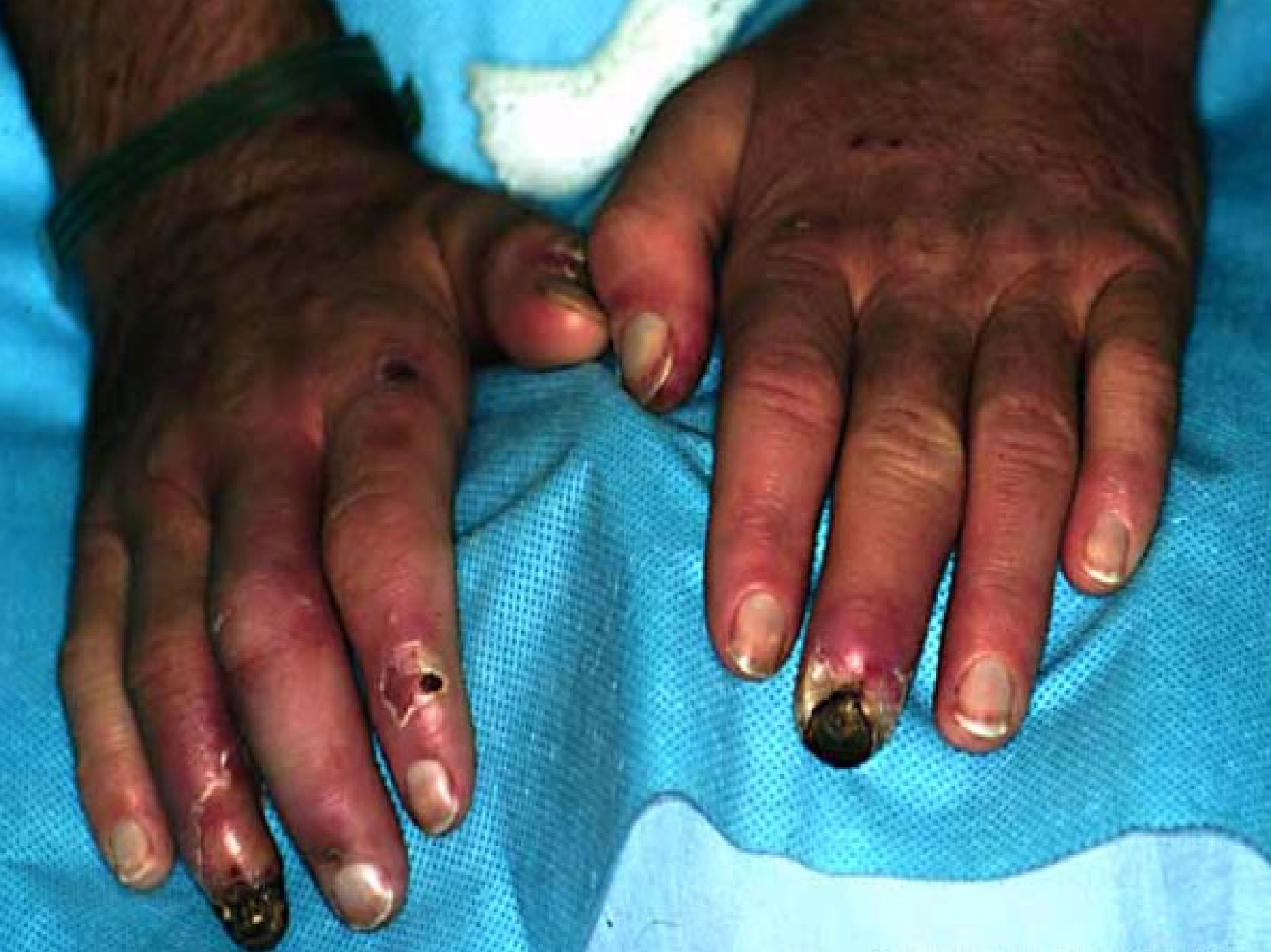
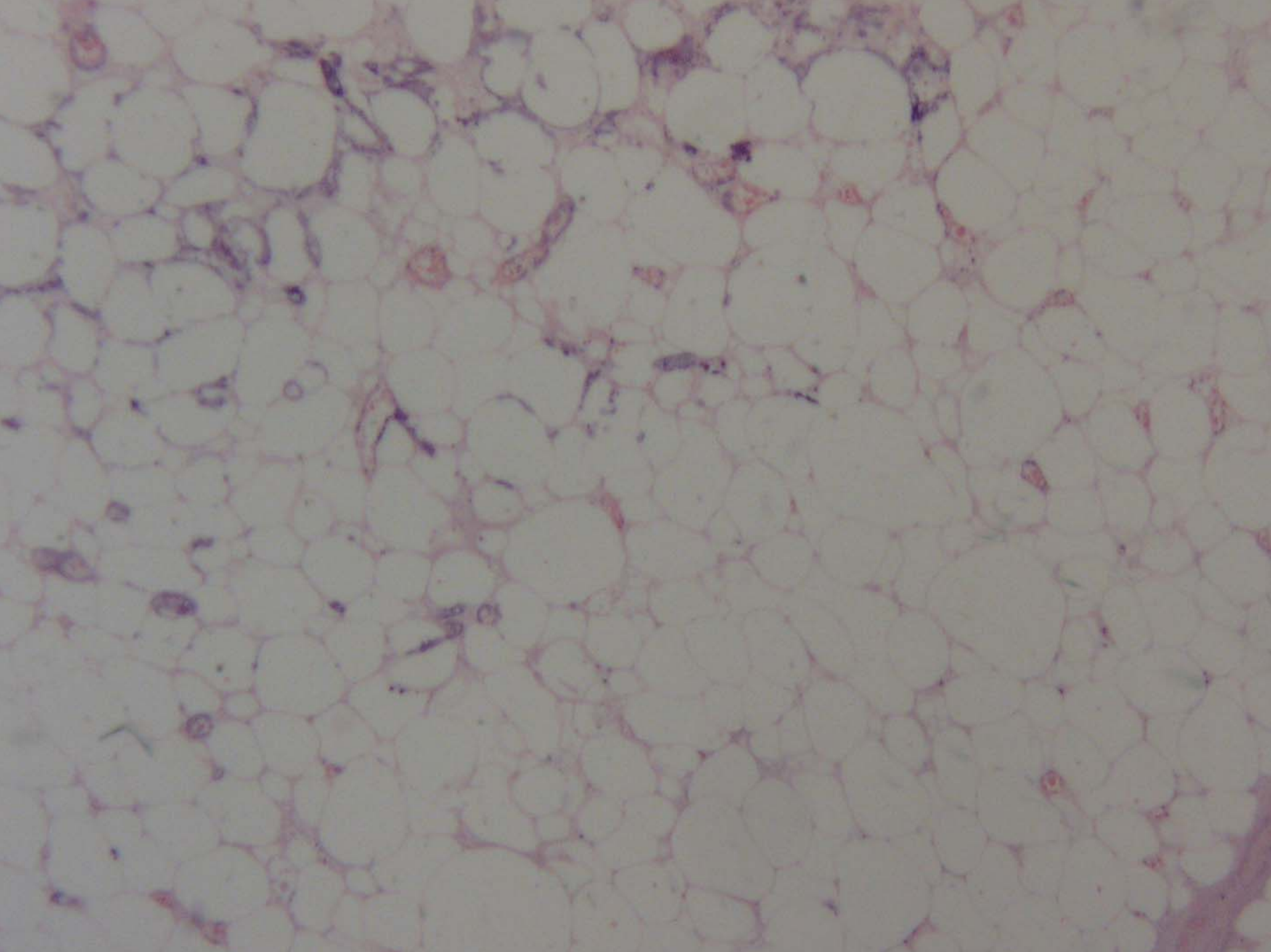
Dermatopathologic Emergencies!

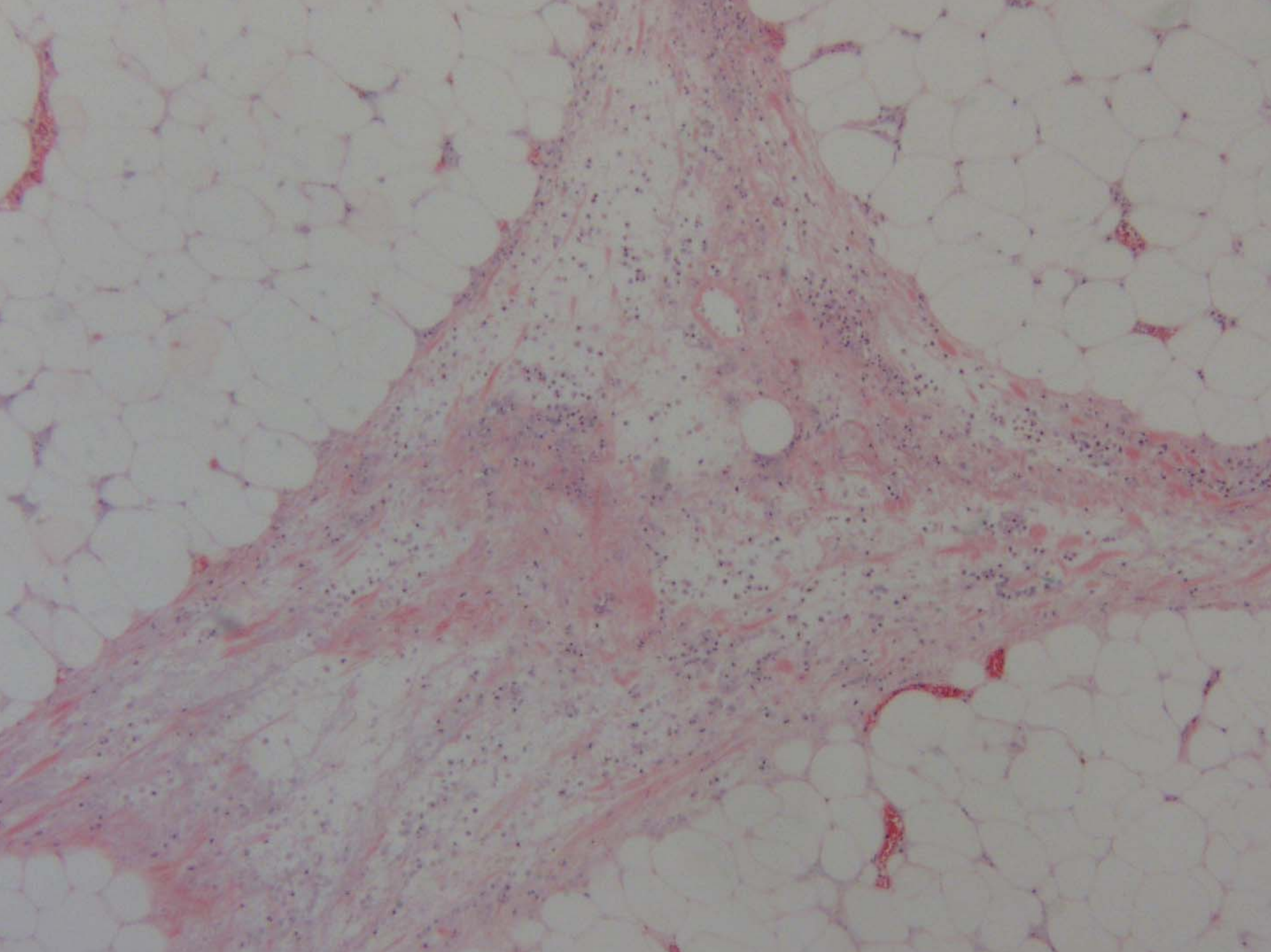
Paul K. Shitabata, M.D.
Dermatopathologist
APMG

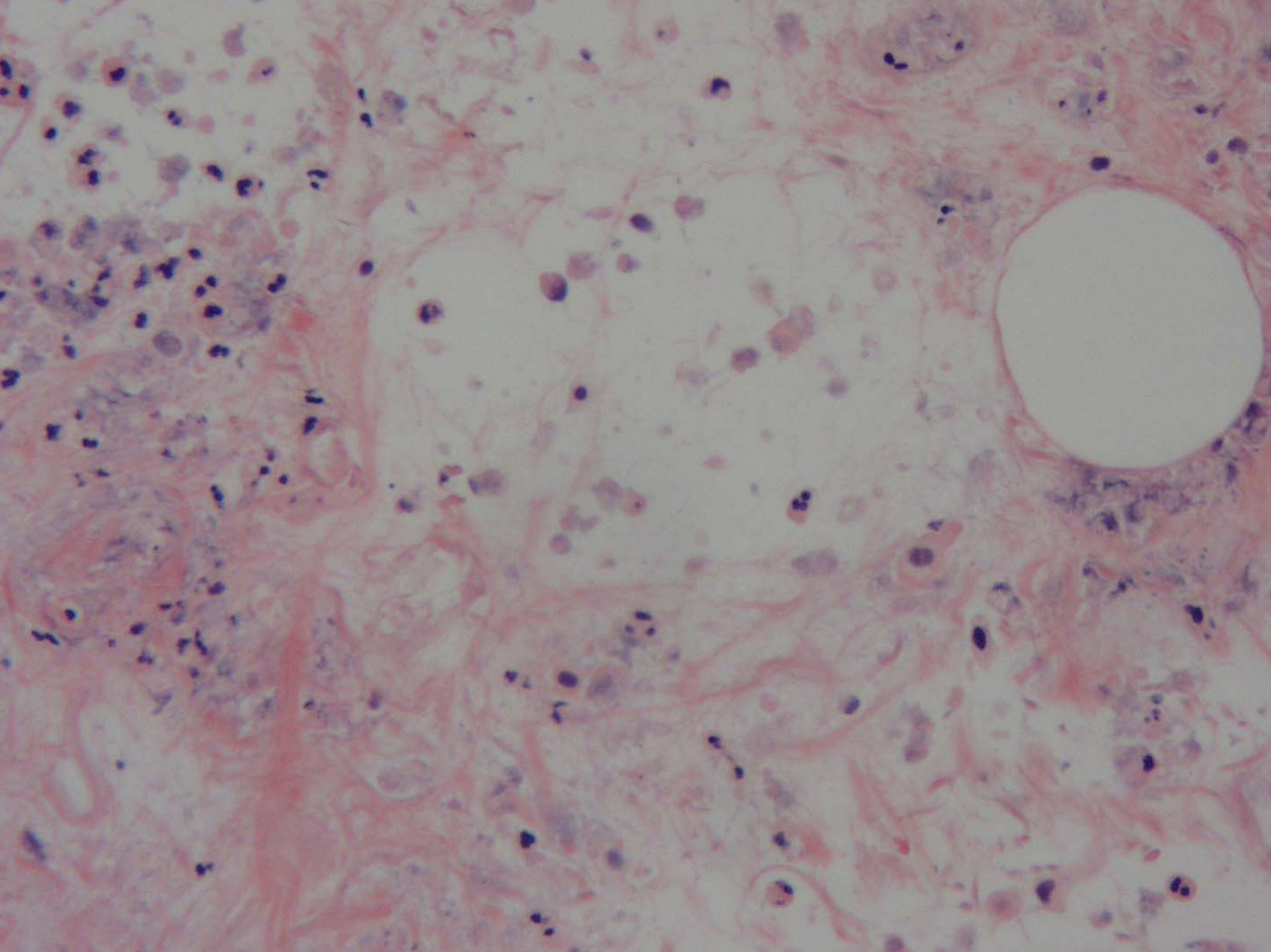
History

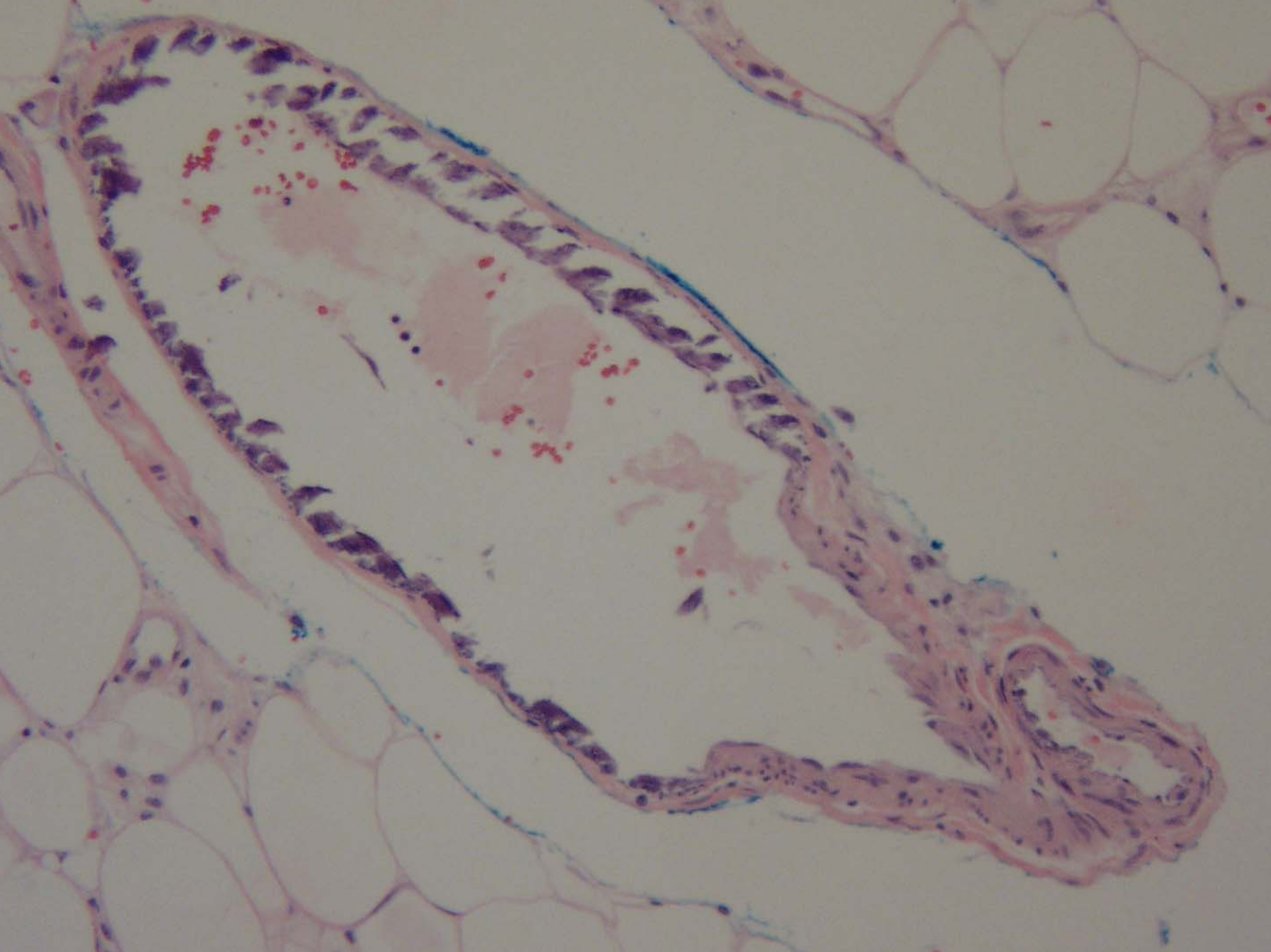
- 82 F, four year hx on dialysis
- Acute onset of painful subQ nodules on distal extremities
- Incisional bx with cultures

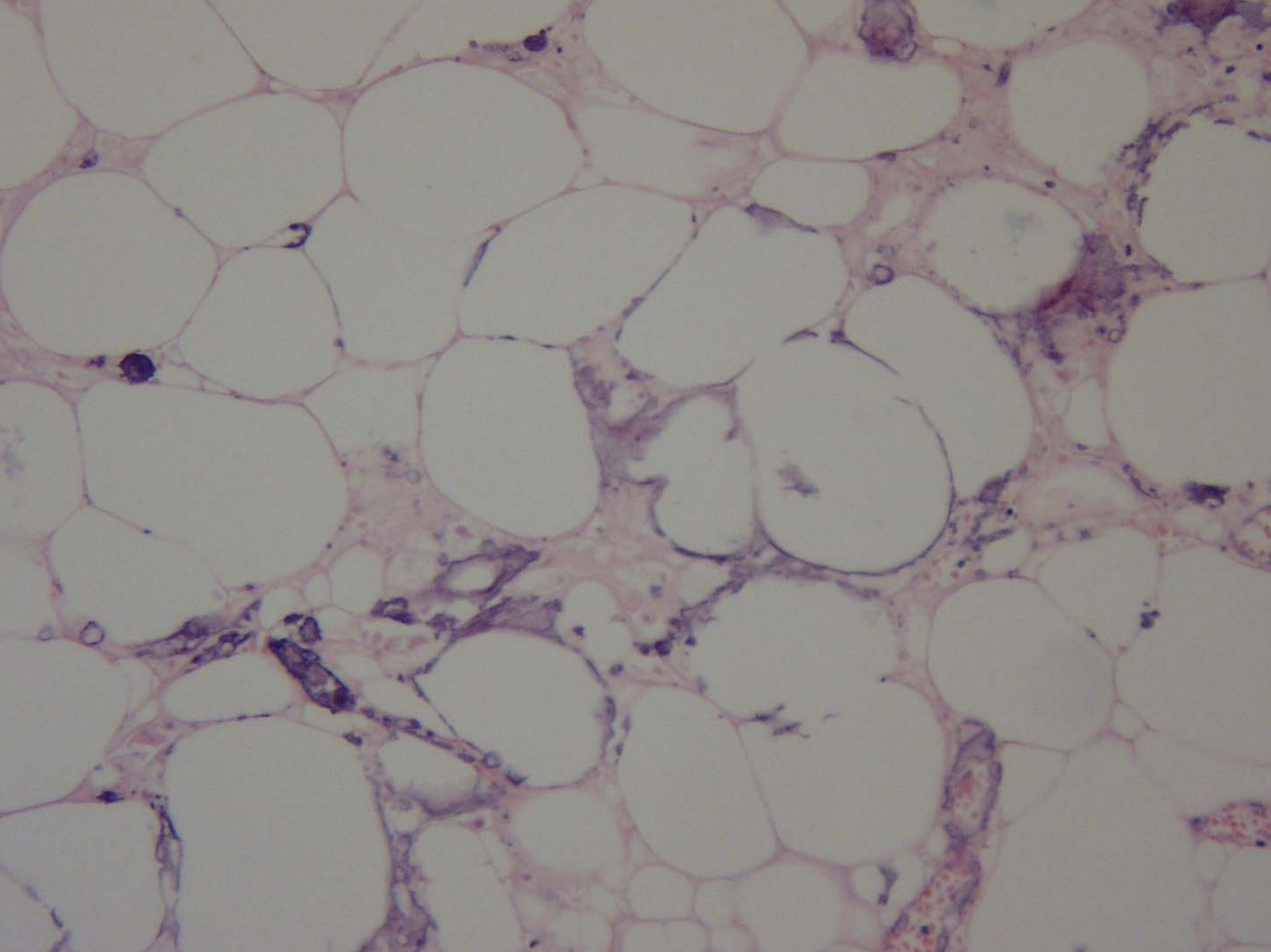


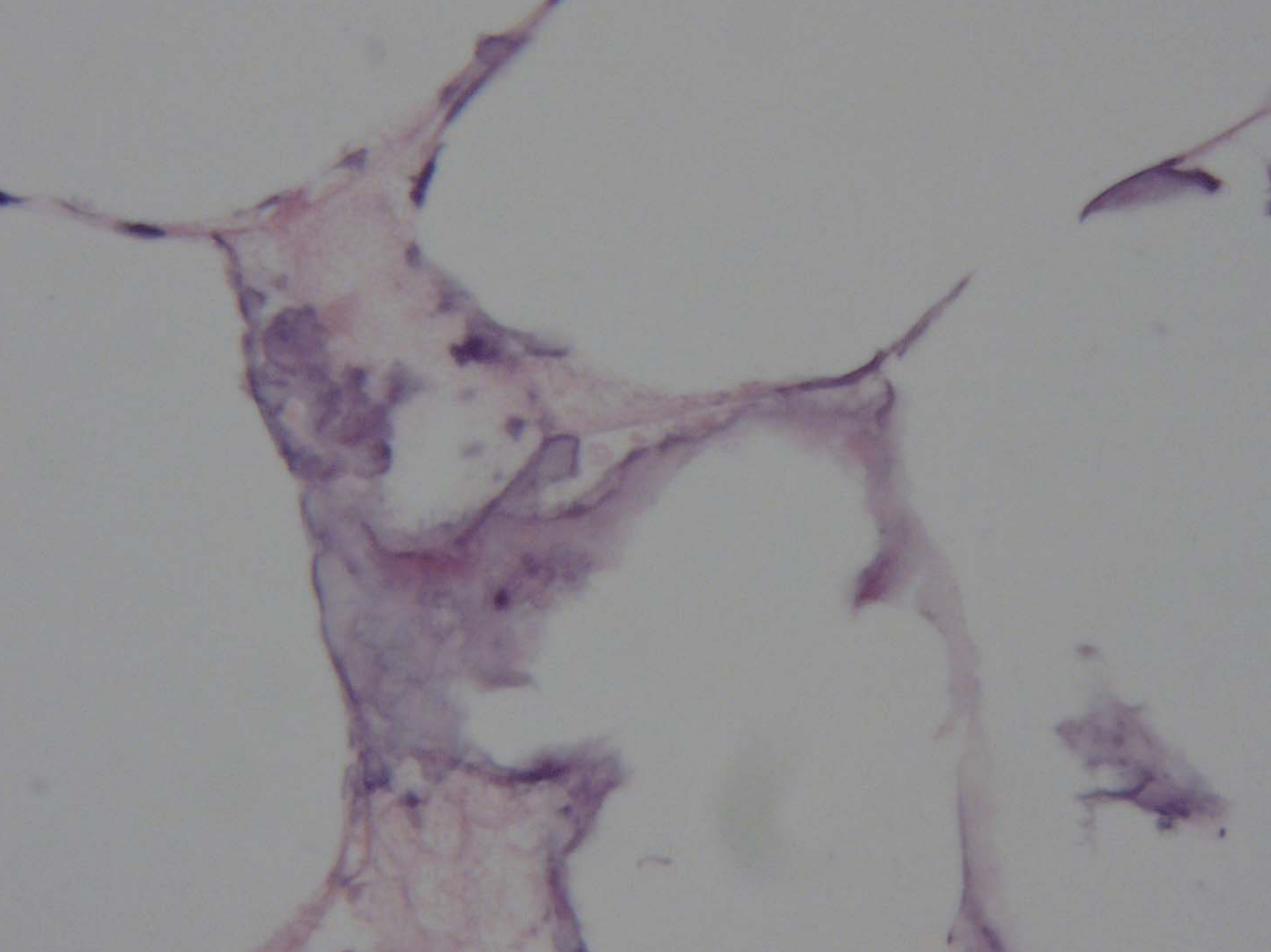


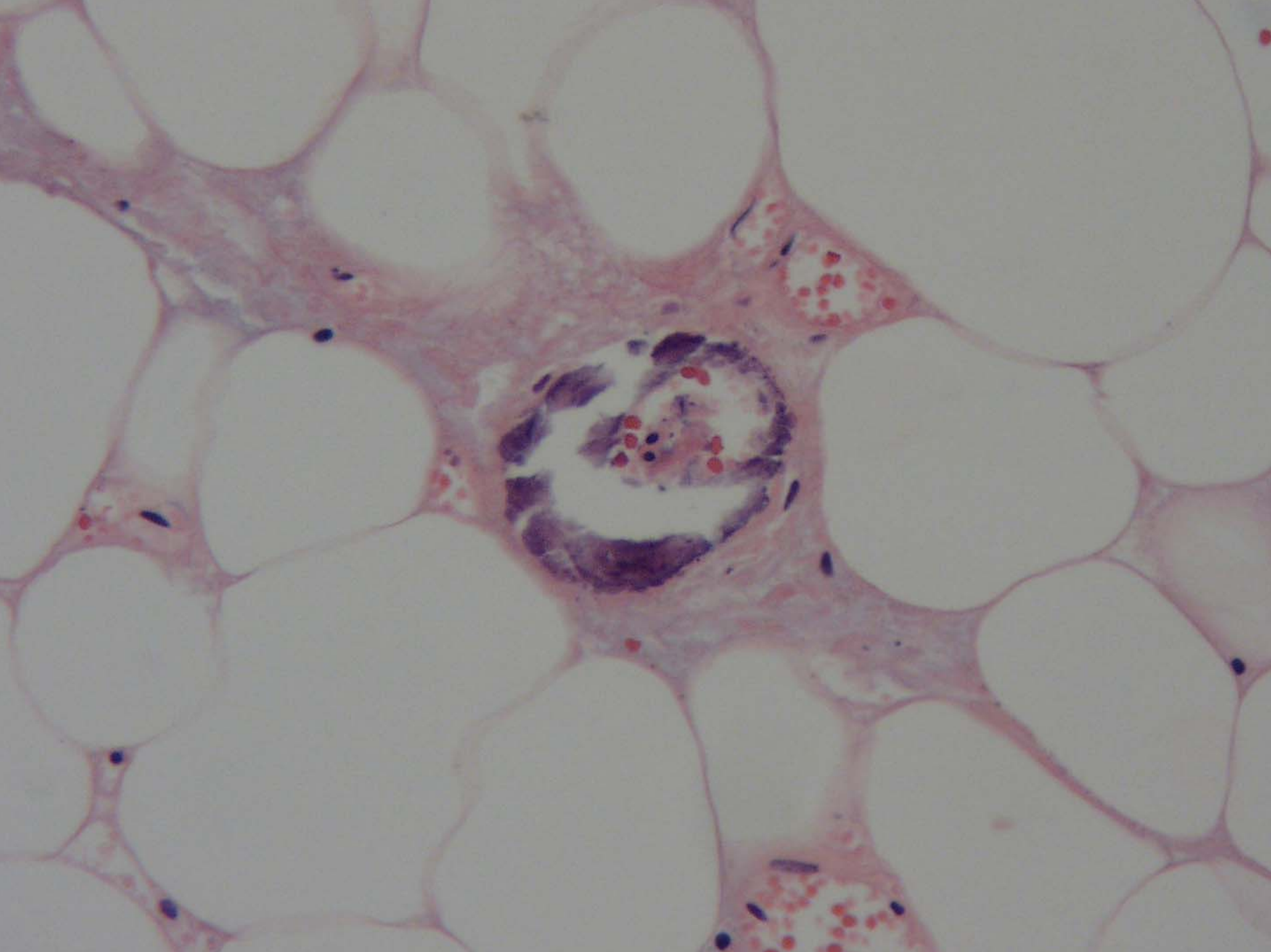


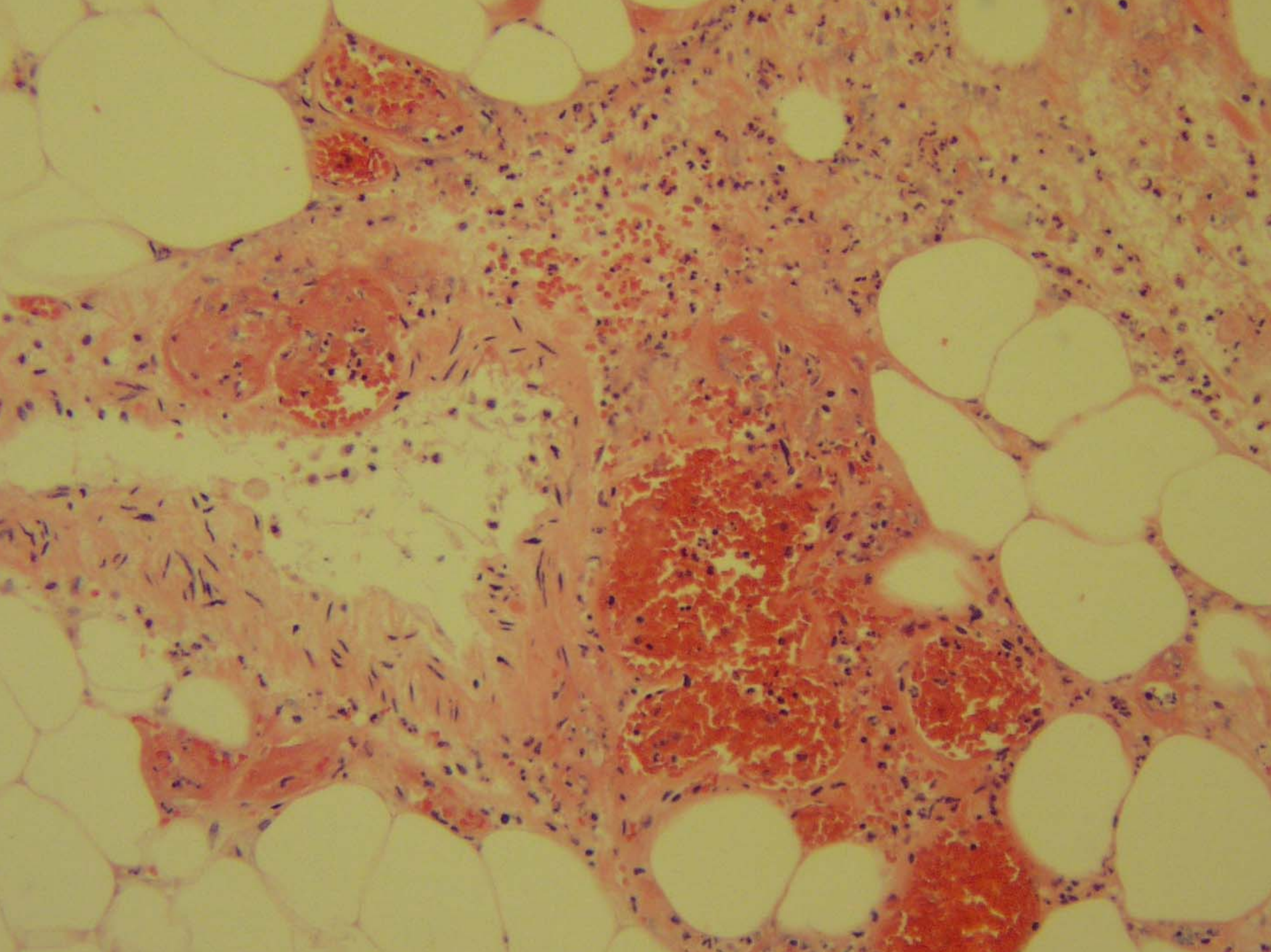


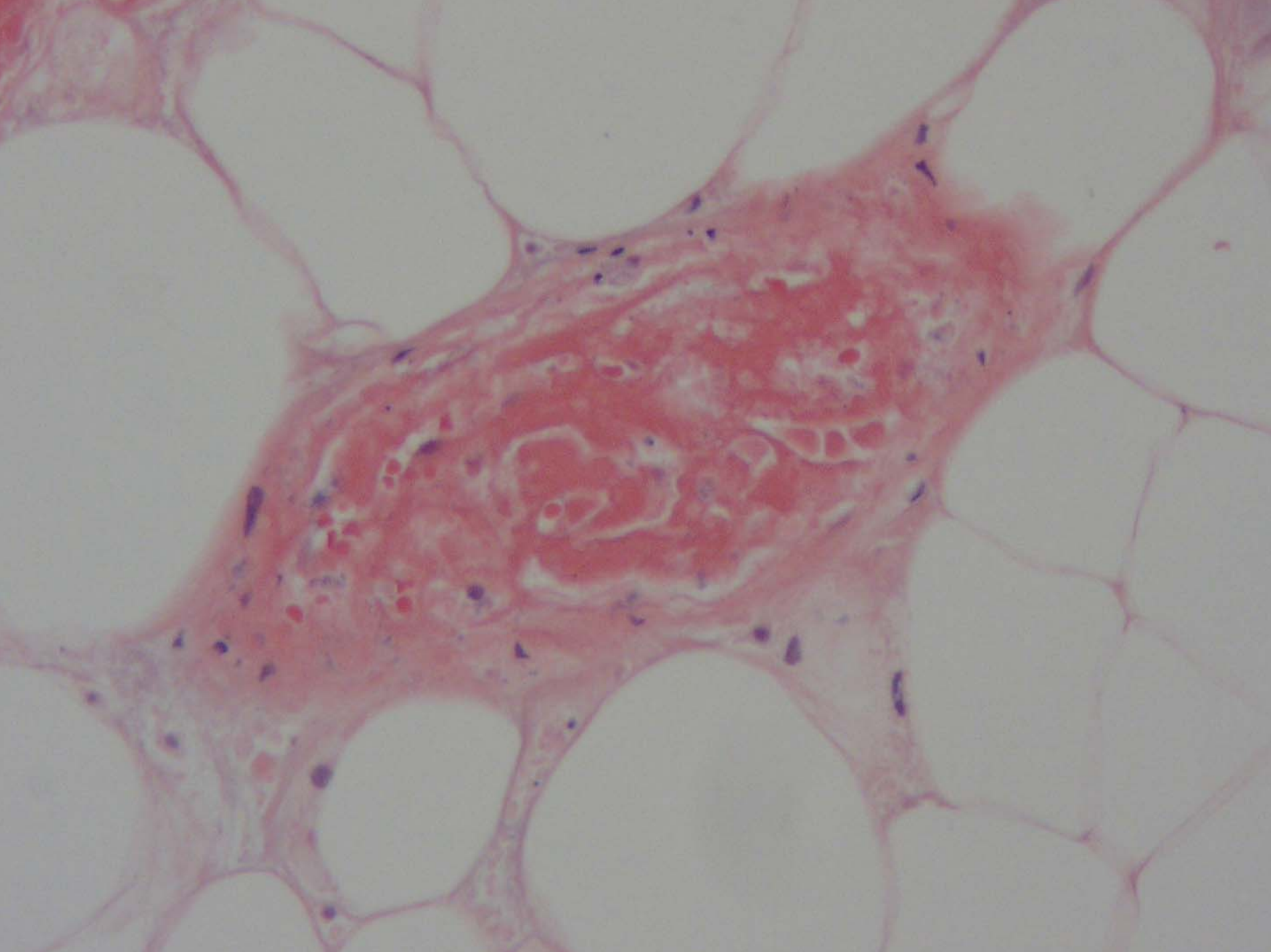


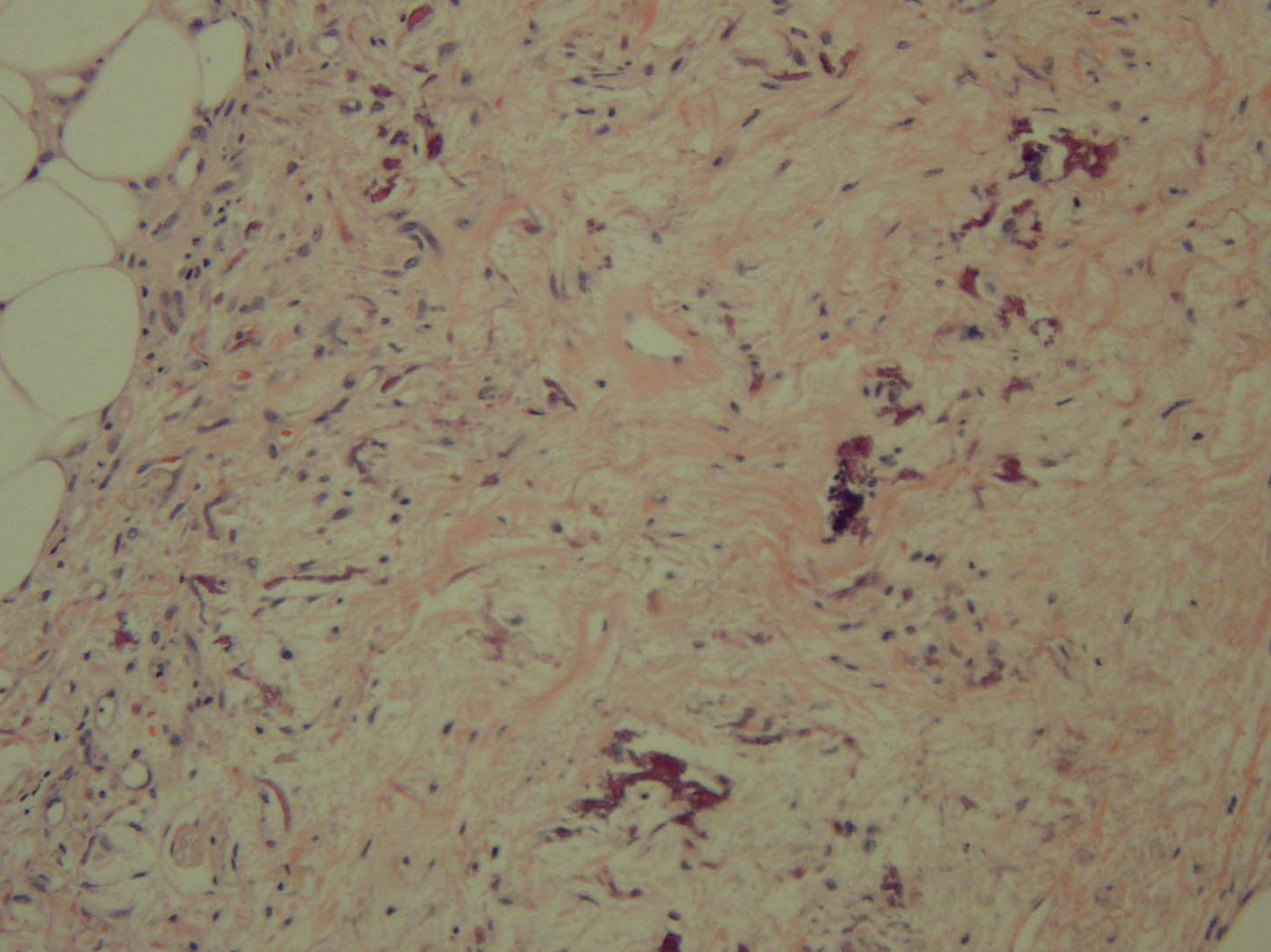


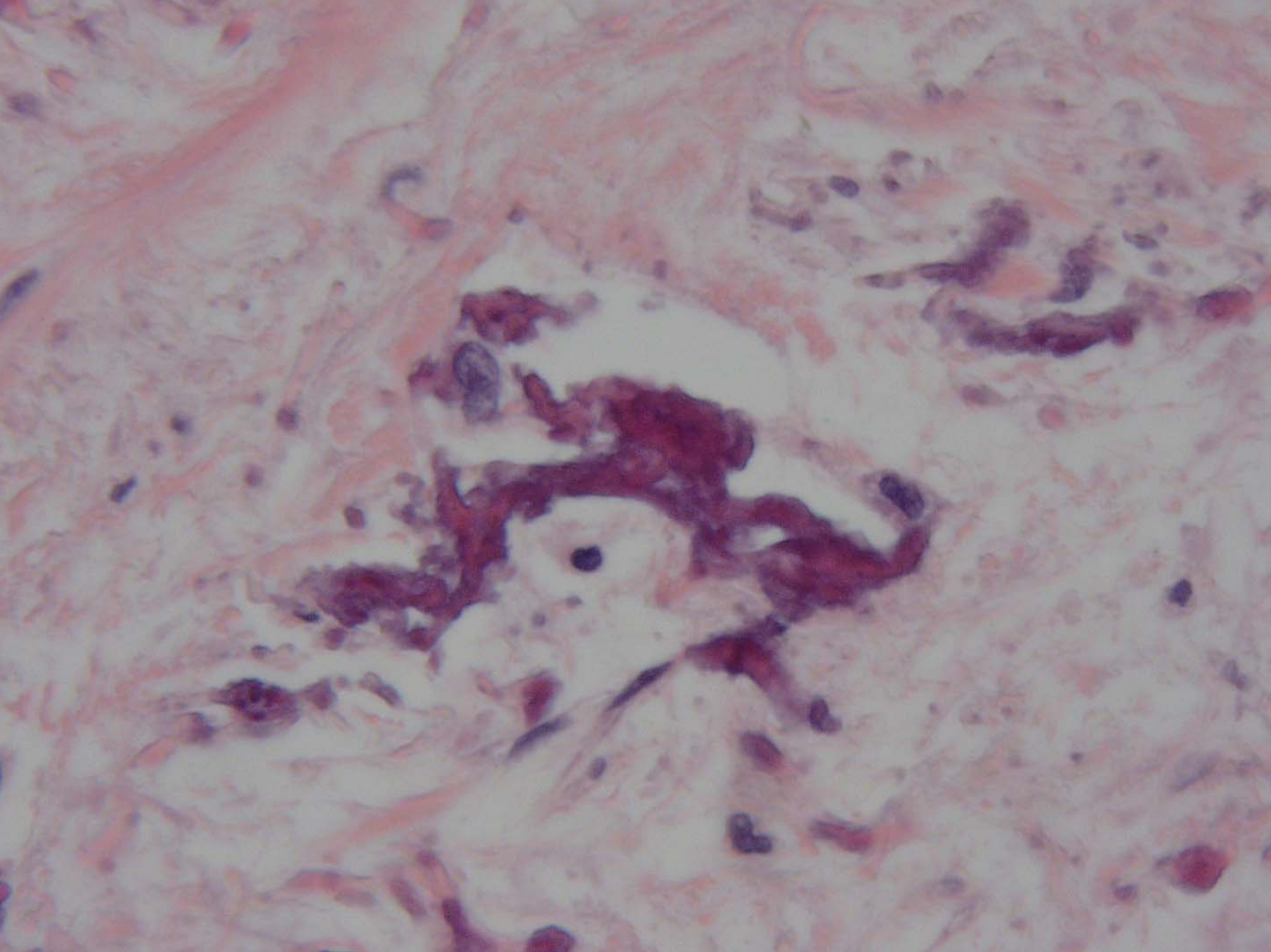












Calciphylaxis

- 1-4% of the ESRD population
  - Probably rare in general population
- Mortality/Morbidity
  - Mortality rate 60-80%
  - Leading cause of death is sepsis from infected, necrotic skin lesions
  - Mortality rate is higher in patients with proximal disease than in those with only distal or acral disease
- More prevalent in whites
- F:M 3:1
- 6 months to 83 years
  - Mean age of 48 years
  - Younger patients with longer duration of renal replacement therapy more predisposed

Clinical

- Increased risk
  - Obesity
    - Increased where body fat is most abundant, the thighs, buttocks and lower abdomen
  - Glucocorticoid exposure

Pathogenesis

- Multifactorial
  - Associated disorders chronic renal failure, hypercalcemia, hyperphosphatemia, an elevated calcium-phosphate product and secondary hyperparathyroidism
  - Hypercoagulable conditions including protein C and protein S deficiencies
- Selye's Rat model
  - Hypersensitivity induced by a set of "sensitizing" agents
  - Calcinosis occurred only in those subsequently subjected to a group of challengers, and only after a critical lag time
  - Sensitizing events and agents included nephrectomy and exposure to parathyroid hormone and vitamin D
  - Challengers included egg albumin and metallic salts

Radiologic

- Plain films uniformly demonstrate an arborization of vascular calcification within the dermis and subcutaneous tissue
  - Common in ESRD and not specific for calciphylaxis

Histopathology

- Incisional biopsy is usually diagnostic with subcutaneous tissue sampled
- Calcification within the media of small and medium-sized arterioles with extensive intimal hyperplasia and fibrosis
- Mixed inflammatory infiltrate occurs frequently
- Subcutaneous calcium deposits with panniculitis and fat necrosis may sometimes be found
- Vascular microthrombi are frequent

Treatment

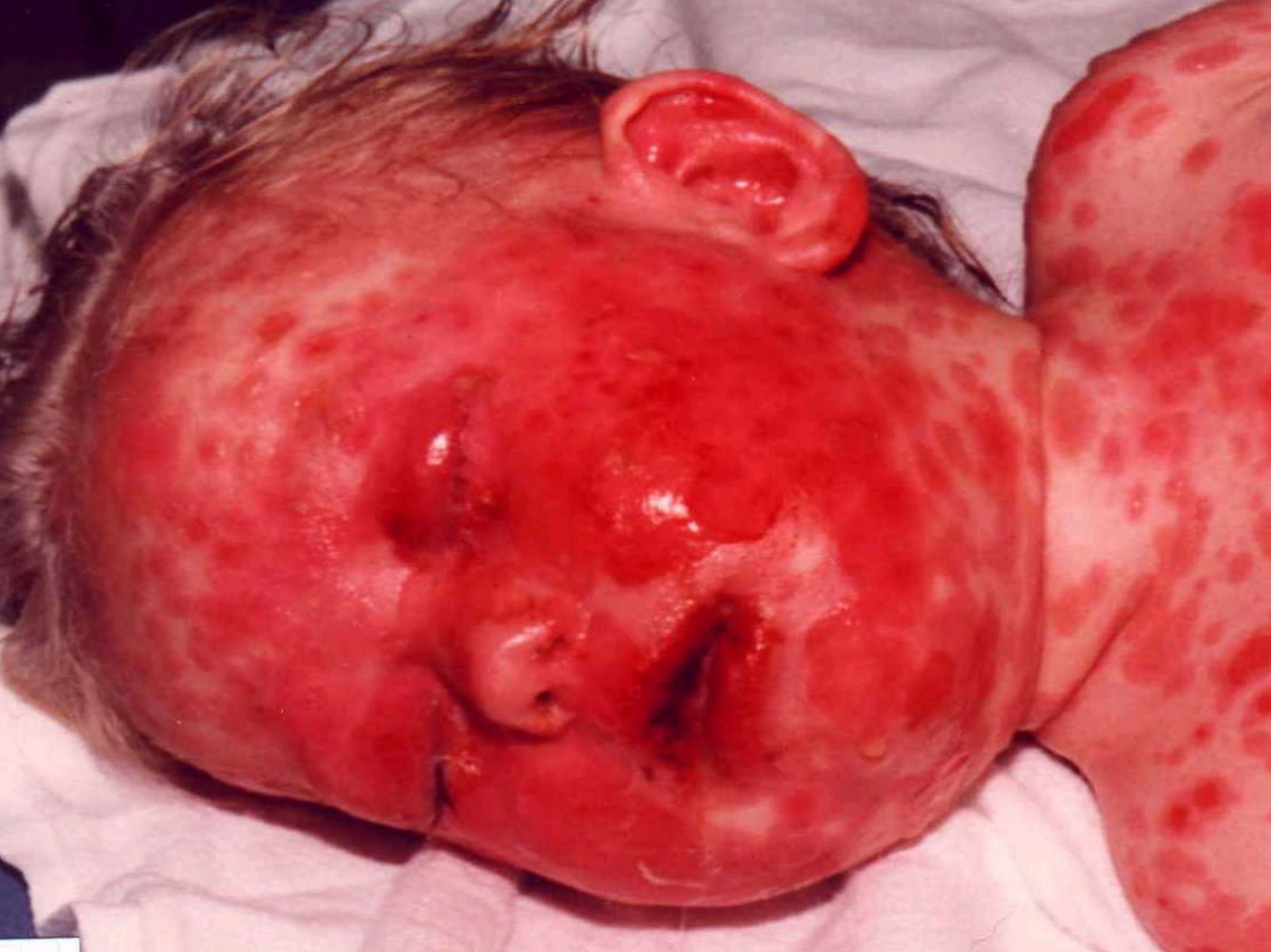
- Supportive
- Total or subtotal parathyroidectomy with autotransplantation
- Avoid glucocorticoids

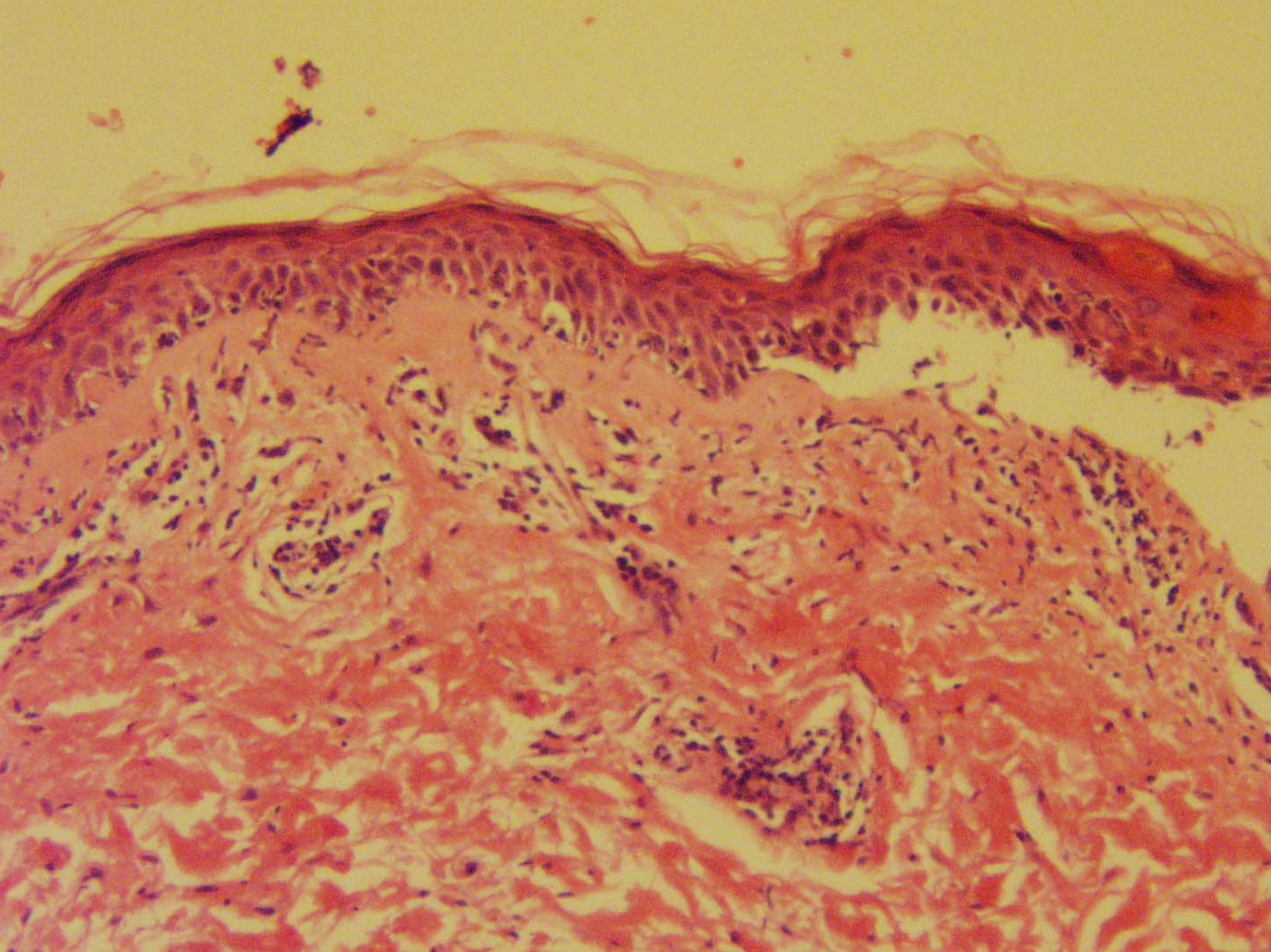
Differential Diagnosis

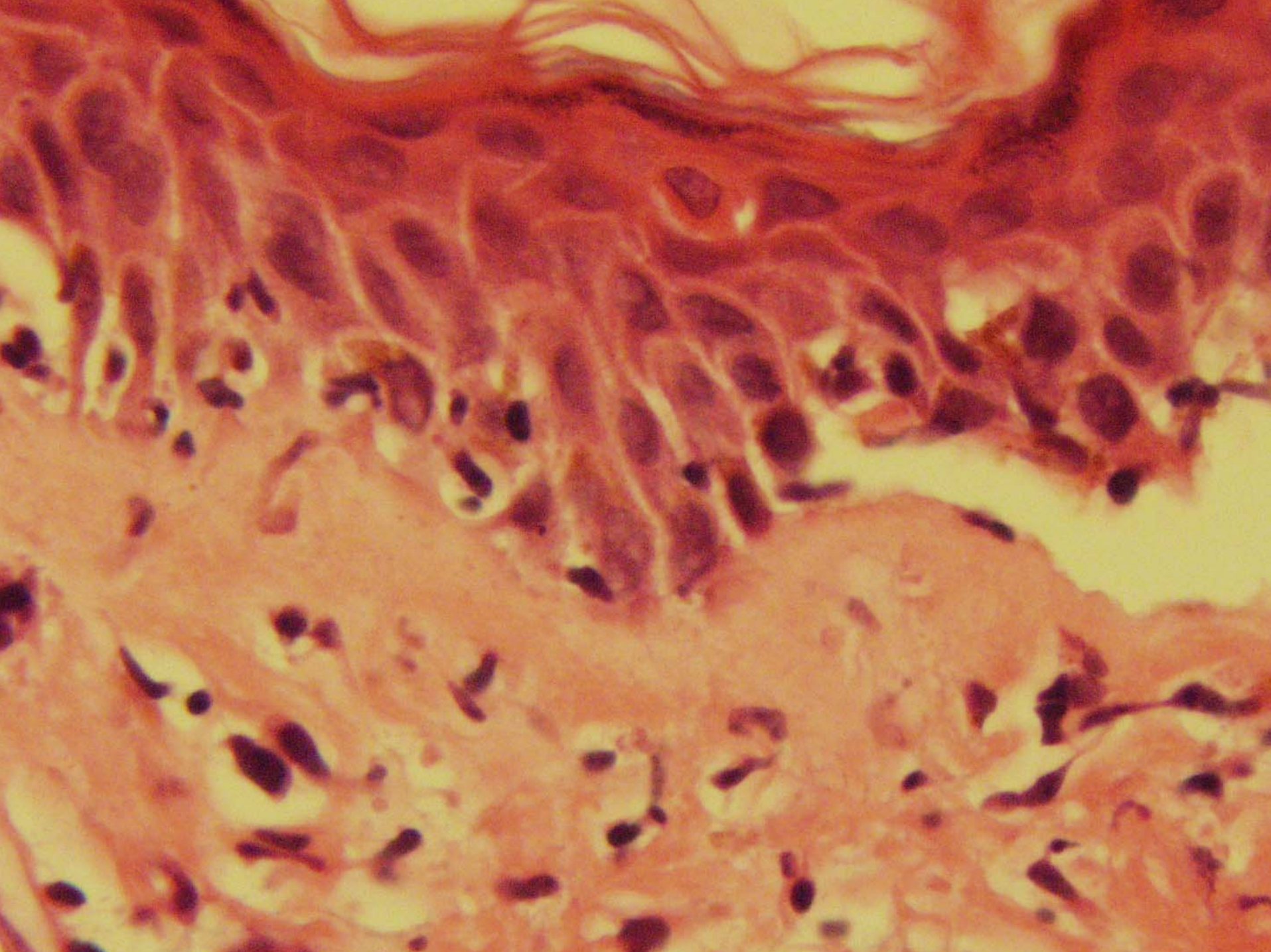
- Infectious panniculitis
- Vasculitis
- Thrombotic disorder

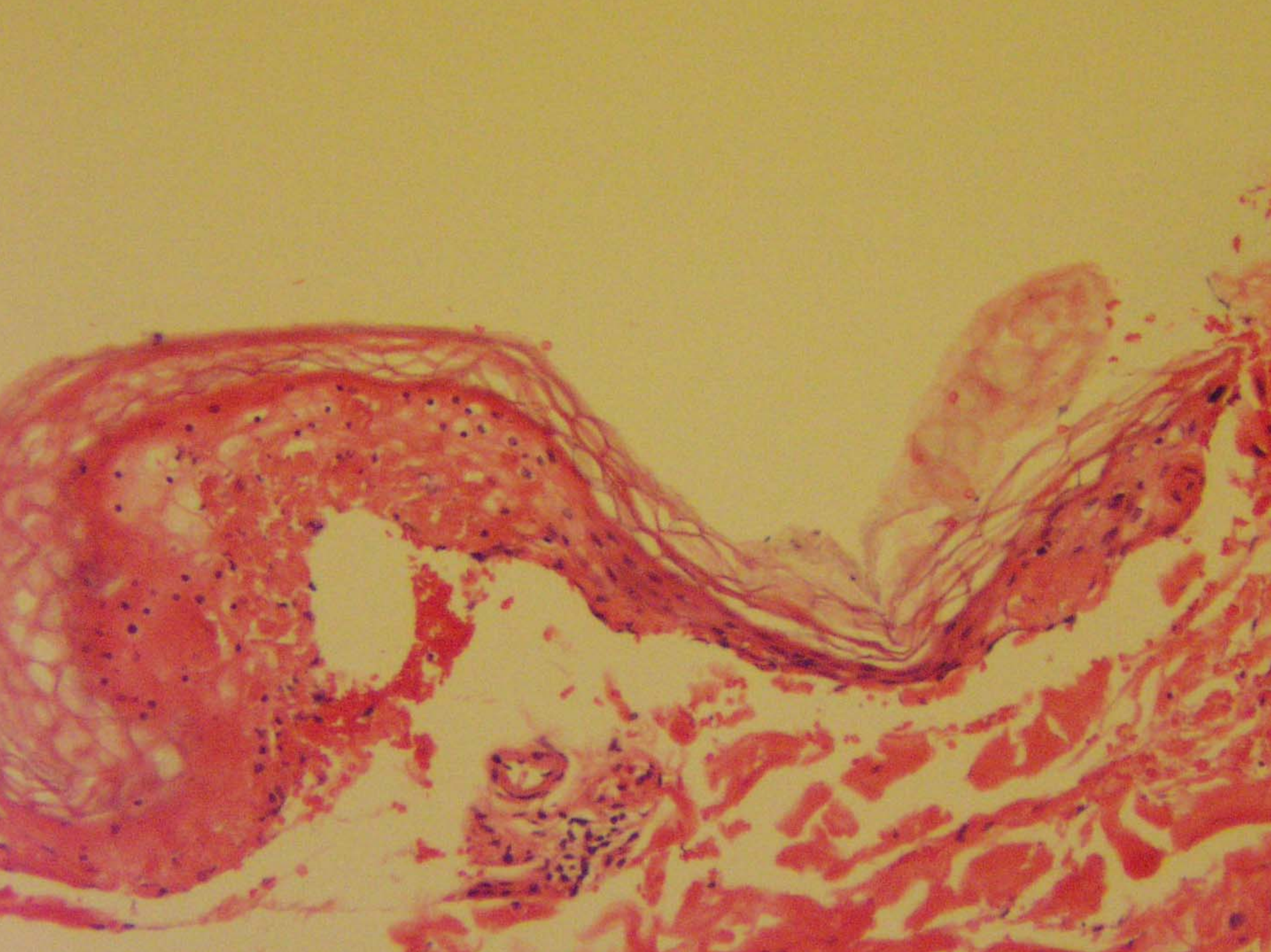
History

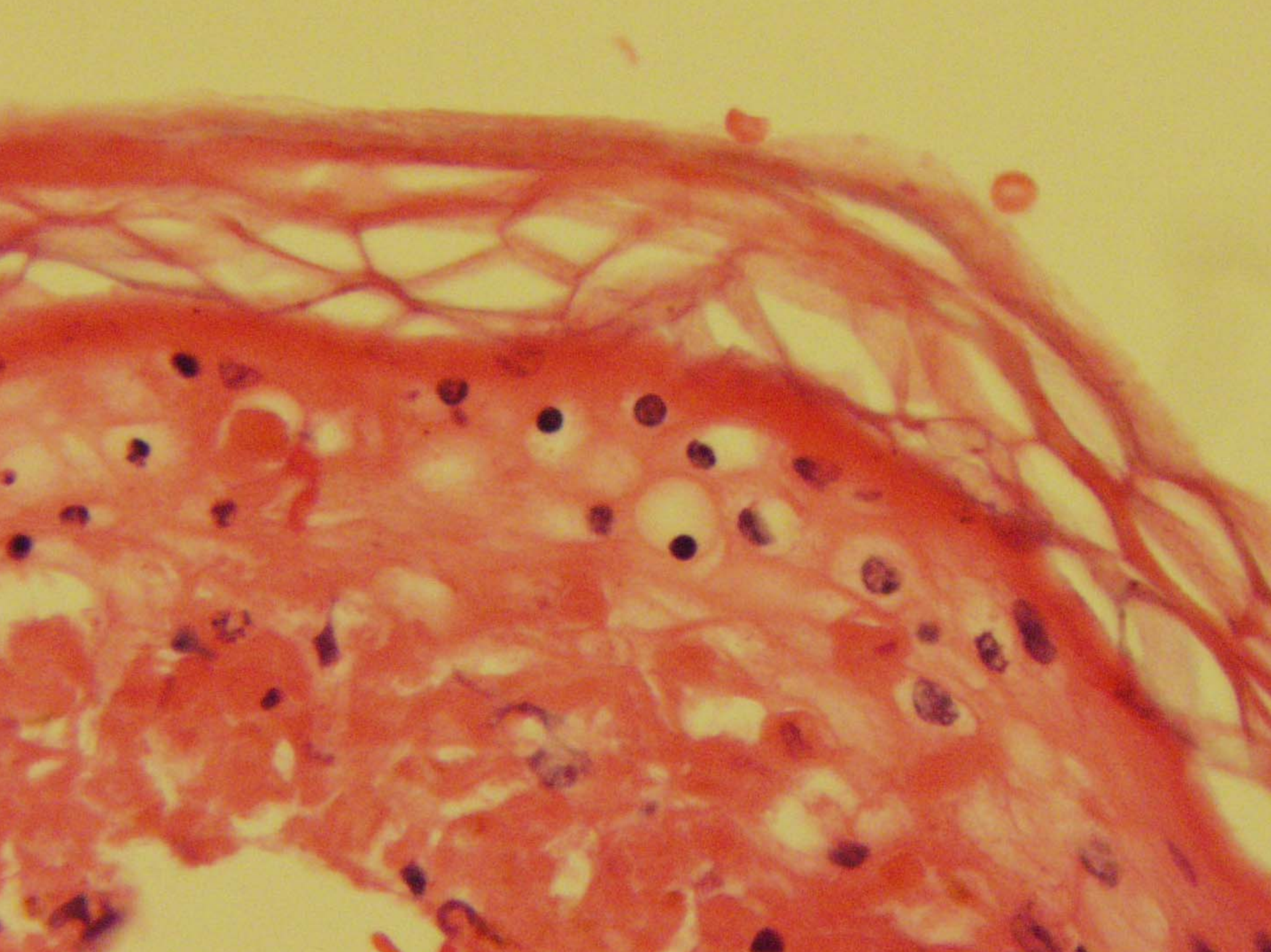
- 24 year old epileptic patient on Phenobarbital
- Developed rapid onset of painful erythematous lesions over most of body including mucous membranes











Toxic Epidermal Necrolysis

- Prodromal symptoms may precede skin lesions by 1-2 weeks
  - Fever is the most common symptom.
  - Upper respiratory infection–like symptoms, such as malaise, anorexia, headache, sore throat, cough, nausea, vomiting, and diarrhea, are present.
- Skin is diffuse, erythematous, and painful, and tender skin lesions
  - Scalp usually is spared
  - Erythematous morbilliform or discrete macules that rapidly coalesce and become patches of loose skin (Nikolsky sign)
- Mucous membranes blisters
- Fever
- Bilateral purulent conjunctivitis, which manifests as edema, crusting, and ulceration with pain and photophobia
  - Pain and photophobia
- Bronchopneumonia in 30% with ventilatory support

TEN vs. SJS

- Arch Dermatol 2002 Aug;138(8):1019-24
- Survey from 1989 to 1995 of 1800 hospital departments in Europe
  - 552 patients and 1720 control subjects.
- Erythema multiforme major differences
  - Younger males
  - Frequent recurrences
  - Less fever
  - Milder mucosal lesions
  - Lack of association with collagen vascular diseases, human immunodeficiency virus infection, or cancer
  - Recent or recurrent herpes was the principal risk factor for erythema multiforme majus (etiologic fractions of 29% and 17%, respectively) and had a role in Stevens-Johnson syndrome (etiologic fractions of 6% and 10%) but not in overlap cases or toxic epidermal necrolysis
  - Drugs had higher etiologic fractions for Stevens-Johnson syndrome, overlap, or toxic epidermal necrolysis (64%-66%) than for erythema multiforme major (18%)

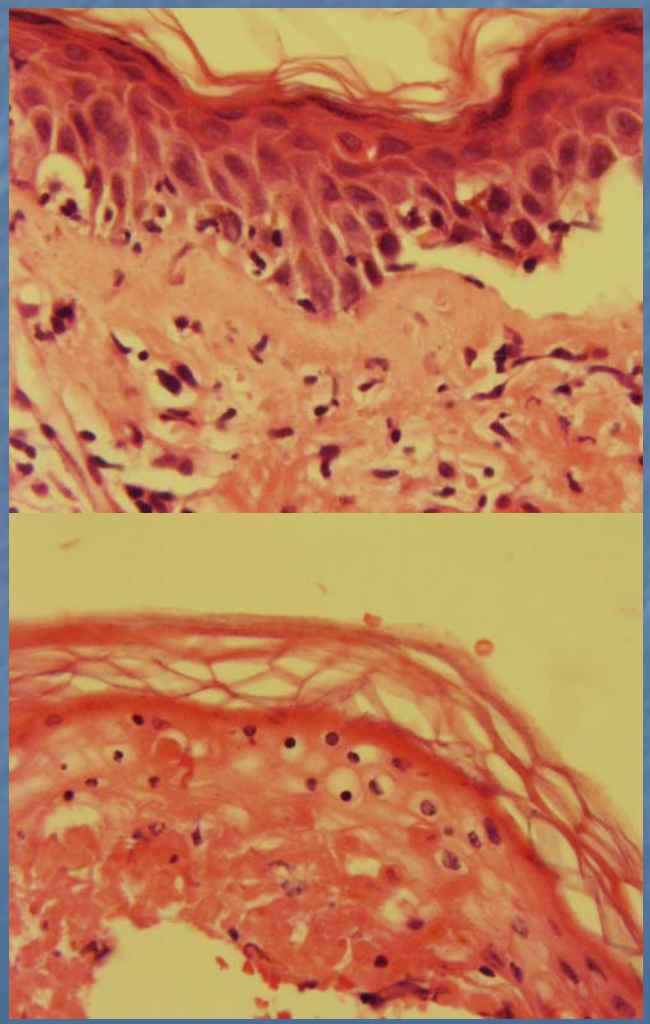
Working Classification

- Bullous erythema multiforme
- Recurrent erythema multiforme
- Persistent erythema multiforme
- Stevens-Johnson syndrome
- Overlap Stevens-Johnson syndrome/toxic epidermal necrolysis
  - (epidermal detachment between 10-30%)
- Toxic epidermal necrolysis with spot
  - (widespread purpuric macules or target lesions)
- Toxic epidermal necrolysis without spots

TEN

- TEN may present with generalized erythema rapidly progressing to blisters and shedding of skin
- Mortality may be up to 35%
- Unlike erythema multiforme, drugs are implicated in the majority of cases
  - Sulfonamides and sulfones
  - Pyrazolone derivatives (eg, phenylbutazone, oxyphenbutazone, phenazone)
  - Antibiotics (eg, aminopenicillins, trimethoprim, cephalosporins, ciprofloxacin, doxycycline, erythromycin, tetracycline)
  - Anticonvulsants (eg, phenytoin, phenobarbital, and carbamazepine)
  - Nonsteroidal anti-inflammatory drugs
  - Allopurinol
  - Antituberculosis drugs (eg, thiacetazone, isoniazid)
- Majority of cases are idiopathic

TEN Histopathology



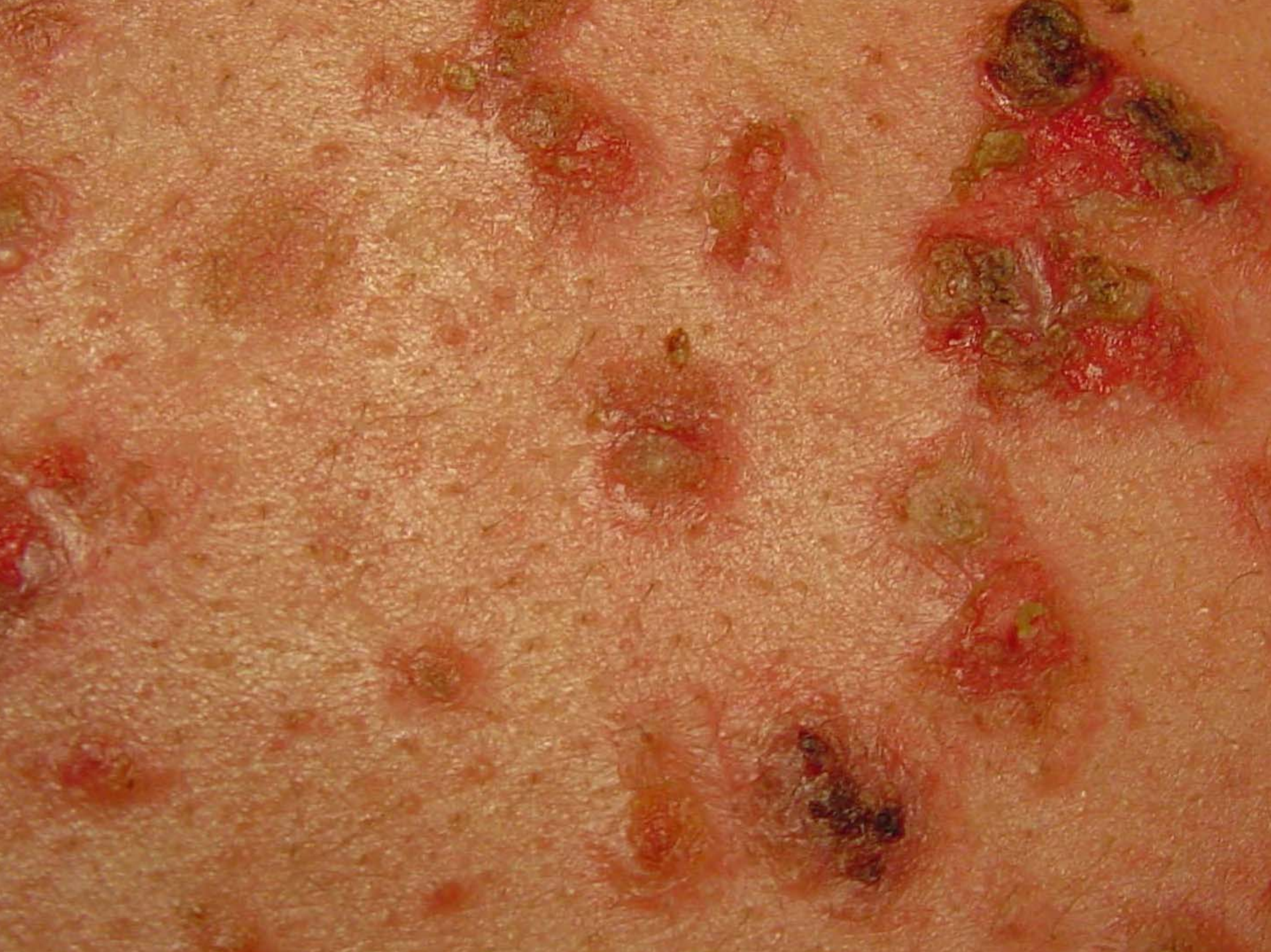
- Acute onset of interface dermatitis
- Minimal inflammatory infiltrate
- Usually detachment of epidermis from dermis
- May show extensive epidermal necrosis

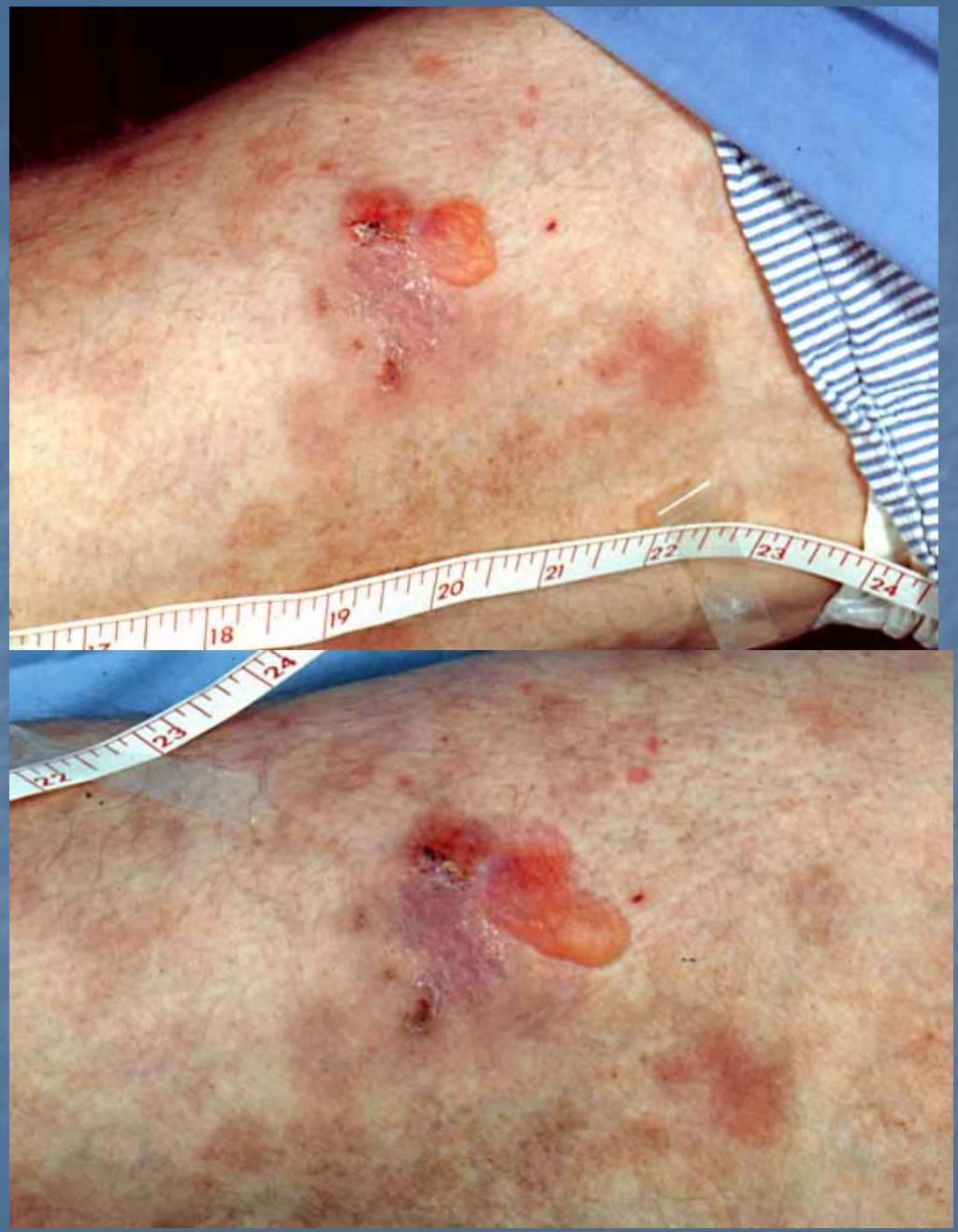
Differential Diagnosis

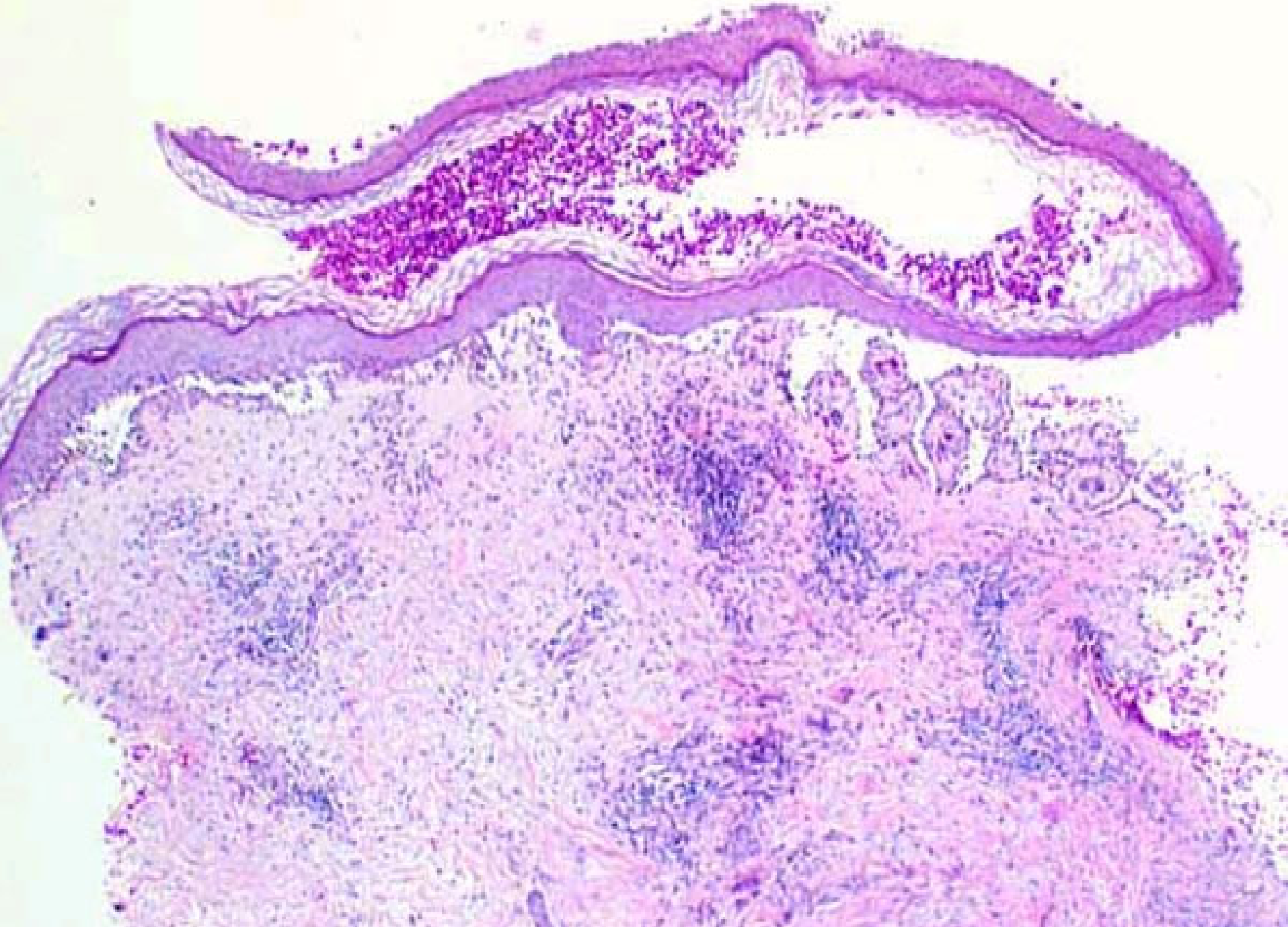
- Erythema multiform/SJS
- Staphylococcal Scalded Skin Syndrome
- Epidermolyisis Bullosa

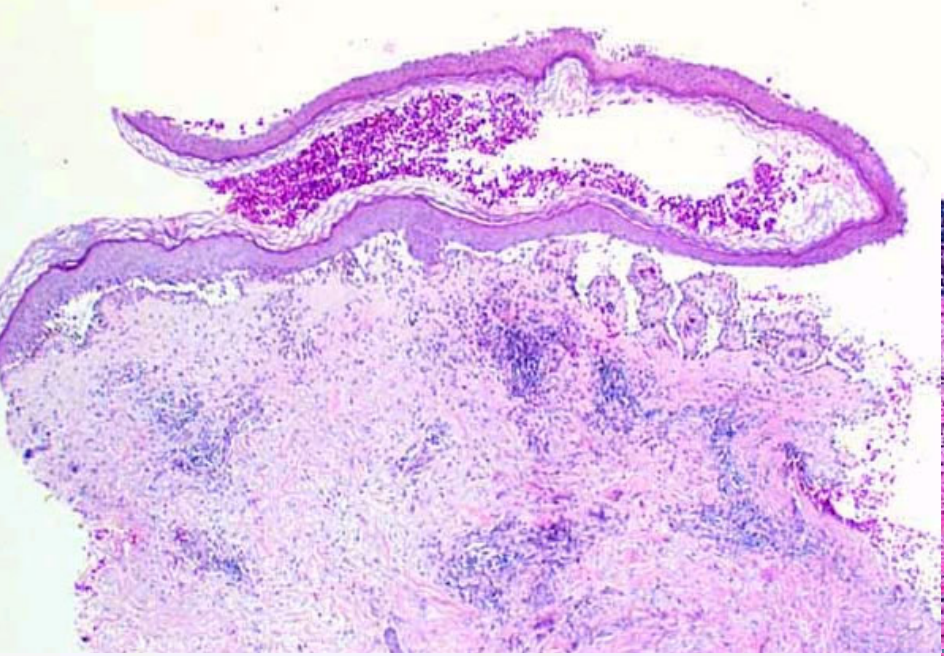
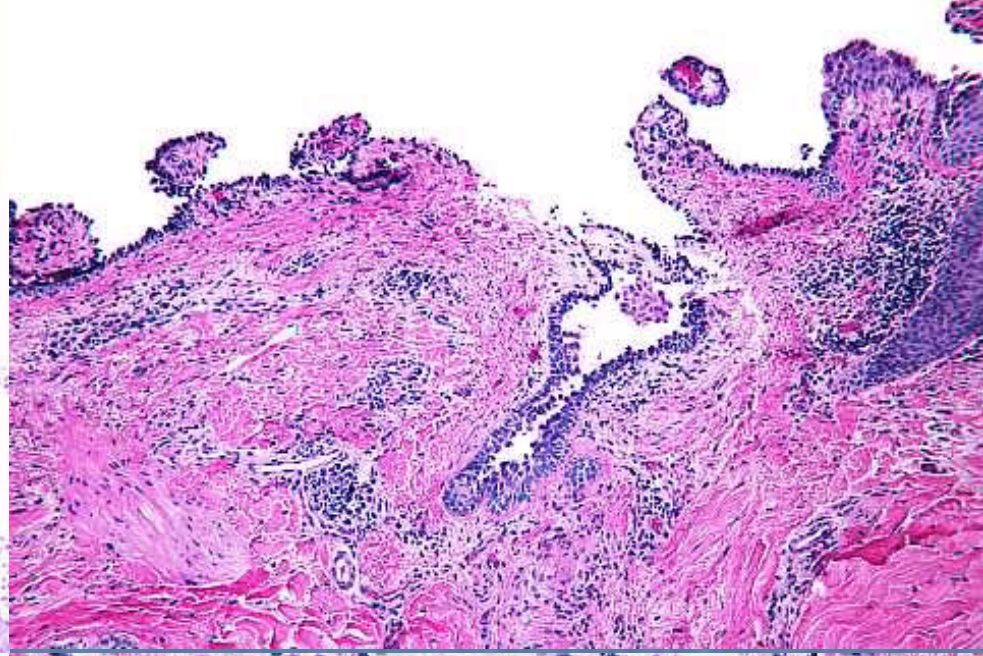
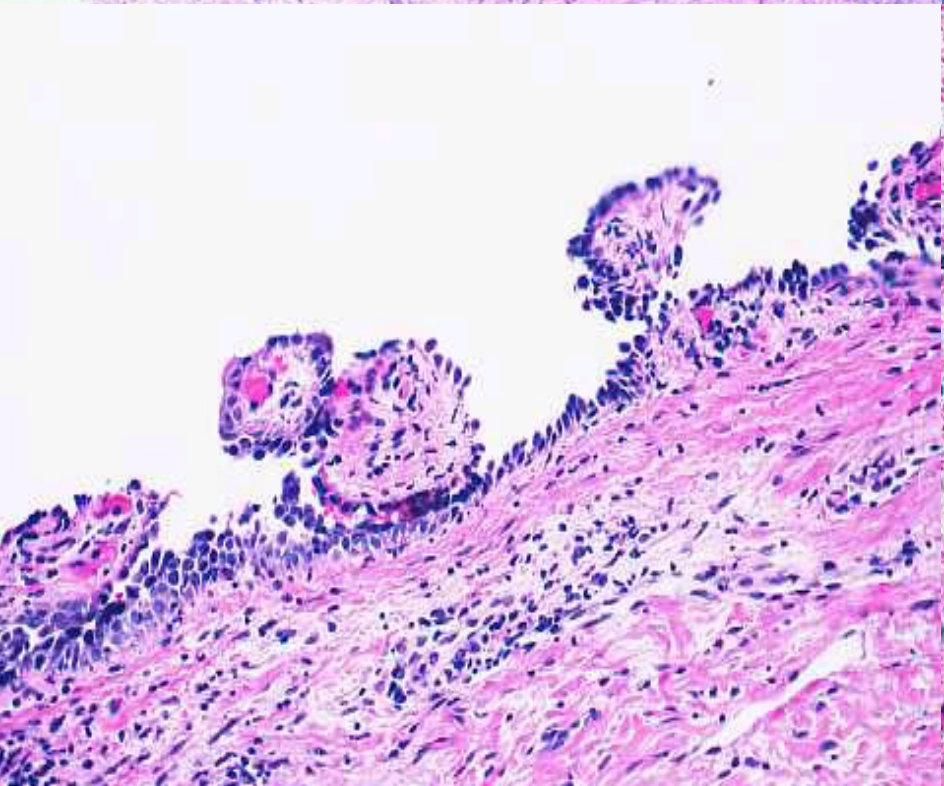
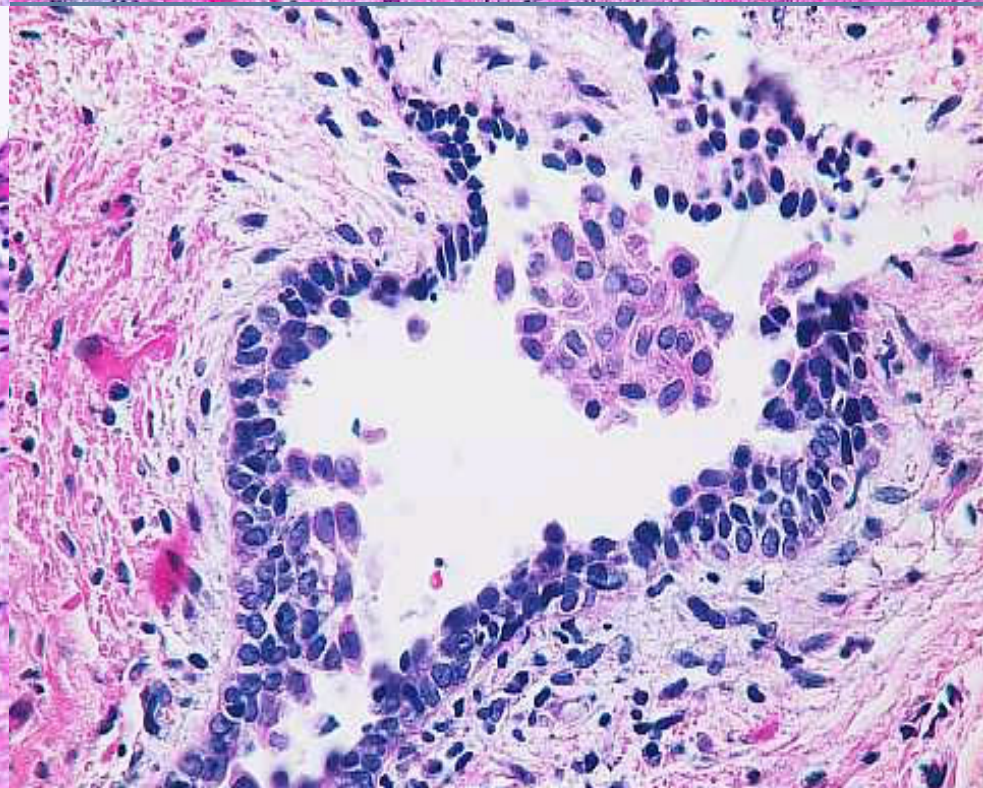
History

- 35 year old F
- 1 month history of blistering lesions over most of body, oral lesions
- Monogamous relationship for 10 years





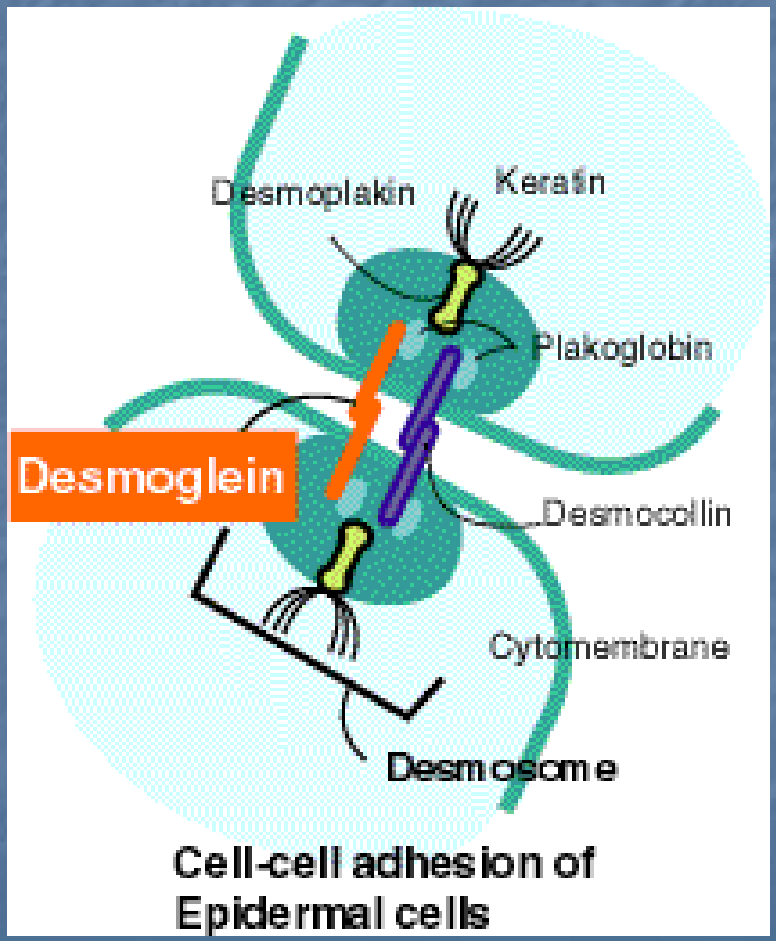


Pemphigus Vulgaris

- Mucosal lesions in 50-70% of patients
- Heal without scarring unless secondary infections
- Incidence high in regions where the Jewish population is predominant
  - Jerusalem 1.6 per 100,000
  - Connecticut, incidence was 0.42 per 100,000
  - Finland 0.76 per million

Pathophysiology



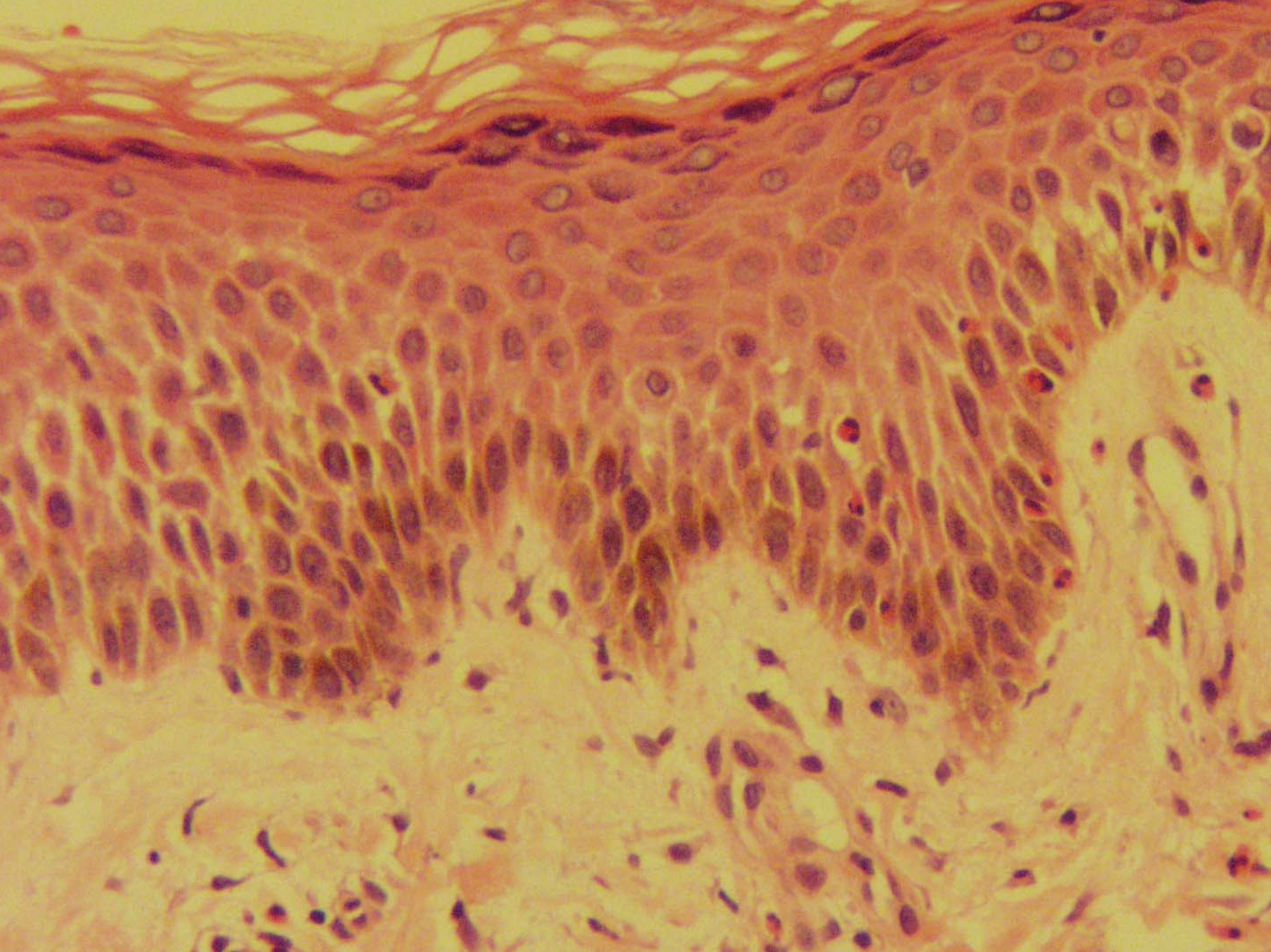
- Autoimmune blistering diseases
  - Binding of autoantibodies to the desmosomal cadherins desmoglein 1 and 3
  - Complement also interacts
  - DIF shows intraepidermal intracellular distribution

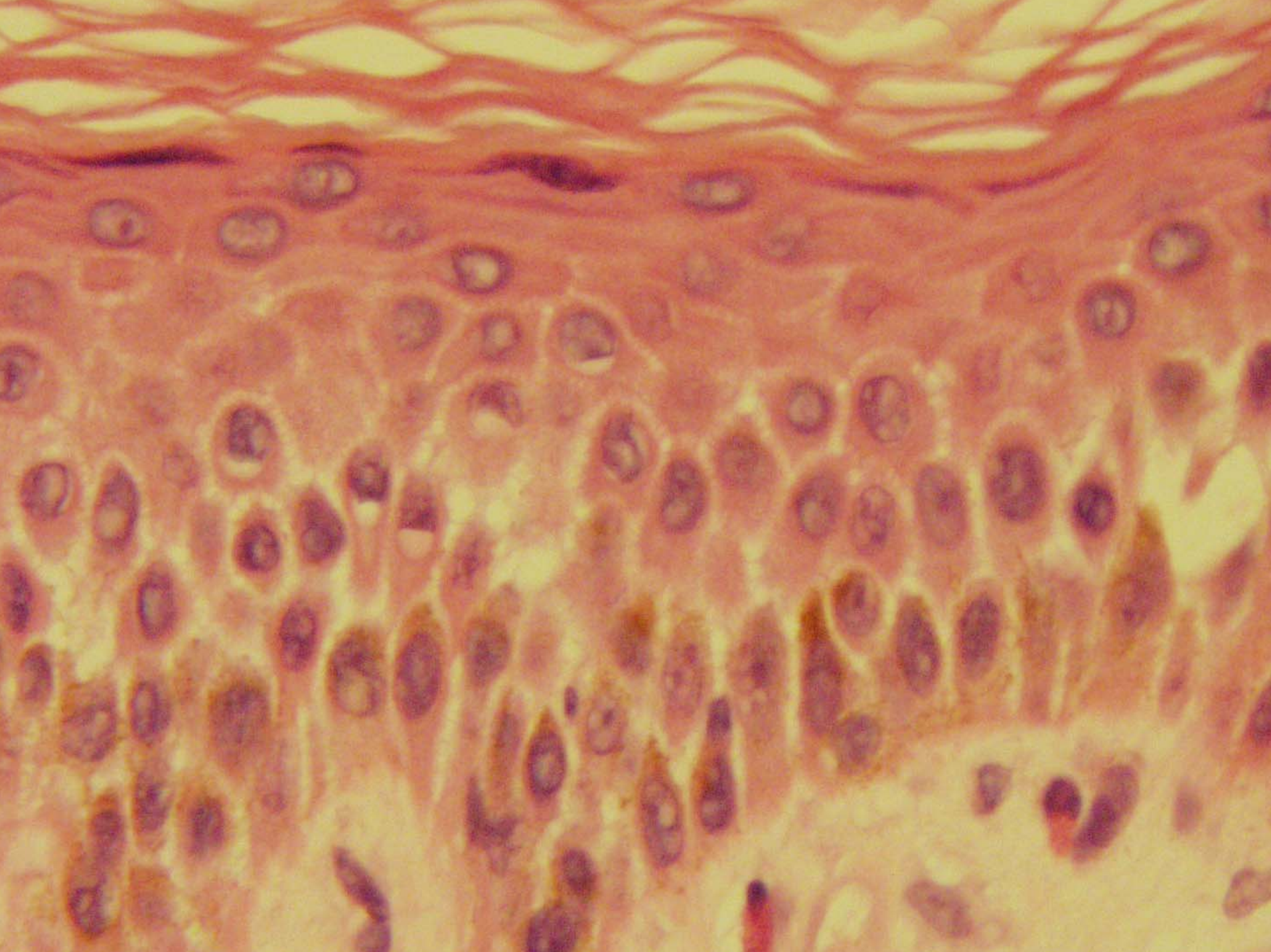
Causes and Associations

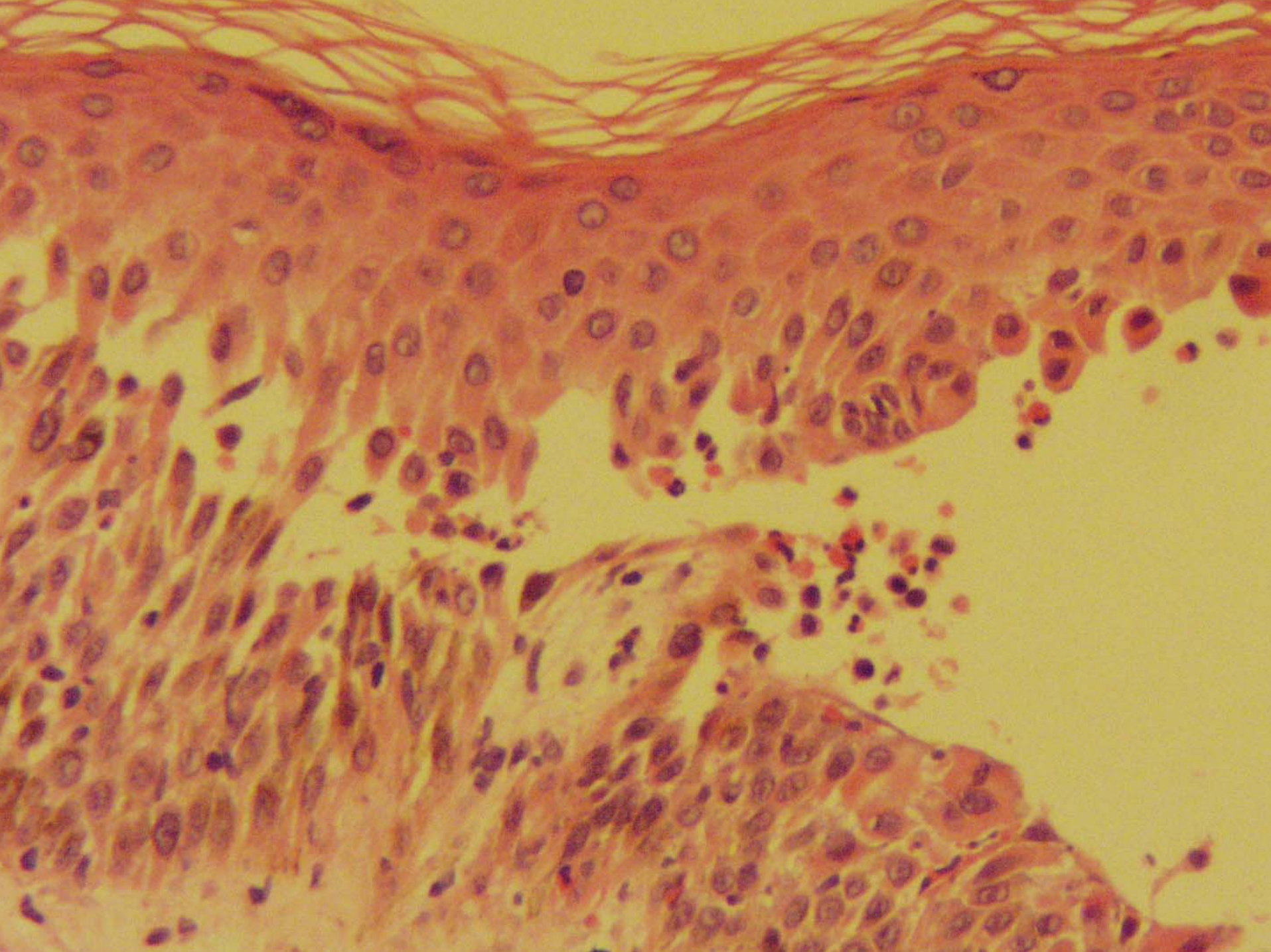
- PEMPHIGUS is proposed to denote the many causes of the disease
  - PEsticides
  - Malignancy
  - Pharmaceuticals
  - Hormones
  - Infectious agents
  - Gastronomy
  - Ultraviolet radiation
  - Stress

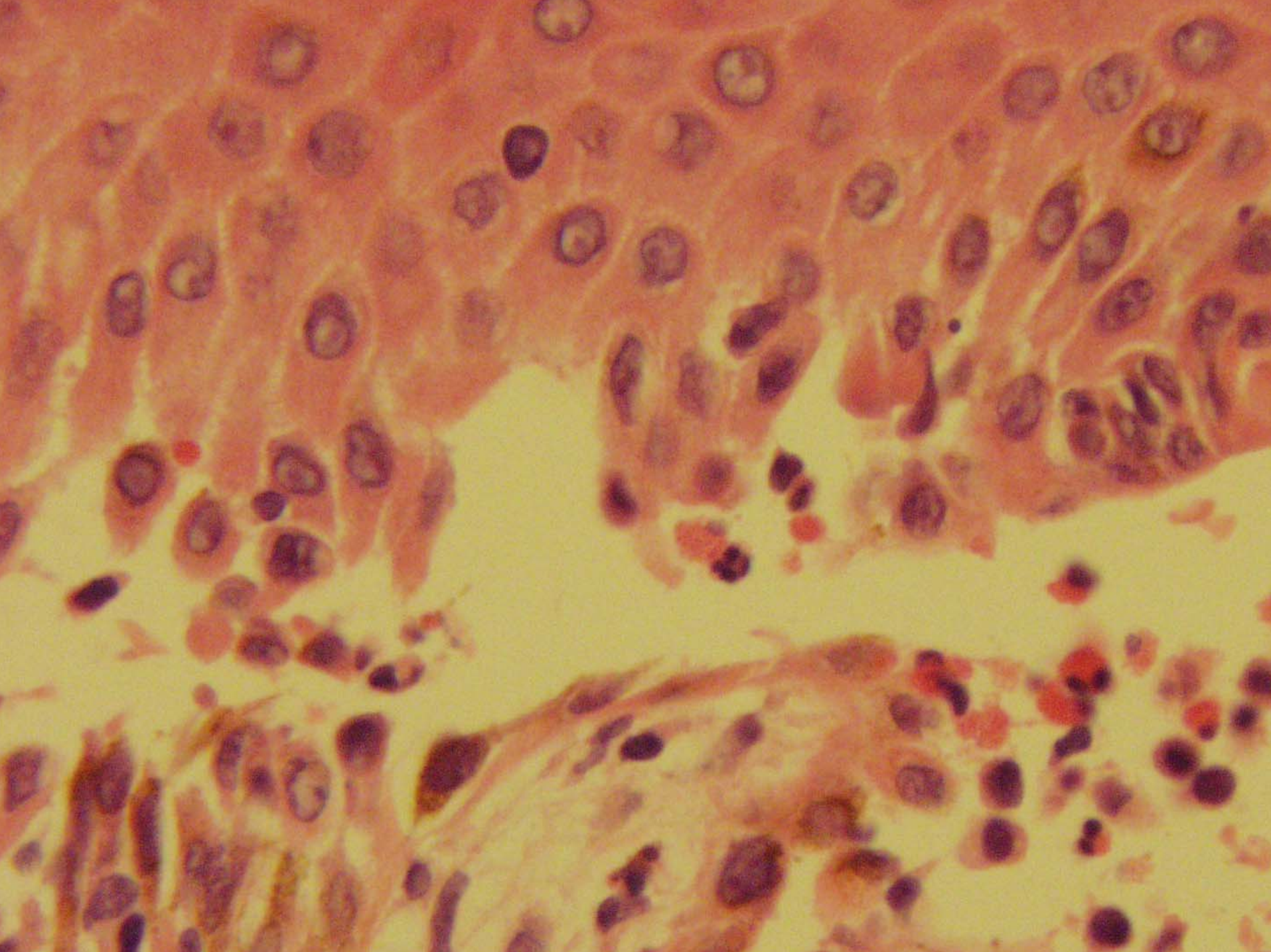
Histopathology

- Intradermal blister with acantholysis
- Suprabasal epidermal cells separate from the basal cells to form clefts and blisters
  - Basal cells tombstone appearance
  - Blister cells with acantholysis
- Tzank preparation shows acantholytic cells
- Blistering is preceded by eosinophilic spongiosis

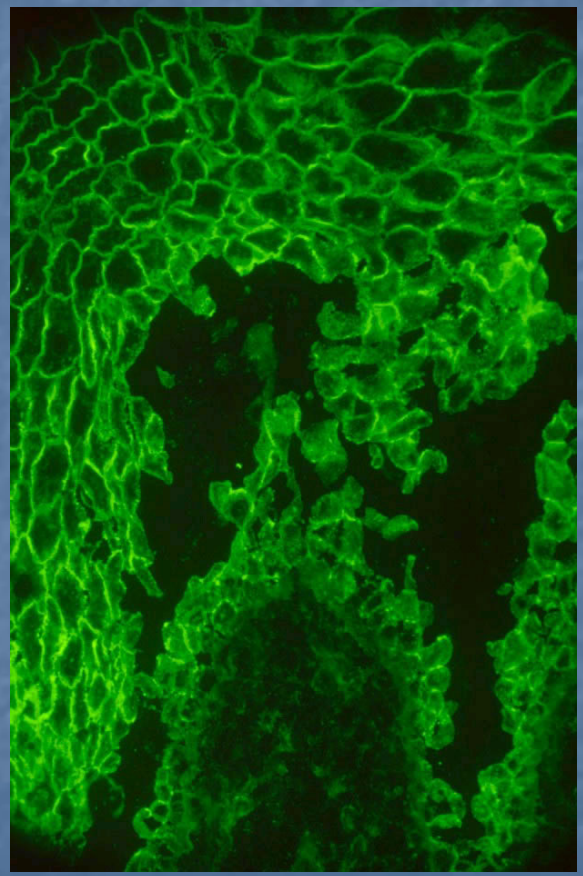








Laboratory



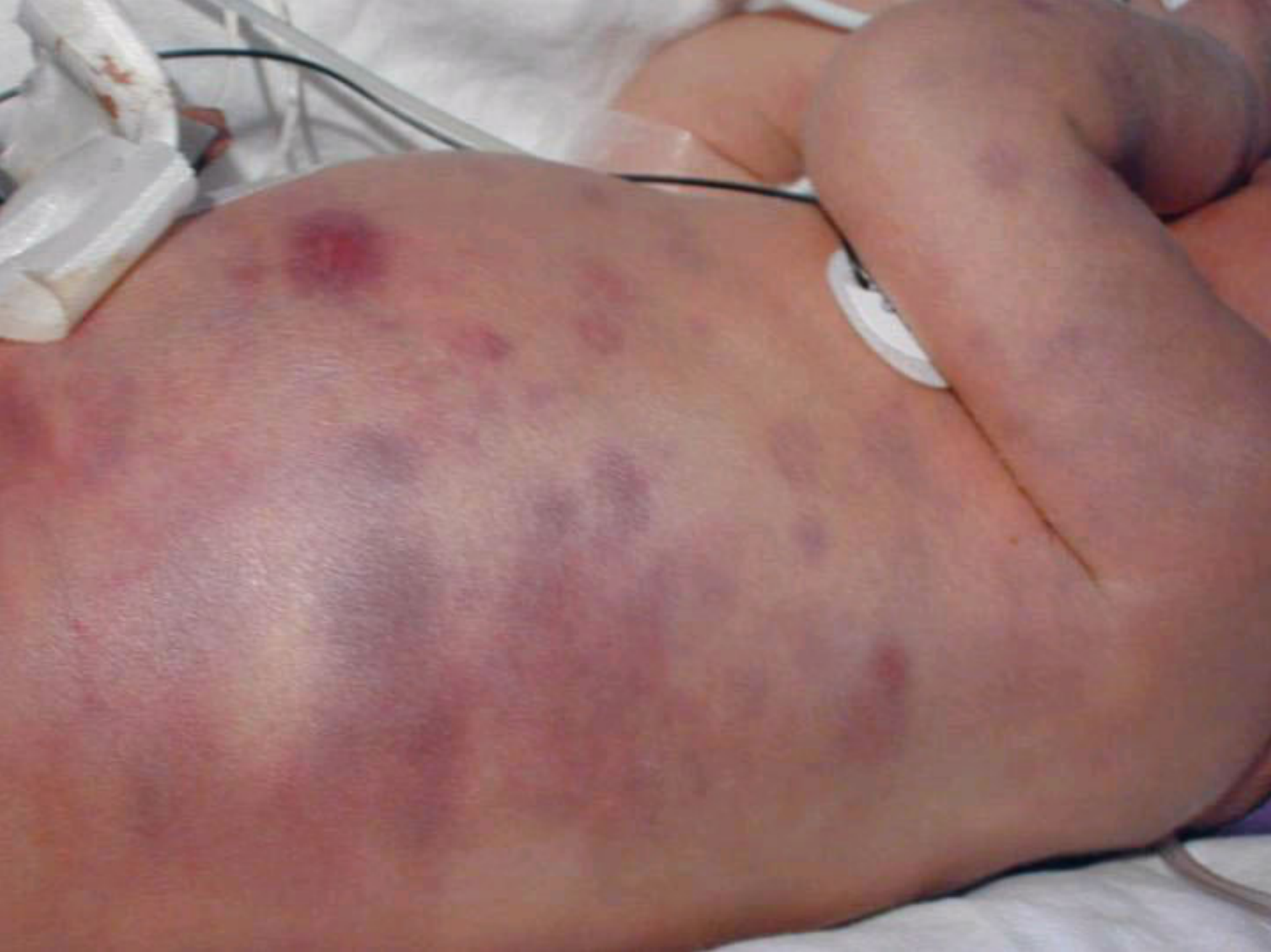
- Best location for DIF is normal perilesional skin
  - DIF performed on lesional skin may give false-positive results
  - Direct immunofluorescence (DIF) on normal-appearing perilesional skin
- Indirect immunofluorescence (IDIF) using the patient's serum if DIF is positive
  - Preferred substrate for IDIF is monkey esophagus or salt-split normal human skin substrate.
- DIF shows IgG deposited intercellular keratinocytes
  - IgG1 and IgG4 are the most common subclasses
  - C3 and IgM less frequent
  - DDX: Pemphigus vegetans, pemphigus foliaceus, and pemphigus erythematosus

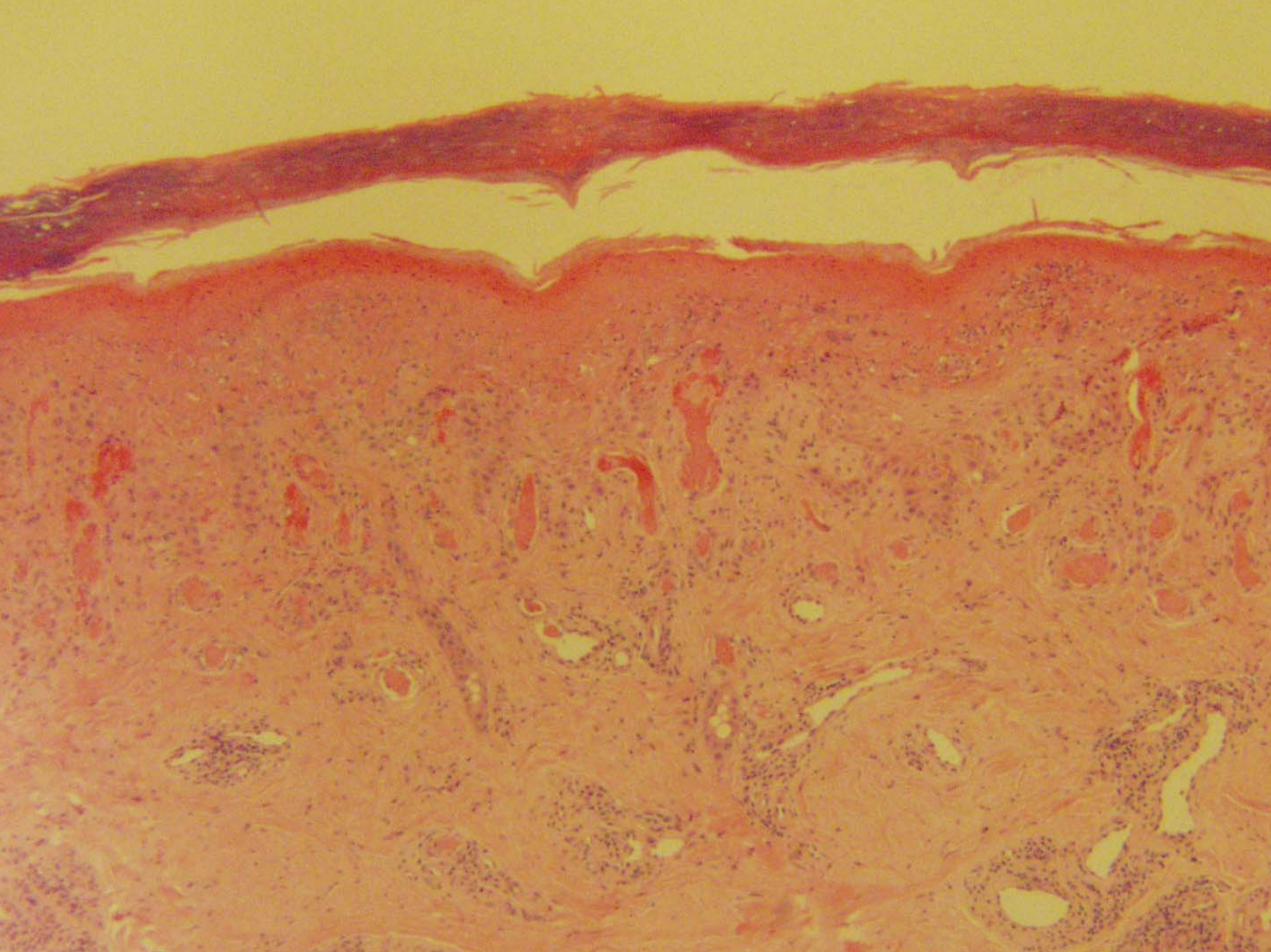
Differential Diagnosis

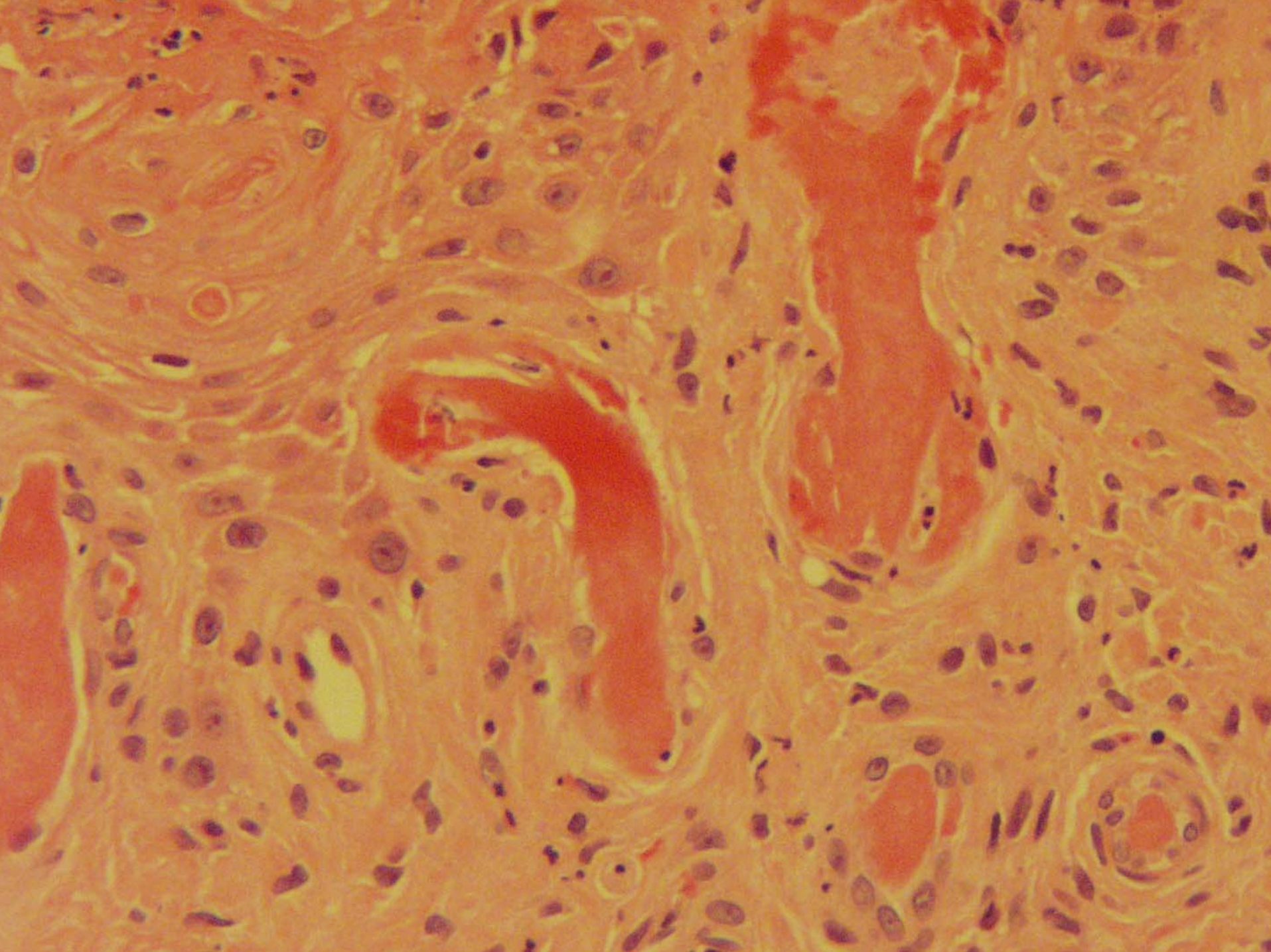
- Hypersensitivity reaction
- Bullous pemphigoid, urticarial stage
- Grover’s disease

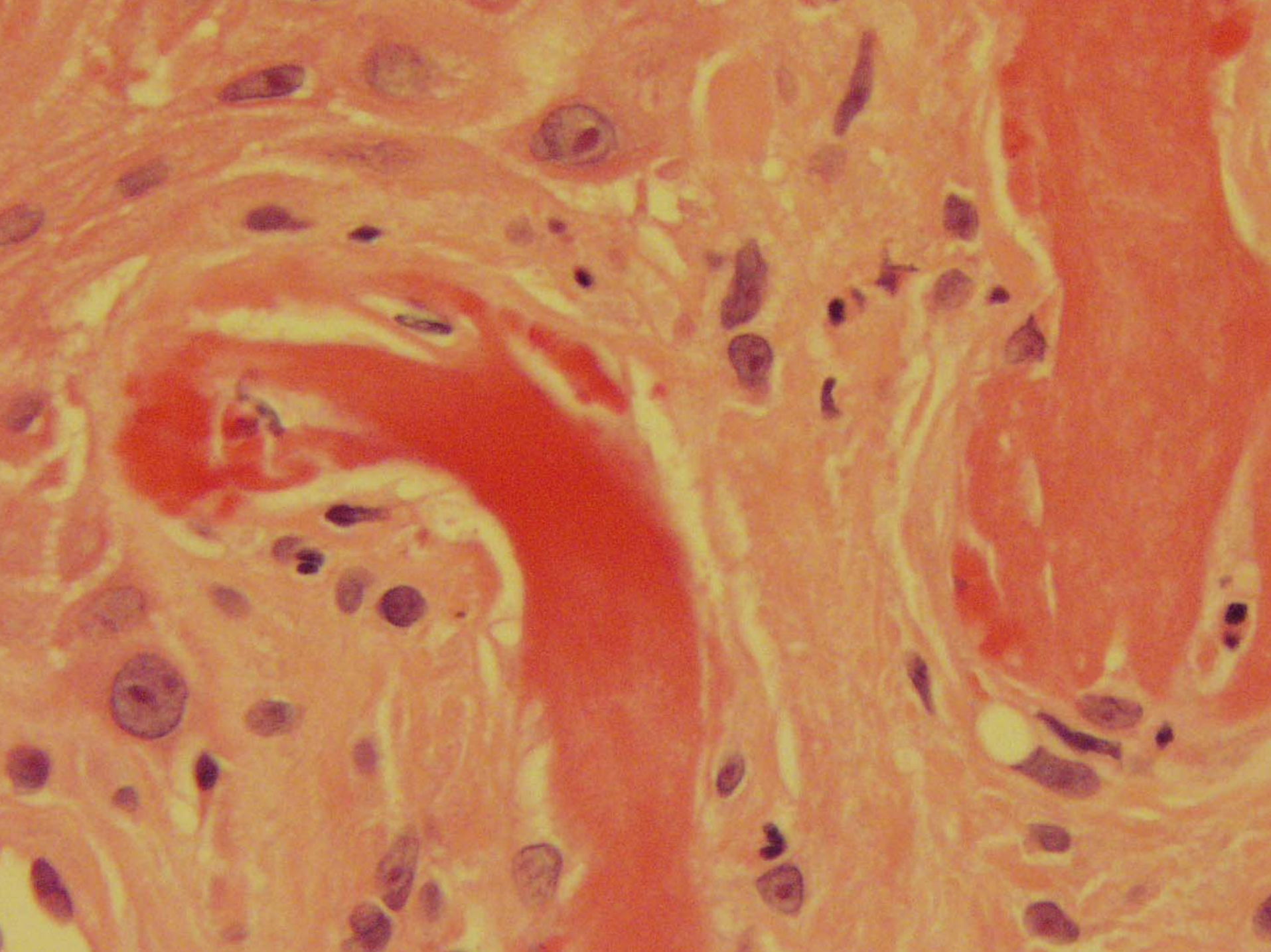
Case Study

- Newborn with septicemia
- Diffuse hemorrhagic and ecchymosed areas over body
- Blood cultures pending
- Vaginal cultures on mother pending









D.I.C.

- Acute disseminated intravascular coagulation-Usually hemorrhagic
  - Most common etiology is infection (gram-positive and gram-negative septicemia, typhoid fever, Rocky Mountain spotted fever, viremia, and parasites)
  - Obstetric patients (abruptio placentae, amniotic fluid embolism, hypertonic saline abortion, and eclampsia)
  - Acute tissue injuries (snakebites, necrotizing enterocolitis, freshwater drowning, heat stroke, brain and crush injury, renal homograft rejection, dissecting aortic aneurysm, and hemolytic transfusion reactions)
  - Homozygous protein C and S deficiency, factor V Leiden, severe liver disease, heparin-induced thrombocytopenia
- Subacute or chronic disseminated intravascular coagulation-Usually thrombotic
  - Malignancies, especially mucin-producing adenocarcinomas (Trousseau syndrome)
  - Retained dead fetus also can create a prothrombotic state.
  - Giant cavernous hemangiomas, chronic renal disease, venous thrombosis, pulmonary embolus, and marantic endocarditis

Laboratory Evaluation

- Screening tests PT and aPTT, platelet count, and fibrinogen
  - If results of all tests are abnormal, diagnosis is most likely
- **D-dimer test**
  - Positive test confirms the formation of both thrombin and plasmin
  - Thrombin cleaves fibrinogen to liberate fibrinopeptides A and B, leaving fibrin monomer
  - Thrombin also activates factor XIII to induced soluble cross-linked fibrin monomer to becomes insoluble
  - When plasmin forms, it cleaves insoluble, cross-linked, fibrin monomer that is held together by its D domains
  - Liberates a dimer of the D domain
- **Fibrin (split) degradation products (FDPs)**
  - Only measure plasmin-cleaved fibrinogen or fibrin
  - When findings are positive, FDPs do not indicate thrombin formation
  - In cases of severe DIC, fibrin monomer findings can be negative

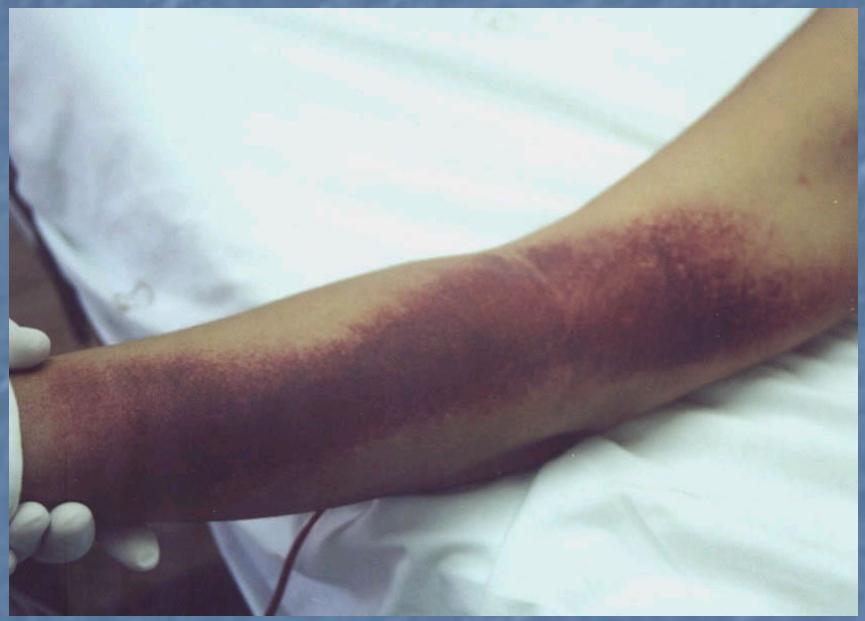
Histopathology

- Rarely biopsied
- Extensive epidermal and dermal necrosis
- Fibrin thrombi with secondary vasculitic changes

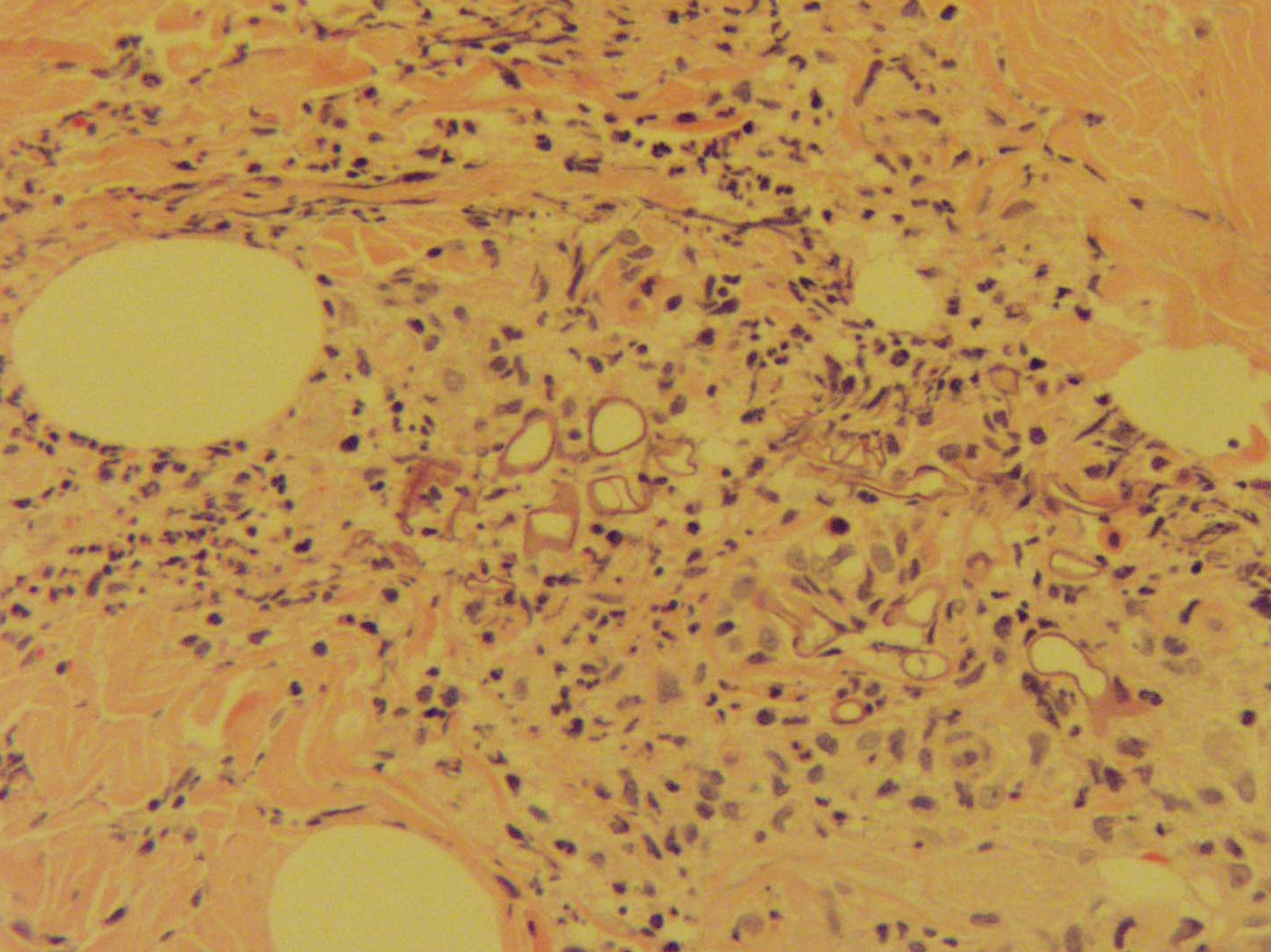
Differential Diagnosis

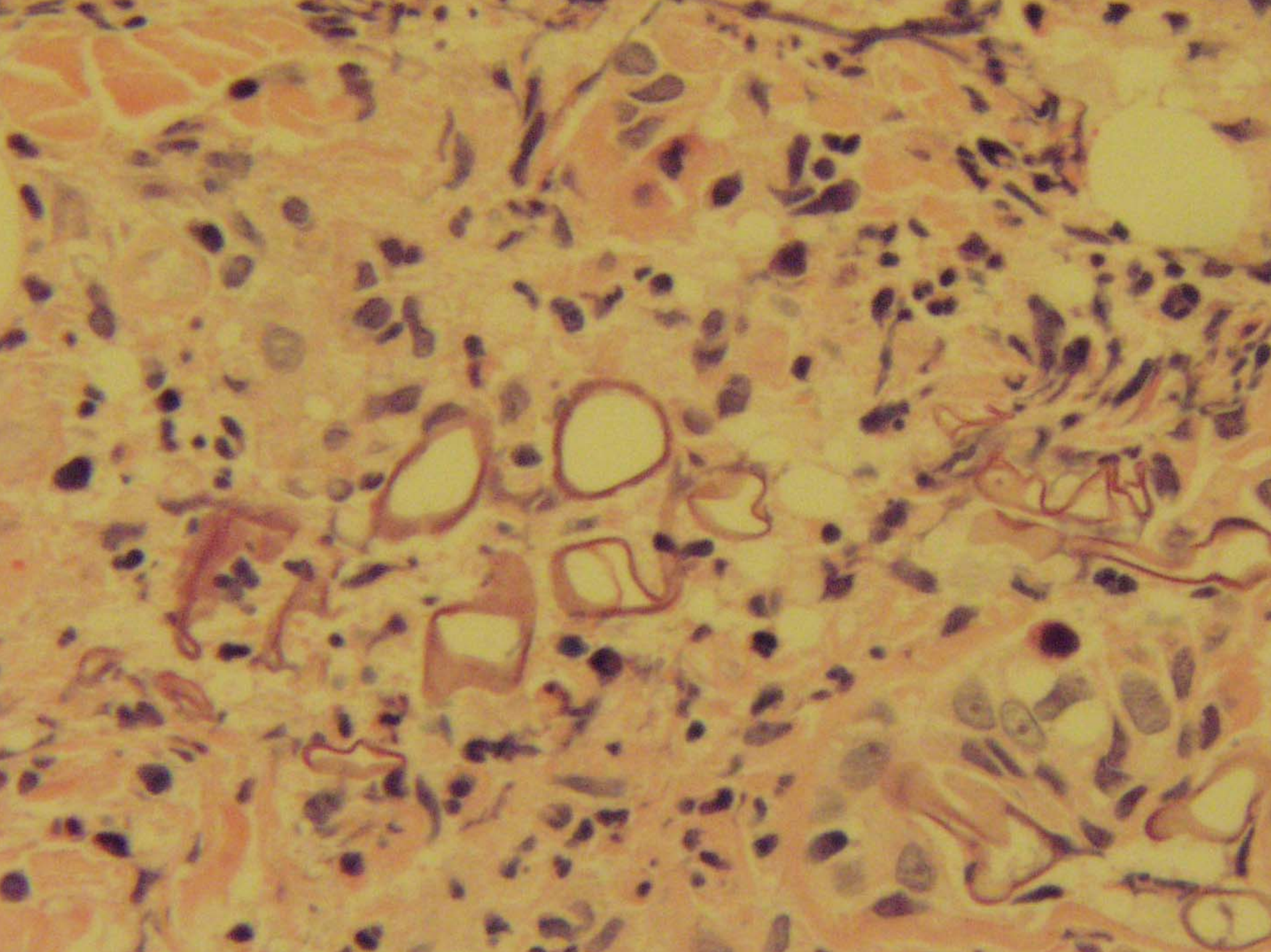
- TTP/Hemolytic-Uremic syndrome
- Anti-phospholipid antibody syndrome
- Cryoglobulinemia
- Warfarin/Coumadin necrosis
- Heparin-Induced Thrombocytopenia

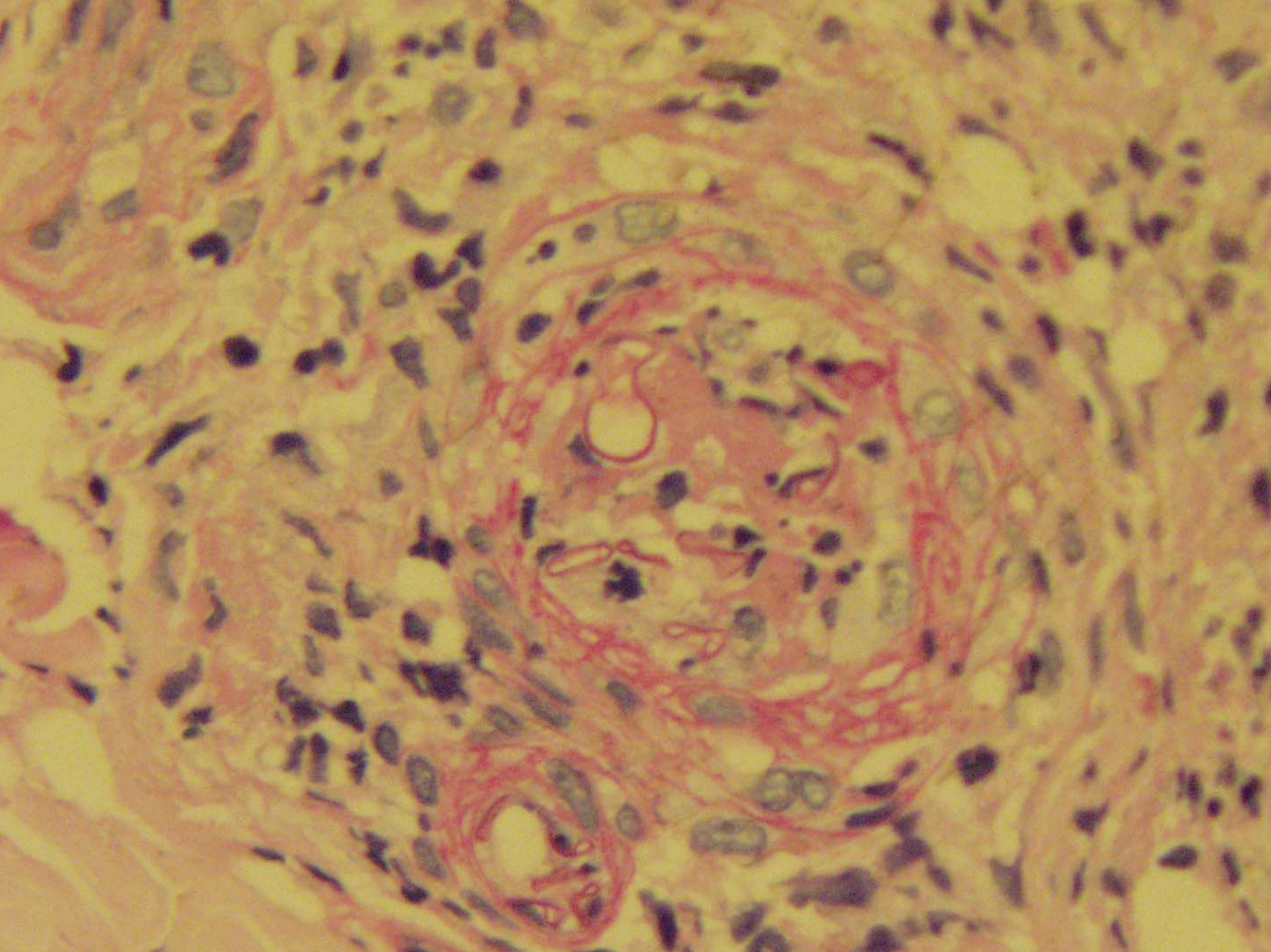
History



- 54 M with ANNL, status post induction chemotherapy
- Developed painful ecchymotic patches near IV sites



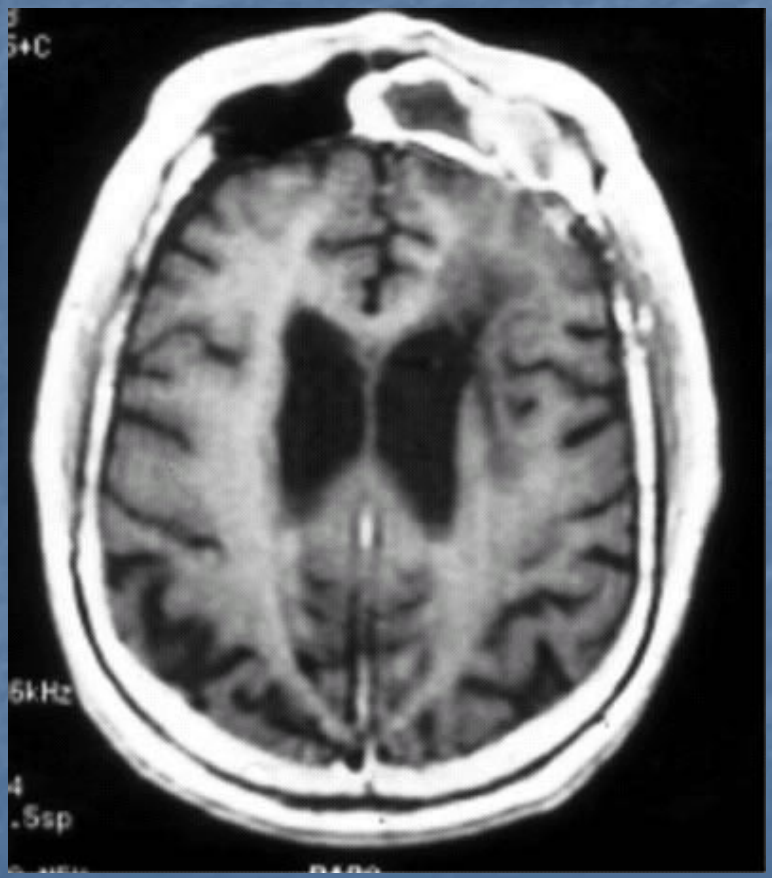




Mucormycosis

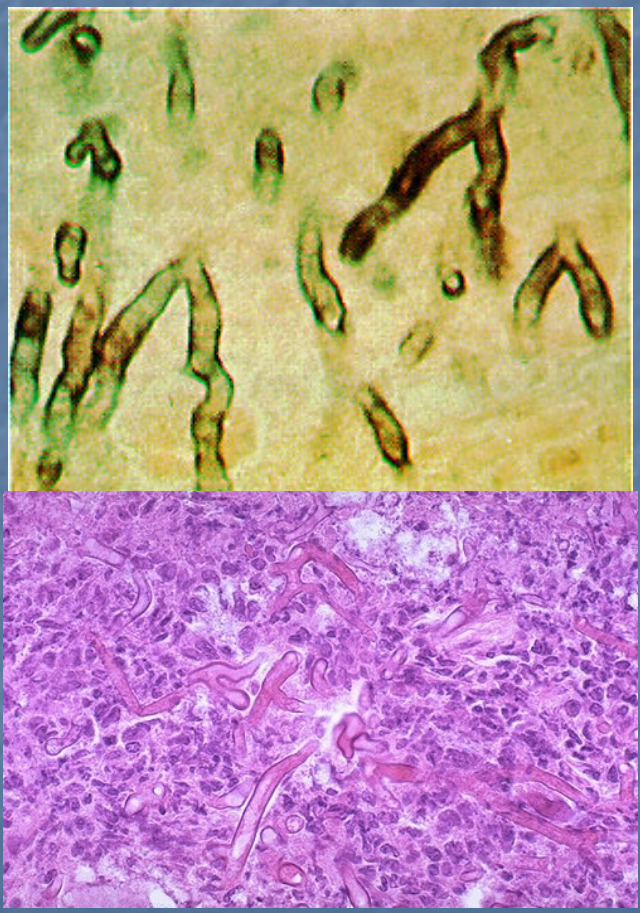
- Rhinocerebral mucormycosis most common type
- Cutaneous disease may be primary or part of disseminated infection
  - Associated with occlusive therapy in immunocompromised patients
  - Prematurity

Radiologic Findings



- Rhinocerebral form with left frontal sinus bony dehiscence seen on CT
- Extension of disease on to dura seen on MRI

Histopathology

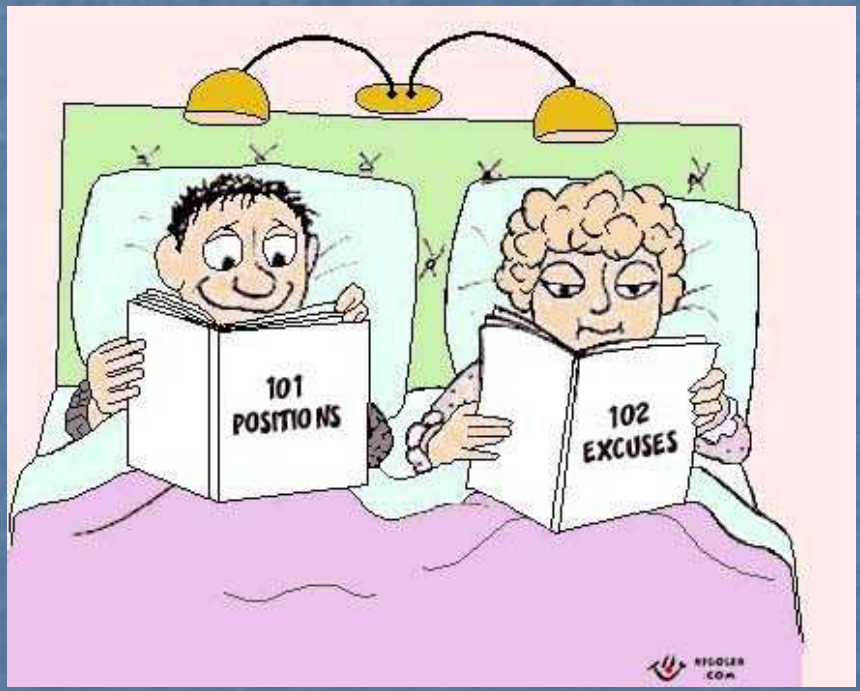


- Wide branching hyphae
- Vascular invasive
- Inflammatory infiltrate variable depending upon immune status of patient

Differential Diagnosis

- Apsergillus
- Candida

Questions



- Know how to listen, and you will profit even from those who talk badly.

--Plutarch
(46 AD - 120 AD)