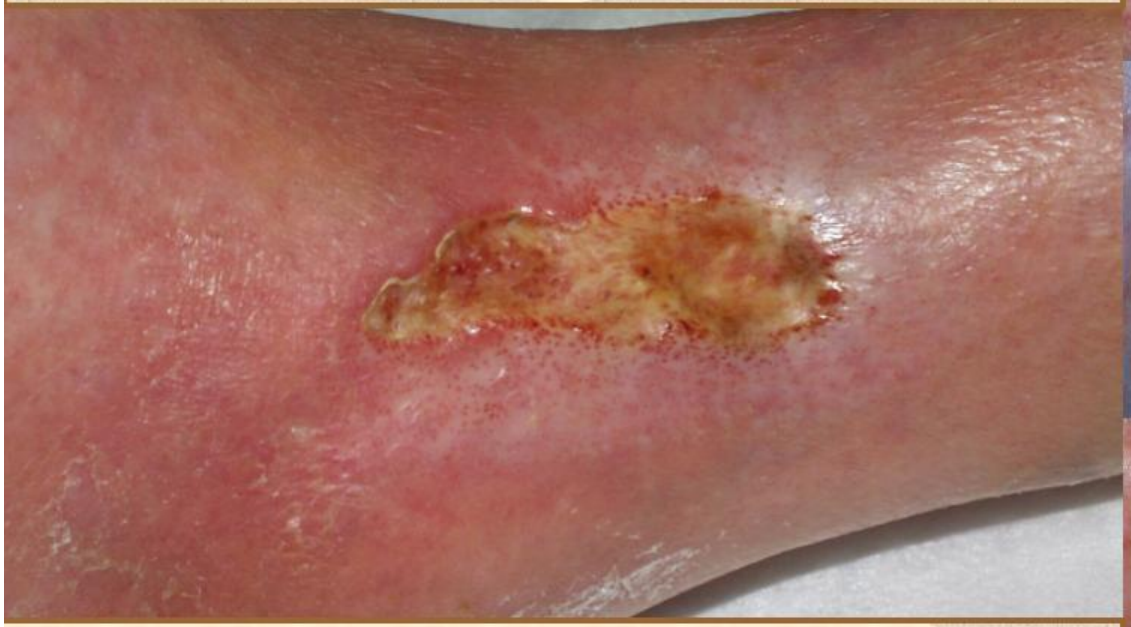


69F, active rheumatoid, hx miscarriage

no wound repair with basic care

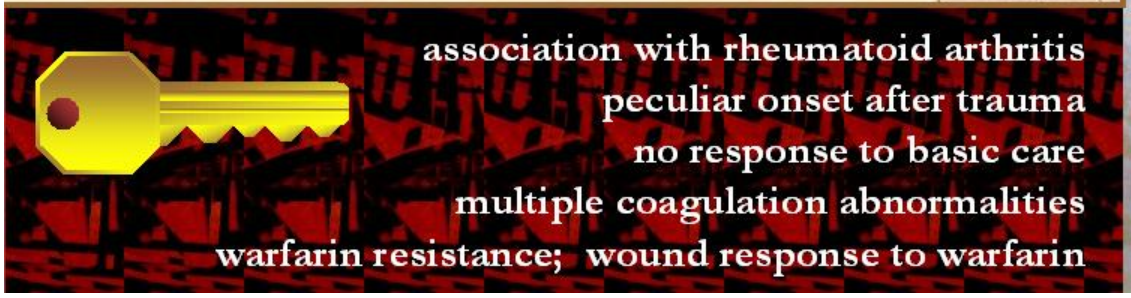
factor V Leiden heterozygous,
proteins C & S low, homocysteine high

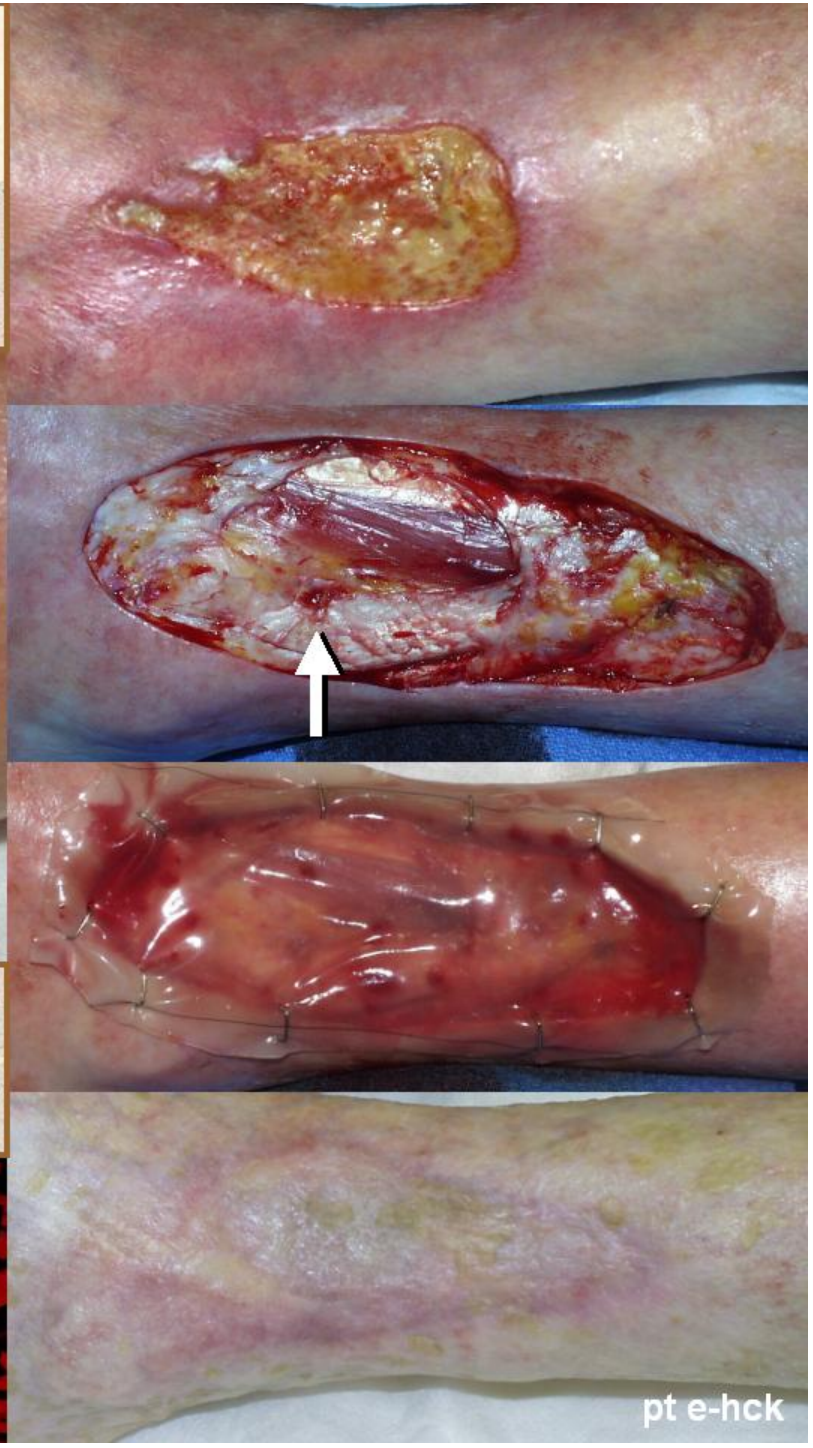
TcPO2s - periwound ischemia; ABI 0.93



hypercoagulable on warfarin; doses adjusted

healed with warfarin, hyperbaric O_2, and integra





76F, scleroderma

progressive necrosis; no wound module

multi-hypercoagulopathy

treated by warfarin and integra

died from pulmonary embolus
after withdrawal of warfarin

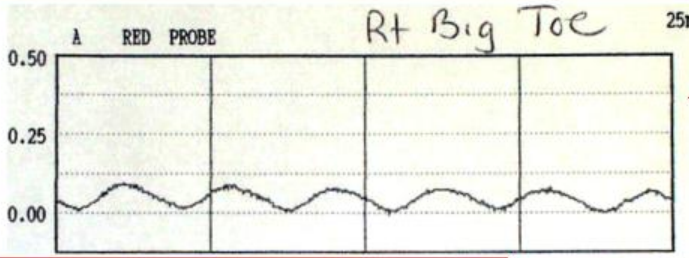
sed rate	56	<30
C-reactive protein	7.4	< 0.5
ANA	1:1280	<1:40
fibrinogen	477	150 - 350
plasminogen	> 150	70 - 130
protein S	58	72 - 157
cardiolipin IgM	134	< 15 = negative > 80 = high pos

pathergy

large vessel status

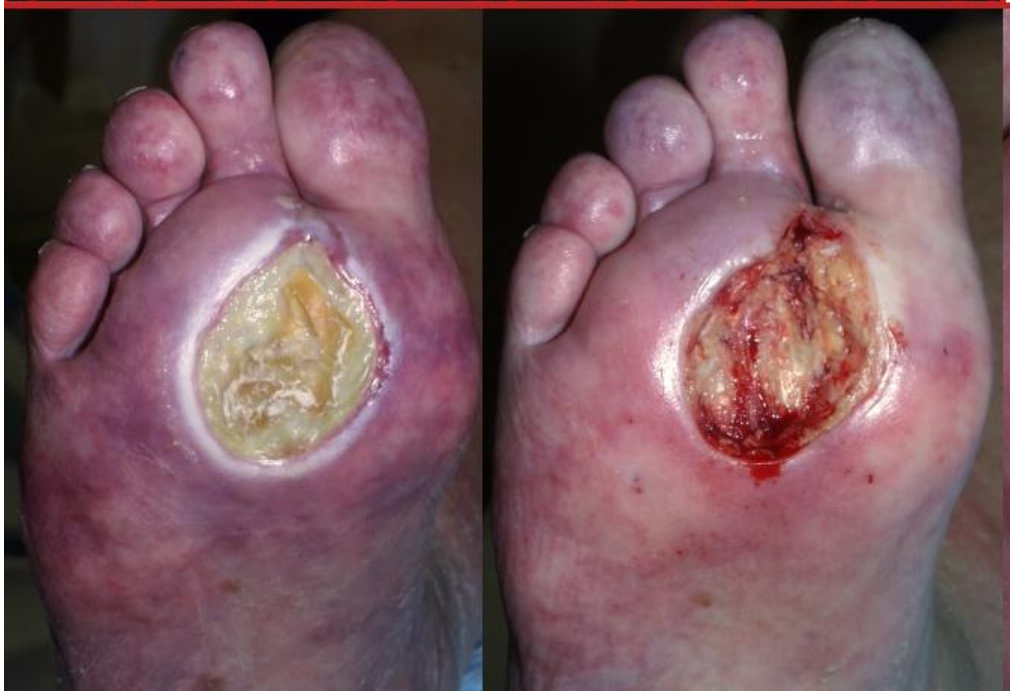
association with scleroderma

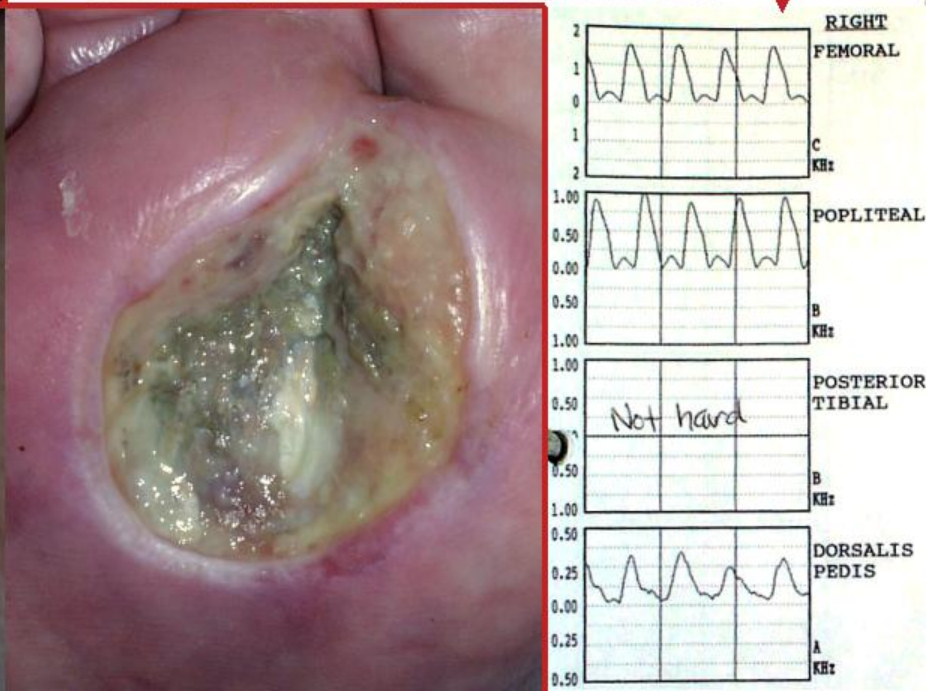
thrombosis after withdrawal of warfarin



ppg

doppler





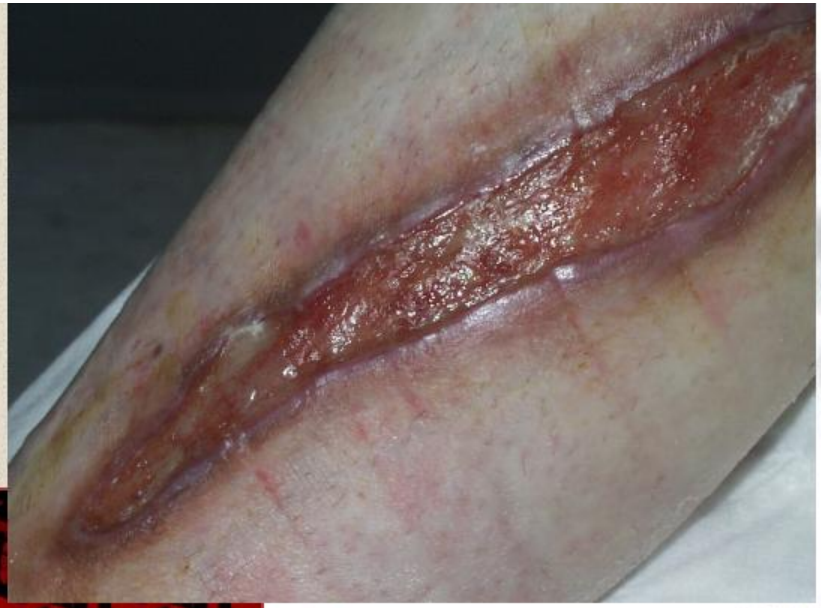
38F, lupus

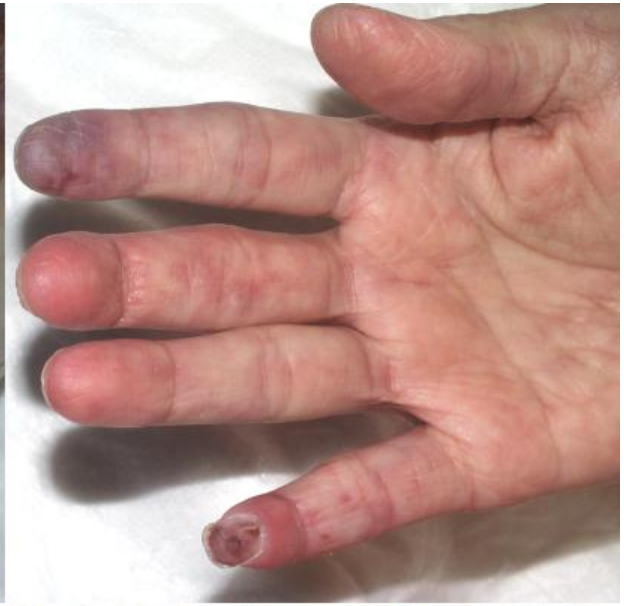
progressive necrosis;
no wound module

protein S deficient
elevated cardiolipin

no response to
any other therapy;

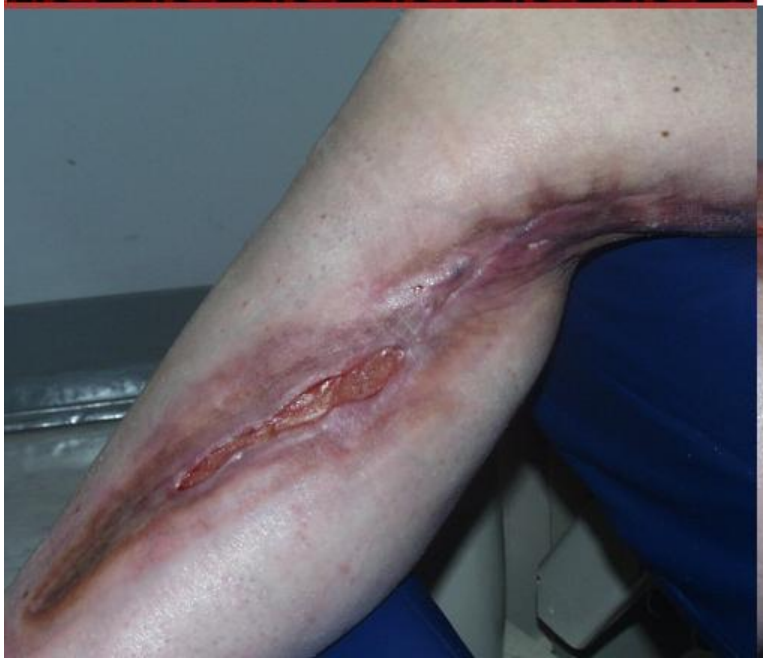
prompt response
to warfarin

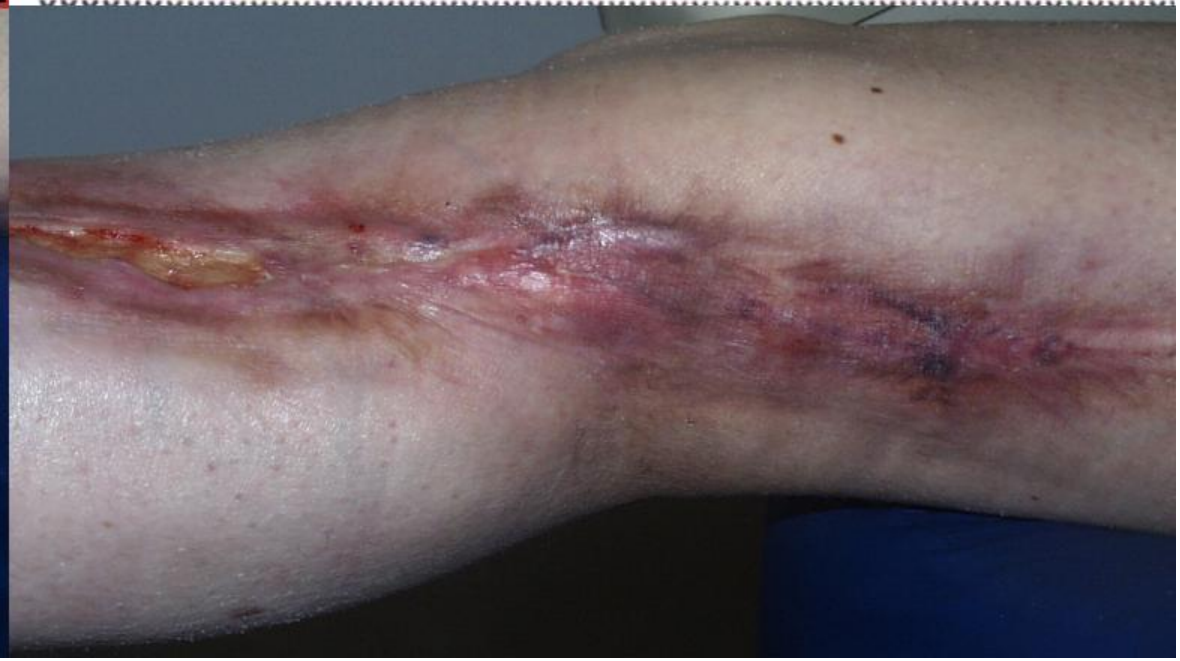




lupus
typical history and exam
no response to basic care
confusion with vasospasm
prompt response to anticoagulation

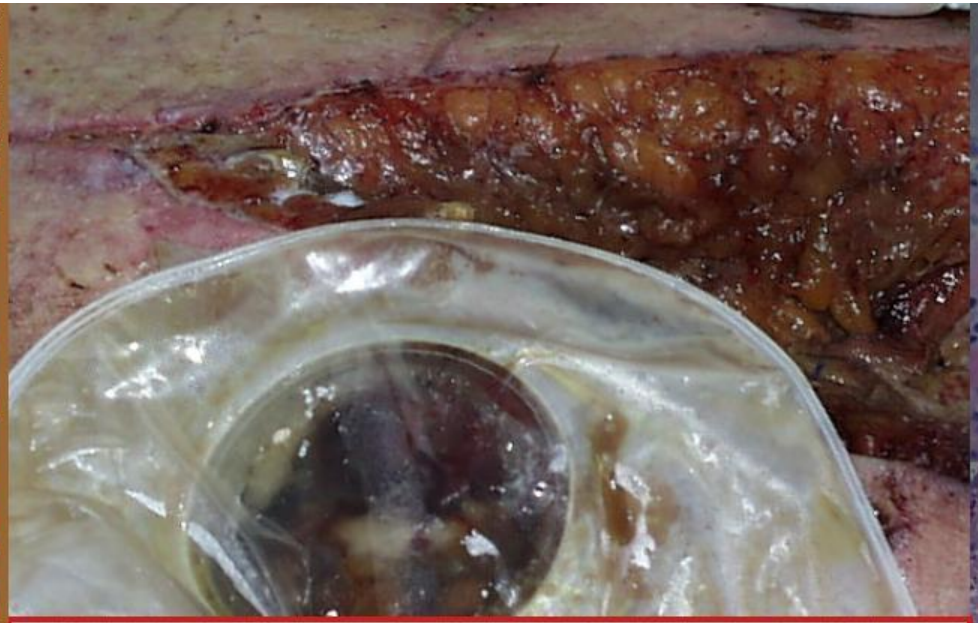
********** VALUES OUTSIDE OF REFERENCE RANGE		
* PROTEIN S ACTIVITY	40	L
* CARDIOLIPIN IgG	36	H
* CARDIOLIPIN IgM	44	H

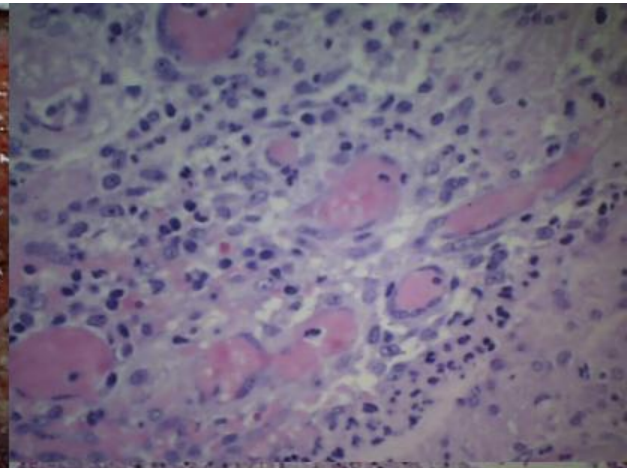


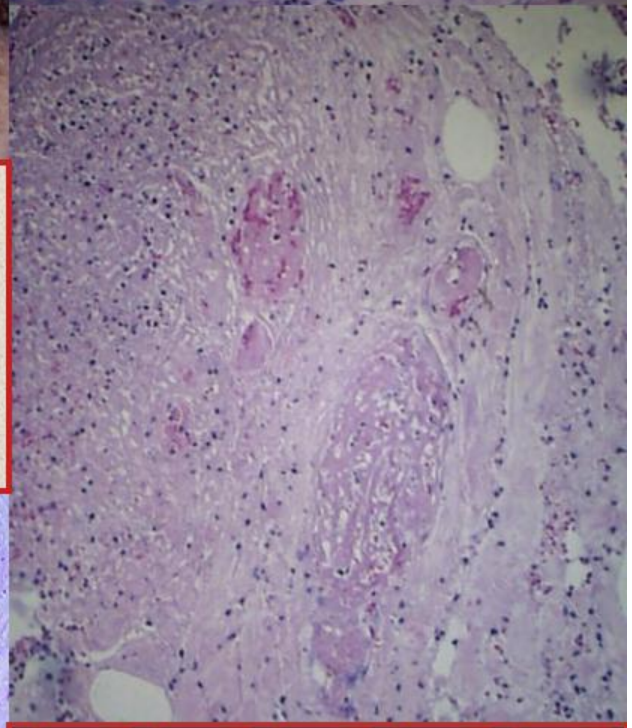


CLINICAL PROFILES

- Young or healthy people
- Association with connective tissue disorders
- **Fatal complications**
- Patients with other risks or diagnostic confusion
- Patients who do not or who may have these disorders
- Re-evaluating old patients







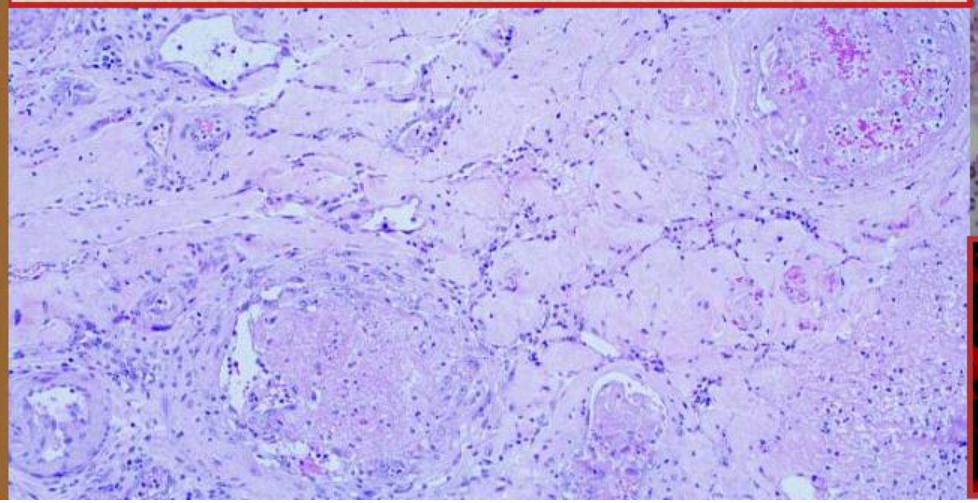
62 M: diverticular colo-vesical fistula

hx dvt/pe, finger necrosis from minor injury

multiple operations with progressive necrosis of bowel and abdominal wall

activated protein C deficiency

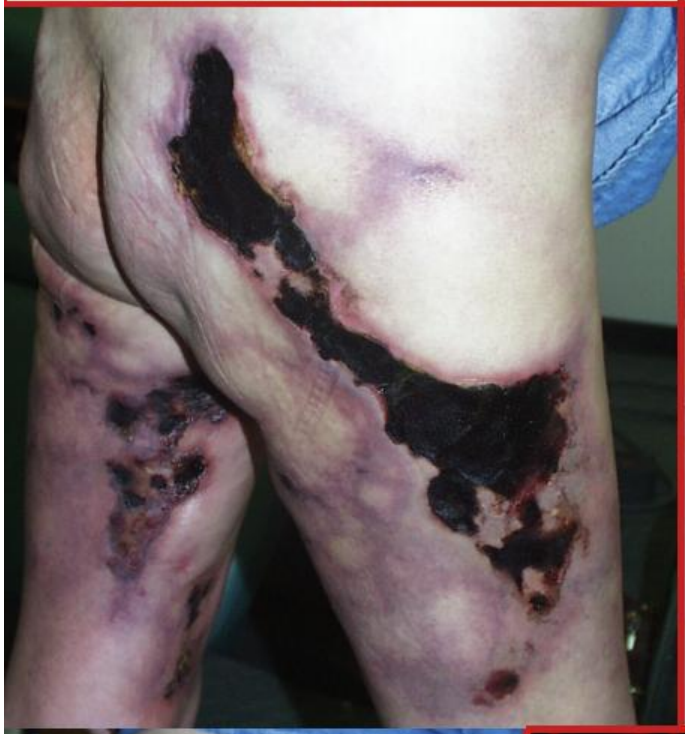
anticoagulation, hbo, other rx suggested

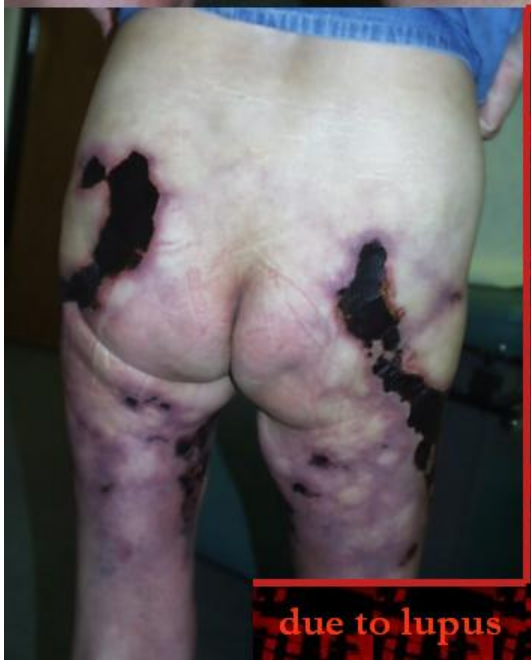


history of thrombosis
pathergy
positive histology
multiple infarctions
multiple wound complications

35F, acute lupus protein S deficient

58M, coronary angioplasty activated protein C resistant





multiple infarctions

multiple wound complications

triggered by warfarin

misdiagnosed as pyoderma

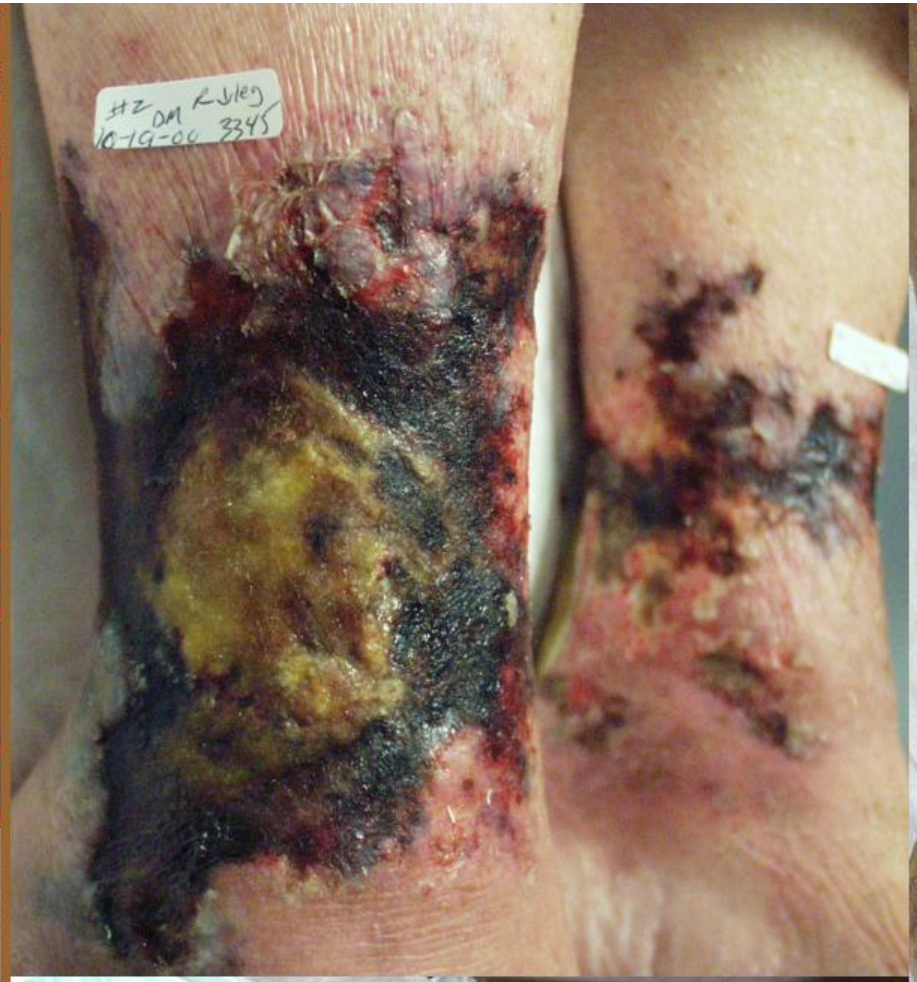
incompetent wounds

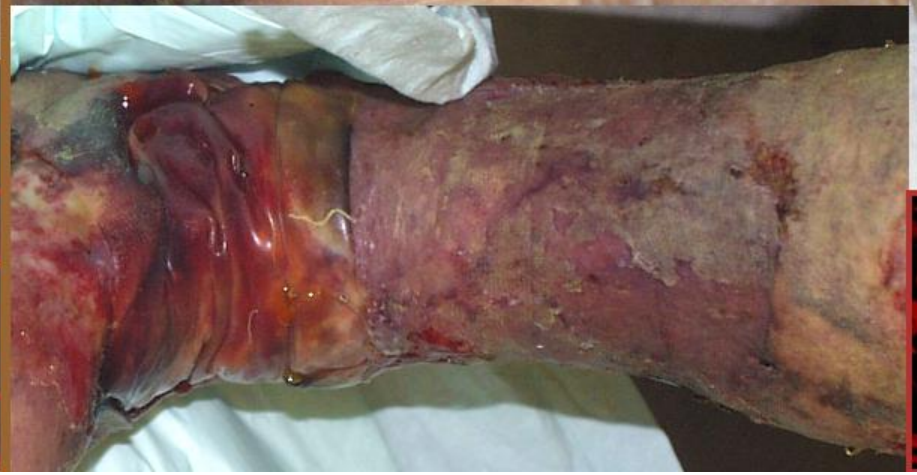
microthrombosis only

due to lupus

CLINICAL PROFILES

- Young or healthy people
- Association with connective tissue disorders
- Fatal complications
- Patients with other risks or diagnostic confusion
- Patients who do not or who may have these disorders
- Re-evaluating old patients





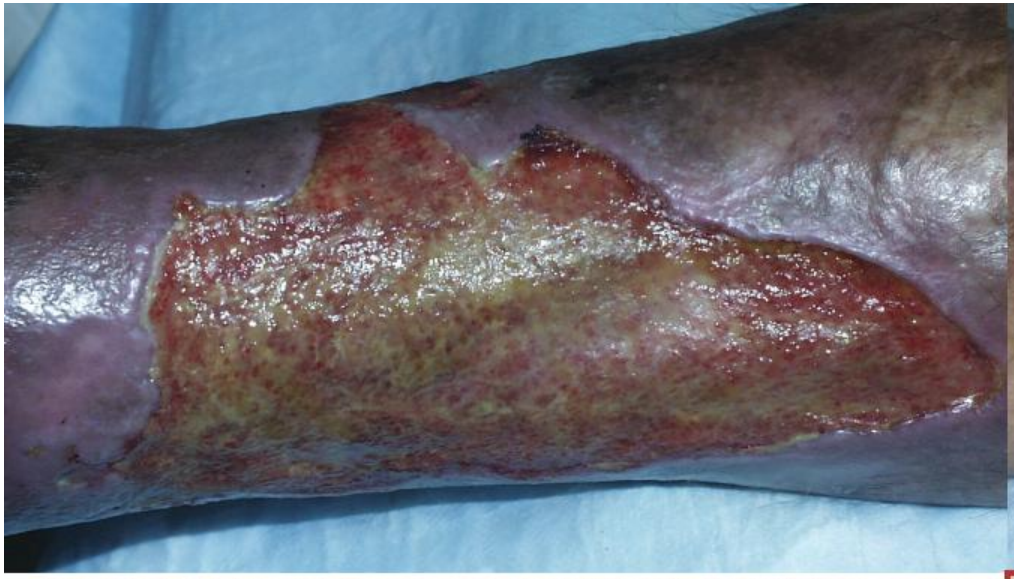
67F, aso/pvod

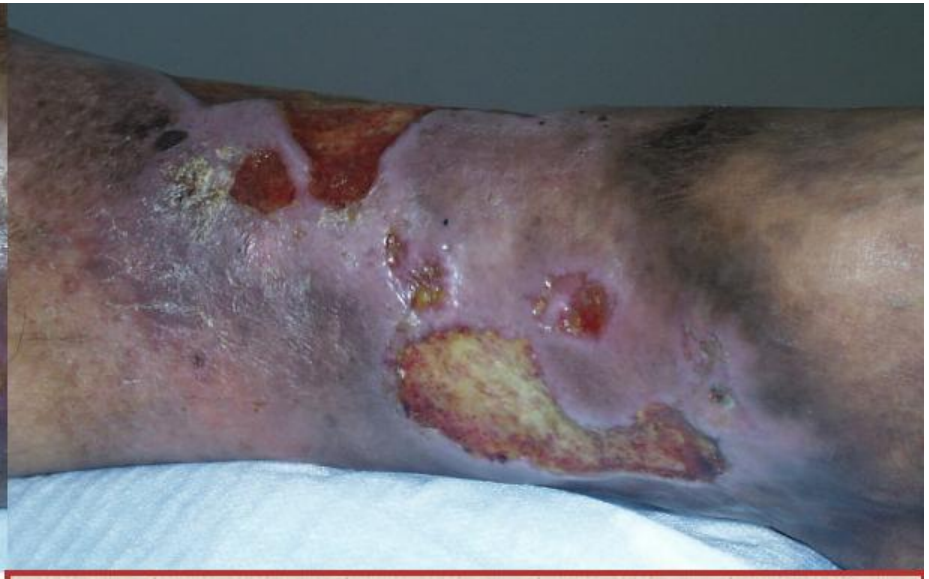
progressive leg necrosis

antithrombin-3 deficiency

healed by warfarin, hbo, and integra

mixed pathologies
history and wounds typical
response to anticoagulation





********** VALUES OUTSIDE OF REFERENCE RANGE **********		
* RDW	16.3	H
* CHOLESTEROL	236	H
* TRIGLYCERIDE	269	H
* LDL CHOLESTEROL, CALC.	155	H
* VLDL CHOLESTEROL	45	H
* CHOL/HDL RATIO	6.6	H
* C-REACTIVE PROTEIN (CRP)	35.4	H
* HOMOCYSTEINE	14.5	H
* ANA SCREEN	Positive	
* ANA TITER	1:80	
* ANA PATTERN	Speckled	
* CHOLESTEROL, SERUM	249	H
* BETA LIPOPROTEINS	INCREASED	*
* PRE-BETA LIPOPROTEINS	INCREASED	*
* SERUM APPEARANCE	OPALESCENT	*
* PLASMINOGEN ACTIVITY	>150	H
* PROTEIN C ACTIVITY	158	H
* FIBRINOGEN	699	H

****

CARDIOLIPIN IgM	16

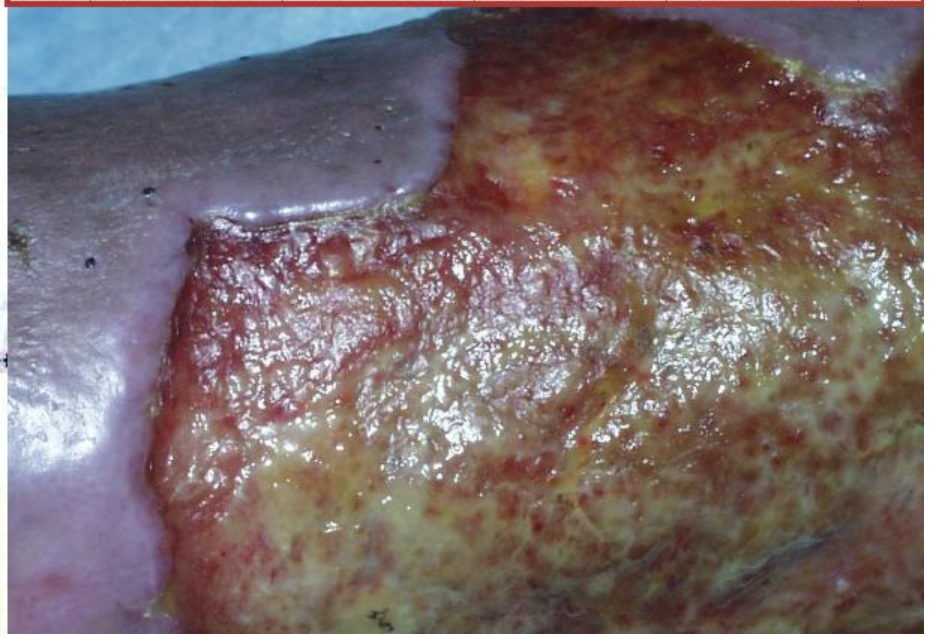
Reference Range for Cardiolipin IgM

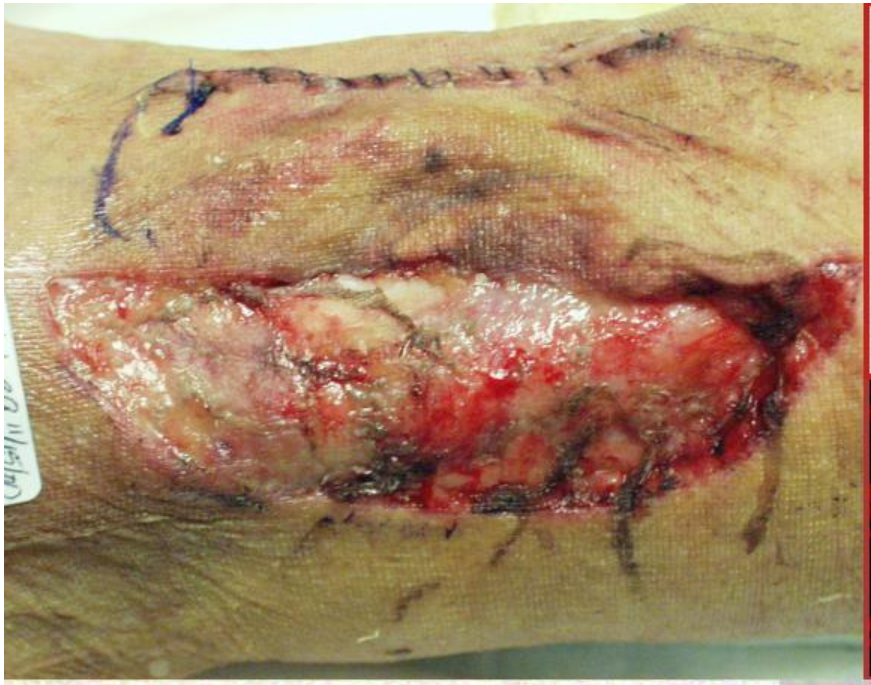
IgM Result:	Interpretation:
<12	Negative
12-20	Indeterminate
21-80	Low to Medium Positive
>80	High Positive

35M, dm, hyperlipidemia, aso/pvod

leg ulcers many years

hypercoagulability ? immunopathy ?



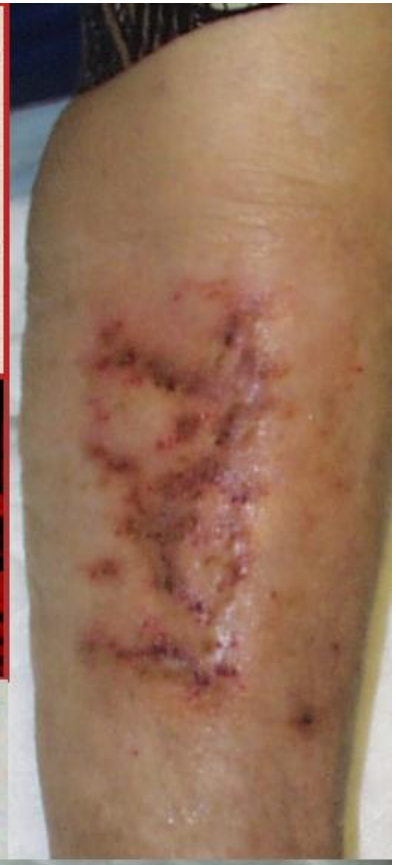


72F, chronic ankle ulcer

necrosis, dehiscence, delayed healing after surgery

protein C & cardiolipin abnormalities

warfarin for future problems

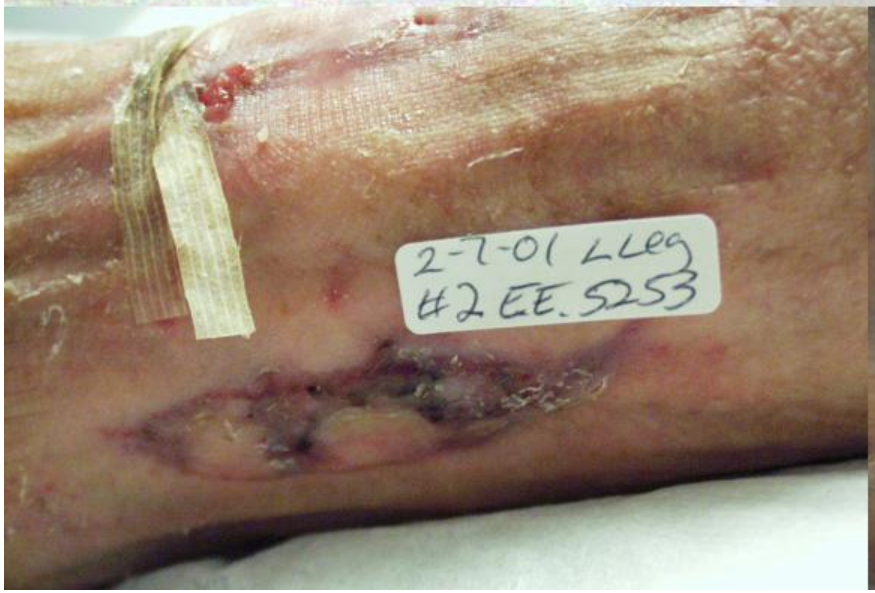


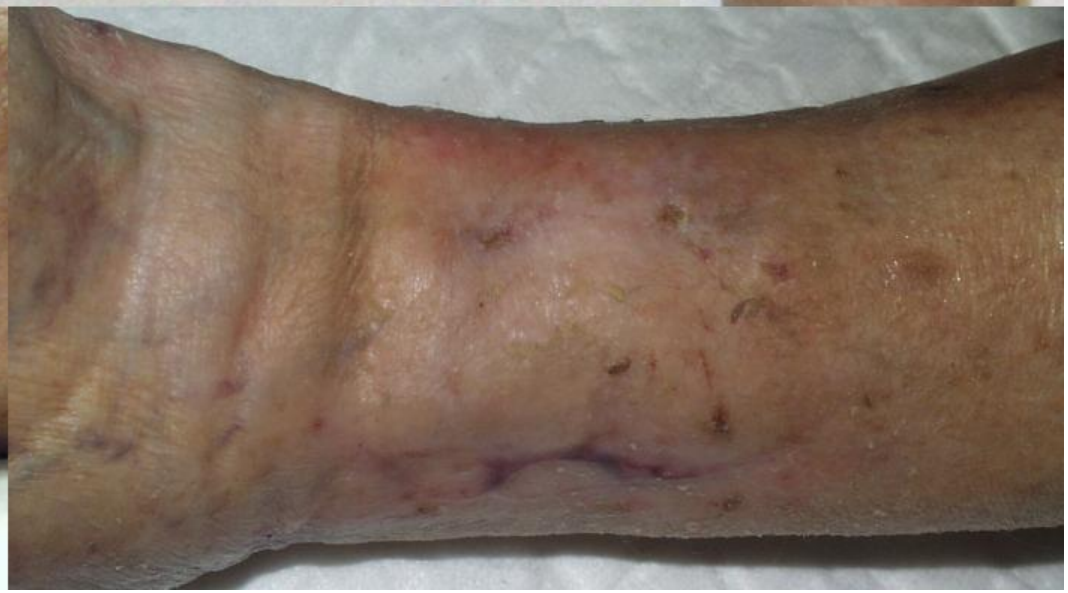
********* VALUES OUTSIDE OF REFEREN

* PROTEIN C ACTIVITY	131	H
* CARDIOLIPIN IgM	36	H

****

TEST	
ANA QUANT	1:320*
ANA PATTERN	HOMOGEN*





CLINICAL PROFILES

- Young or healthy people
- Association with connective tissue disorders
- Fatal complications
- Patients with other risks or diagnostic confusion
- Patients who do not or who may have these disorders
- Re-evaluating old patients

MOLECULAR GENETICS REPORT: FACTOR II PROTHROMBIN

Accession # 01-132-1428

Result	Allele Size	
Normal Genotype	345 bp	Homozygous

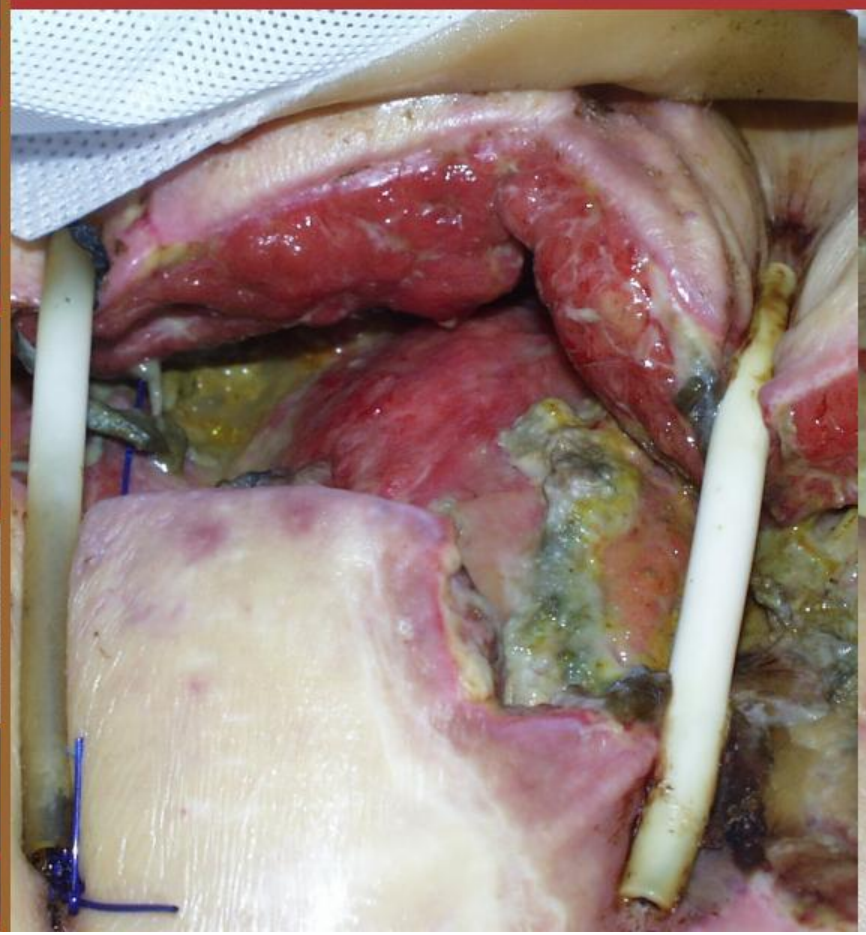
INTERPRETATION: This patient shows evidence for being homozygous for the **normal** 345 bp allele for the Prothrombin gene (mutation in which has been shown to be associated with increased plasma prothrombin concentrations and a subsequent increased risk for venous Thrombosis).

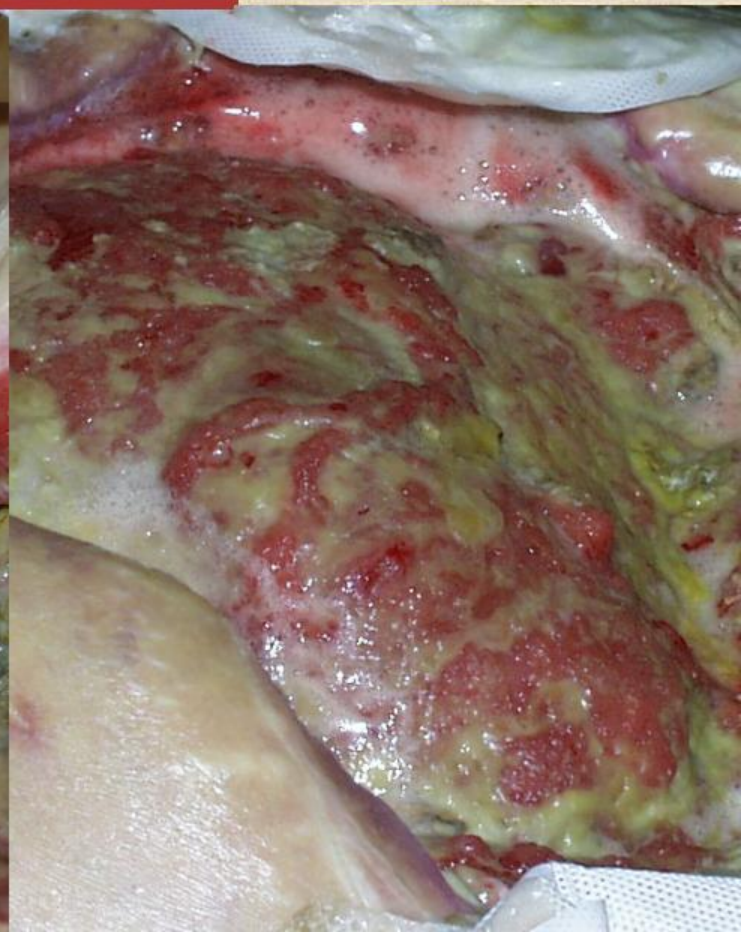
COMMENT: This result should be interpreted in the context of available clinical findings. This result does not rule out increased prothrombin or an increased risk for venous Thrombosis due to other factors.

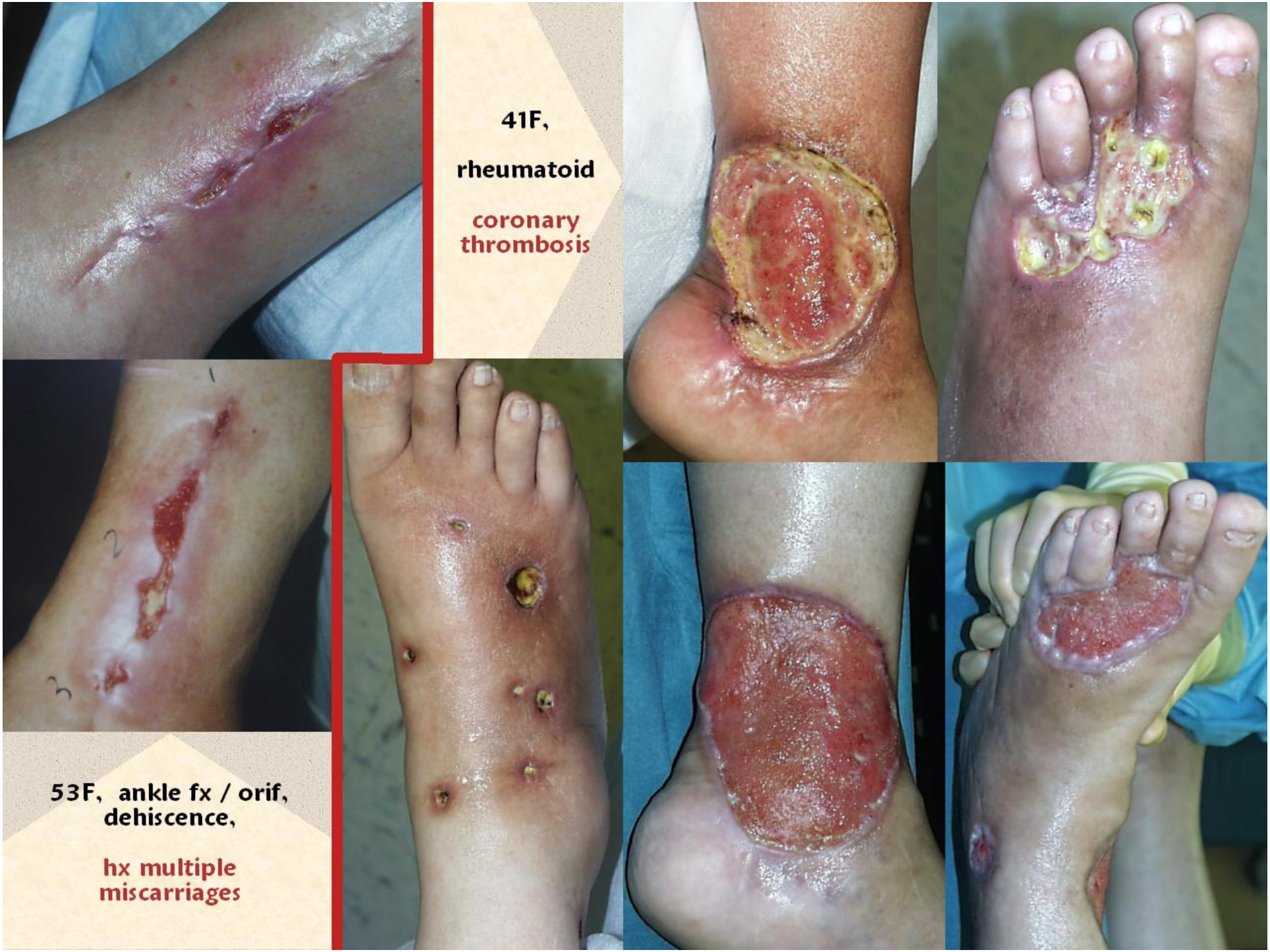
60F, iliac vein injury and ligation,

subsequent dopplers: venous thrombosis

74F, peritonitis, fistulas, dehiscence






41F,
rheumatoid
coronary thrombosis
53F, ankle fx / orif, dehiscence,
hx multiple miscarriages

CLINICAL PROFILES

- Young or healthy people
- Association with connective tissue disorders
- Fatal complications
- Patients with other risks or diagnostic confusion
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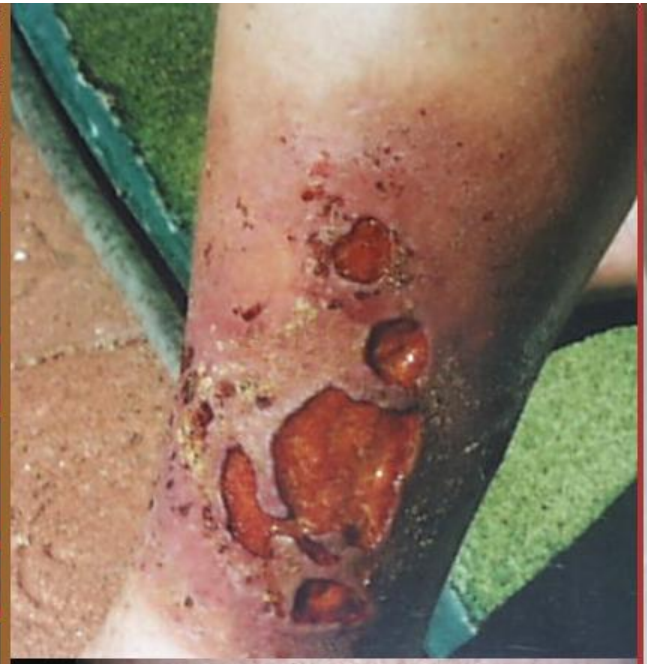
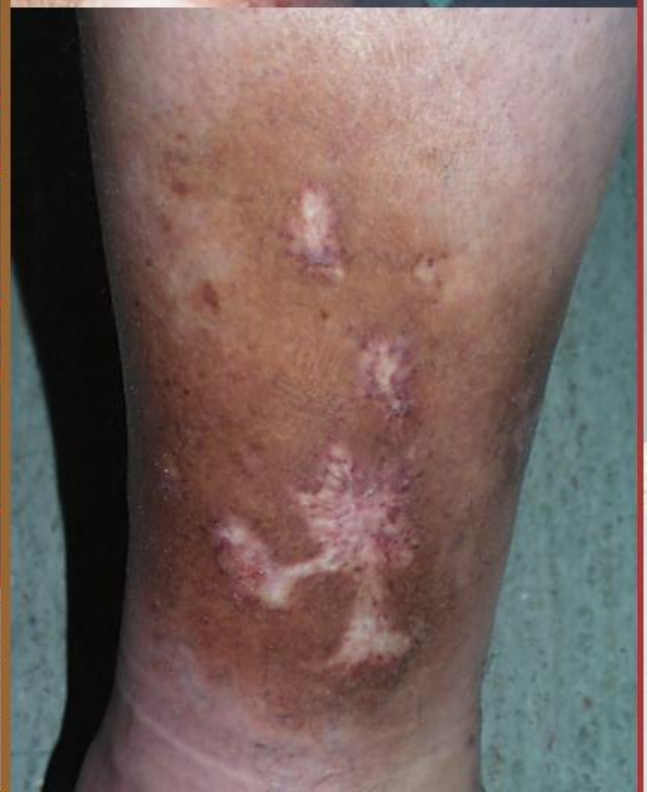
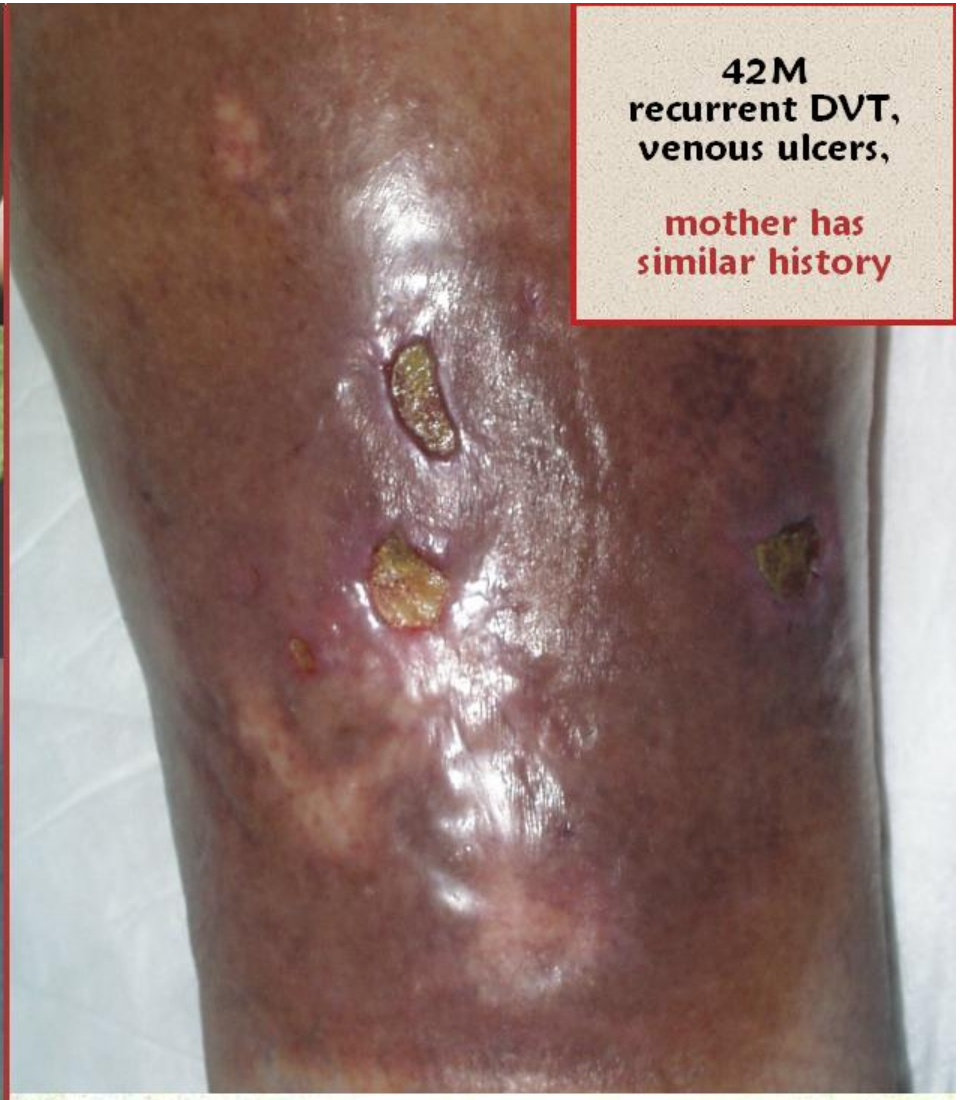






42M
recurrent DVT, venous ulcers,

mother has similar history

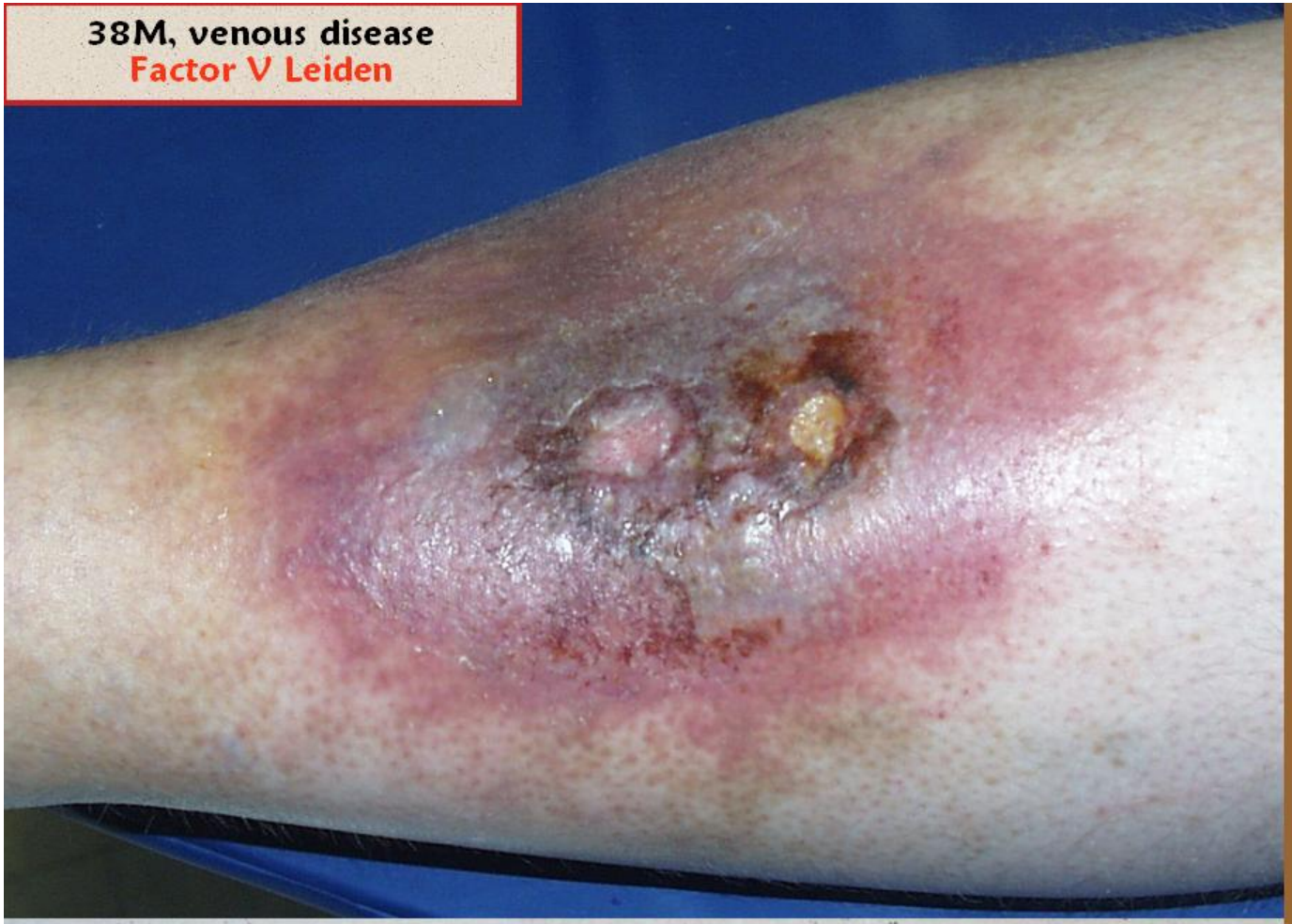
HOMOCYSTEINE	16.1	H	5.4–11.9

********** VALUES OUTSIDE OF REFERENCE RANGE *****

* FACTOR V LEIDEN MUTATION	HETEROZYGOUS	
* ANTI-THROMBIN III ACTIVITY	74	L
* PROTEIN C ANTIGEN	68	L
* CARDIOLIPIN IgA	15	H
* CARDIOLIPIN IgG	66	H

****

38M, venous disease
Factor V Leiden

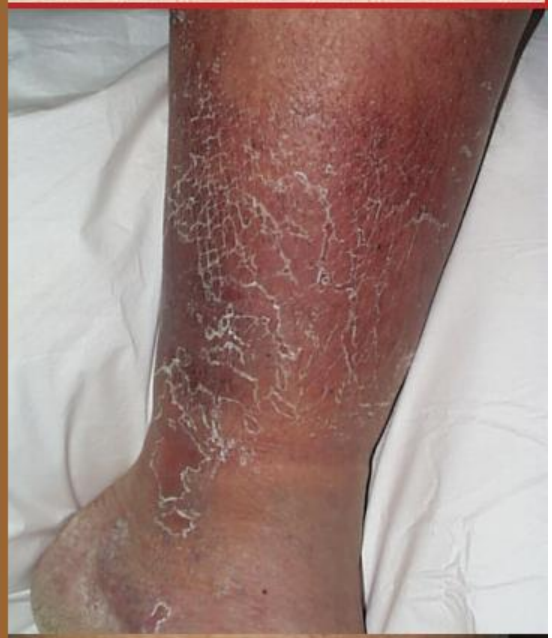


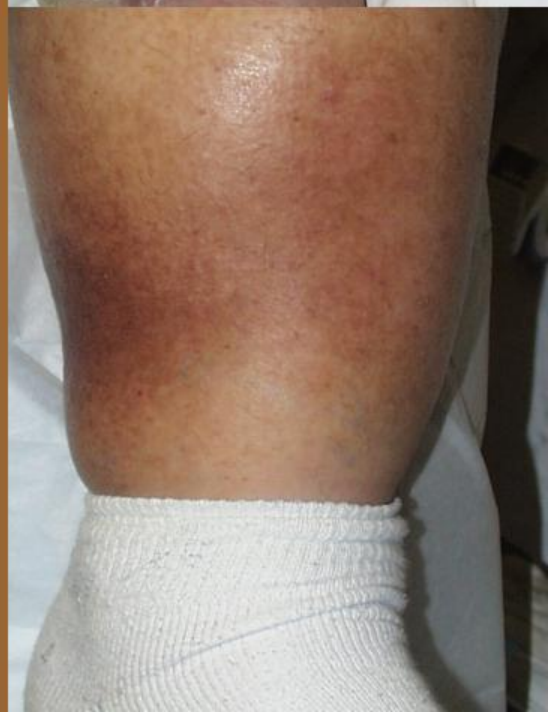
REASON FOR CONSULTATION: Deep venous thrombosis.

Dear Dr. Van den Broeck:

I had the pleasure of seeing Mr. Hendrix in clinic for evaluation of his history of deep venous thrombosis. The patient did have a blood test after his last visit. CMP was okay. CBC was okay. PT was 22. PTT was elevated at 42, INR 2.1, anti-thrombin was 22, protein C was slightly low at 68, protein S 80, and activated protein C resistance was in the normal range of 1.03. Fibrinogen was 415, factor II mutation negative, lupus anticoagulant negative, and homocysteine normal at 9.9. The patient did have testing done for factor V lightened gene mutation, which came back abnormal. He is heterozygote for this mutation, which can predispose the patient for having underlined thrombosis. The patient did undergo maximum study and the PTT was corrected. The patient has no complaints.

42M, venous disease
Factor V Leiden



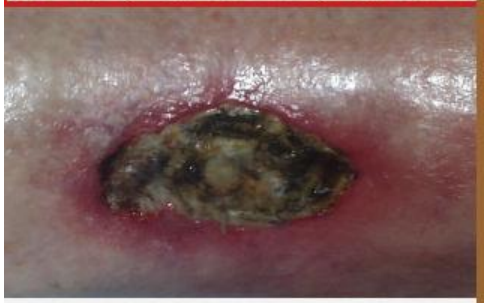


MISCELLANEOUS

80F, progressive refractory leg ulcers

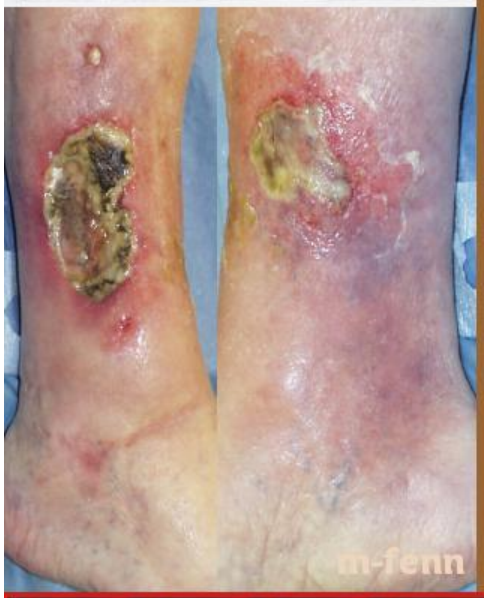
Died from CVA before any rx

Proteins C & S deficient



FIBRINOGEN	386H
PROT C ACTIVITY	12C
PROT S ACTIVITY	43L

H=High, L=Low, C=Critical



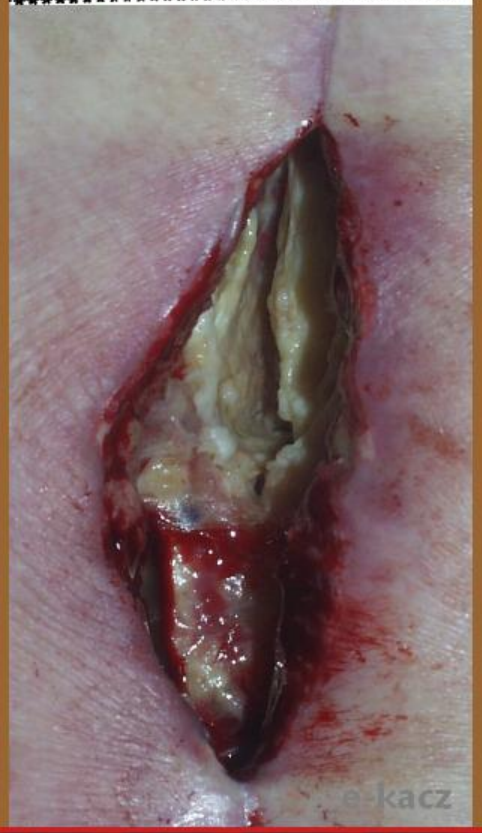
67F, back surgery necrosis and dehiscence

Jehovah's Witness

family history venous dx

Factor V Leiden

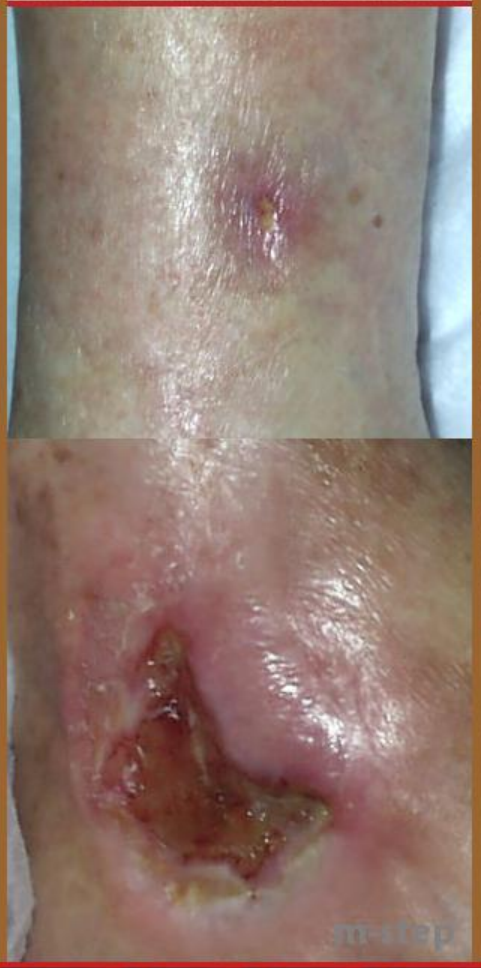
********** VALUES OUTSIDE OF REF	
FACTOR V LEIDEN MUTATION	HETERZ
PLASMINOGEN ACTIVITY	135
PROTEIN C ACTIVITY	136
FIBRINOGEN	640



88F, unhealed ankle and leg ulcers, 60 years

multiple miscarriages

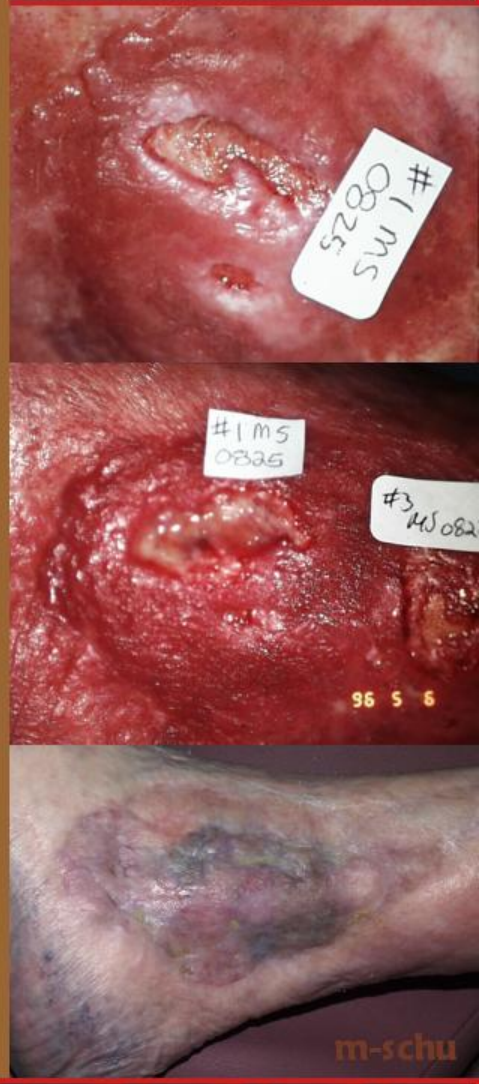
anticardiolipins elevated cryofibrinogen



74F, recurrent ankle ulcers 30 years

hx multiple DVT

platelet & coagulopathy



long history, acute history, pathergy, multiple failed surgery, miscarriages, family history, recurrent pathology, characteristic patterns of disease, refractory to treatment, hypercoagulability

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

CASE 12-1996

PRESENTATION OF CASE

An 18-year-old woman was admitted to the hospital because of hepatomegaly and ascites.

The patient had been in excellent health until four weeks earlier, when she started taking norethindrone–ethinyl estradiol tablets. Four days later, she began to have abdominal "bloating" and discontinued the medication; she continued to vomiting. Her physician gain of 3.6 kg over a peri abdominal distention. A results of tests of liver f the abdomen showed dist physician subsequently d mographic (CT) scan o firmed the presence of as enlarged.

Four days before admi amination of the abdom paracentesis yielded 3 li contained 160,000 red ce white cells per cubic mill phocytes; the total prote deciliter. Microscopical vealed no microorganism showed no malignant-ty patient had increasing a fever, and she entered an

The patient was not se ination three months e menses were normal; her curred 23 days before ad tions. She had traveled t met and to Israel two ye in moderation and did no

There was no recent his

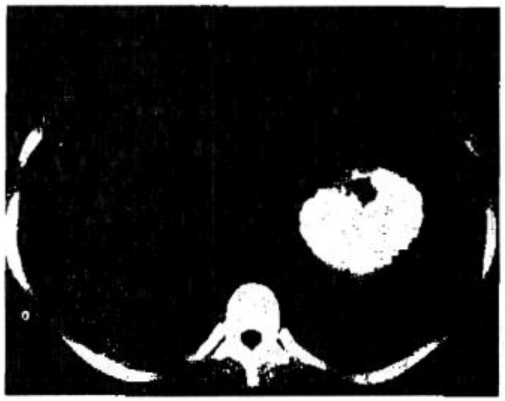


Figure 1. Axial CT Scan at the Level of the Portal-Vein Bifurcation. Obtained without the Intravenous Administration of Contrast Material, Showing Ascites and an Enlarged Spleen. Barium is present in the stomach.

Table 1. Hematologic Values.

VARIABLE	2 DAYS BEFORE ADMISSION	ON ADMISSION
Hematocrit (%)	Normal	43.1
Mean corpuscular volume (μm³)		78
Erythrocyte sedimentation rate	Normal	
[illegible] (per mm³)		13,000
[illegible] (%)		
[illegible]		71
[illegible]		4
[illegible]		23
[illegible]		2
[illegible] (per mm³)	133,000	225,000
[illegible] (sec)	15	14.1*
[illegible] time	37	40.7

* [illegible] seconds

[illegible] fever, lymphadenopathy, back or bone [illegible] pruritus, menstrual changes, abdomi- [illegible] risk factors for infection with the human [illegible] virus.

[illegible] examination was normal except for as- [illegible]ble liver edge 2 cm below the right cos- [illegible] spleen was not felt. No icterus or lym- [illegible]as found, and the rectal examination

[illegible]laboratory tests were performed (Table [illegible]brin-split products was positive, with a [illegible]an 40 and less than 66 μg per milliliter [illegible]<10; value usually considered abnor- [illegible] conjugated bilirubin concentration was [illegible]liter (9 μmol per liter), and the total bil- [illegible]ation was 1.5 mg per deciliter (26 μmol [illegible]-glutamyltransferase concentration was [illegible] normal range, 7 to 33). The values for

Case reported April 1996

18 F, healthy

starts birth control pills

→

Budd-Chiari
hepatic vein thrombosis

→

Protein C deficiency

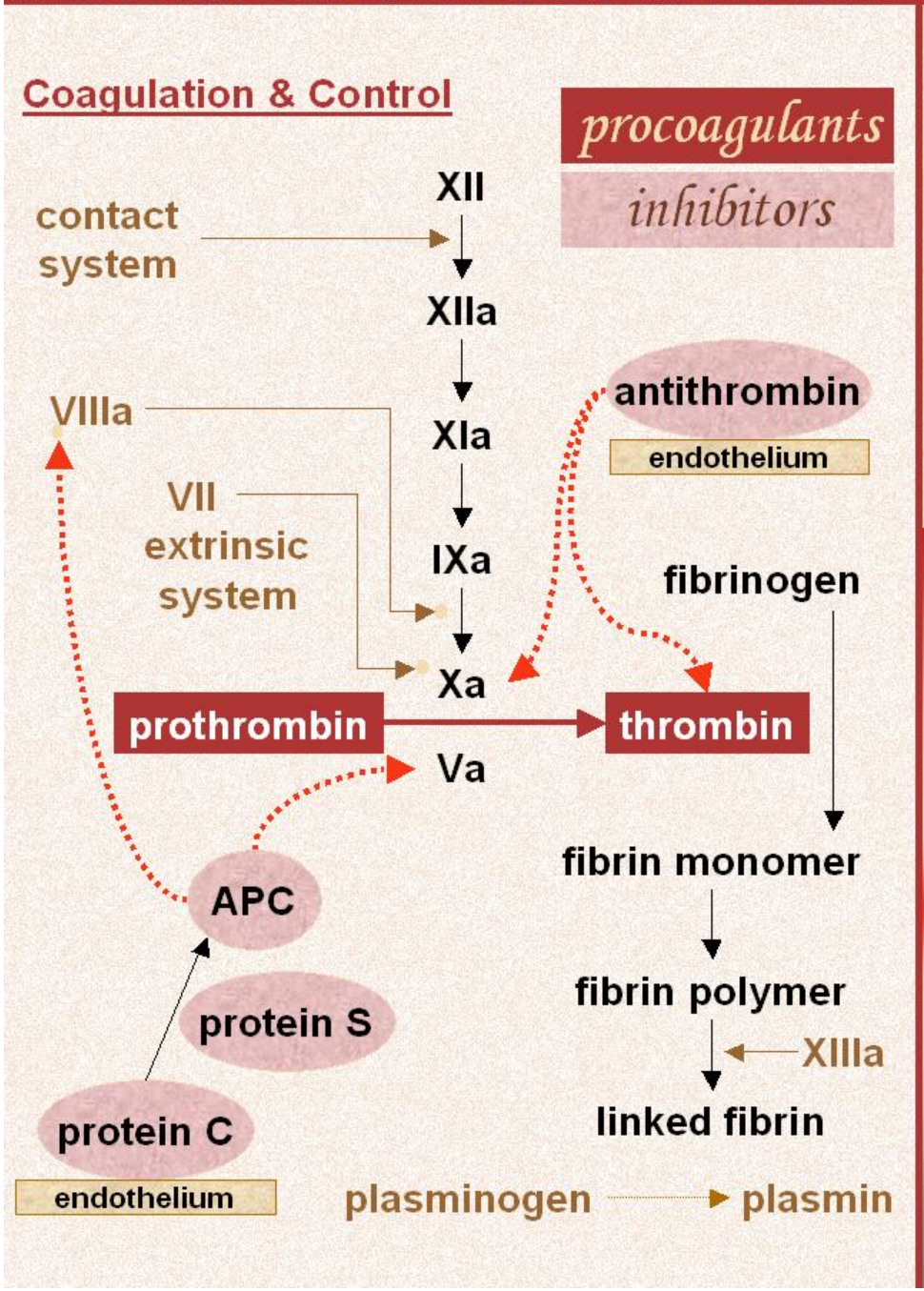
→

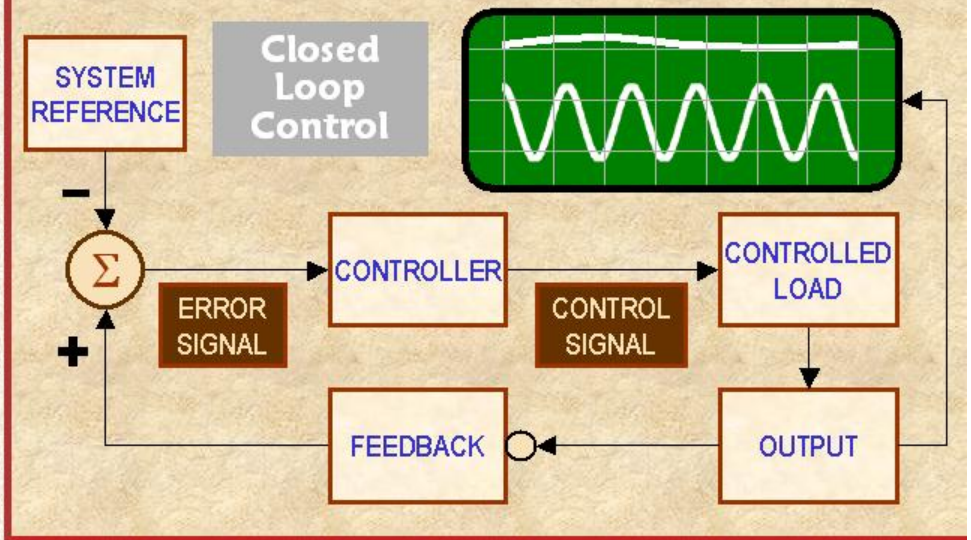
liver necrosis - liver transplant
(protein C normal after transplant)

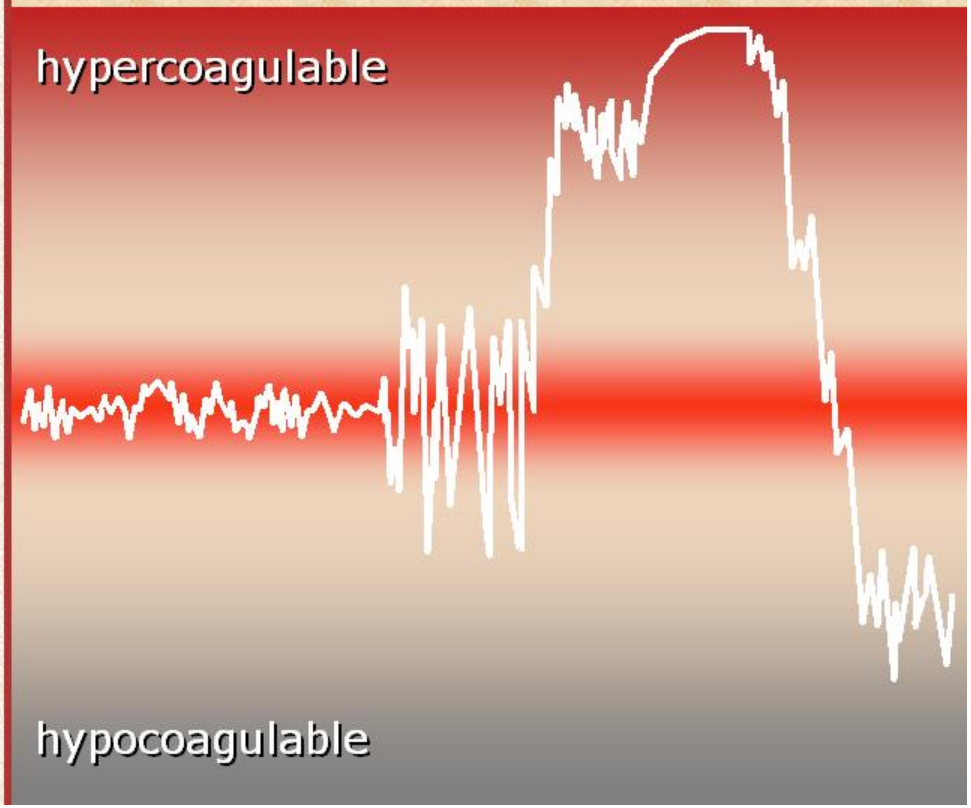
Nothing about this case, neither workup nor management, should be considered adequate or appropriate in 2001

missed diagnoses
pointless laparotomy
catheterization without thrombolysis
liver necrosis

THE PHYSICS OF COAGULATION AND THROMBOSIS







TREATMENT OF HYPERCOAGULABILITY

anticoagulation essential

warfarin: roller coaster ride inr
keep inr higher than usual
pretreat with heparins (warfarin necrosis)

heparins: in lieu of warfarin?
heparin versus synthetics

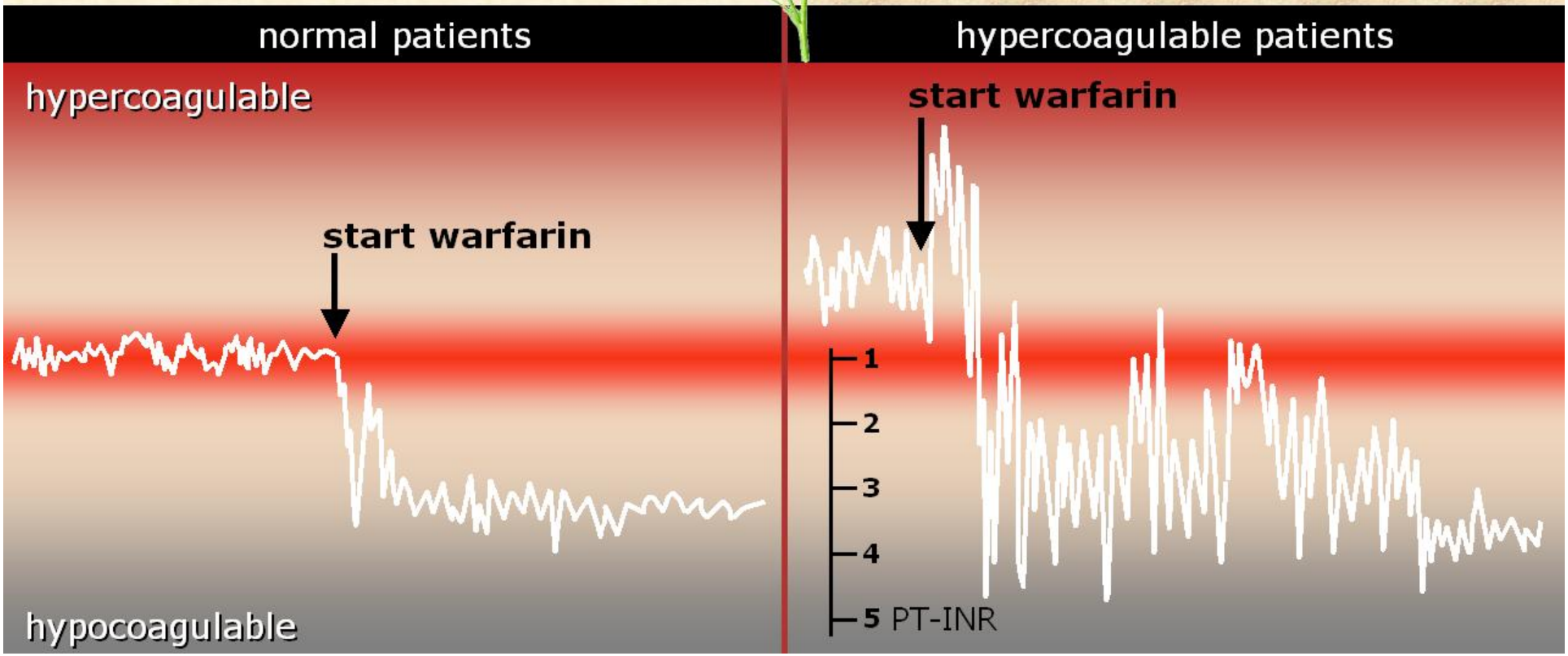
short term versus long term rx
assess other risks
episodic or continuous?

treat or pretreat for surgery
restoring blood to dynamical balance
do not stop anticoagulants
do not operate until anticoagulated

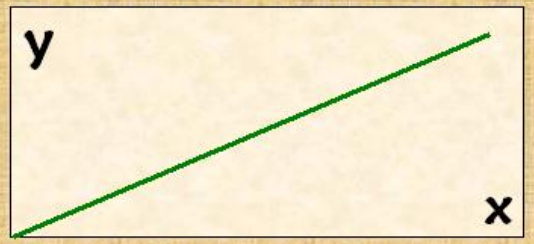
remove thrombus or not?
thrombolysis
thromboembolectomy

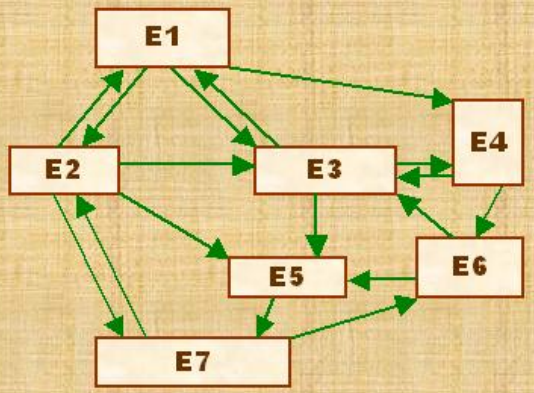
usual principles of treating thrombosis

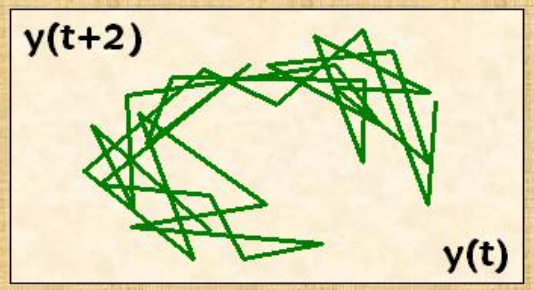
anticoagulation essential



Why do patients become hypercoagulable?







Hypercoagulability is a dynamical disease.

Example: *output = rate x volume* ($\varphi = r \times v$)

A LINEAR SYSTEM

Piston rate — **Stroke volume**

$$d\varphi = v\,\partial r + r\,\partial v$$
$$\partial\varphi = v\,\partial r$$
$$\partial\varphi = r\,\partial v$$

Pump output

A NON-LINEAR SYSTEM

Heart rate ⇄ **Stroke volume**

$$d\varphi = v\,\partial r + r\,\partial v$$
$$v = f(\varphi, r)$$
$$r = f(\varphi, v)$$

Cardiac output

The thrombosis trigger threshold becomes more sensitive.

What have we been missing?

THE

SEATS and CAUSES

OF

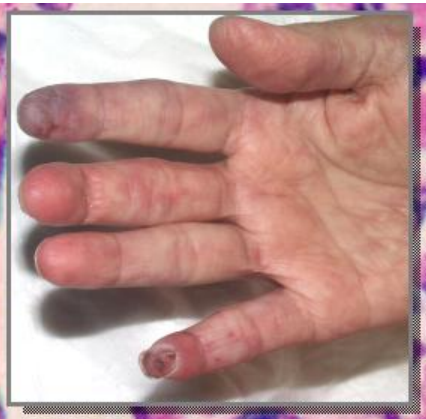
DISEASES

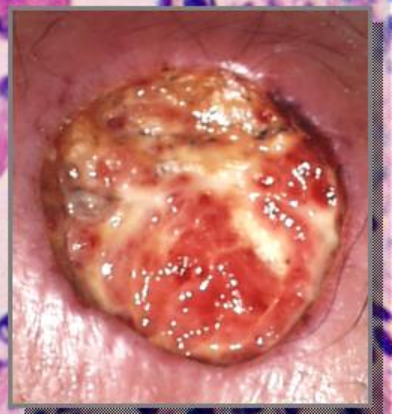
INVESTIGATED BY ANATOMY.

BOOK the SECOND.

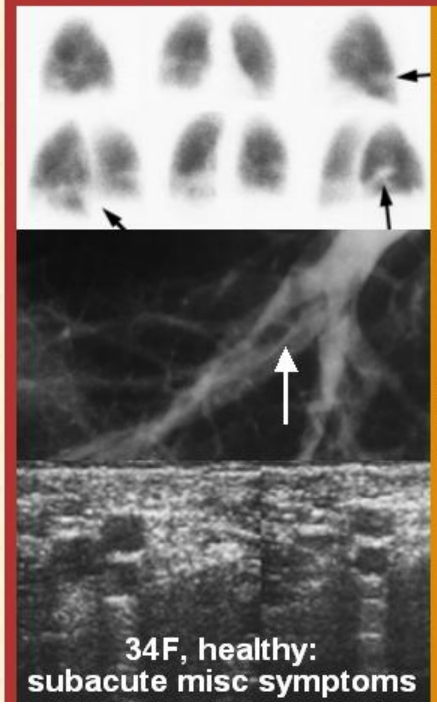
Of DISEASES of the THORAX.

Zz 2



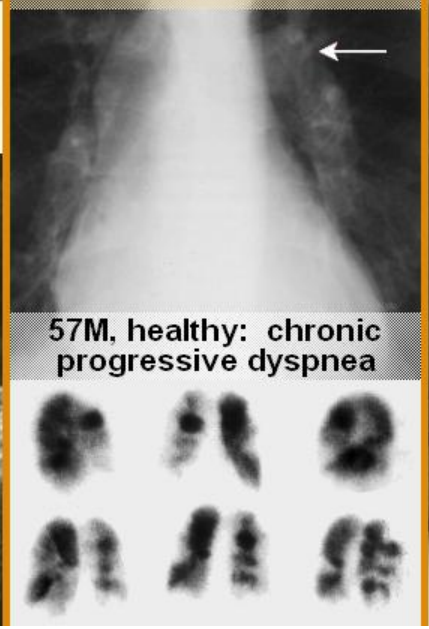


lupus glomerulonephritis
focal thrombotic glomerulonephritis
rapidly progressive glomerulonephritis
glomerulonephritis of chronic liver disease

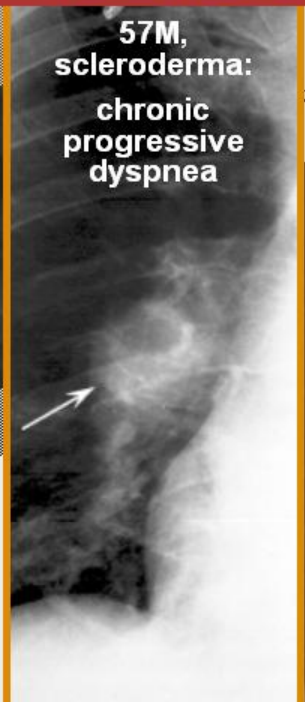


34F, healthy:
subacute misc symptoms

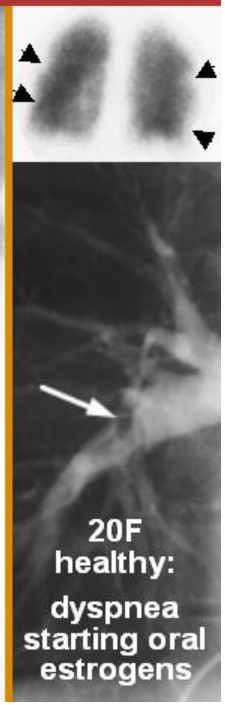
pulmonary thrombosis



57M, healthy: chronic progressive dyspnea



57M, scleroderma:
chronic progressive dyspnea



20F healthy:
dyspnea starting oral estrogens

SUMMARY

Hypercoagulable disorders

Be aware that these disorders exist. Be alert to their presence.

❊ ❊ full spectrum of thrombo-embolic problems ❊ ❊

refractory, recurrent, frustrating

(until diagnosis made)

what are we missing?

Diagnosis

current history

past history

family history

exclude other diagnoses

hypercoagulable screen

rheumatoid screen

other laboratory studies

acute care

prophylaxis

modified care

customary principles

❊ ❊ ❊ ❊ ❊ ❊ ❊

antithrombotic therapy essential

care of sequelae

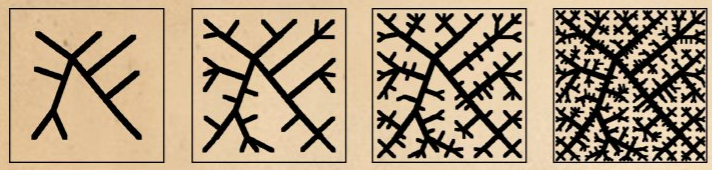
thrombolysis

ancillary modalities

Treatment

Marc E. Gottlieb, MD, FACS
A Professional Corporation

PLASTIC & RECONSTRUCTIVE SURGERY
Board Certification ••• ••• ••• *Plastic Surgery* ••• *Hand Surgery* ••• *General Surgery*



Specializing in the treatment, reconstruction, and management of
Acute and chronic wounds • Diseases and defects of the soft tissues • Injuries, diseases, and defects of the hand and extremities • Defects of the head and trunk

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Hypercoagulability: Prethrombotic and Microthrombotic Disorders

Original presentation February 24, 2000, Maui
at the Boswick Burn and Wound Meeting

Further presentations & updates, 2001, 2003, 2004, 2005

Most recent presentation, October 27, 2005, Phoenix
at WOCN, Rocky Mountain Chapter, Annual Meeting