SSSSSSSSS

Dr A Yeung
CICU, RHTSK

History

- M/48, single, clerk, NSND, no drug abuse
- Hx of obesity, ?eczema on topical herbs
- Admitted x fever/dry cough x few days
- Associated with diffuse erythematous rash one week before admission, followed by skin peeling
- Erythema already subsided on admission

P.E.

- Feverish
- Grossly obese, estimated BMI>35
- Poor hygiene
- HS dual, no murmur
- Chest clear
- Abd soft, no tenderness or organomegaly
- GCS full, neck soft, no focal neurology
- Multiple patches of ?septic spots, folliculitis with desquamation
- Mucosa intact

P.E.

P.E.

P.E.

Progress

- ECG : AF, VR ~160/min, no ischemic changes
- CXR : increased CTR, mild congestion
- Pus swab and blood culture done
- Given empirical Tazocin

Progress

- Noted sudden drop in GCS to E4M5-6V4 twelve hours after admission
- Associated with decreased R side movement
- Septic shock
- Taken to ICU x further management

CT Brain

Progress

- Further drop in GCS and labile breathing
- Intubated electively

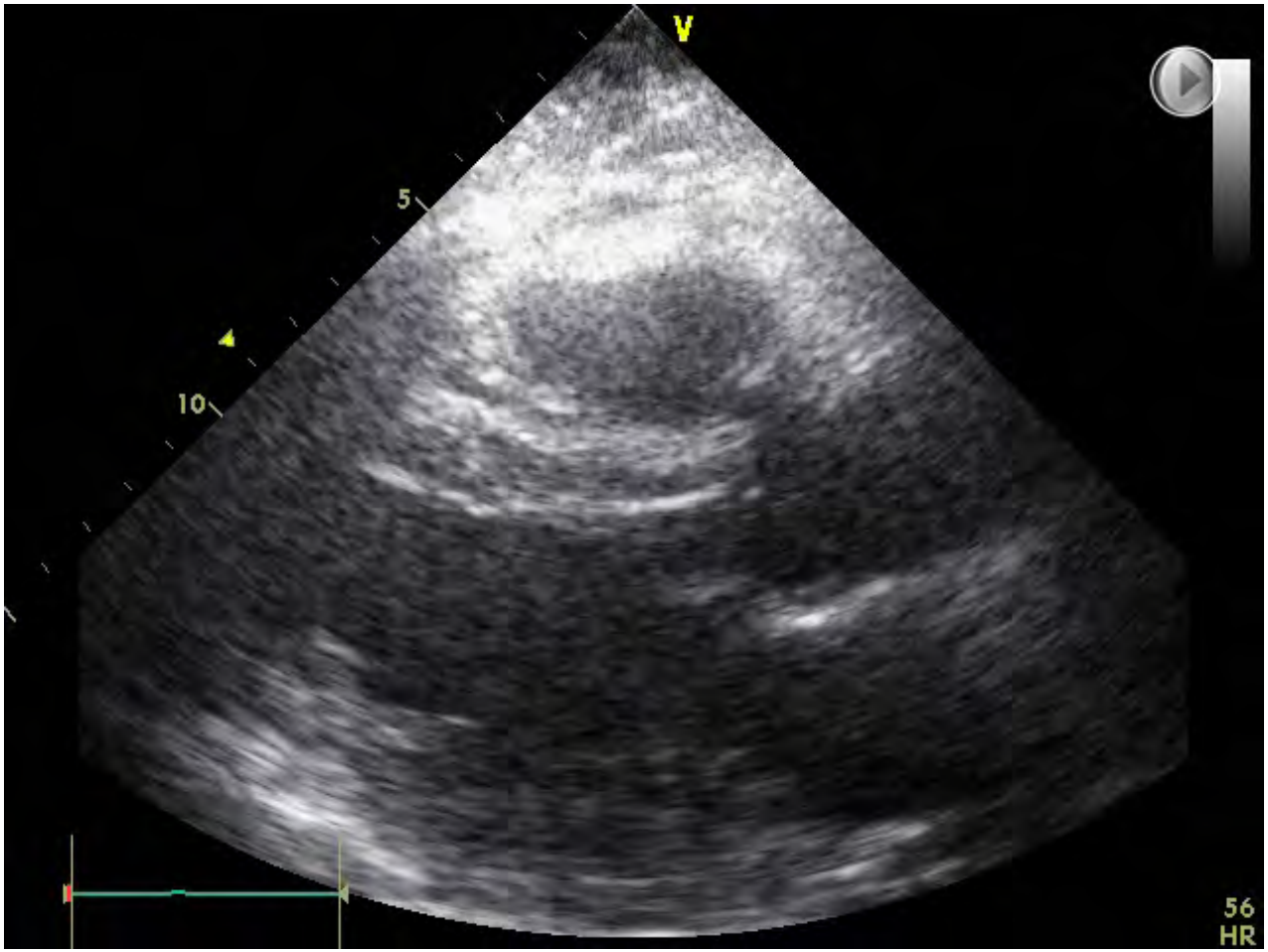
Progress

- Bedside USG abd :
  - GB wall mildly thickened, no pericholecystic fluid, liver normal, CBD not dilated, bilateral kidneys normal

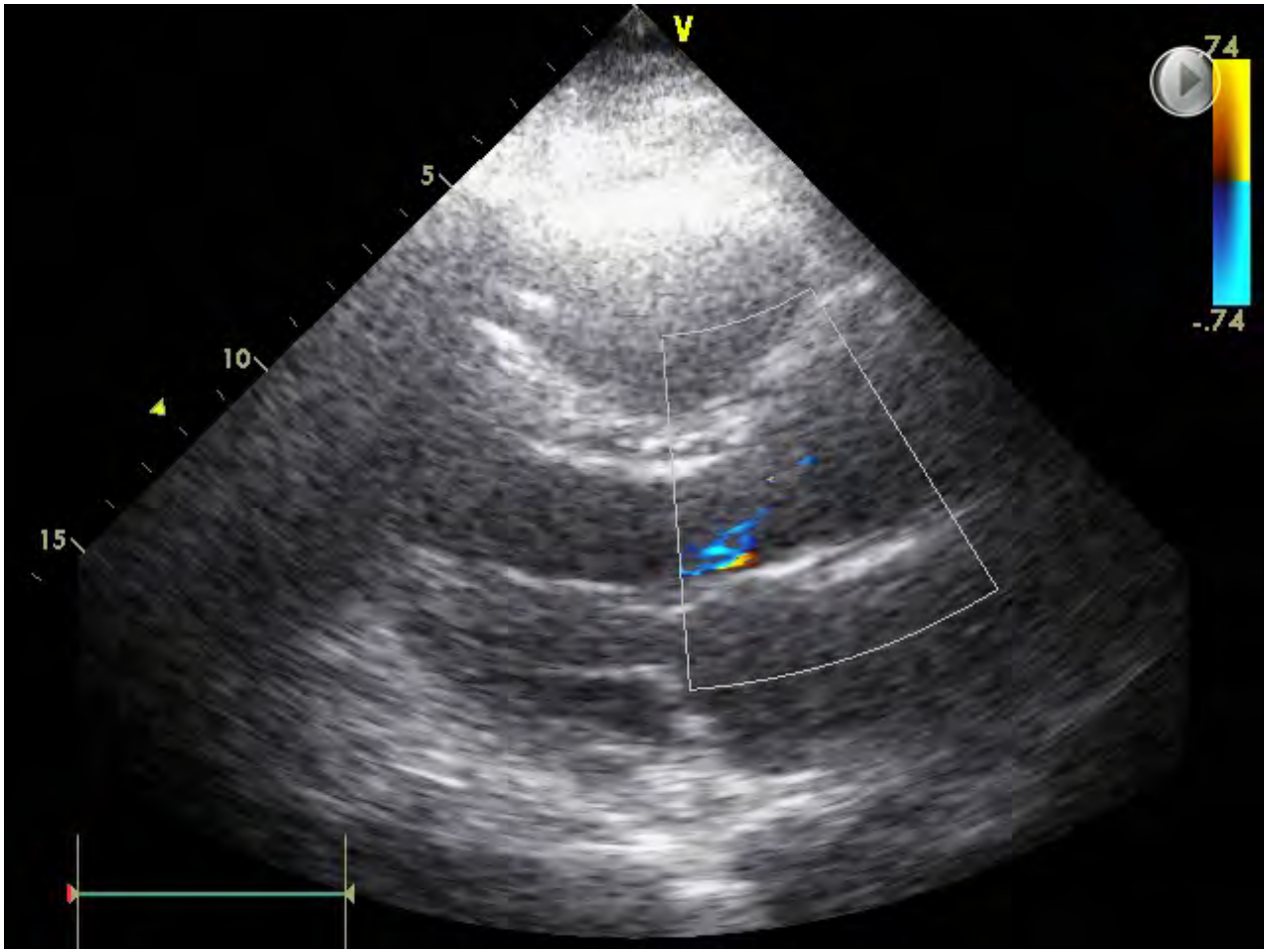
TTE

- Fair echogenicity due to gross obesity

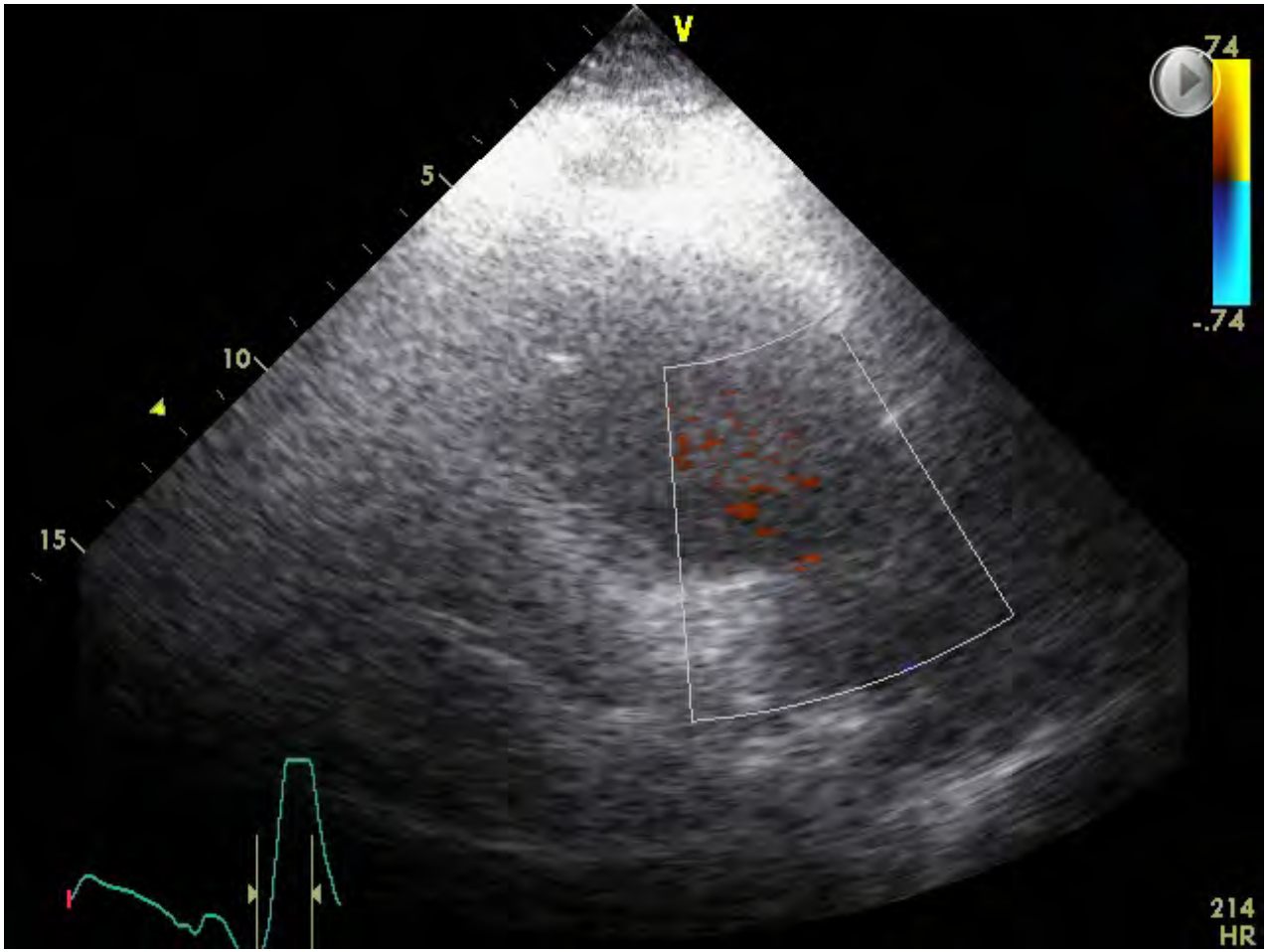
TTE



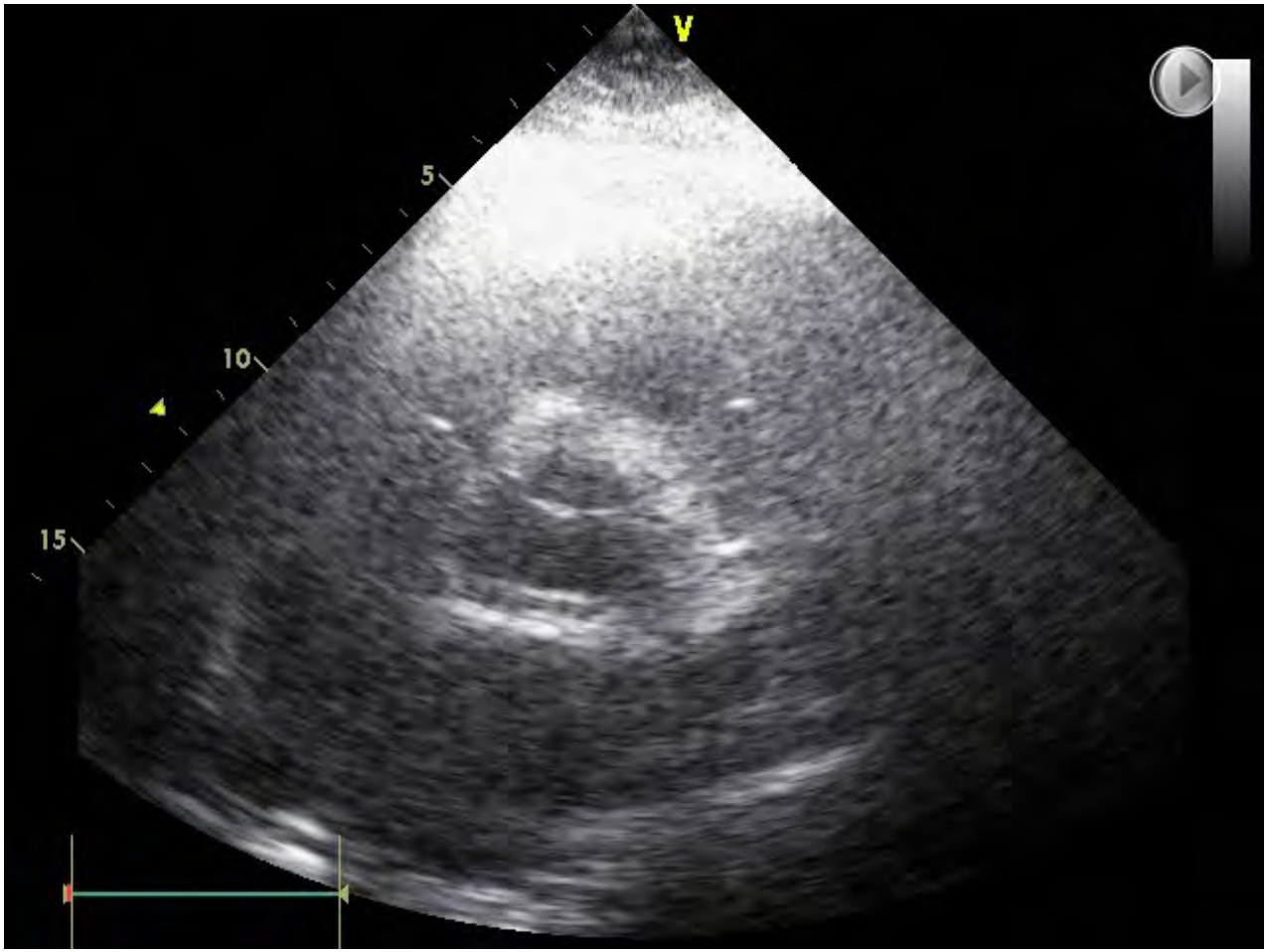
TTE



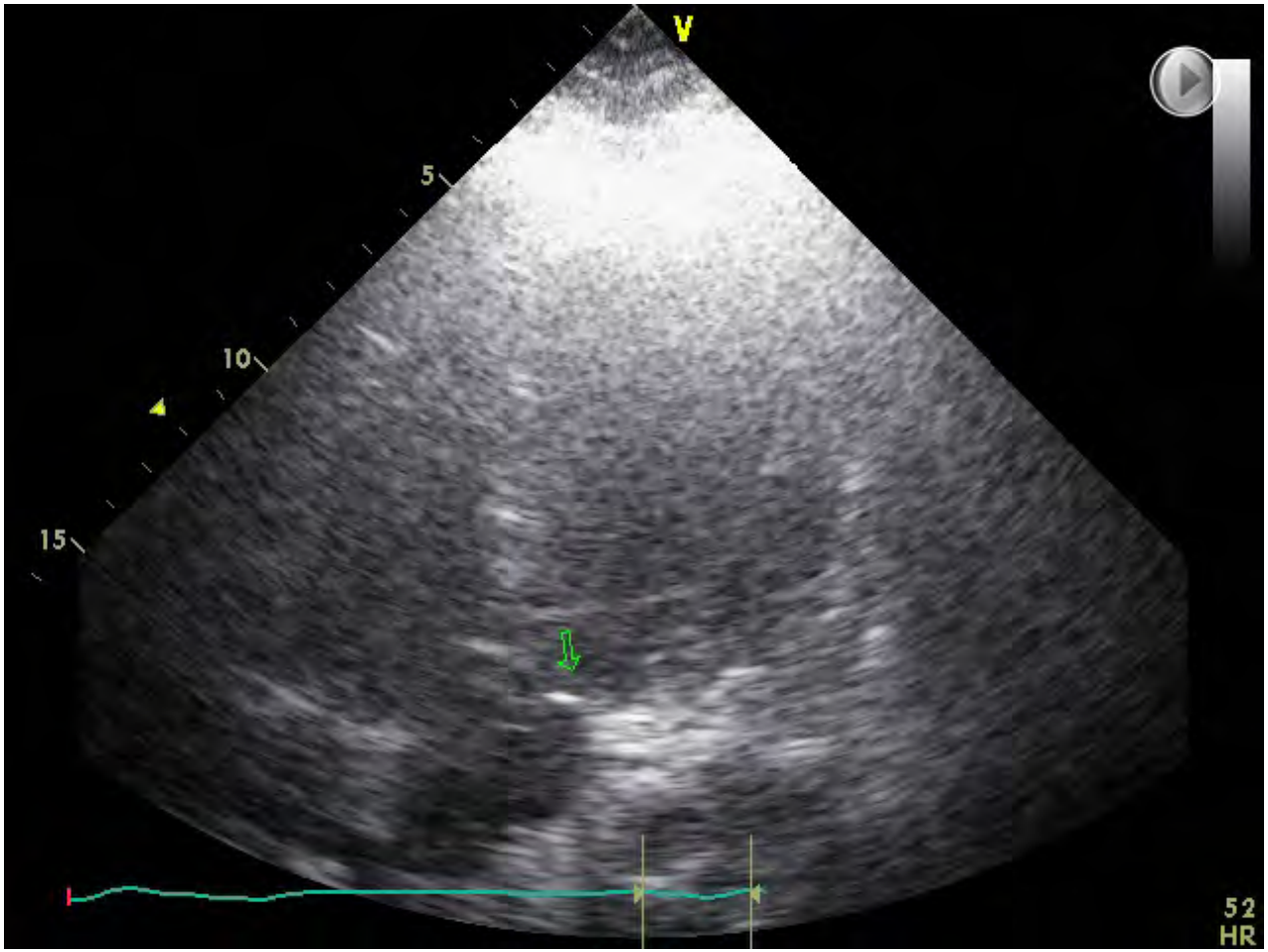
TTE



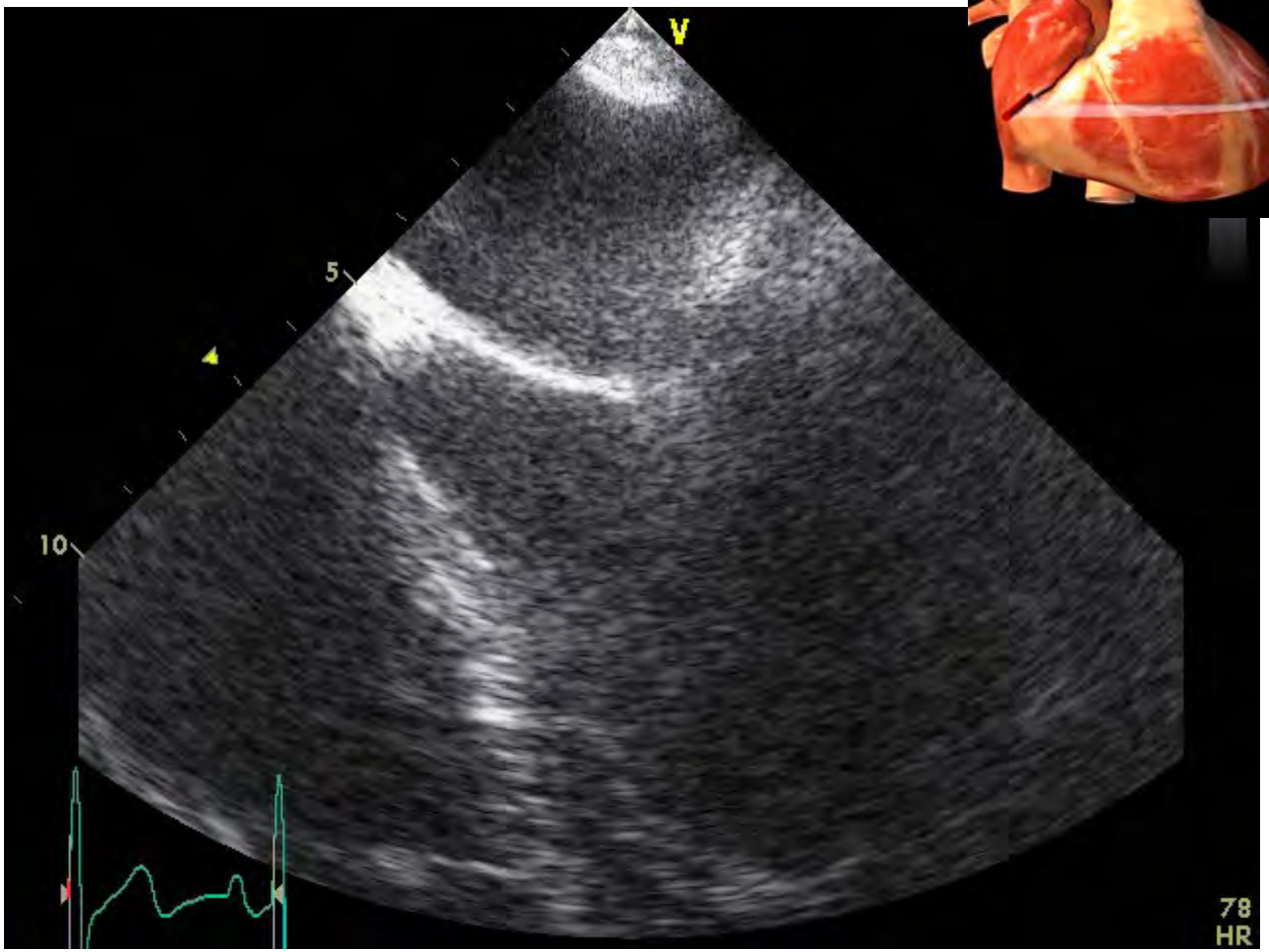
TTE



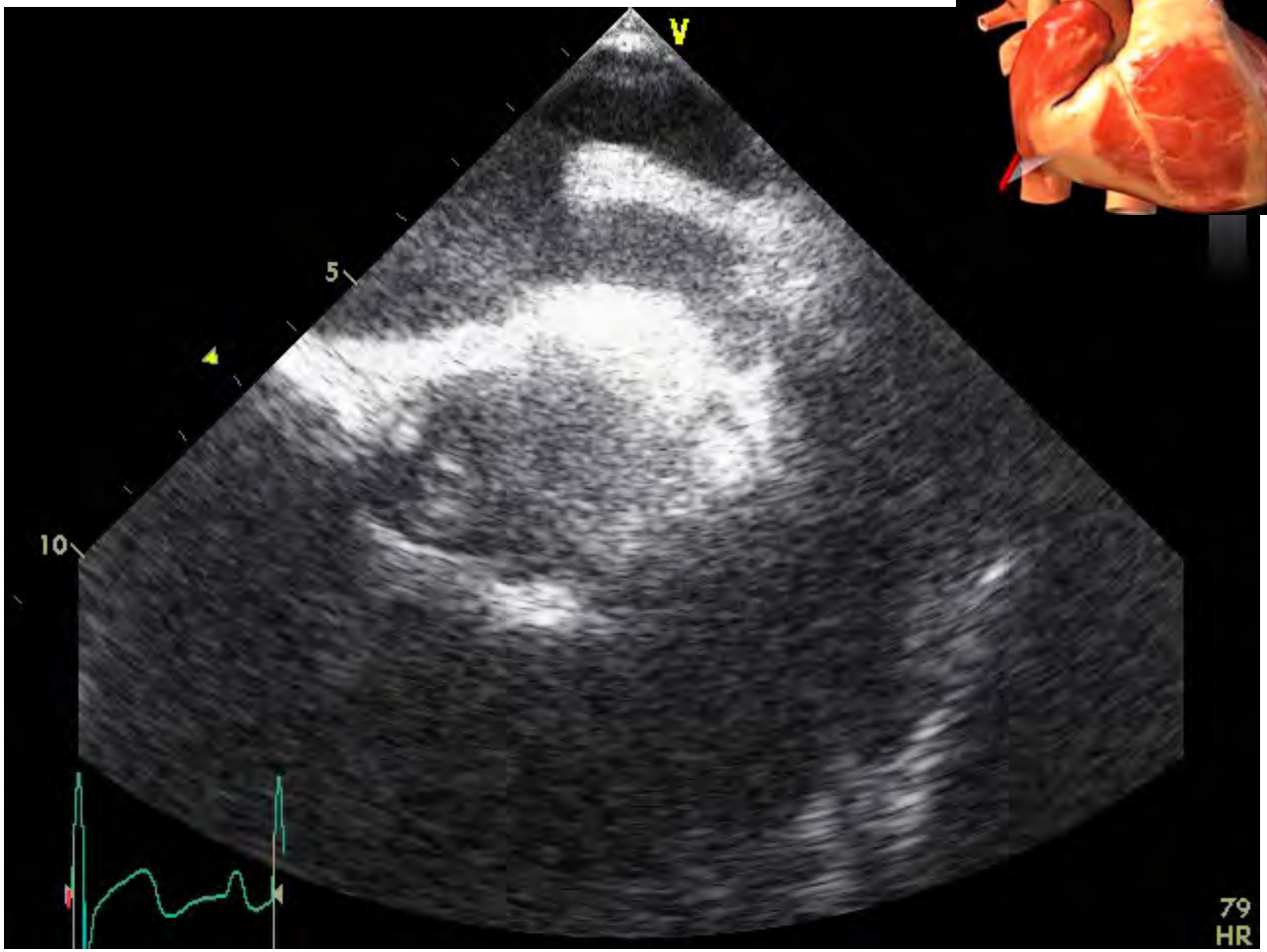
TTE



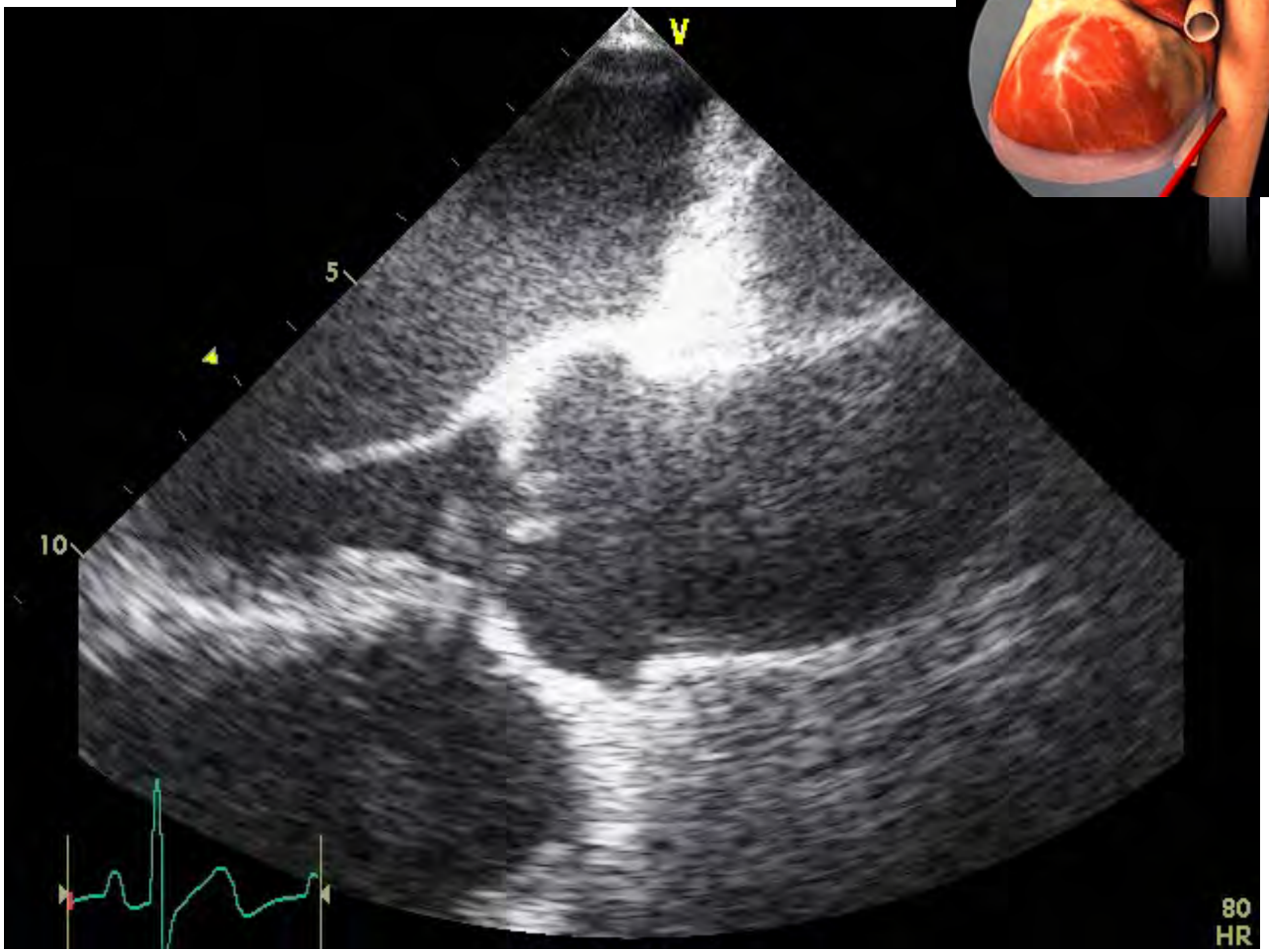
TEE

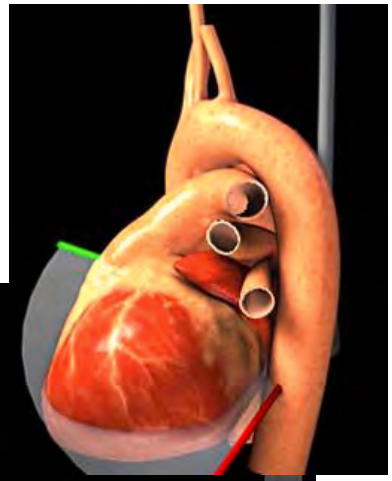


TEE



TEE





Progress

- Blood culture x 2 : GPC
- Pus swab : GPC
- Imp: folliculitis with IE and cardioembolic stroke
- Seen by neurologist : not to start aspirin or anticoagulation as high risk of hemorrhagic transformation

Repeat CT Brain

CT Report

- Newly noted heterogenous hypodense/ isodense changes in large area of R parietal-temporal region, with extension to R insular cortex and external capsule. ?Infarct/abscess
- L MCA infarct
- Small infarcts, abscesses or cerebritis over L frontal lobe

Question

- How to explain the diffuse erythematous rash and subsequent patchy desquamation?
- Proceeded to skin biopsy

Skin Biopsy

- Presence of subcorneal clefts
- No epidermal necrosis, spongiosis, subepidermal blister formation or vacuolar degeneration
- Superficial dermis : mild perivascular chronic inflammatory infiltrate
- No vasculitis or viral inclusion
- Gram stain and fungal stain are negative
- Diagnosis : Staphyloccocal scaled skin syndrome

Progress

- Given IE dose of Vancomycin/Gentamicin then Cloxacillin/Gentamicin (MSSA)
- Chlorhexidine bathing BD
- Folliculitis subsided
- Fever down, repeated blood cultures –ve
- Best GCS E2VTM3
- Consulted QMH CTS : not for surgical intervention as high hemorrhagic risk with cardiopulmonary bypass

Progress

- Tracheostomy done, weaned off ventilator
- Discharged to general ward on Day 12
- Relatives agree DNACPR in view of poor neurology
- Succumbed 20 days after ICU discharge

Summary

- A patient with extensive MSSA folliculitis complicated by Septicemia, infective endocarditis, Staphylococcal Scalded Skin Syndrome, multiple Septic embolic Stroke
- SSSSSSSSS

Discussion

- Staphylococcal Scalded Skin Syndrome
- Neurological complications of IE

Staphylococcal Scalded Skin Syndrome

- First reported 1972
- Other names :
  - Ritter von Ritterschein disease
  - Ritter disease
  - Lyell disease
  - Staphylococcal epidermal necrolysis
- Spectrum
  - Bullous impetigo to SSSS

Clinical Features

- Primarily in neonates and infants
- Diffuse erythema followed by flaccid bullae and wrinkling or widespread erosions
- No mucosal involvement
- Nikolsky's sign +ve

SSSS in Adults

- Uncommon
- <50 cases reported
- Usually in patients with renal insufficiency or immunocompromised
- Less than 5 cases reported in apparently immunocompetent adults – believed to be due to heavy load of Staphyloccus aureus

Opal, S.M.; Johnson-Winegar, A.D.; Cross, A.S. Staphylococcal scalded skin syndrome in two immunocompetent adults caused by exfoliatin B-producing Staphylococcus aureus. J. Clin. Microbiol. 1988

Pathophysiology

- An infection caused by S. aureus commonly at sites such as oral/nasal cavities, throat, umbilicus
- Production of Epidermolytic toxins A and B (ETA and ETB)
- ETA and ETB are proteases with high substrate specificity which selectively hydrolyze desmosomal proteins in skin
- Prevalence of ETA does not differ significantly among MRSA and MSSA

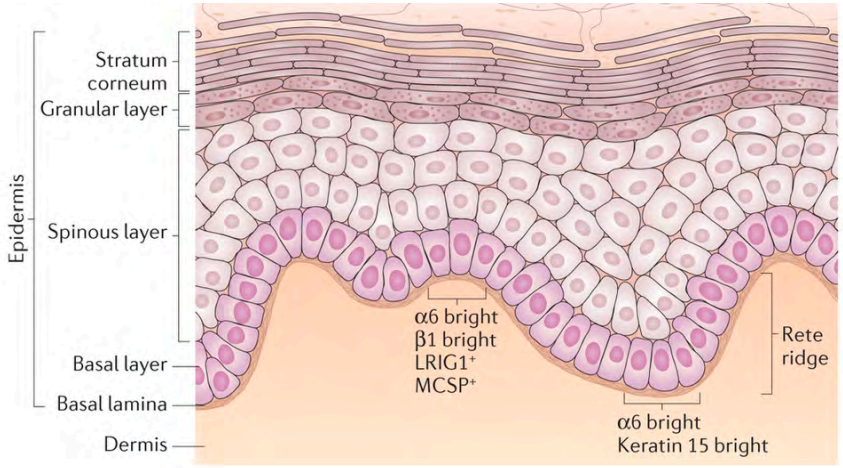
Toxins (Basel). May 2010; 2(5): 1148–1165.

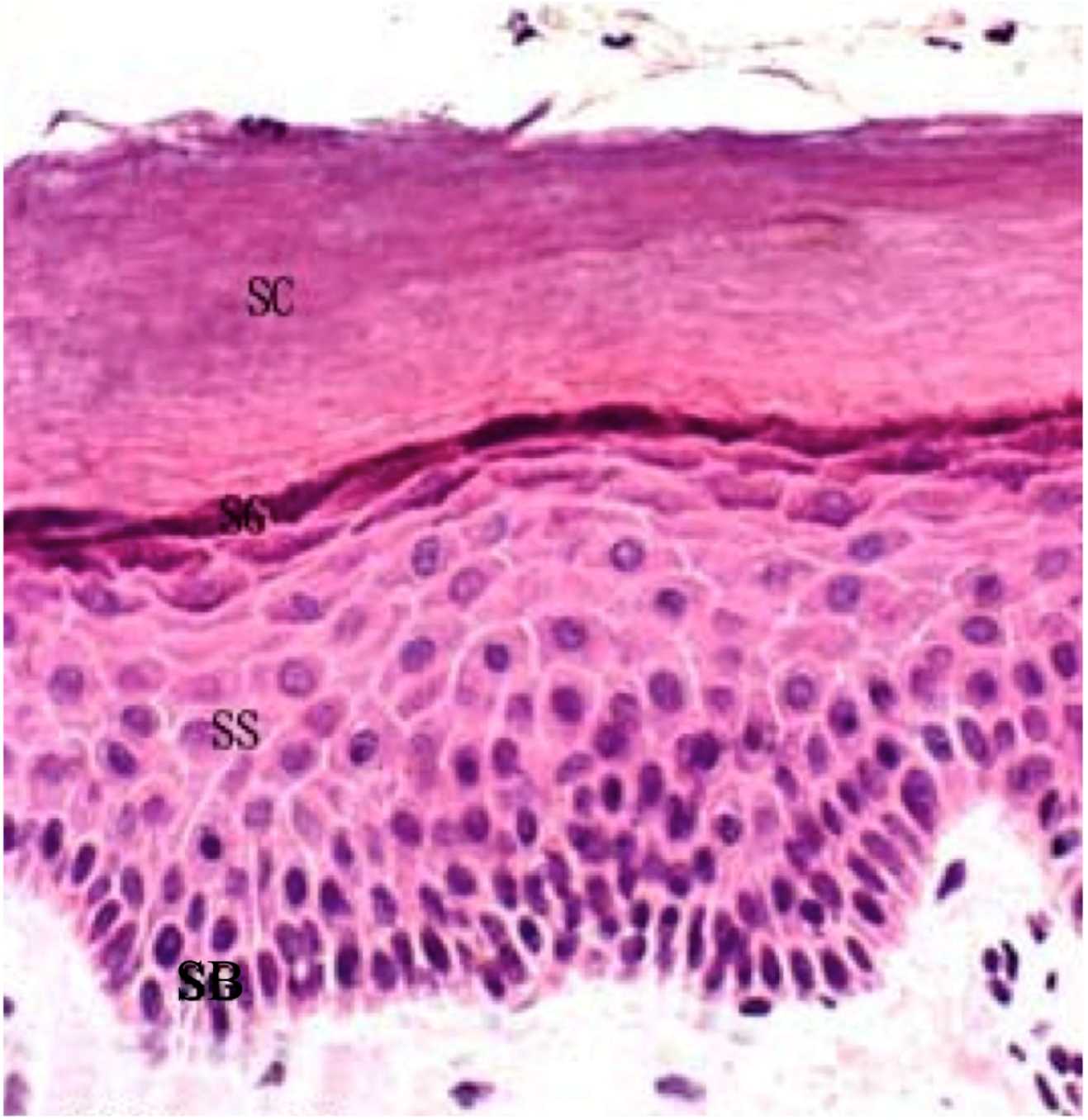
Histology of Normal Skin

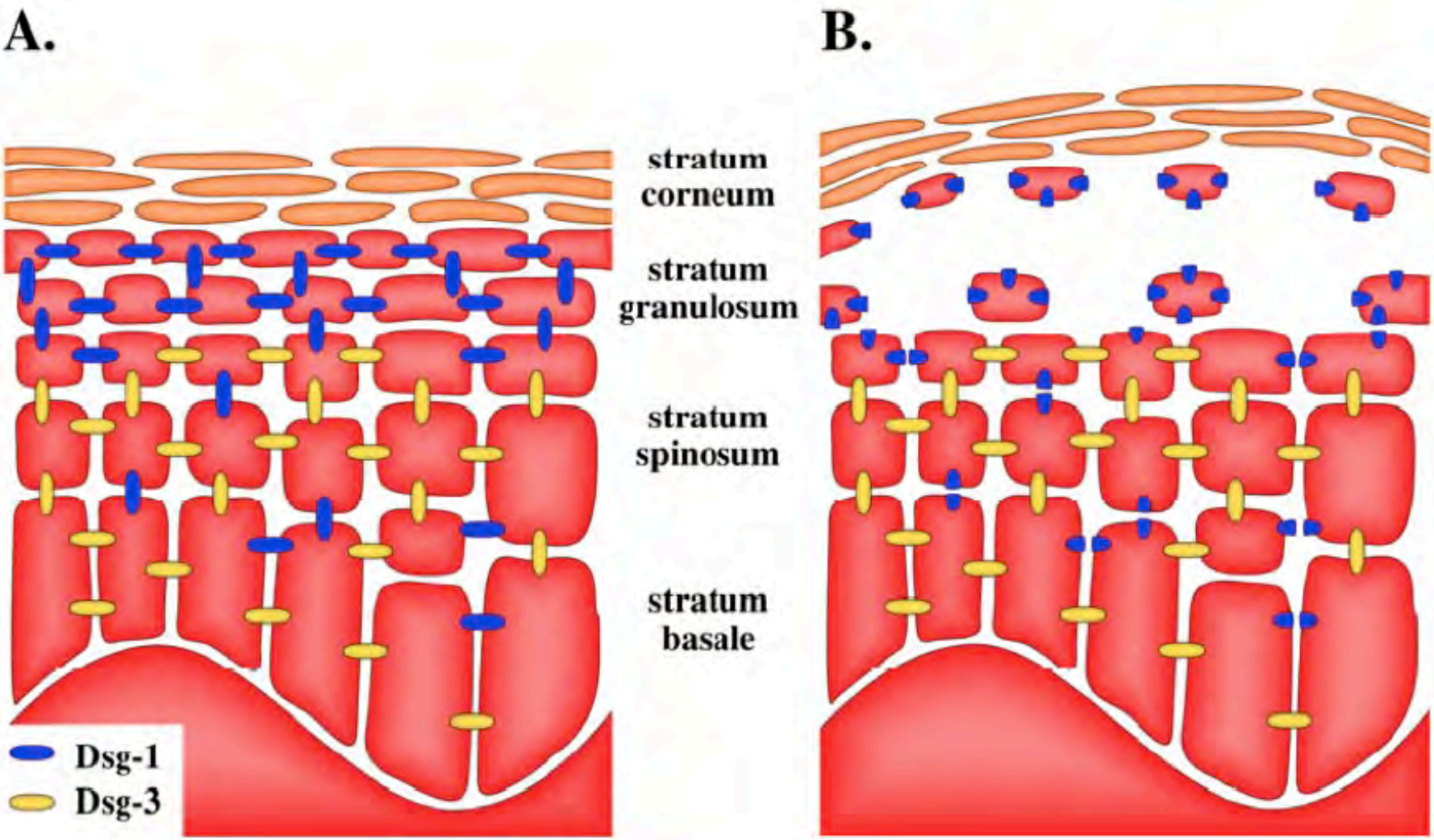
- Skin is made up of 2 layers : epidermis and dermis
- Dermis contains the skin appendages, e.g. sebaceous glands, hair follicles, vessels, sweat glands, sensory organs, etc.

Histology of Normal Skin

- Epidermis consists of 5 layers, from top to bottom :
  - Stratum lucidum
  - Stratum corneum
  - Stratum granulosum
  - Stratum spinosum
  - Stratum basale

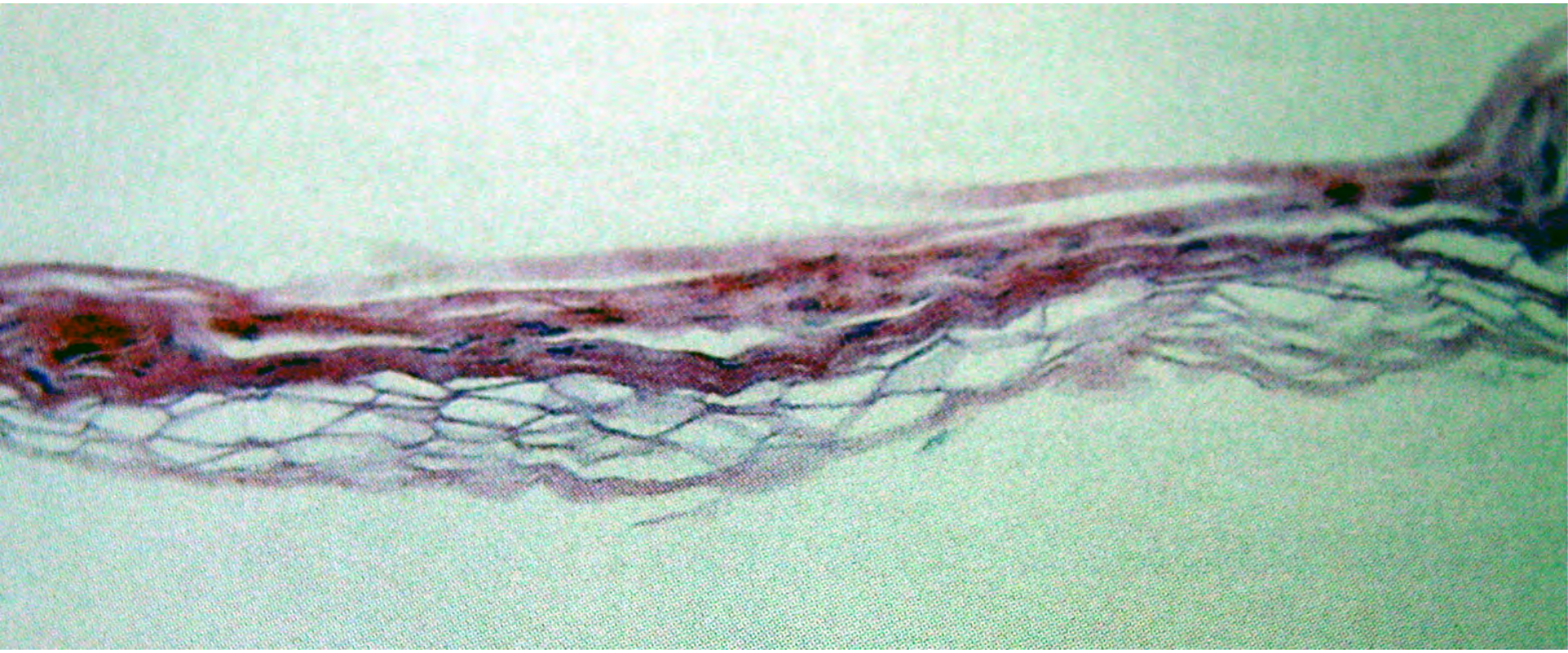



SC
SG
SS
SB



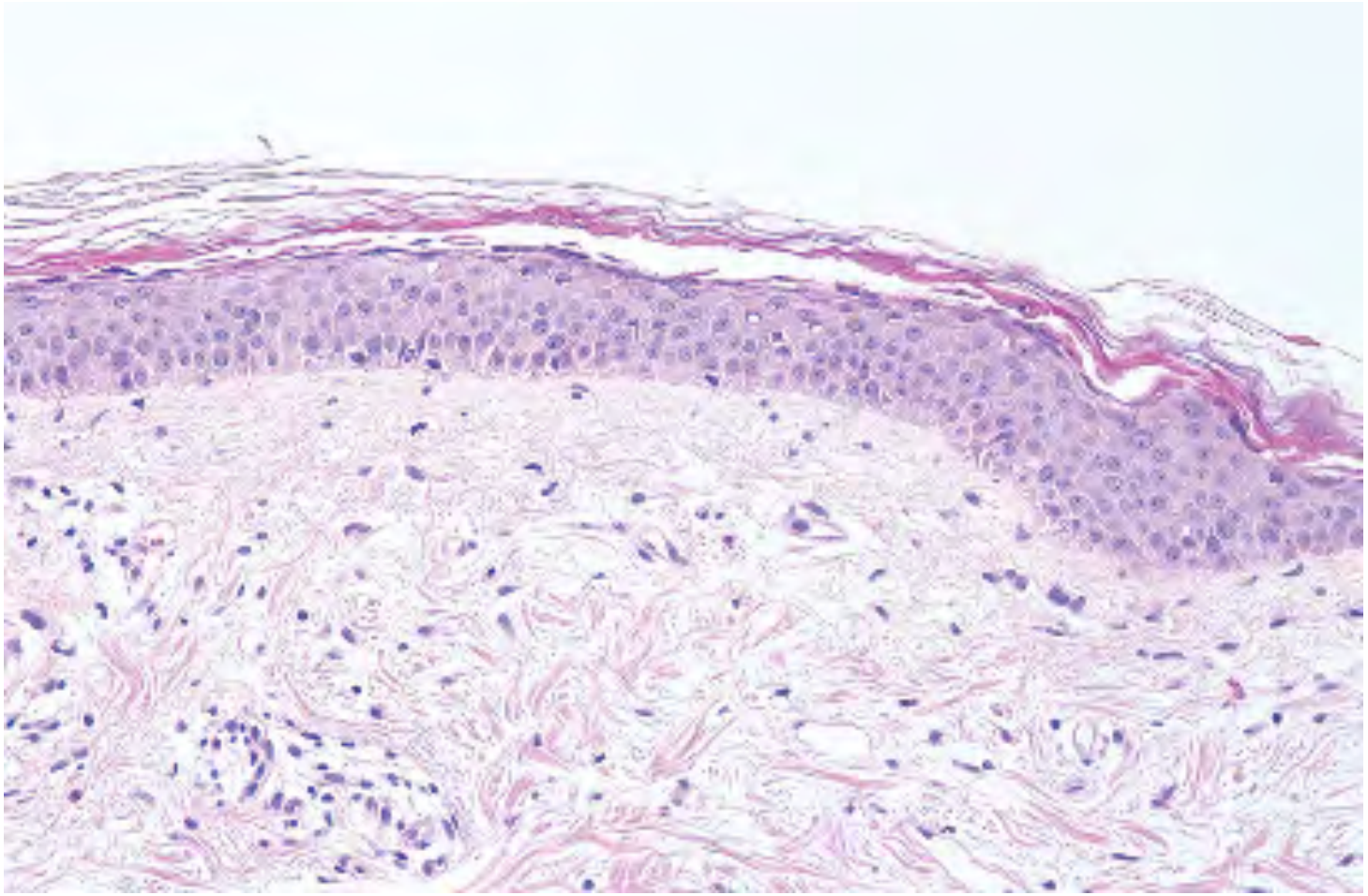
The ETs selectively hydrolyze Dsg-1

Histology of SSSS



Desquamated epidermis is limited to stratum corneum and small portion of granular layer

Histology of SSSS



Why SSSS not common in adults?

- Hypotheses :
  - ?neutralizing antibodies
  - Increased renal clearance of ETA and ETB in mature kidneys

Diagnosis

- Clinical + Presence of S. aureus in nasal, conjunctival, pharyngeal, umbilical, or other swabs
- Full-thickness skin biopsy
- Immunological assay of Staphylococcal ETA or ETB (not routinely a/v)

Treatment

- Supportive
- Rehydration
- Topical wound care
- Antibiotics for S. aureus

Prognosis

- Mortality among children with treatment <5%
- Mortality among adult 20-59% due to comorbidities

Cribier, B.; Piemont, Y.; Grosshans, E. Staphylococcal scalded skin syndrome in adults. A clinical review illustrated with a new case. J. Am. Acad. Dermatol. 1994

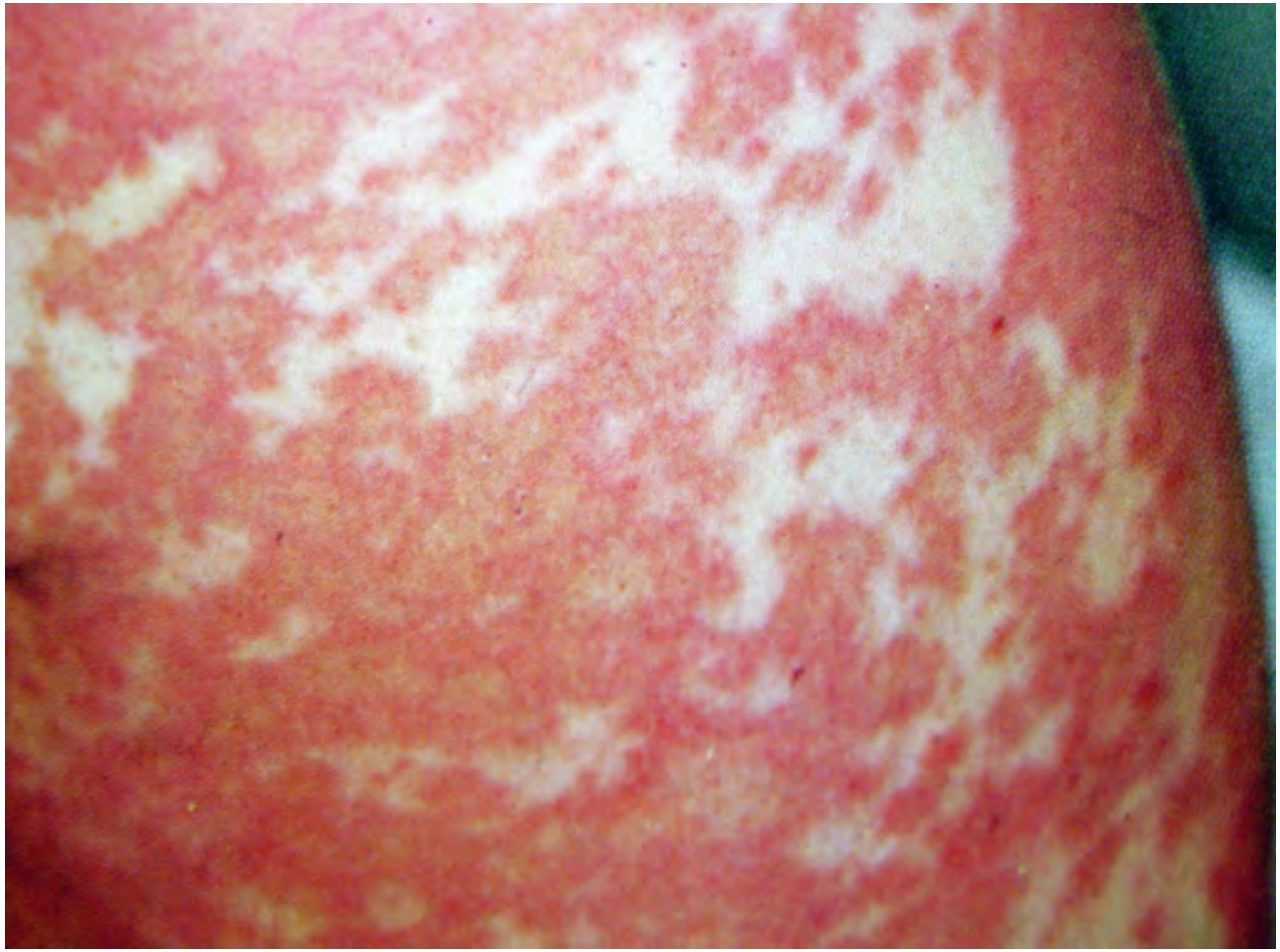
DDx

- Toxic epidermal necrolysis (TEN)
- Toxic shock syndrome (TSS)
- Pustular psoriasis
- Pemphigus

TEN

- Prodromal constitutional symptoms invariably precede mucocutaneous manifestations: malaise, fever, headache, cough, rhinorrhea
- Large, poorly defined erythematous or purpuric macules appear and coalesce to form large bullae
- Sheets of epidermis desquamate
- >30% BSA
- +ve Nikolsky's sign
- Mucosal involvement

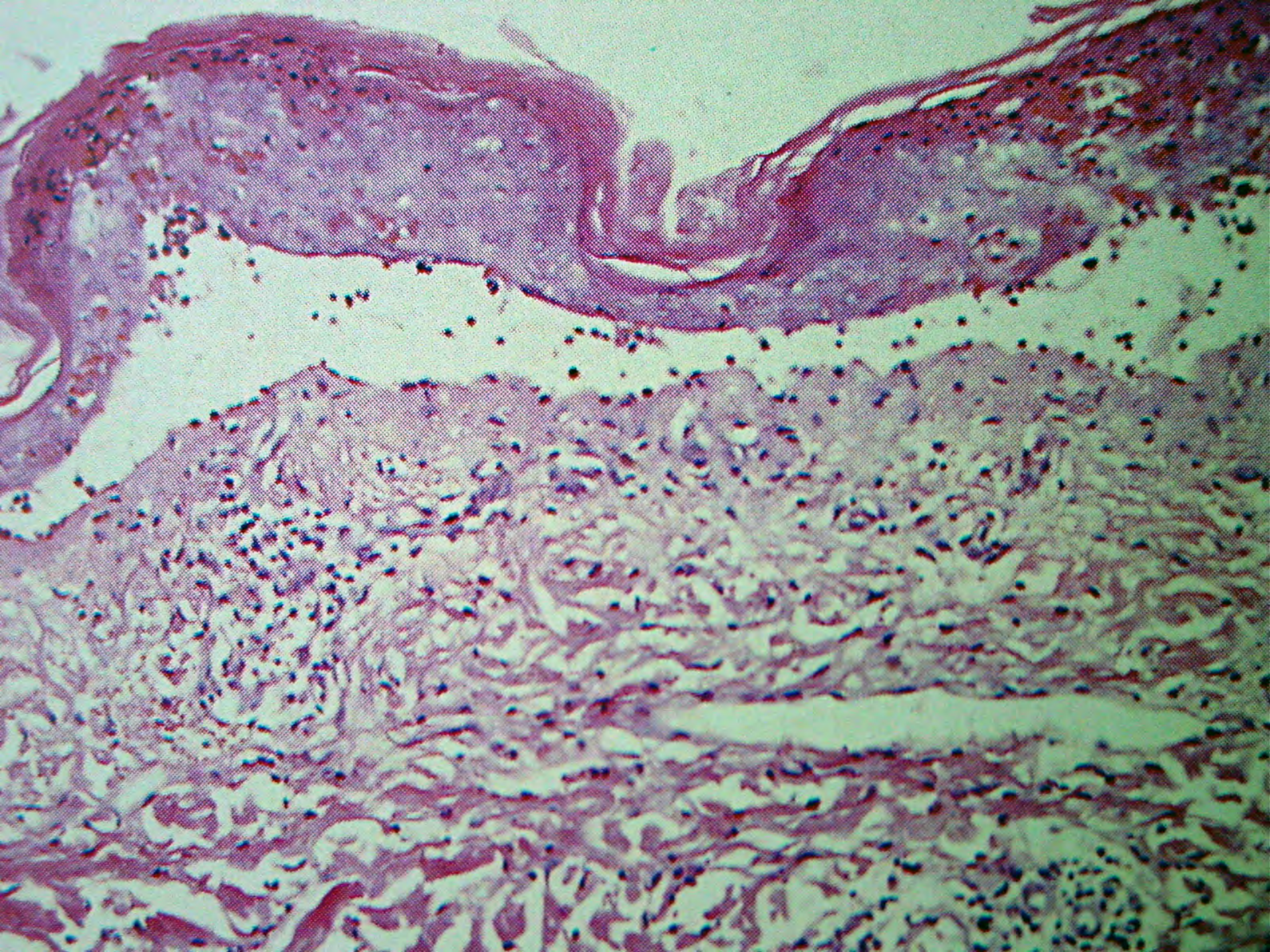
TEN



TEN

Histology

- TEN
  - Full thickness epidermal necrosis and subepidermal blister
  - The entire epidermis is present in the desquamated sheets
  - Dermal inflammation less marked



Why need to differentiate?

- TEN : routine antibiotic may cause harm
- SSSS : antibiotics needed

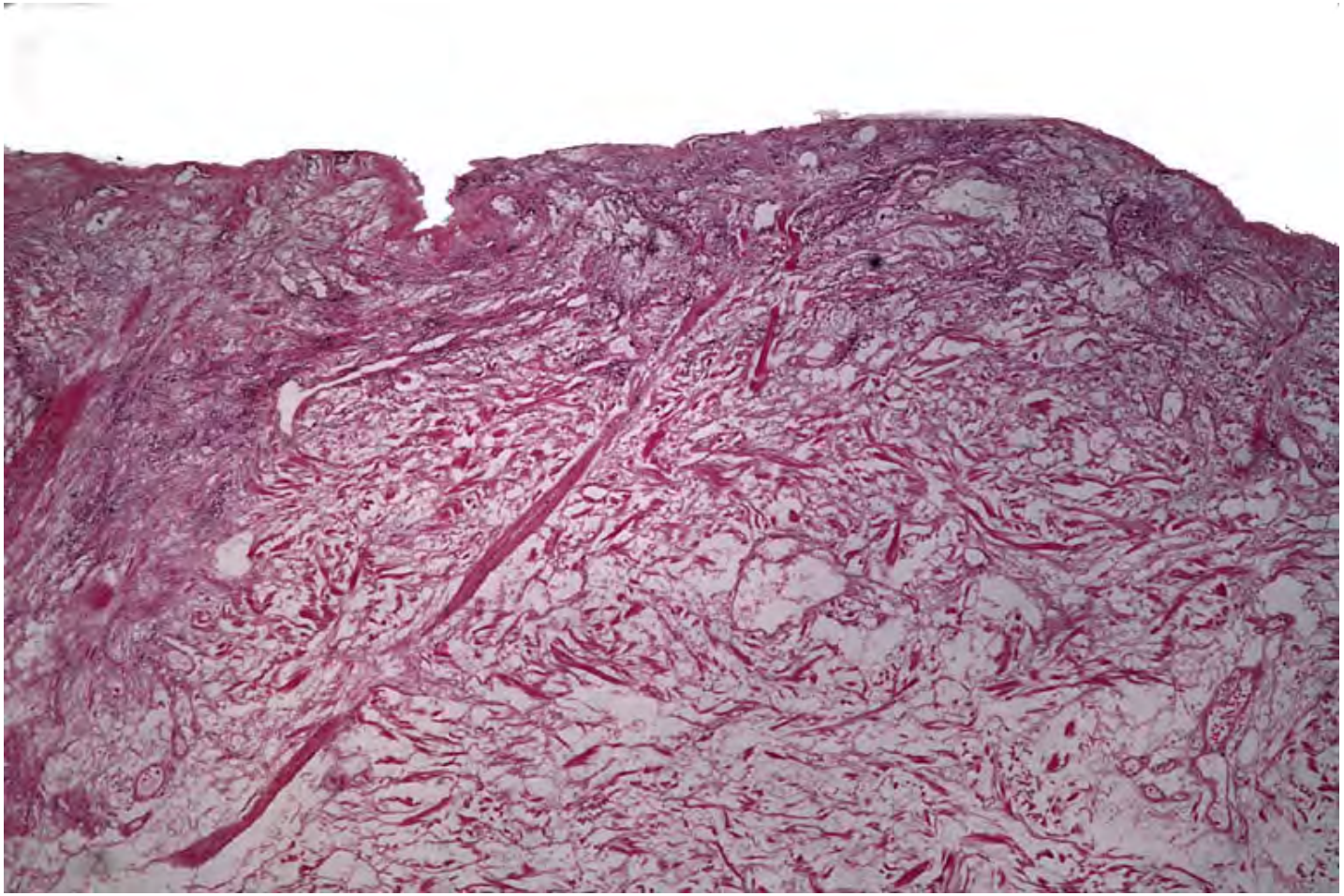
TSS

- Associated with tampon use. Other assoc. : abscesses, postpartum wound, burns, IVDA, etc.
- Occurs in persons of all ages and sexes
- Presents with diffuse macular erythroderma, most prevalent on trunk, followed by peeling

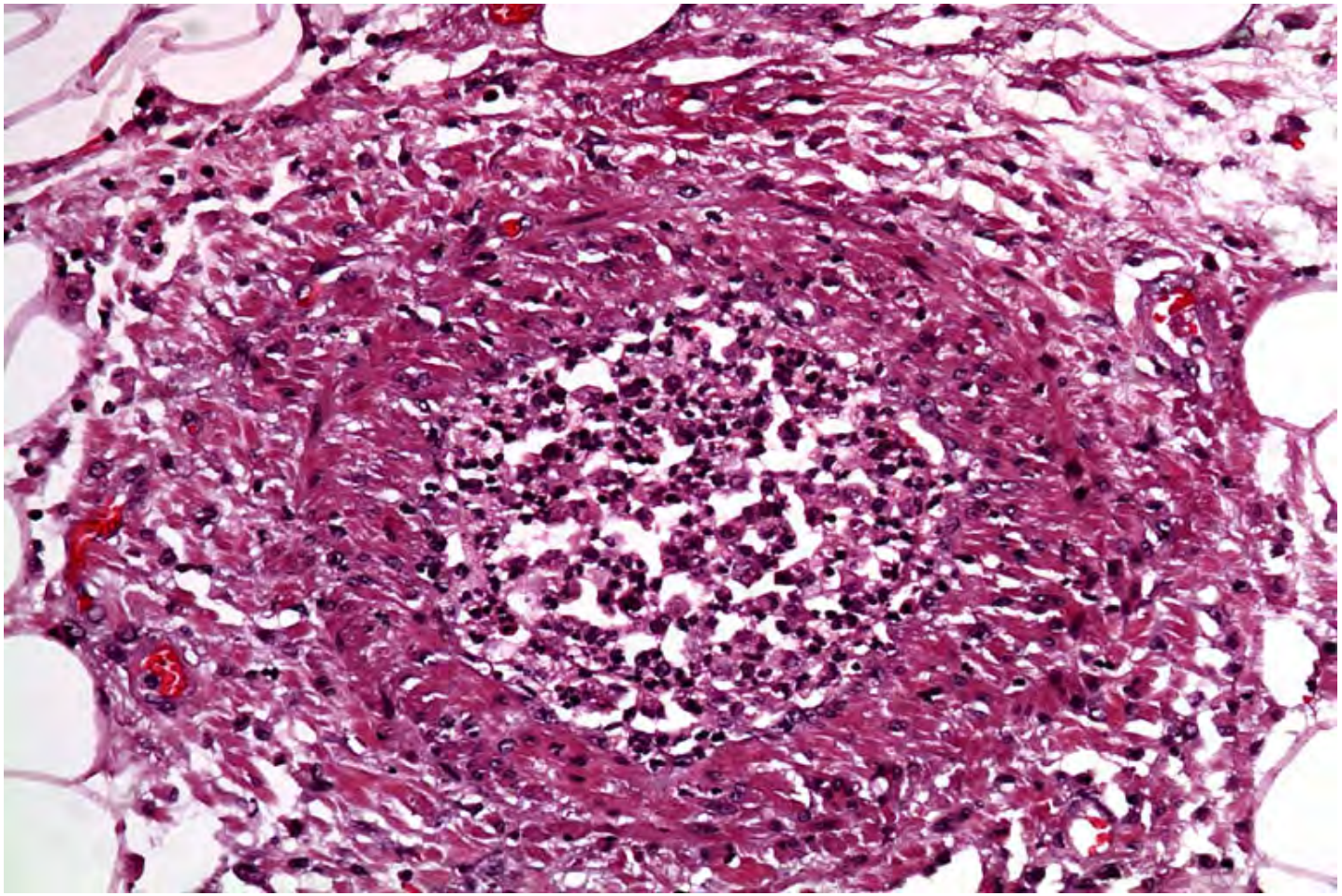
Histology

- TSS :
  - Keratinocyte necrosis at all levels of epidermis
  - Ballooning degeneration may be present
  - Papillary dermis characterized by diffuse, prominent edema
  - Perivascular lymphocytic infiltrate

Epidermal and Dermal Necrosis in TSS



Vasculitis in TSS



Pathophysiology of TSS

- S. aureus related epidermal toxin, known as toxin 1 (TSST-1) or enterotoxin B or C act as superantigens that bind to major histocompatibility antigens and stimulate cytokine production (TNF, interleukin-1) by macrophages
- Streptococcal related TSS are associated with group A Streptococcus infection (necrotizing fascilitis/myositis), caused by pyrogenic exotoxins

Staphylococcal TSS

Clinical Criteria

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
  - Gastrointestinal: vomiting or diarrhea at onset of illness
  - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
  - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
  - Hepatic: total bilirubin, alanine aminotransferase enzyme, or asparate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
  - Hematologic: platelets less than 100,000/mm^3
  - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

Streptococcal TSS

Table 1. Case definition of streptococcal toxic-shock syndrome (streptococcal TSS)

I. Streptococcal TSS
   A. Isolation of group A *Streptococcus*
      1. From a sterile site
      2. From a nonsterile body site
   B. Clinical signs of severity
      1. Hypotension
      2. Clinical and laboratory abnormalities (requires two or more of the following):
         a) Renal impairment
         b) Coagulopathy
         c) Liver abnormalities
         d) Acute respiratory distress syndrome
         e) Extensive tissue necrosis, i.e., necrotizing fasciitis
         f) Erythematous rash

Definite Case = A1 + B(1+2)
Probable Case = A2 + B(1+2)

TSS

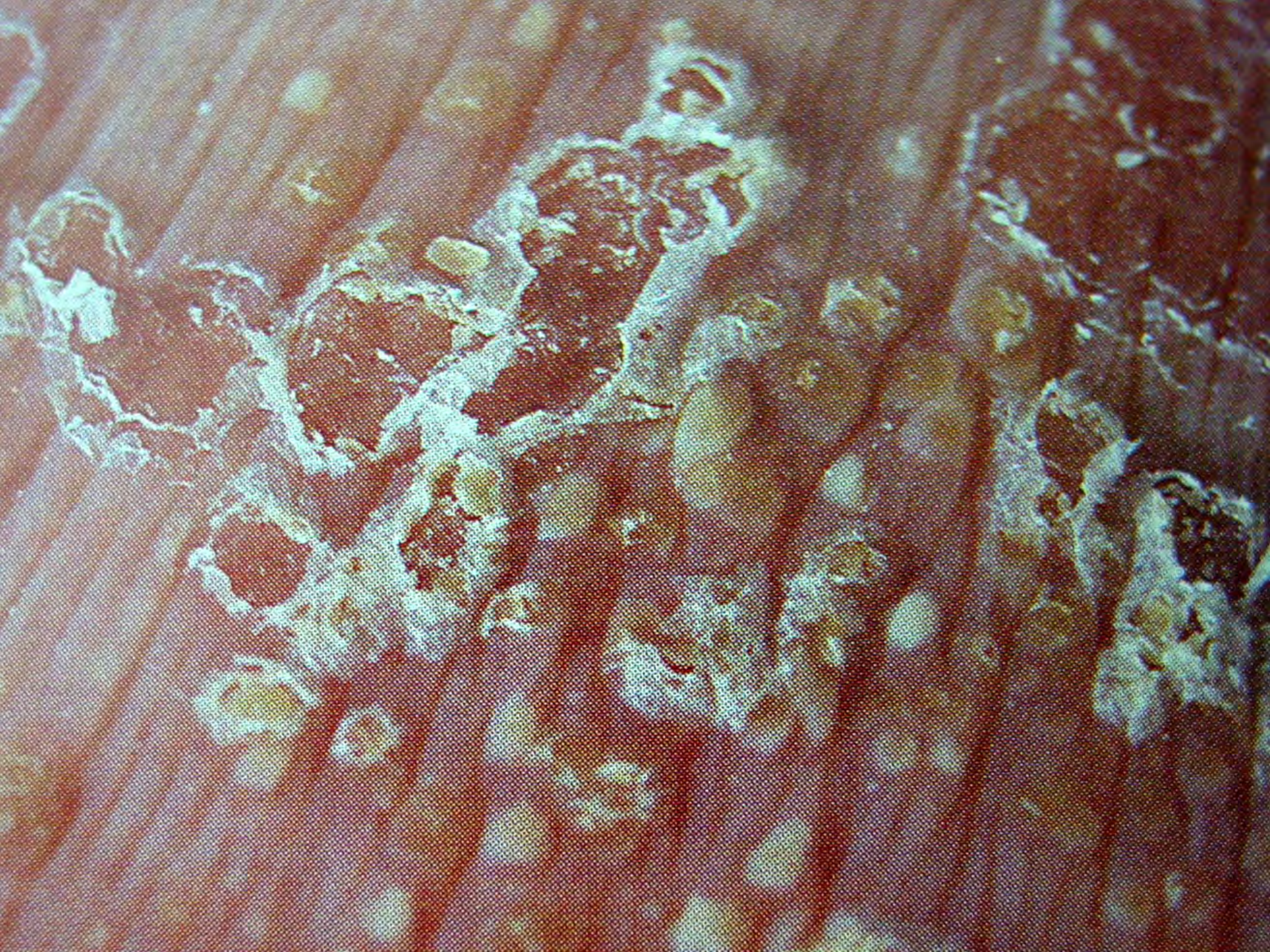
- Differentiate from SSSS
  - TSS usually a clinical diagnosis
  - SSSS usually occurs in neonates/infants
  - SSSS usually has no multisystem involvement
  - SSSS tends to start from head and neck region while TSS starts from trunk
  - Less blister formation in TSS

Psoriasis

- A relapsing and remitting condition, characterized by well circumscribed, red-pink plaques covered by layers of silvery white scale
- Prominent on knees, elbows, trunk and scalp
- Variants: guttate, erythrodermic and pustular psoriasis

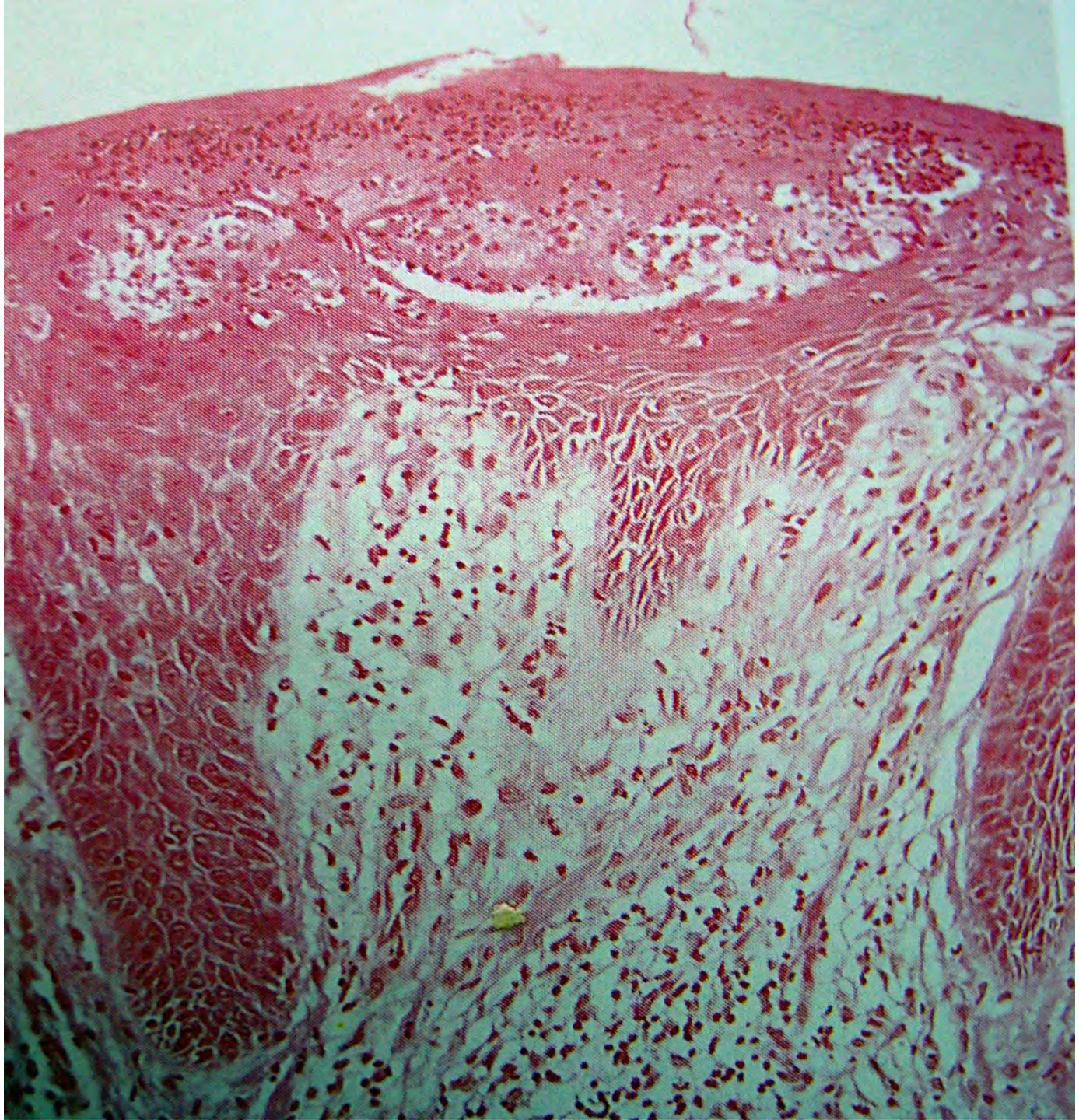
Pustular Psoriasis

- Uncommon form of psoriasis with widespread pustules on an erythmatous background
- Generalized or localized
- Typically in adults



Histology

- Pustular psoriasis:
  - Accumulations of neutrophils in epidermis, forming a pustule
  - Plus other features of psoriasis, namely, parakeratosis, thickened epidermis, suprapapillary thinning



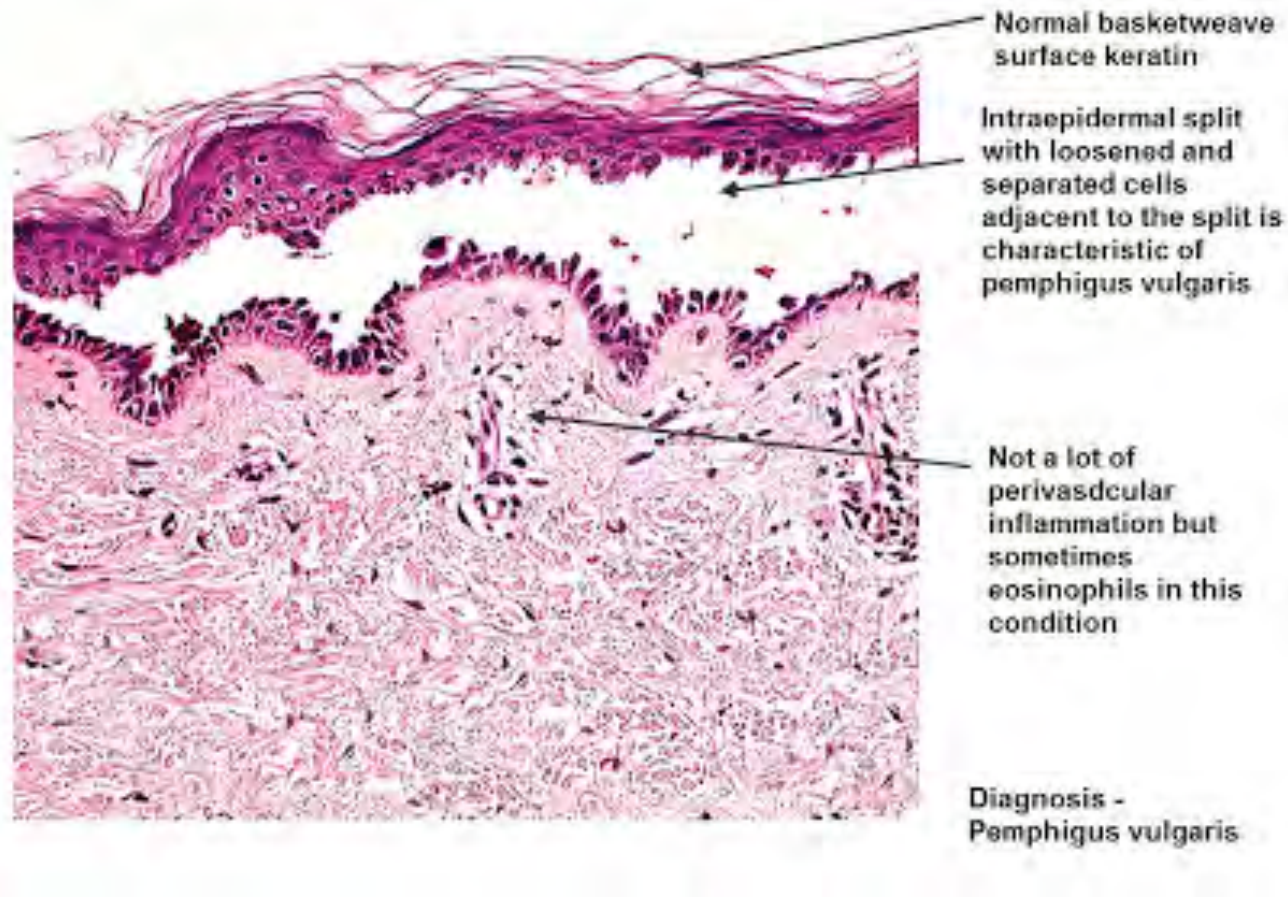
Treatment

- Rehydration
- Correct electrolytes
- Methrotrexate, Cyclosporine, Steroid, PUVA
- Antibiotics not indicated unless signs of infection

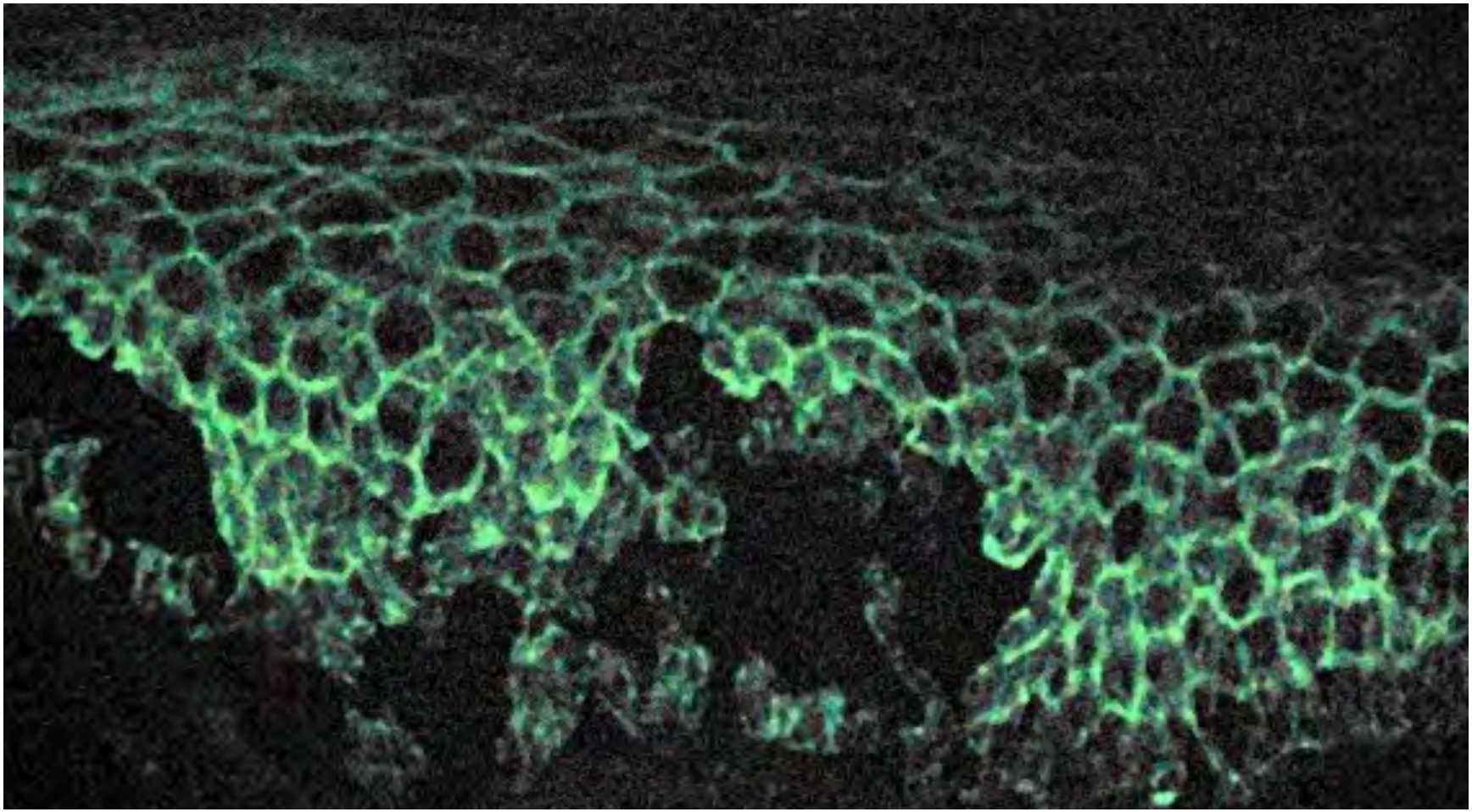
Pemphigus

- Autoimmune, intraepithelial blistering disease
- Affects skin and mucosal membrane
- Mediated by circulating autoantibodies against desmosomes in epidermis
- Cutaneous lesions usually arises on healthy-appearing skin
- Nikolsky's sign +ve

Histology


Normal basketweave surface keratin
Intraepidermal split with loosened and separated cells adjacent to the split is characteristic of pemphigus vulgaris
Not a lot of perivasdcular inflammation but sometimes eosinophils in this condition
Diagnosis - Pemphigus vulgaris

Immunofluorescence using an anti-IgG antibody



Neurological Complications of IE

Neurological Complications of IE

- TIA
- Embolic stroke
- ICH
- Mycotic aneurysm
- Meningitis
- Cerebral abscess
- Encephalopathy

Neurological Complications of IE

- Most neurological Cx occur early during course of IE
- 20-40% in IE patients
- 37-55% in IE patients requiring ICU care

Sonneville et al. Annals of Intensive Care 2011, 1:10

TIA/Embolic Stroke

- >40% affects MCA
- Incidence decreases with appropriate antibiotics
  - 4.82/1000 patient days in first week to 1.71/1000 patient days in second week
- Higher risks if :
  - Mitral valve vegetation
  - Prosthetic valve vegetation
  - Larger vegetation >10mm
  - Mobile vegetation
  - S. aureus

Sonneville et al. Annals of Intensive Care 2011, 1:10

TIA/Embolic Stroke

- No indication for initiation of antithrombotic drugs (thrombolytic drugs, anticoagulant or antiplatelet) during active phase of IE
- In patients already receiving oral anticoagulant, it should be replaced by unfractionated heparin for at least 2 weeks with close monitoring

Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL, ESC Committee for Practice Guidelines: **Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC).** *Eur Heart J* 2009, **19**:2369-2413.

?Aspirin

- No convincing data to support its initiation
- Interruption of antiplatelet therapy is not recommended in the absence of bleeding

ICH

- 12-30% of neurological Cx of IE
- Hemorrhagic transformation of ischemic infarcts by septic emboli is involved in 1/3
- Other mechanisms involved :
  - Thrombocytopenia
  - Anticoagulation therapy
  - Rupture mycotic aneurysm
- MRI reveals an even higher incidence of microbleeds

Intracranial Mycotic Aneurysms

- Relatively rare, <10% neurological Cx of IE
- Septic embolization to vasa vasorum
- ICMA multiple in 25% of cases
- Most common in distal branches of MCA
- Streptococci > S. aureus > others
- CT angiography and MRA able to detect ICMA >5mm
- Monitoring with serial imaging is needed
- Most resolve with appropriate antibiotics
- May need neurosurgery if mass effect or enlarging despite antibiotics

Meningitis

- Septic or aseptic response to brain ischemia or hemorrhage
- 2-20% of patients with IE
- Up to 40% of neurological Cx of IE
- May add fluoroquinolone or rifampicin if S. aureus

Brain Abscess

- Reported in 13% of patients with IE
- Mostly S. aureus

Sonneville R, Mirabel M, Hagège D, Tubach F, Vignon P, Perez P, Lavoué S, Kouatchet A, Pajot O, Mekontso-Dessap A, Tonnelier JM, Bollaert PE, Frat JP, Navellou JC, Hyvernat H, Ait Hssain A, Tabah A, Trouilet JL, Wolff M: **Neurologic complications and outcomes of infective endocarditis in critically-ill patients: the ENDOREA prospective multicenter study.** *Crit Care Med* 2011.

Table 2. Indications for Surgery in IE

Circulation. 2010;121:1141-1152

Congestive heart failure*
Congestive heart failure caused by severe aortic or mitral regurgitation or, more rarely, by valve obstruction caused by vegetations
Severe acute aortic or mitral regurgitation with echocardiographic signs of elevated left ventricular end-diastolic pressure or significant pulmonary hypertension
Congestive heart failure as a result of prosthetic dehiscence or obstruction
Periannular extension
Most patients with abscess formation or fistulous tract formation
Systemic embolism†
Recurrent emboli despite appropriate antibiotic therapy
Large vegetations (>10 mm) after 1 or more clinical or silent embolic events after initiation of antibiotic therapy
Large vegetations and other predictors of a complicated course
Very large vegetations (>15 mm) without embolic complications, especially if valve-sparing surgery is likely (remains controversial)
Cerebrovascular complications‡
Silent neurological complication or transient ischemic attack and other surgical indications
Ischemic stroke and other surgical indications, provided that cerebral hemorrhage has been excluded and neurological complications are not severe (eg, coma)
Persistent sepsis
Fever or positive blood cultures persisting for >5 to 7 days despite an appropriate antibiotic regimen, assuming that vegetations or other lesions requiring surgery persist and that extracardiac sources of sepsis have been excluded
Relapsing IE, especially when caused by organisms other than sensitive streptococci or in patients with prosthetic valves
Difficult organisms
S aureus IE involving a prosthetic valve and most cases involving a left-sided native valve
IE caused by other aggressive organisms (*Brucella, Staphylococcus lugdunensis*)
IE caused by multiresistant organisms (eg. methicillin-resistant *S aureus* or vancomycin-resistant enterococci) and rare infections caused by Gram-negative bacteria
Pseudomonas aeruginosa IE
Fungal IE
Q fever IE and other relative indications for intervention
Prosthetic valve endocarditis
Virtually all cases of early prosthetic valve endocarditis
Virtually all cases of prosthetic valve endocarditis caused by *S aureus*
Late prosthetic valve endocarditis with heart failure caused by prosthetic dehiscence or obstruction, or other indications for surgery

Implications of Neurologic Complications during Cardiac Surgery

- Risk of cardiopulmonary bypass :
  - Hemorrhagic transformation due to heparin
  - Hypotension further exacerbate cerebral ischemia

Controversies

- In many series, surgery independently associated with lower mortality ?selection bias
- Early (within 72 hours) vs late (delay 2 weeks)

Recommendations

- The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis by the European Society of Cardiology
  - After a silent cerebral embolism or TIA, surgery is recommended without delay if indication remains
  - After a stroke, surgery indicated for heart failure, uncontrolled infection, abscess or persisting high embolic risk should not be delayed
  - After ICH, surgery must be postponed for at least 1 month
- This recommendation does not apply to comatous patients

Eur Heart J 2009

Cardiac Surgery : Factors to Consider

Table 2 Cardiac surgery in ICU patients with IE and neurologic complications

Surgery possible if required	Surgery to be delayed or contraindicated
Heart failure, uncontrolled infection, abscess, high embolic risk	
Silent neurologic complications (CT scan, MRI)	Severe comorbidities
Transient ischemic attack	Severe septic shock
Stroke	Stroke and coma or extensive neurologic deficit
Microbleeds or very small hemorrhagic lesions	Intracranial hemorrhage (other than microbleeds or very small hemorrhagic)
Meningitis	Meningitis and coma (rare)
Brain abscess	Brain abscess associated with intracranial hypertension
Small ICMA	Very large or enlarging ICMA

Prognosis

- Mortality for IE : 18%
- Mortality with prosthetic valve IE : 22-33%
- Mortality for patients with IE requiring ICU care : 45-57%

Sonneville et al. Annals of Intensive Care 2011, 1:10

Take Home Messages

- Think of SSSS in blistering adult patients with renal impairment or immunocompromised
- May consider full-thickness skin biopsy if in doubt
- Poor prognosis for those with IE requiring ICU care
- Early appropriate antibiotics for IE to minimize neurological complications
- ?Early cardiac surgery if indicated

Questions?

THANK YOU