CALCIPHYLAXIS

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WHAT IS IT?

- **C**alcific uremic arteriolopathy (CUA), also called calciphylaxis, is a disorder of small-vessel calcification associated with the development of progressive cutaneous plaques and ulcers due to ischemia

Hans Selye

- Approximately 45 years ago, Hans Selye published Calciphylaxis, which described induction of soft-tissue calcification in rodents.

- **Selye's definition of calciphylaxis**
- "a condition of induced systemic hypersensitivity in which tissues respond to appropriate challenging agents with a precipitous, though sometimes evanescent, local calcification

PREVALENCE

- estimated prevalence of CUA in ESRD patients is 4.1%.
- **Manitoba**
- Of the 59 patients that developed calciphylaxis, 54 were on PD, 4 were on HD, and 1 was in predialysis. In the PD population, the mean yearly incidence from 1998 to 2003 was 4.5/100 patient-years, falling to 1.3/100 patient-years in 2004-2006

- Gipstein et al published the first case series in 1976, describing 11 patients with ESRD who developed medial calcinosis of the arteries and painful ischemic ulcer

- **Women** are affected by calciphylaxis 5 times more frequently than men,
- **obesity** (body mass index (30 kg/m2) is approximately 4 times more common in dialysis patients with calciphylaxis when compared with dialysis patients without calciphylaxis.

Factors Associated with Development of Calcific Uremic Arteriolopathy

- **End-stage renal disease**
- Hemodialysis
- Calcium–phosphate product > 55 mg2/dL2
- Prolonged hyperphosphatemia
- Warfarin use
- **Diabetes mellitus**
- **Obesity**
- Hypercoagulable states
- Protein malnutrition
- Caucasian race
- Elevated alkaline phosphatase
- Female

TABLE

Established and suspected risk factors for calciphylaxis

Confirmed risk factors*	Presumed risk factors
Chronic renal insufficiency (especially dialysis patients and after renal transplantation)	Vitamin K deficiency/therapy with vitamin K antagonists (phenprocoumon, warfarin)
Secondary/tertiary hyperparathyroidism	Fetuin-A deficiency (inflammation)
Hyperphosphatemia	Adynamic bone disease
Increased calciumphosphate product (e.g. combination of active vitamin D with calcium-containing phosphate binders)	Deficiency of other calcification inhibiting systems (e.g. pyro-phosphates)
Female gender	Genetic factors?
Diabetes mellitus	
Obesity	
Hypalbuminemia (malnutrition, inflammation)	

* Based on epidemiological studies and case reports

Table 1. Causes of nonuremic calciphylaxis[a]

Cause	No. of Cases (%)
Primary hyperparathyroidism	10 (27.8)
Malignancy[b]	8 (22.2)
Alcoholic liver disease	6 (16.7)
Connective tissue diseases[x]	4 (11.1)
Diabetes	2 (5.5)
Chemotherapy-induced protein C and S deficiency	1 (2.8)
Crohn disease	1 (2.8)
Osteomalacia treated with nadroparin calcium	1 (2.8)
POEMS syndrome	1 (2.8)
Vitamin D deficiency	1 (2.8)
Weight loss	1 (2.8)
CKD (not ESKD)	1 (2.8)

Table III. Clinical features of 15 nondialysis patients with calciphylaxis

Patient No.	Estimated GFR*	Warfarin use	Prednisone use	Comorbidities
1	>60	Yes	Yes	Polymyositis, Sjögren's syndrome
2	41-60	Yes	Yes	Autoimmune hepatitis
3	41-60	No	Yes	Rheumatoid arthritis
4	41-60	No	No	Chronic ethanol abuse
5	20-40	Yes	Yes	
6	20-40	Yes	Yes	Sarcoidosis
7	20-40	No	Yes	Sarcoidosis
8	20-40	Yes	No	Cholangiocarcinoma
9	20-40	Yes	Yes	Systemic lupus erythematosus
10	20-40	Yes	Yes	Systemic lupus erythematosus
11	20-40	Yes	No	Diabetes mellitus
12	20-40	No	Yes	Ethanol-related steatohepatitis
13	<20	No	Yes	Pemphigus foliaceus
14	<20	Yes	Yes	Osteoporosis
15	<20	No	Yes	Osteoporosis, diabetes mellitus

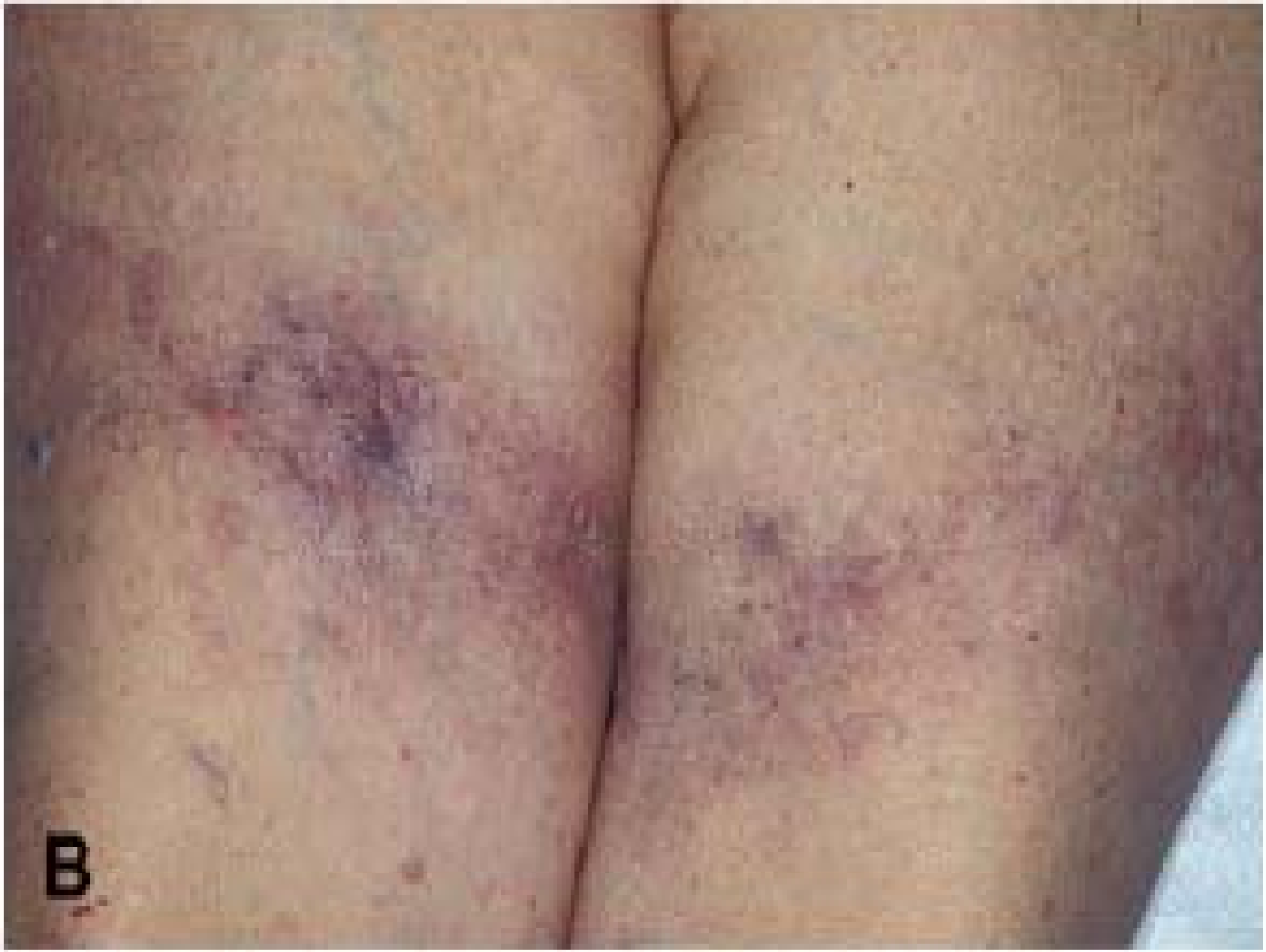
GFR, Glomerular filtration rate.
*Estimated (Cockcroft-Gault) GFR, mL/min.

CLINICAL FEATURES

- The diagnosis of CUA is suspected by clinical findings, namely severe painful necrotic skin ulceration in patients

CLINICAL

- The initial cutaneous changes present as tender serpiginous, indurated plaques or livedo reticularis, with palpable subcutaneous deposits of calcium or thickened blood vessels. There may be surrounding pallor or ecchymosis and associated hyperaesthesia.
- The hallmark clinical feature of CUA is severe pain that is often refractory to standard analgesics. Ulceration is likely a late presentation of disease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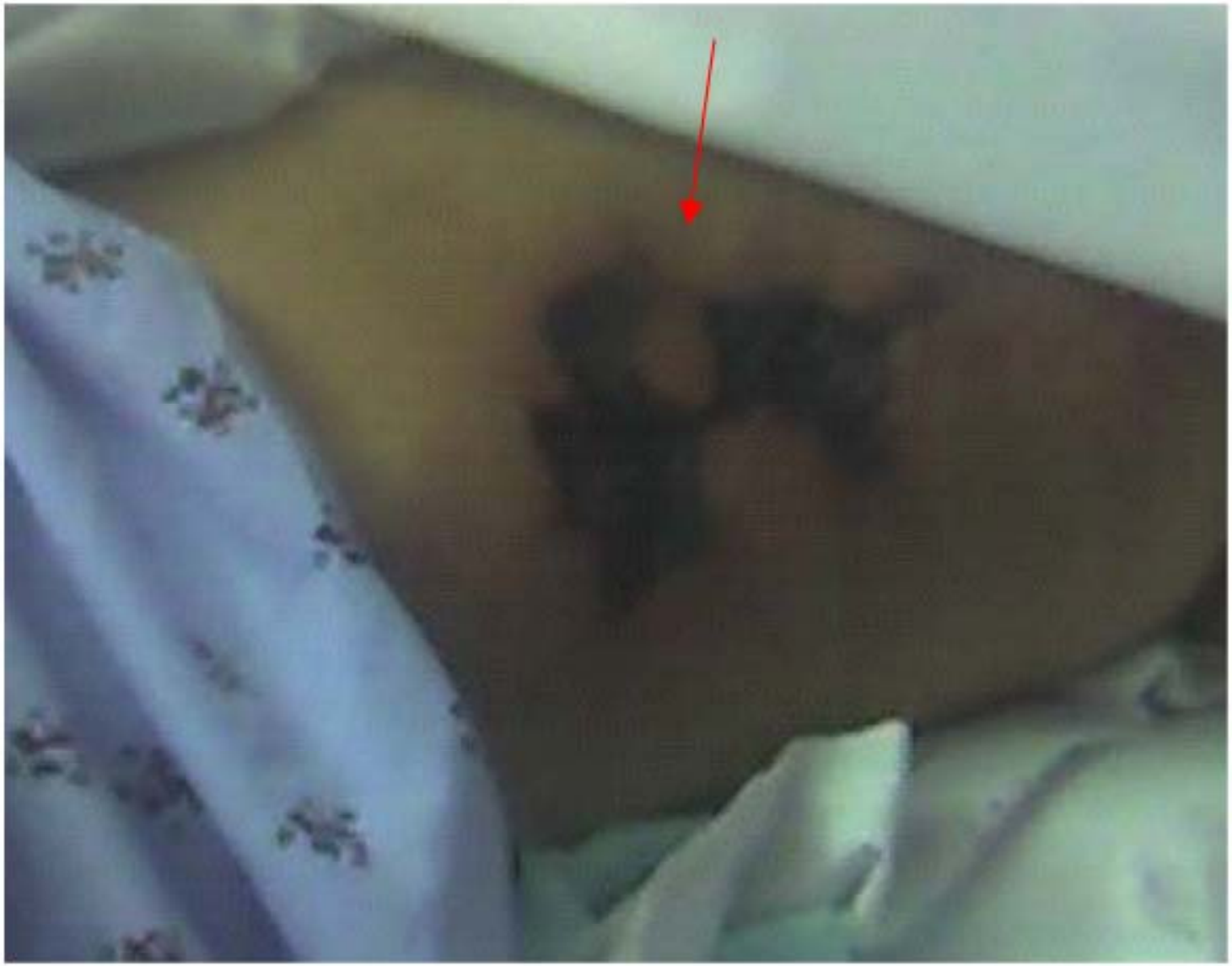
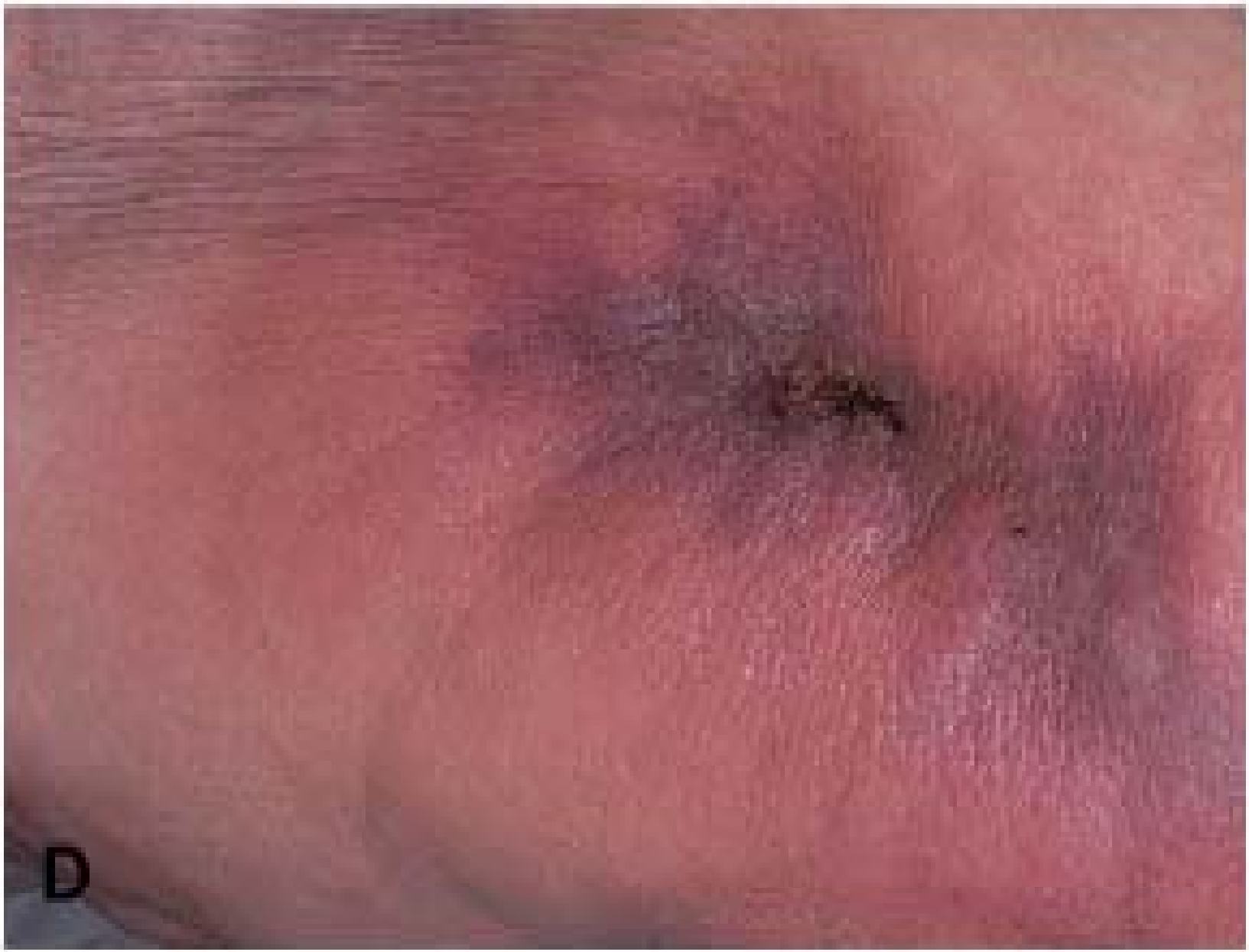


TYPES

- proximal (on the trunk/buttocks/face)
- distal (extremities).
- Cardiac ,penile, pulmonary , pancreatic and ocular CUA presentations of this unusual disease may occur but are rare.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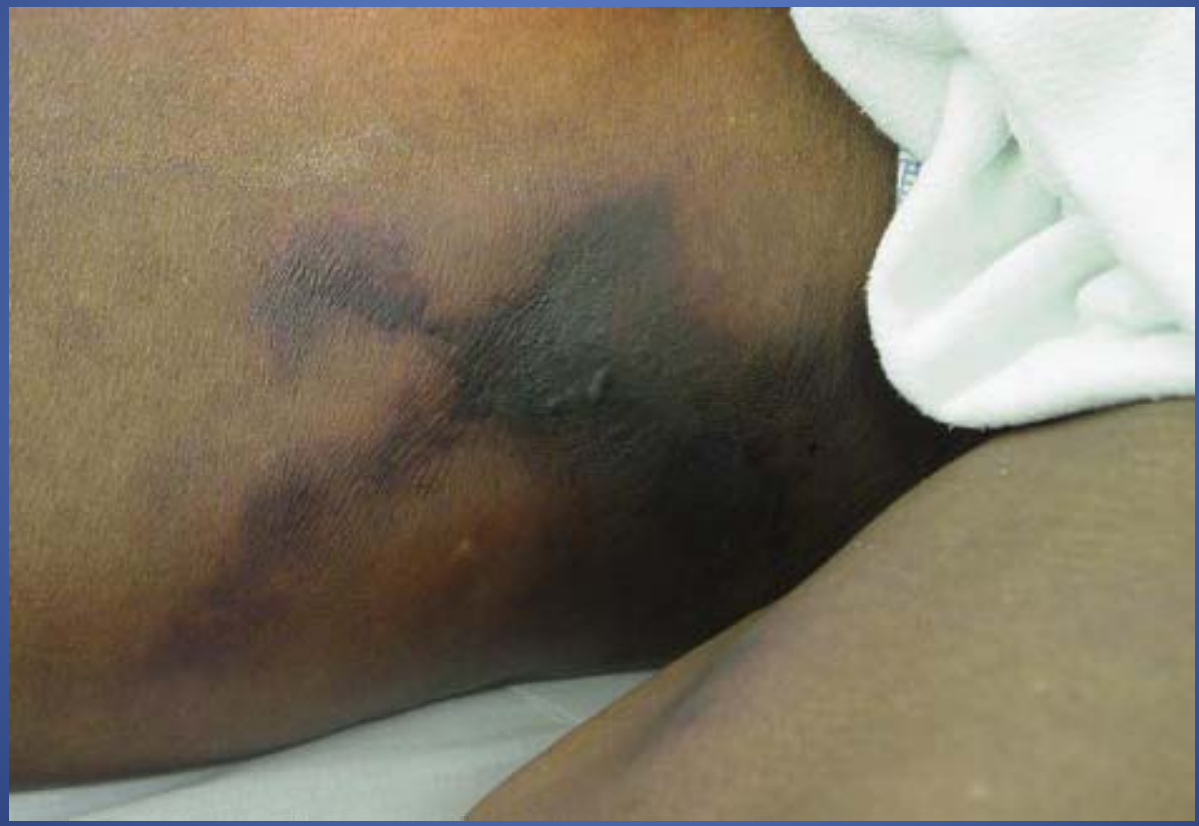


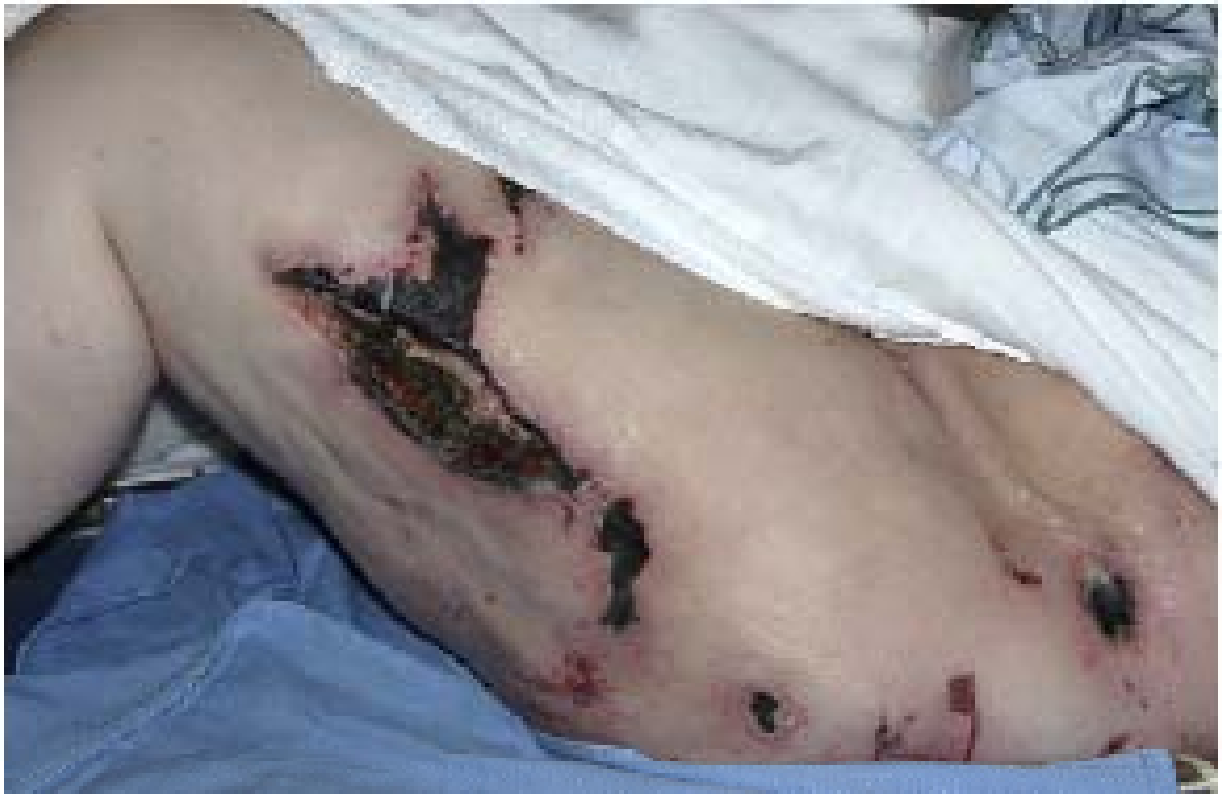
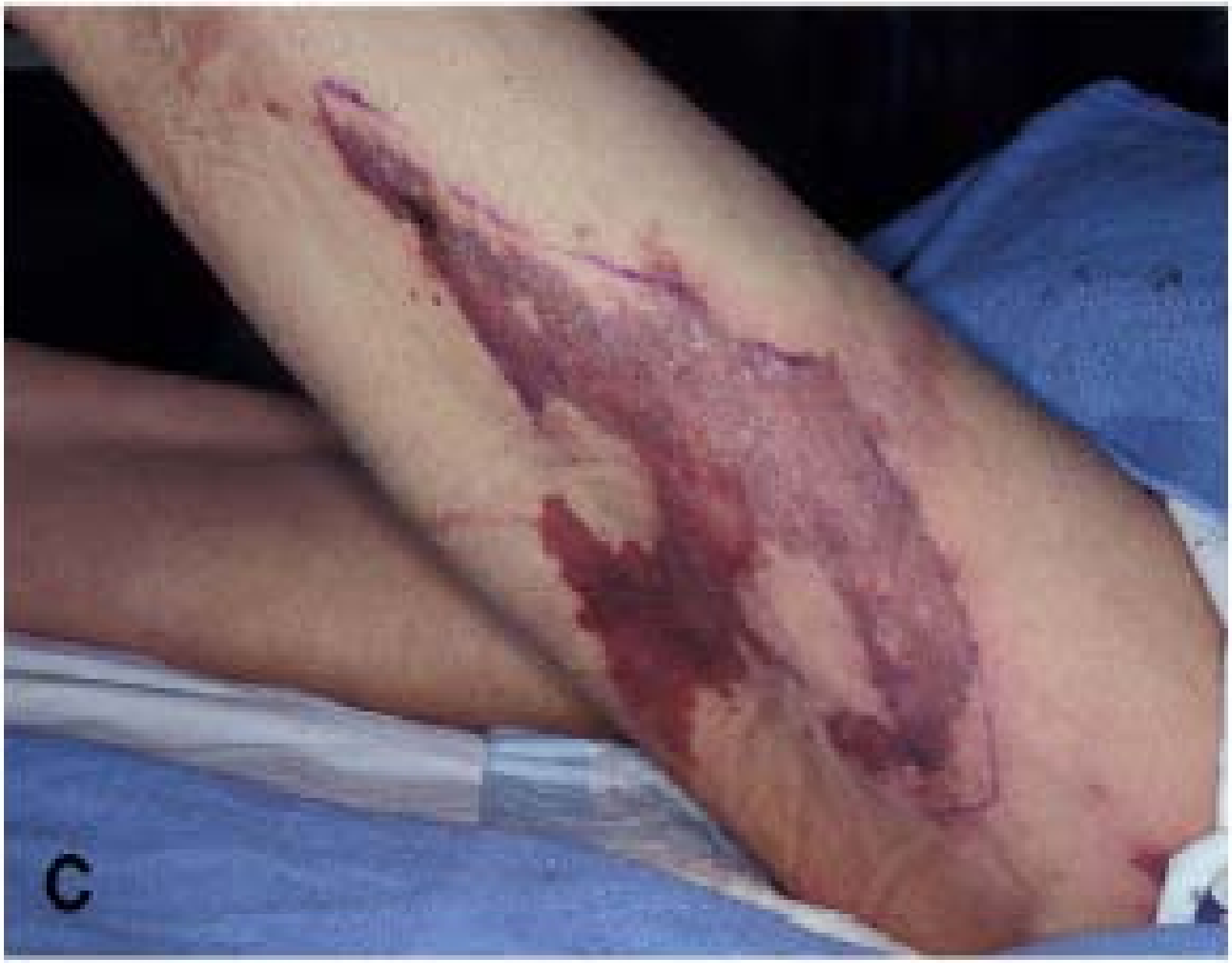


Fig 2. Photograph of clinical findings of calciphylaxis shows multiple areas of ischemic purpura, necrosis, and ulceration of thigh, hip, and abdomen.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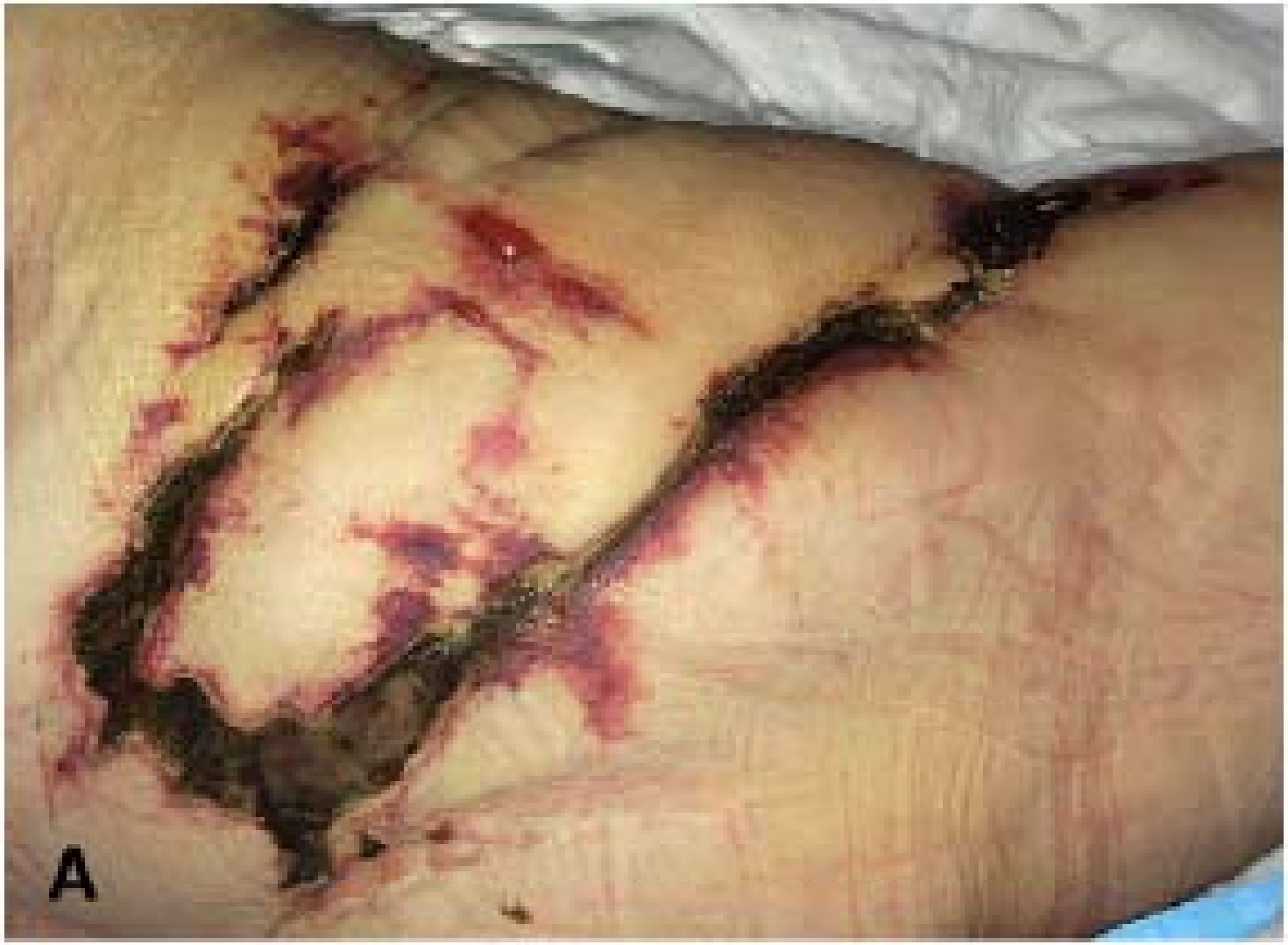
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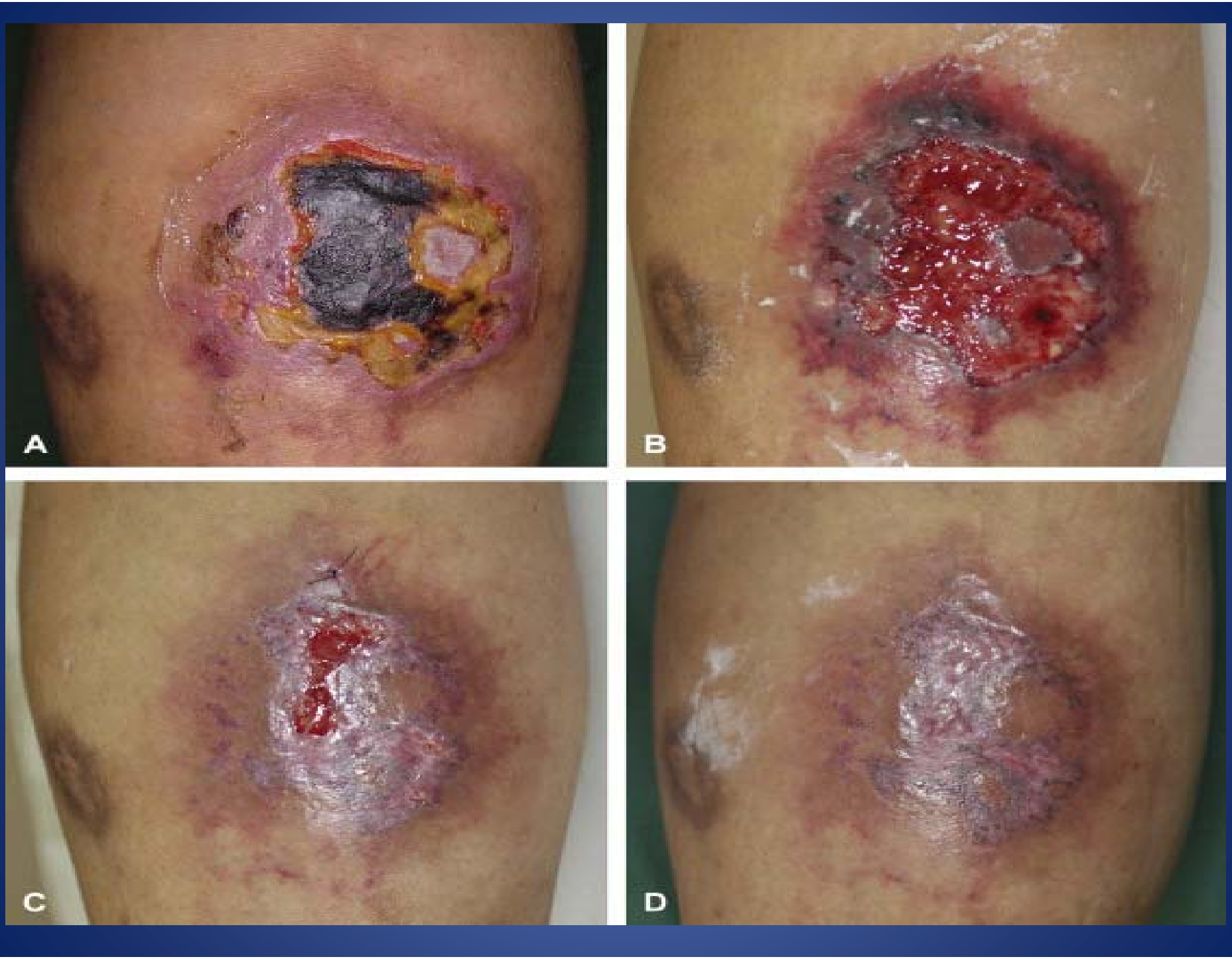
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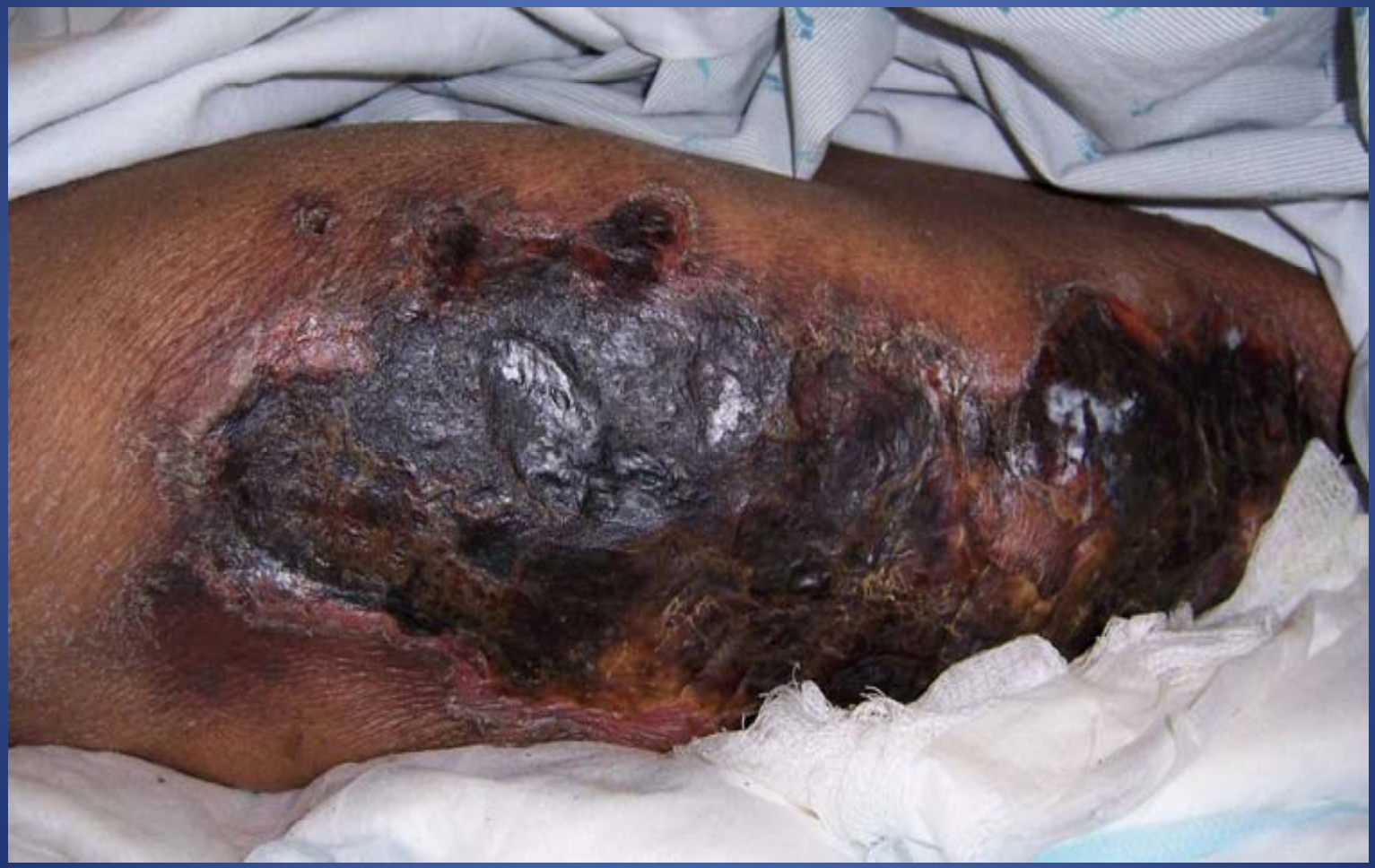
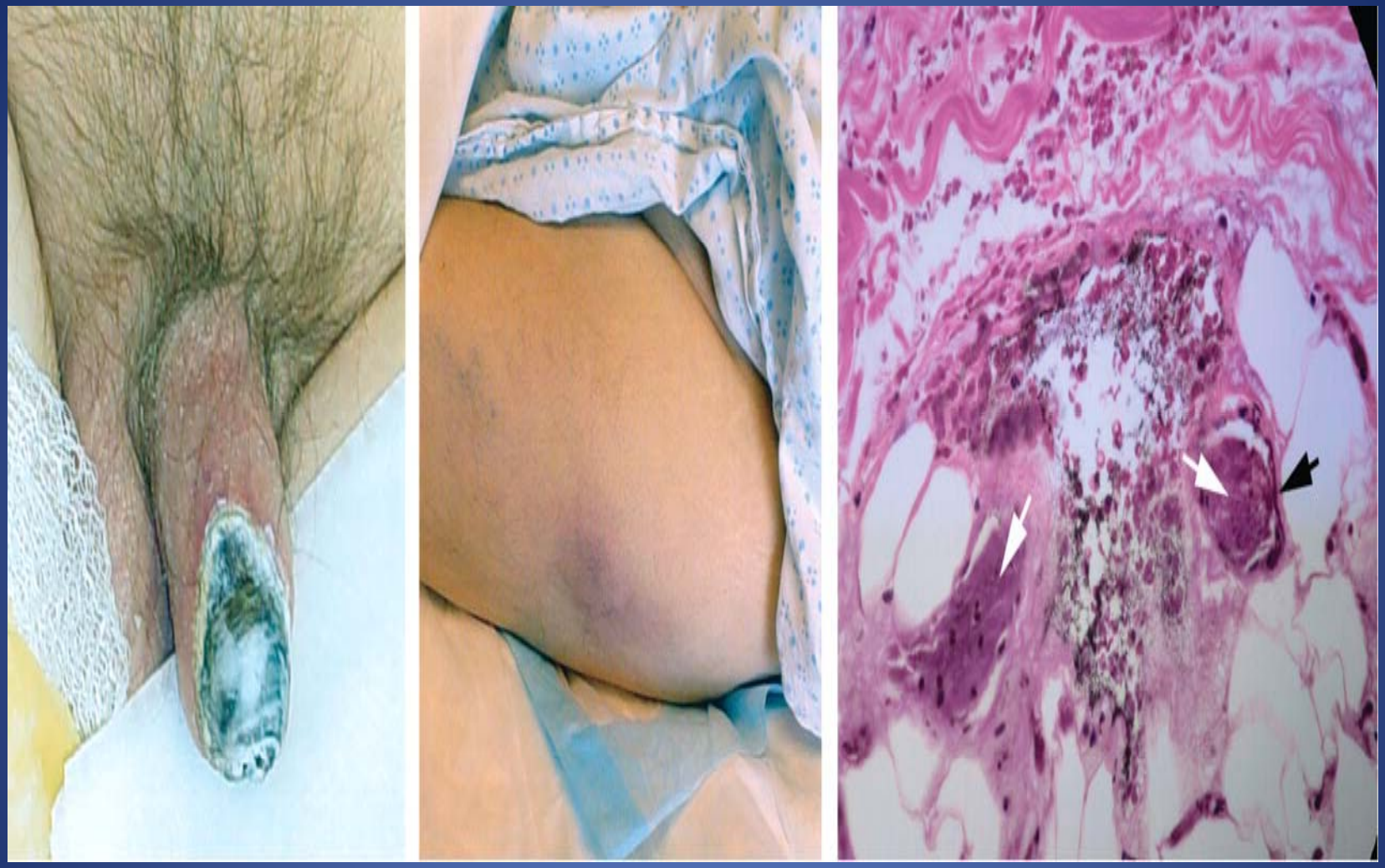




Rifkin B. S., Perazella M. A. Mayo Clin Proc. 2006;81:9-9

Table I. Demographic and clinical characteristics of cases and controls

	Total cases (n = 64)	Nondialysis cases (n = 15)	Dialysis cases (n = 49)	Dialysis controls (n = 98)	Odds ratio* (*P* value)
Mean age (range), y	59 (36-93)	60 (40-93)	59 (36-78)	58 (36-78)	N/A
Gender, No. (%)					
Male	11 (17)	1 (7)	10 (20)	20 (20)	N/A
Female	53 (83)	14 (93)	39 (80)	78 (80)	N/A
Comorbid diagnoses, No. (%)					
Diabetes mellitus	27 (42)	5 (33)	22 (45)	40 (41)	1.18 (.637)†
Hepatobiliary disease‡	14 (22)	5 (33)	9 (18)	2 (2)	8.00 (.007)†
					14.9 (.002)§
Autoimmune/inflammatory‖	25 (39)	9 (60)	16 (33)	23 (23)	1.58 (.236)†
Median body mass index	30.0	28.0	30.2	26.6	1.10 (<.001)†
Body mass index >30, No. (%)	33 (52)	7 (47)	26 (53)	22 (22)	3.91 (<.001)†
					4.77 (<.001)§

Table I. Cont'd

	Total cases (n = 64)	Nondialysis cases (n = 15)	Dialysis cases (n = 49)
General distribution of lesions, No. (%)			
Proximal	39 (61)	7 (47)	32 (65)
Distal	17 (27)	7 (47)	10 (20)
Both proximal and distal	8 (12)	1 (7)	7 (14)

Specific location of lesions, No. (%)			
Legs	59 (92)	15 (100)	44 (90)
Arms	6 (9)	1 (7)	5 (10)
Trunk	19 (30)	3 (20)	16 (33)
Buttocks/hips	14 (22)	5 (33)	9 (18)
Genitalia			

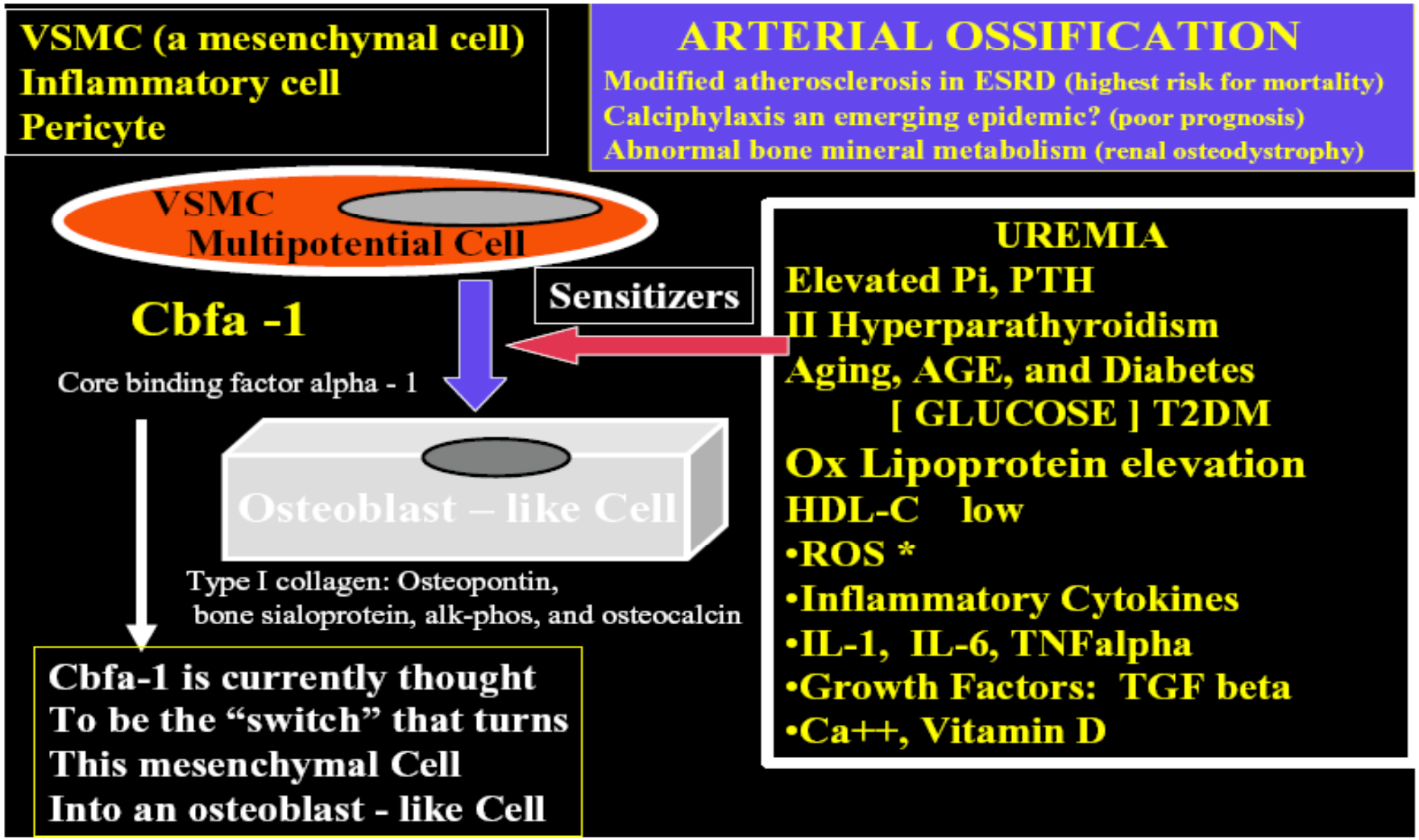
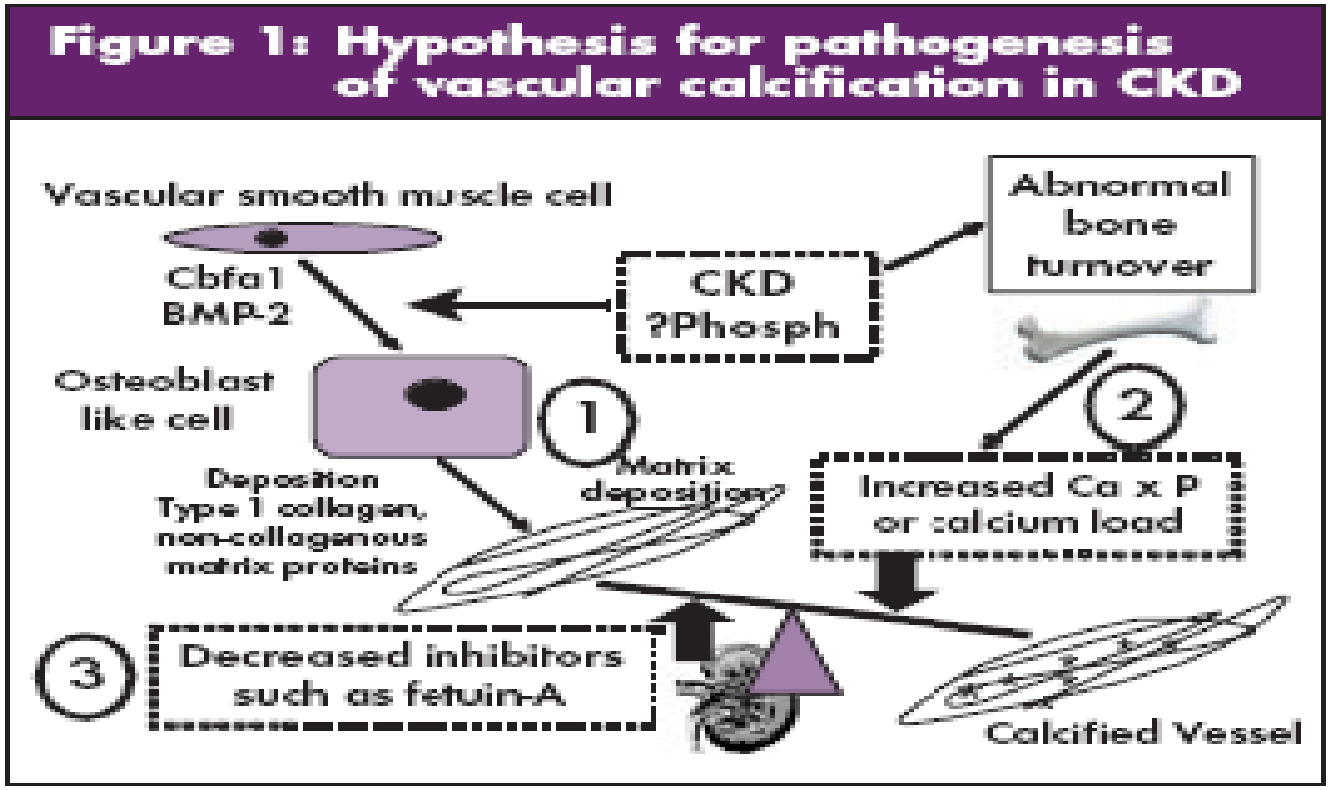


Figure 6
Sensitizers and the Cbfa-1 "protein switch" to transform mesenchymal cells into osteroblast-like cells. This slide demonstrates the transformation of the pluripotent mesenchymal VSMC and pericyte into an osteoblast-like cell. It reveals the importance of the ossification sensitizers and core binding factor alpha-1 Cbfa-1 emphasizing their important role in VOC.

Pathogenesis



Adapted from Chen and Moe.[95]

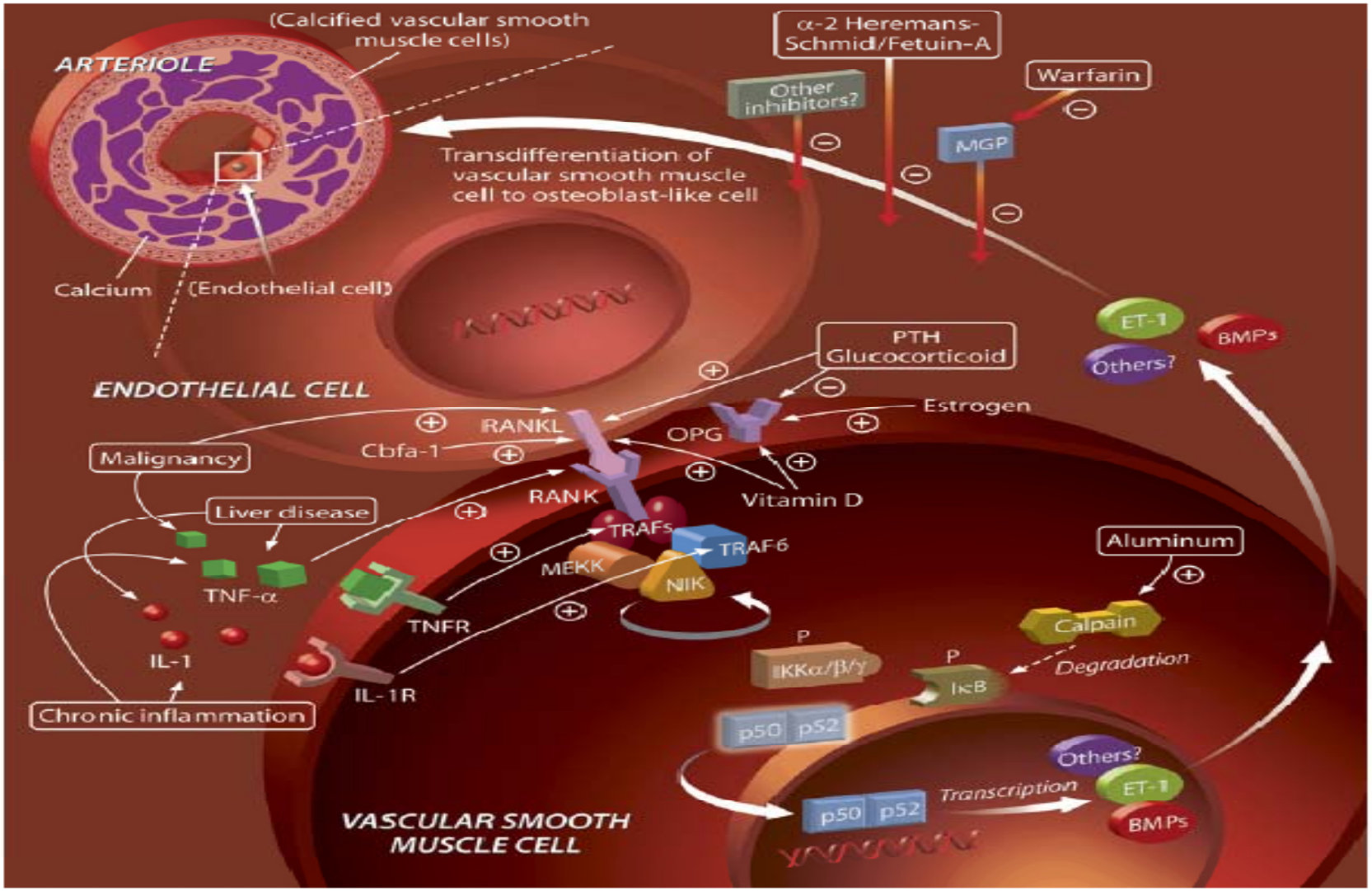
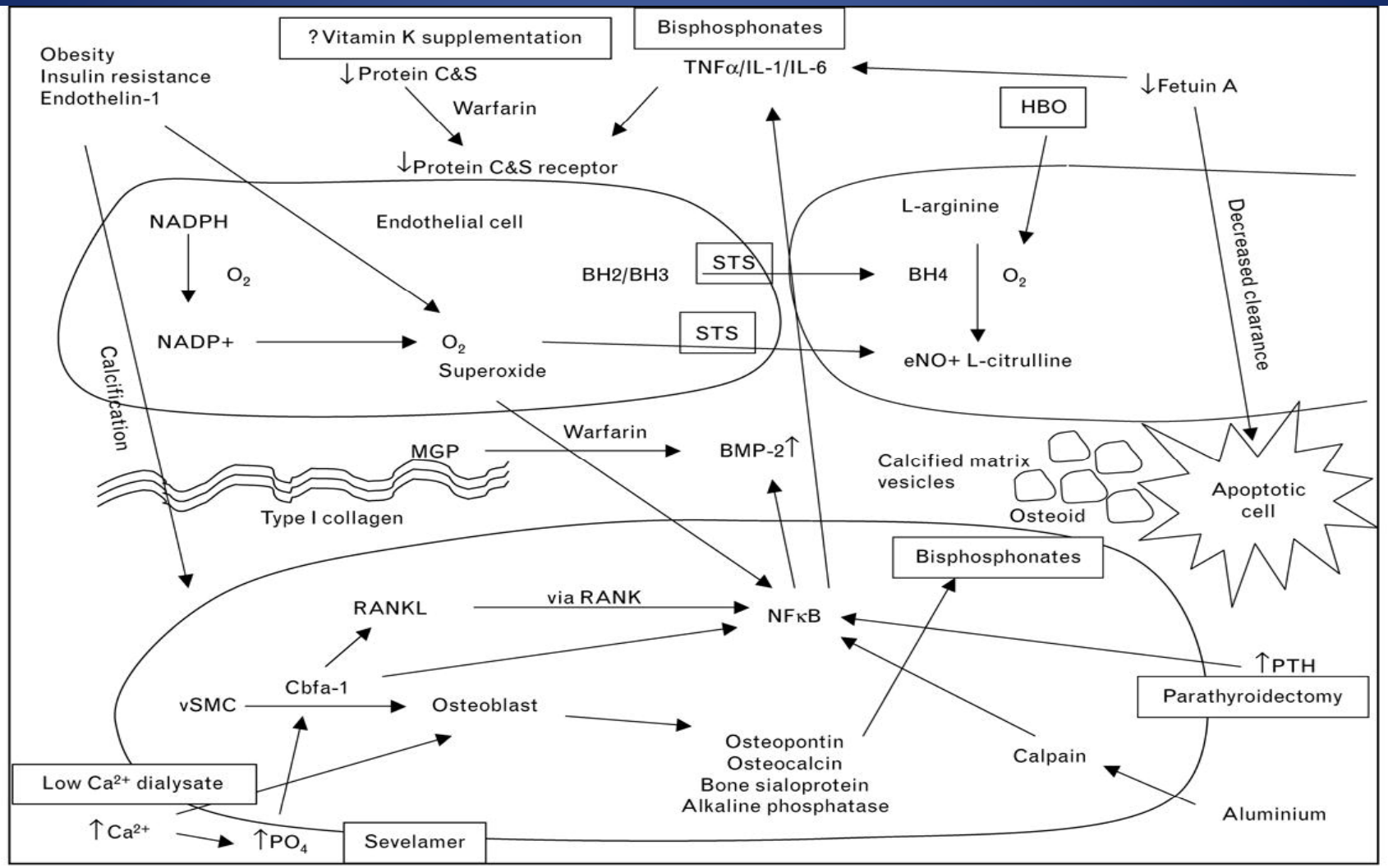
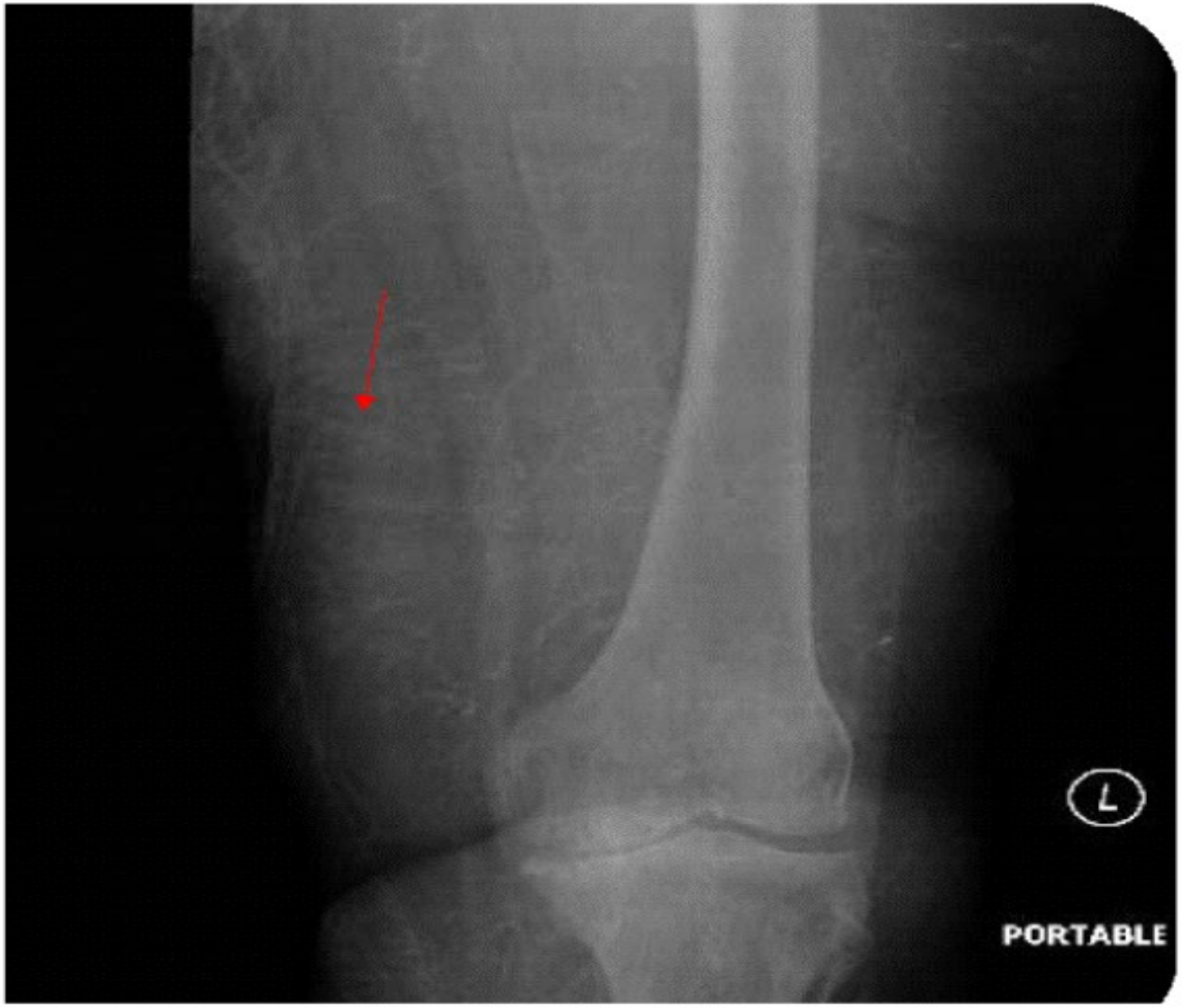


Fig 5. Schematic illustration for proposed molecular pathogenesis of calciphylaxis. *BMP*, Bone morphogenic protein; *Cbfa-1*, core-binding factor α/runt-related transcription factor; *ET*, endothelin; *IκB*, nuclear factor κ-B (NFκB) inhibitor; *IKKα/β/γ*, NFκB inhibitor α, β, and γ complex; *IL*, interleukin; *IL-1R*, IL-1 receptor; *MEKK*, mitogen-activated kinase 1; *MGP*, matrix Gla protein; *NIK*, NFκB-inducing kinase; *OPG*, osteoprotegerin; *PTH*, parathyroid hormone; *p50/p52*, NFκB subunits 1/2; *RANK*, receptor activator of NFκB; *RANKL*, ligand of RANK; *TNF*, tumor necrosis factor; *TNFR*, TNF-α receptor; *TRAF*, TNF receptor–associated factor.

- Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B.
- Weenig RH.
- J Am Acad Dermatol. 2008 Mar;58(3):458-71. Epub 2008 Jan 18. Review



Both the endothelial cell (the arterial wall intima) and vascular smooth muscle cell (constituting the arterial medial layer) are phenotypically and functionally altered by changes in the microenvironment. Uncoupling of endothelial nitric oxide synthase increases formation of reactive oxygen species, although this process can be reversed by STS. Osteogenic differentiation of the vascular smooth muscle cells is critically dependent upon Cbfa-1, leading to down-regulation of smooth muscle gene expression and up-regulation of bone-forming proteins. The text within boxes highlights available treatment options and their sites of action. BH2/BH3/BH4, di-/tri-/tetrahydrobiopterin; BMP, bone morphogenic protein; Ca^{2+}, calcium ion; Cbfa-1, core-binding factor alpha 1; eNO, endothelial nitric oxide; HBO, hyperbaric oxygen; IL-1, interleukin 1; IL-6, interleukin 6; MGP, matrix Gla protein; NFκB, nuclear factor κ B; PO_4, phosphate; PTH, parathyroid hormone; RANK(L), receptor activator of NFκB (ligand); STS, sodium thiosulphate; TNFα, tumour necrosis factor alpha; vSMC, vascular smooth muscle cell.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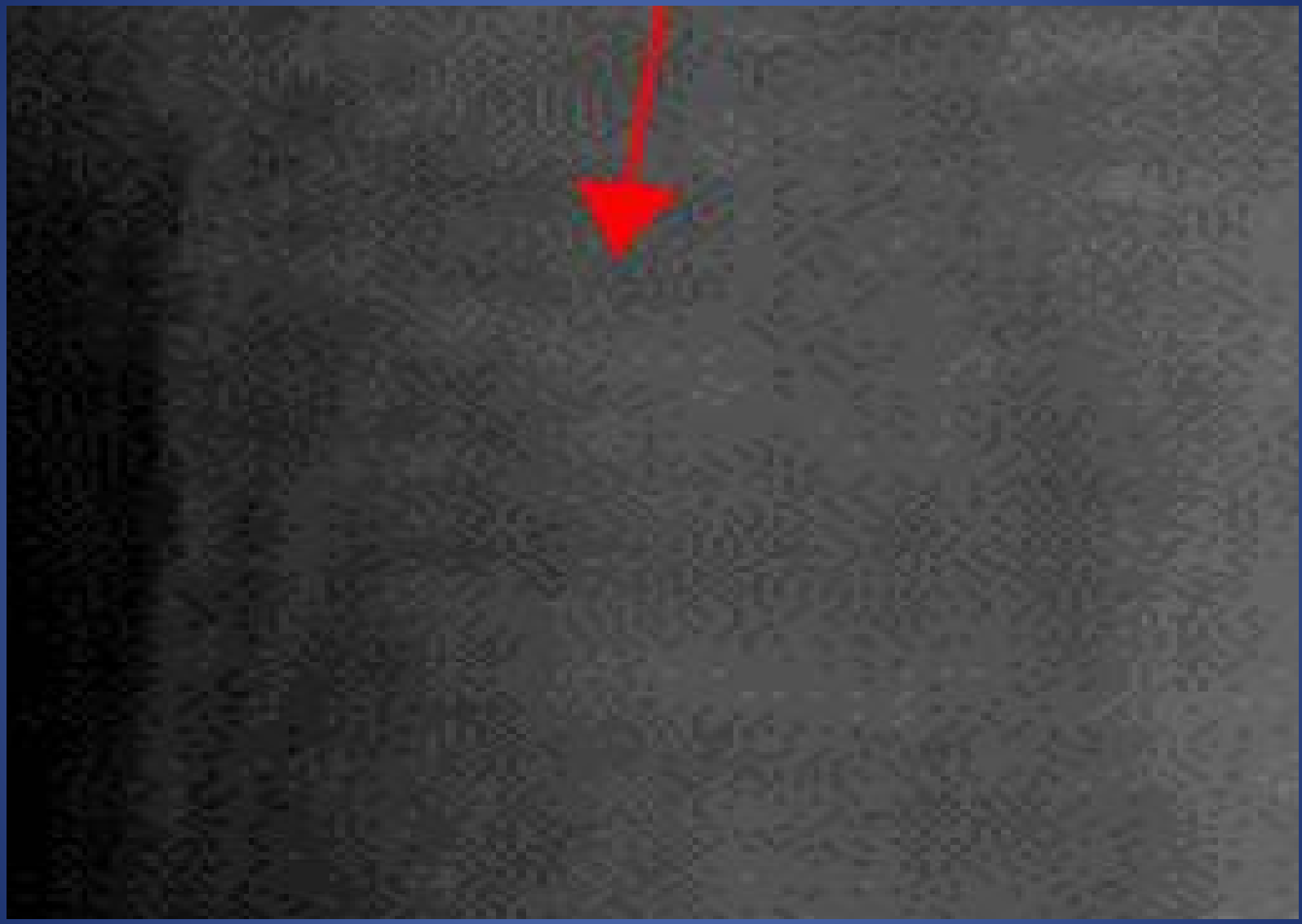

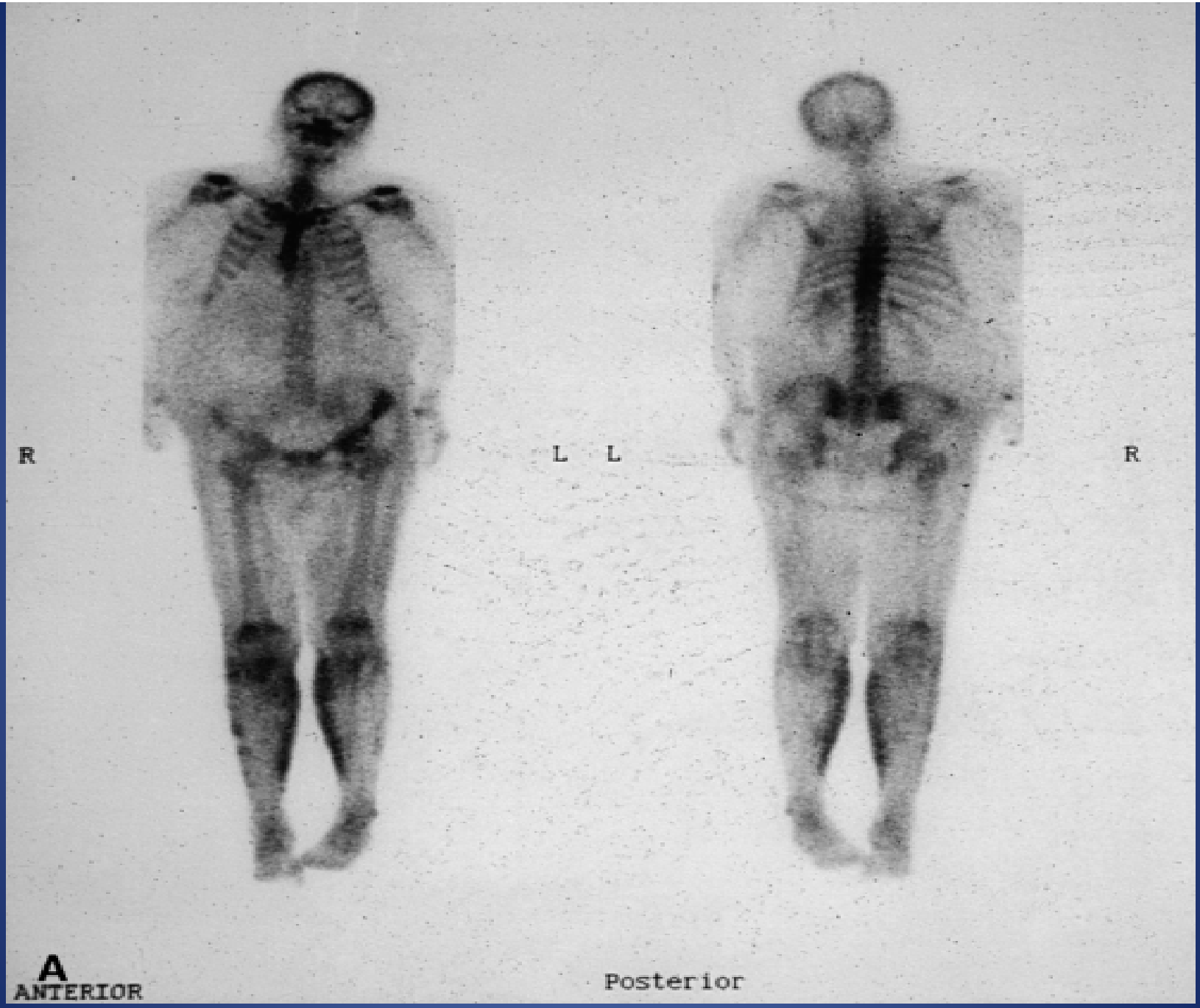
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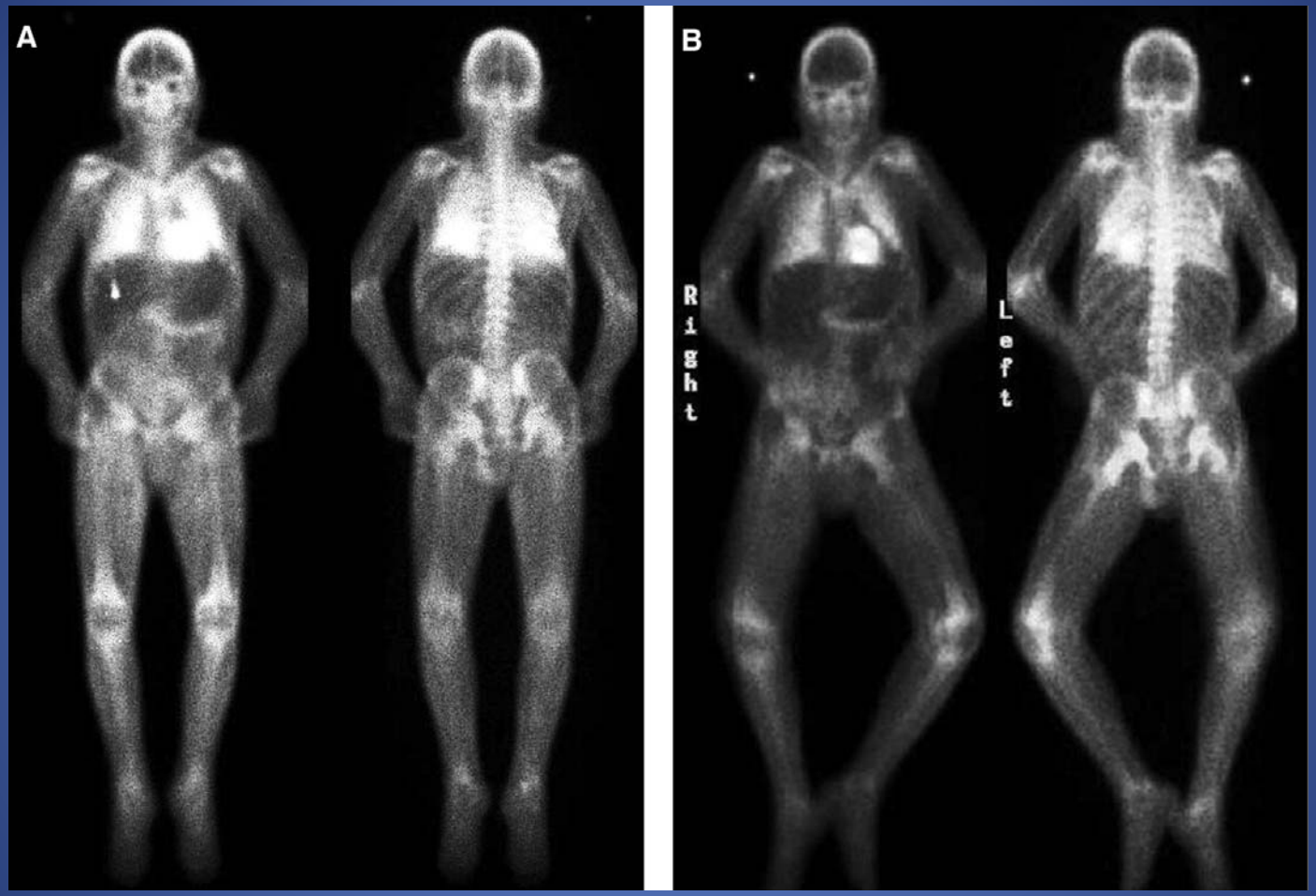
R
A
ANTERIOR
Posterior

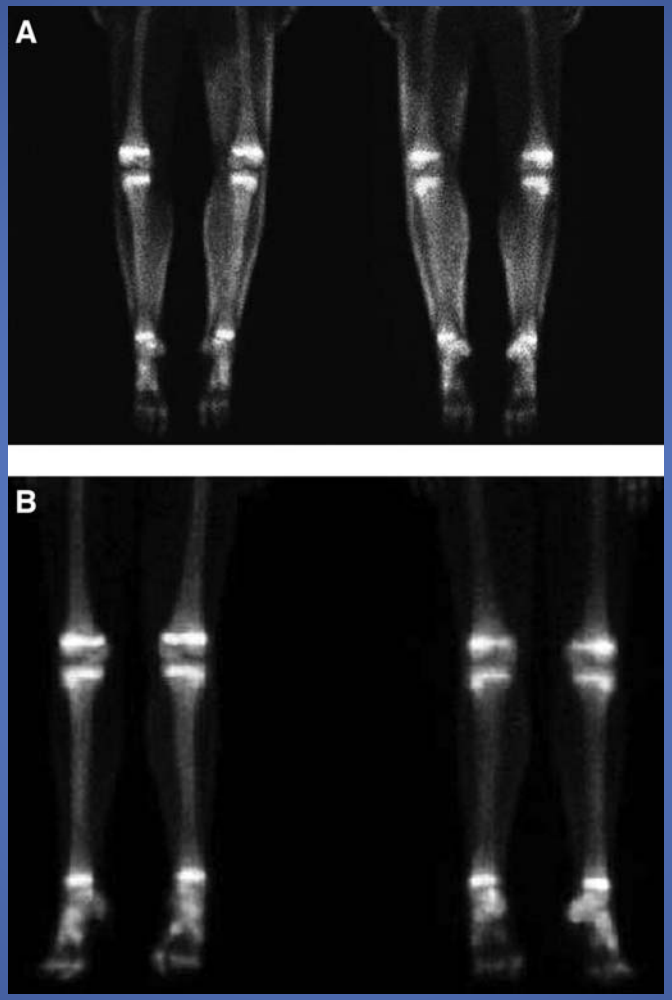
Figure 1. (A) Initial three-phase bone scan demonstrating soft tissue accumulation in thighs, distal femur, proximal tibia, and forearms



Araya, C. E. et al. Clin J Am Soc Nephrol 2006;1:1161-1166

CJASN

Figure 2. (A) There is abnormal soft tissue activity in the skin surface of both lower legs, consistent with calcific uremic arteriolopathy



Araya, C. E. et al. Clin J Am Soc Nephrol 2006;1:1161-1166

CJASN

- Panniculitis may also be evident, and this remains the precursor of tissue necrosis that may extend to the subcutaneous fat.
- A giant cell reaction may also occur.The obliterative vasculopathy is not limited to arterial profiles, and both venules and capillaries can be affected.

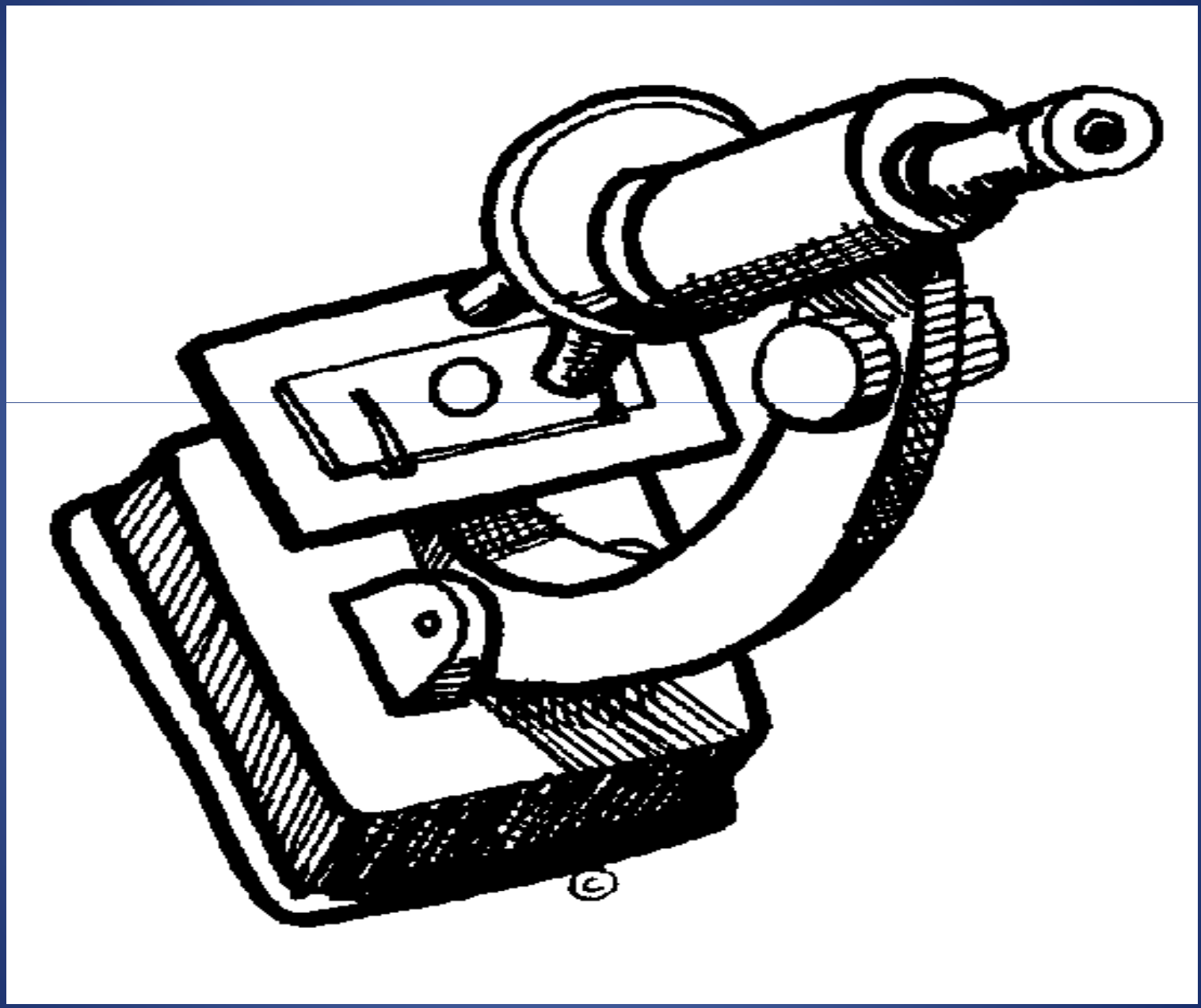
- A modern definition of Selye's calciphylaxis(calciphylactic hypersensitivity) includes a disease that is caused by certain genetic aberrations, medications,hormones, deficiency states, inflammatory mediators, and other stimuli that are equivalent to Selye's sensitizers and challengers. These sensitizers and challengers directly or indirectly activate NFkB and result in bone pathology (osteopenia, osteoporosis,osteomalacia, osteolysis, and high- and lowturnover bone disease) and vascular calcification.

PTH

- For patients with calciphylaxis, PTH levels range from low to high, indicating that a PTH abnormality may be a cofactor in the pathogenesis of the disease, but it is not diagnostic of calciphylaxis. Moreover, for patients receiving chronic hemodialysis, no statistically significant difference was observed in PTH levels of patients with calciphylaxis relative to controls.

Skin Biopsy

- The role of cutaneous biopsy in the diagnosis of calciphylaxis is controversial, with fears that the traumatization itself can lead to ulceration and infection. However, only a biopsy allows a reliable diagnosis.



- Histology
- The hallmark histological finding is small vessel (up to 600mmdiameter) calcification (the primary event), intimal proliferation ,endovascular fibrosis and intravascular thrombosis.

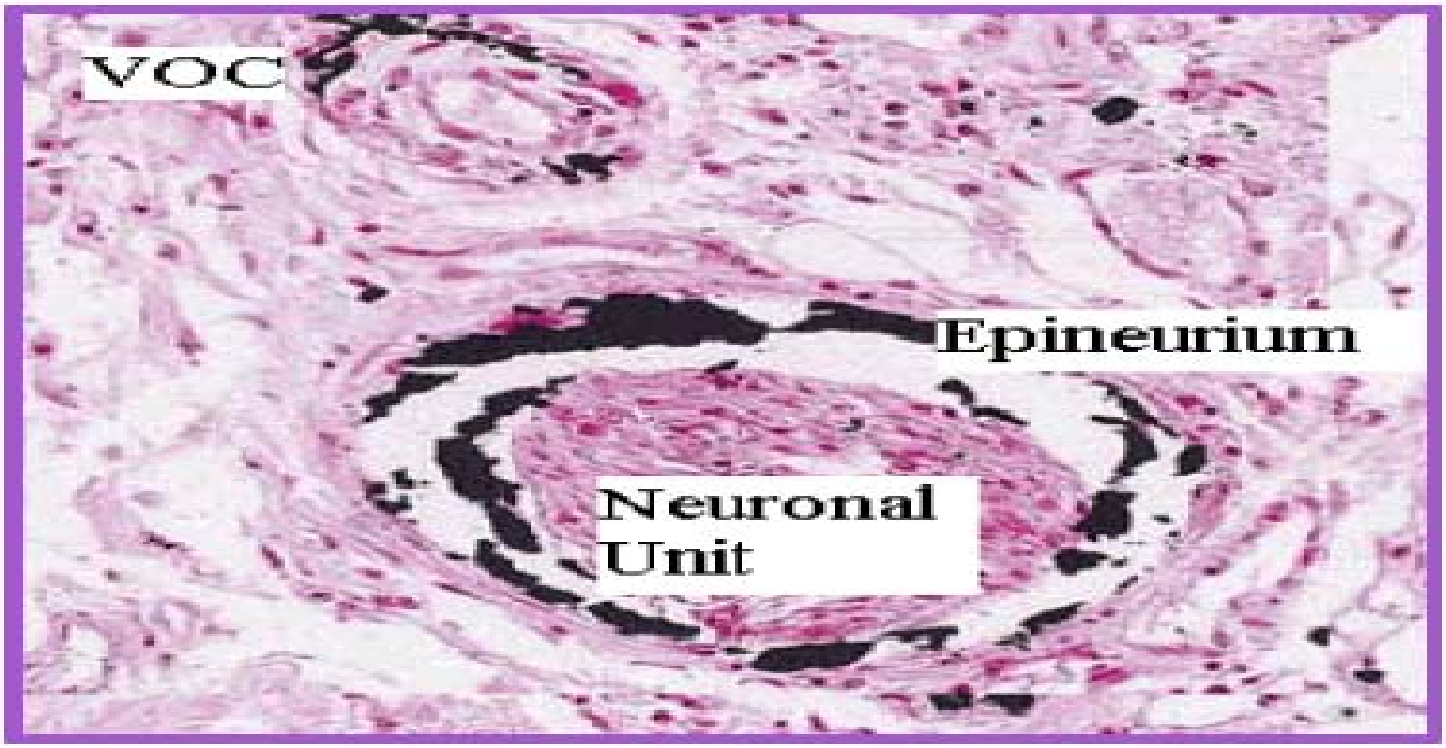
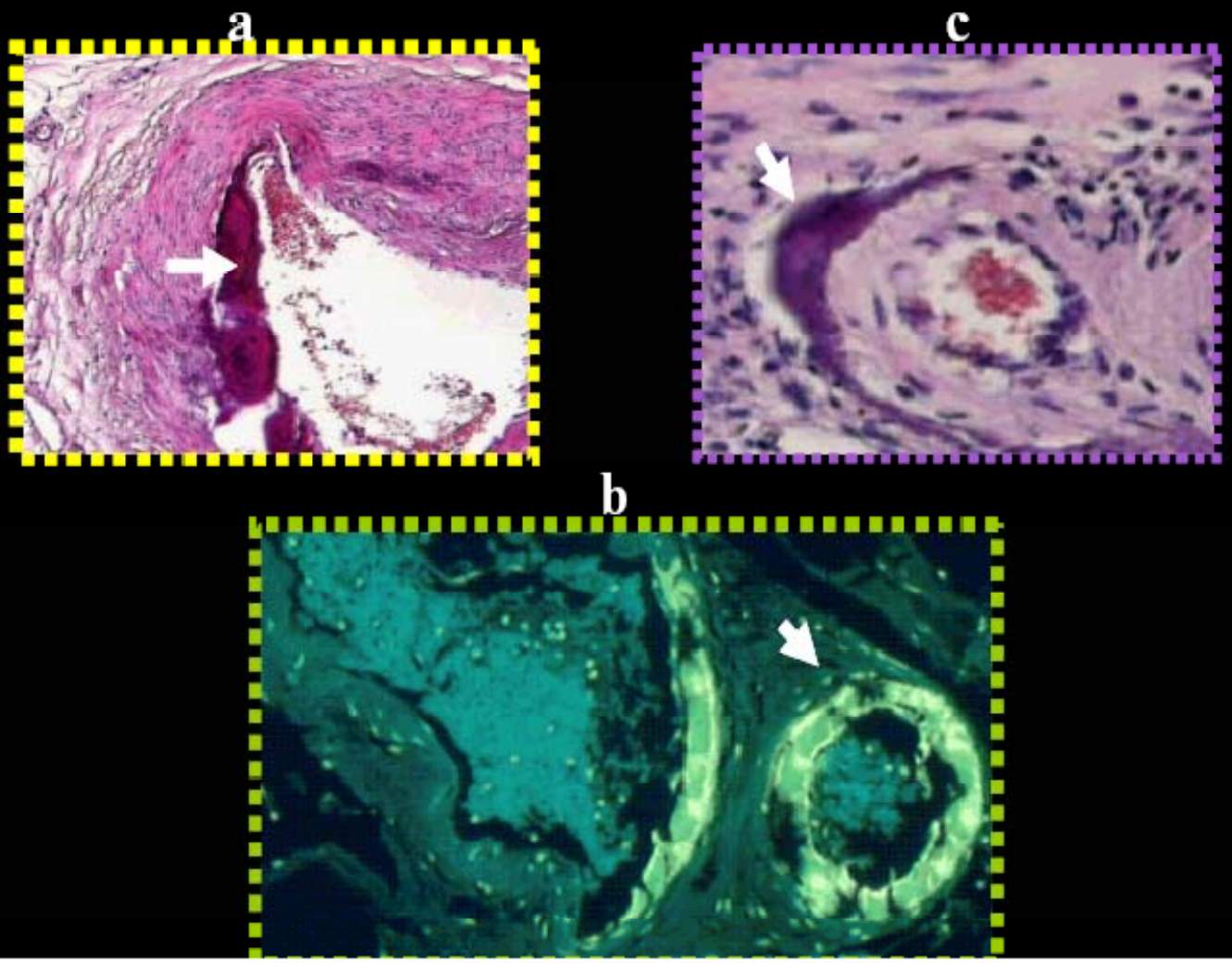
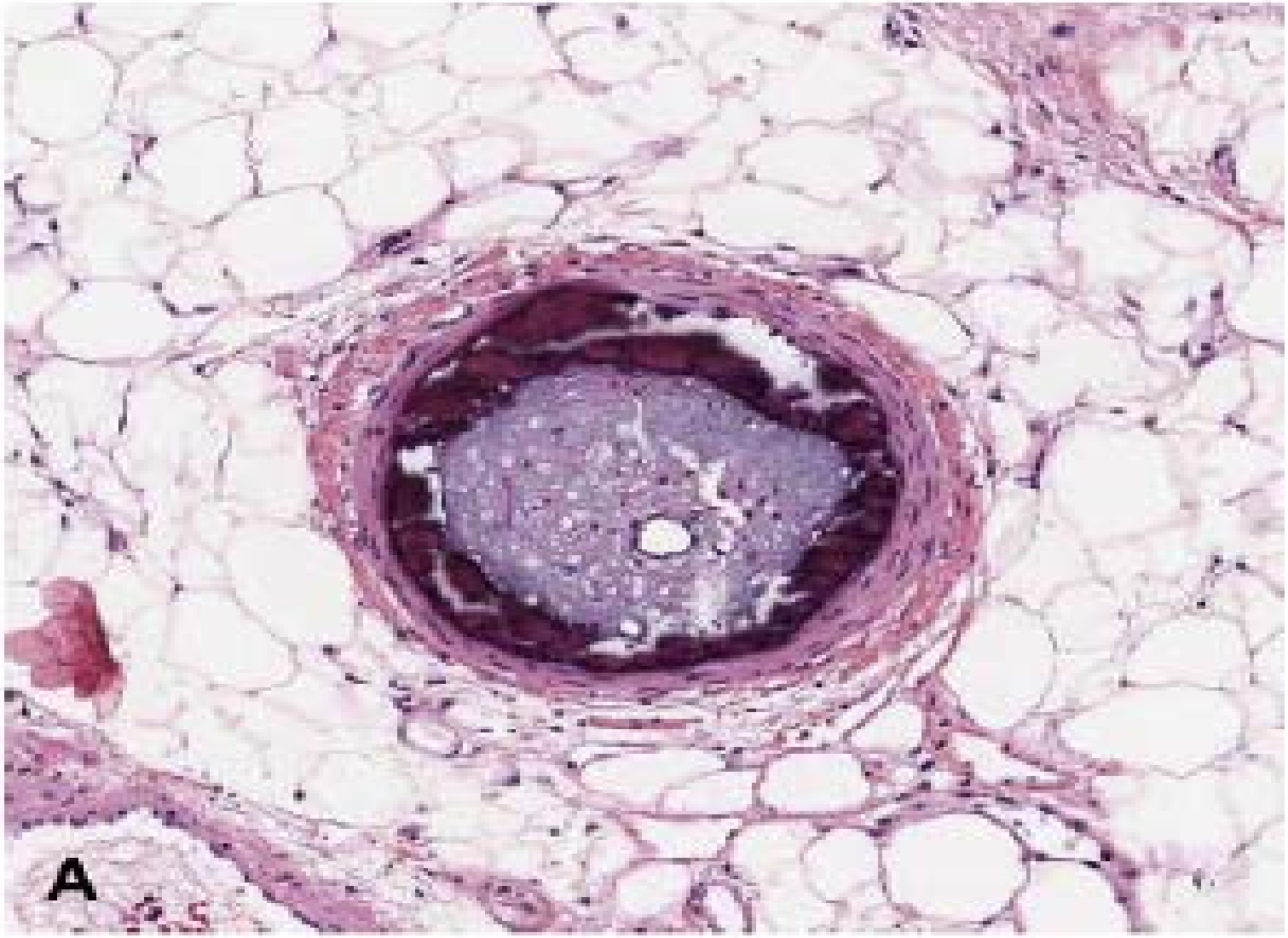
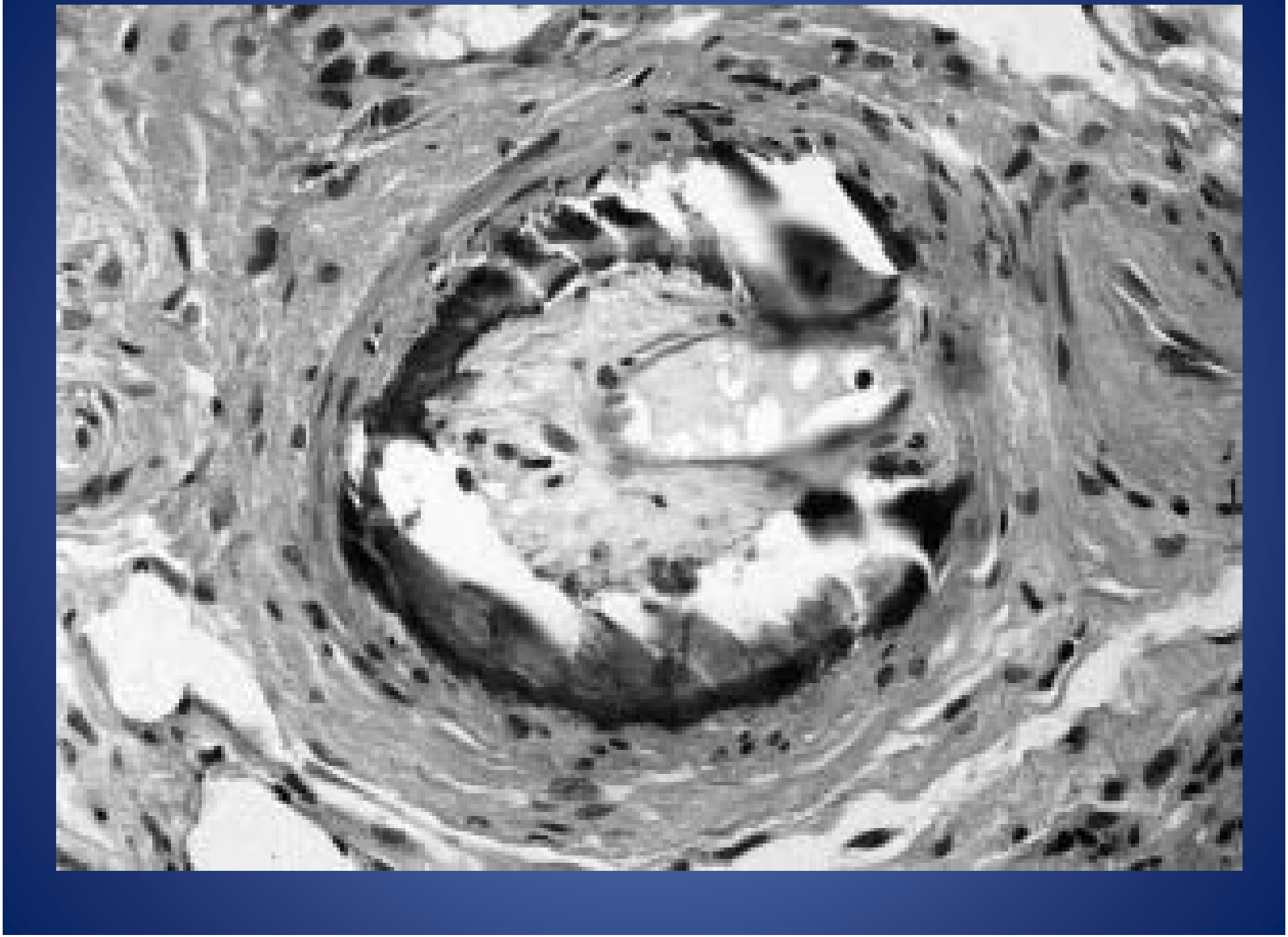


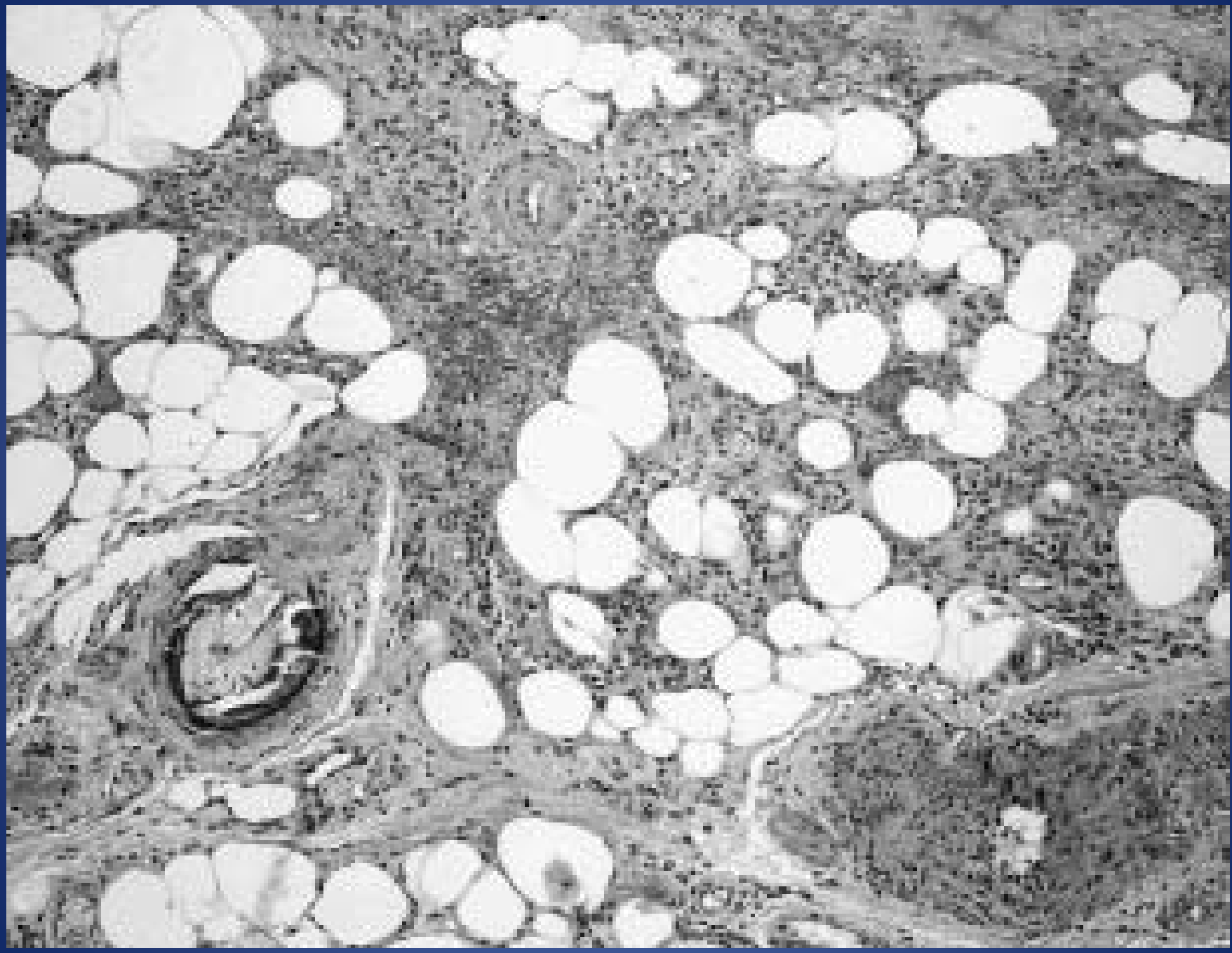
Figure 10
Neuronal calciphylaxis. This image demonstrates not only medial calcification of an arteriole but also calcification of the epineurium of a peripheral neuronal unit within the subcutaneous tissue of a patient with systemic CPLX. This is from the same patient and breast biopsy tissue as in figure 7. Calcium stains black in this von Kossa stain.

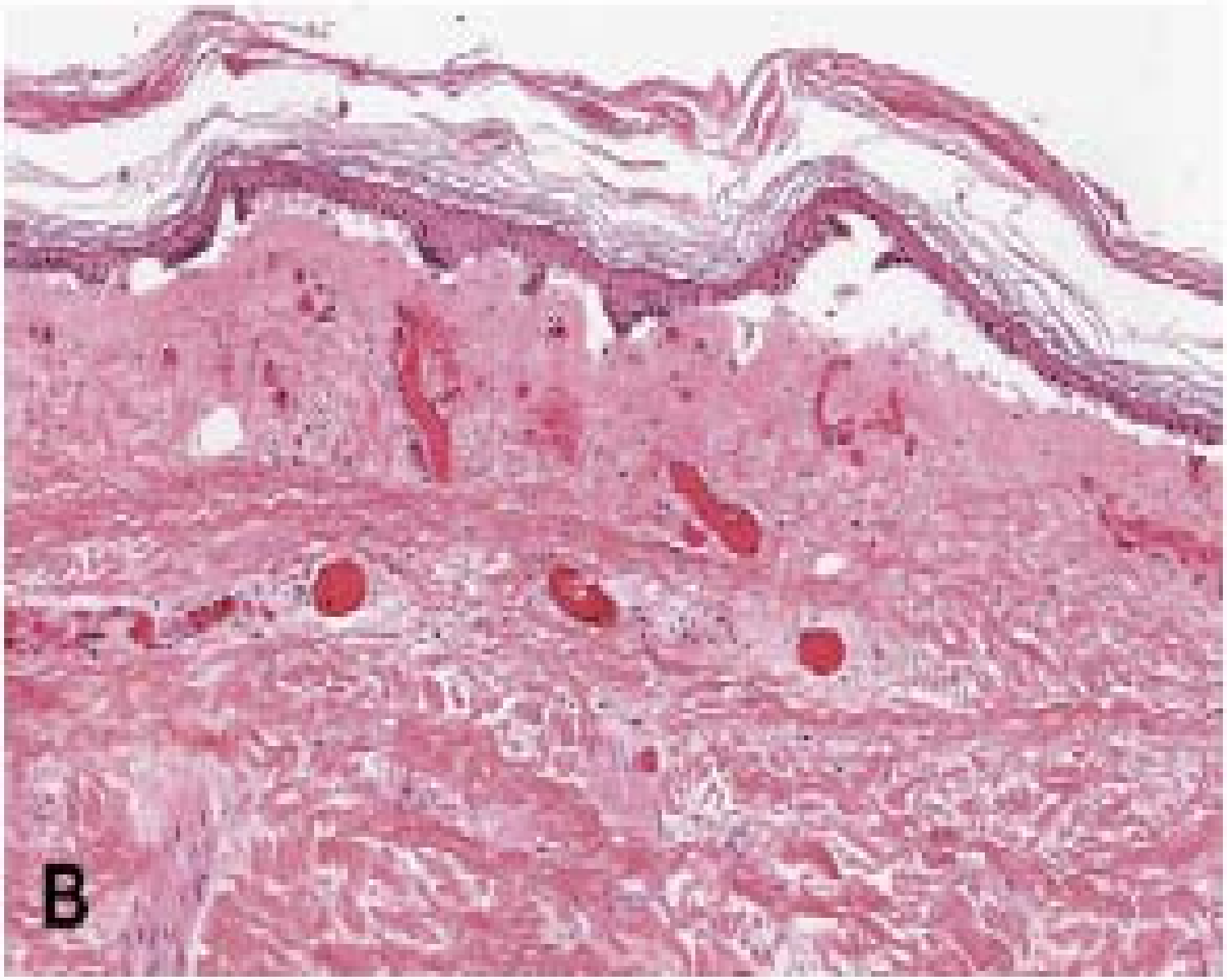
Histological findings from breast biopsy 2003:
Calciphylaxis
Vascular calcification involving intima (a), media (b), adventitia (c)




A



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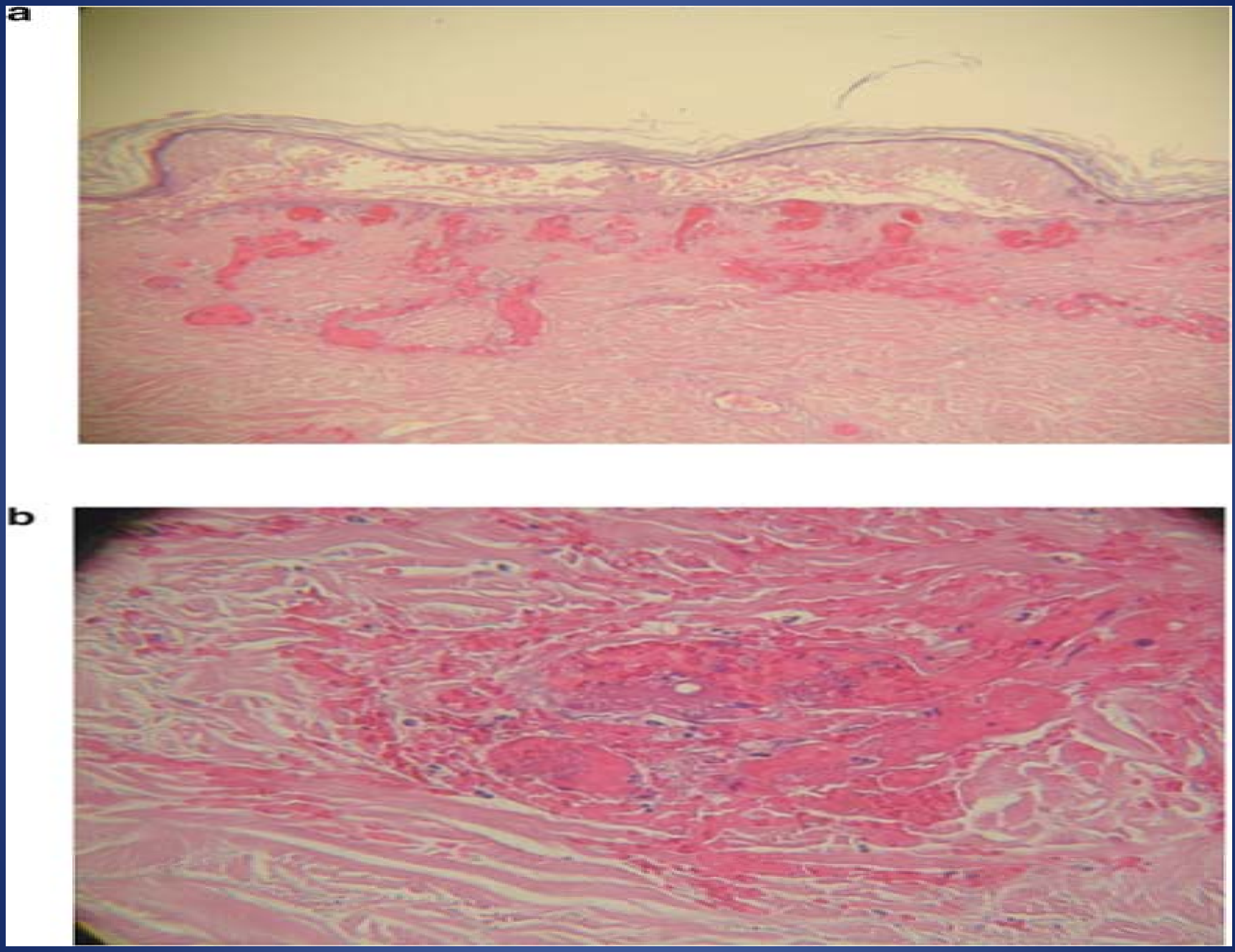
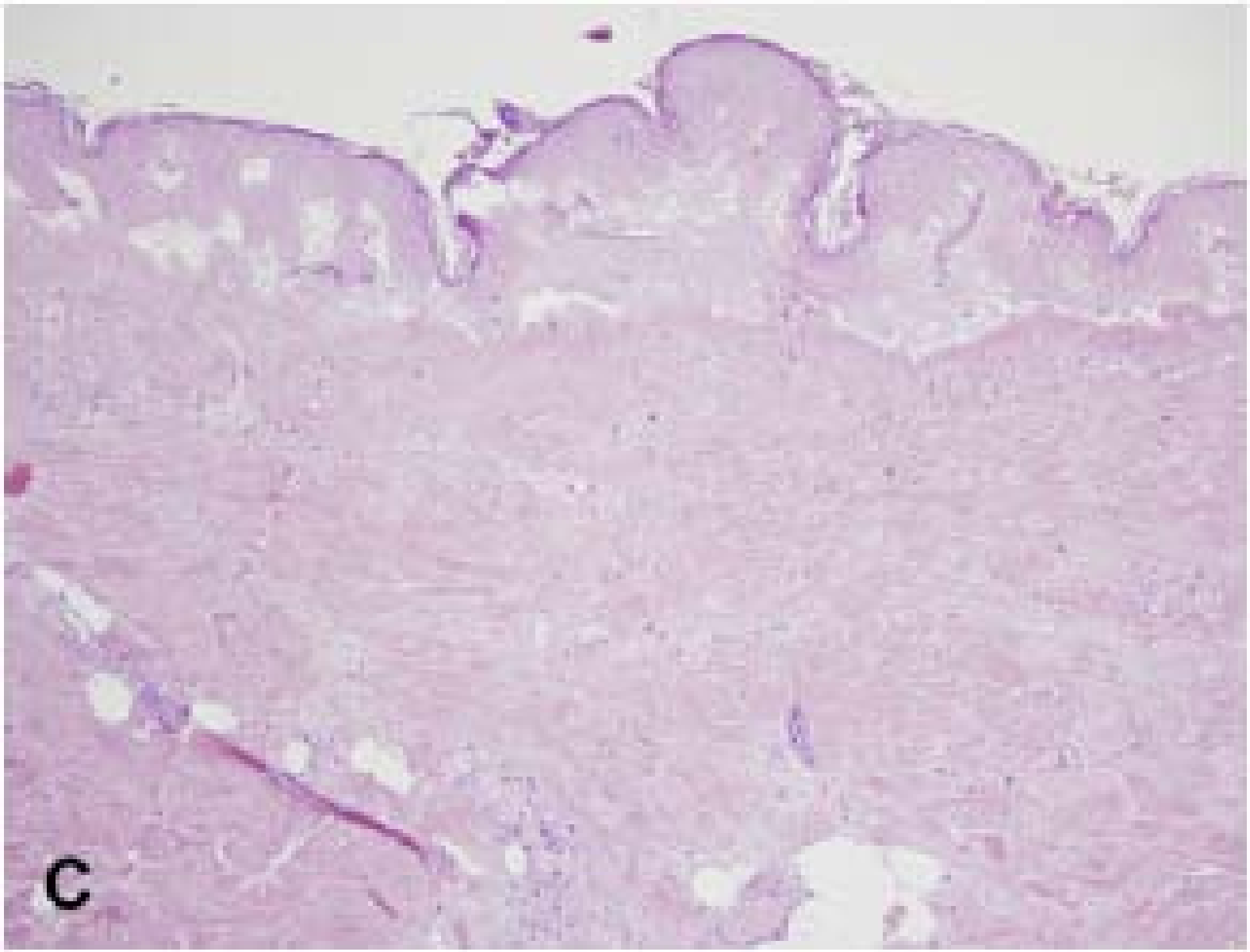

a
b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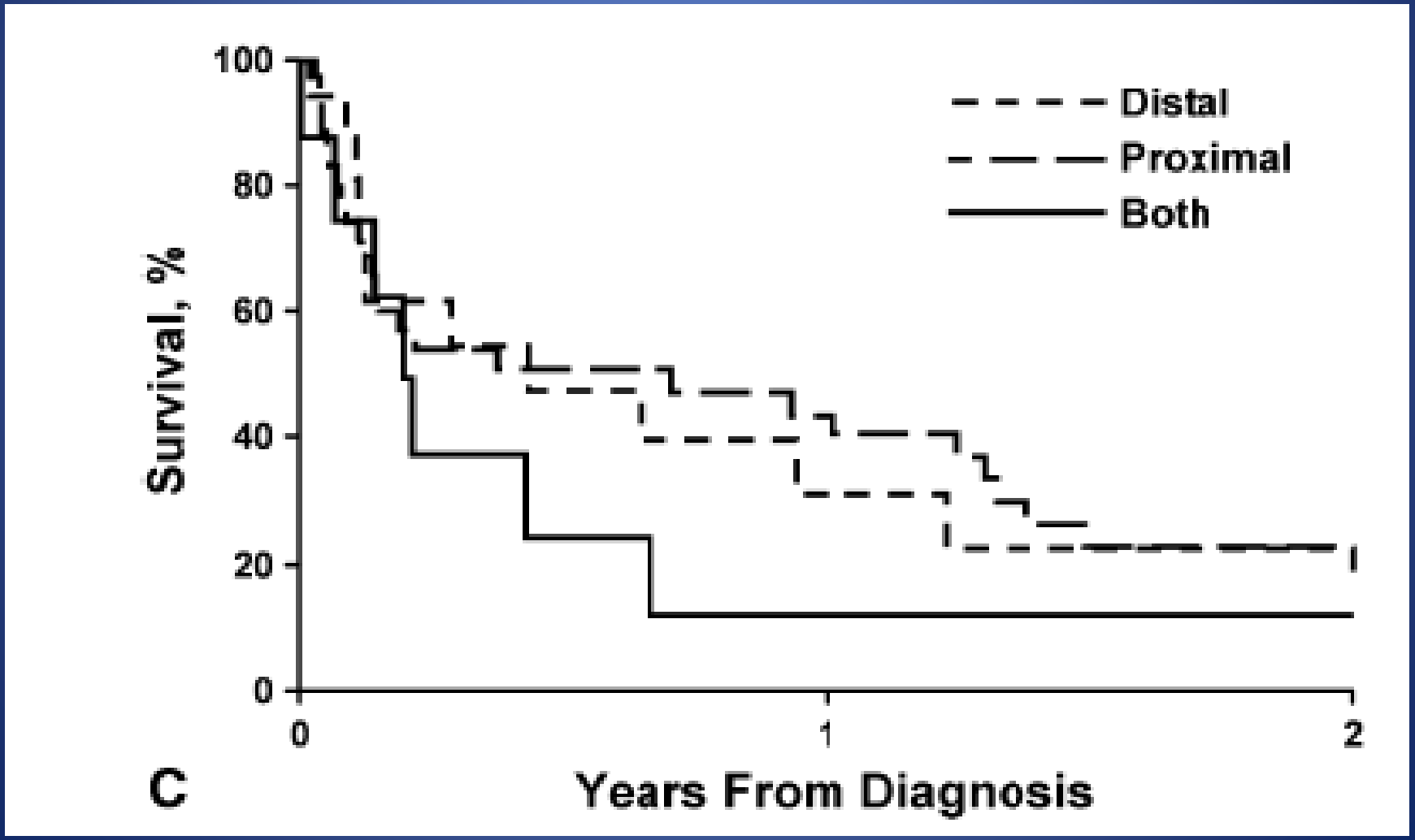
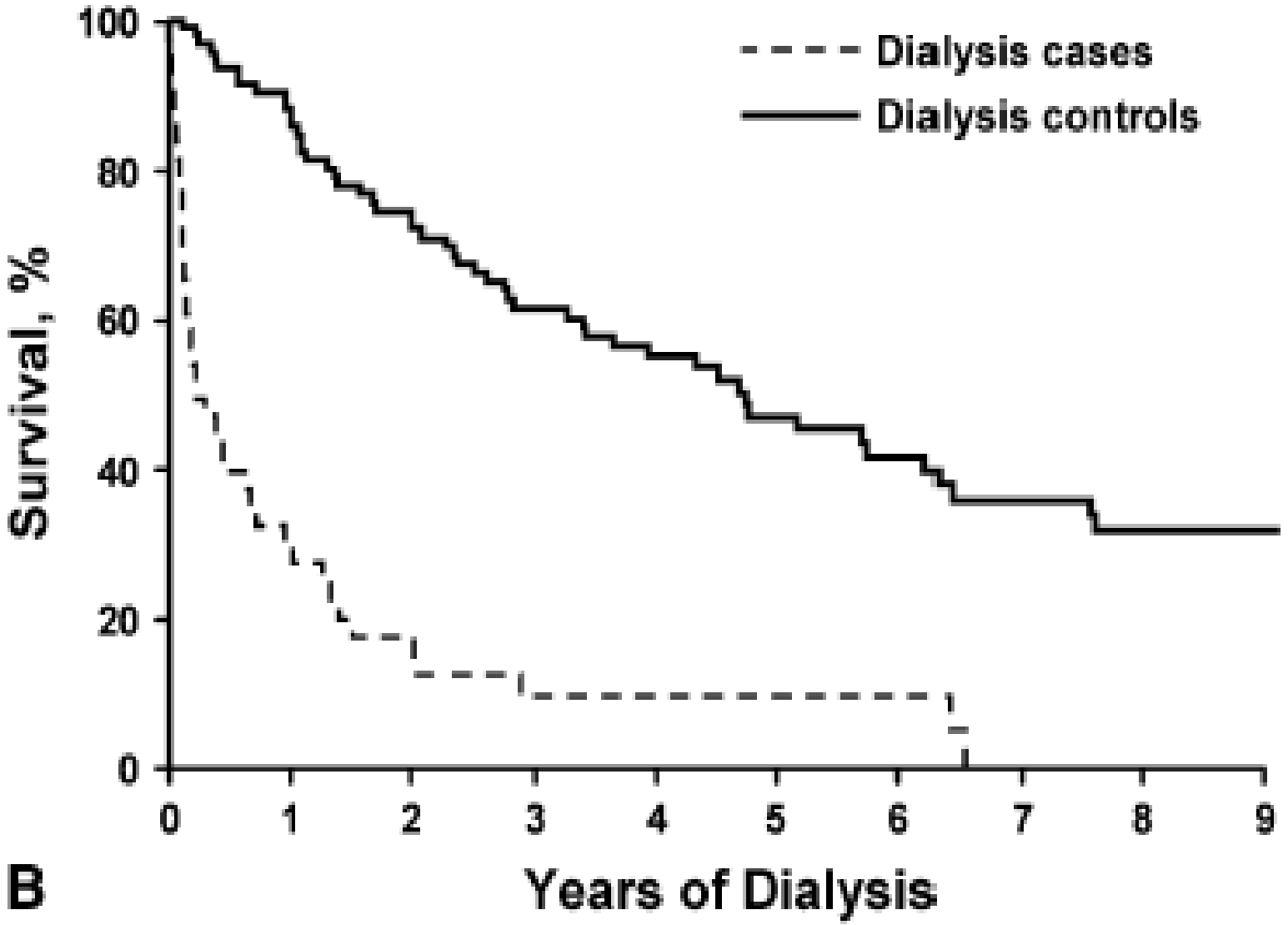
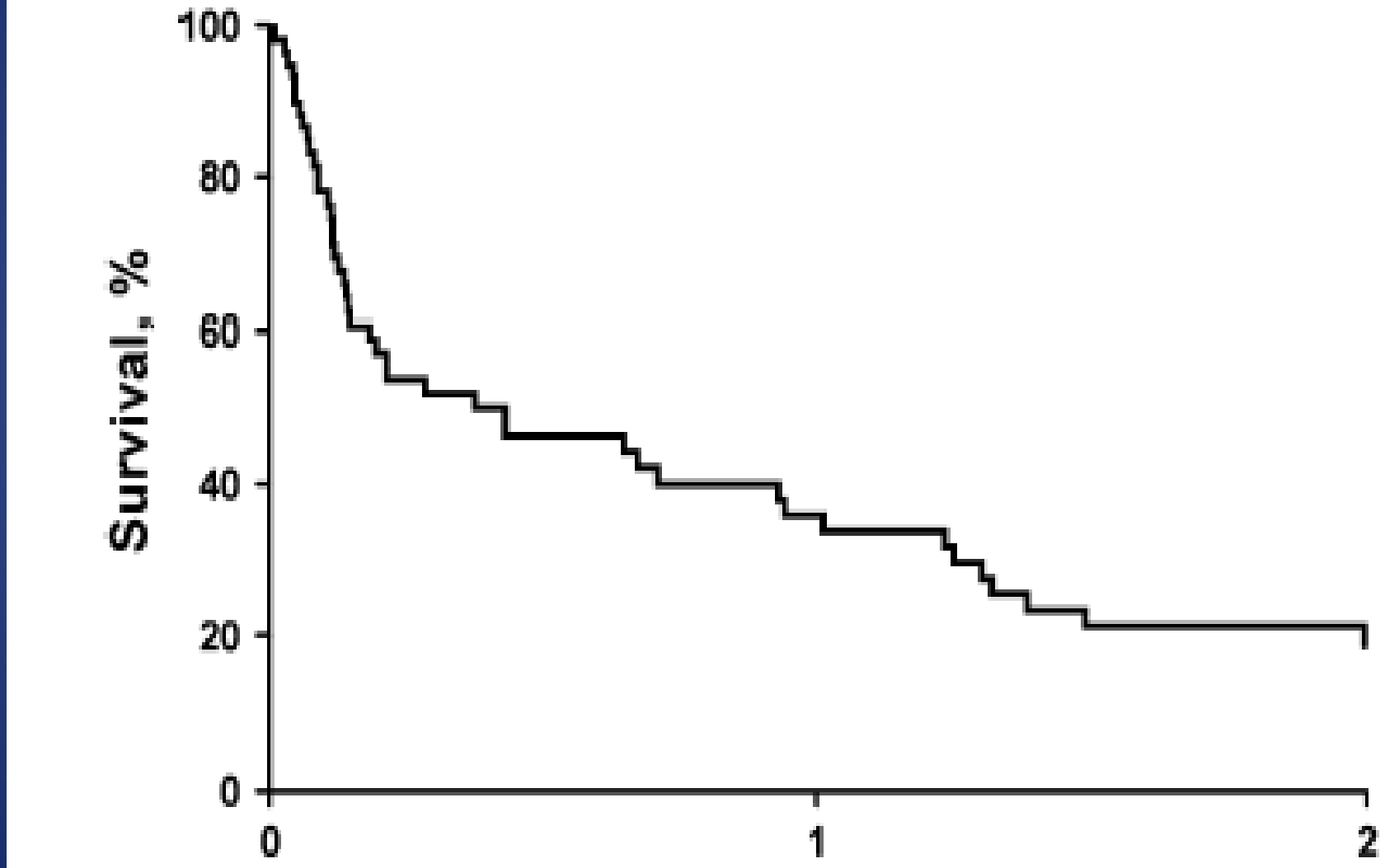
MORTALITY RATE-

- mortality rate at 6 months
  33% in patients with CUA who presented only with cutaneous plaques
- **80%** once ulceration developed

Factors assoc with outcome




Dialysis cases
Dialysis controls
Survival, %
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
B
Years of Dialysis


Survival, %
100
80
60
40
20
0
0
1
2

BOX

Therapeutic approaches to calciphylaxis

General

- Reduction of the calcium phosphate product (phosphate binders, increase of dialysis dose, reduction of calcium supply, reduction or discontinuation of vitamin D therapy)
- Parathyroidectomy in secondary or tertiary hyperparathyroidism
- Antibiotics for ulceration and signs of inflammation
- Professional, interdisciplinary wound management

Potential

- Discontinuation of a therapy with vitamin K antagonists, switch to heparin or antiplatelet agent
- Cinacalcet for secondary hyperparathyroidism, if necessary for tertiary hyperparathyroidism and contraindication for parathyroidectomy
- Biphosphonates, caution: adynamic bone disease
- Sodium thiosulfate as early rescue therapy for severe courses
- Hyperbaric oxygen therapy

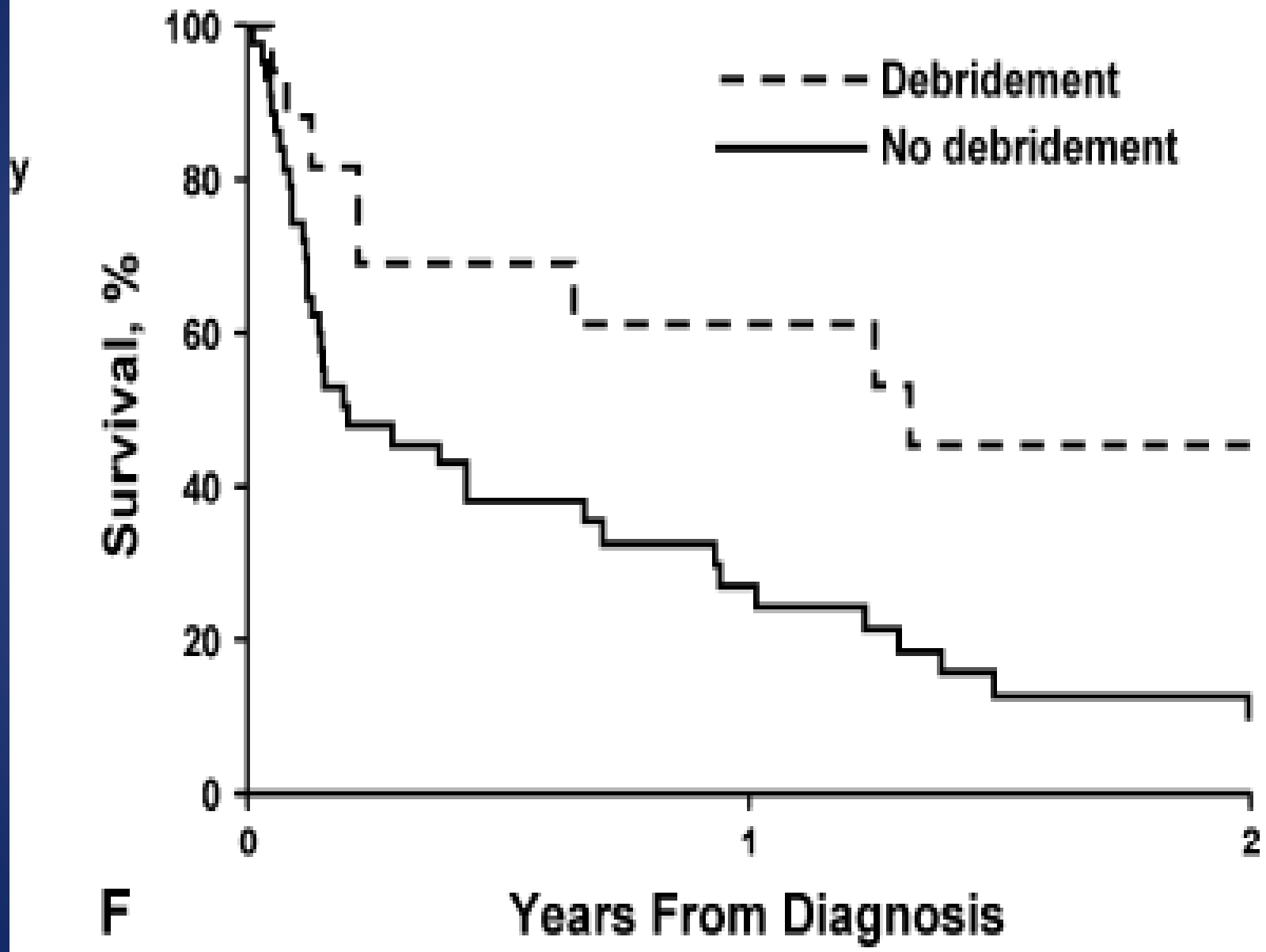
Perspectival

- if appropriate, high dose vitamin K replacement?
- if appropriate, fetuin-A induction with anti-inflammatory therapeutics?

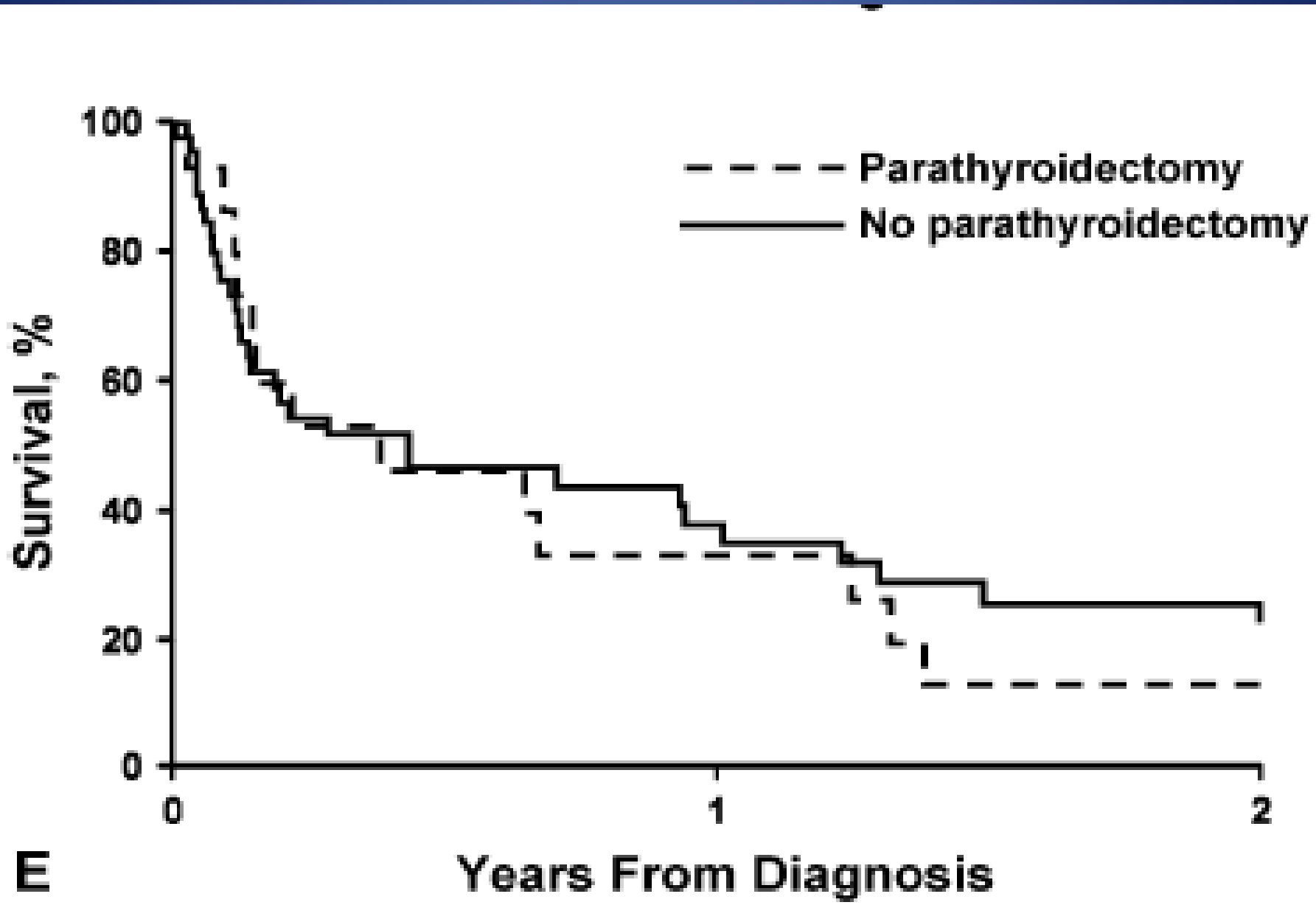
Based on the Cochrane Classification, the general recommendations also reach only evidence level IV because in view of the relative rarity of the disease condition no clinical studies of high methodological quality are available. The therapeutic approaches designated potential and perspectival are based on experimental pathophysiological findings or single case reports. The Calciphylaxis Register is intended to open the way for prospective controlled studies with the aim of improving the level of evidence.

Operative Treatment

- subtotal or total parathyroidectomy
- serial wound débridement or amputation.


Debridement
No debridement
Survival, %
100
80
60
40
20
0
0
1
2
Years From Diagnosis

F


Parathyroidectomy
No parathyroidectomy
Survival, %
100
80
60
40
20
0
0
1
2
Years From Diagnosis

E

Nonoperative Therapy

BOX

Therapeutic approaches to calciphylaxis

General

- Reduction of the calcium phosphate product (phosphate binders, increase of dialysis dose, reduction of calcium supply, reduction or discontinuation of vitamin D therapy)
- Parathyroidectomy in secondary or tertiary hyperparathyroidism
- Antibiotics for ulceration and signs of inflammation
- Professional, interdisciplinary wound management

Potential

- Discontinuation of a therapy with vitamin K antagonists, switch to heparin or antiplatelet agent
- Cinacalcet for secondary hyperparathyroidism, if necessary for tertiary hyperparathyroidism and contraindication for parathyroidectomy
- Biphosphonates, caution: adynamic bone disease
- Sodium thiosulfate as early rescue therapy for severe courses
- Hyperbaric oxygen therapy

Perspectival

- if appropriate, high dose vitamin K replacement?
- if appropriate, fetuin-A induction with anti-inflammatory therapeutics?

Based on the Cochrane Classification, the general recommendations also reach only evidence level IV because in view of the relative rarity of the disease condition no clinical studies of high methodological quality are available. The therapeutic approaches designated potential and perspectival are based on experimental pathophysiological findings or single case reports. The Calciphylaxis Register is intended to open the way for prospective controlled studies with the aim of improving the level of evidence.

Sodium Thiosulfate

- Based on treatment of calcium urolithiasis,tumoral calcinosis and nephrocalcinosis
- First reported in 2004
- Dose 25g iv tiw after HD

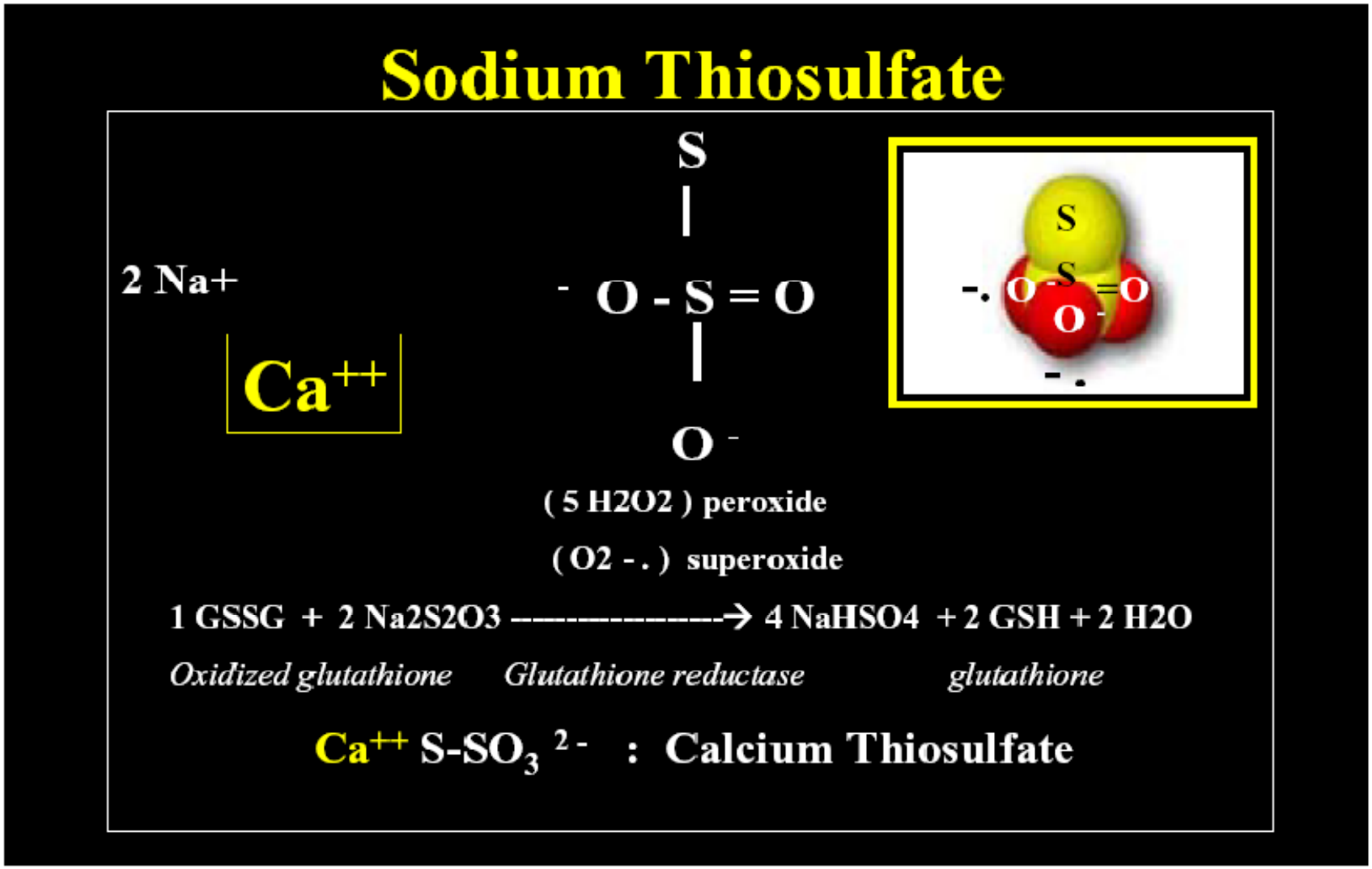


Figure 9
Sodium thiosulfate. This figure demonstrates the chemical structure of sodium thiosulfate, which is an antibrowning, reducing, and antioxidant agent: Capable of donating electrons to re-pair unpaired damaging electrons to be an effective antioxidant as well as a chelator of cations such as the calcium excess in calcific uremic arteriolopathy – CPLX.

Mechanism of Action

- Chelates calcium in the form of calcium thiosulfate salts which are 250-100 000X more soluble than other Ca salts
- Antioxidant properties
- Induces endothelial nitric oxide synthesis and therefore repair endothelium

Side Effects

- Rhinorrhoea,sinus congestion,nausea,vomiting
- Metabolic acidosis

Duration of therapy

- ? 6 months after lesion clears

- Response-improvement pf pain,decreased inflammation and rapid healing of ulcers in weeks

Table 2 Frequently asked questions by physicians who are not familiar with use of sodium thiosulfate in treating patients with calciphylaxis –calcific uremic arteriolopathy (CUA)

Number of patients treated in the literature	There are at least 13 cases described in the literature in Pub Med to date (February 2008) that are indexed (see Table 1)
Methods, frequency, duration, and timing of administration	Intravenous administration with frequency of three times per week, duration of 1 h during the last hour of hemodialysis sessions and one case report of intraperitoneal administration [26]
Most appropriate time to begin treatment	As soon as the diagnosis is made and other therapeutic guidelines have been accomplished
Administration dosage	25 g (two 12.5-g vials diluted in 100 cc of normal saline during dialysis. We currently recommend a test dose of 12.5 g per 100 ml of normal saline to be infused over 1 h. In pediatric patients, a dose of 25 g/1.7m^2 after each hemodialysis session has been used [22] (Table 1)

Duration of therapy	This varies from patient to patient but should be administered for at least 2 months beyond complete healing of skin ulcerations. Relief of pain in days to weeks and healing of skin ulcerations usually requires months
Success rate	In Table 1, there were 12 positive outcomes and one negative outcome [20]
Effectiveness late in the course of the disease	The later in the course of the disease, the effectiveness of any treatment is lessened. However, even if it is late in the disease process, it should be utilized to see if it can help the pain and possibly result in healing skin ulcerations. In Table 1 it is noted that all cases treated to date indicate a rapid and sustained relief of pain within a few weeks and that improvement and healing of skin ulcerations occur in weeks to months
Side effects	If infused too rapidly, this treatment typically will result in rather severe nausea, vomiting, and diarrhea. Araya et al., Brucculeri et al. and Subramaniam et al. have reported an association with metabolic acidosis

Availability	In the USA, STS is readily available for clinical use from American Regent, Shirley, NY. Undoubtedly, there are many other suppliers of this medication globally [23]
Cost	US $25 per 12.5-g vial translating to US $50 per treatment, translating to US $600 per month and US $7,200 per year. This compares favorably with the cost of antirejection medications in the US at an average cost of US $15,000
Oral forms	Available; however, oral treatment of calciphylaxis is not usually recommended because of tolerability due to nausea, vomiting, and diarrhea. Yatzidis used oral STS to prevent calcium stone formation in a dosage of 20 mmol of sodium thiosulfate daily [17]

Issues in Canada

- Cost---approx C$ 100,000 per annum!!!

Frequent Dialysis

- Dialysis 5-6 times a week

TAKE HOME POINTS

- Calcific uremic arteriolopathy (CUA) is seen primarily in patients with end-stage renal disease (ESRD) undergoing dialysis (prevalence, 4.1%).
- Mortality rates approach 80% when infection and sepsis develop.
- CUA is characterized by painful, cutaneous nonhealing wounds in the abdominal and thigh region caused by small-vessel medial wall calcification with intimal proliferation.
- Hyperphosphatemia and a calcium–phosphorus product greater than 55 mg^2/dL^2 in an ESRD patient with a suspicious lesion (resembling lentigo reticularis) suggests the diagnosis.
- Biopsy is helpful for definitive diagnosis but may be associated with development of a nonhealing ulcer.
- Treatment consists of discontinuing sensitizing agents such as warfarin, correcting calcium and phosphorus levels, frequent hemodialysis with low-calcium dialysate, and parathyroidectomy if severe secondary hyperparathyroidism exists.
- Frequent wound débridement, hyperbaric oxygen therapy, and antibiotics for infected lesions may be needed.

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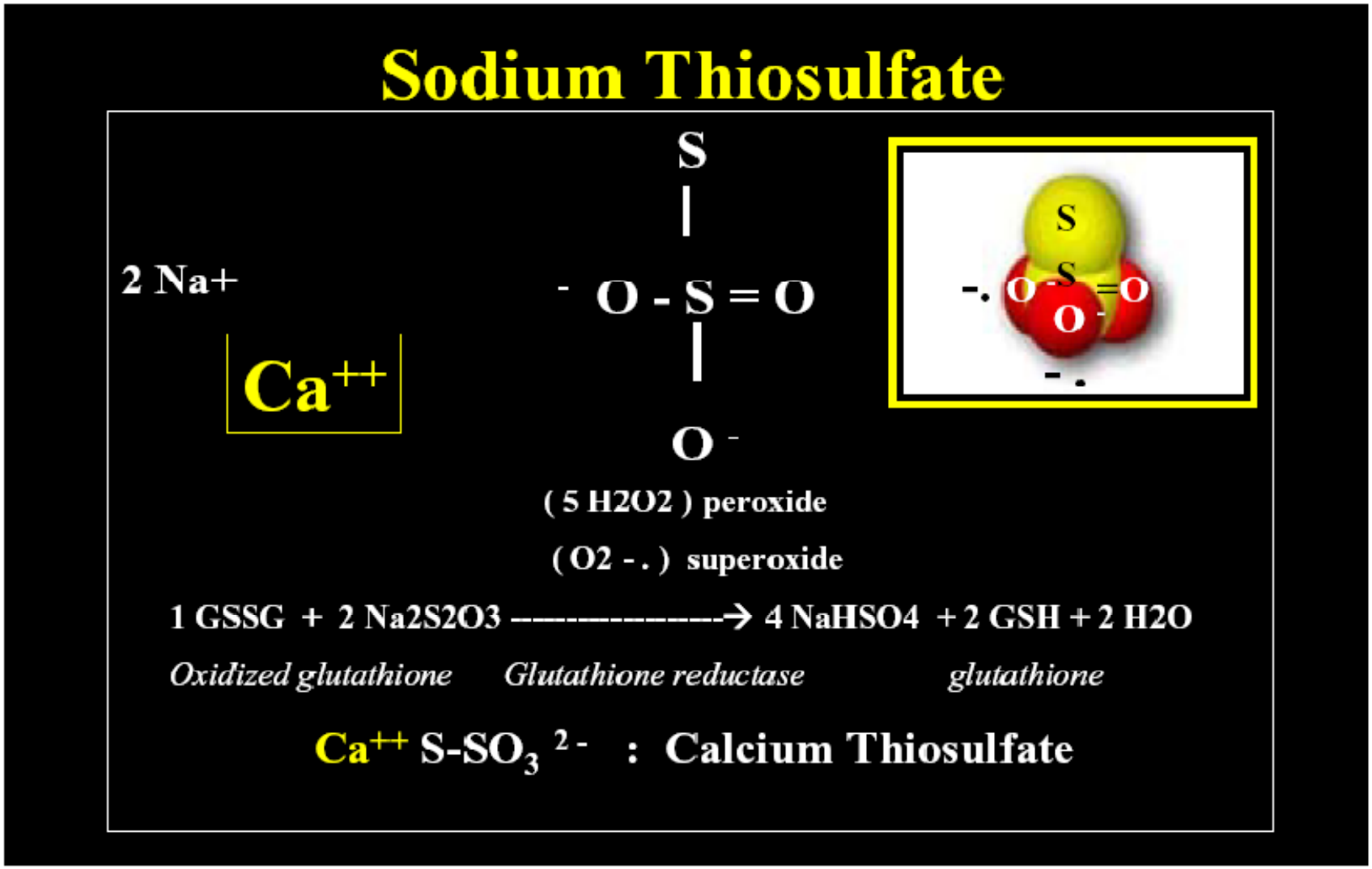

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- Calciphylaxis Registry
-
-
- **Patient Criteria**
-
- Does your patient have both of the following criteria?
-
- Yes No Subcutaneous ischemia with infarcted or necrotic skin lesions
-
- AND
-
- History of secondary hyperparathyroidism with persistently
- elevated calcium x phosphorus product greater than 50 mg^2/dl^2
-