An approach to Inflammatory arthritis

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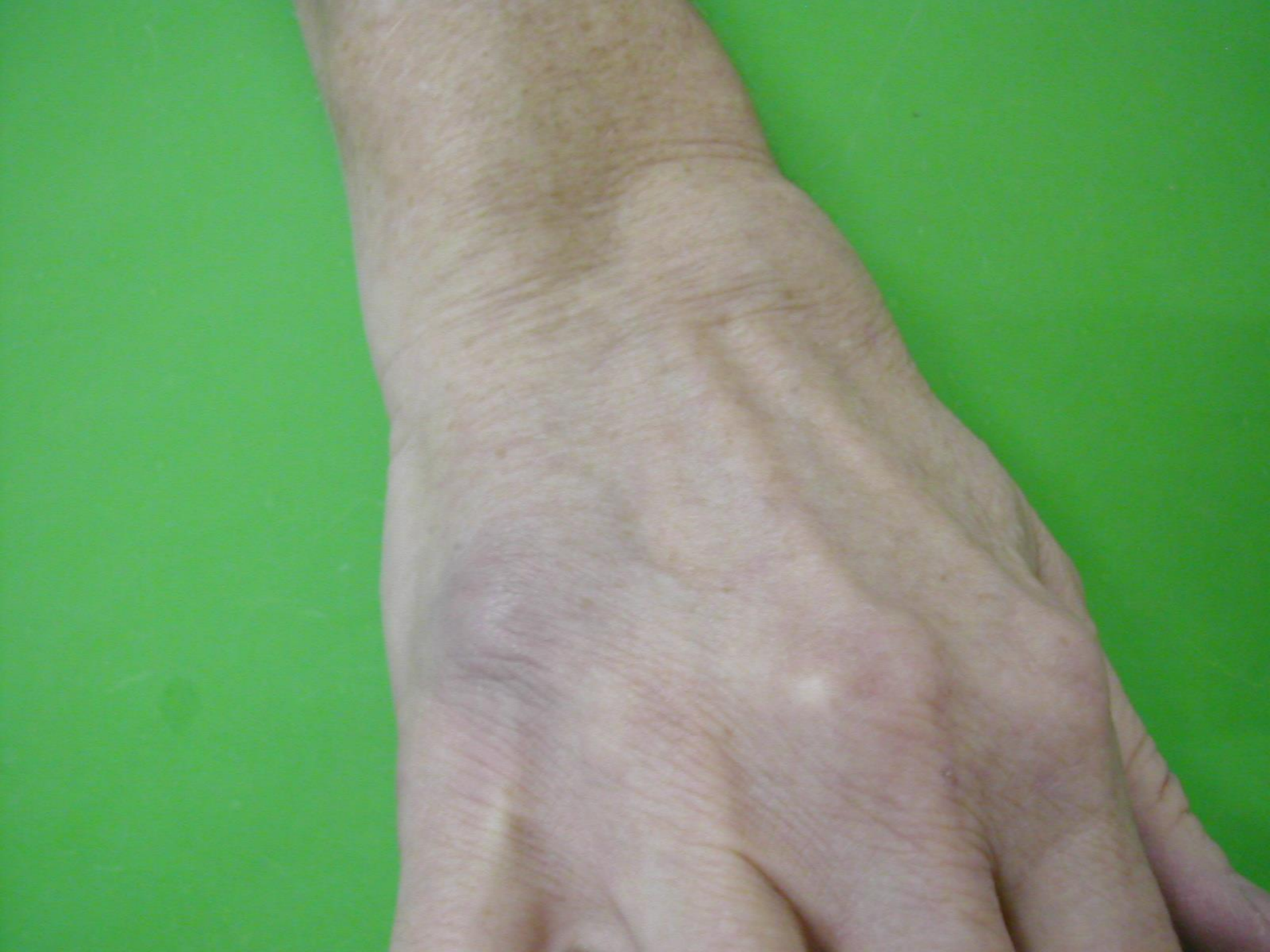
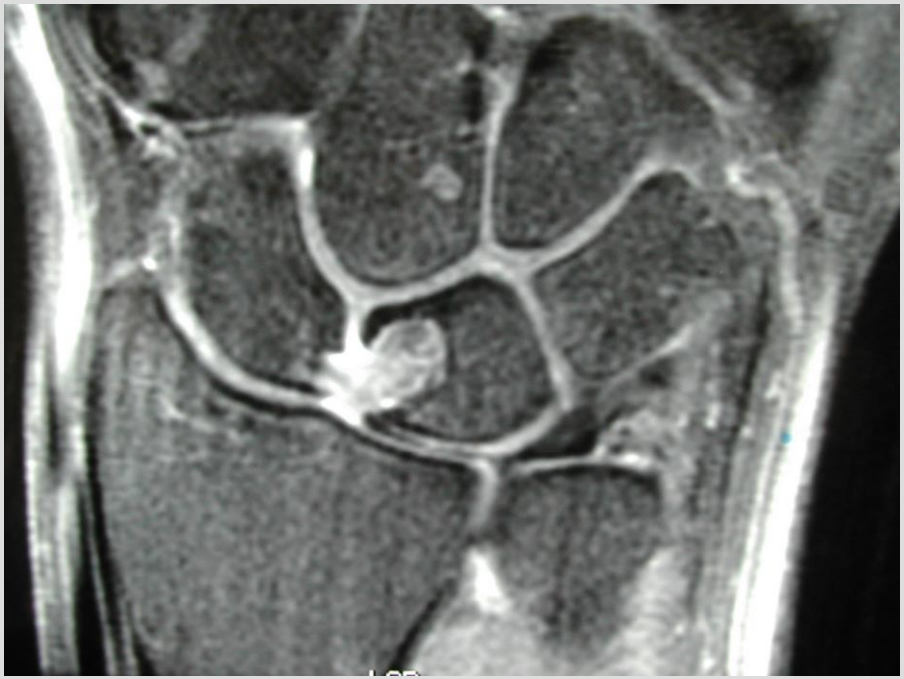
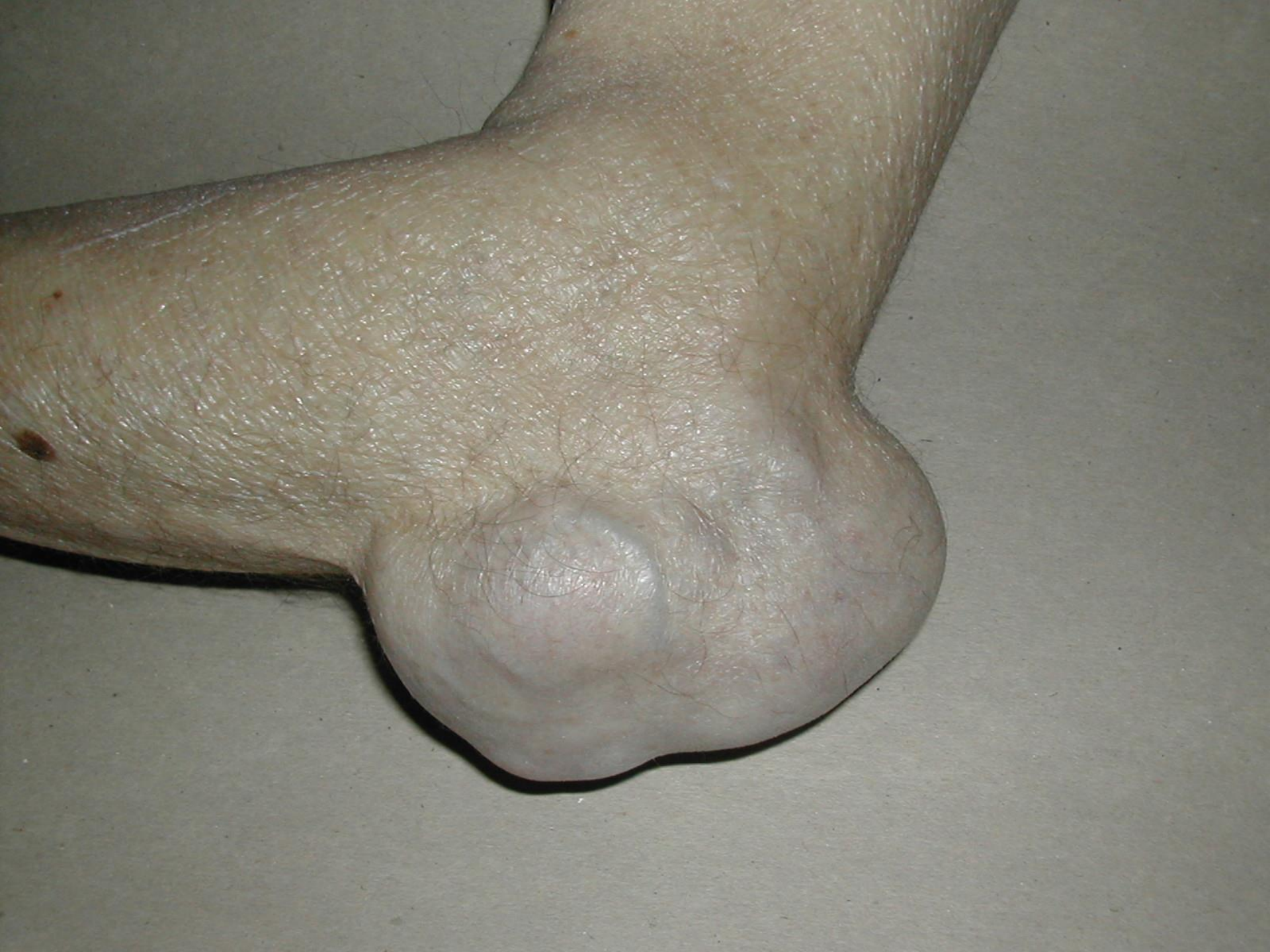
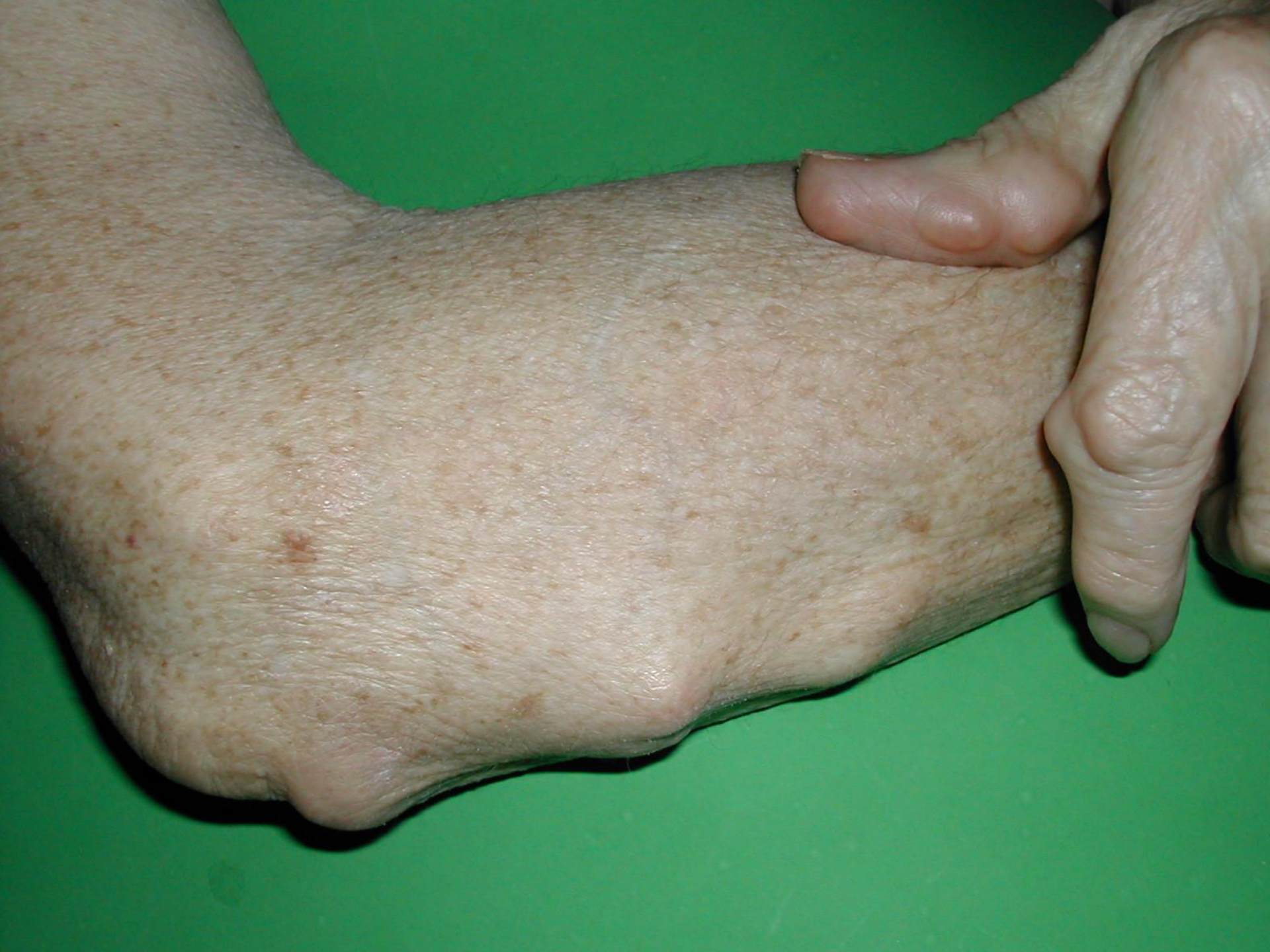
Western Health Rheumatology is an APLAR certified Centre of Excellence

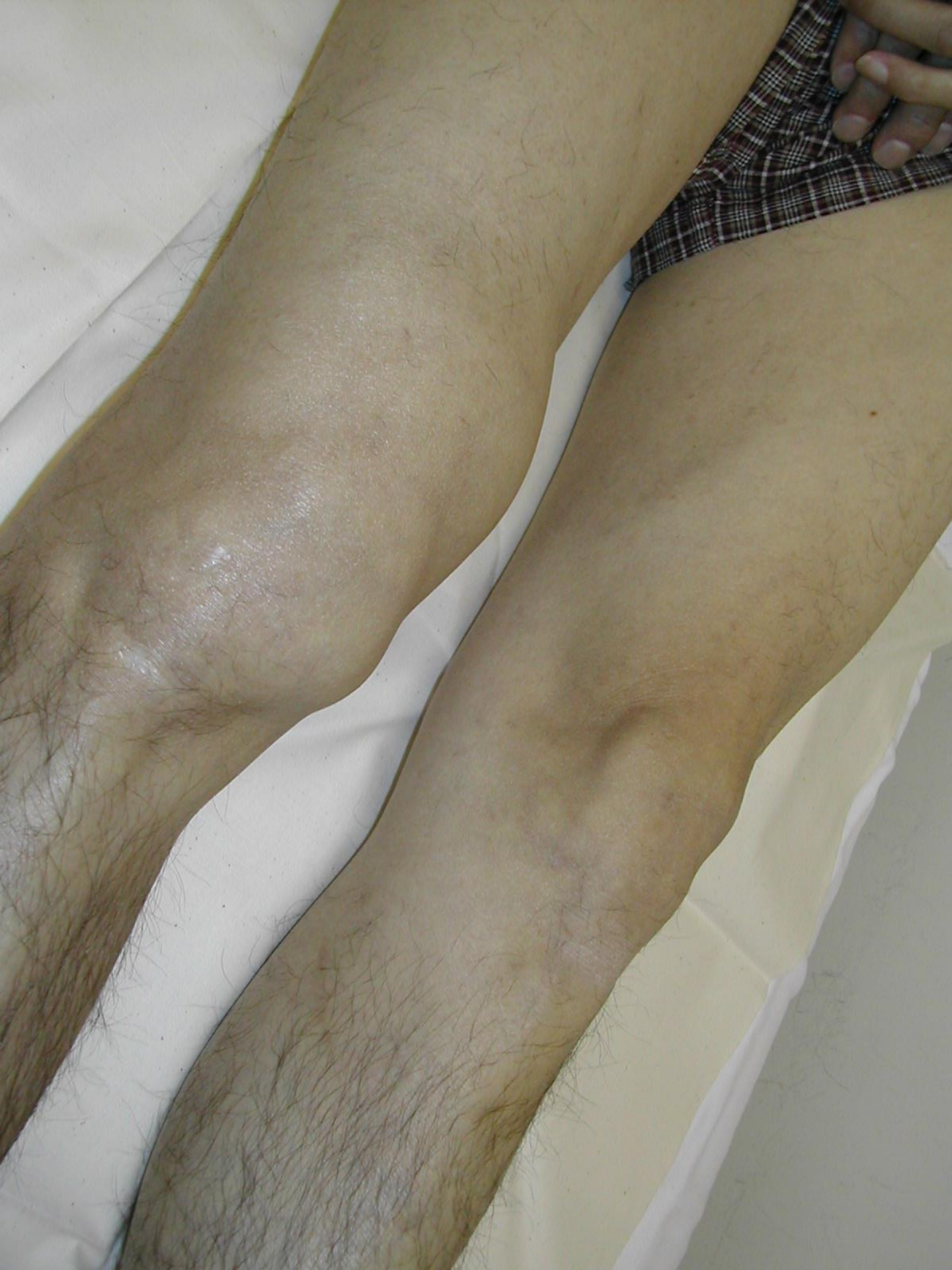


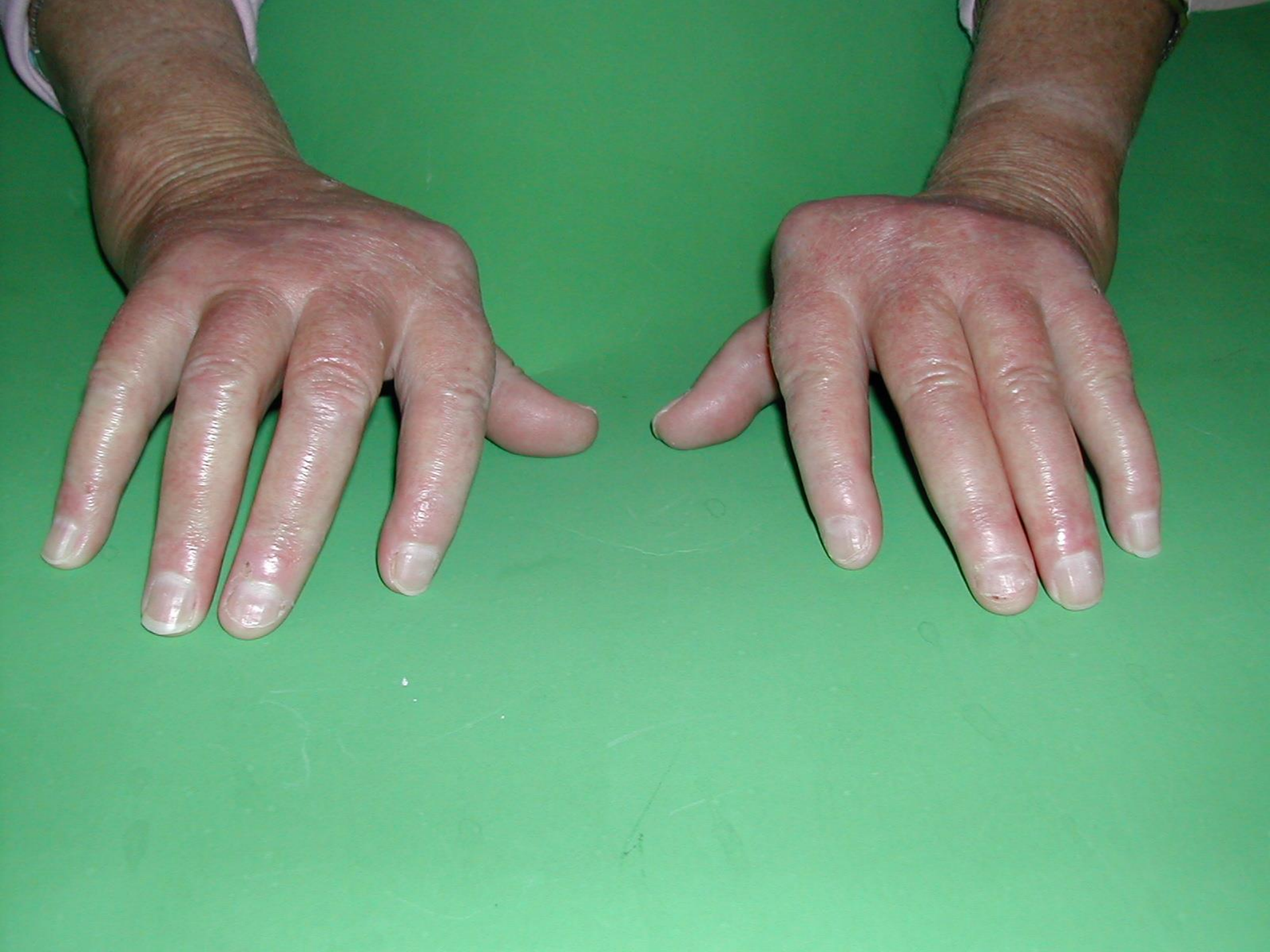
RA wrist – x-ray and MRI

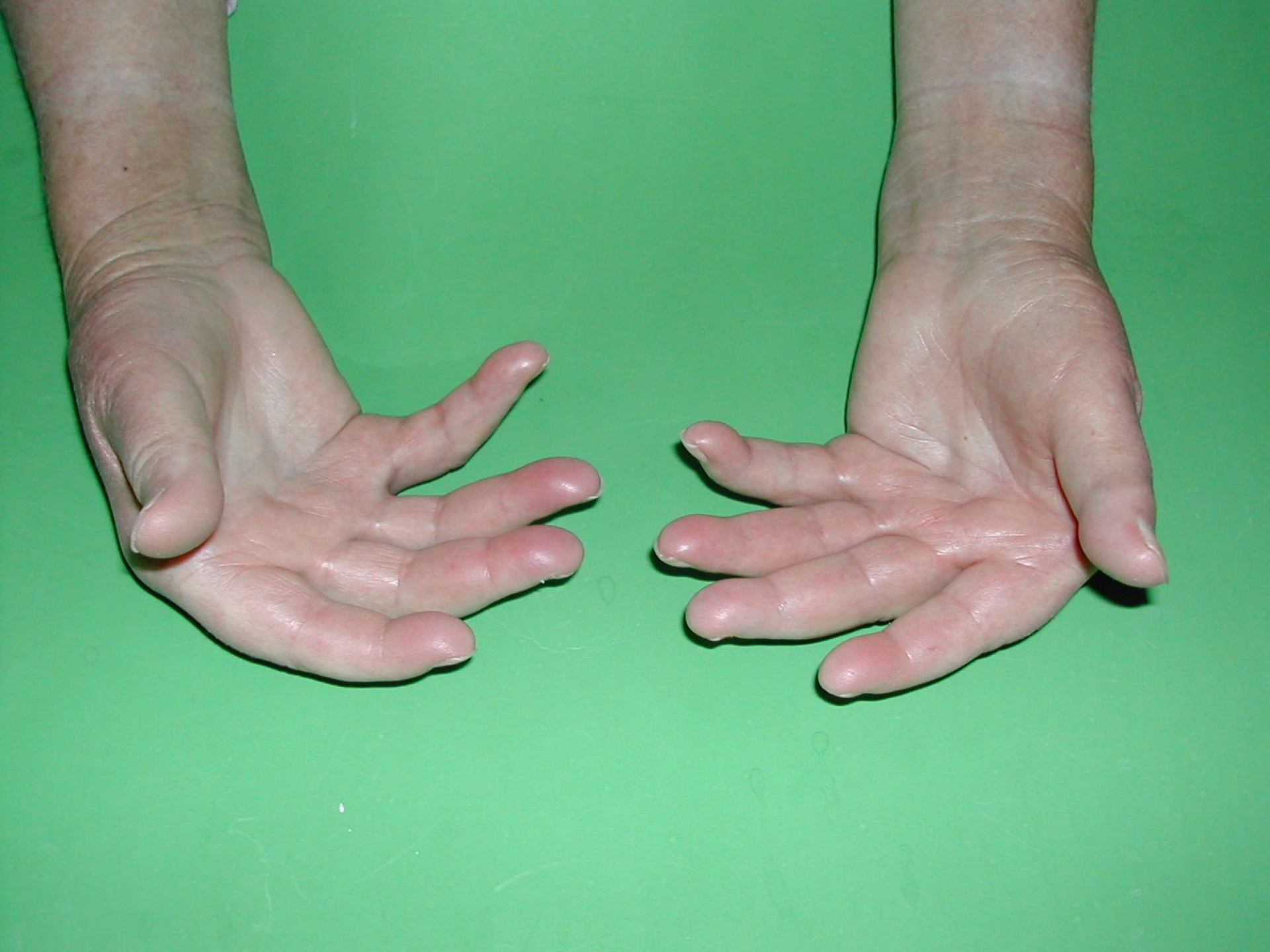


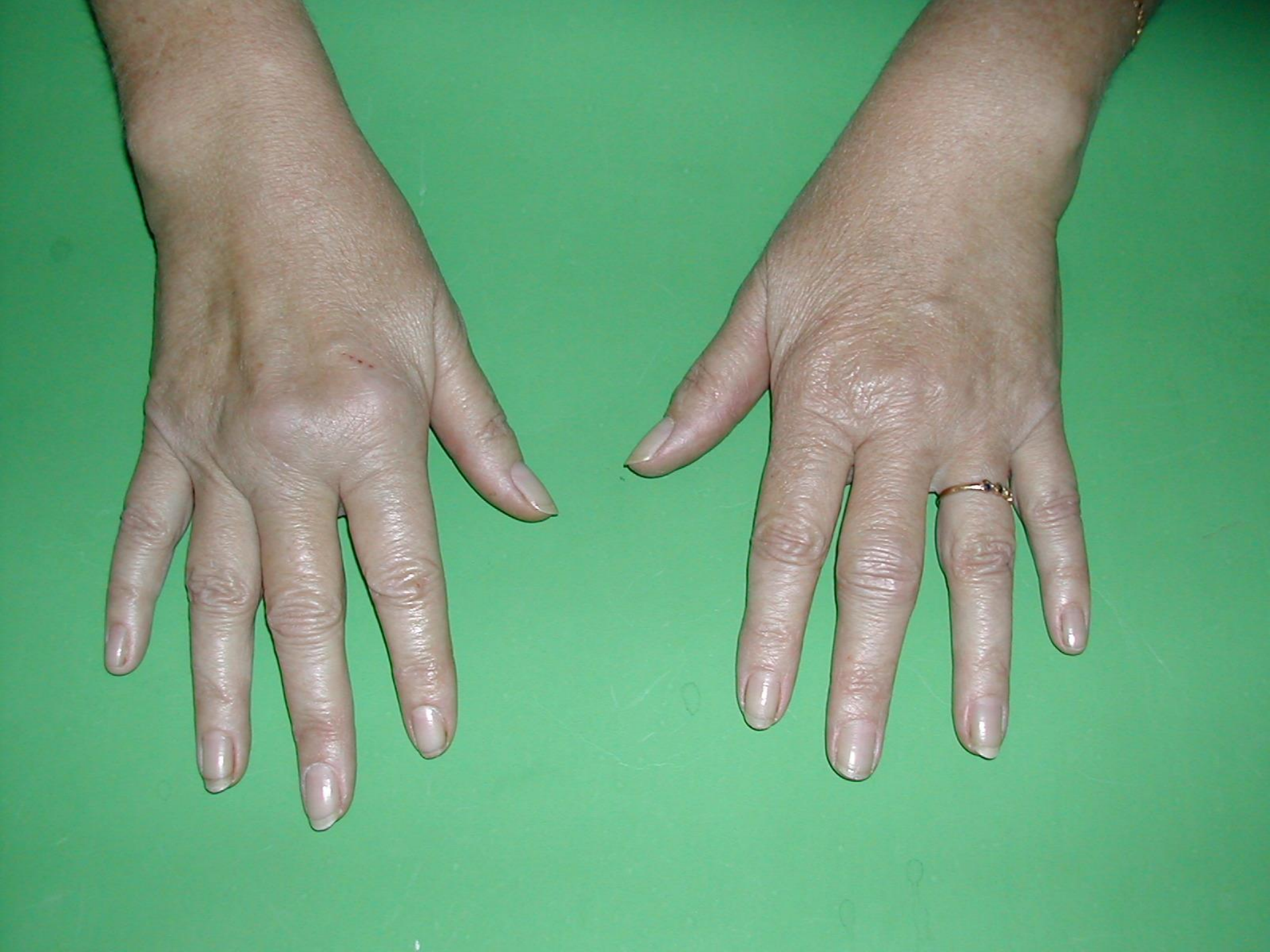


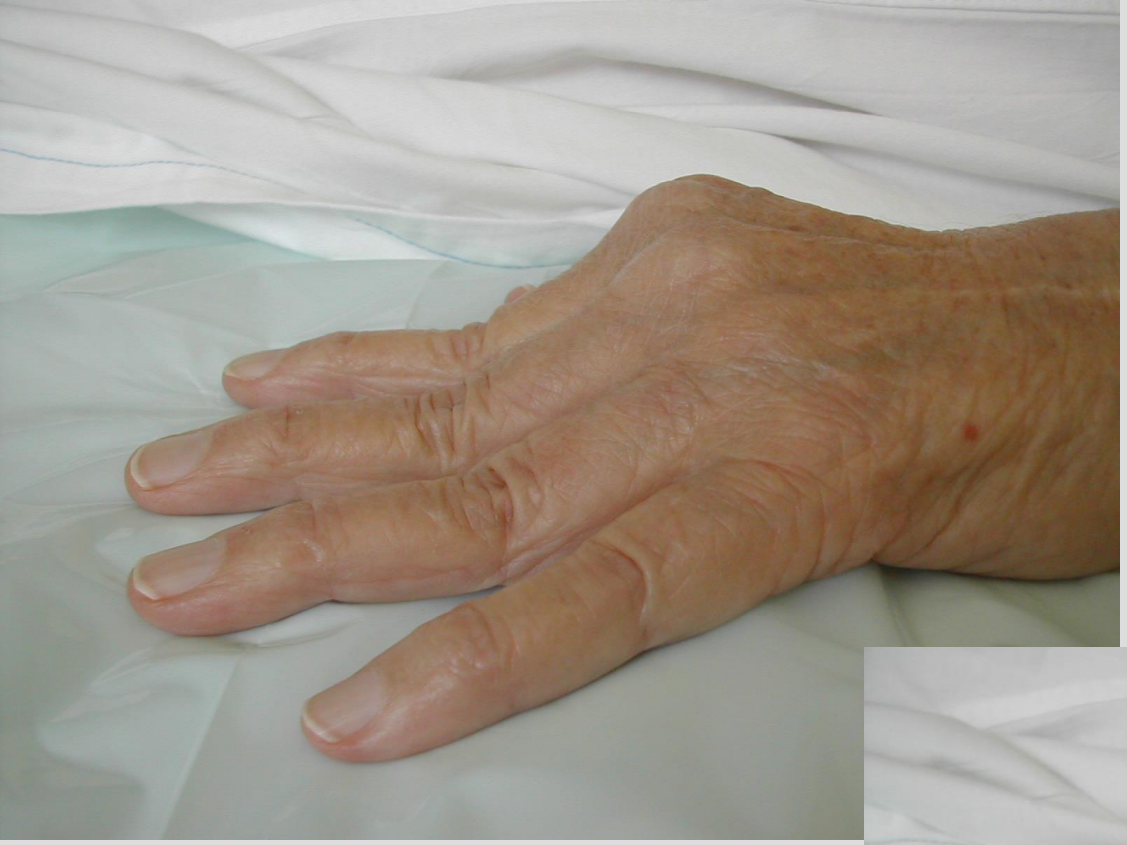




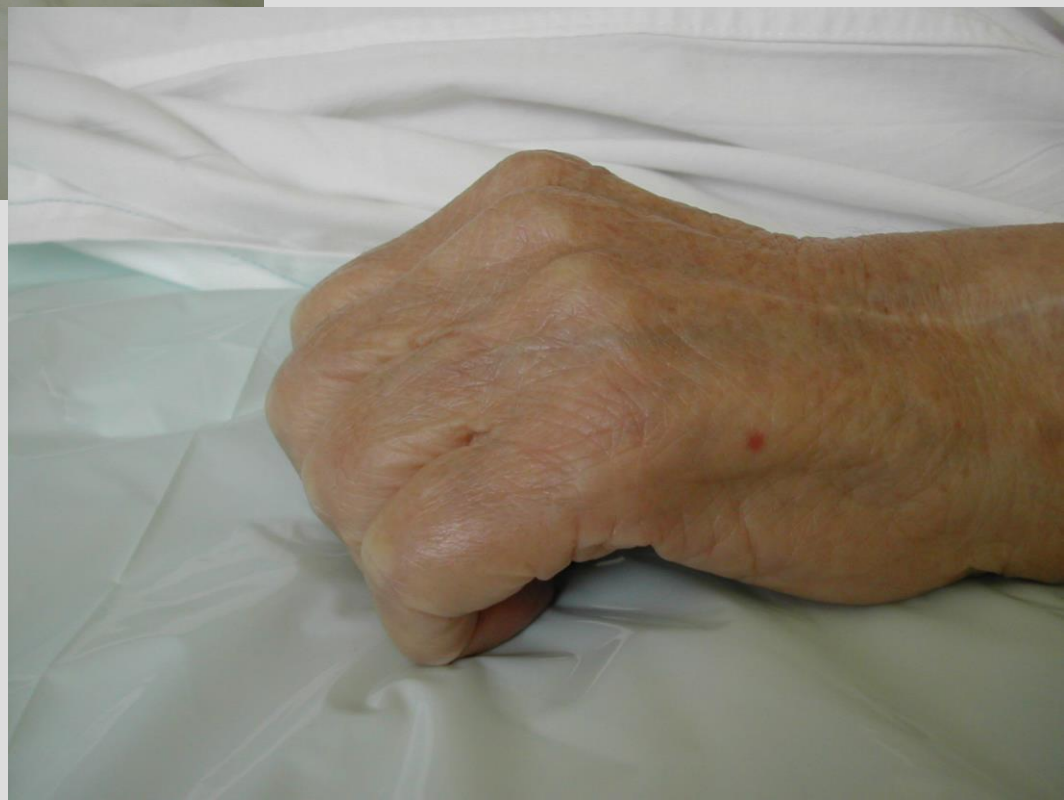








Swan-neck deformity, before & after a clench



DMARDs

- **Disease-modifying antirheumatic drugs (DMARDs)**
  - SAARDs – Slow acting anti-rheumatic drugs
- Slow down disease progression and allow reduction in corticosteroid dose.
- First used in rheumatoid arthritis (hence their name)
  - Crohn's disease, SLE, idiopathic thrombocytopenic purpura.

DMARDs in RA
General Points

- Slow acting (6-8 weeks)
- Marked variability in the response from patient to patient.
- High rate of discontinuation because of either drug toxicity or lack of long-term efficacy.
- Non-specific mechanism of action
  - often unclear

DMARDS
Current Use in RA

- Remain preferred initial treatment for RA
- Introduced early as monotherapy or initial combination therapy
- Effective DMARDs are continued indefinitely
  - Interruption results in disease flares and irreversible joint damage
- Delaying DMARD therapy:
  - reduced likelihood of patients achieving disease remission
    - *Mottonen T et al, Arthritis Rheum 2002*
  - associated with more rapid radiological progression and worse functional outcomes
    - *Egsmose et al, J Rheumatol 1995*

HOW EFFECTIVE ARE THEY?

AMERICAN COLLEGE RHEUMATOLOGY (ACR) criteria:

- **Improvement in tender or swollen joint counts** and improvement in 3/5:
  - **acute phase reactant**
  - **patient assessment**
  - **physician assessment**
  - **pain scale**
  - **disability/functional questionnaire**

ACR 20/50/70 (20%, 50%, 70% improvement)

METHOTREXATE

- Most frequently used DMARD for rheumatoid arthritis.
- Little conclusive evidence of sustained benefit from any combination of DMARDs unless methotrexate is included in the regimen.
- Anti-tumor necrosis factor alpha (anti-TNF) agents are more effective when combined with MTX.
- May provide survival benefit, largely by reducing cardiovascular mortality.
  - 1240 patients with rheumatoid arthritis
    - mortality hazard ratio for methotrexate use compared with no methotrexate use was 0.4 (95% CI 0.2-0.8).
    - The hazard ratio of methotrexate use for cardiovascular death was 0.3 (0.2-0.7), whereas that for non-cardiovascular deaths was 0.6 (0.2-1.2).
    - Other conventional disease-modifying antirheumatic drugs did not have a significant effect on mortality.

  Choi HK; Lancet 2002 Apr 6;359(9313):1173-7.

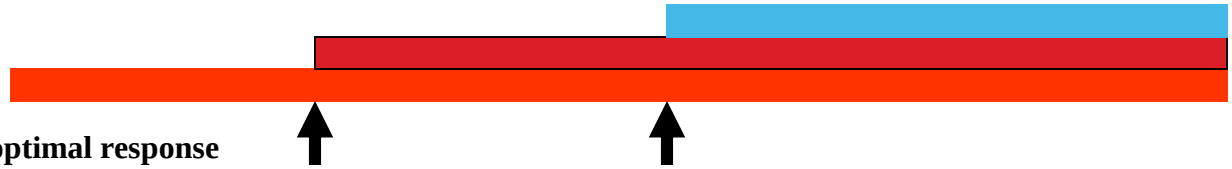
COMBINATION DMARDS

- Generally well tolerated and associated with no significant increase in rate of adverse events compared to monotherapy
- Different combinations and strategies use (see next slides)
- No consensus regarding the most effective strategy or combination of DMARDs in RA
  - Step up combination most commonly practiced to avoid overtreating patients but no evidence it is better

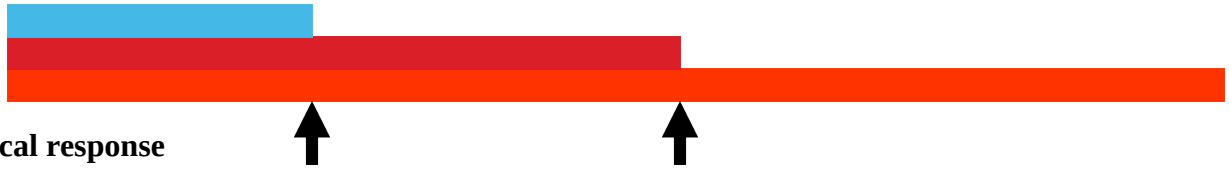
Dale et al, Nature Rheumatology 2007

COMBINATION DMARD STRATEGIES

- **Step-up** (sequential addition of new DMARD)



- **Step down** (initial use of multiple DMARDs with subseqeunt withdrawal once remission is achieved)



- **Parallel approach** (simultaneous use of 2 or more DMARDs)

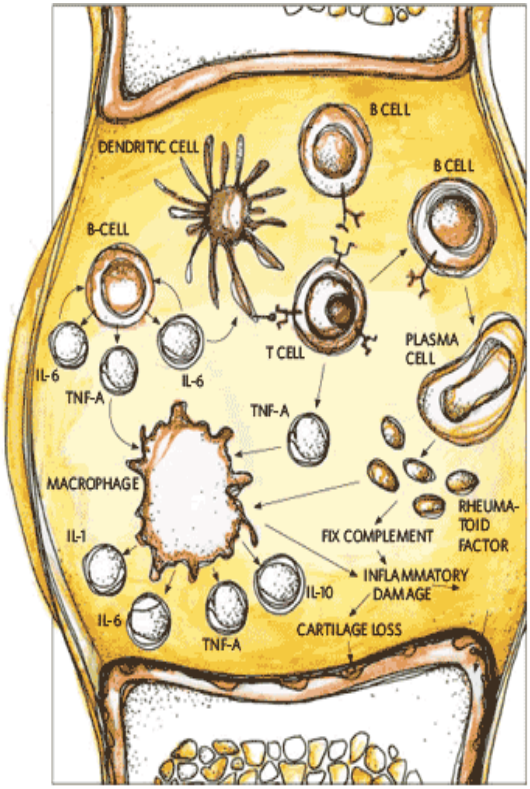
BIOLOGICAL DMARDS

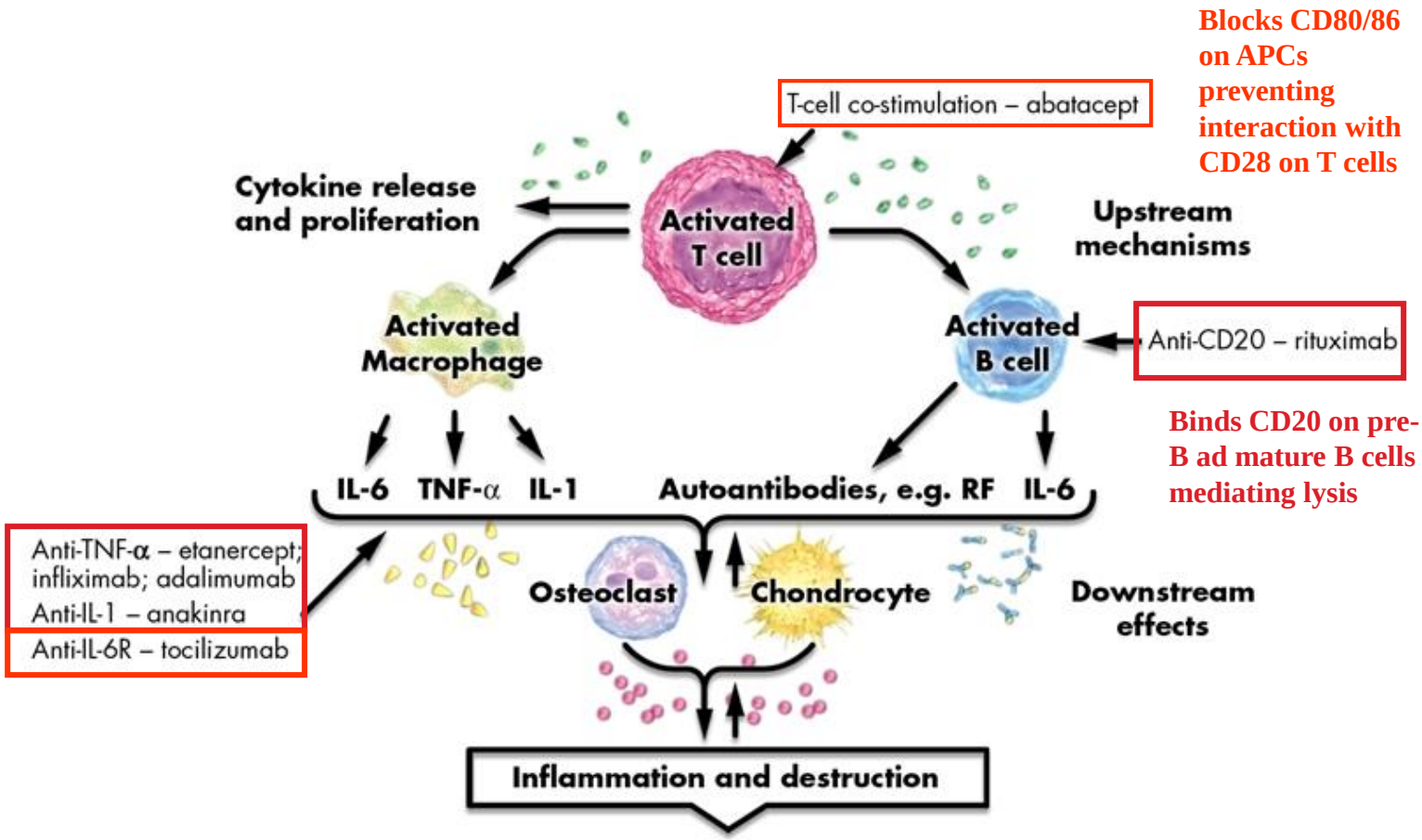
- **Anti-cytokine therapy**
  - Anti-TNF (PBS listed 2003)
    - Infliximab/ (human murine chimeric monoclonal antibody)
    - Etanercept/ Embrel (fully human TNF receptor)
    - Adalimumab/ Humira (recombinant human monoclonal antibody)

    Golimumab (pegly.infliximab), certolizumab (Cimzia)

    Biosimilars
  - Anti-IL-1 Anakinra (ceased to be used)
  - Anti IL-6 Tocilixumab
  - Anti IL-17A Secukinimab
  - Anti IL-23 Uztekinimab
- **B cell depleting antibody** (anti-CD 20)
  - Rituximab/ mabthera (PBS listed 2007)
- **Co-stimulation blocking - T & B cell** (CTLA4-Ig)
  - Abatacept (TGA approved 2007)
  - Small molecules Jak Inhibitor Toficitinib, baracitinib

Others in pipeline mavrilimub (anti GMCSF) etc





- Marc Cohen: *The Internet Journal of Rheumatology*. 2007. Volume 3 Number 1.

BIOLOGICAL DMARDS

Markedly reduce disease activity and slow erosion of joints in majority of patients with RA

- Onset usually rapid

Substantially more expensive than conventional DMARDs Around $22000 per year (price coming down to about 17 000)

Long term experience limited to the last 20 years

- Risk lymphoma in TNF blockade remains controversial/low
- Infection risk
  - TB (latent TB rate at Western Health 8%), reactivation rate 0%
  - Non-TB Hep B / Hep C, others

Biologics
Prescribing in Australia

- 1% population has RA (200, 000) (Ps A, AS)
- Estimated 2% would qualify for PBS criteria for TNF treatment
- Analysis 2003-2005
  - 27970 prescriptions (Etanercept>>>adalimumab>infliximab>anakinra)
  - By July 2005 1% RA population in Australia had been commenced on biologics, increasing to more than 10% in 2018.
  - Western Health figures 2007-2017, 15-20%
  - Compared to 14.9% Sweden in 2003 and 20% in US

Lu, Christine et al, Australia and New Zealand Health, Policy 2007

- Forecast to be A$140 million per annum initially, now just under $2 billion

The funding and use of high-cost medicines in Australia: the example of anti-rheumatic biological medicines

Christine Y Lu*, Kenneth M Williams and Richard O Day

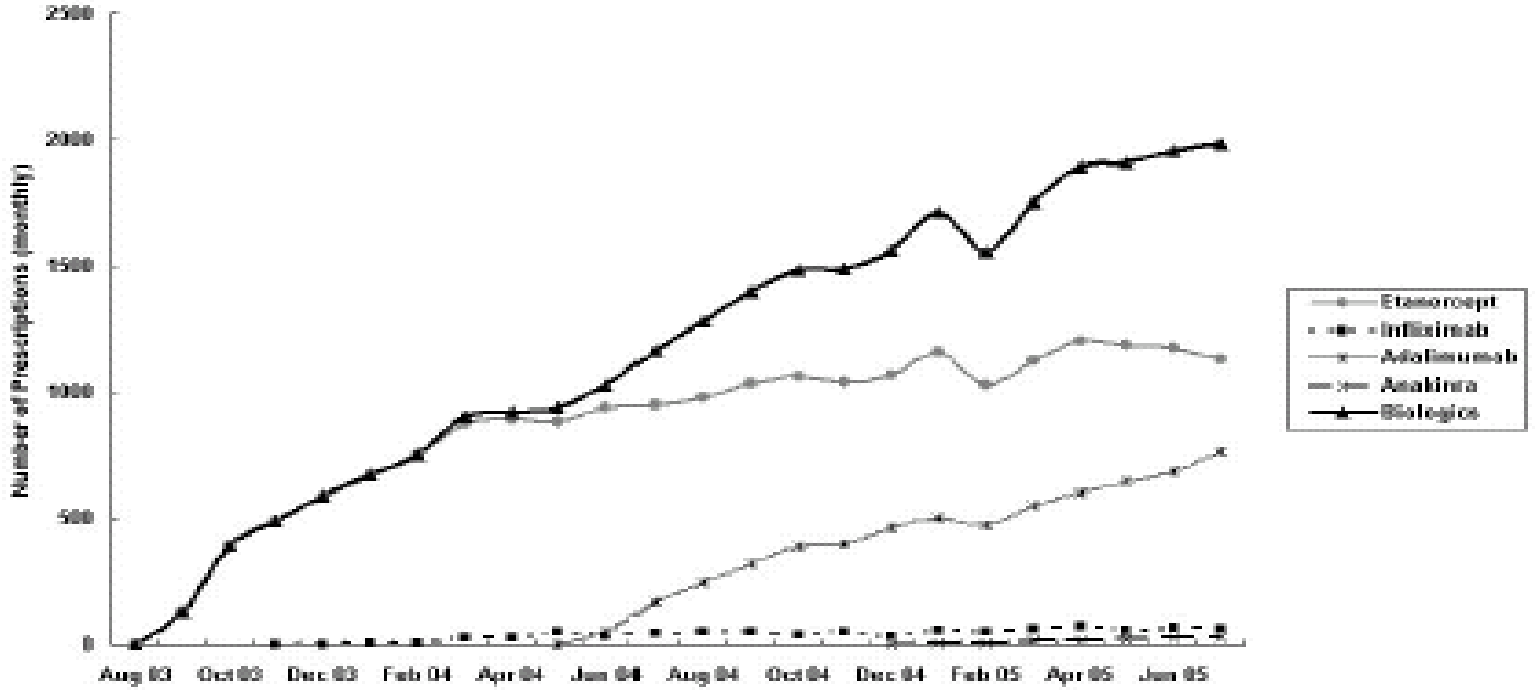
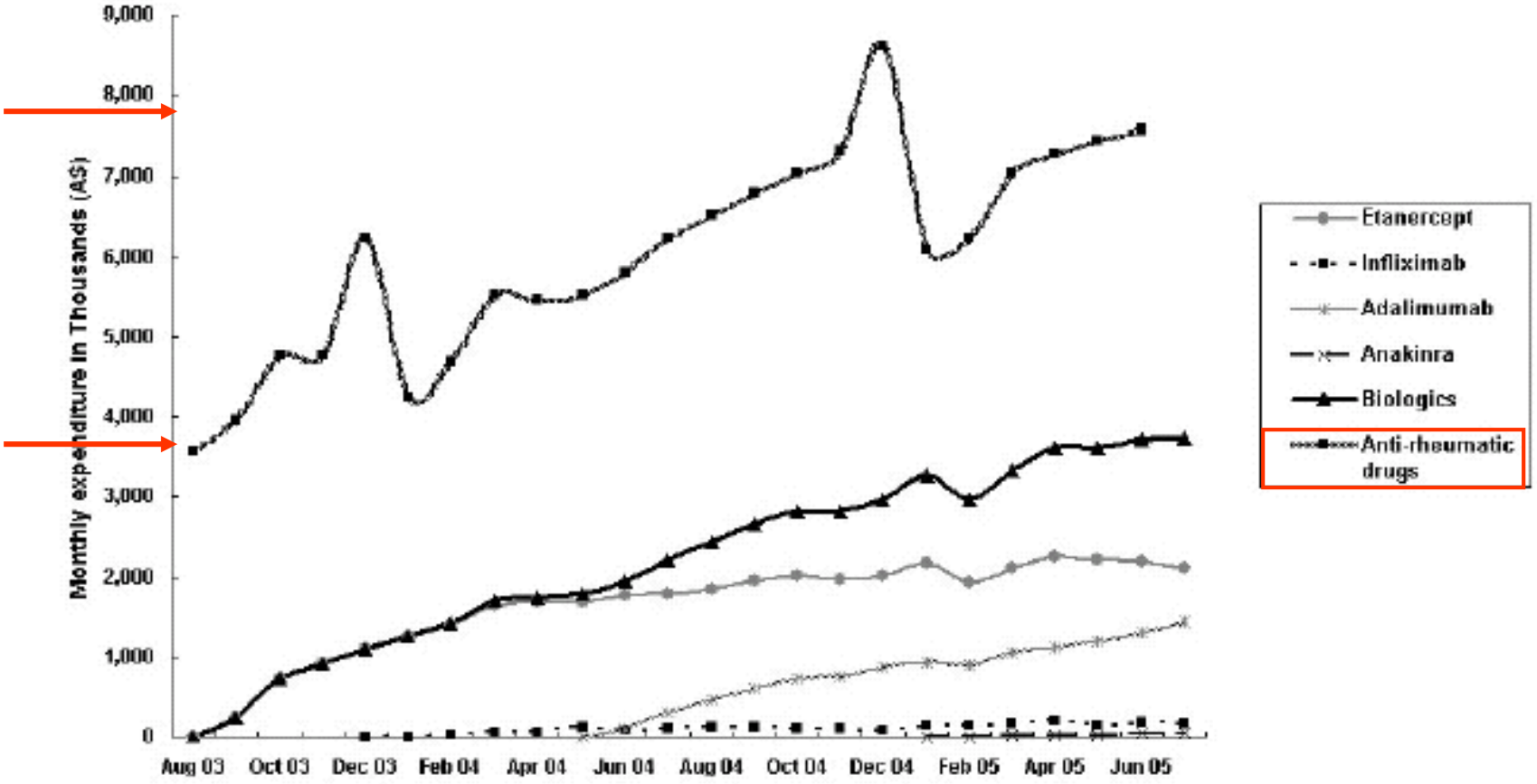


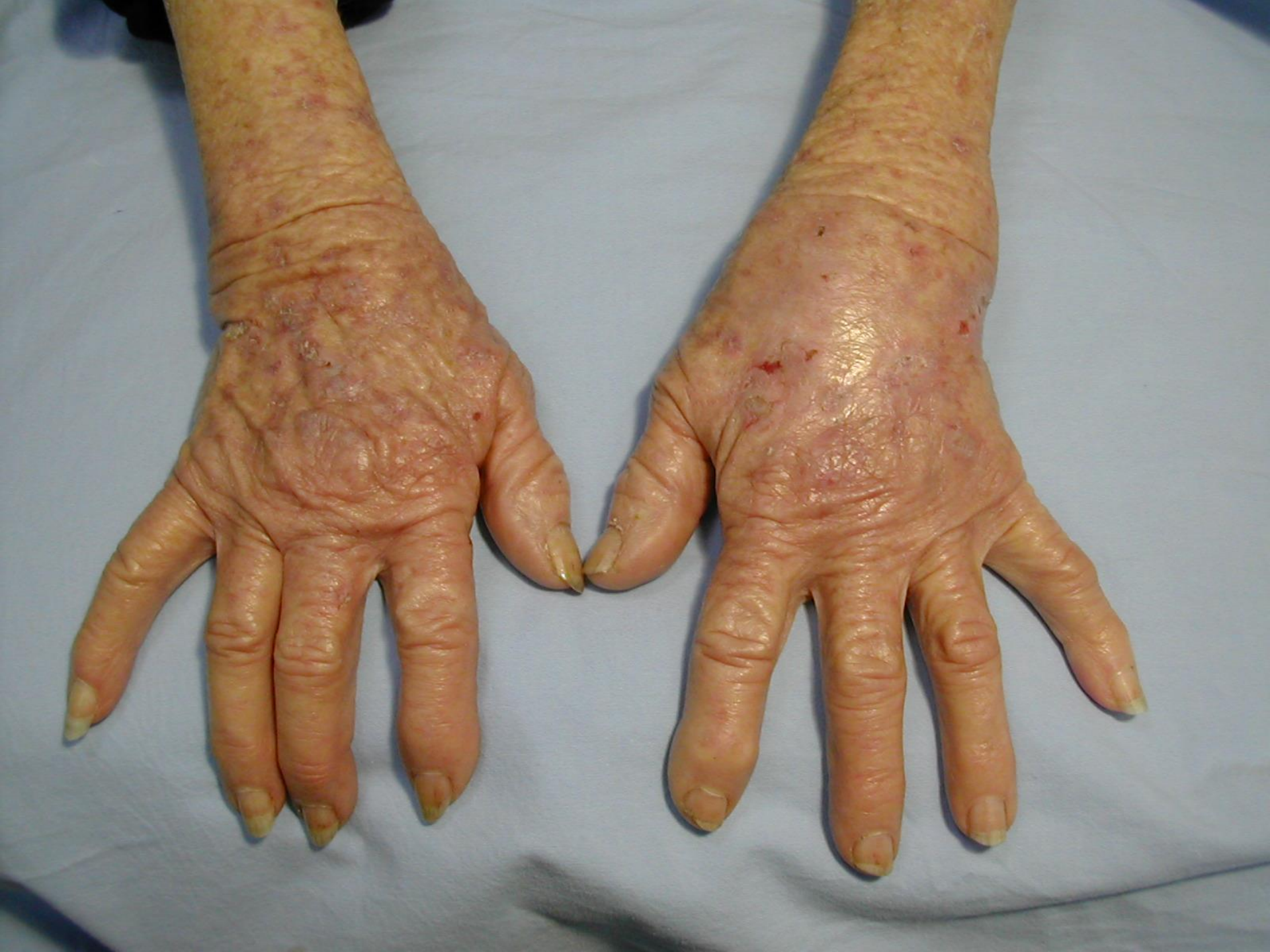
Figure 2
Monthly number of prescriptions for biologics under the PBS and RPBS, by drug, August 2003–July 2005.

Monthly expenditure PBS and RPBS 2003-2005



But

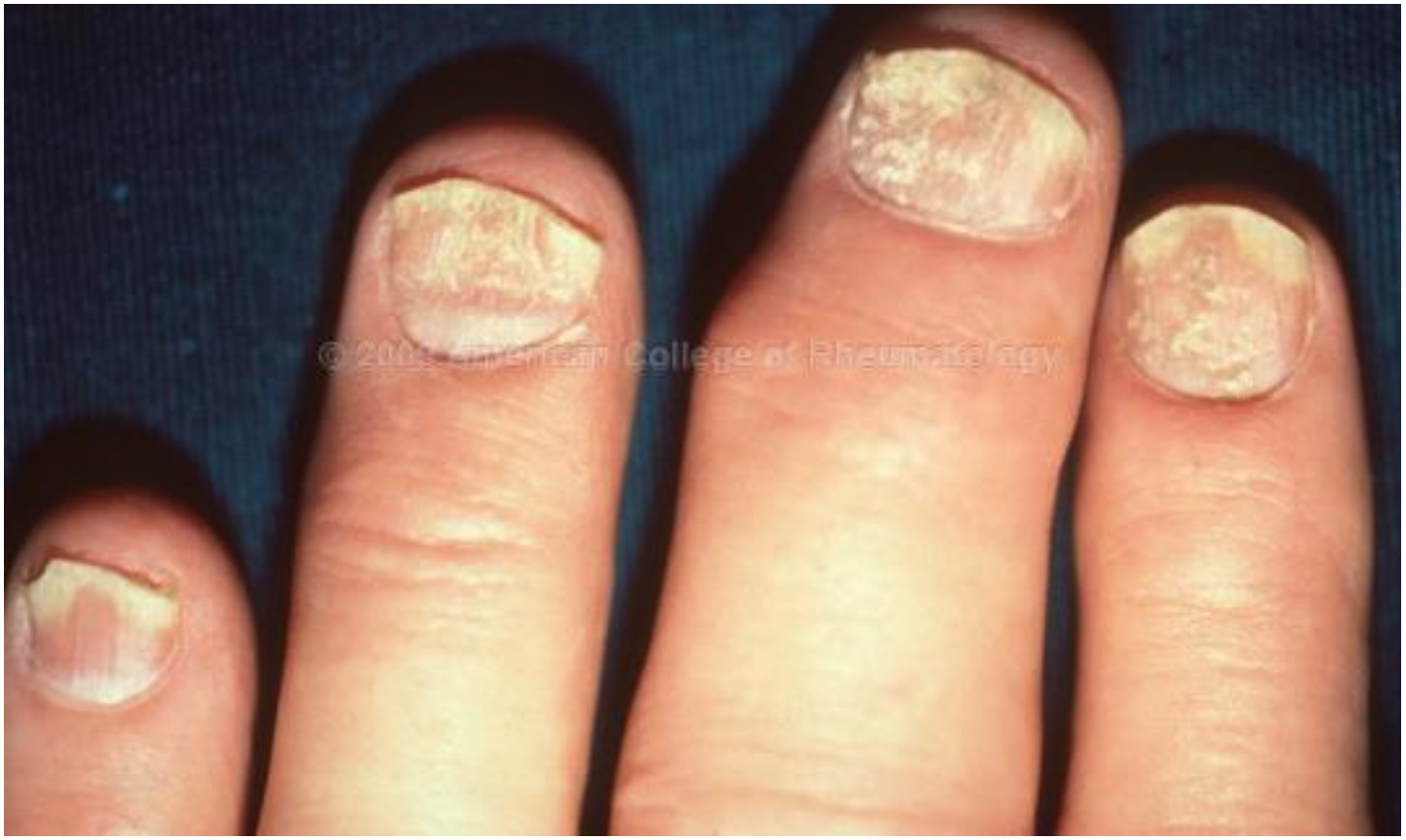
- The cost far outweighs the benefits
- Cost savings, disability, damage, quality of life
- Ability to work, pay taxes, care for others/family, self care, less dependance on system
- Lower morbidities, improved mortality, less admissions, less demand for joint replacement surgery

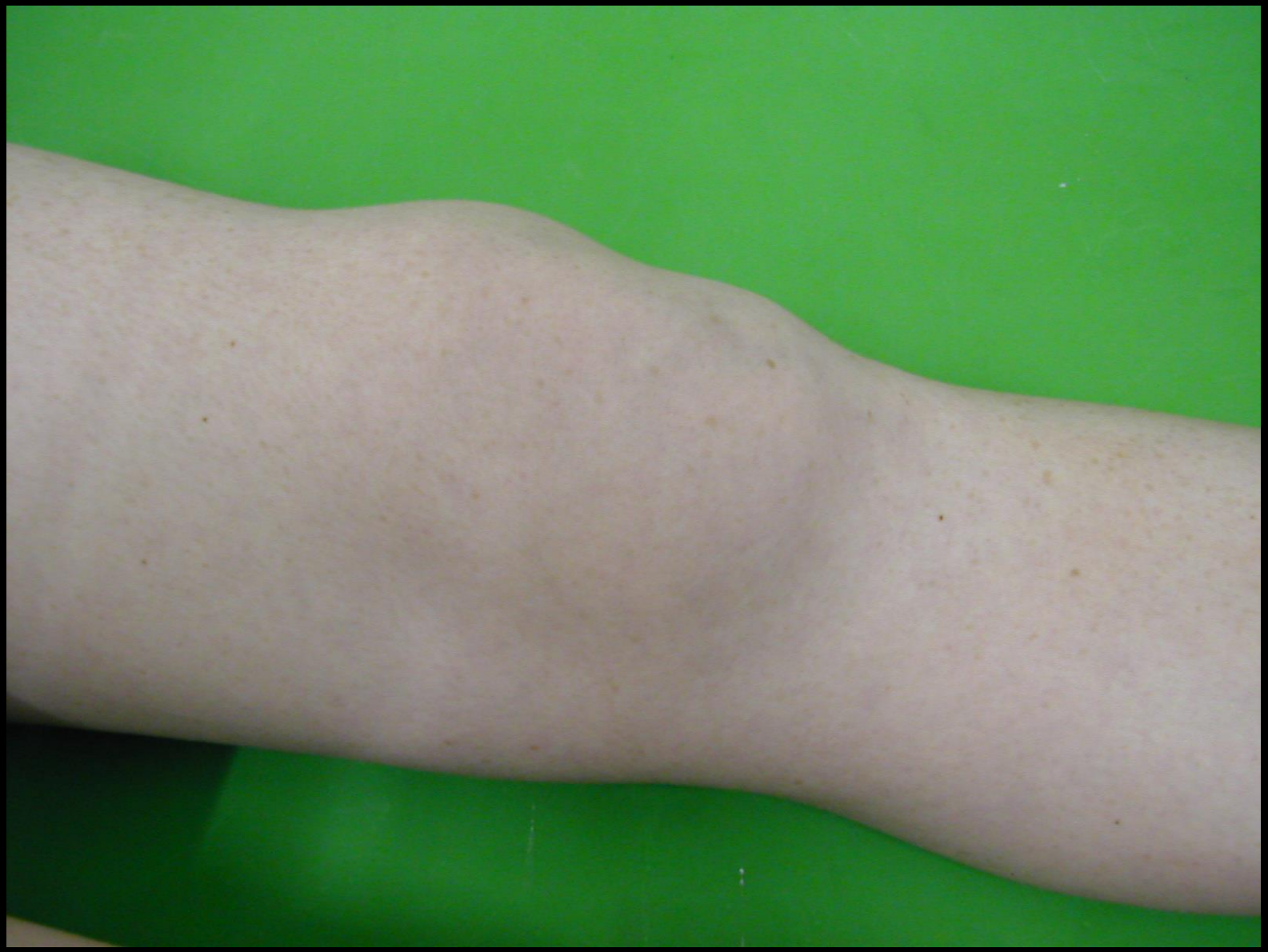


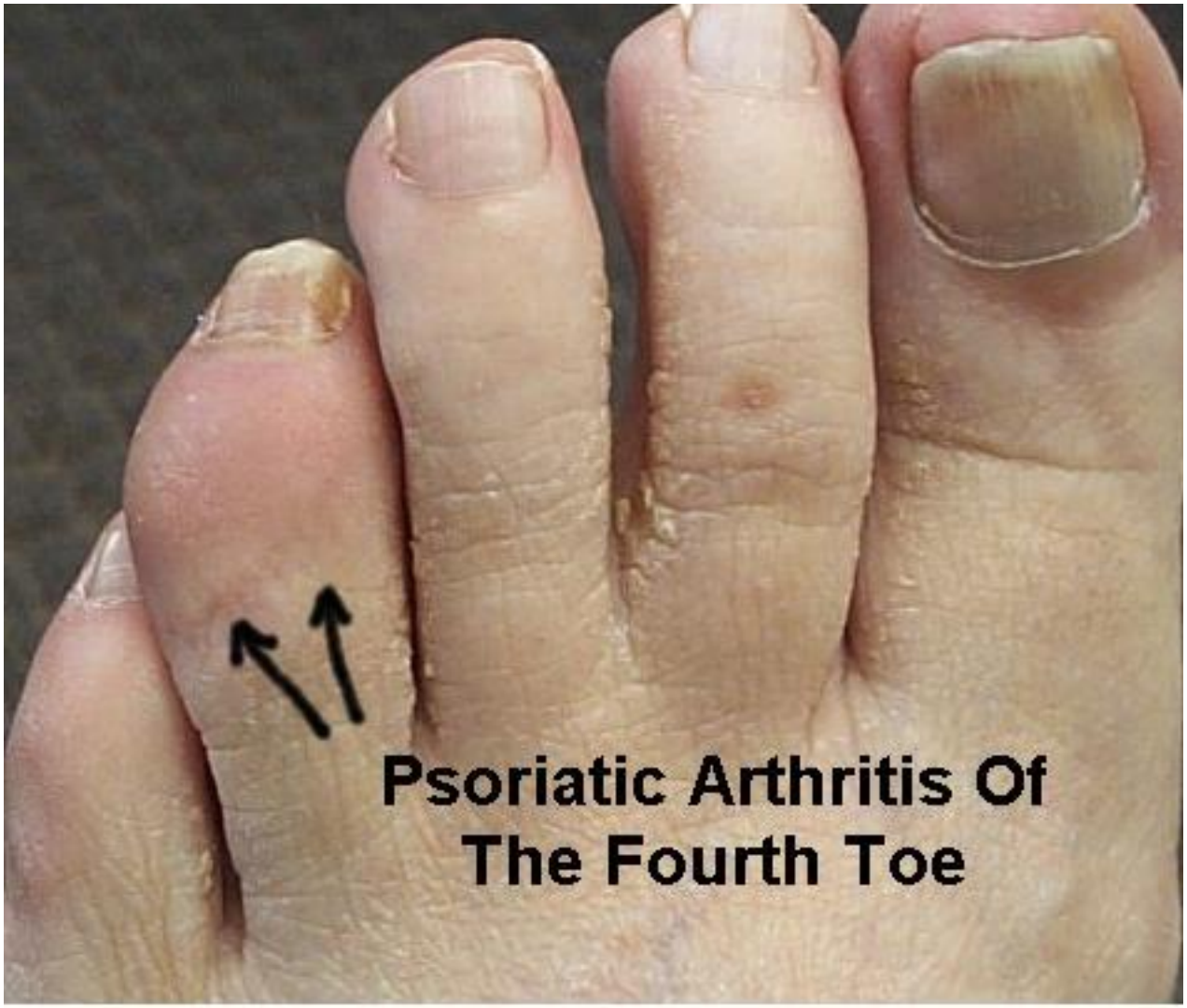
SpA

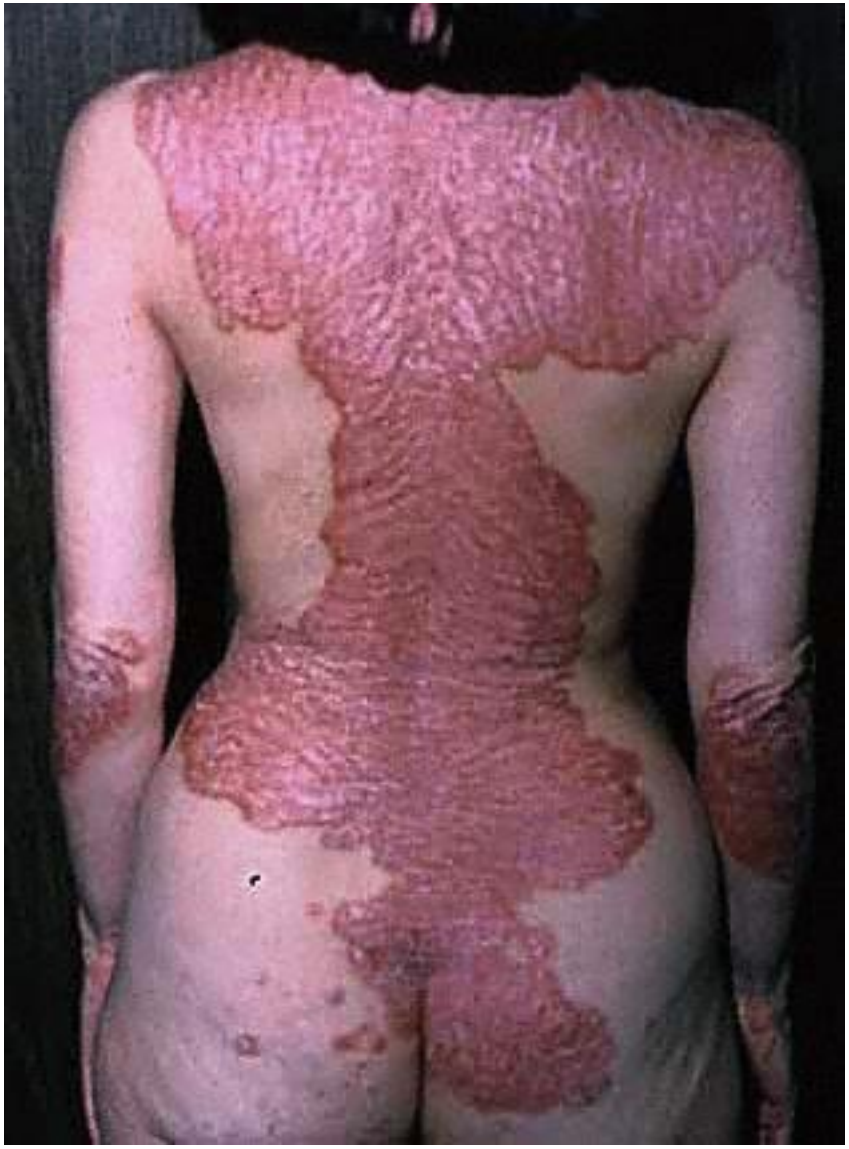
Spondyloarthropathy, Psoriatic arthropathy, seronegative arthropathy

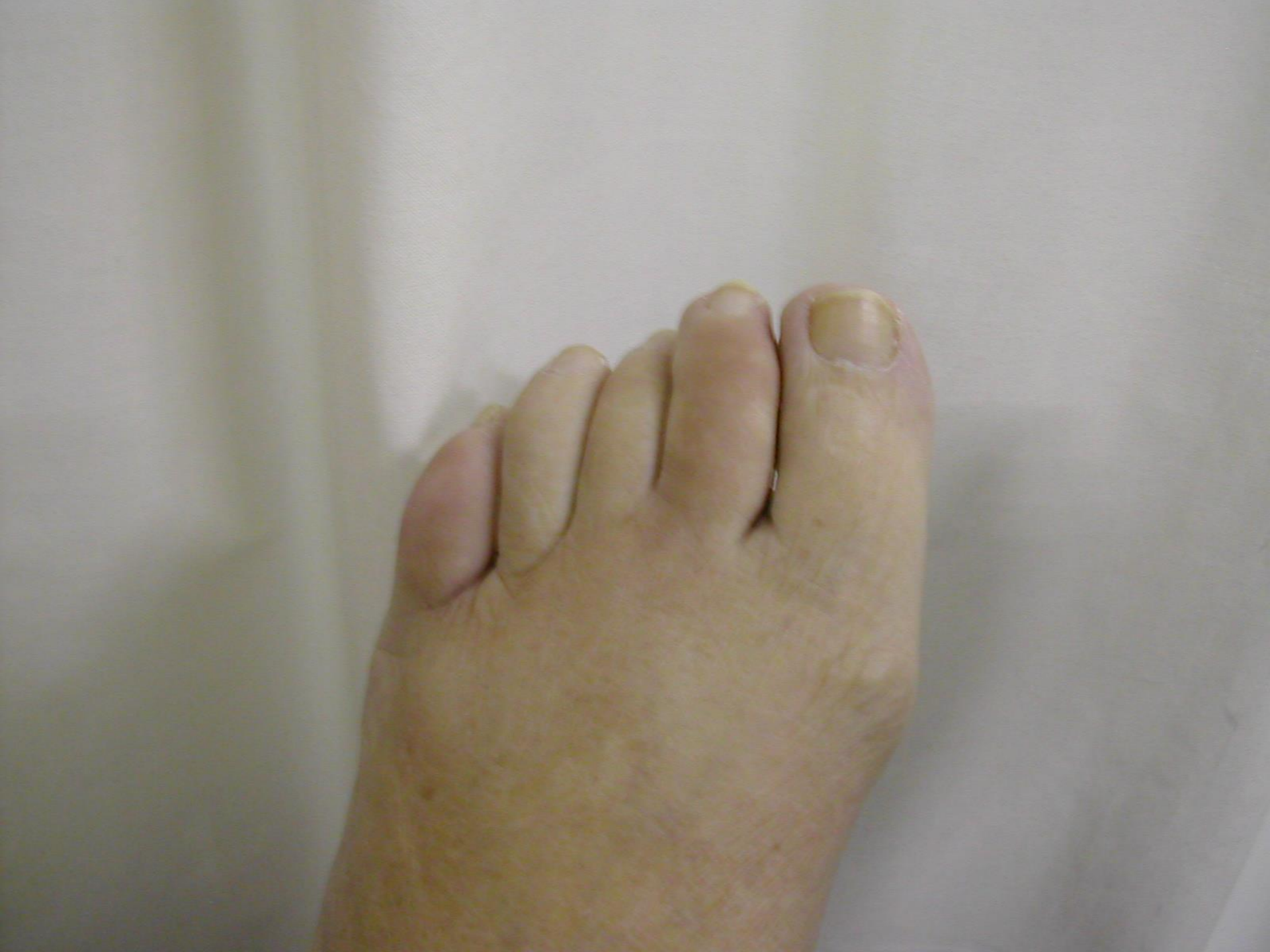
Far more common than originally thought
Can wax and wane, episodic, go into prolonged remission
Inflammatory markers may be normal
Bone scan may be misleading
Inflammation may be more enthesitis
Associated with HLA B 27 in less than 50%
Precede onset of psoriasis
often misdiagnosed as gout, polymyalgia rheumatica, fibromyalgia

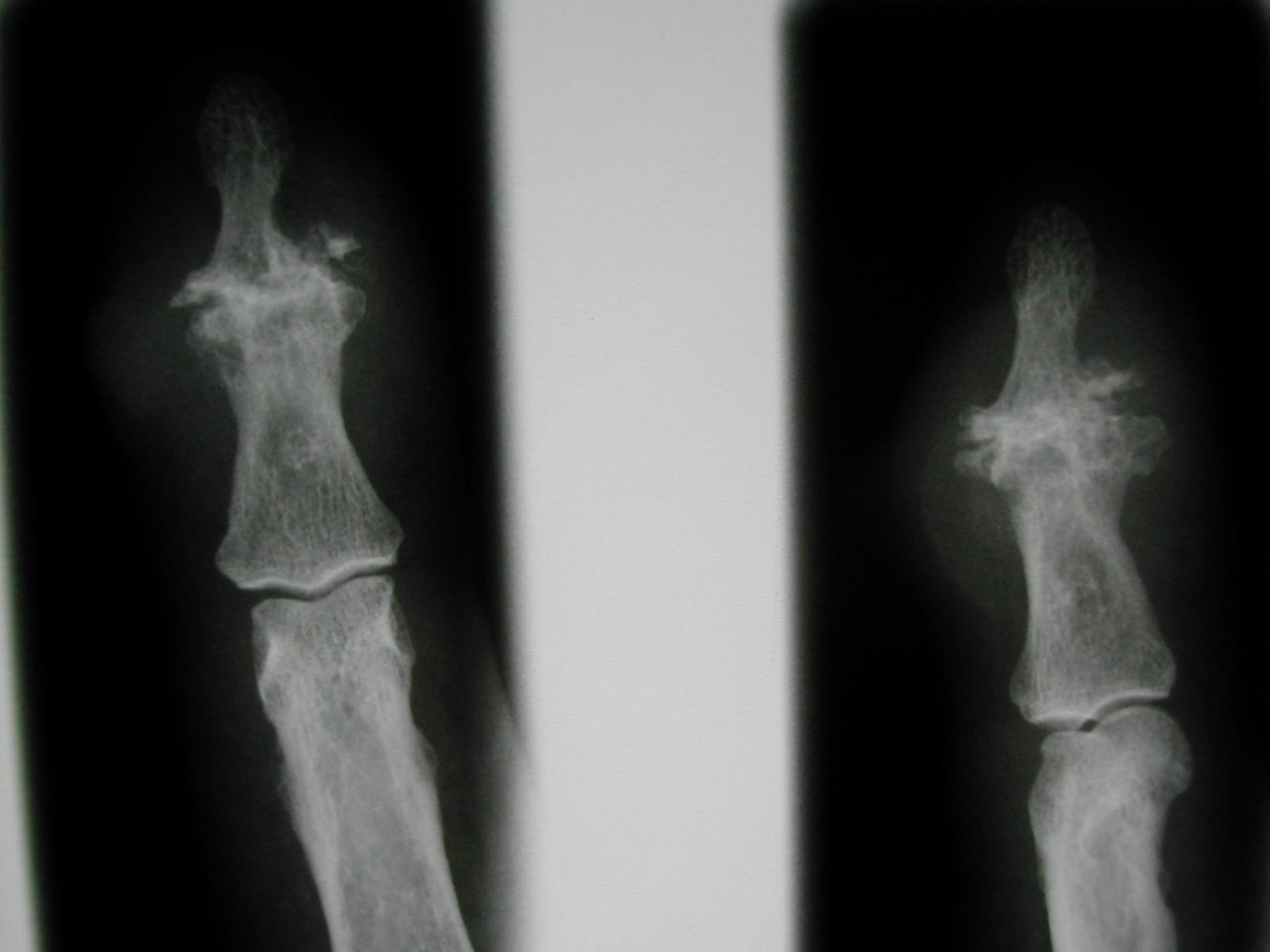


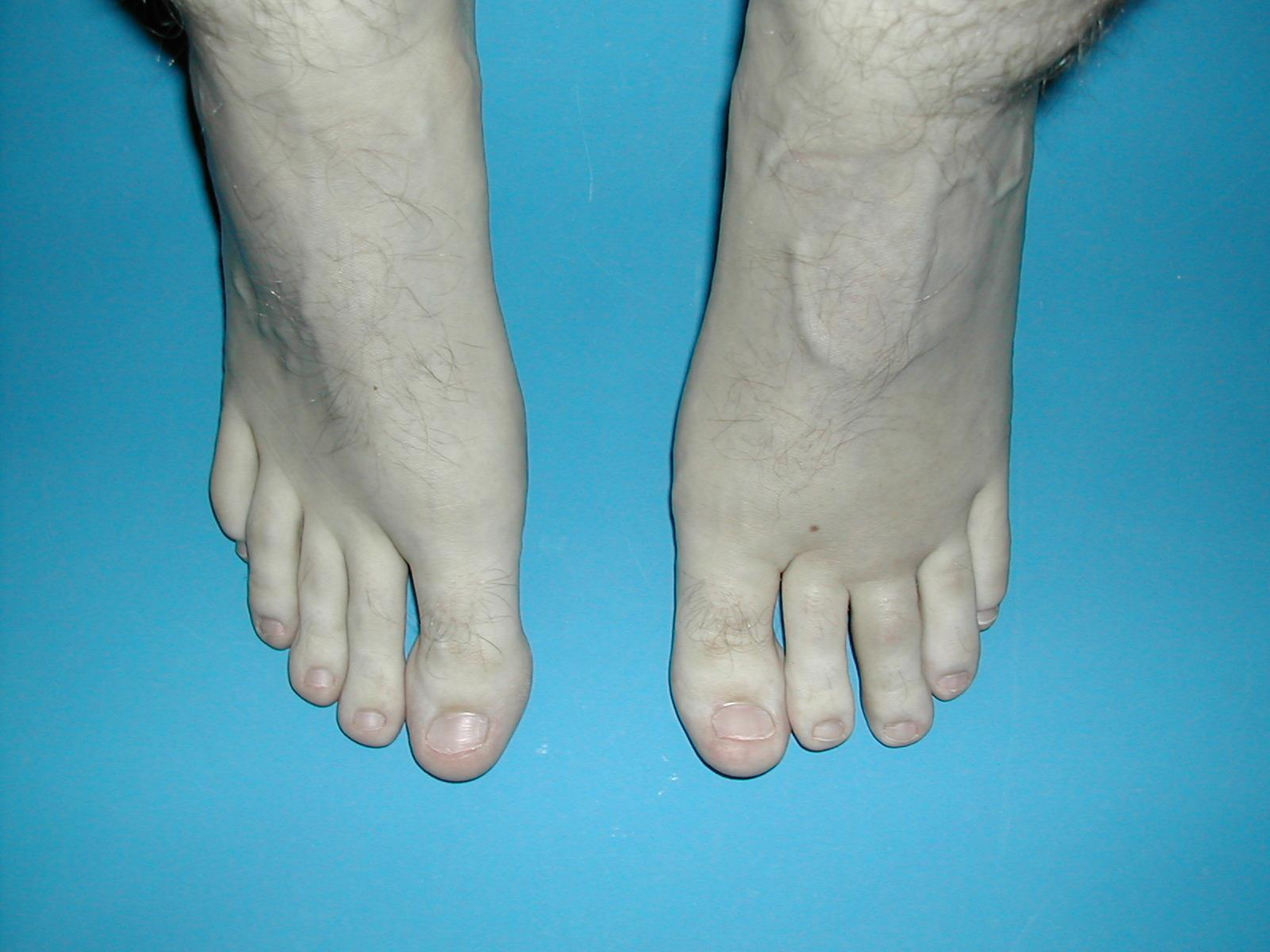


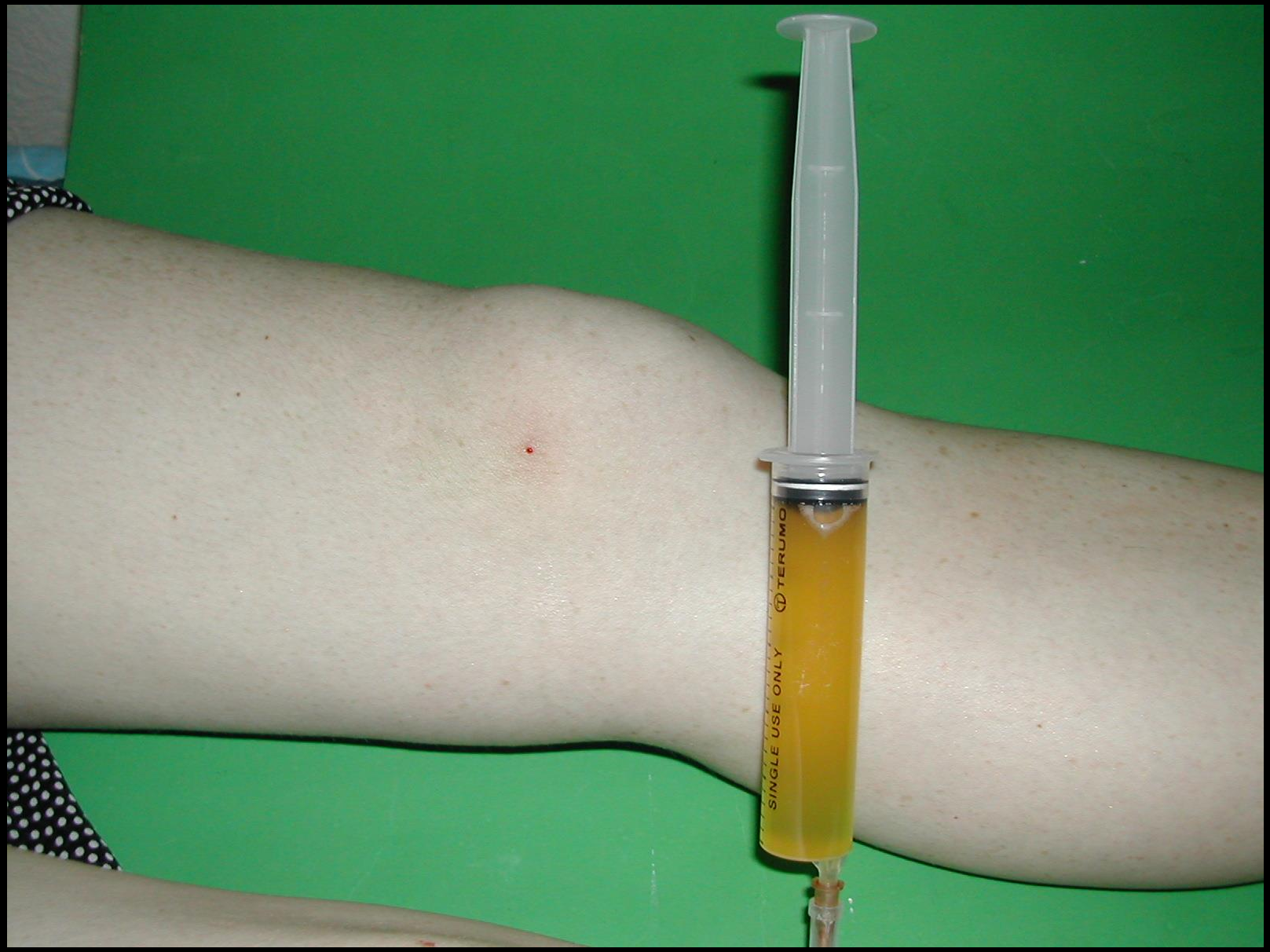

Psoriatic Arthritis Of
The Fourth Toe





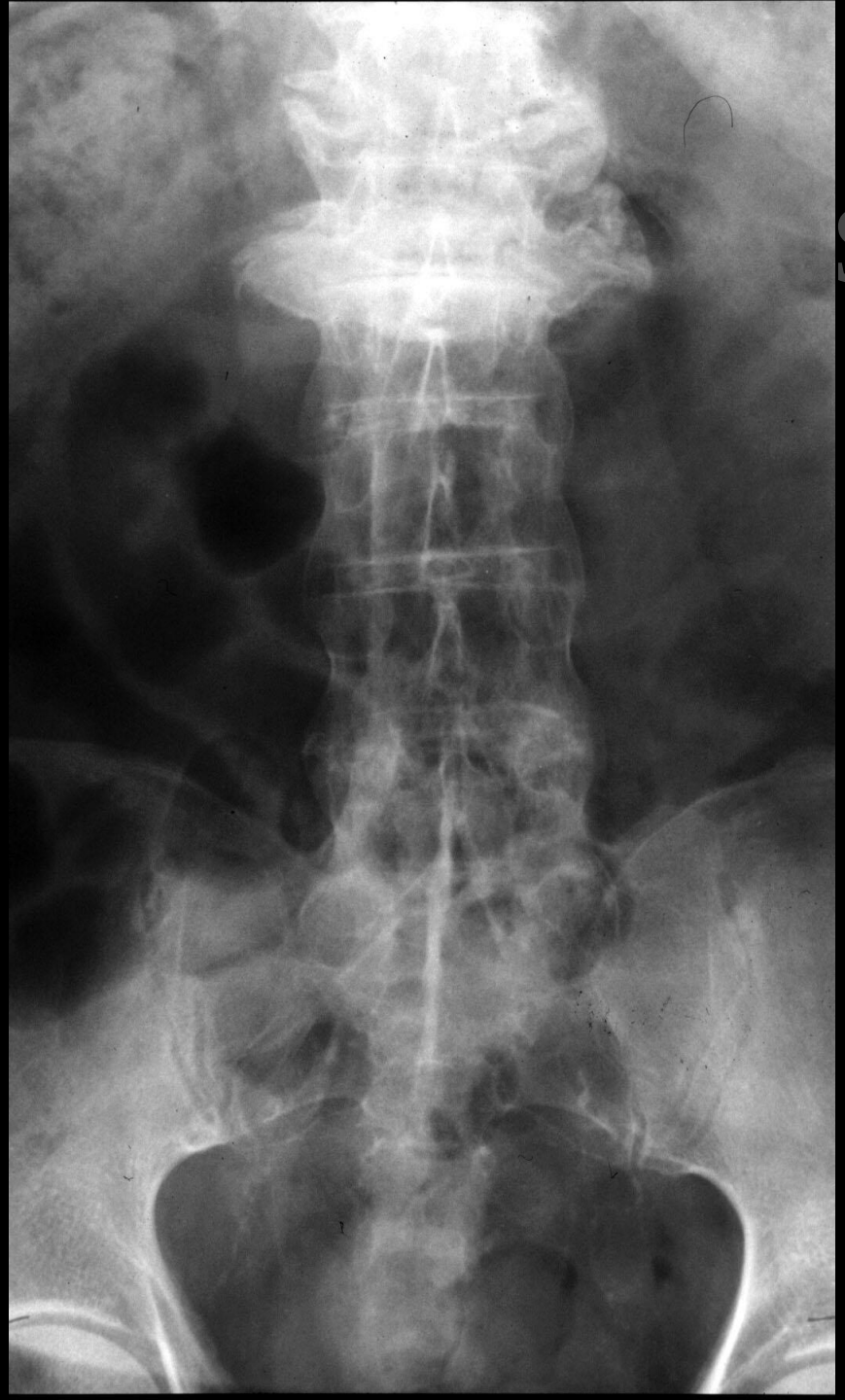
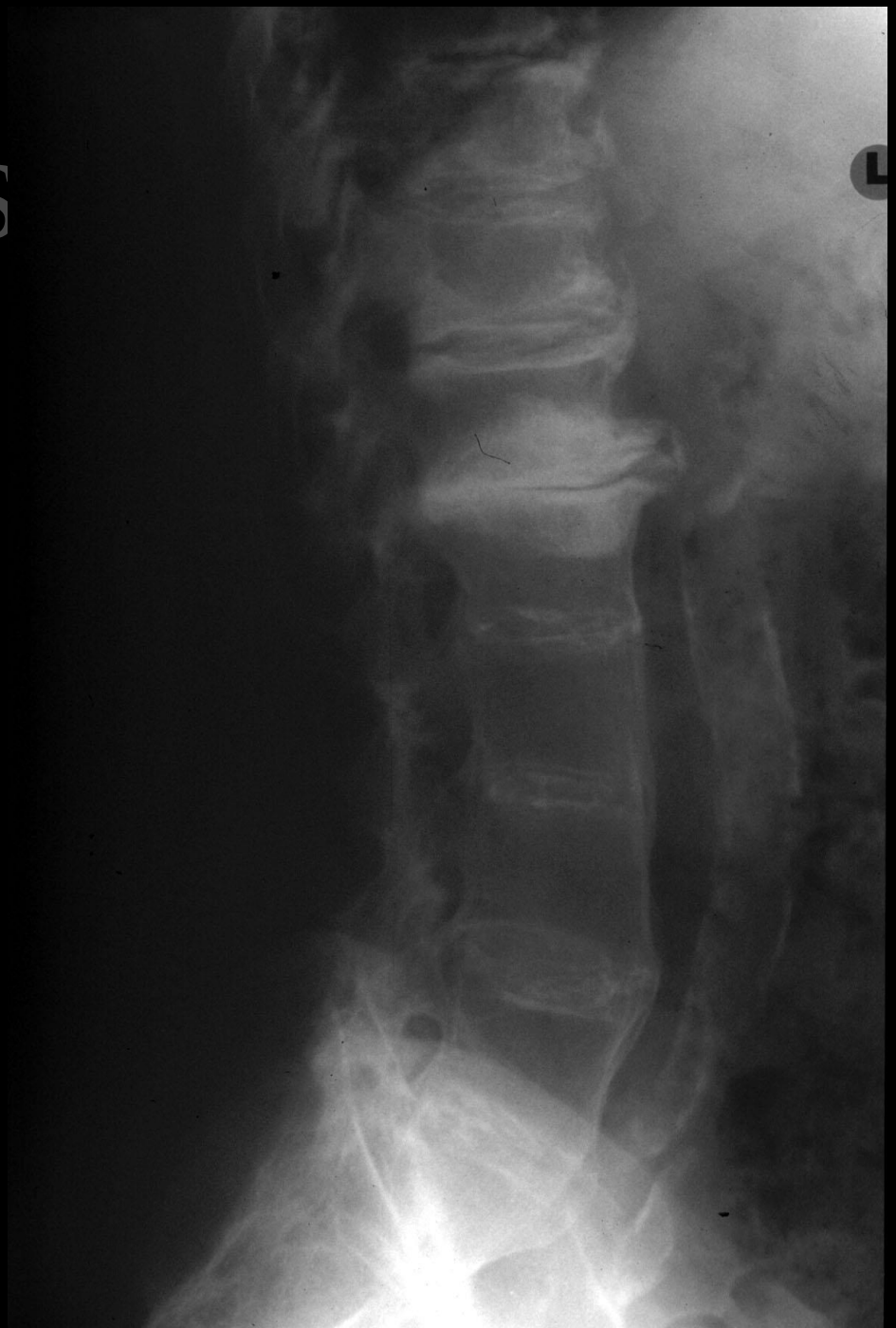


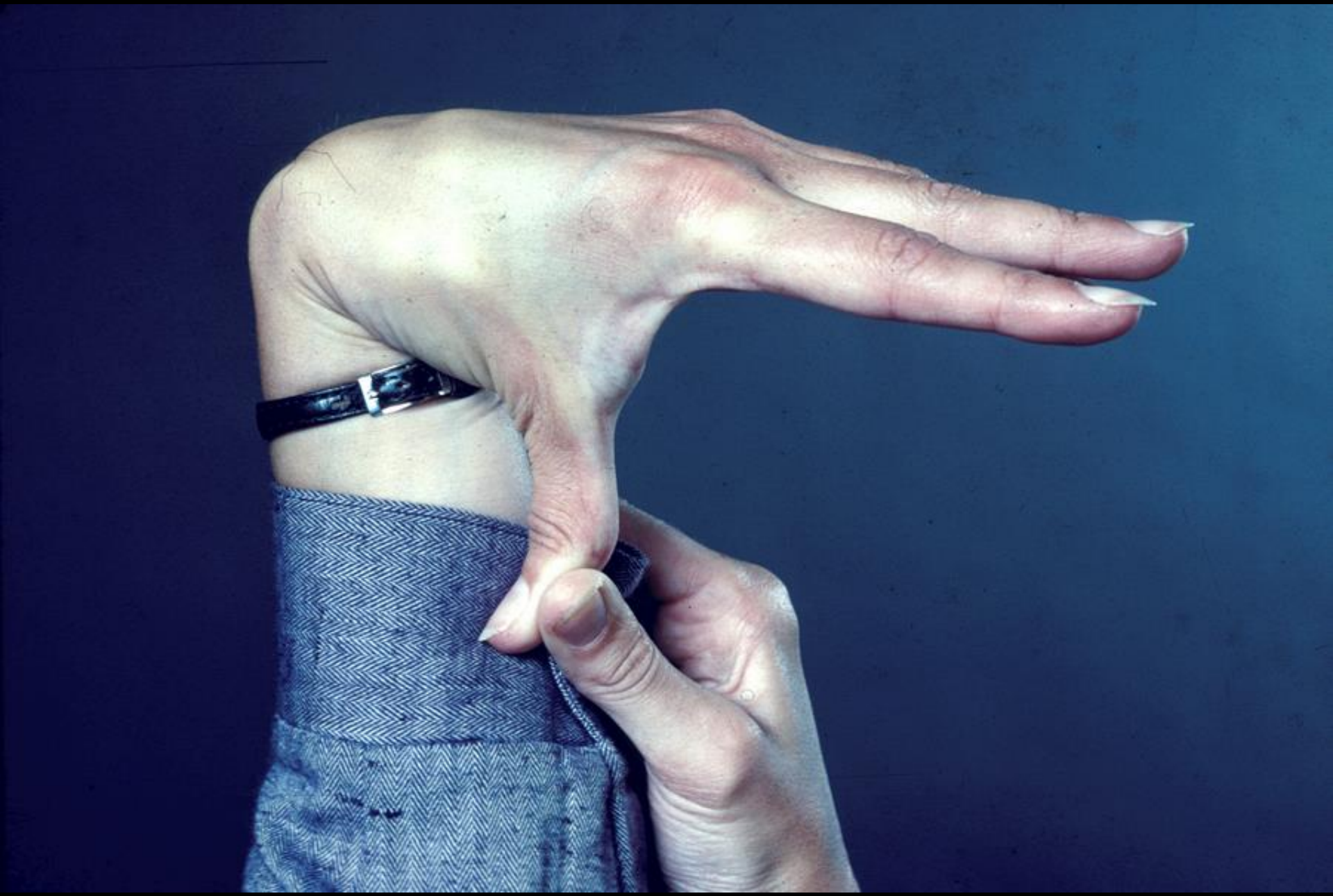


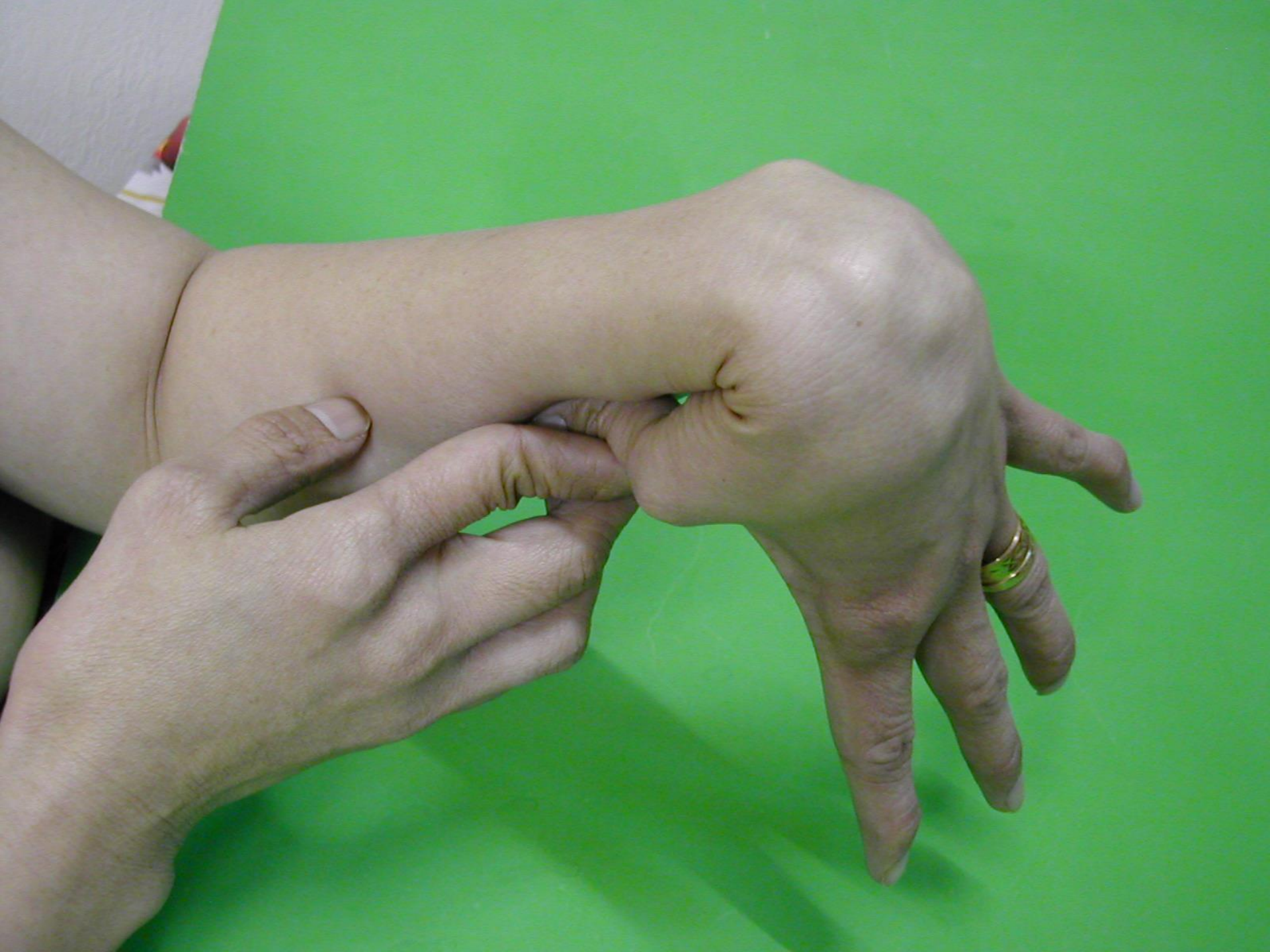

SINGLE USE ONLY
TERUMO

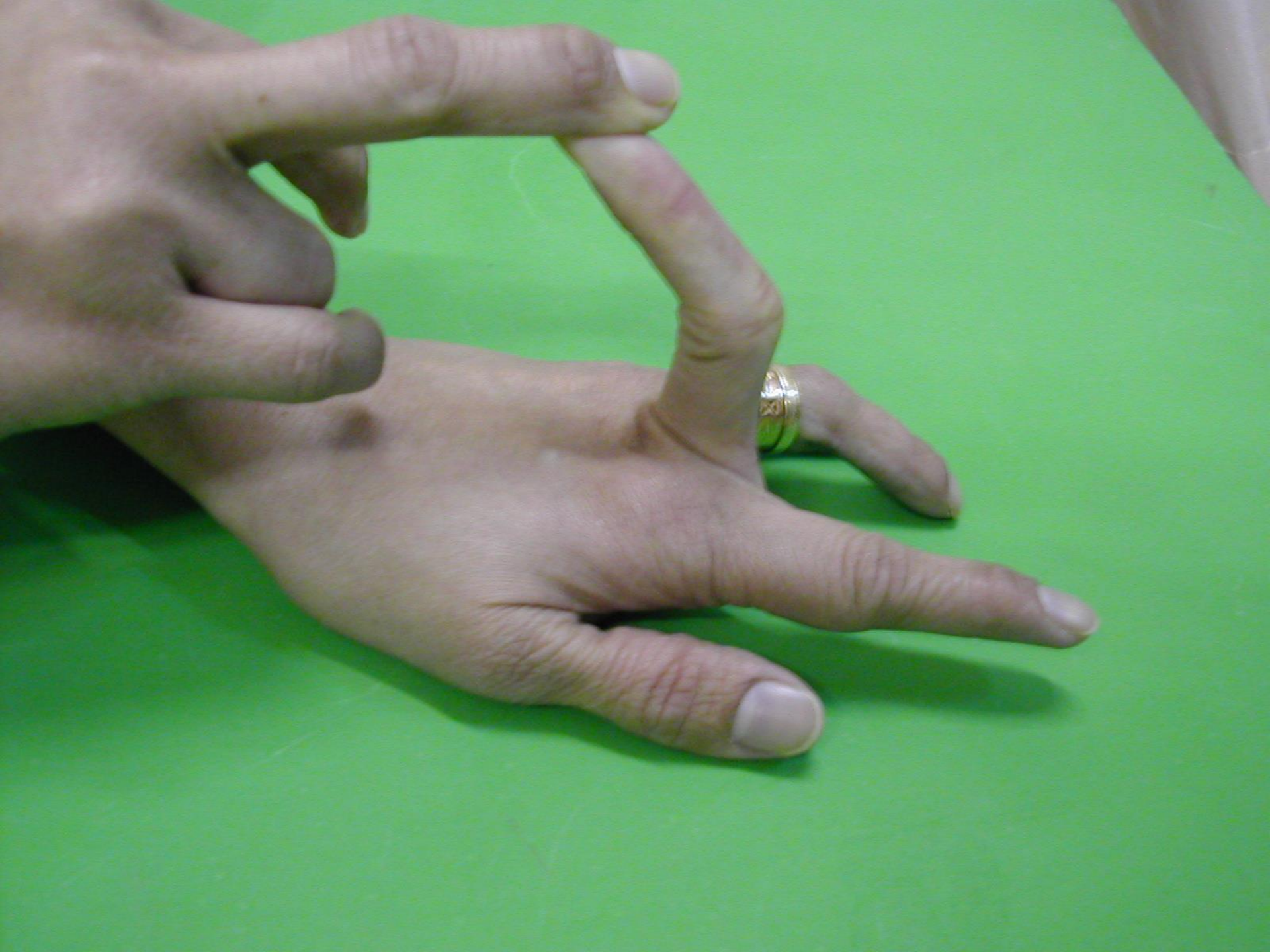
Synovial fluid

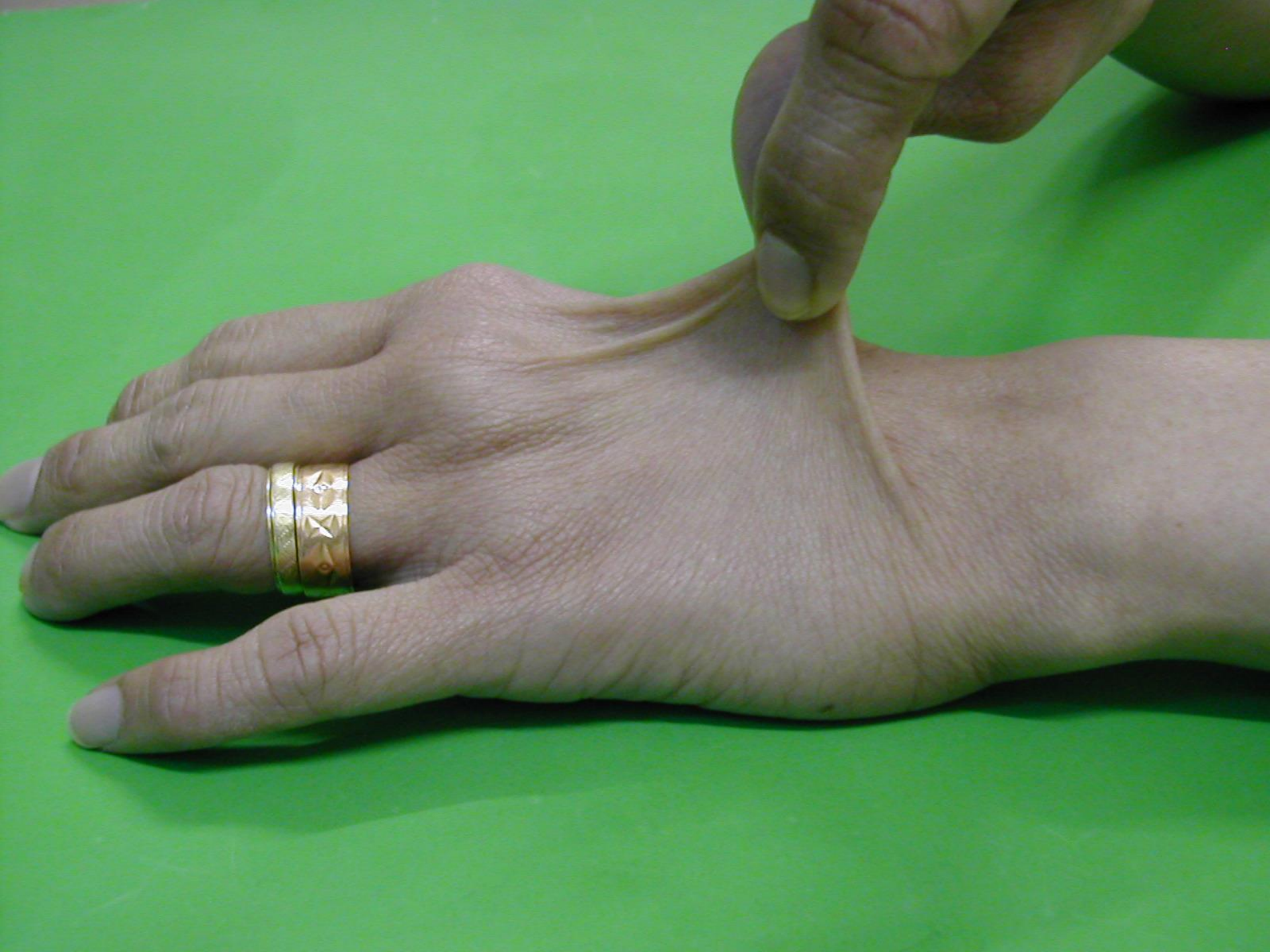
Slightly and moderately opalescent

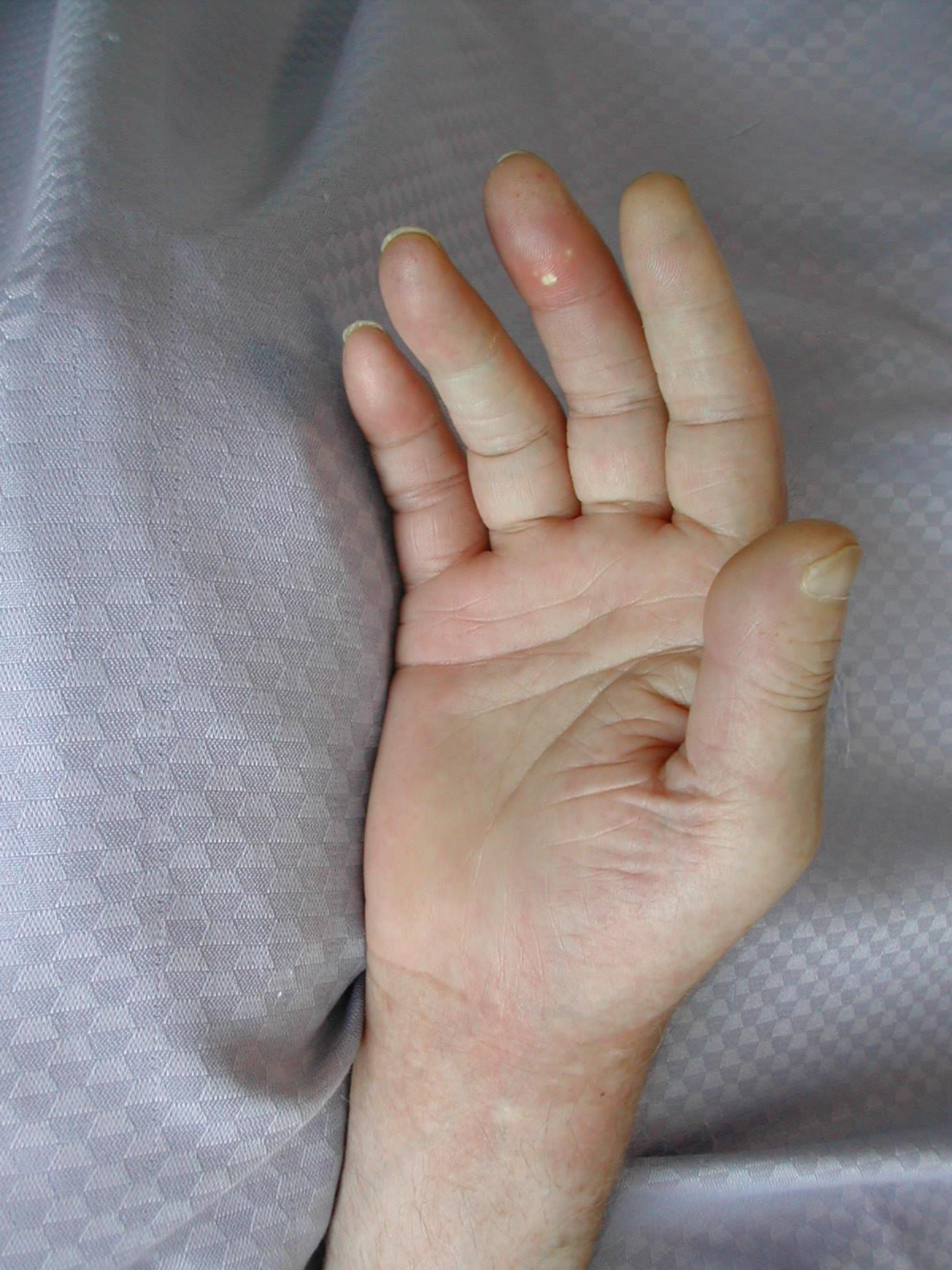



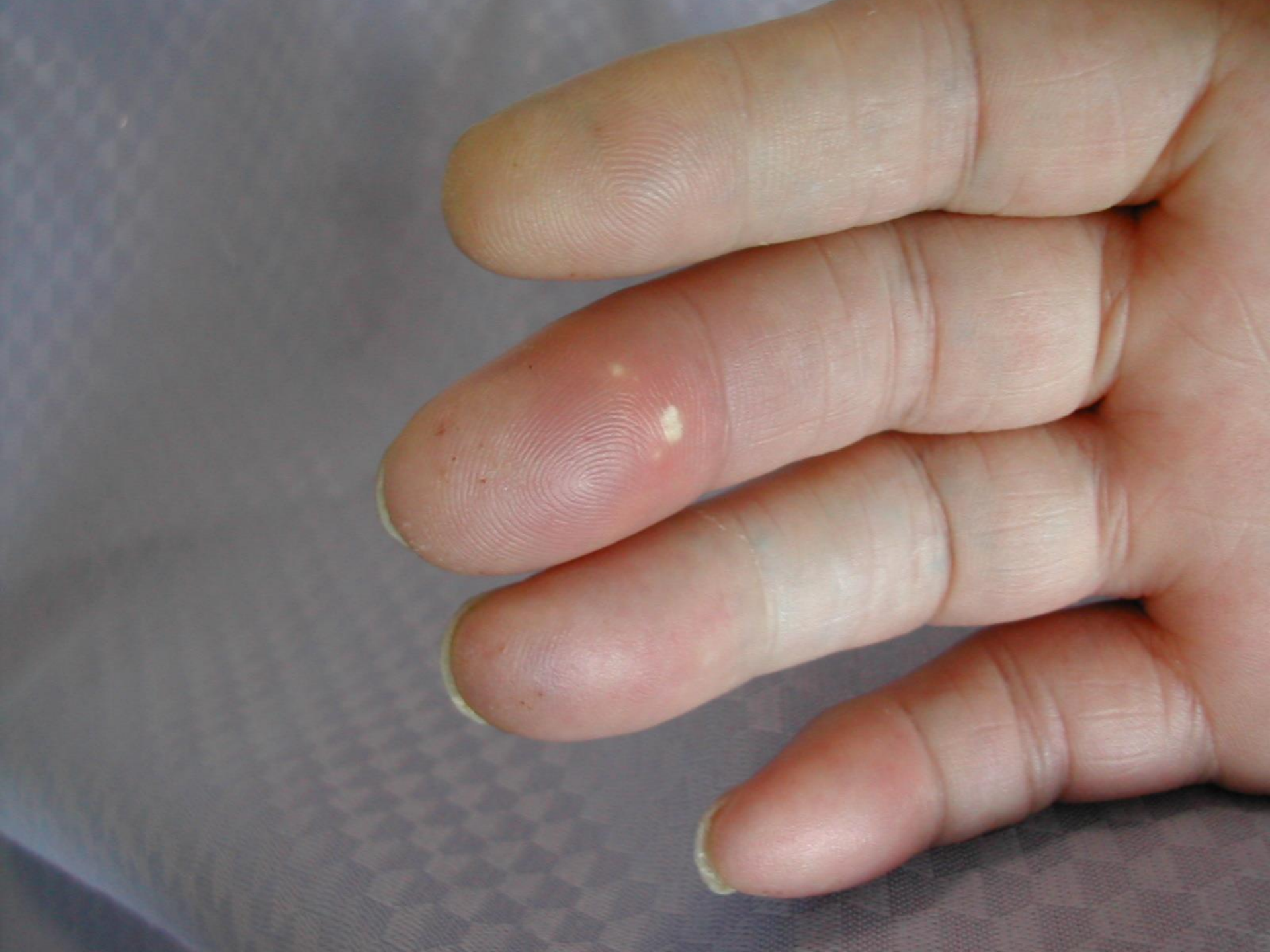


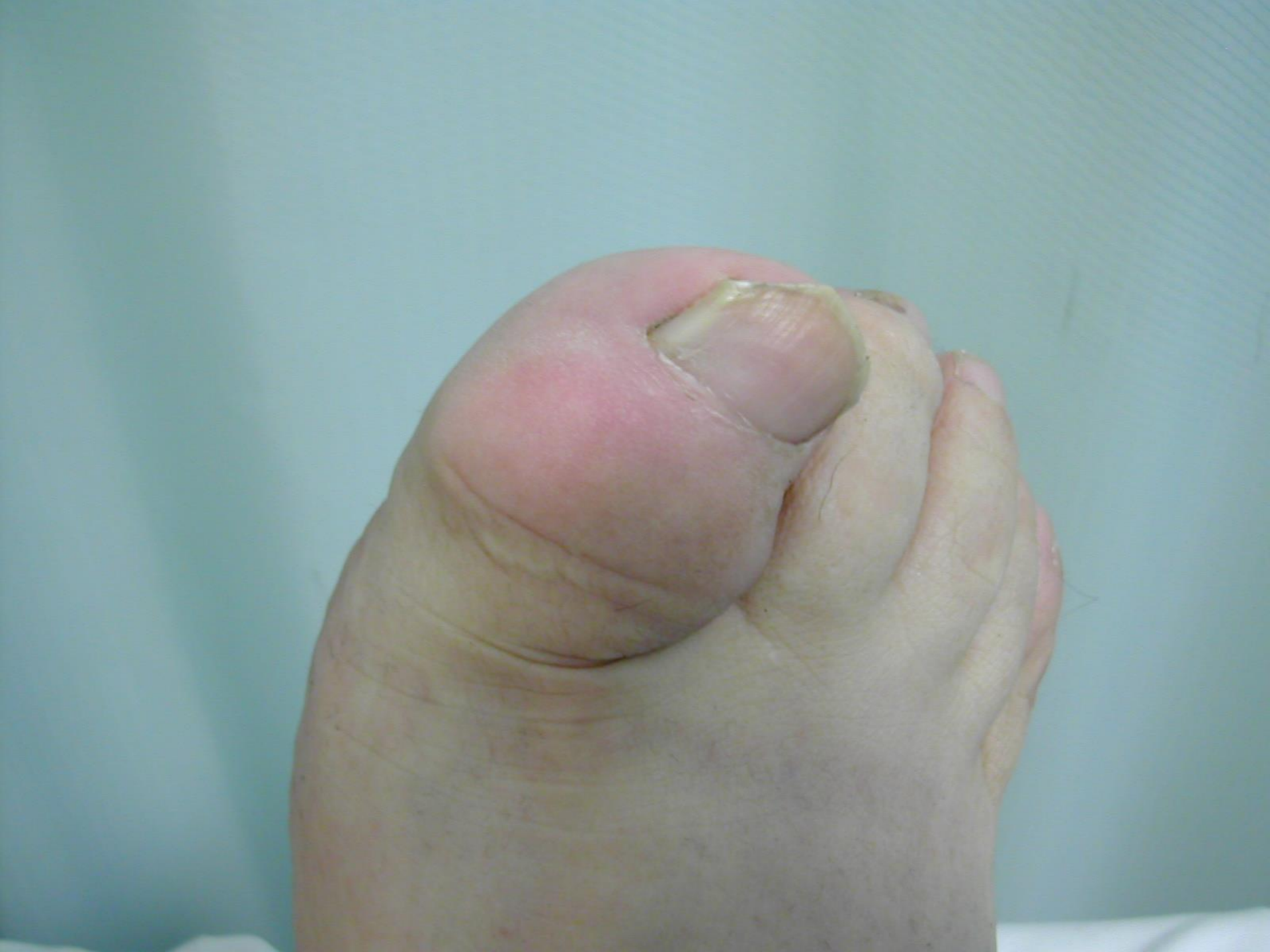


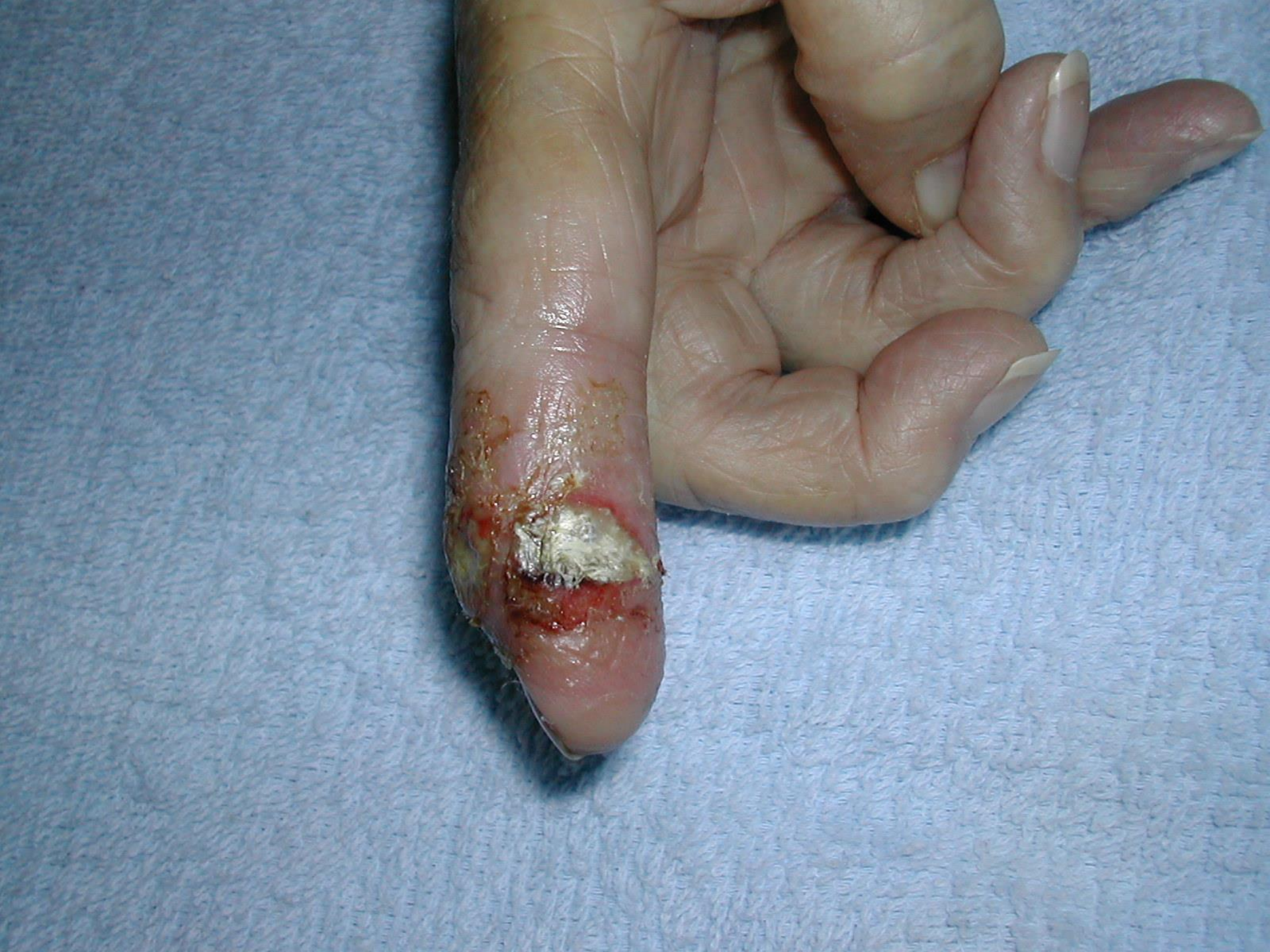




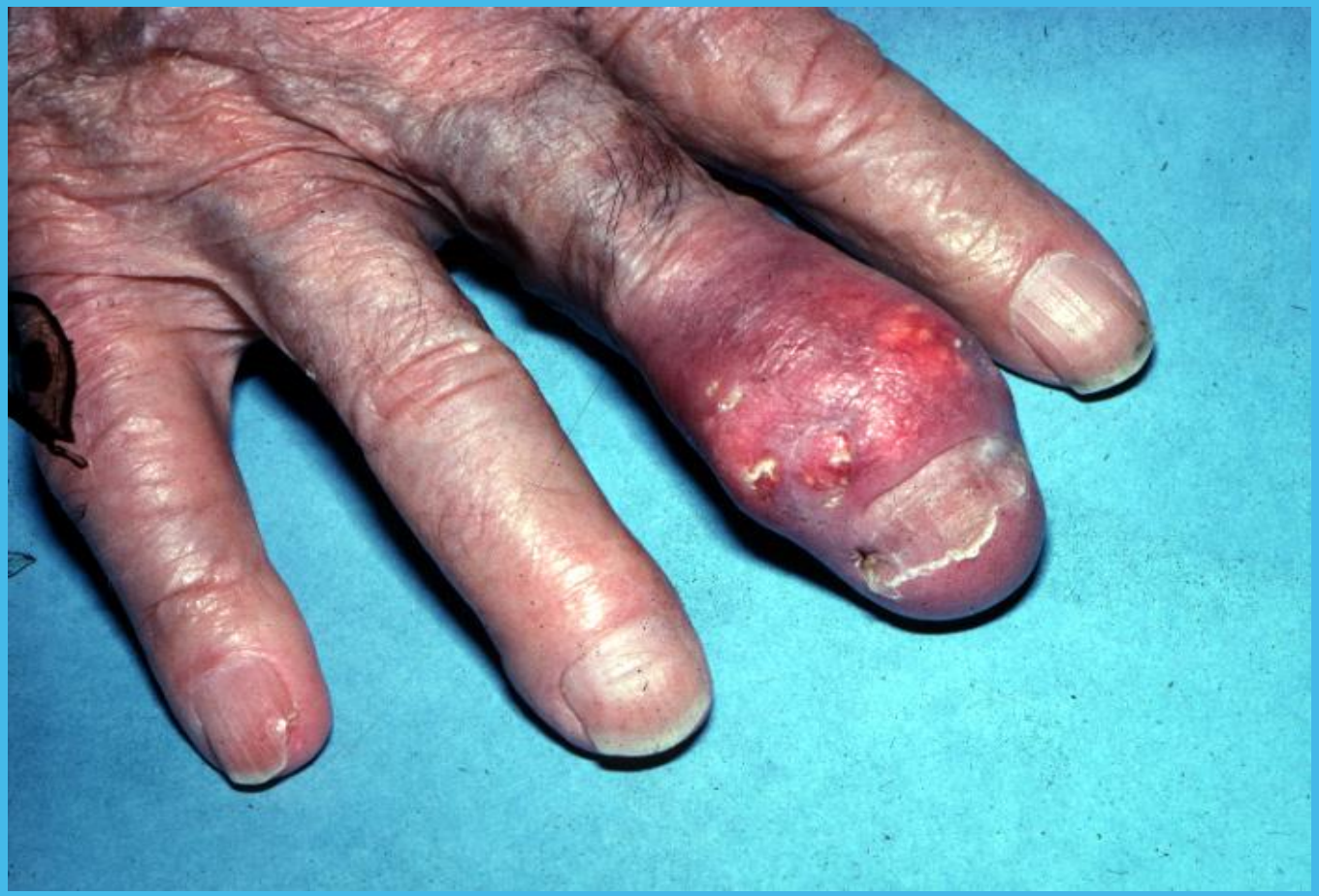




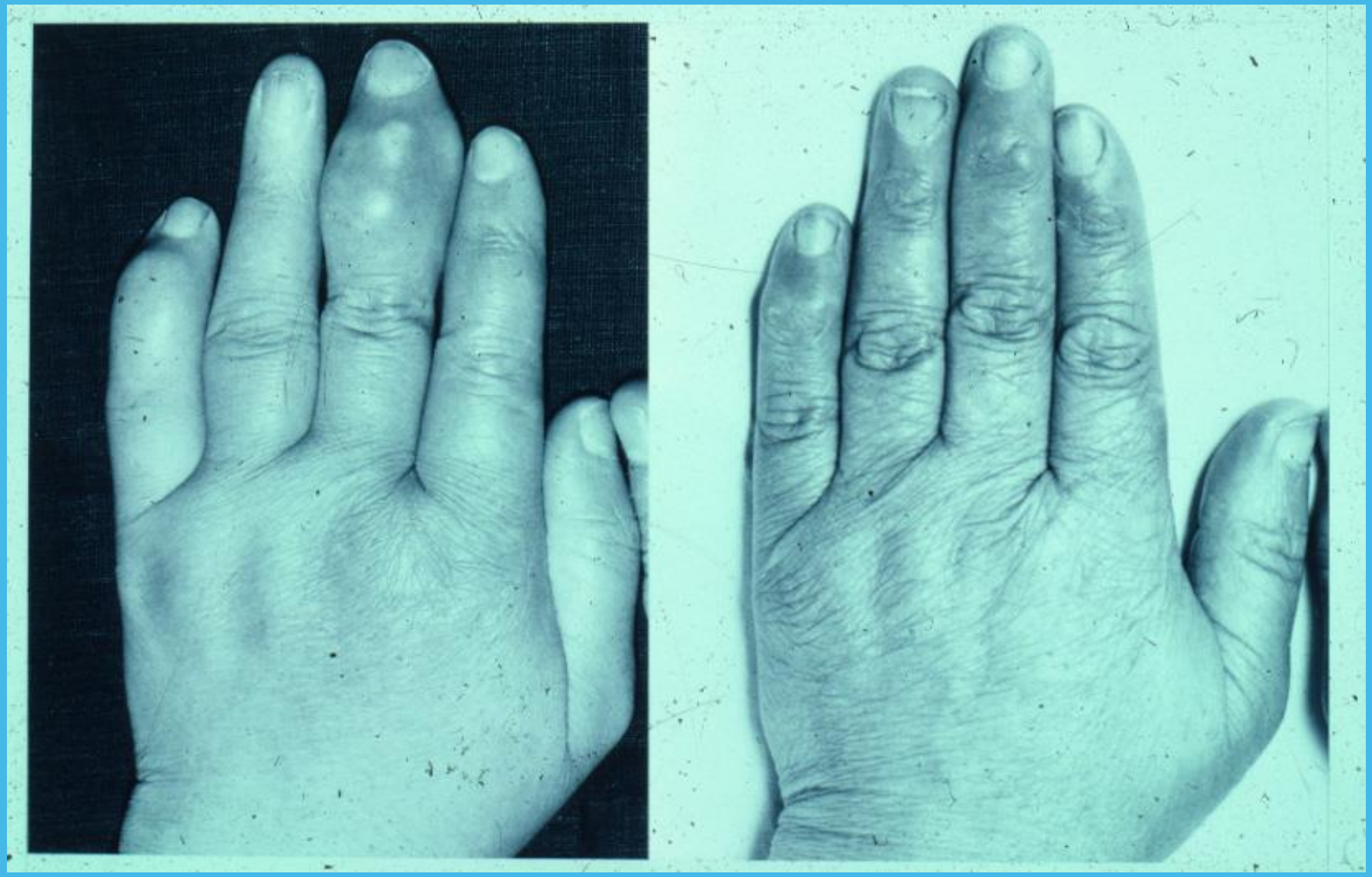




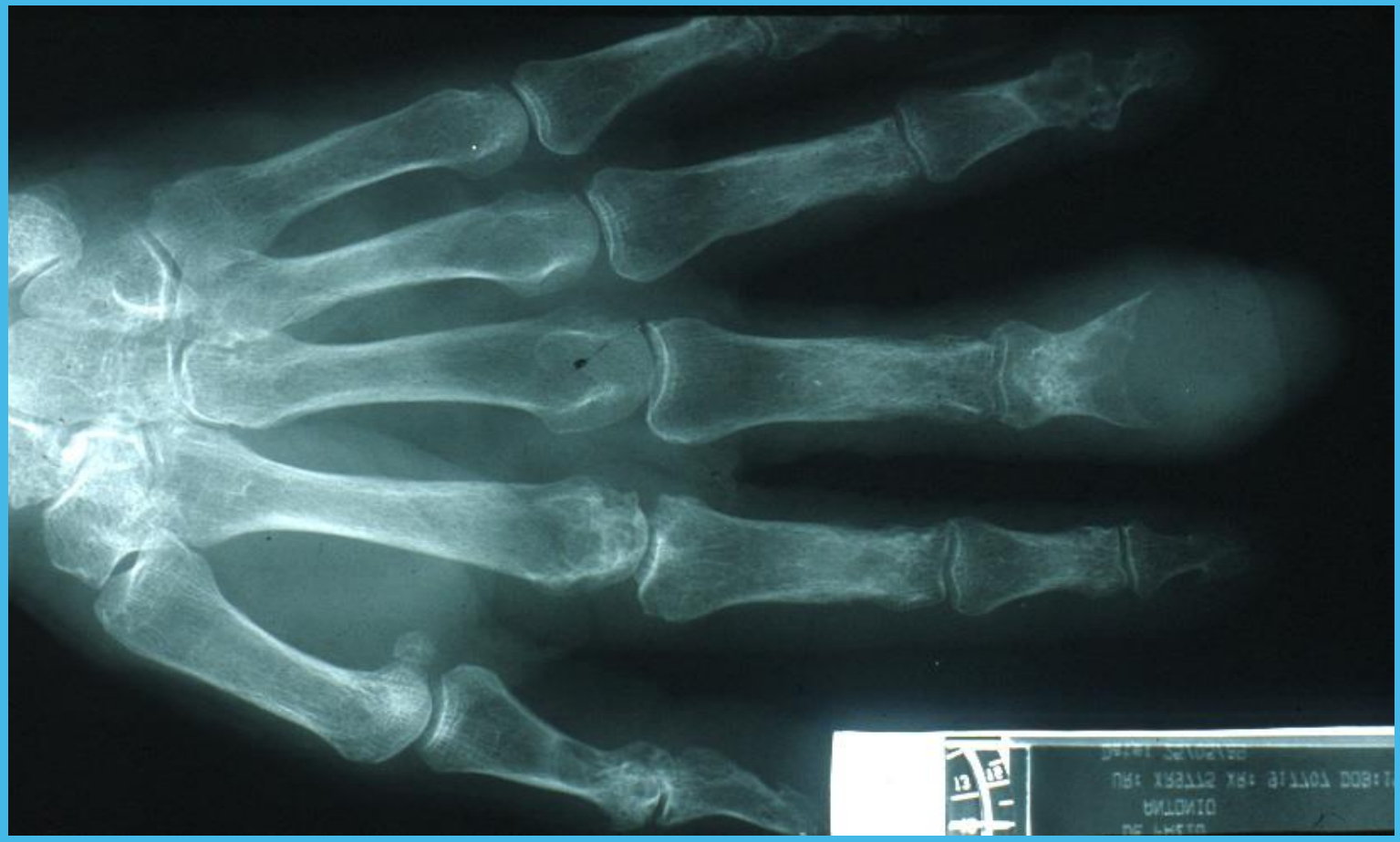
Gout – big DIP tophus



10 years of allopurinol therapy

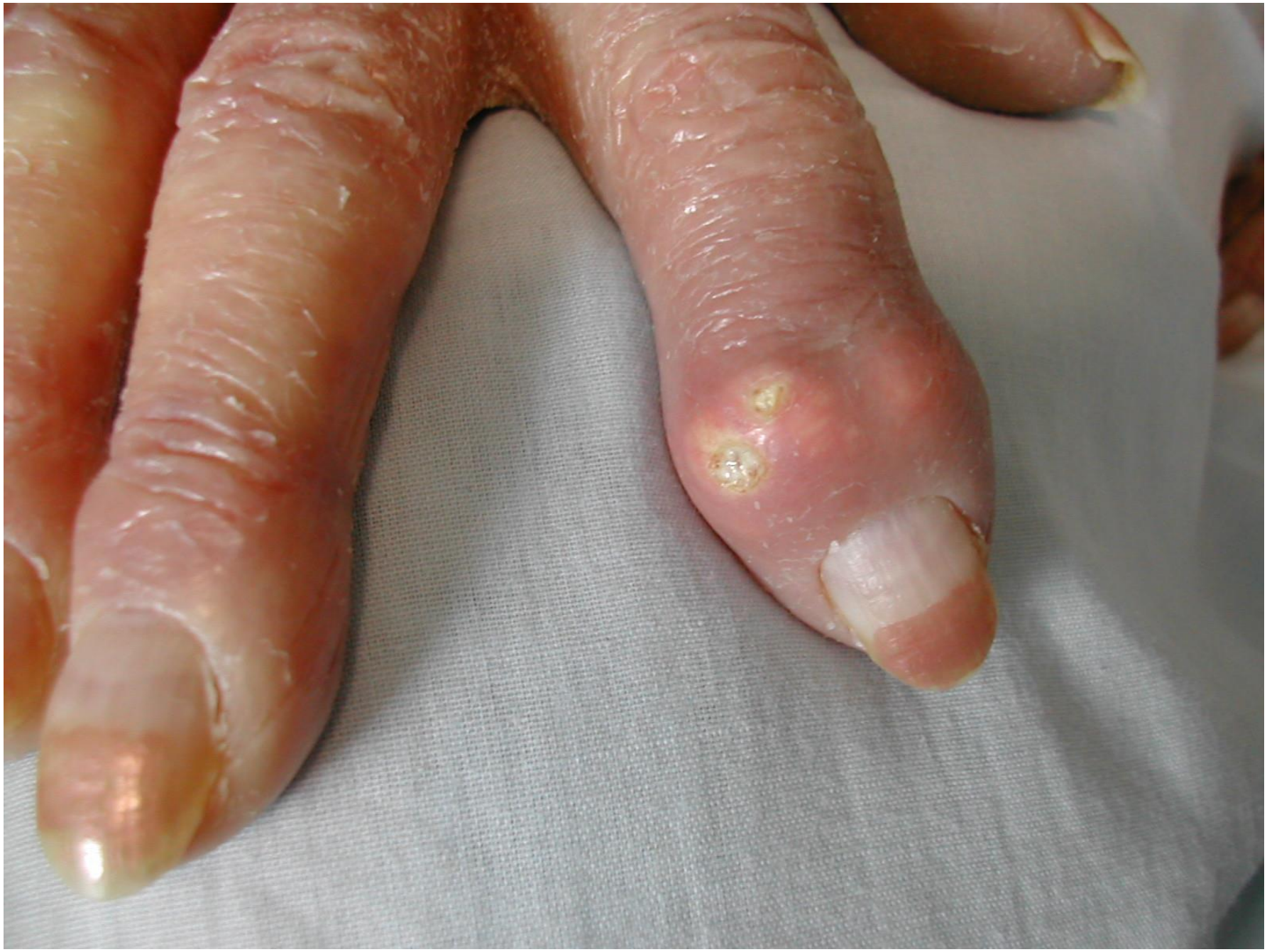


Gout – distal phalanx destruction

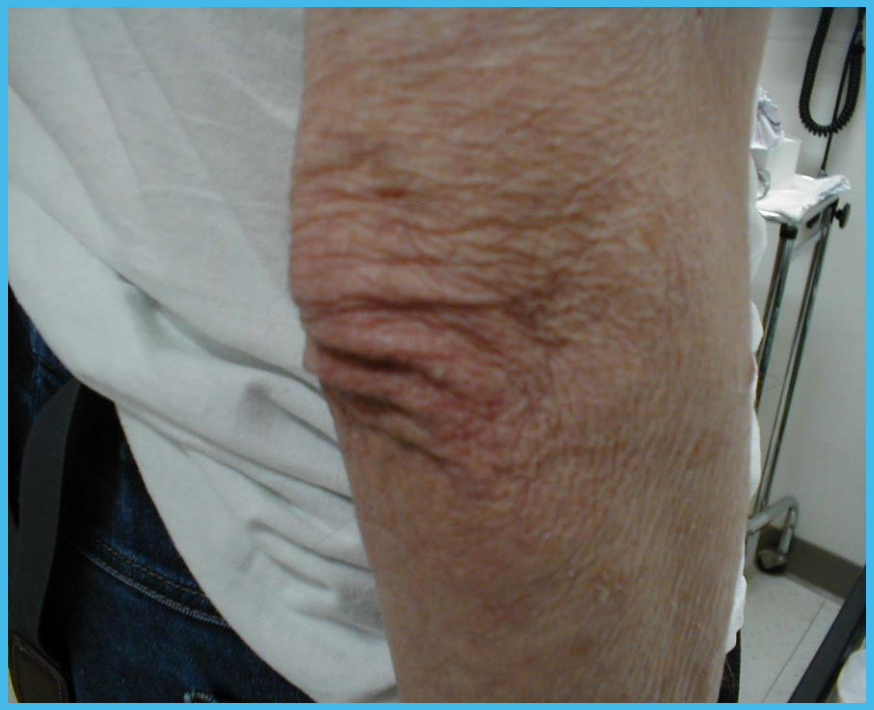


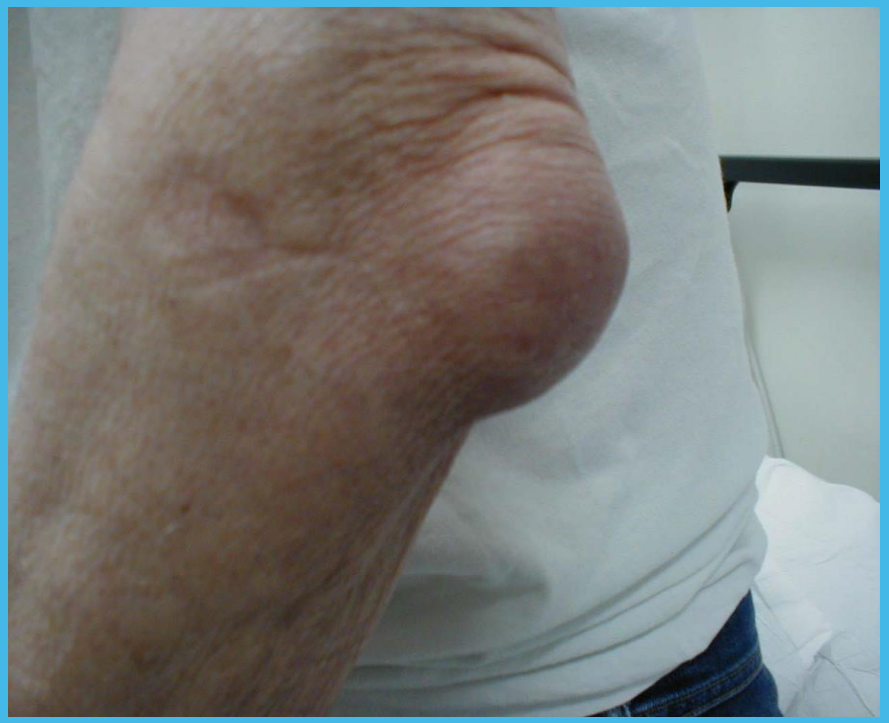
Hippocrates : aphorisms on gout.
(translated by Francis Adams)

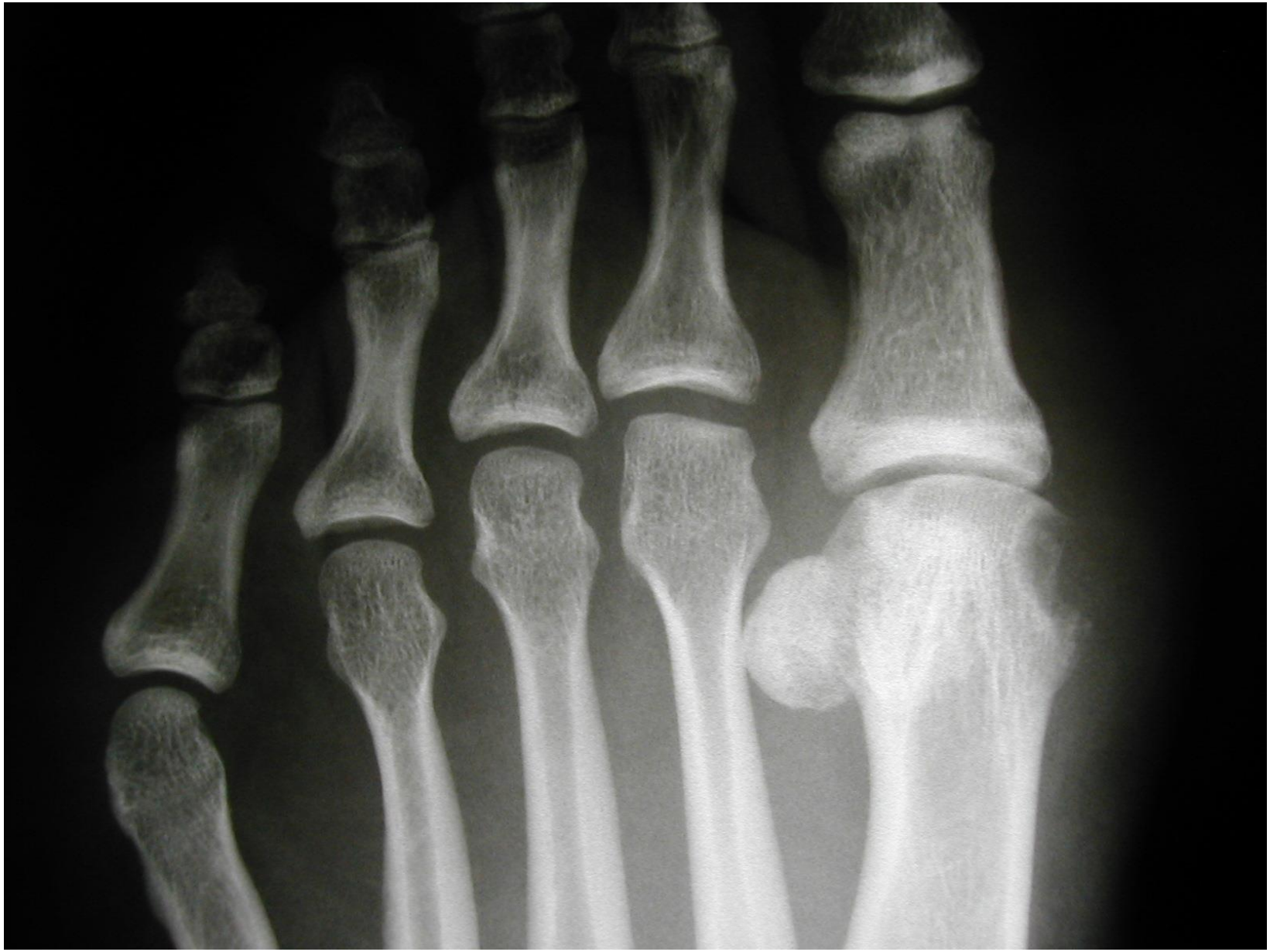
- Eunuchs do not take the gout, nor become bald.
- A woman does not take the gout, unless her menses be stopped.
- A youth does not get gout before sexual intercourse.
- In gouty affections inflammation subsides within 40 days.
- Swellings and pains in the joints, without sores, whether from gout or from sprains, in most cases are relieved by a copious affusion of cold water, which reduces the swelling and removes the pain. For numbness in moderation removes pain.
- Gouty affections become active in spring and in autumn.



Olecranon bursitis

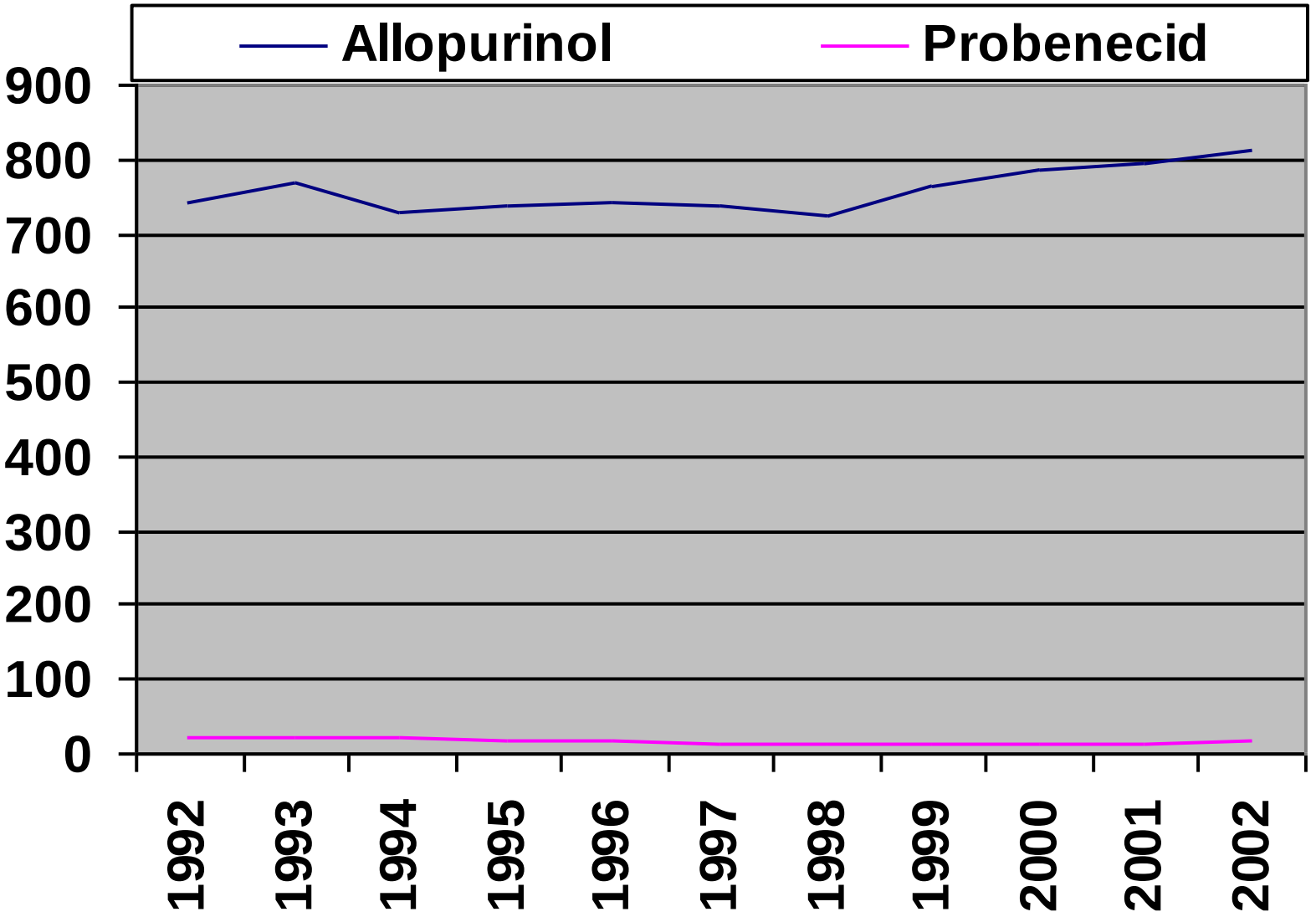


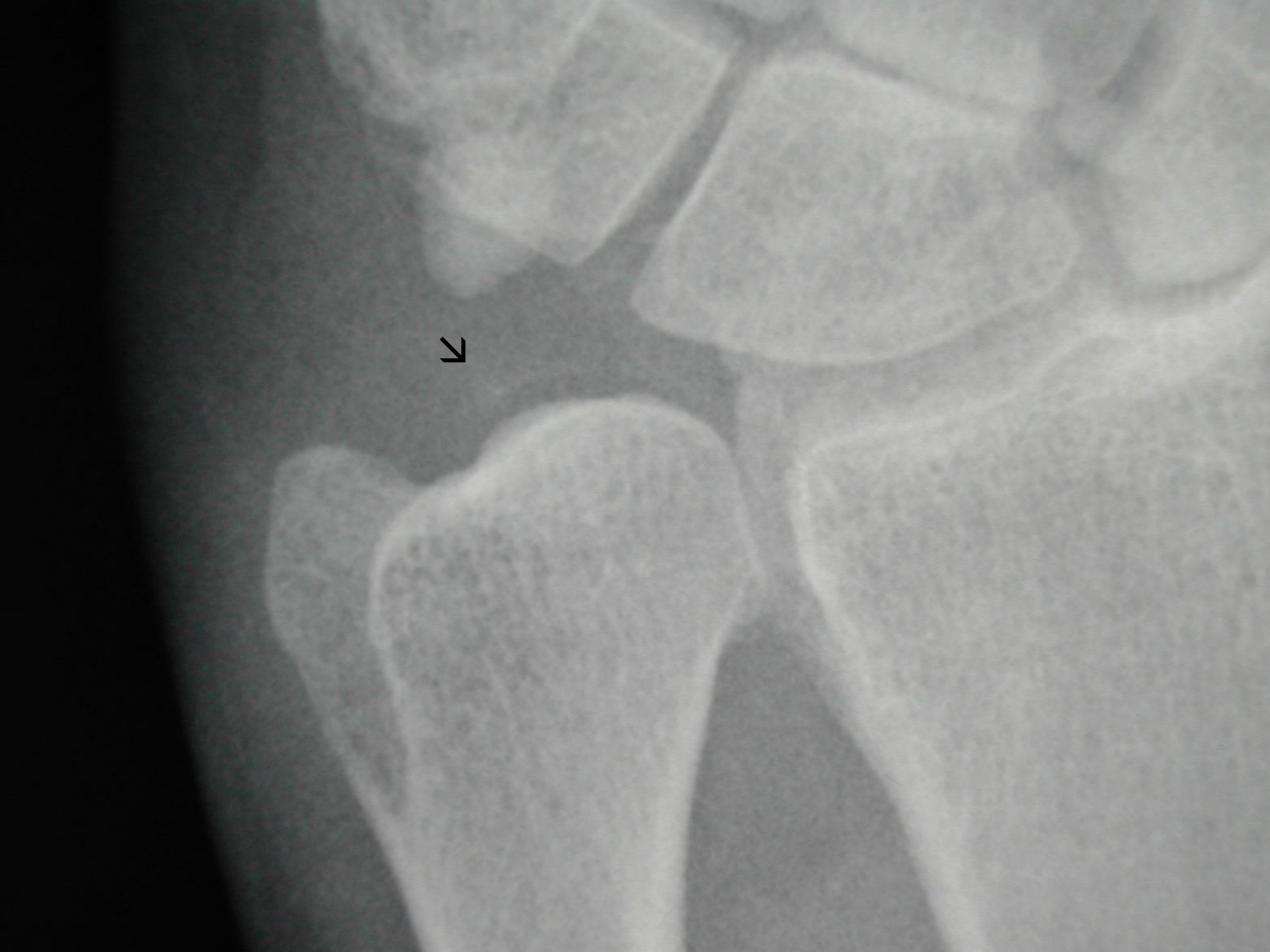


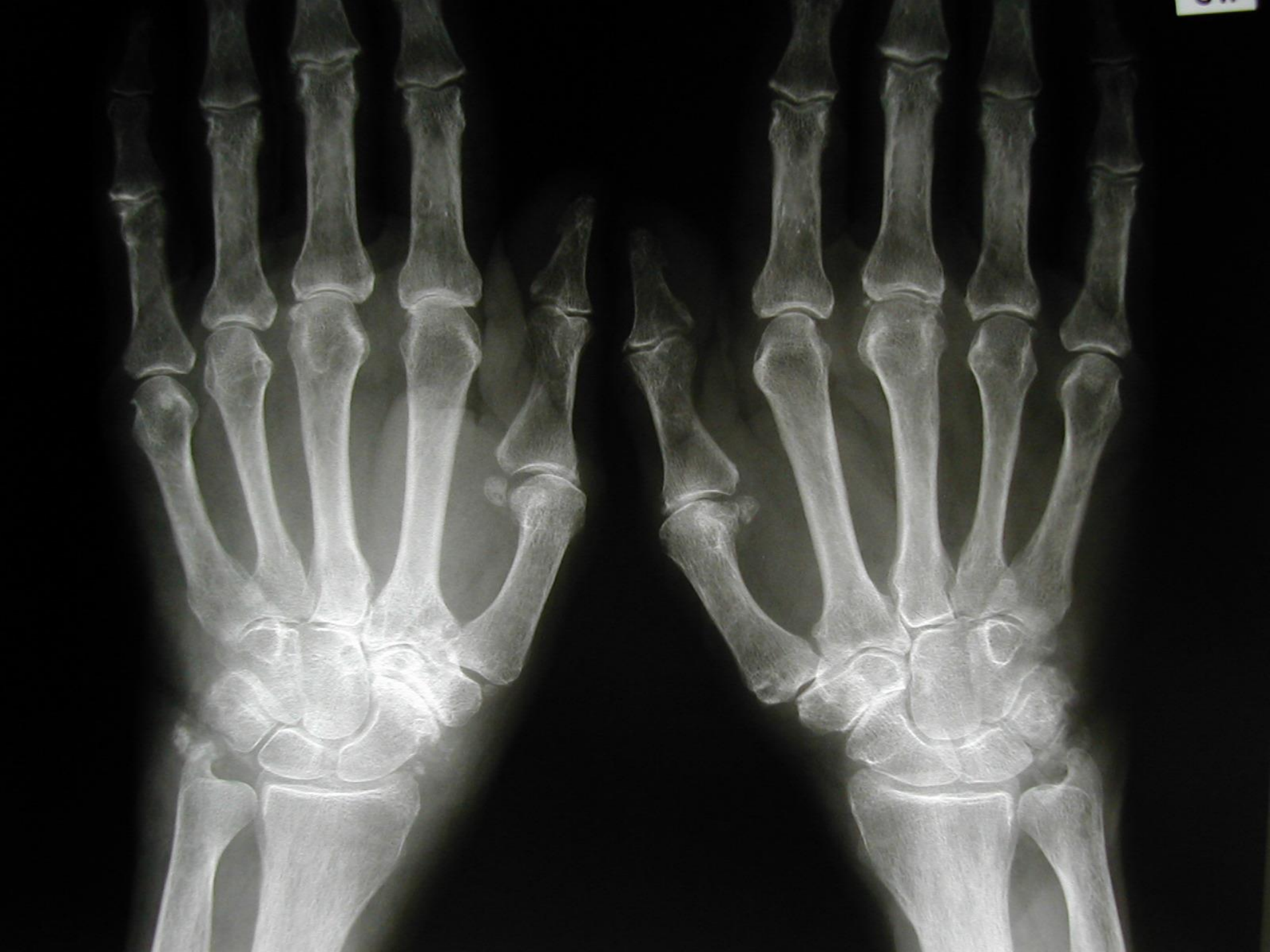


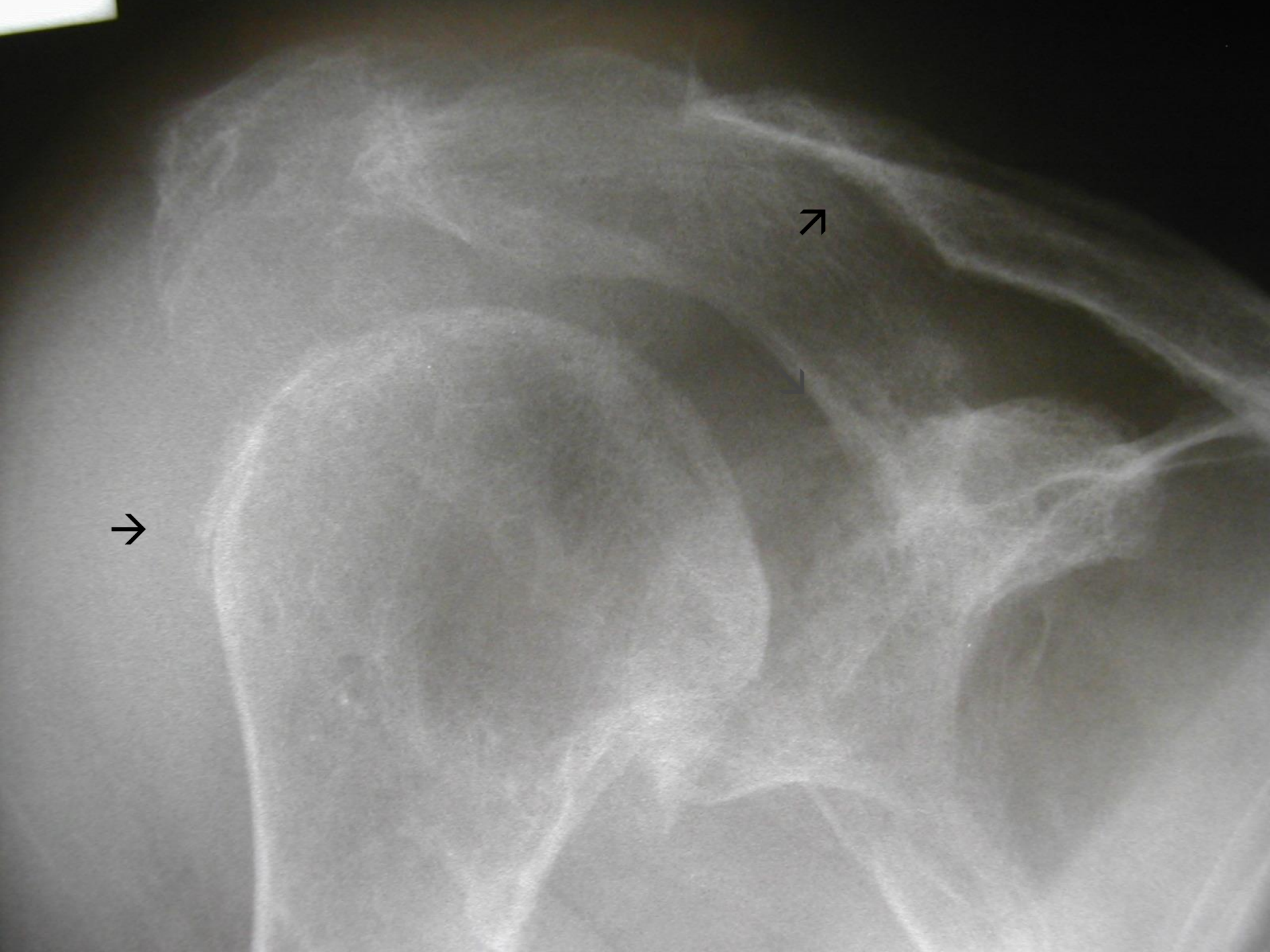
Urate-lowering treatment in Australia

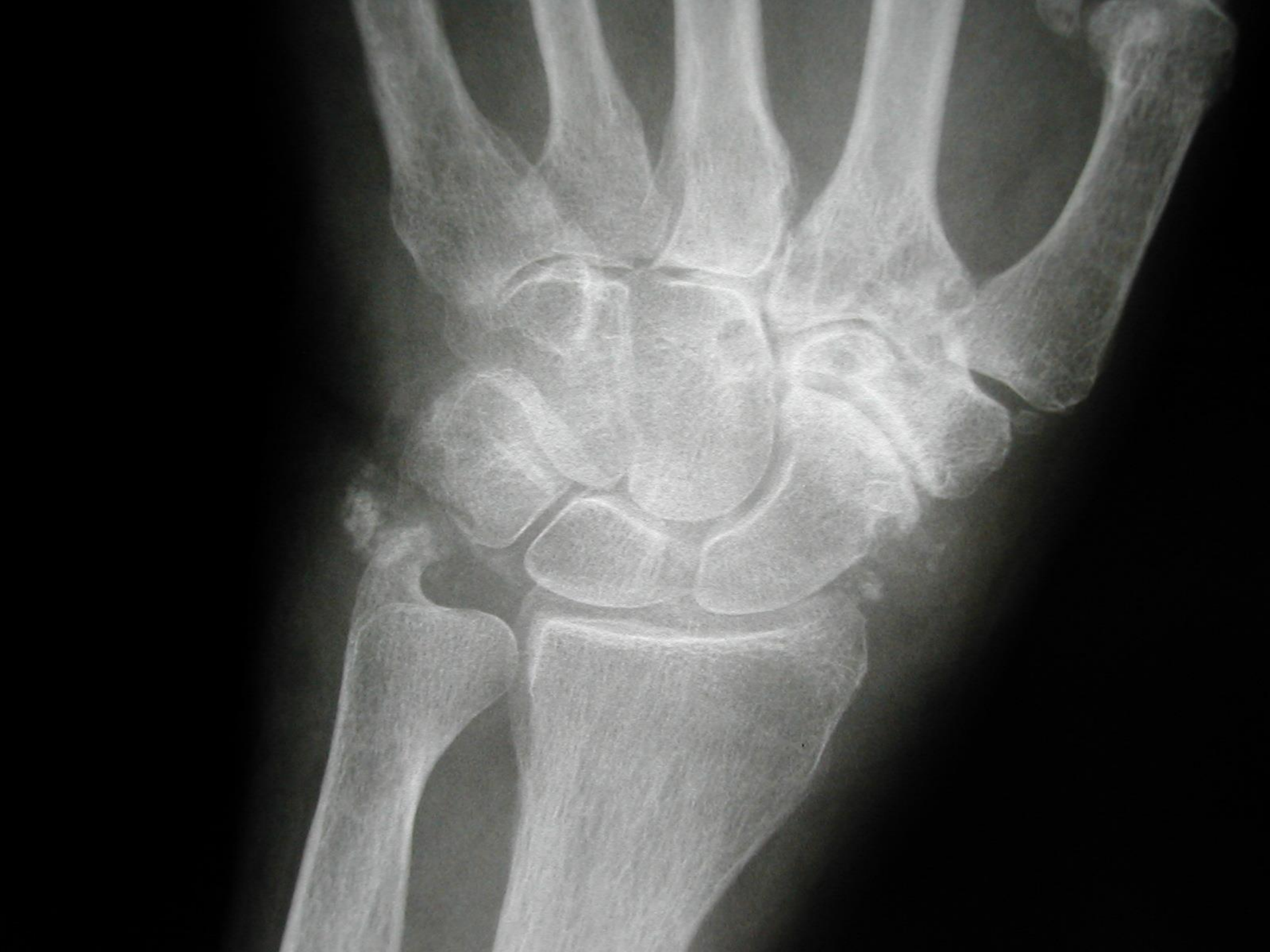
(number of prescriptions in thousands, PBS and RPBS)

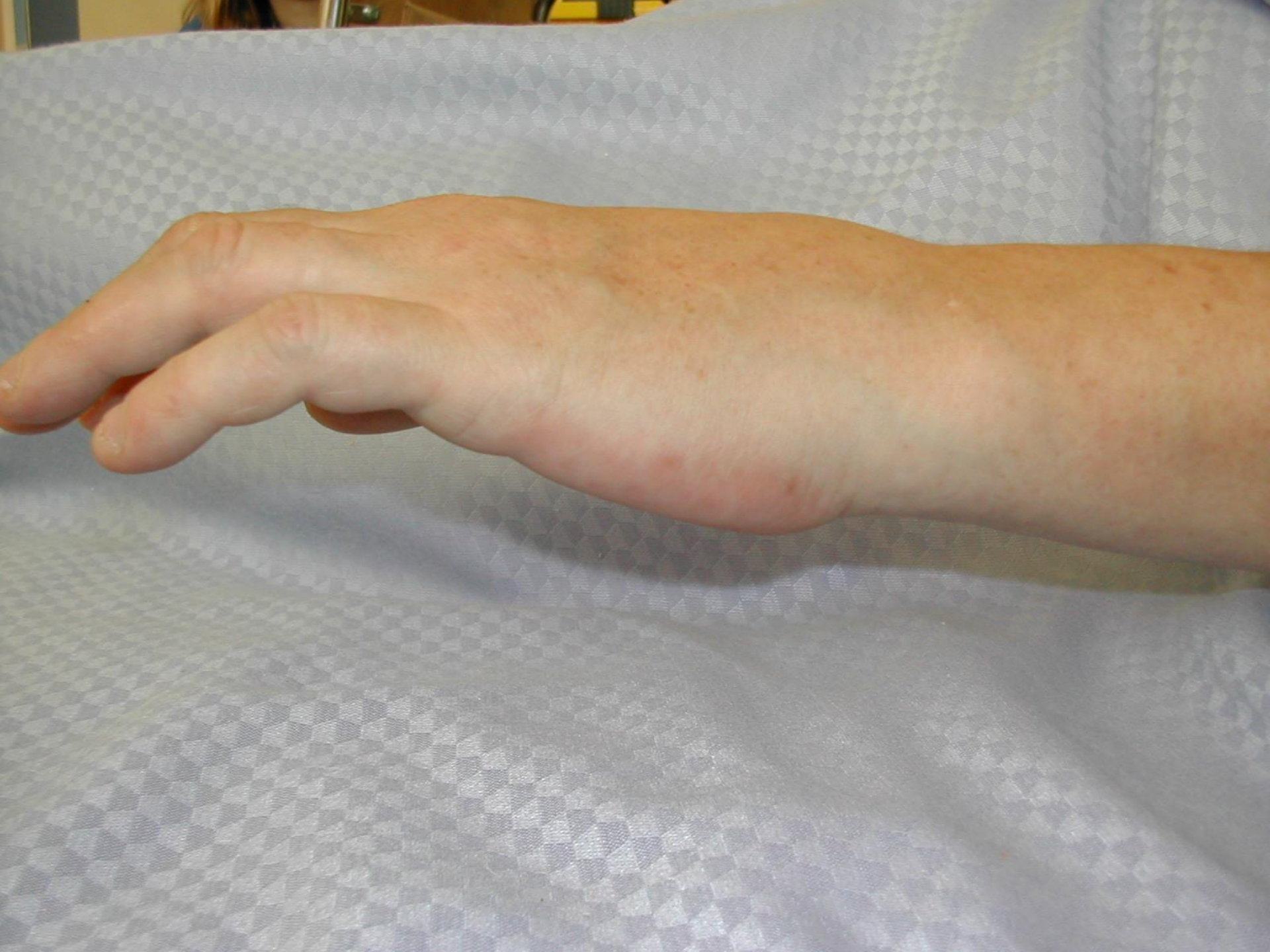


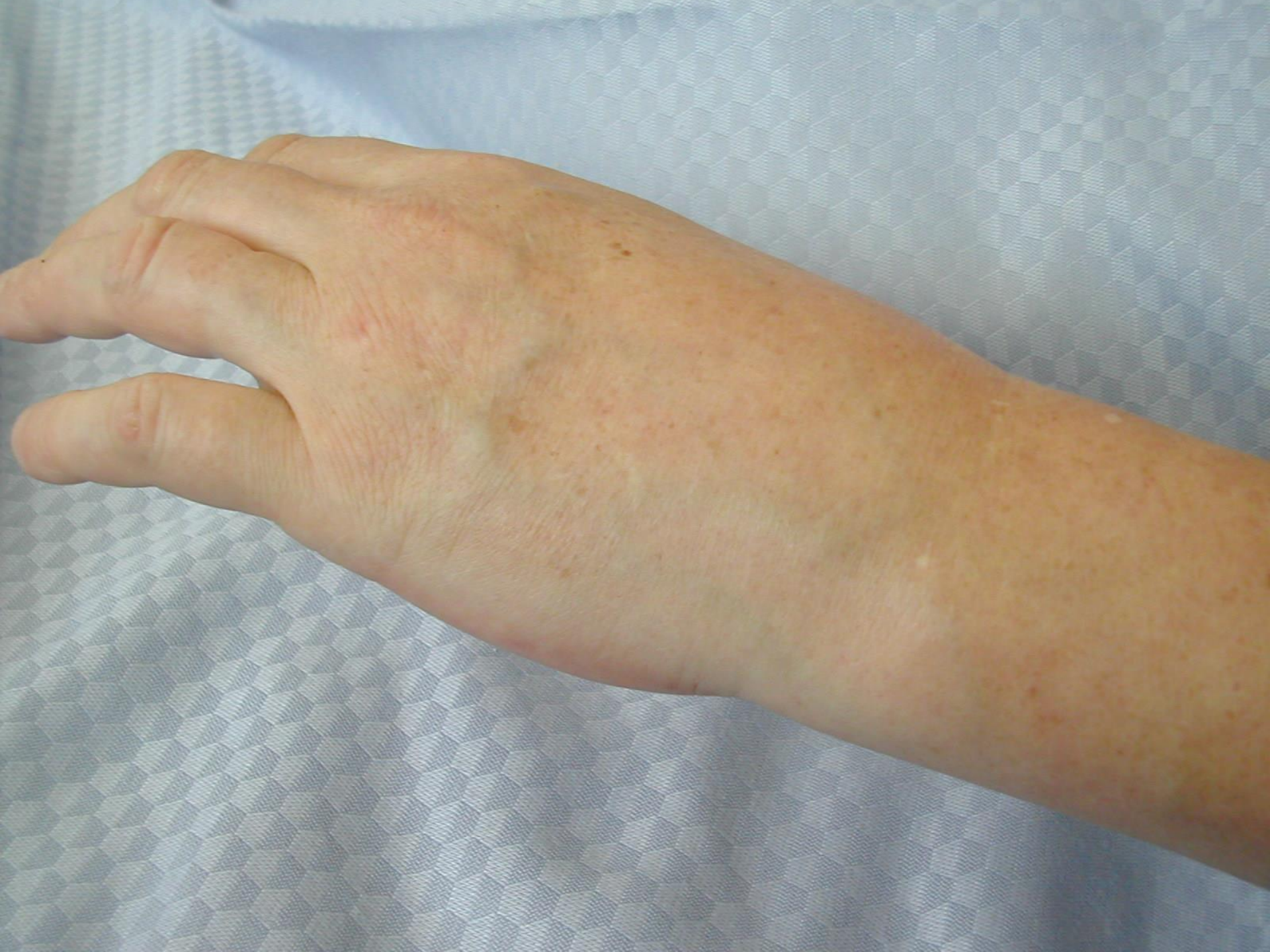


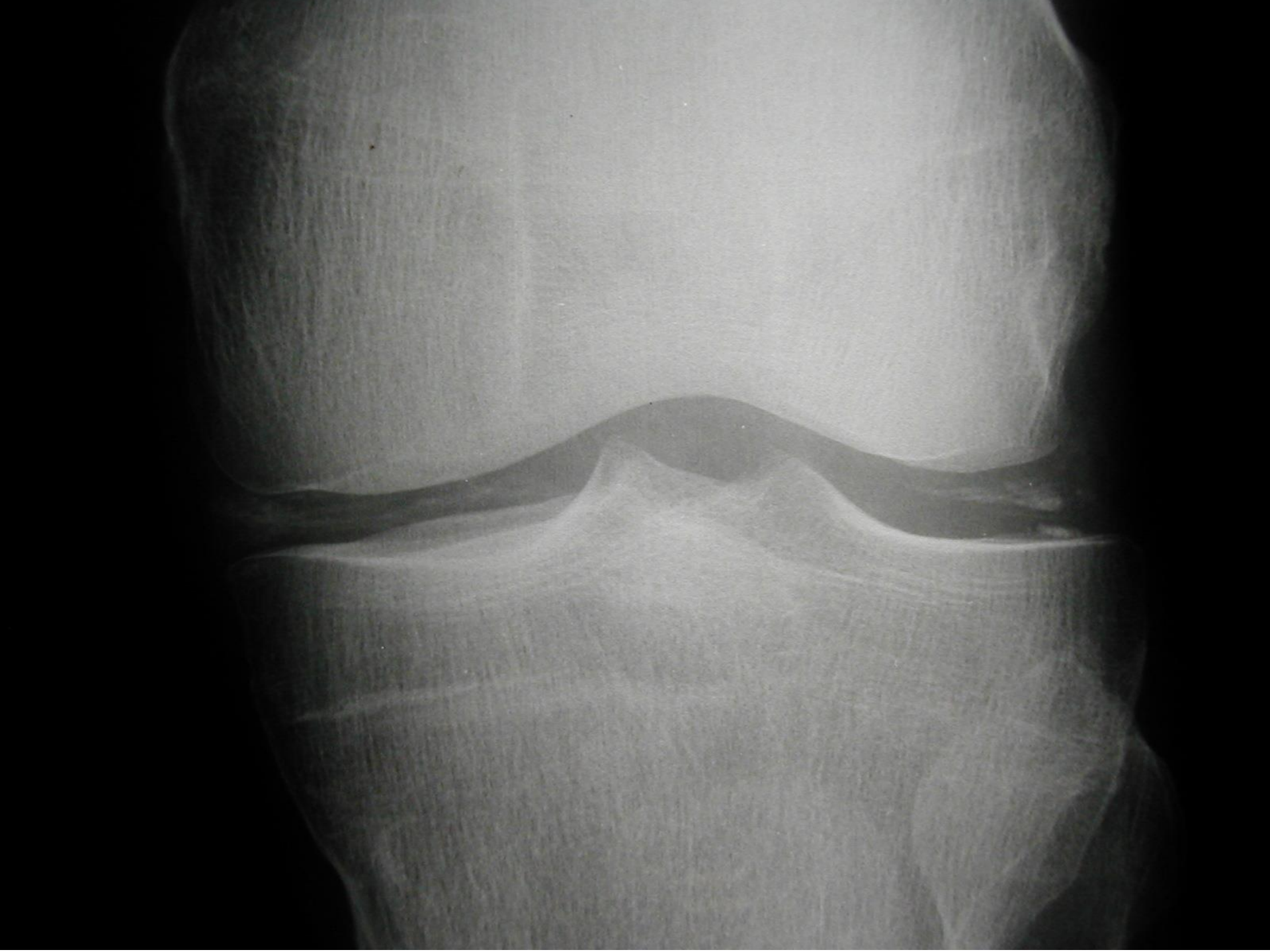


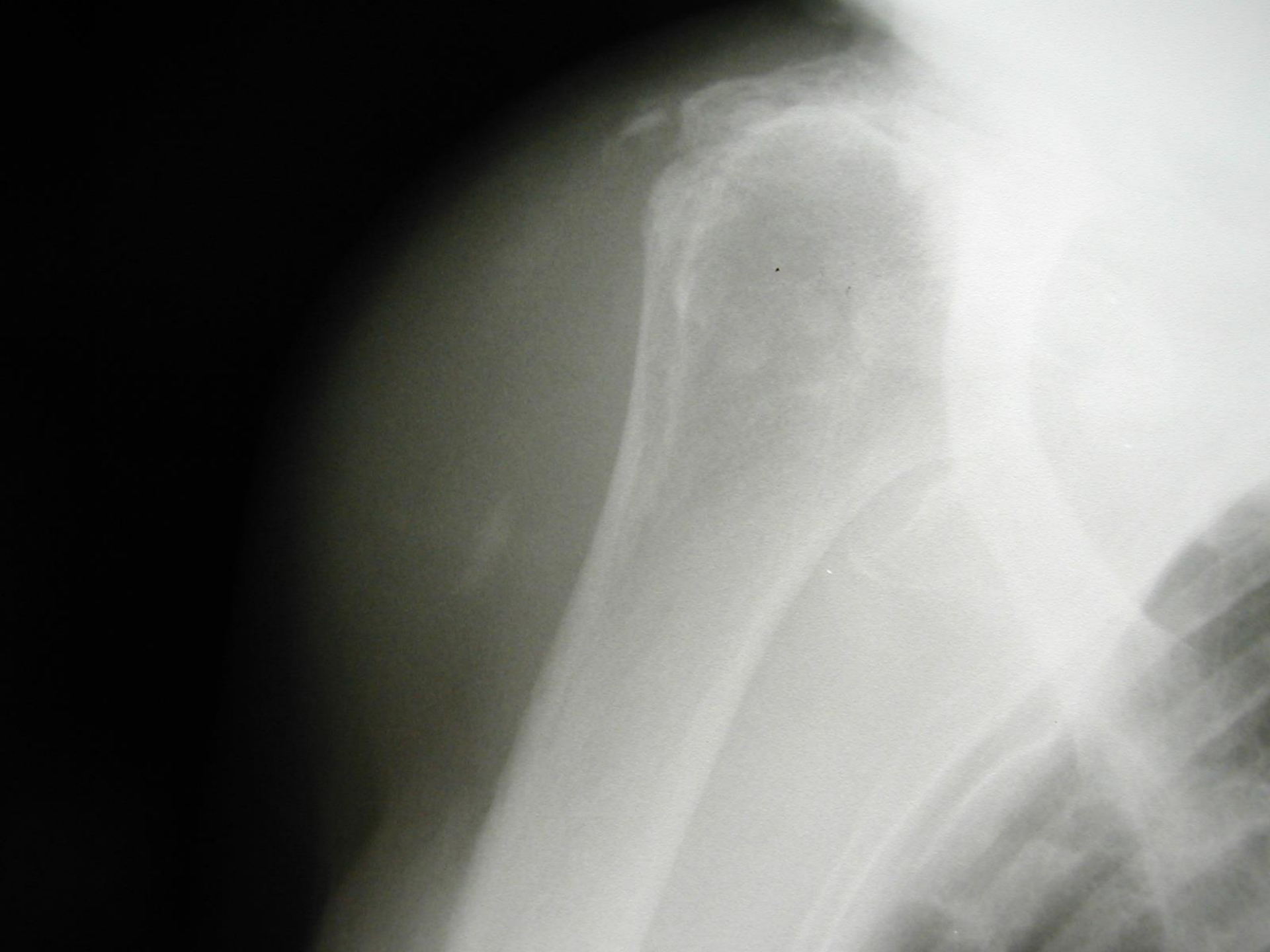


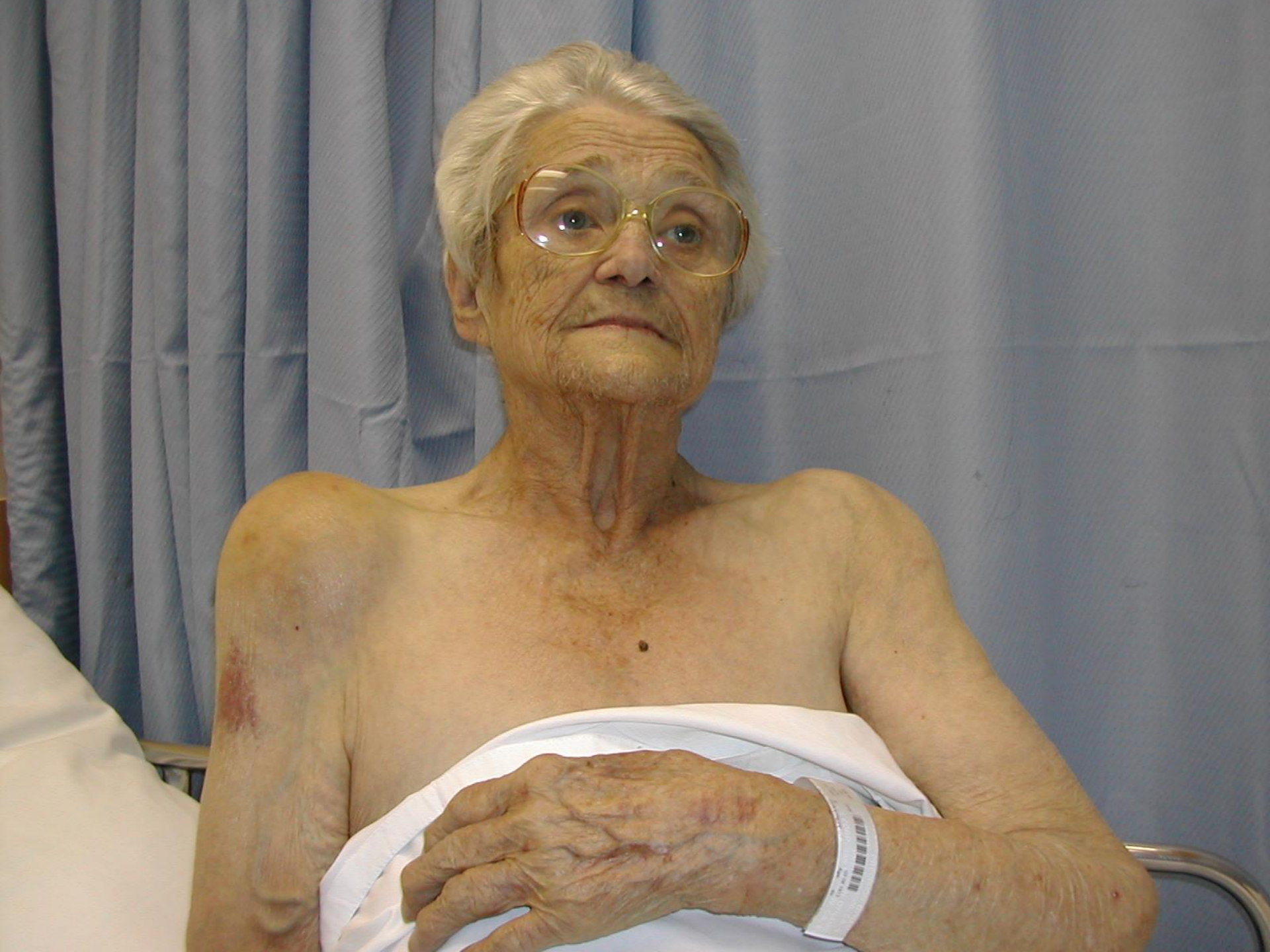












Connective Tissue Disease appendix

Fluorescent ANA patterns

• Speckled	non-specific; ENA
• Nucleolar	scleroderma
• Centromere	CREST
• Homogenous	non-specific; DNA; histones
• Rim (peripheral)	DNA

Titre – disregard 1/120, sit up at 1/640?

ANA

- Insoluble nuclear antigens
  - Anti-DNA
  - Anti-histone
- Soluble nuclear antigens
  - ENA

Extractable Nuclear Antigens

- Sm 30-40% SLE; rare in others
- U_1RNP MCTD (by definition); SLE
- Ro (SS-A) Sjøgren's; SLE
- La (SS-B) Sjøgren's; SLE
- Scl-70 (topoisimerase) Scleroderma
- Jo-1 Dermatomyositis
- Lamin ?
- Unidentified Precipitin Line

“SLE type”

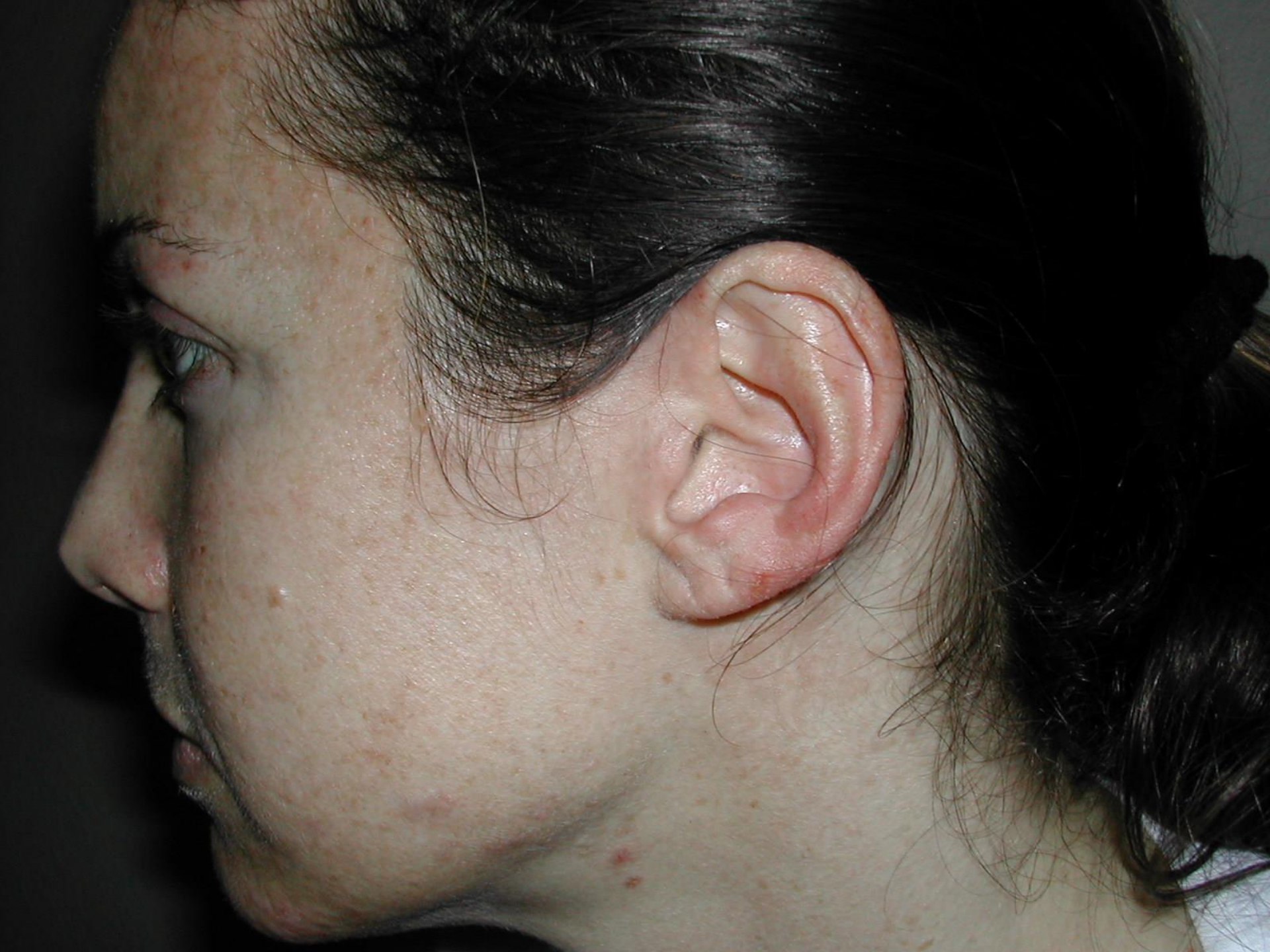
- Young female who is sick, with alopecia, rash, serositis. There are joint pains, but not the luxurious synovitis that one sees with RA.
- Tests show positive ANA, DNA as well and has anaemia, thrombocytopenia, leucopenia and lymphopenia. The complement is often reduced. The urine sediment is often active.
- Differential diagnosis – rheumatoid arthritis and infection.

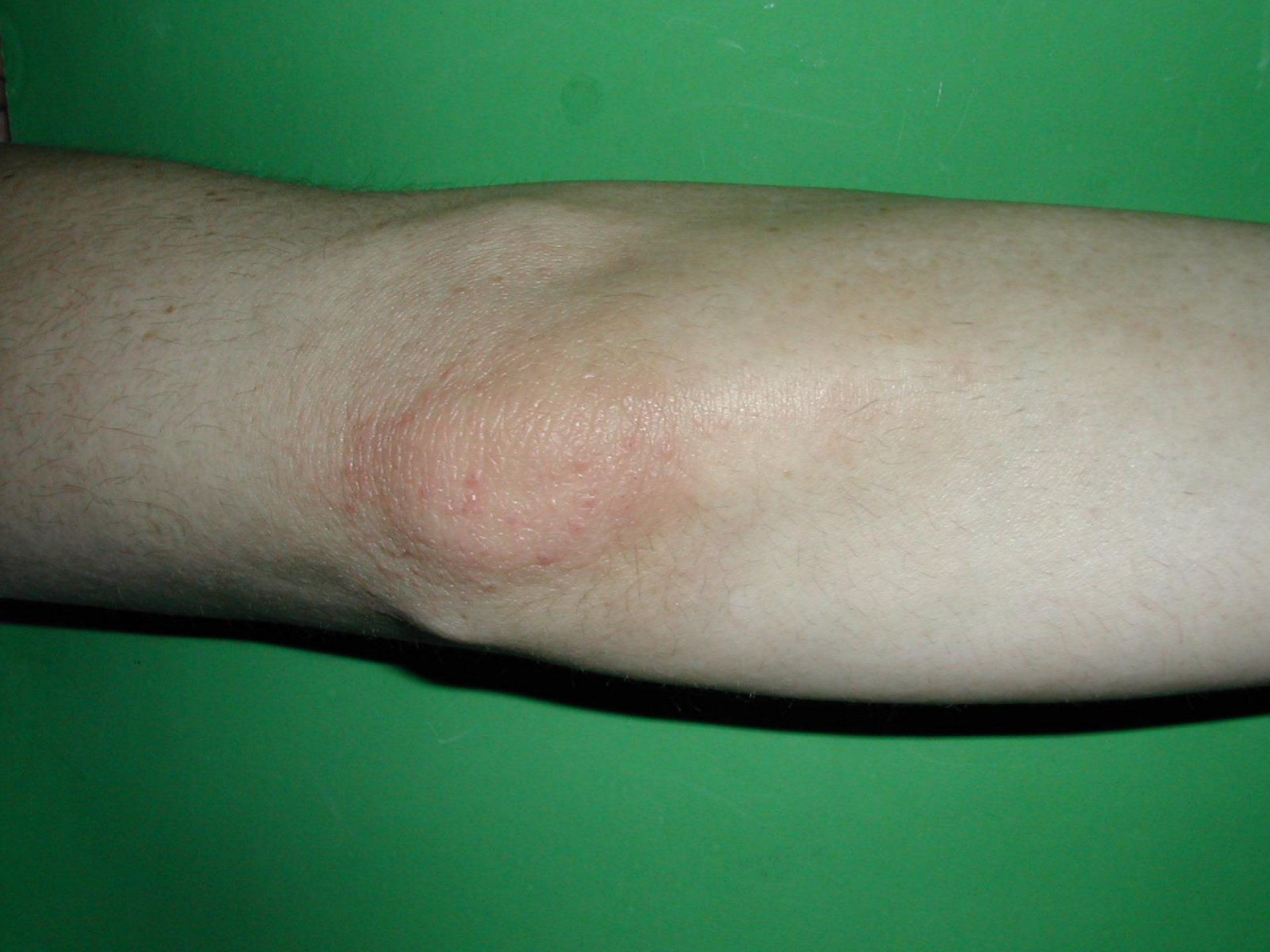
The “antiphospholipid type”

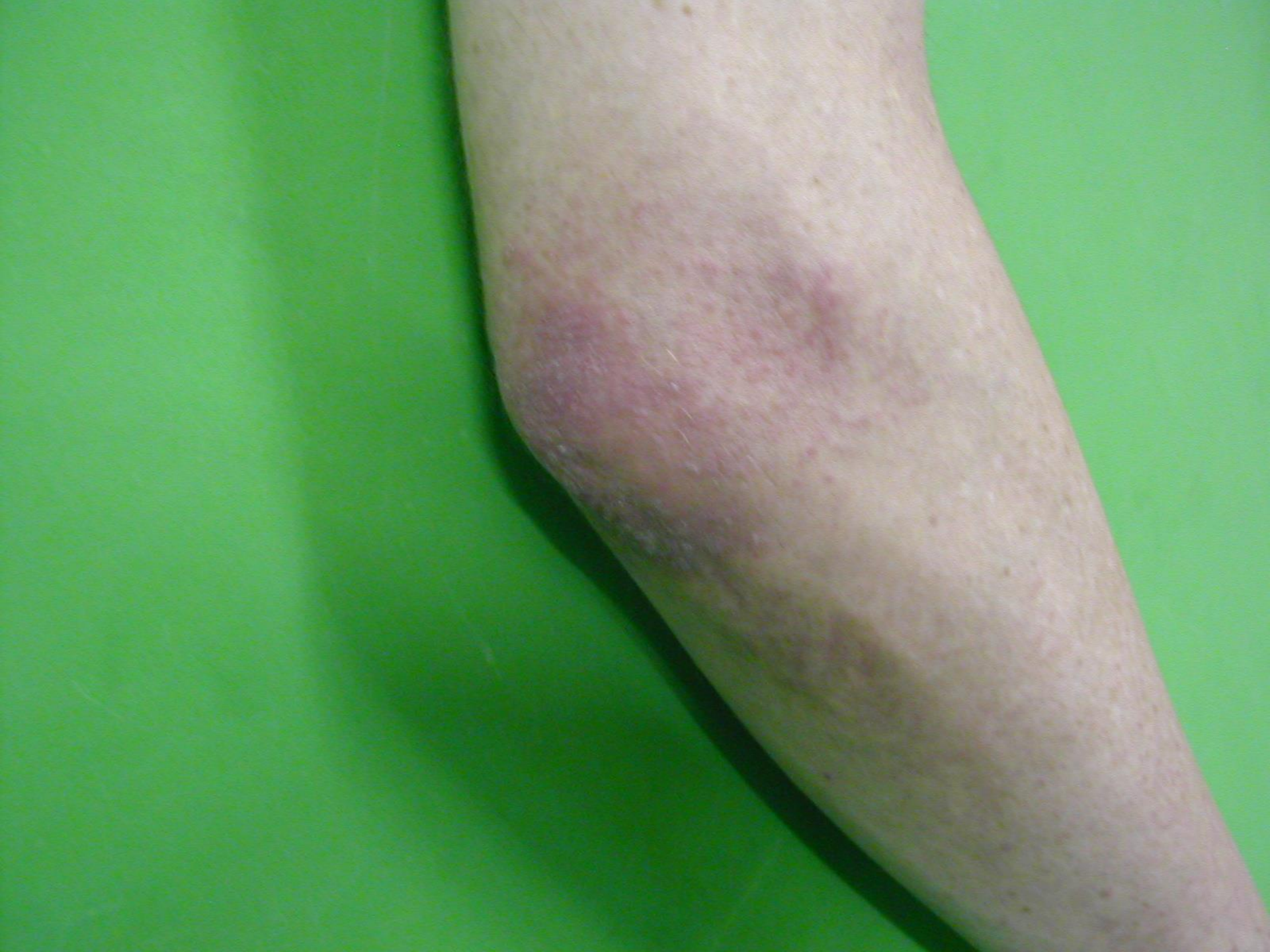
- Young women
- Venous thrombosis, arterial thrombosis, thrombocytopenia, and recurrent mid-trimester abortion.
- Less commonly, livedo reticularis, cutaneous ulceration, endocarditis, CNS manifestations.
- ANA usually positive, may not be specific (check for anti-Ro antibodies).
- Anticardiolipin antibodies (IgG, IgM) in high titre, with or without the lupus anticoagulant.

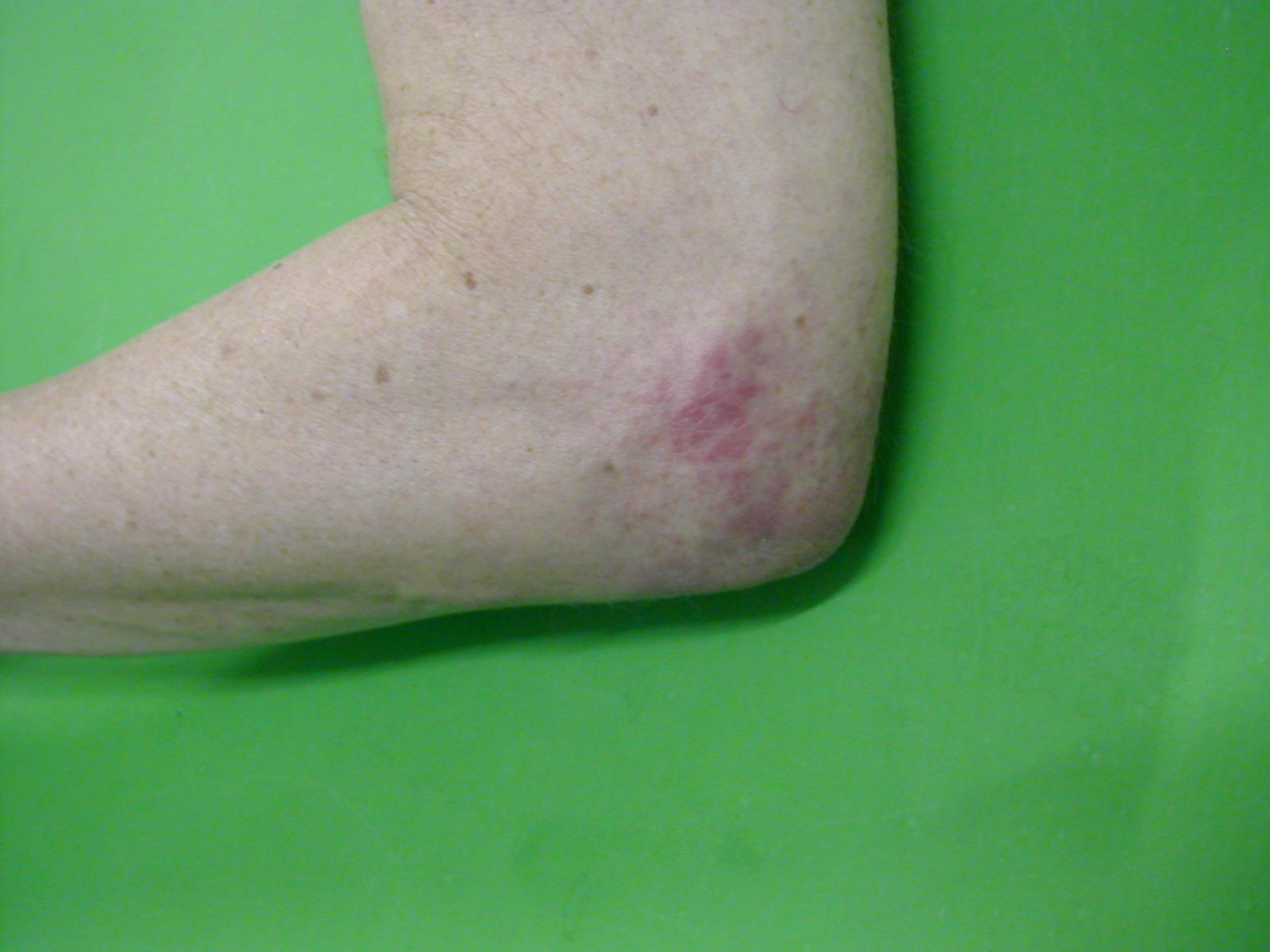
The “PAN type”

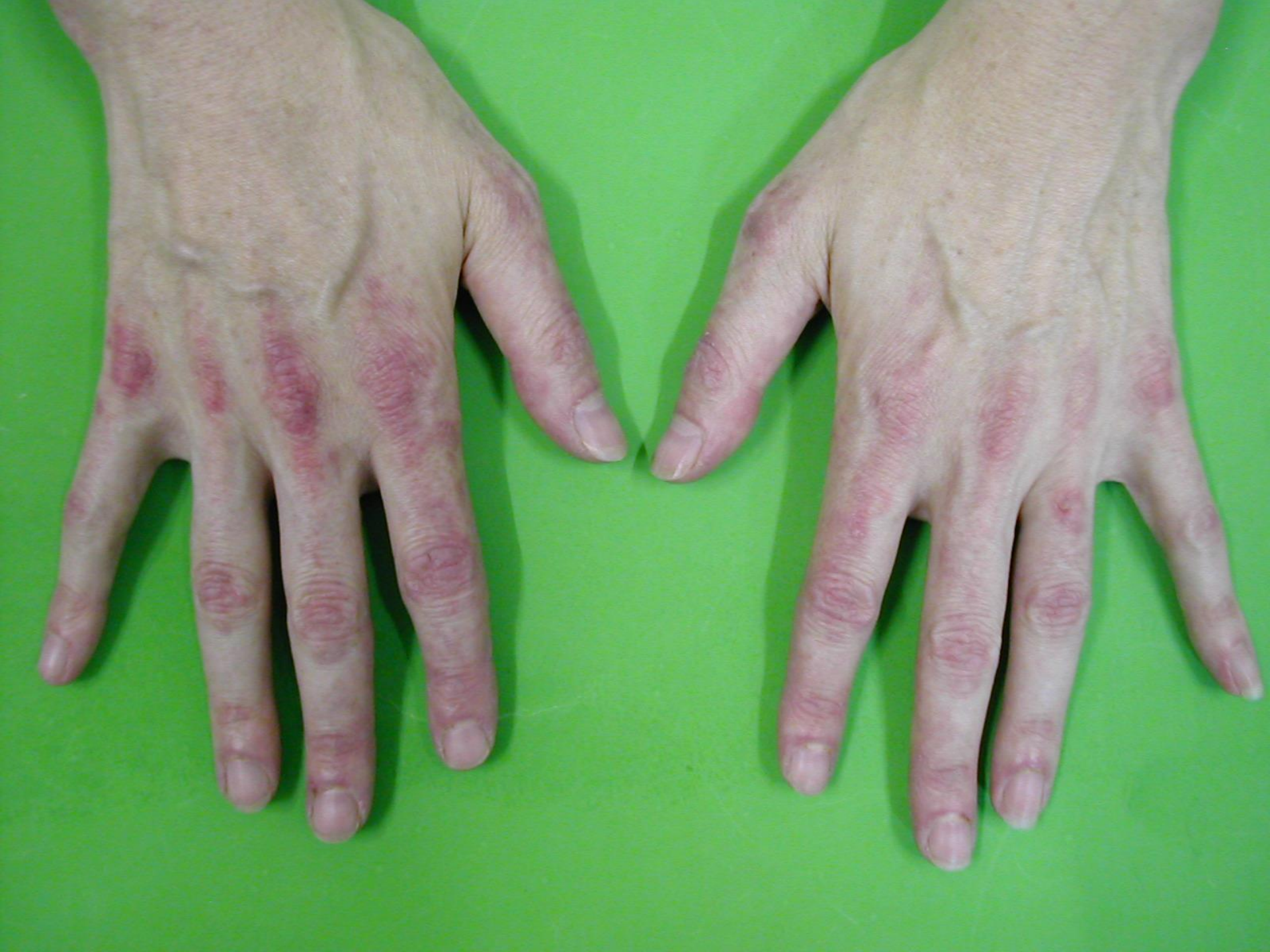
- Middle aged to elderly men and women. Check drug reactions and Hep B, Hep C.
- Vasculitis affecting the medium to large arteries (NB neuropathy).
- The presence of pulmonary involvement and eosinophilia suggests Churg-Strauss syndrome, ENT symptoms Wegener’s granuloma.
- The usual normochromic normocytic anaemia, with leucocytosis. Complement high. The ANA is usually unhelpful – the important test is ANCA.
- Renal function is very important to assess routinely.

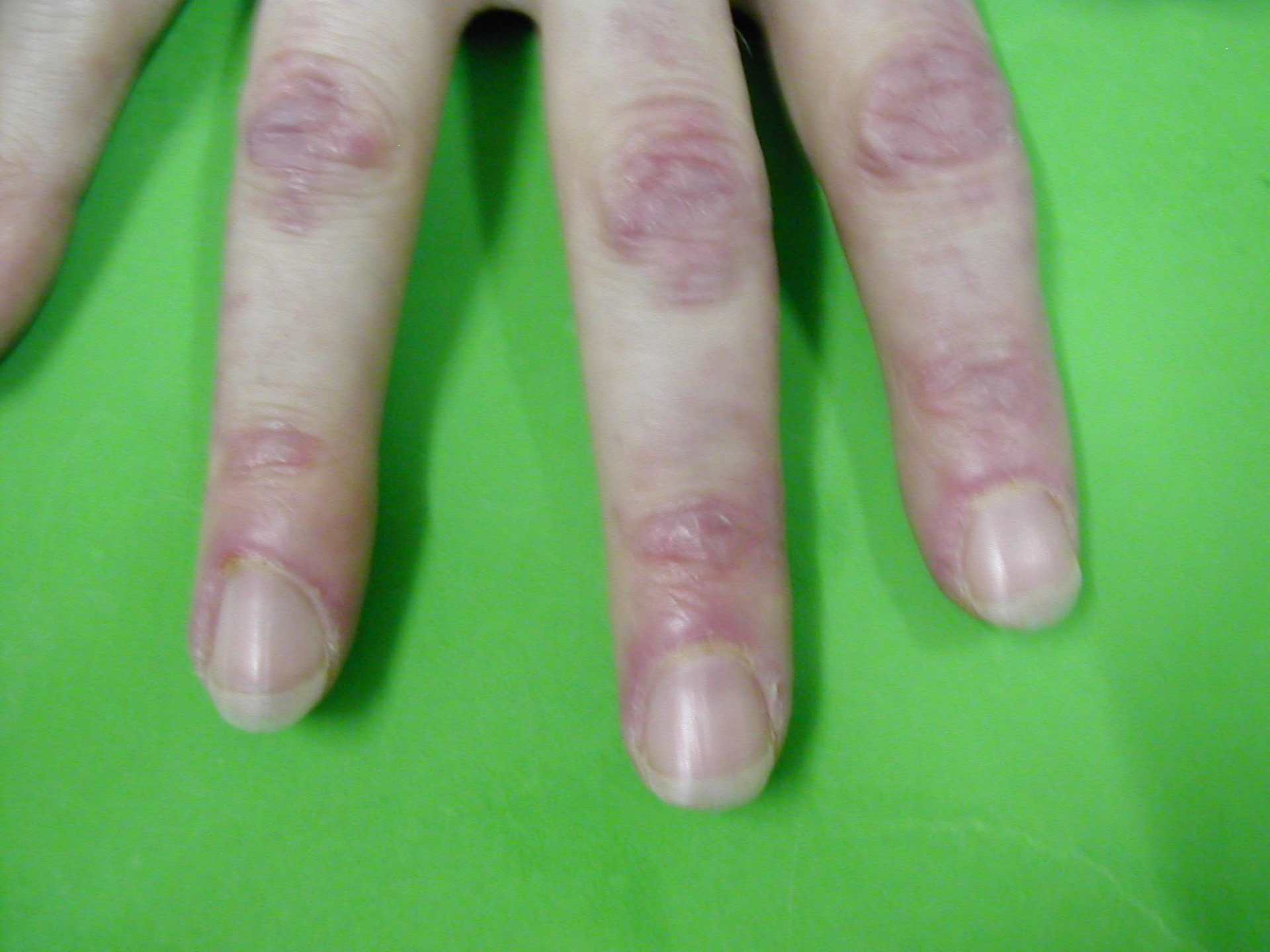


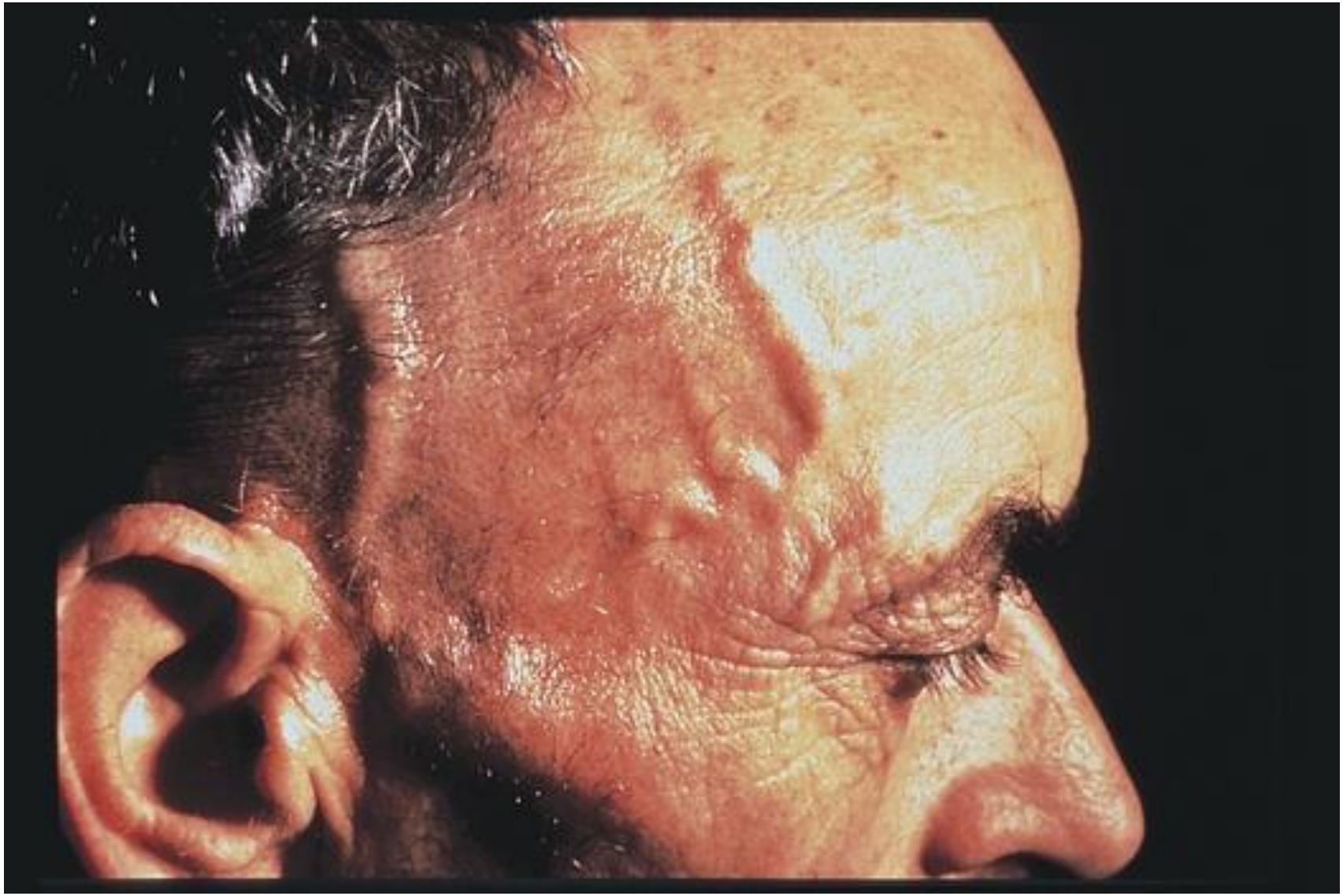


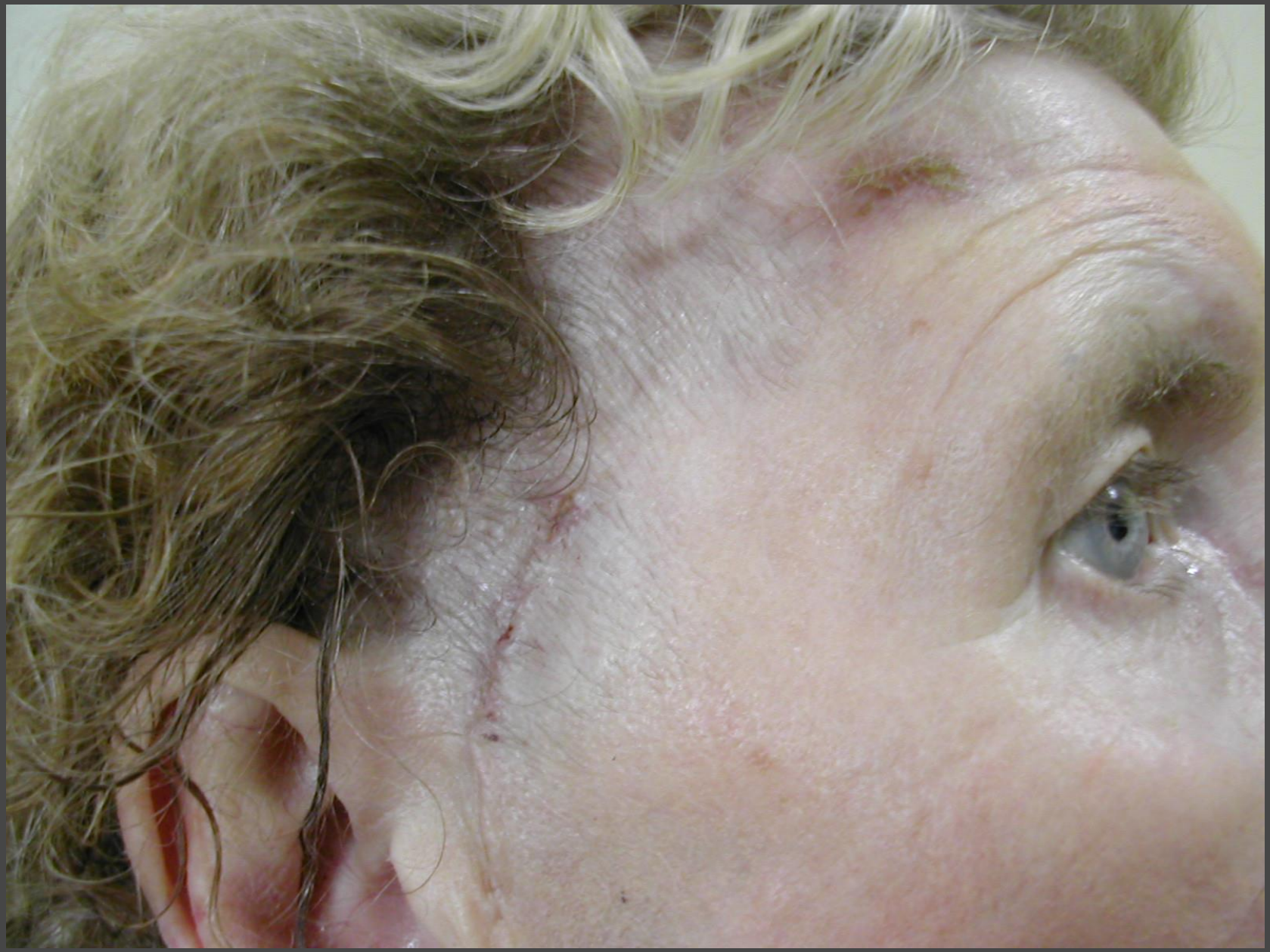


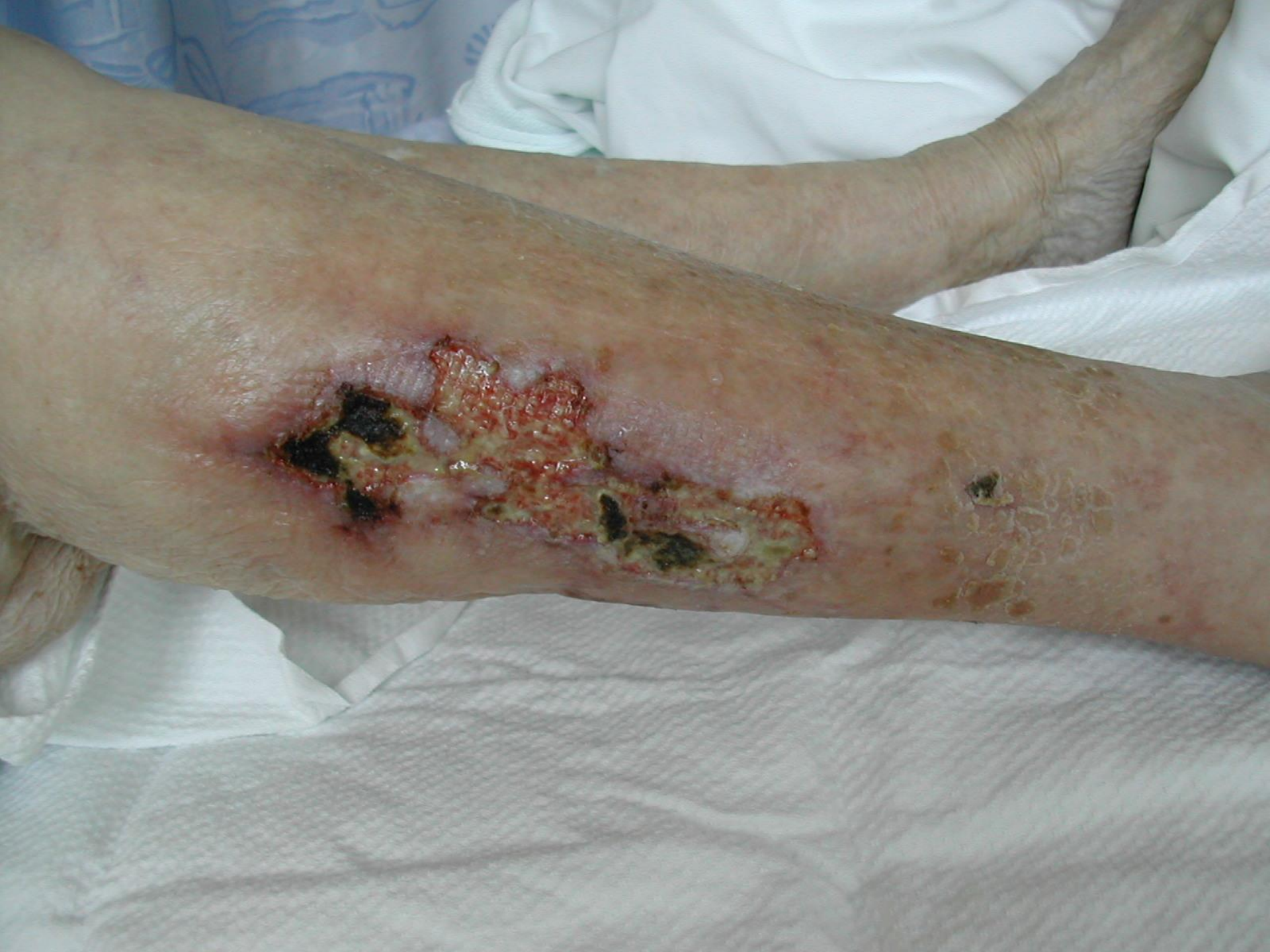


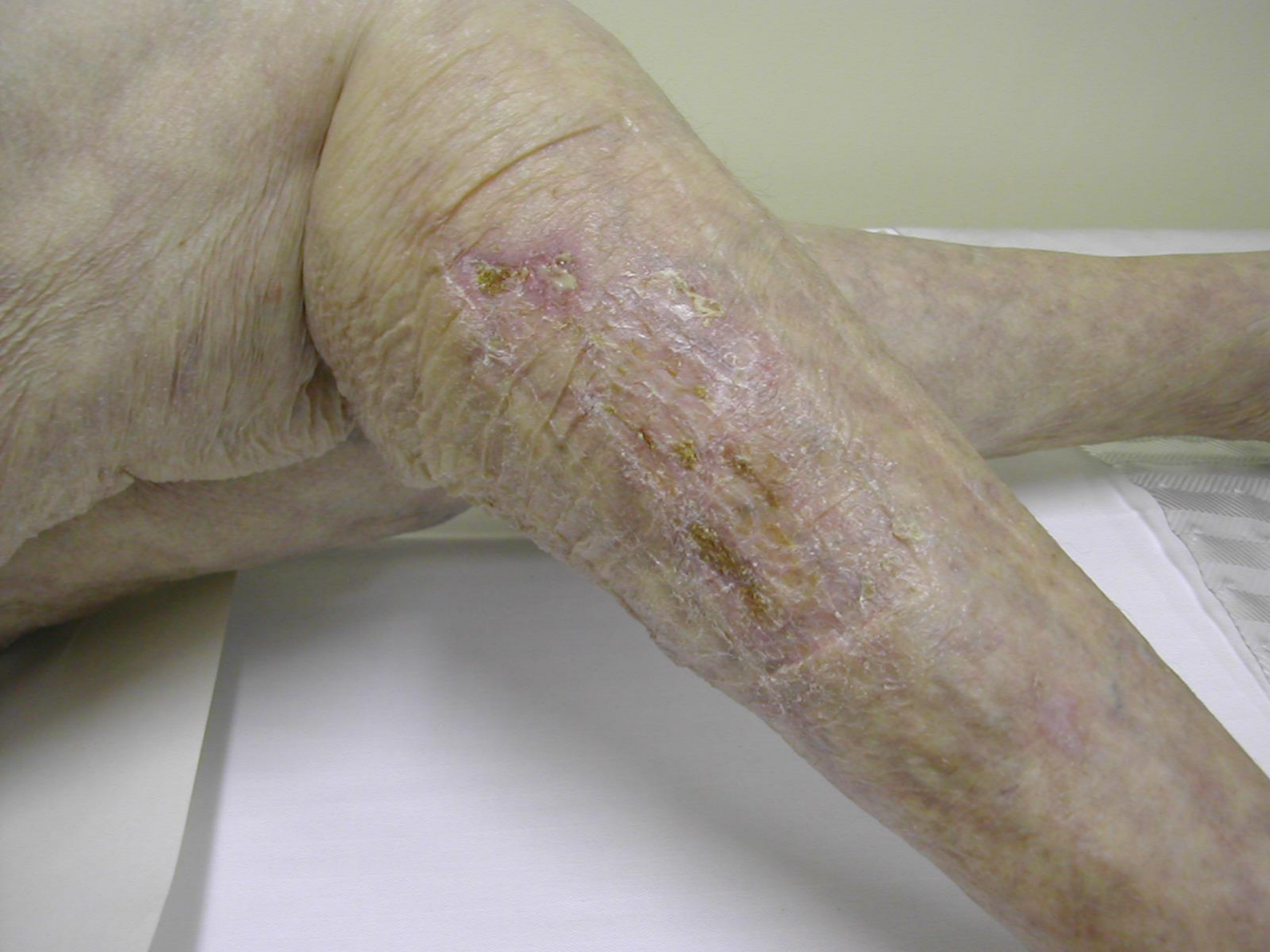


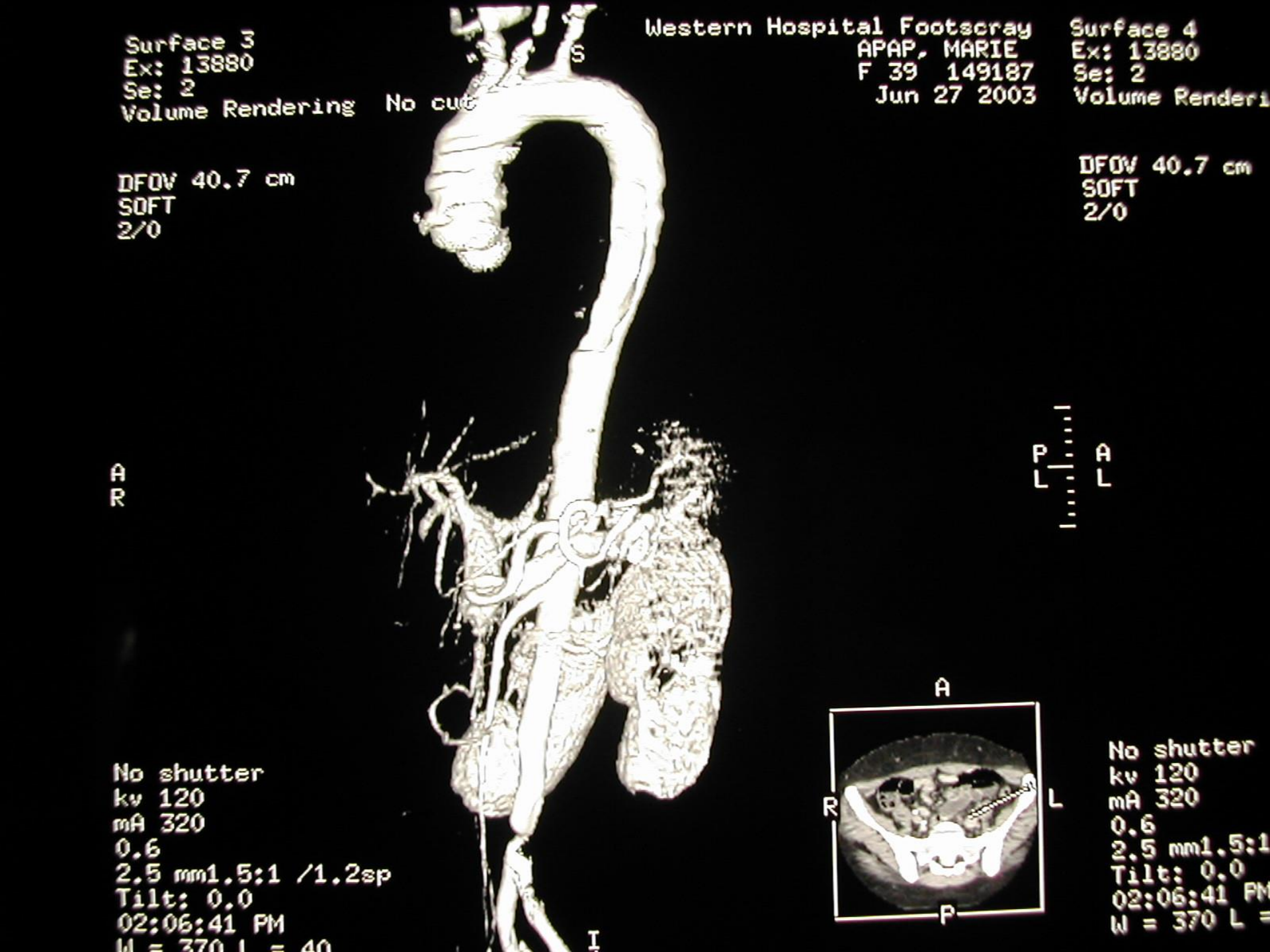








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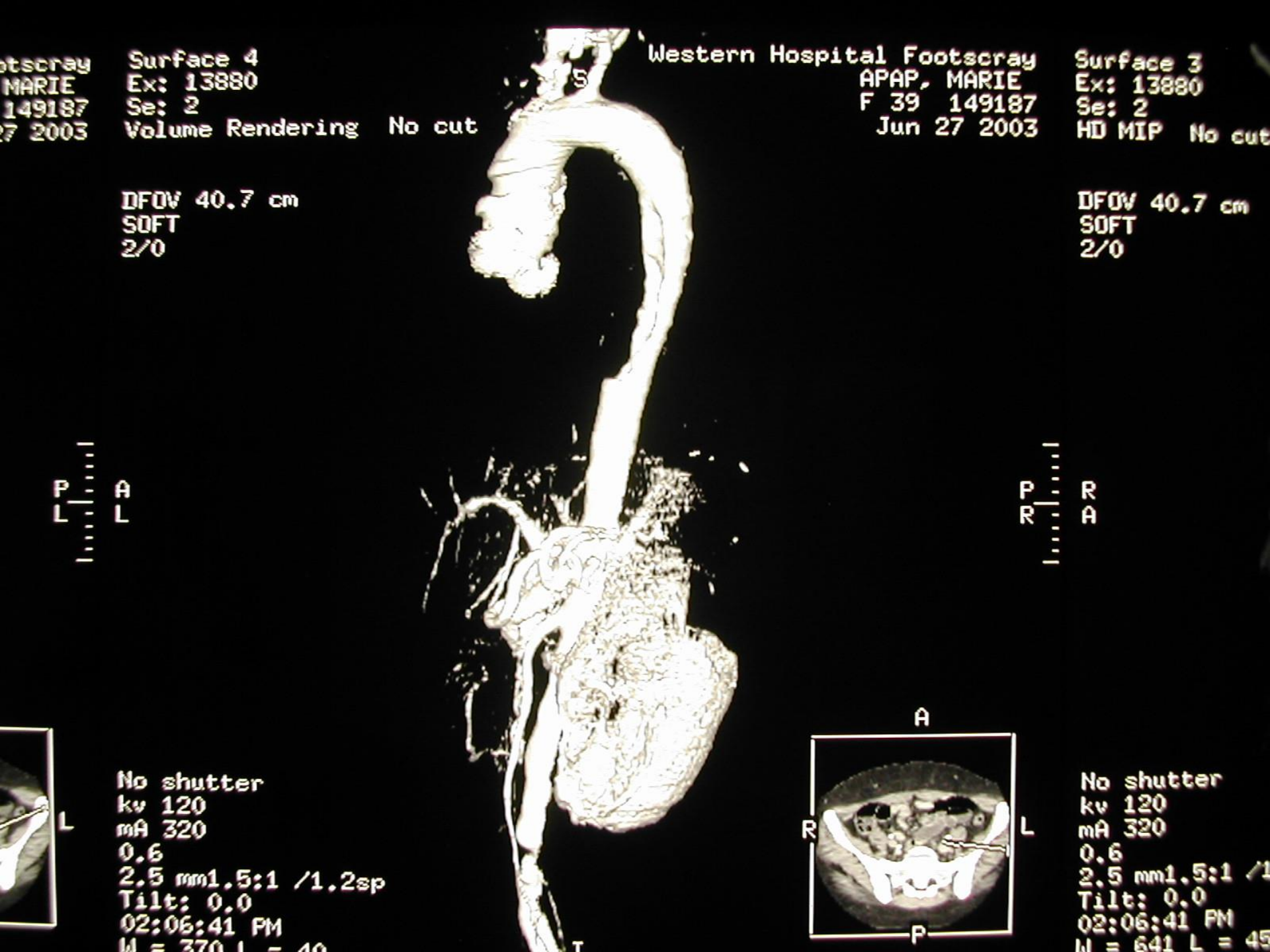
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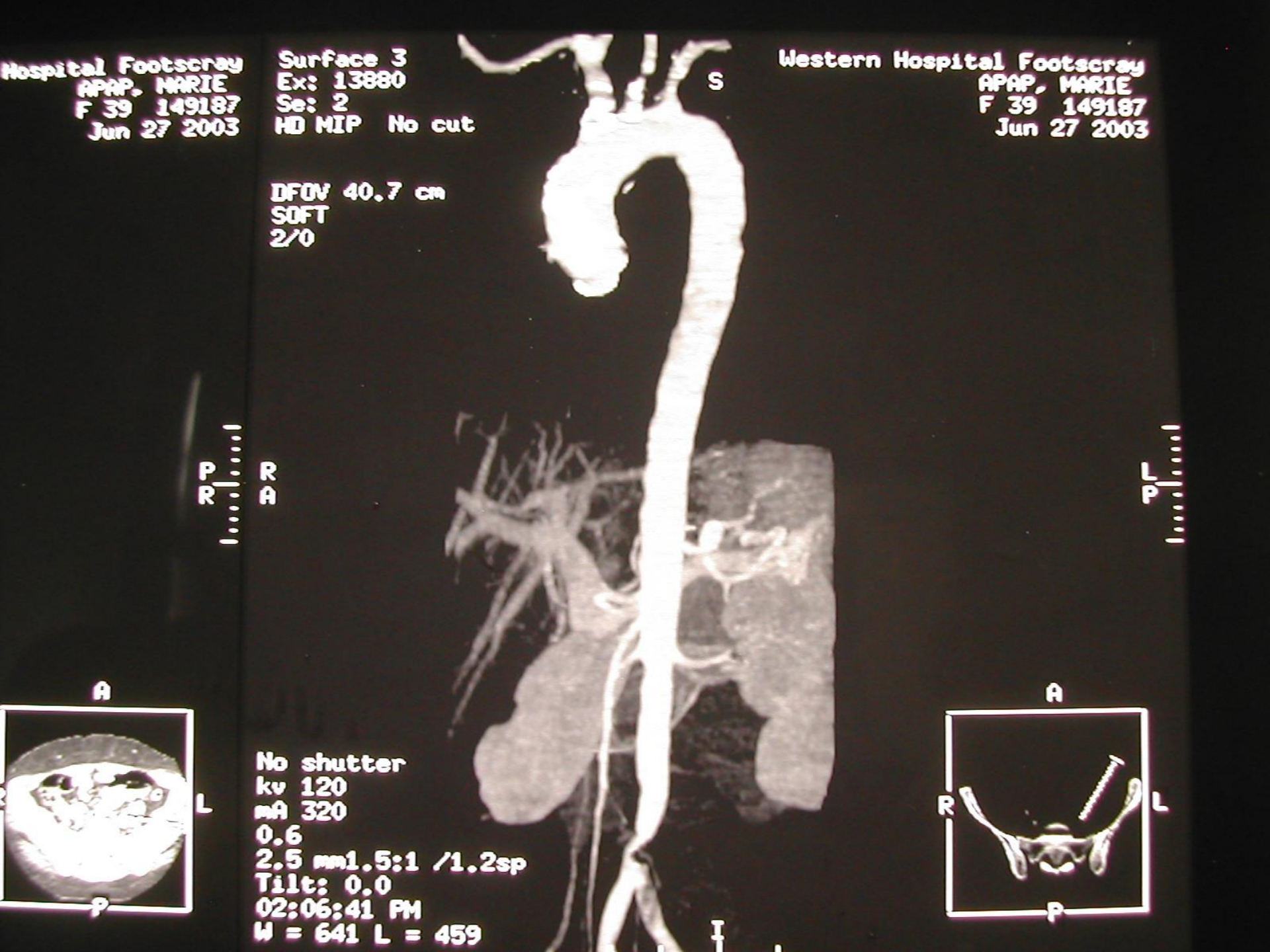
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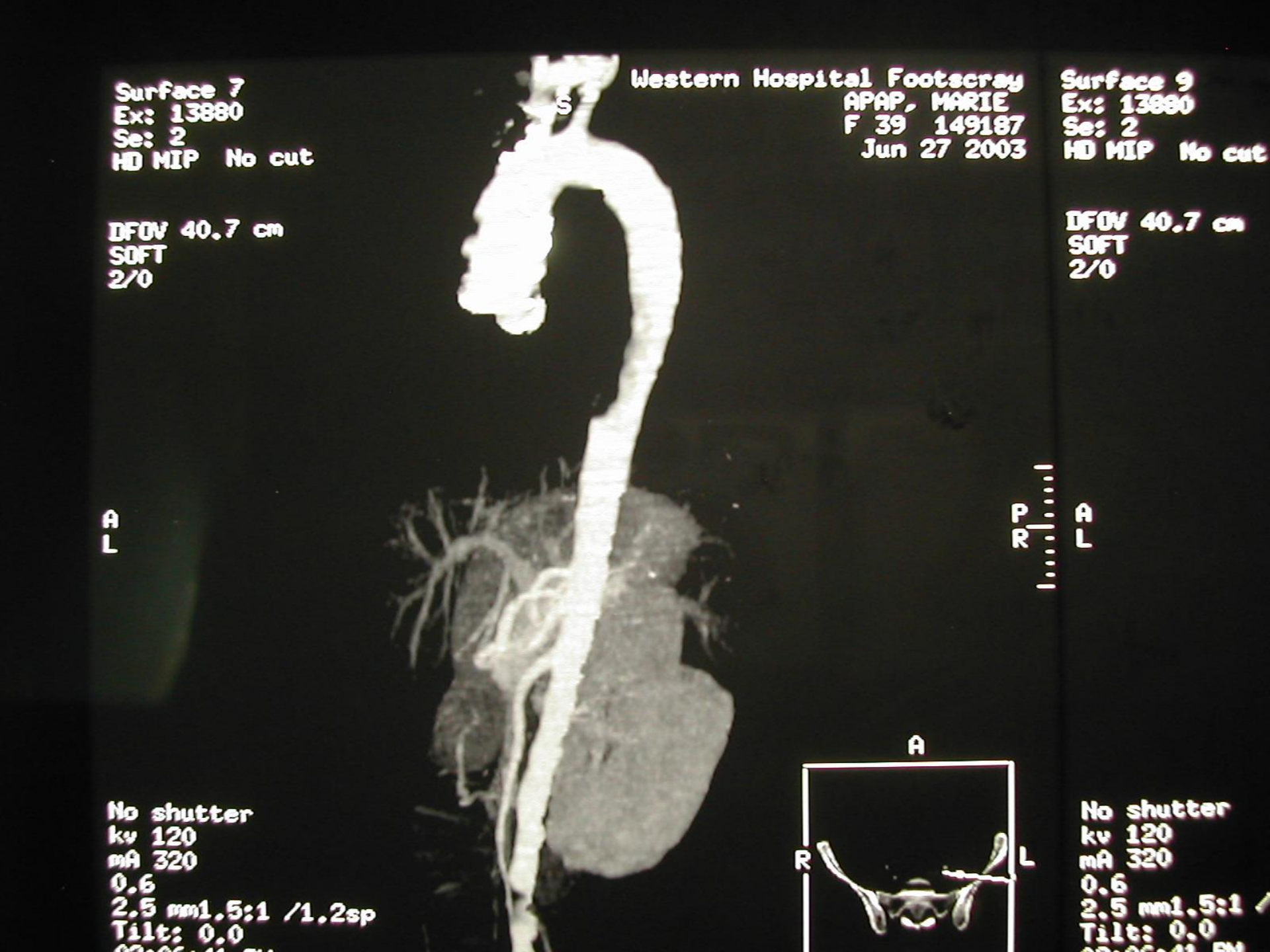
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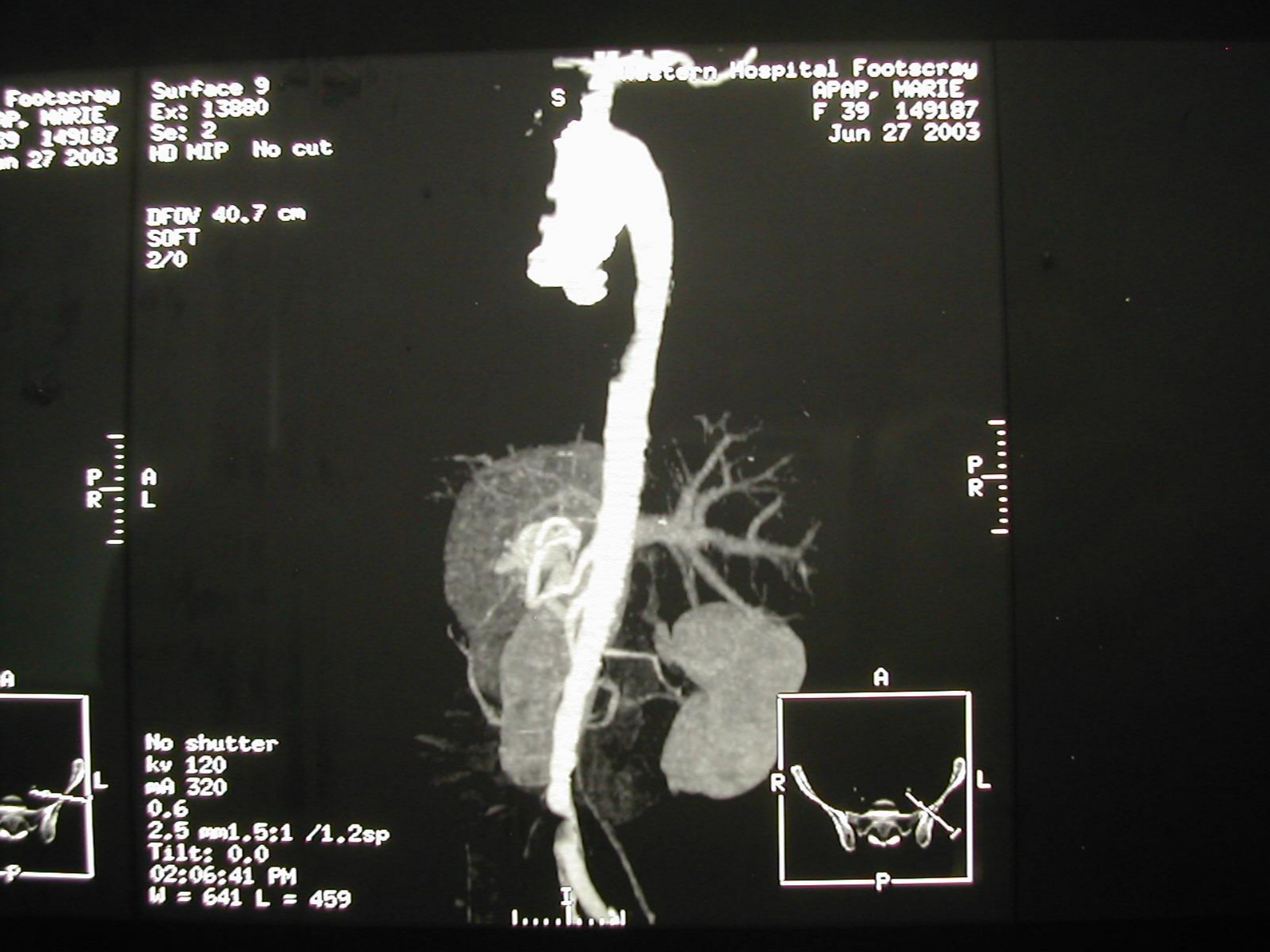
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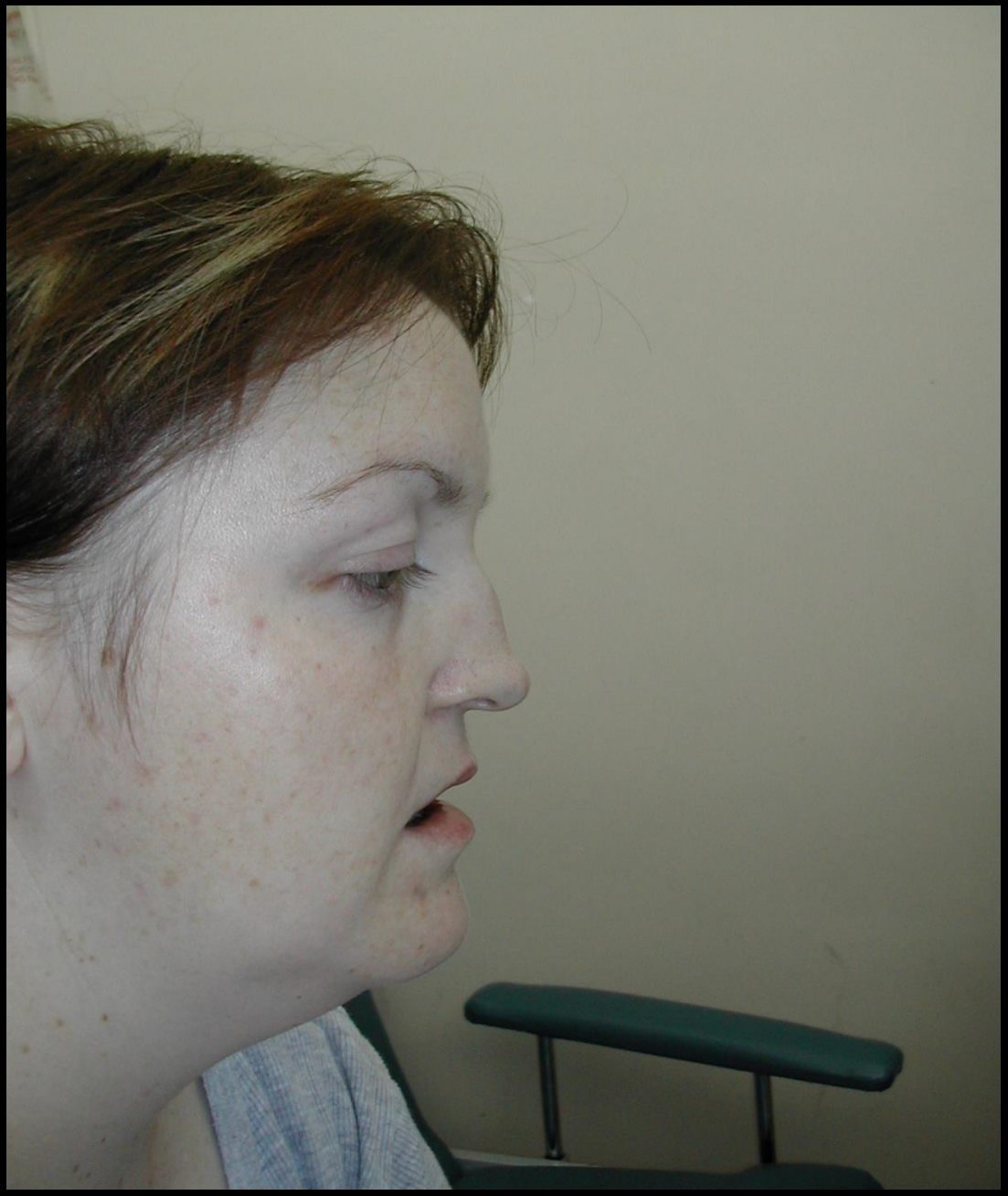

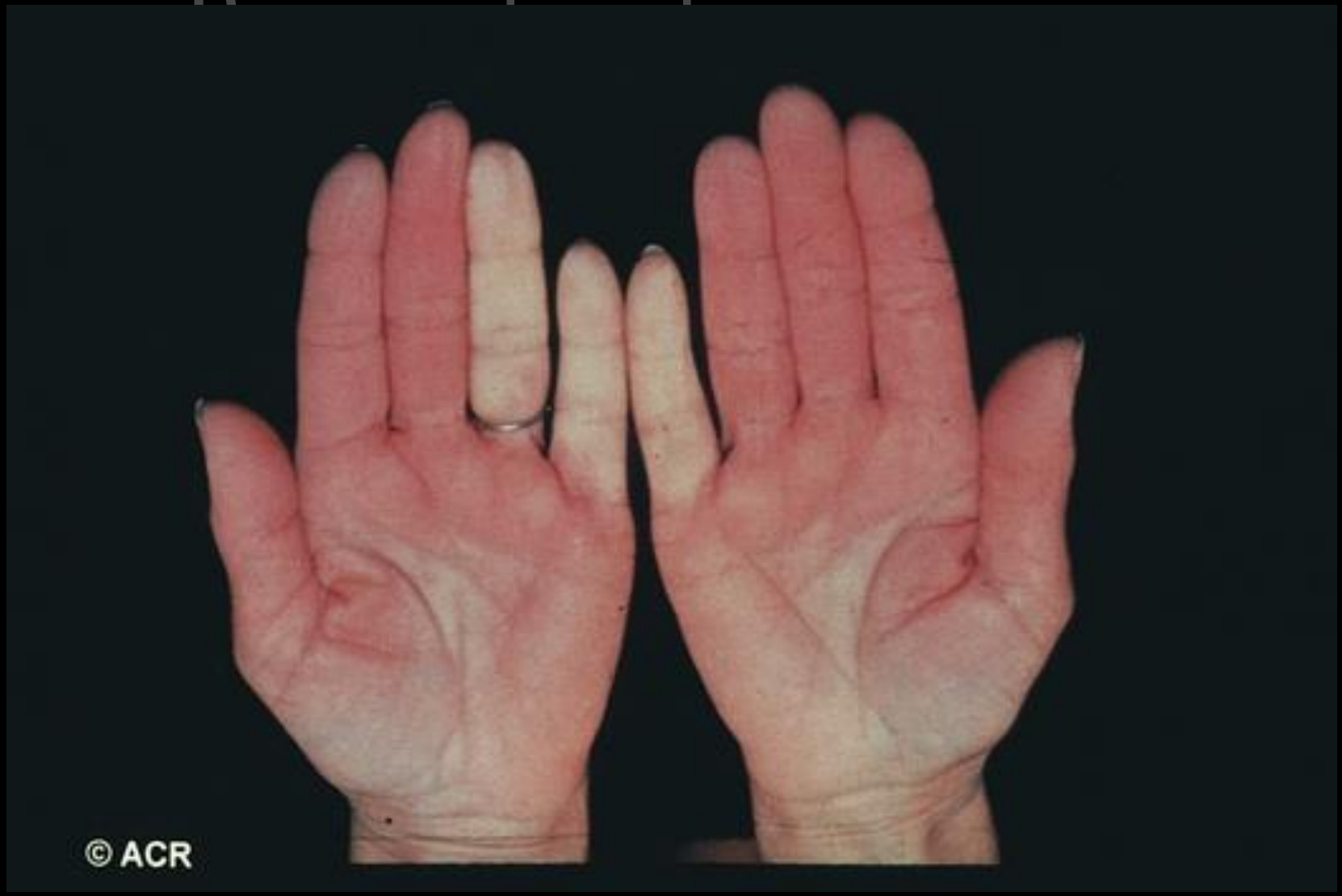
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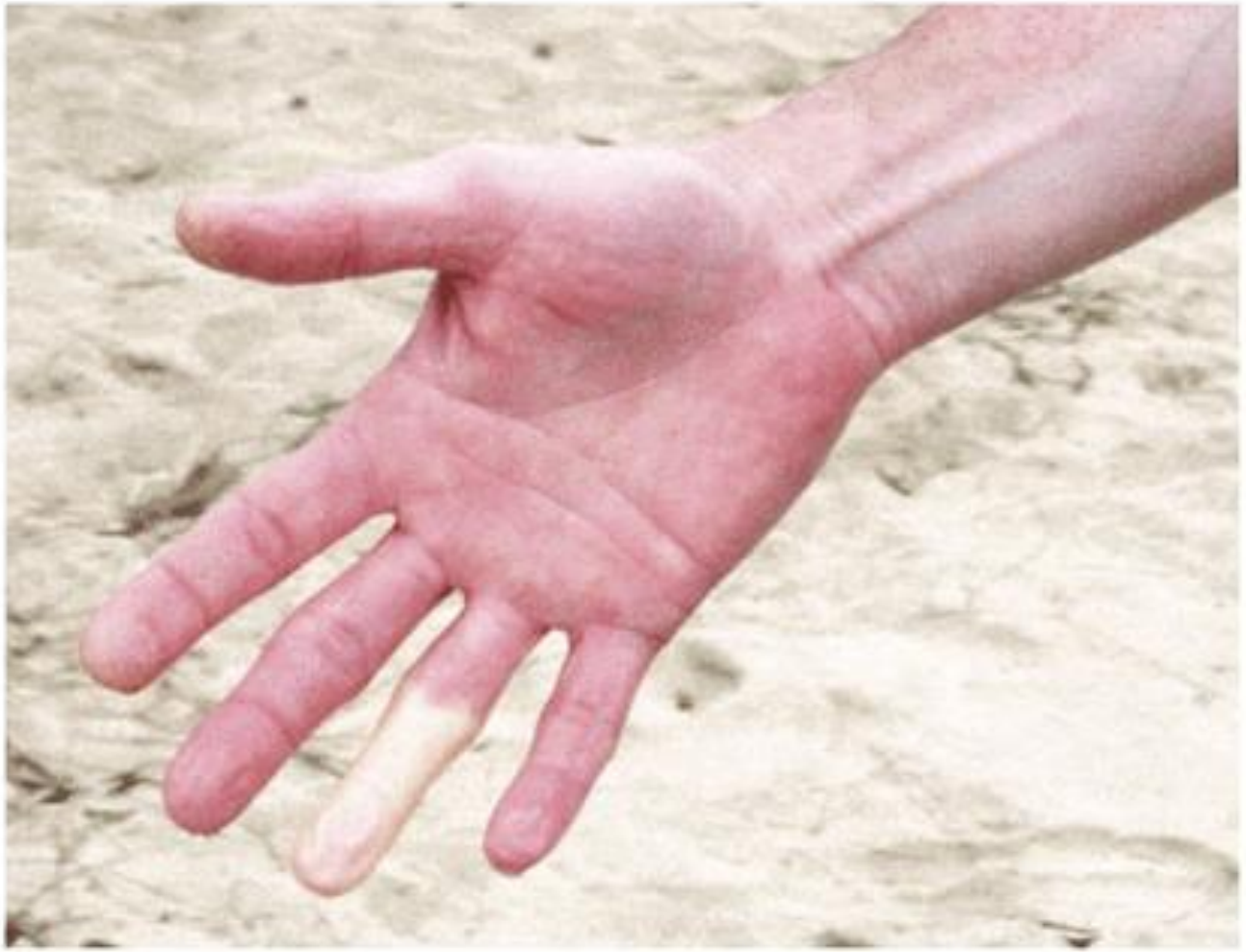

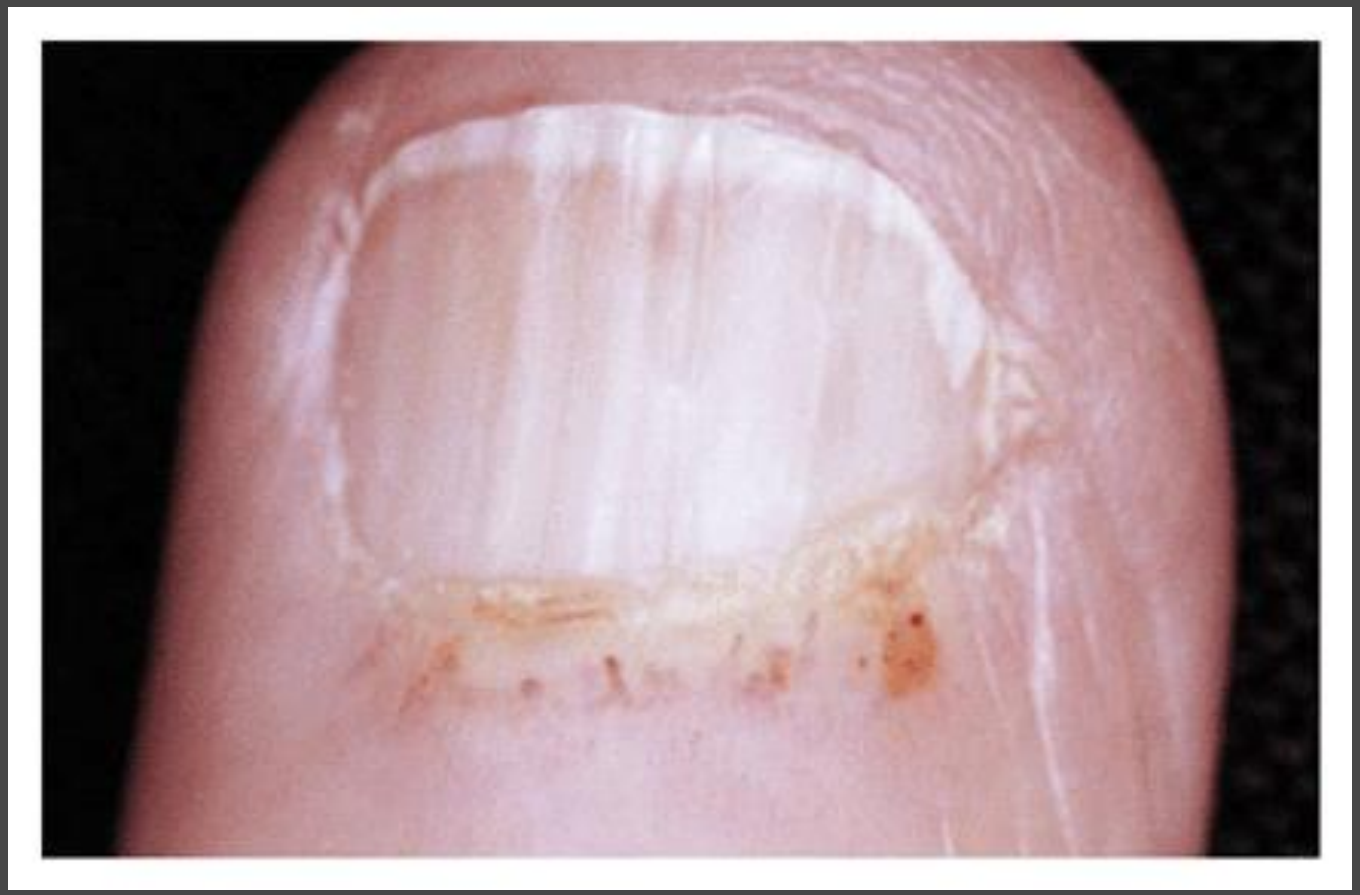

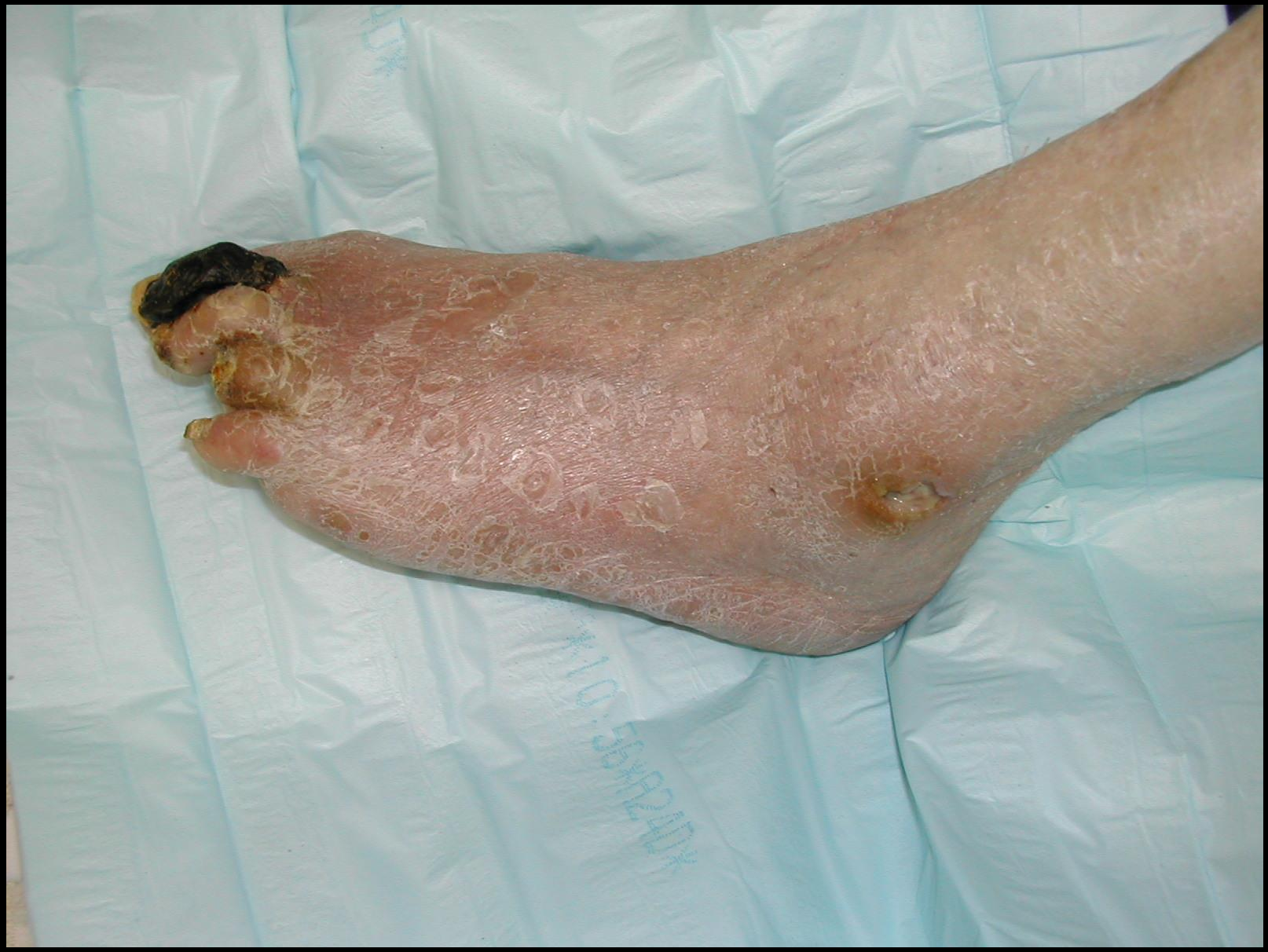

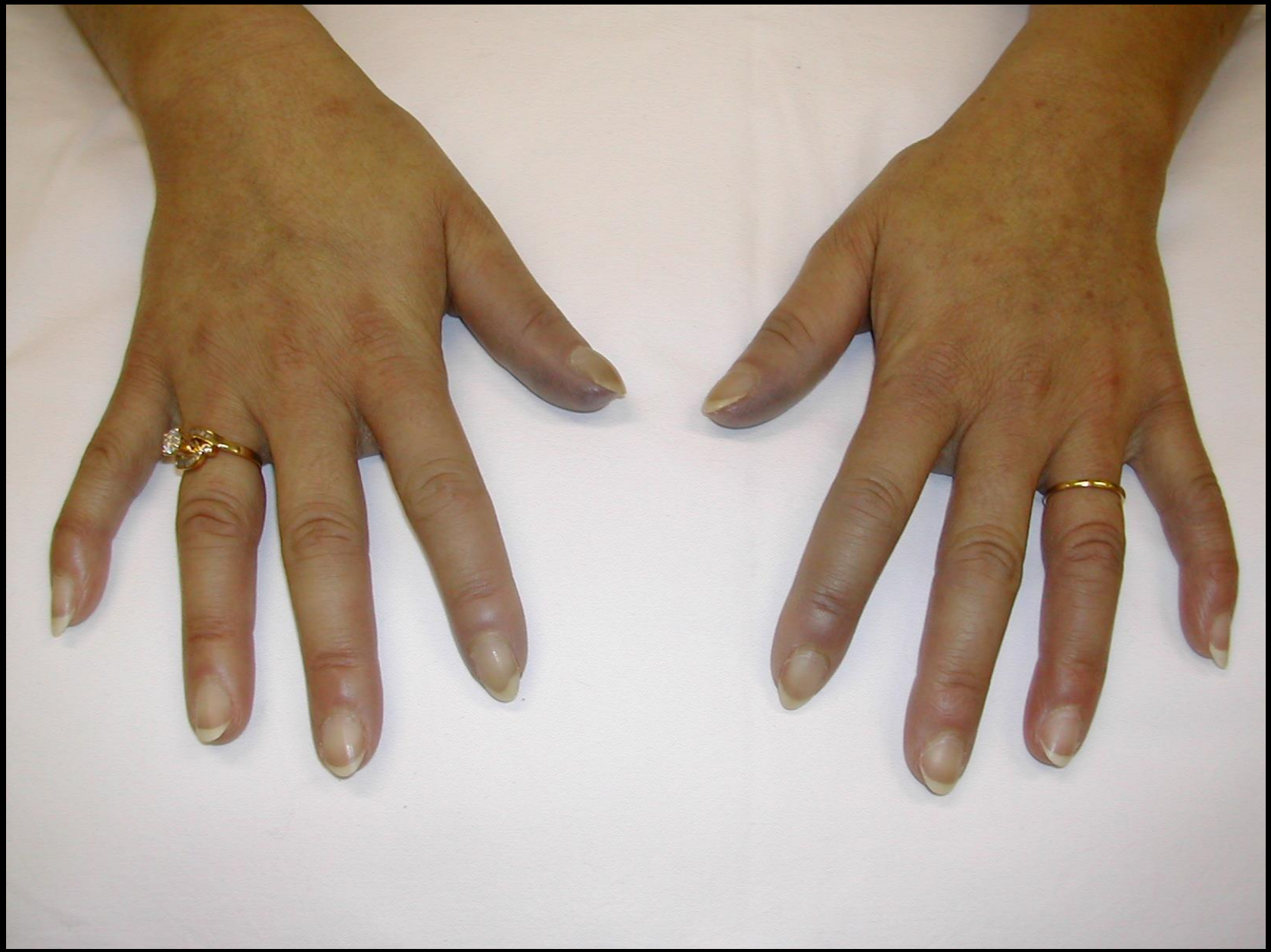

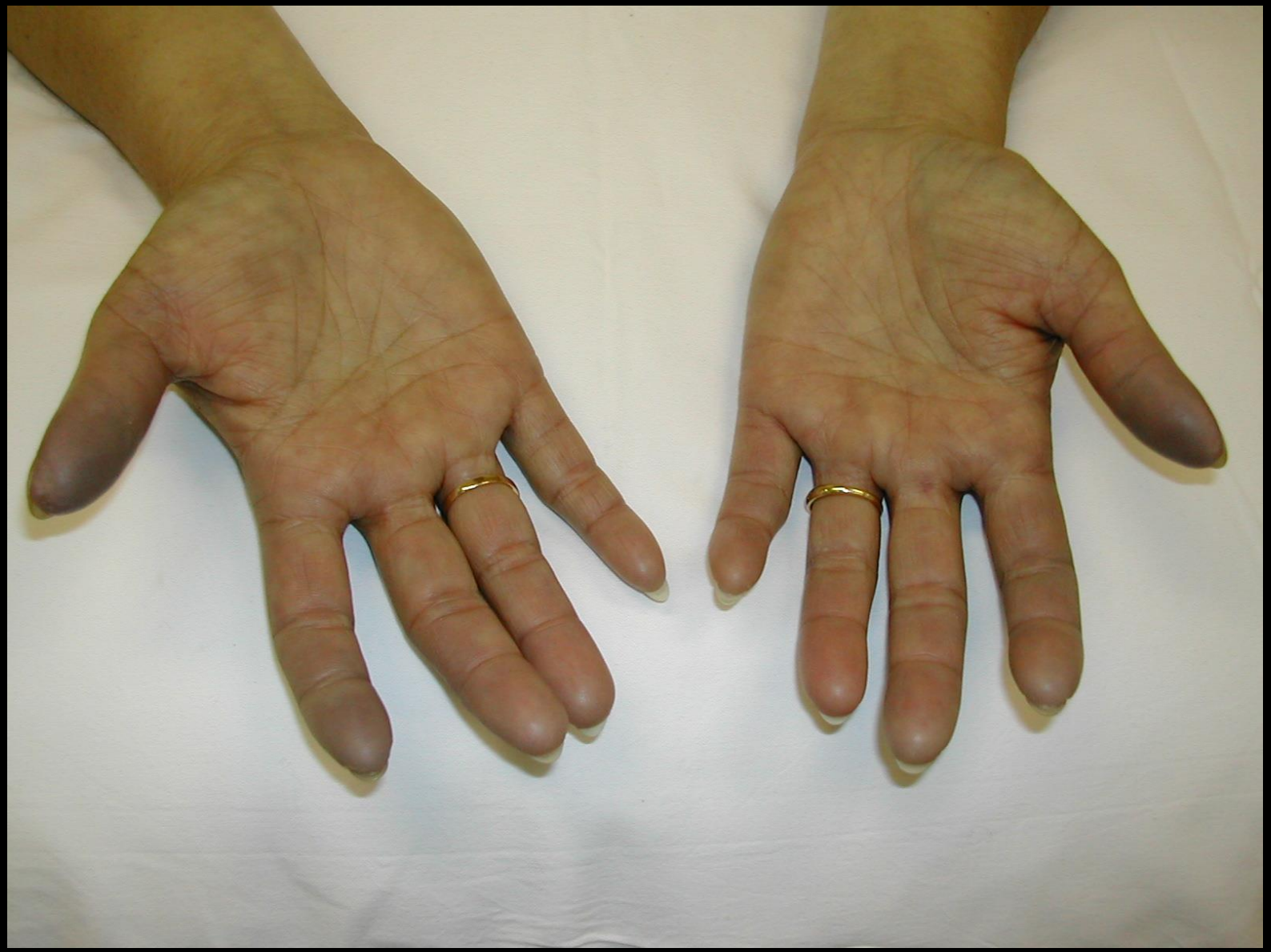

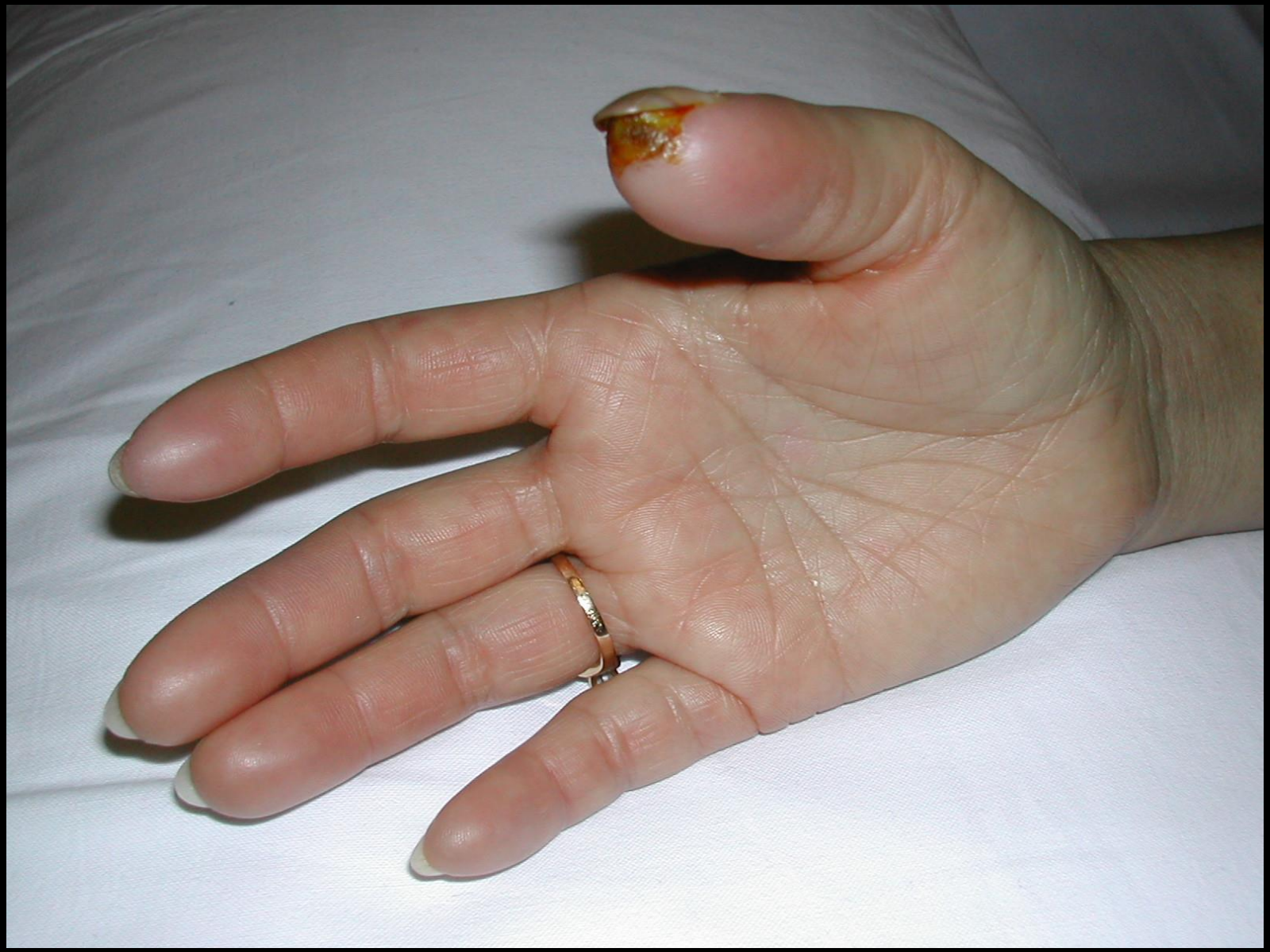

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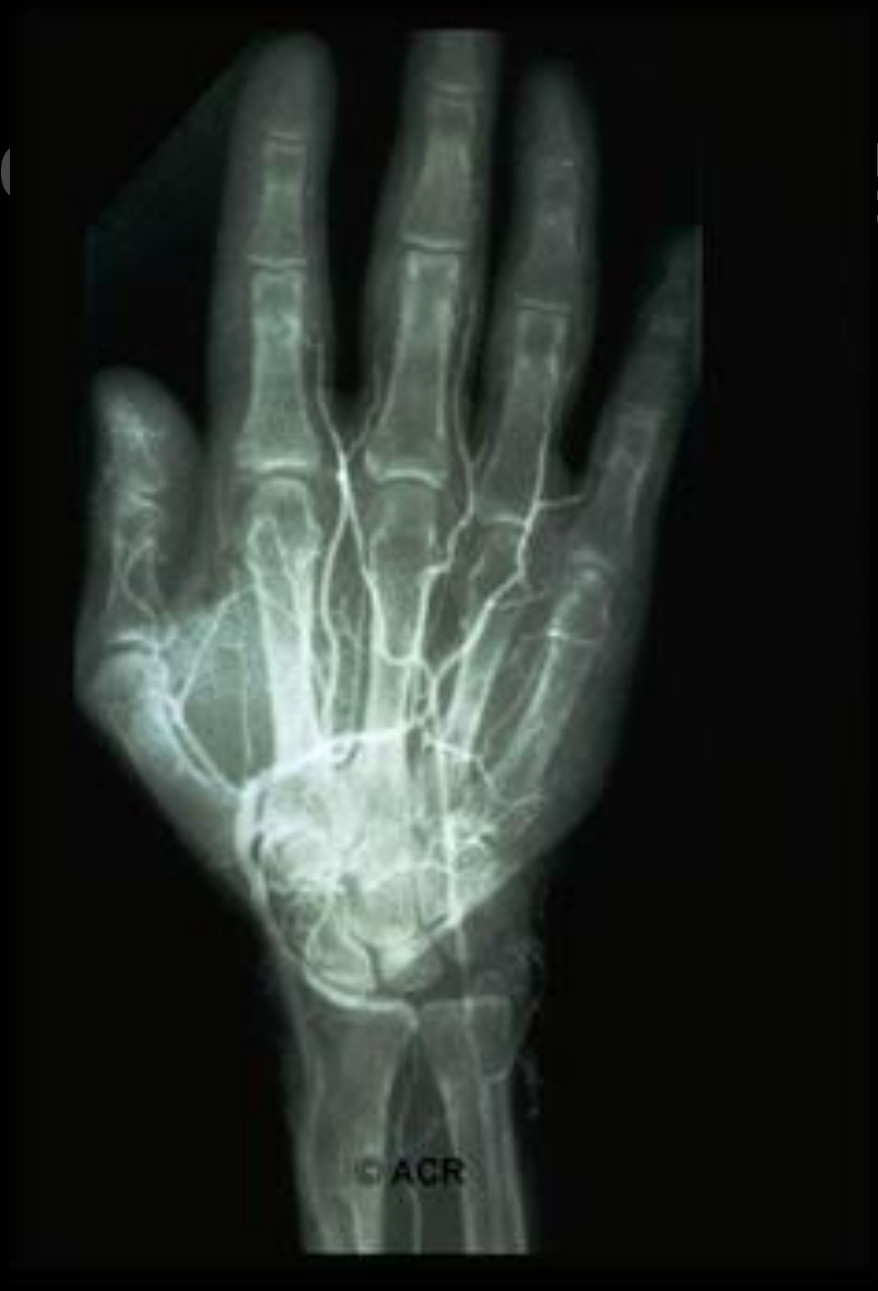

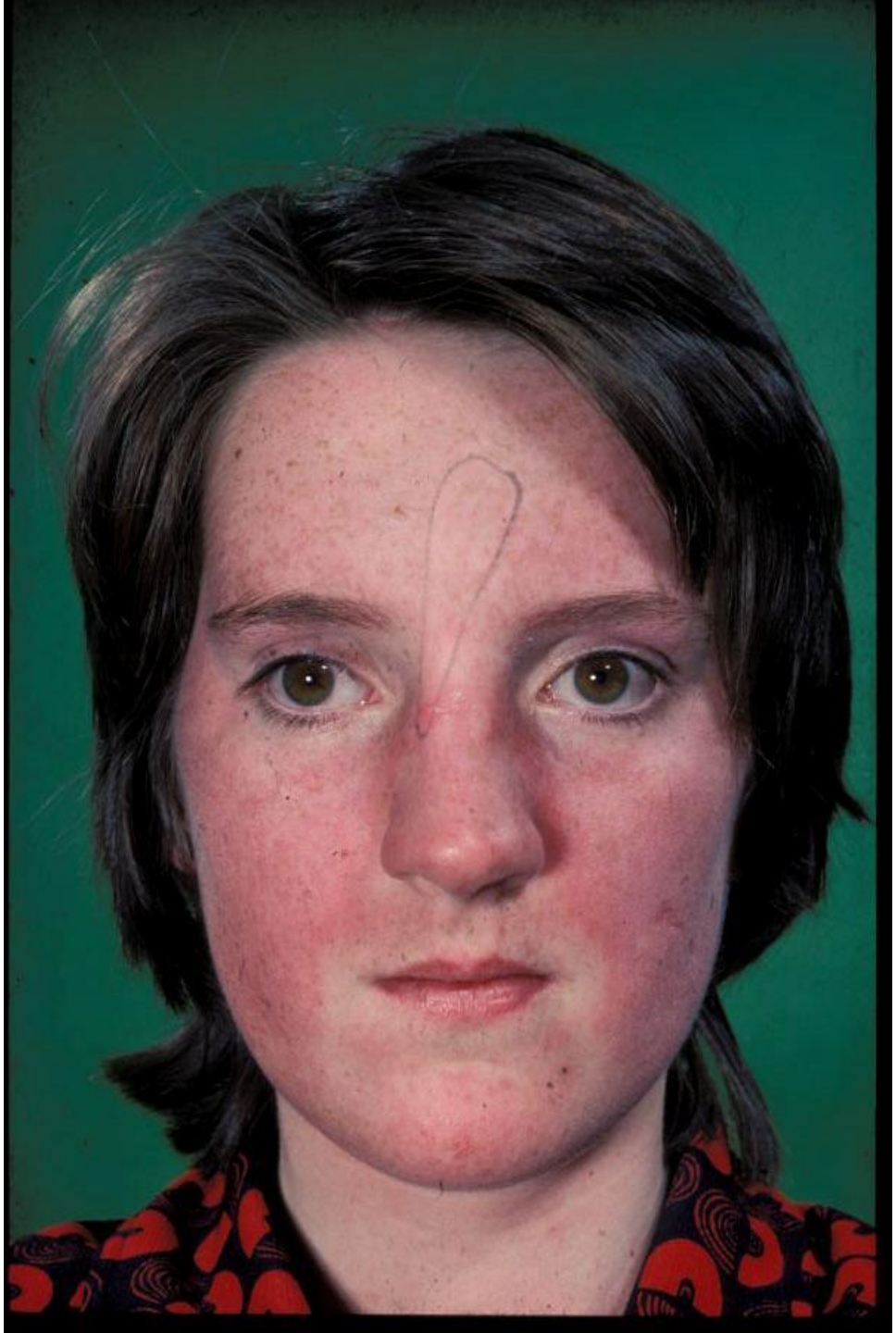

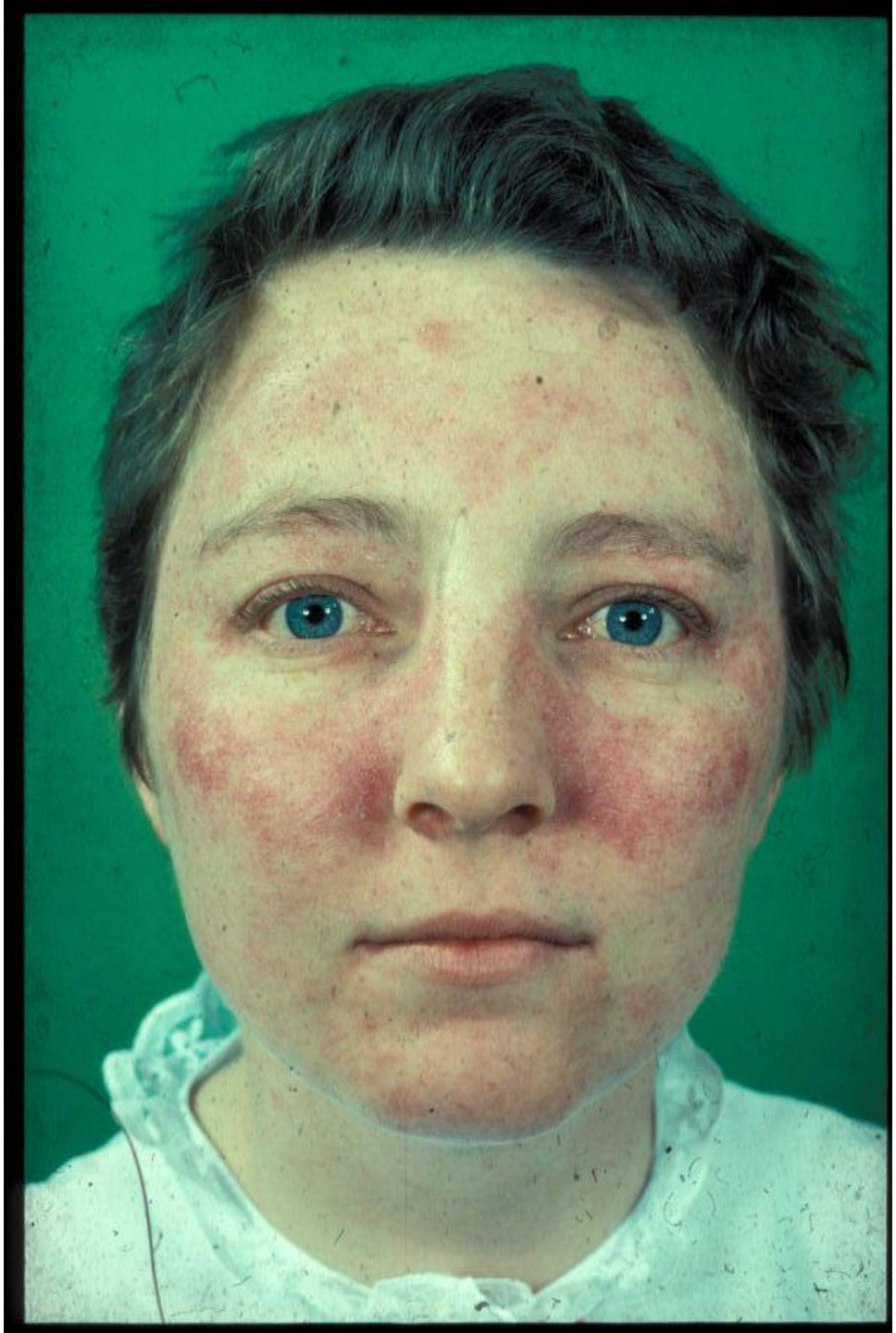

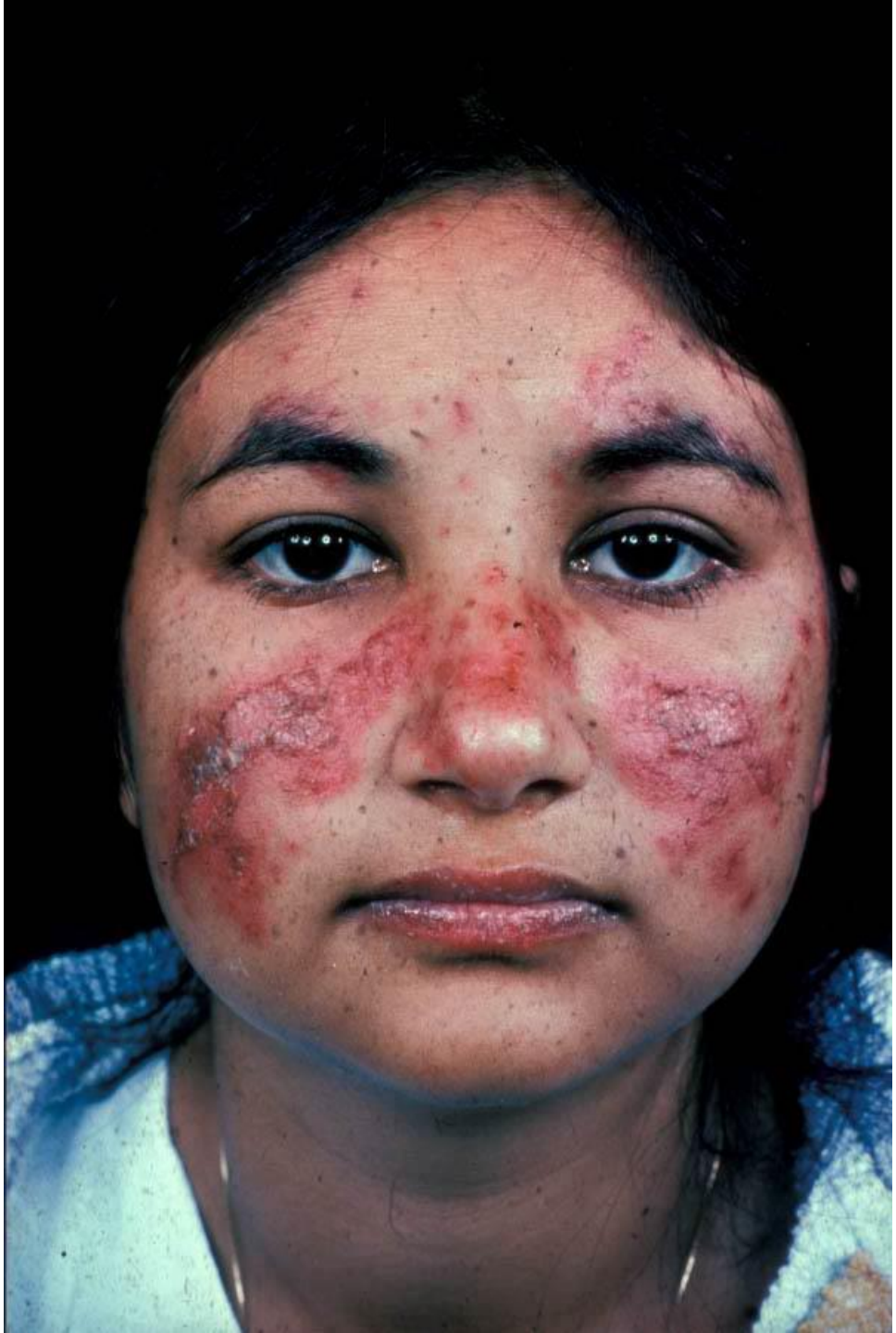

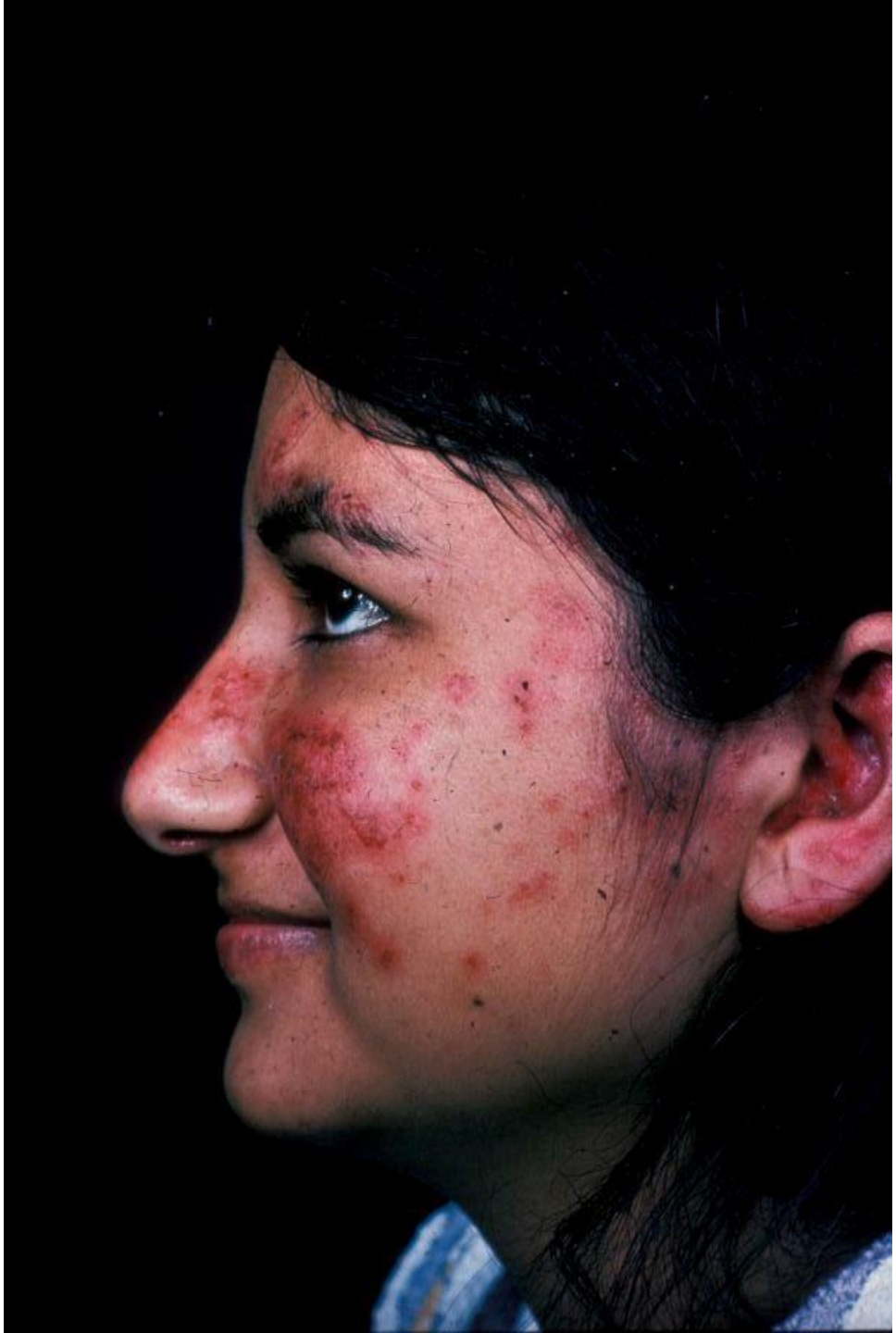

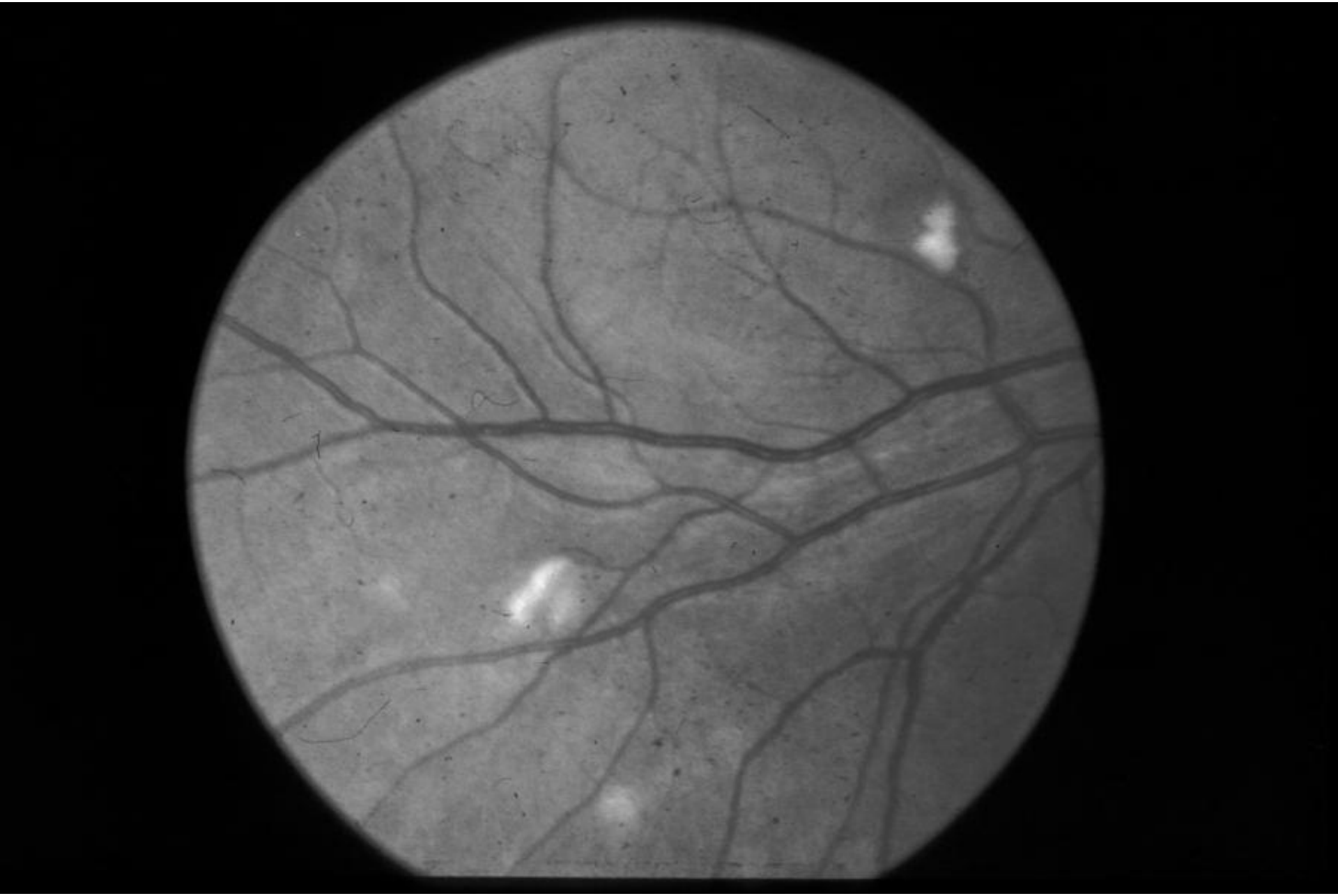

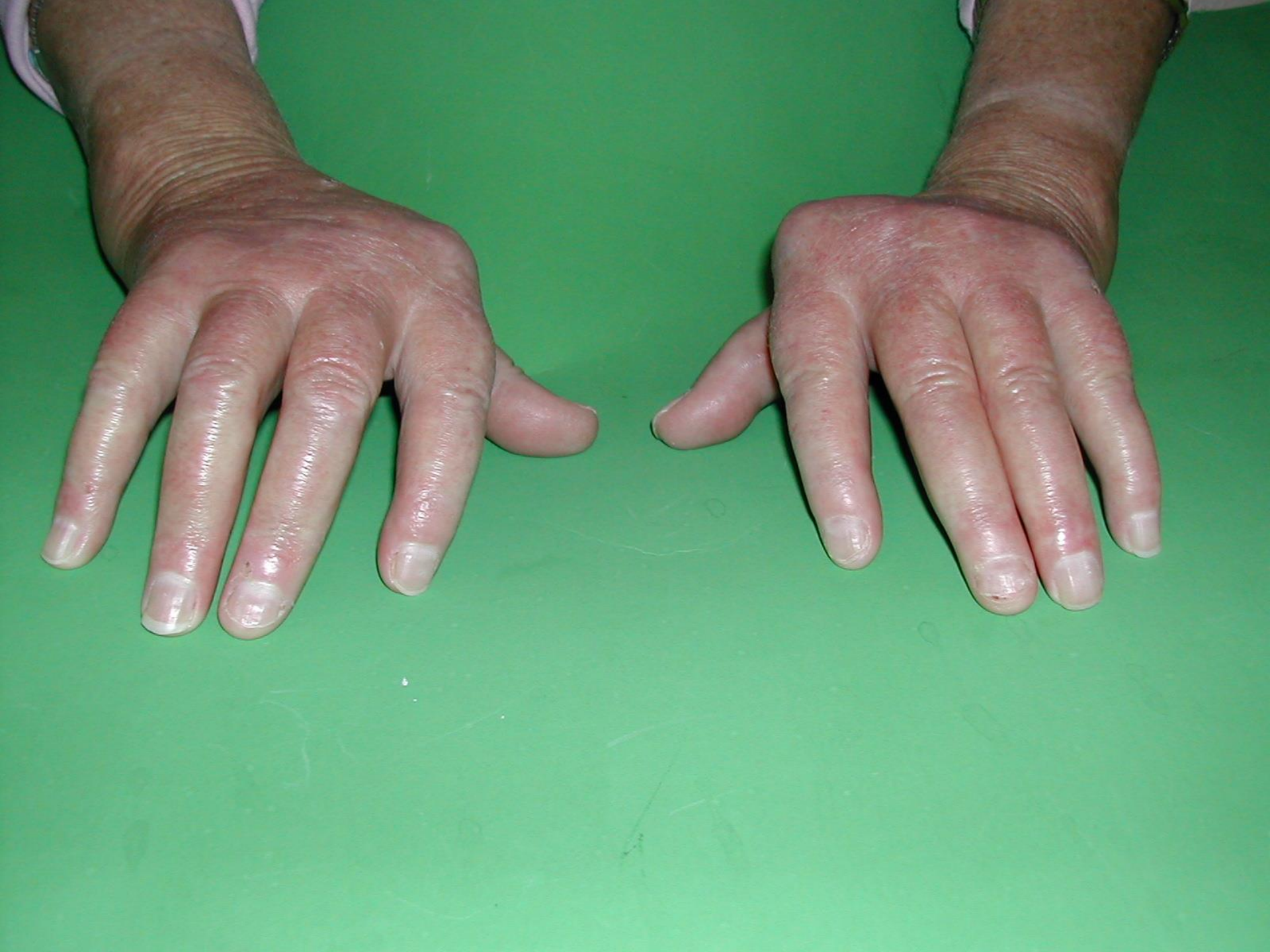

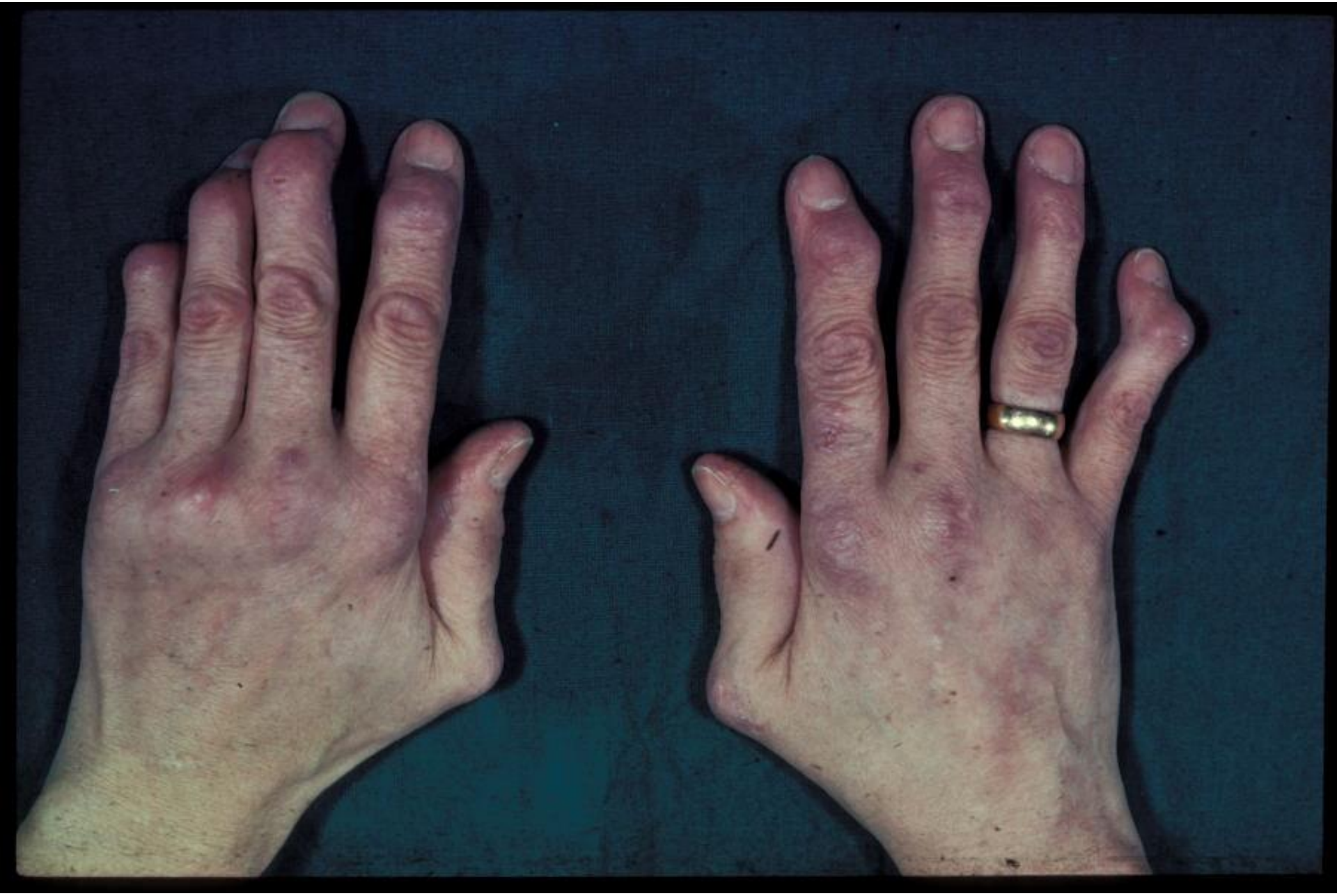

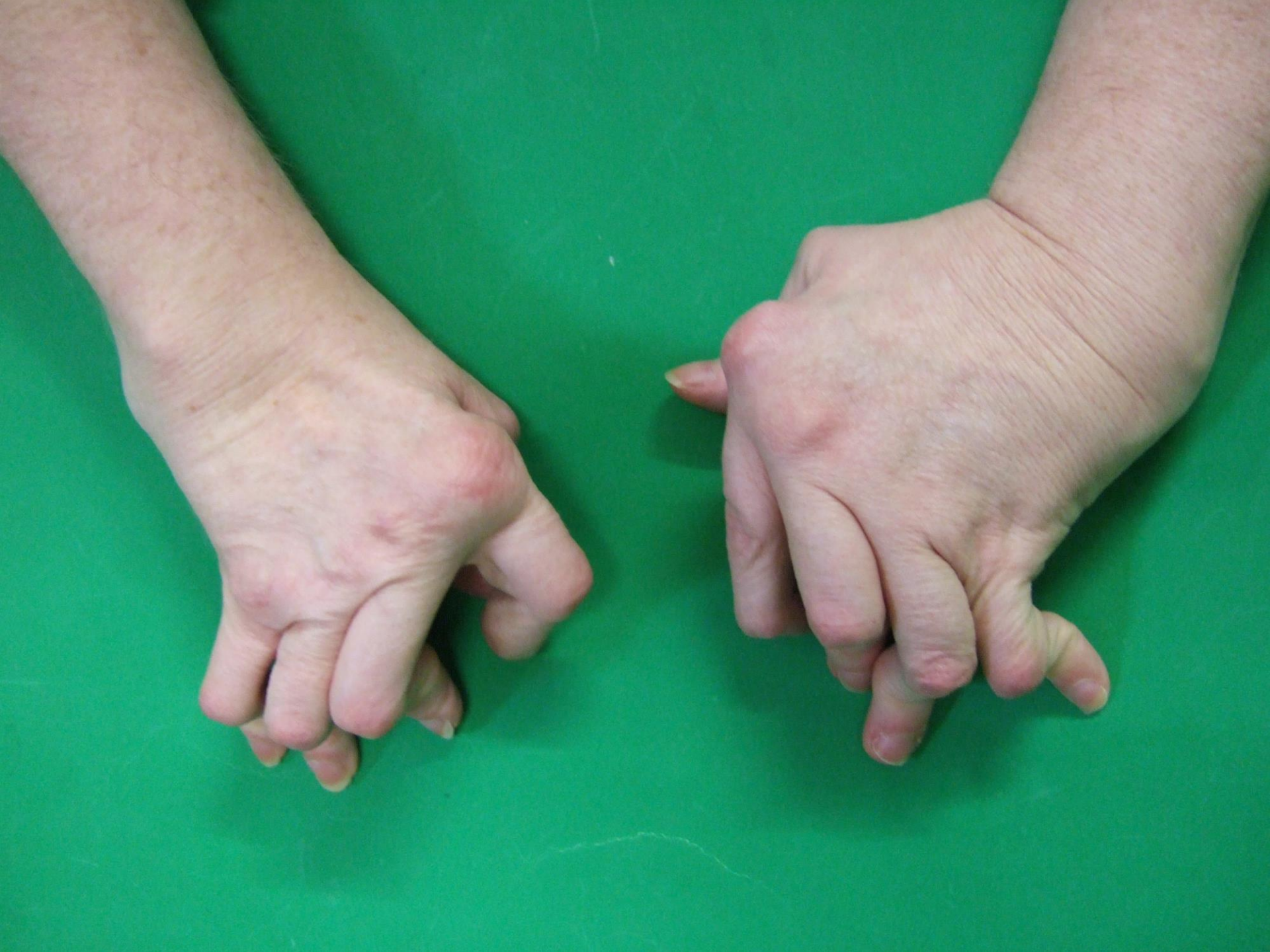

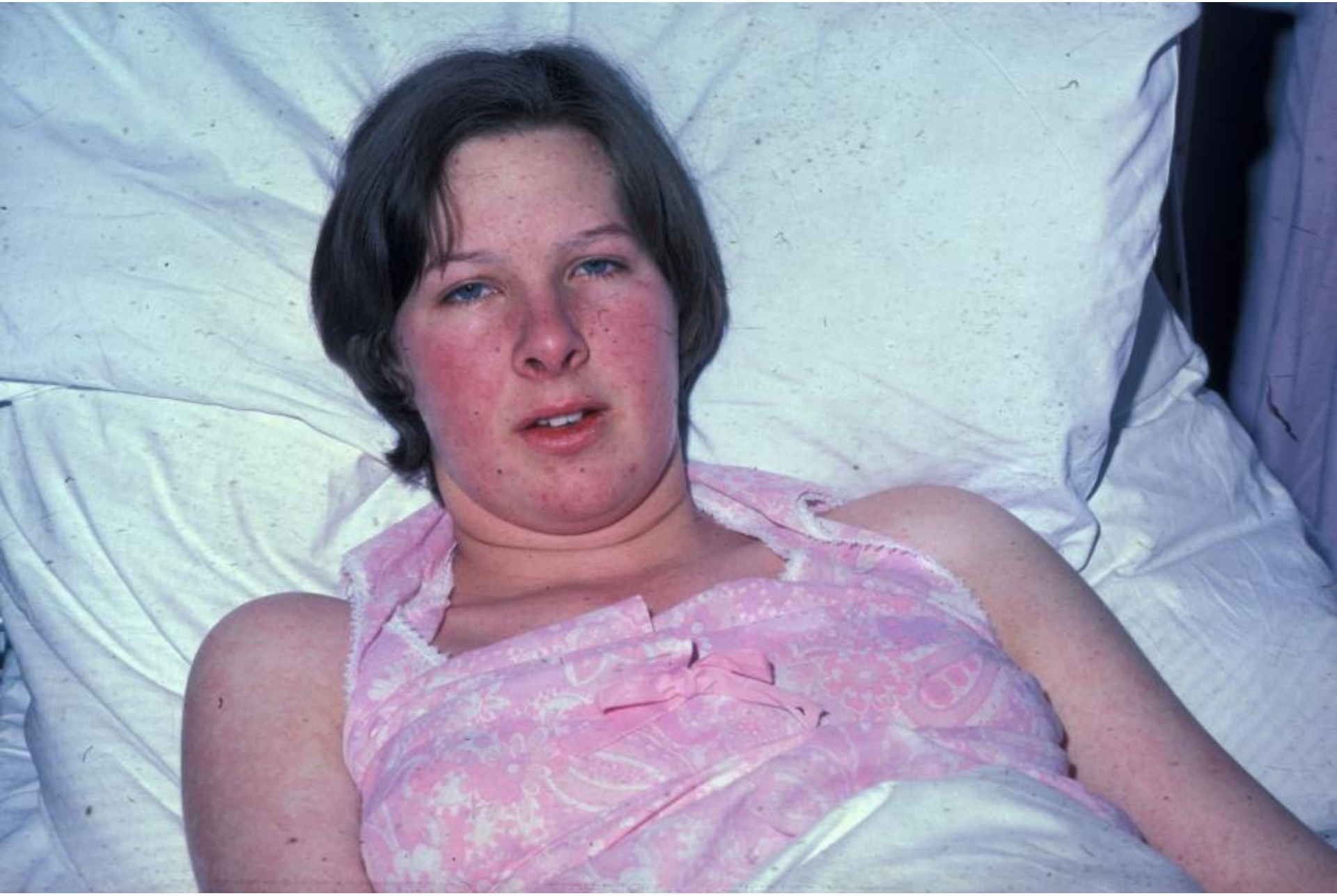

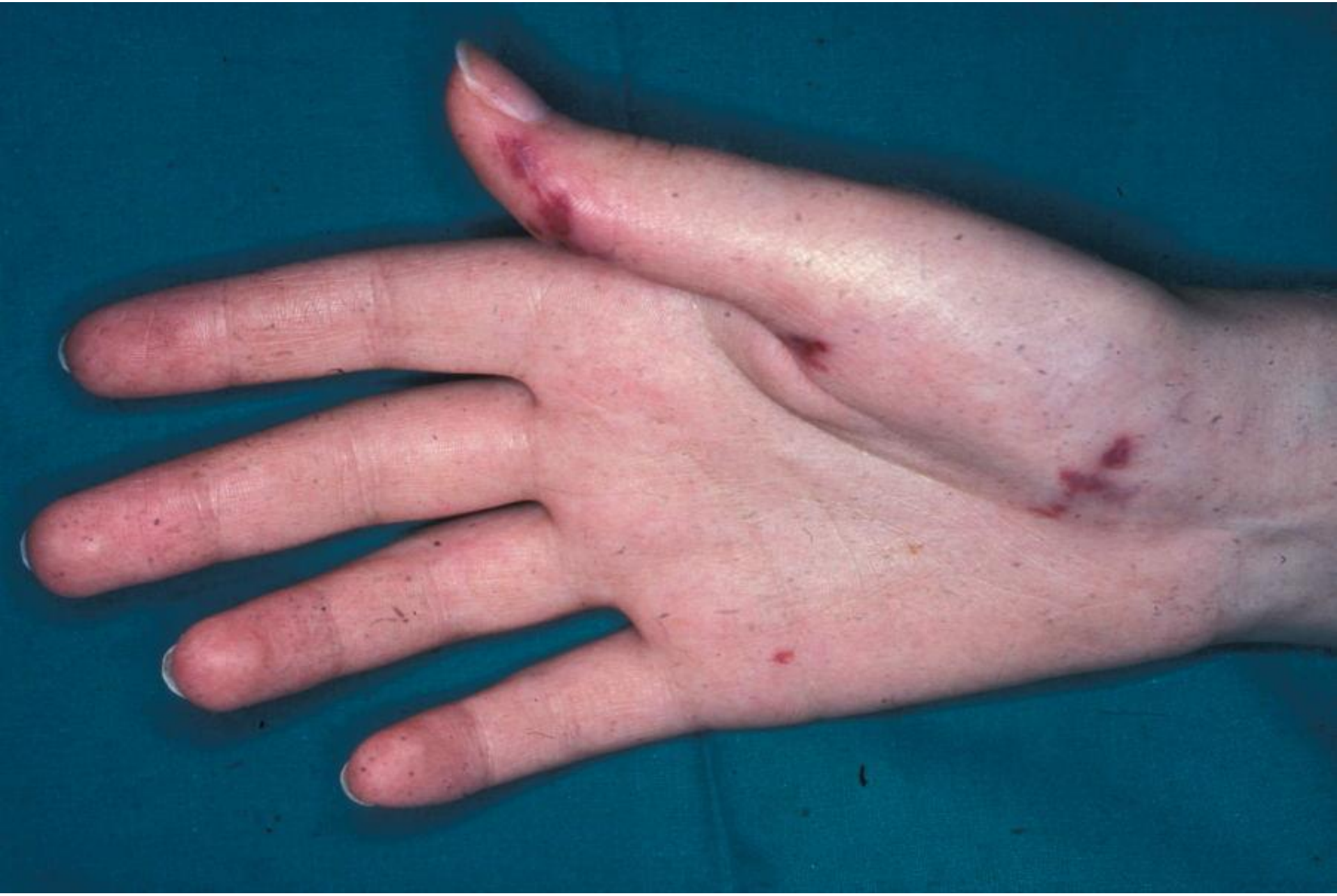

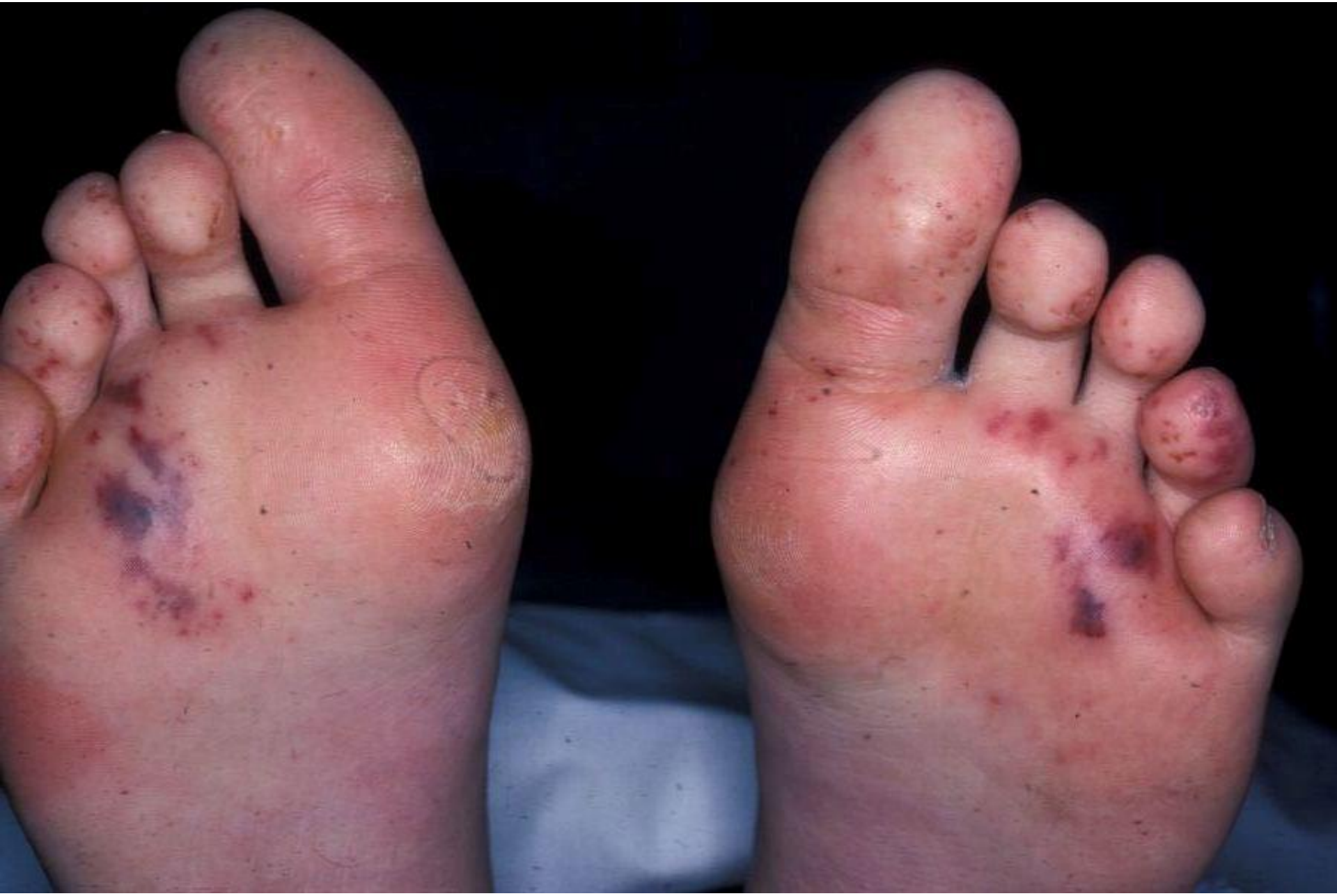

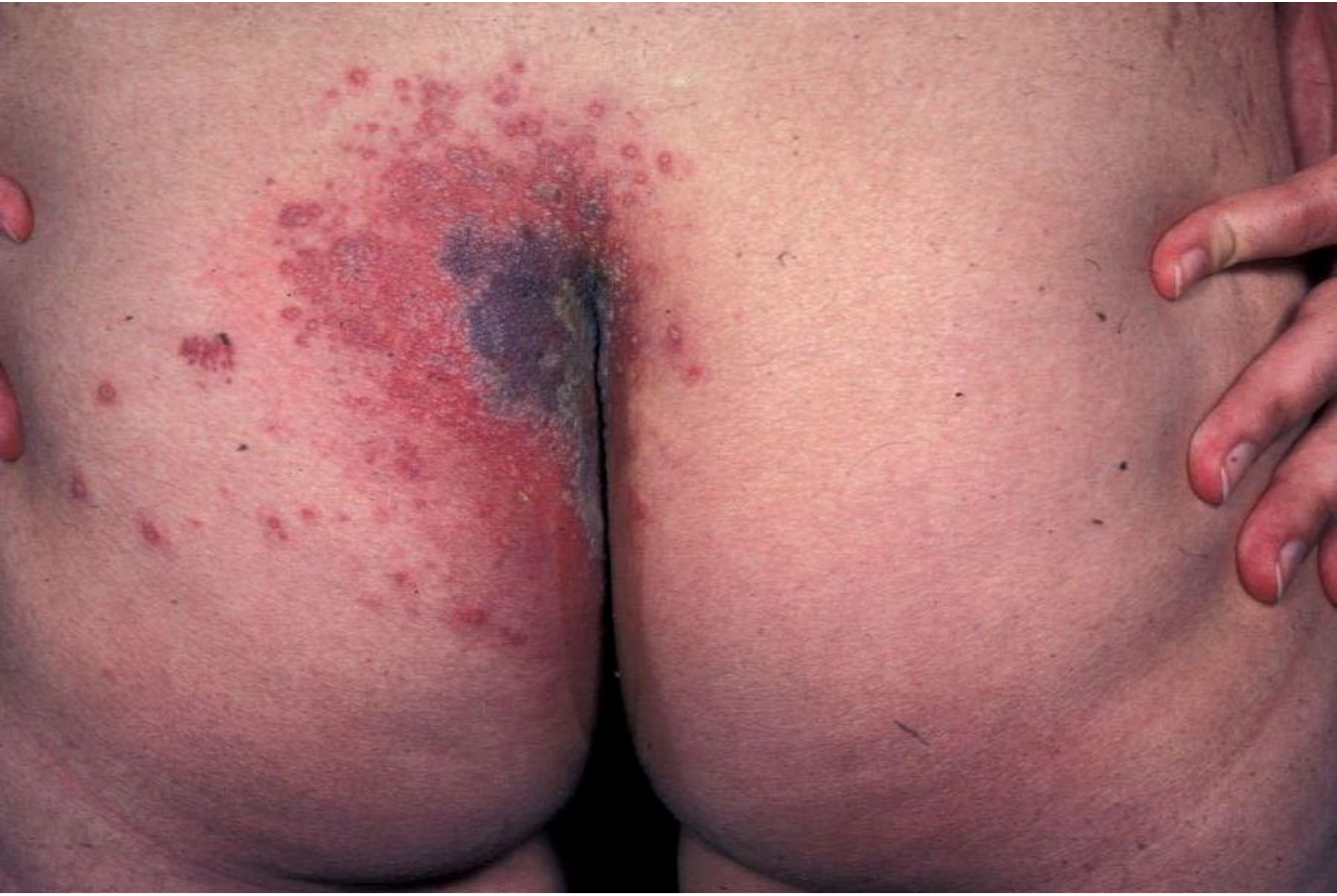

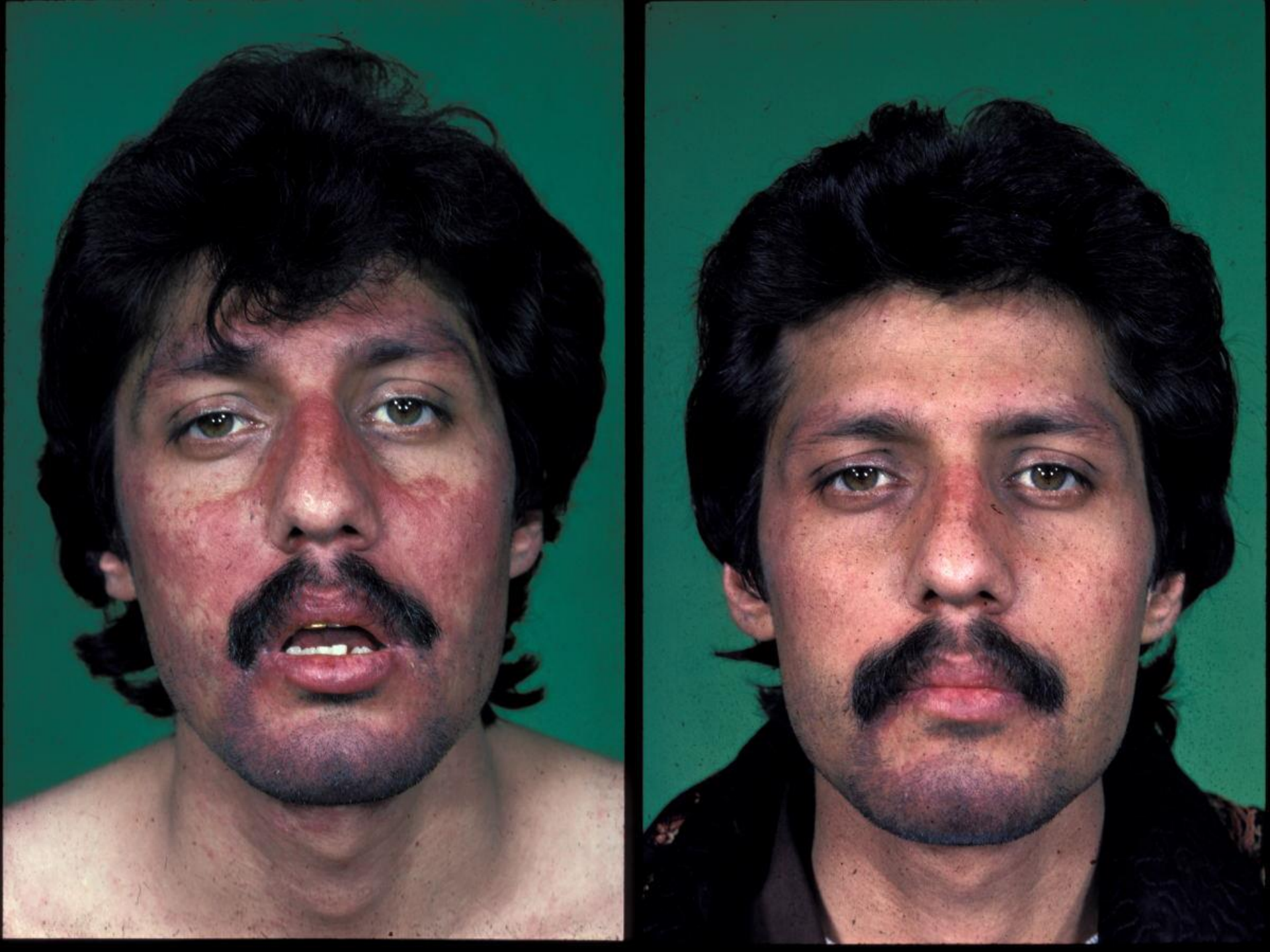

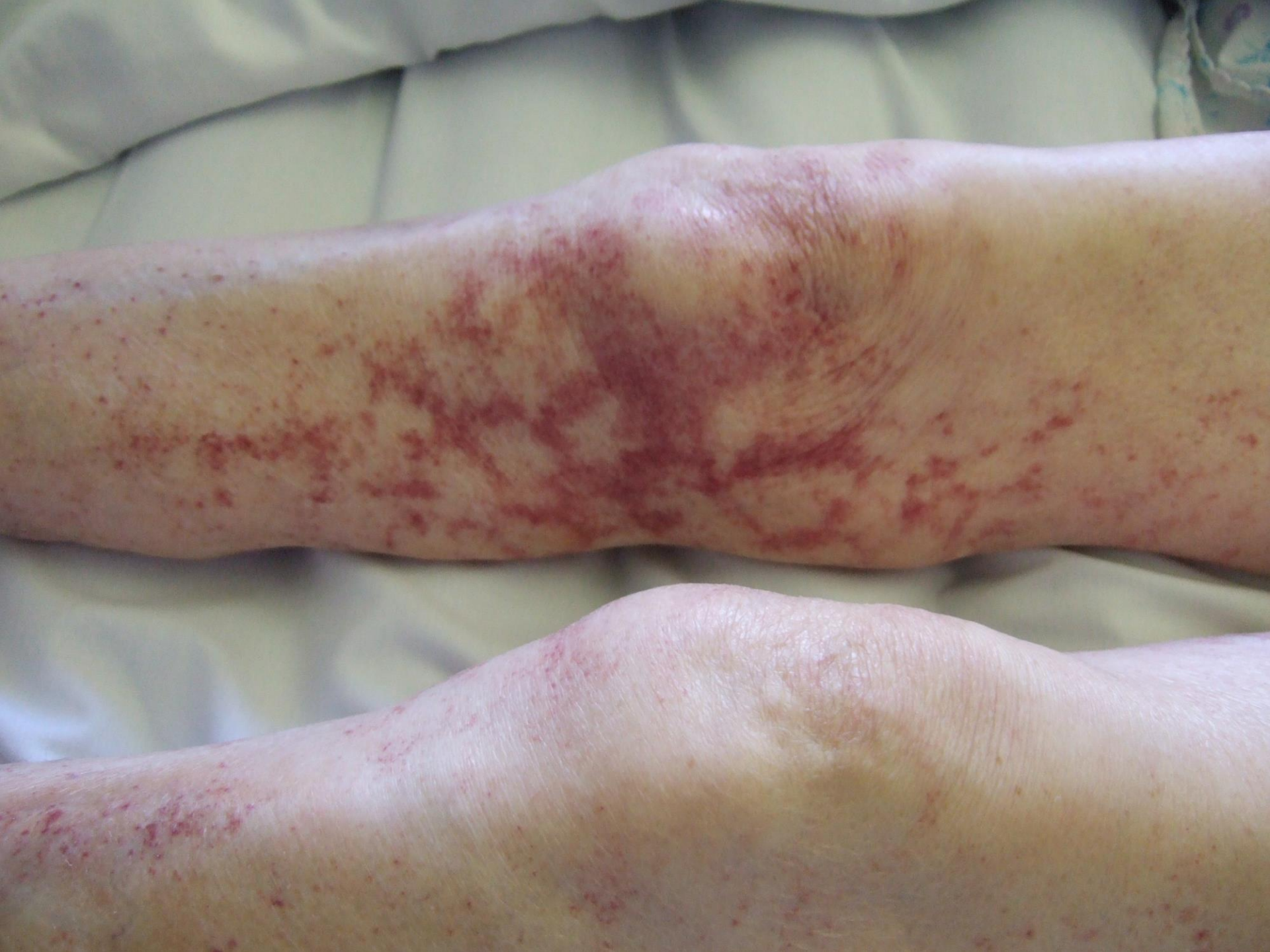

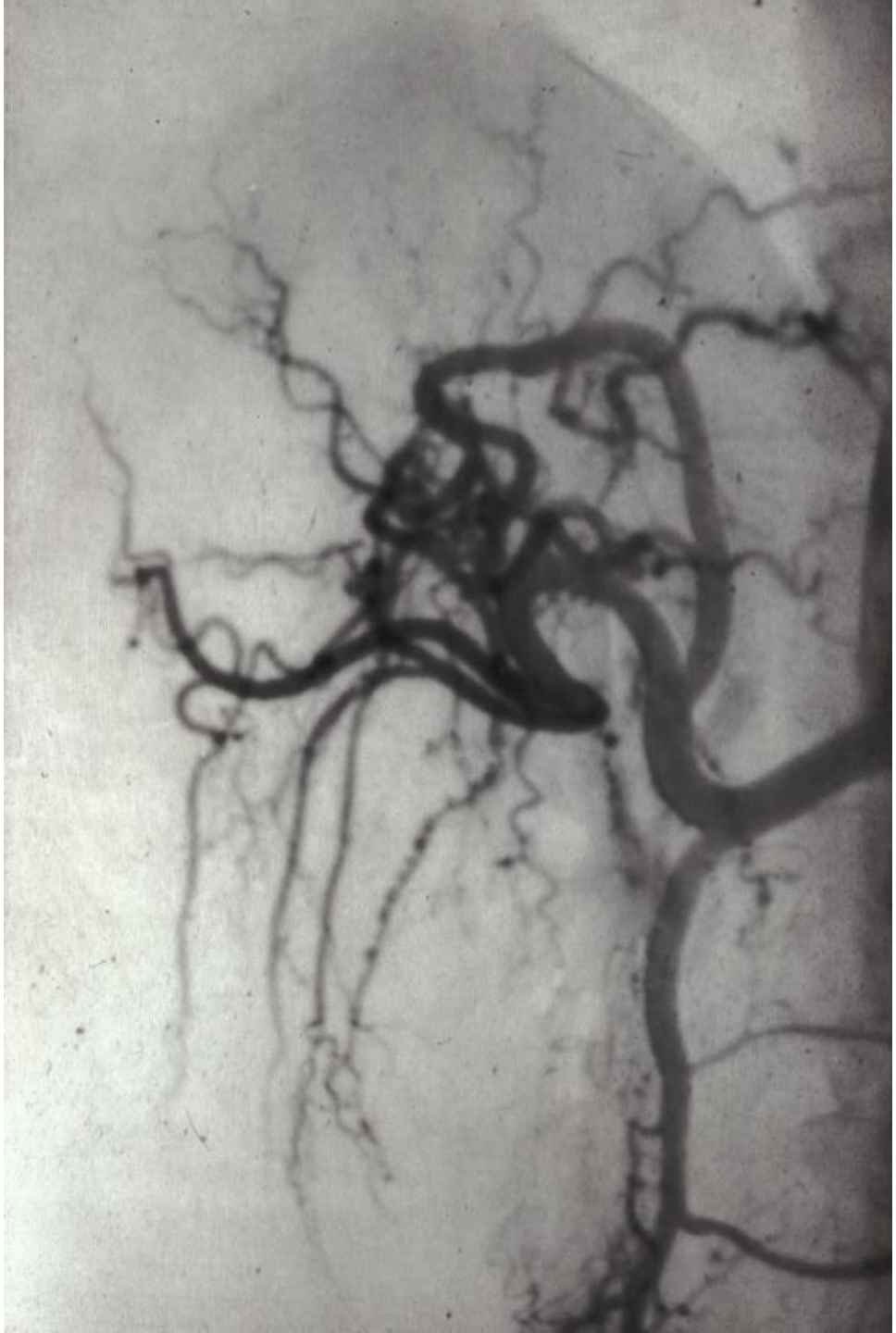

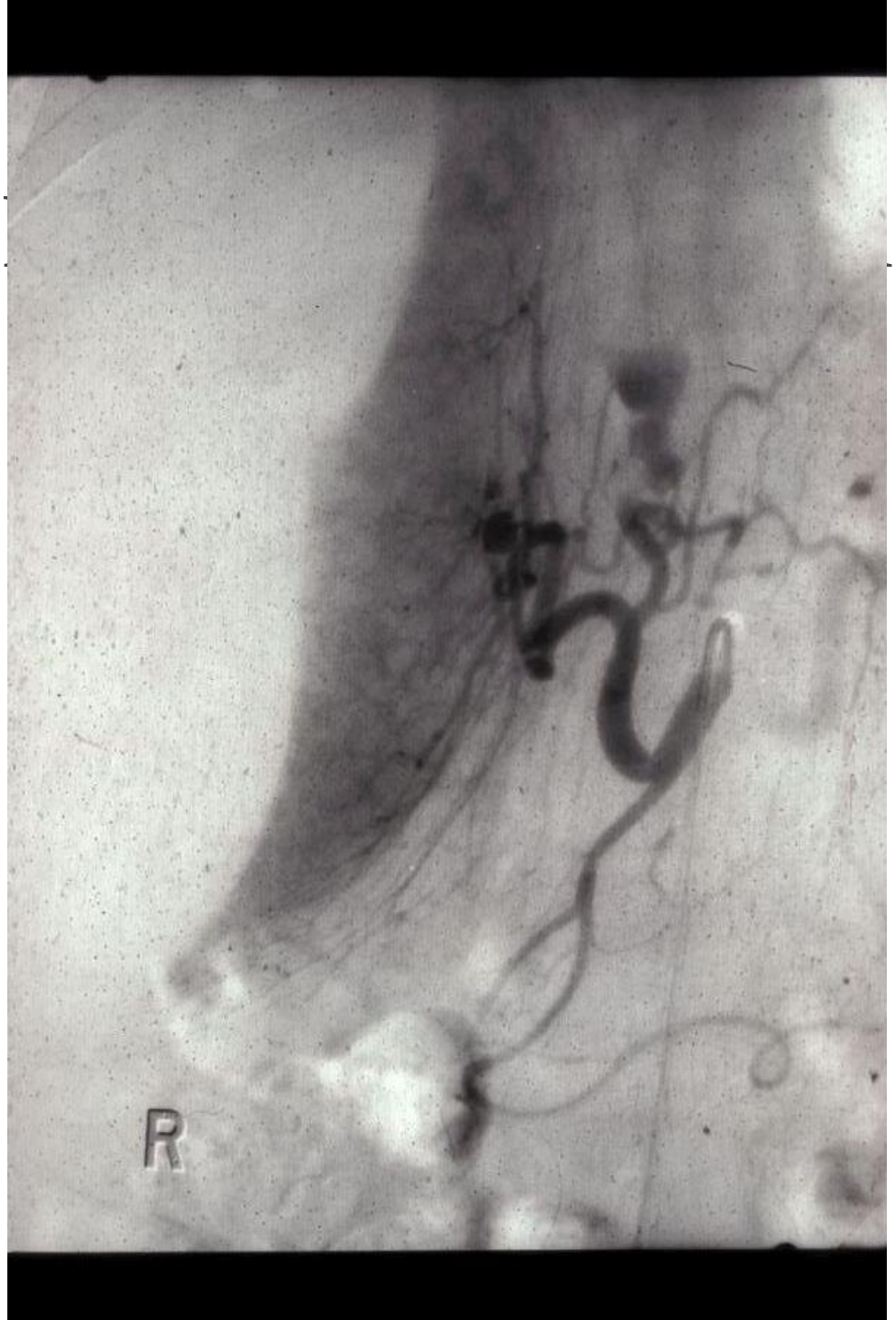
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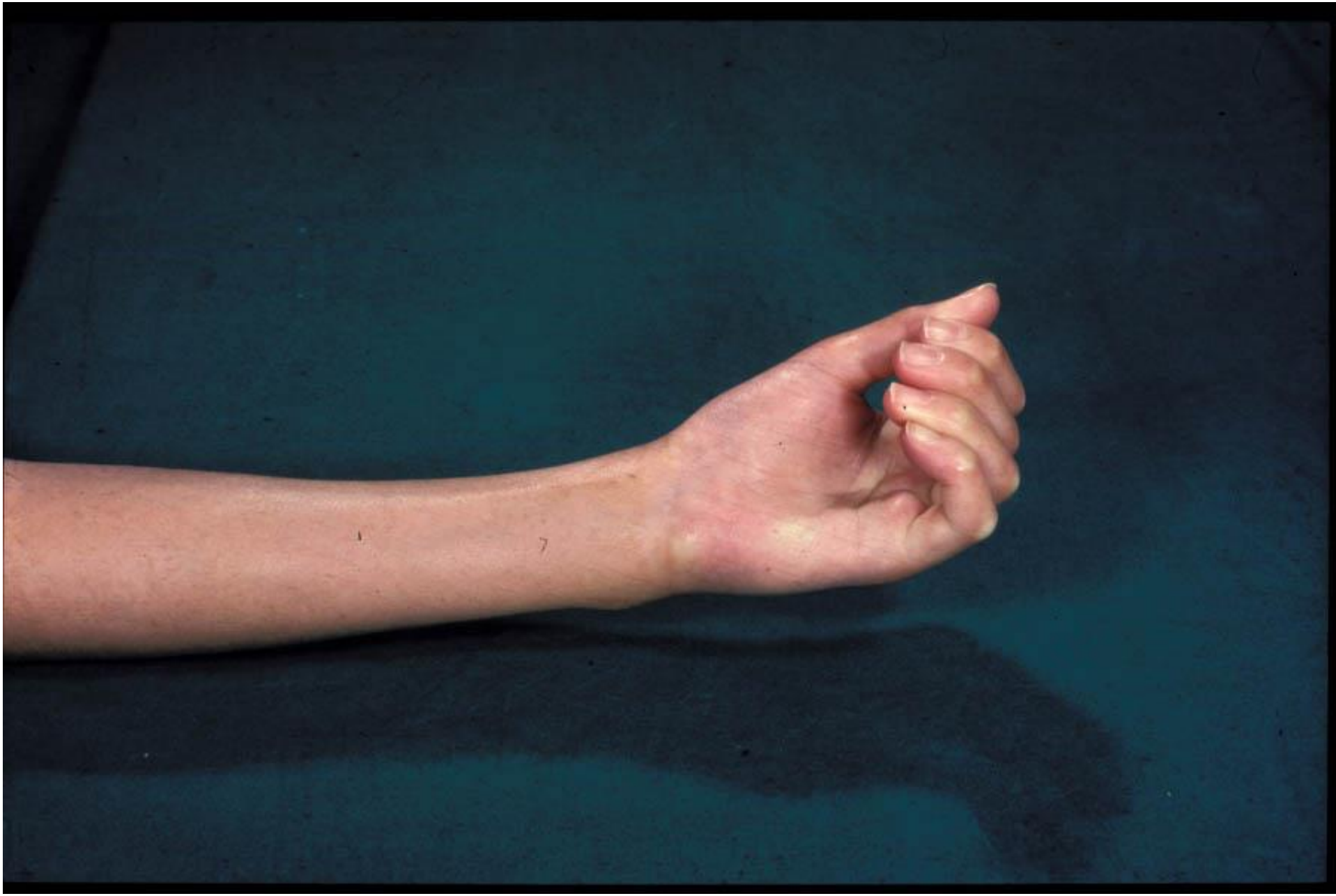
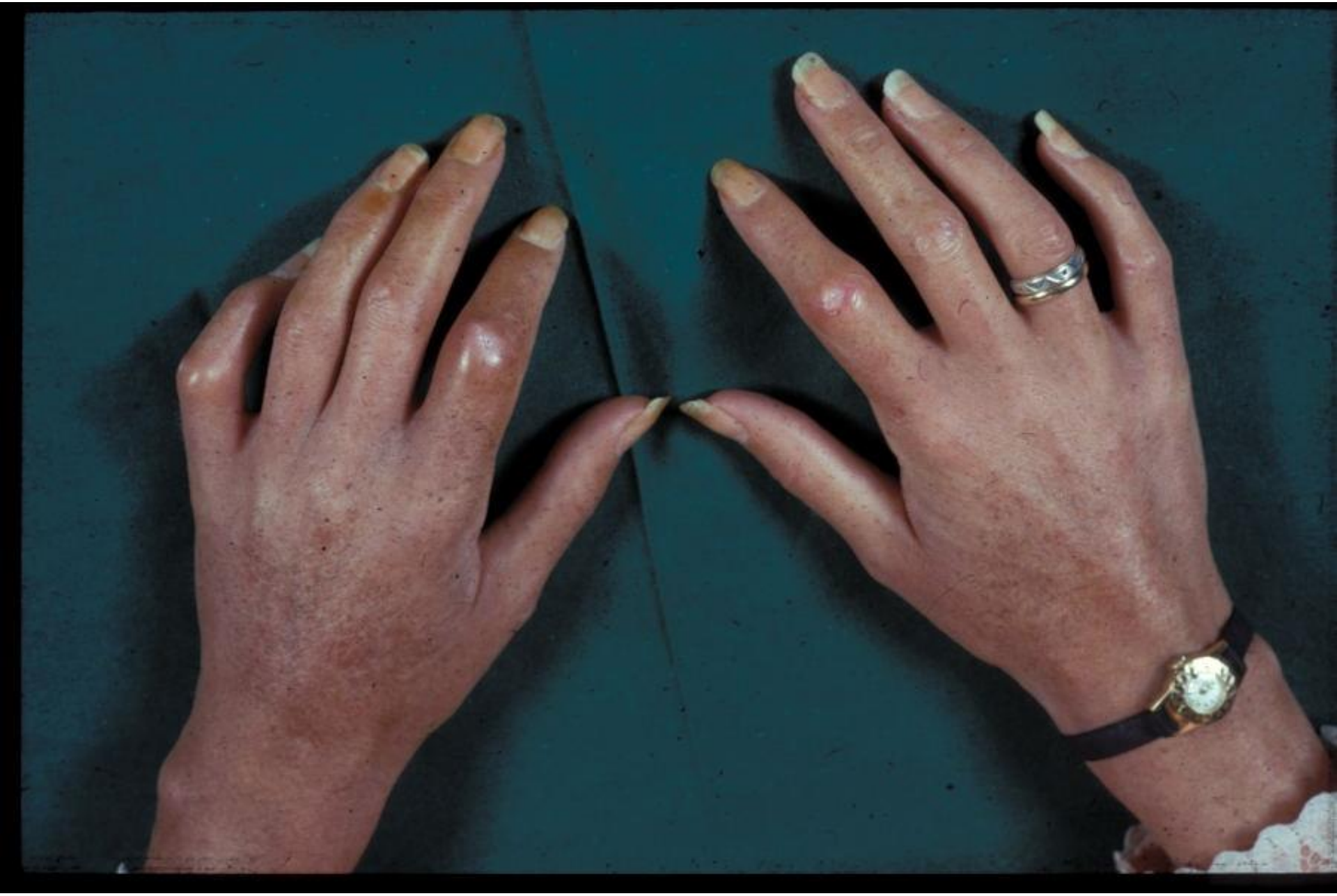
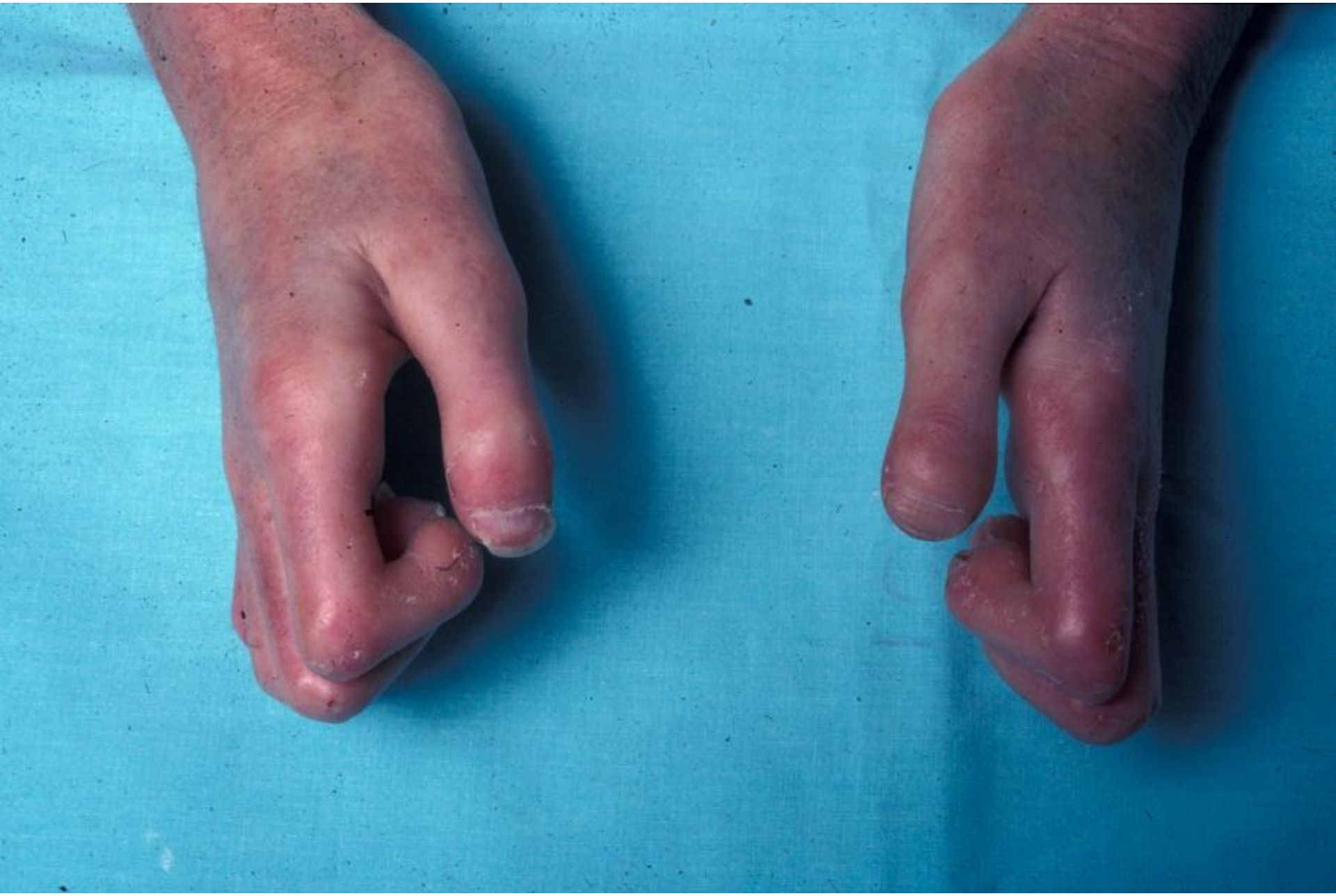
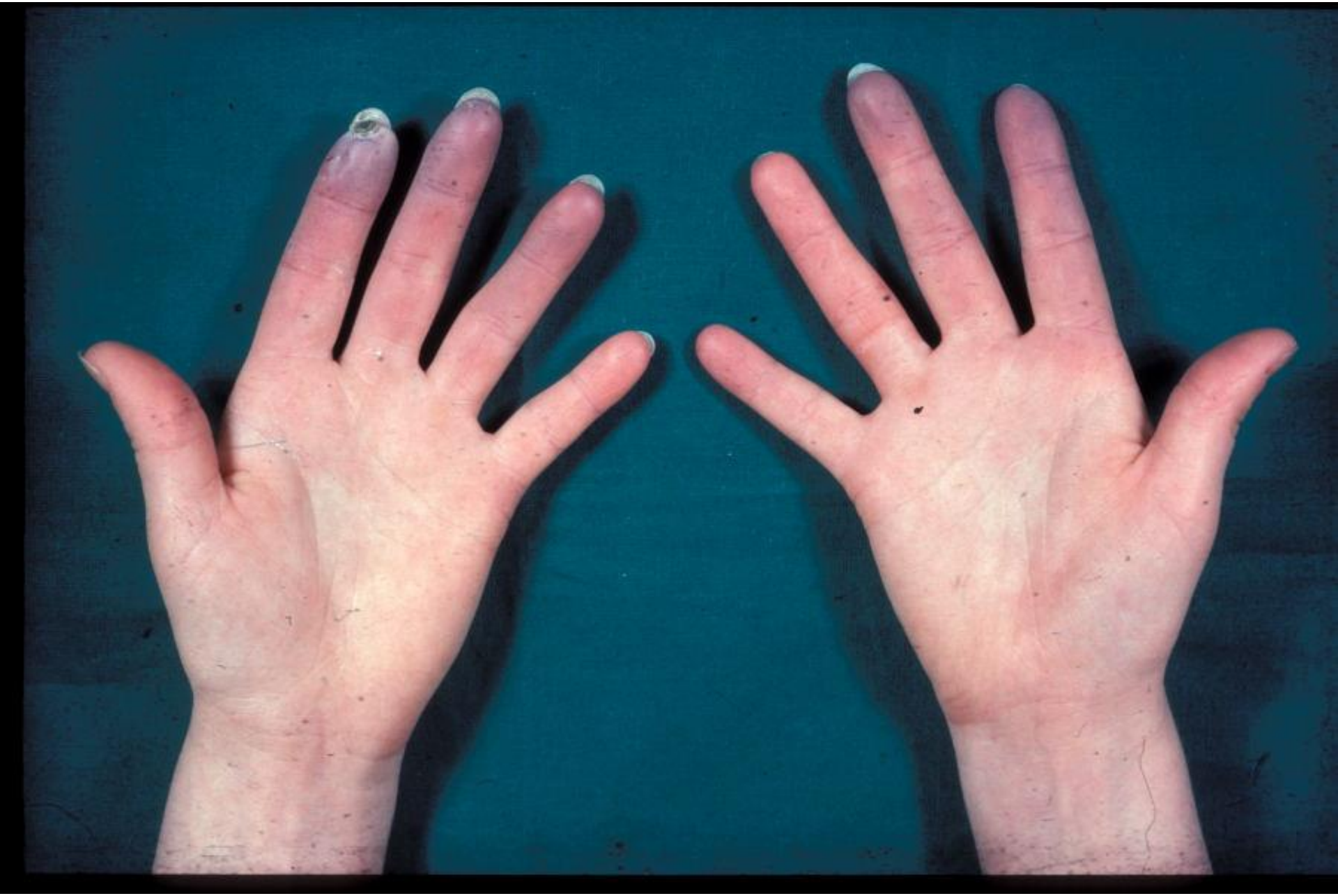
“Scleroderma type”

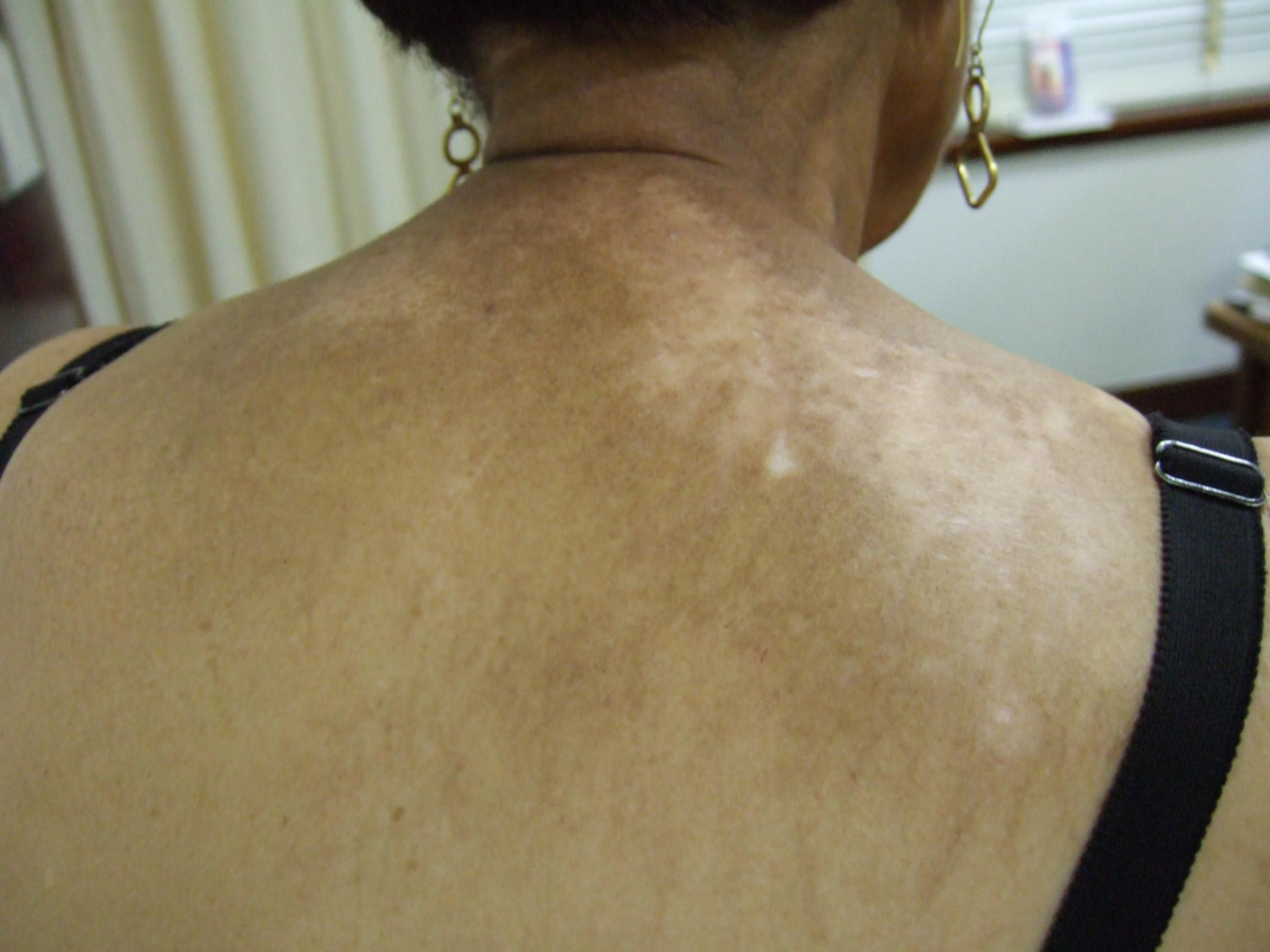
- Middle aged woman with bad Raynaud’s phenomenon, thickened fingers, pinched face ± telangiectasia, and heartburn.
- Check for myostis and calcinosis, vitiligo
- The skin may not be involved proximal to the backs of the hands.
- ANA is often speckled or centromere pattern, with negative DNA and positive ENA.
- Problems to watch out for renal impairment and pulmonary hypertension.
- The MCTD syndrome tends to follow this pattern.

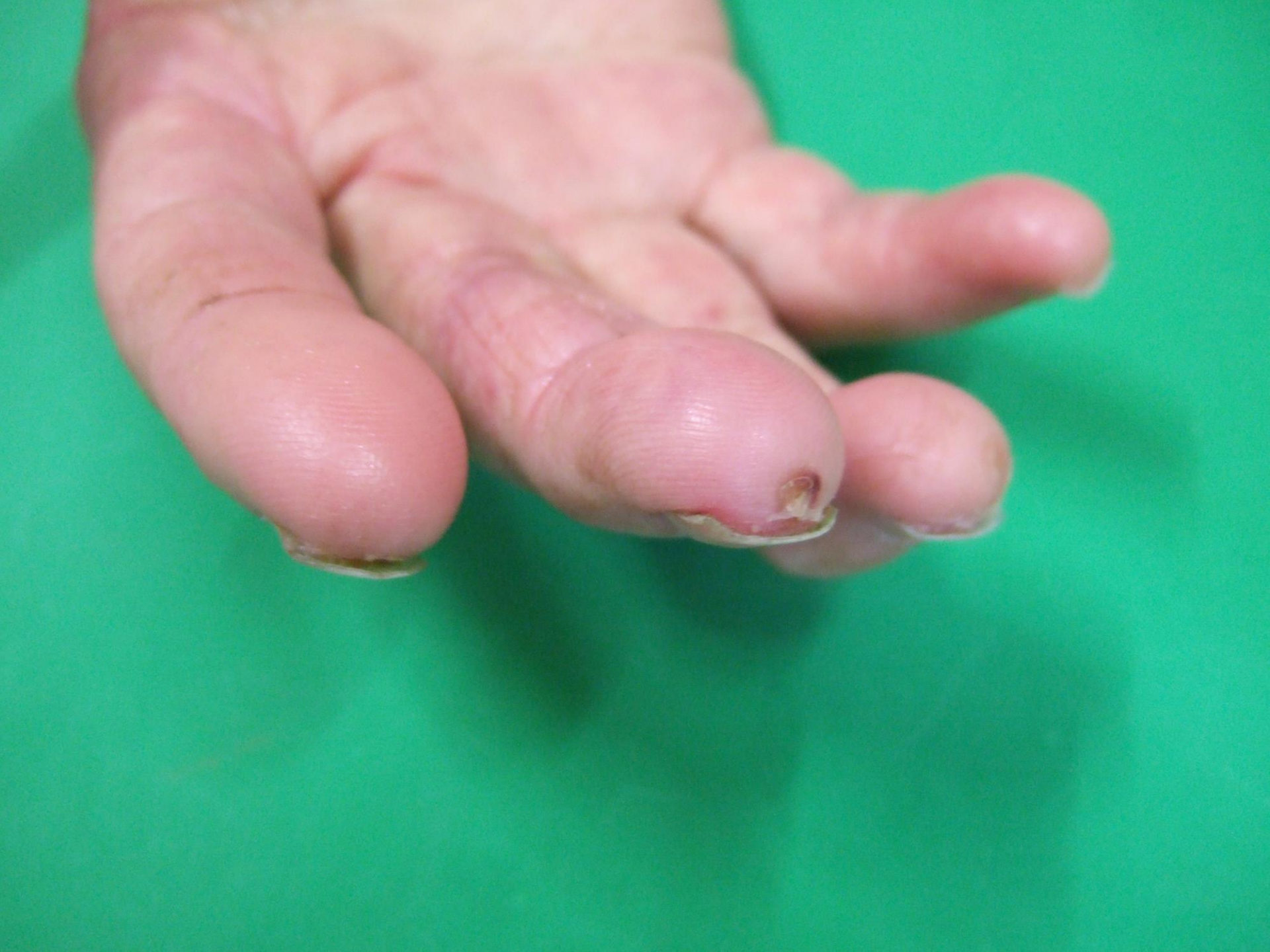


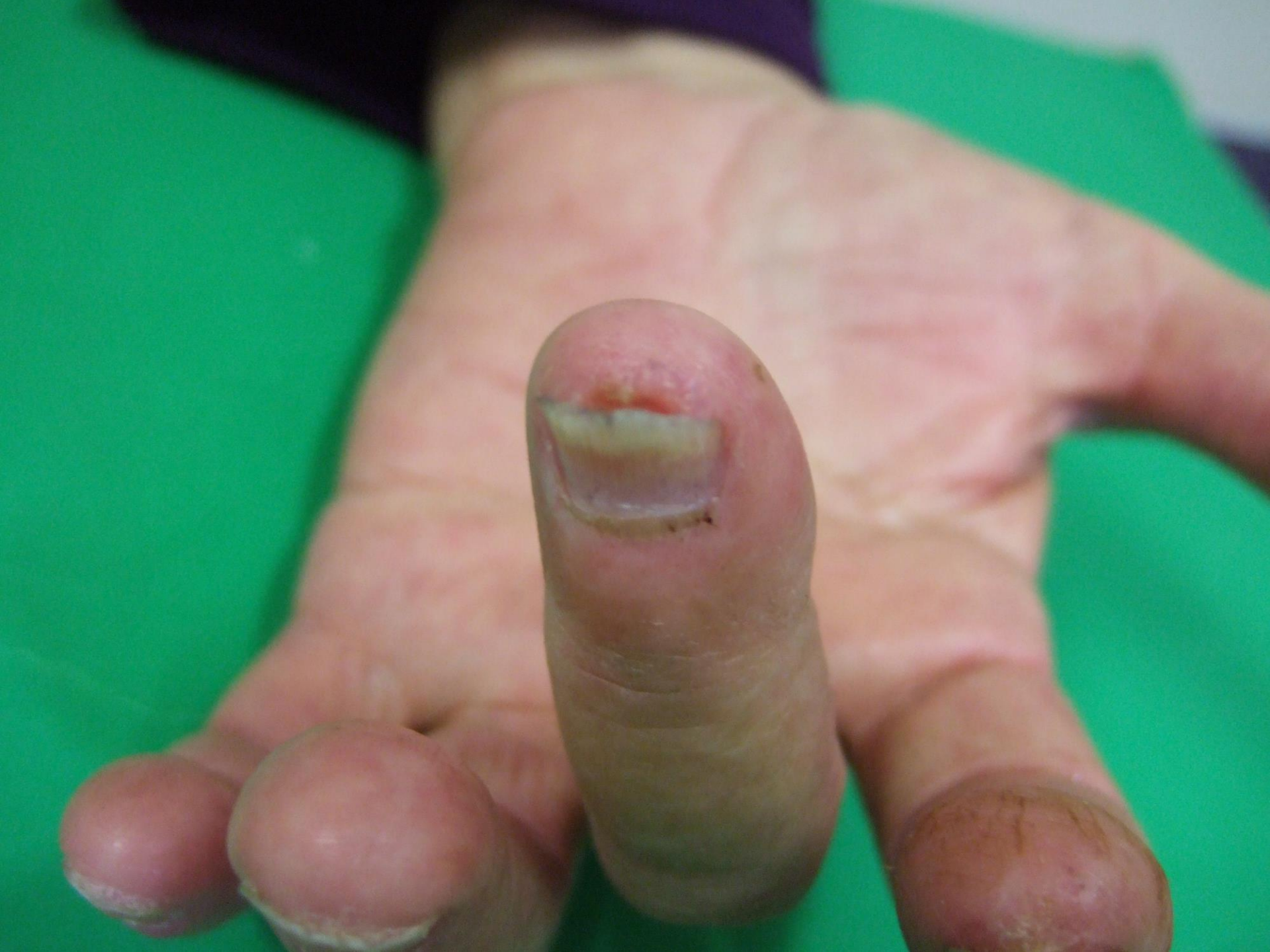


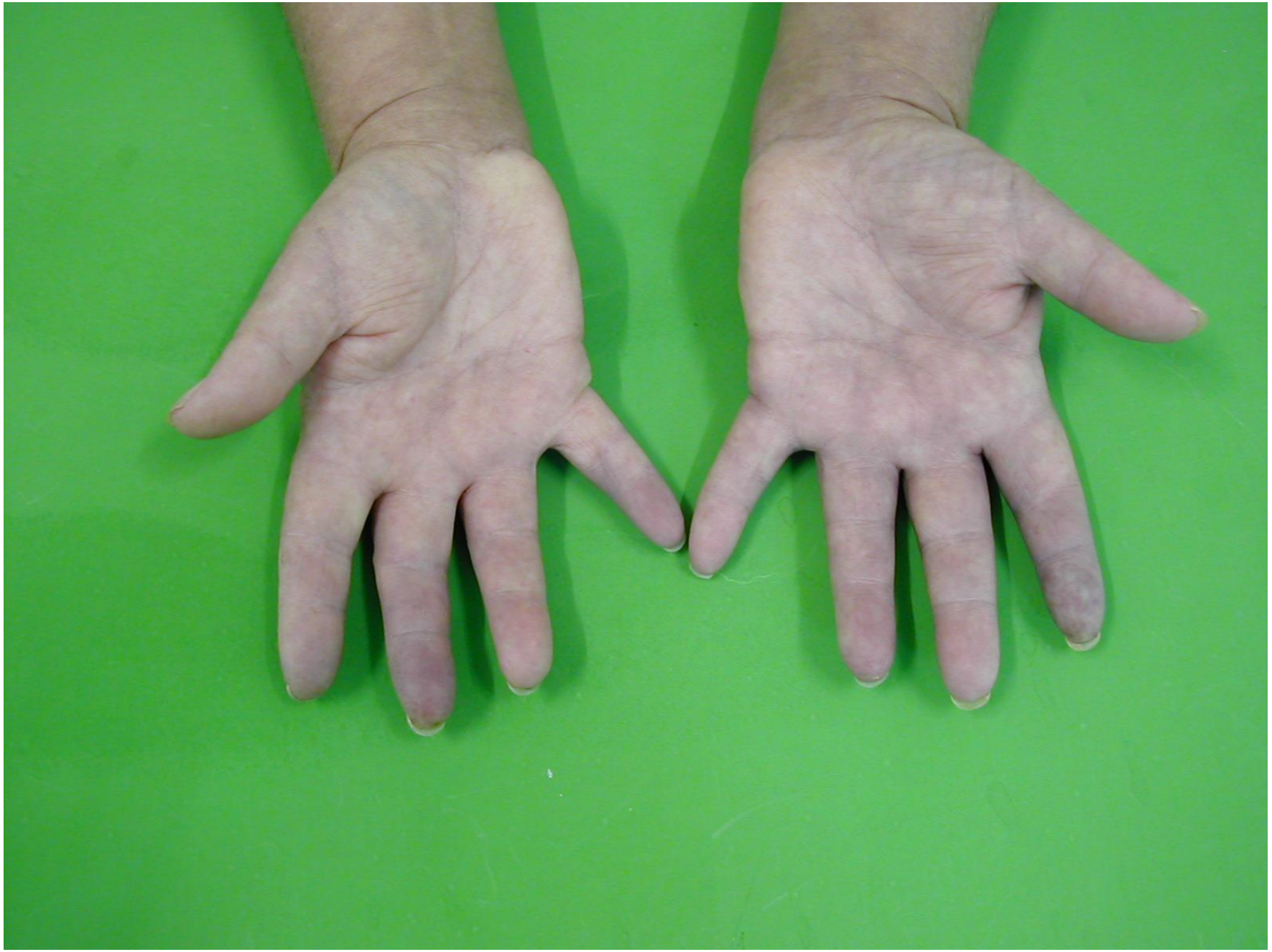


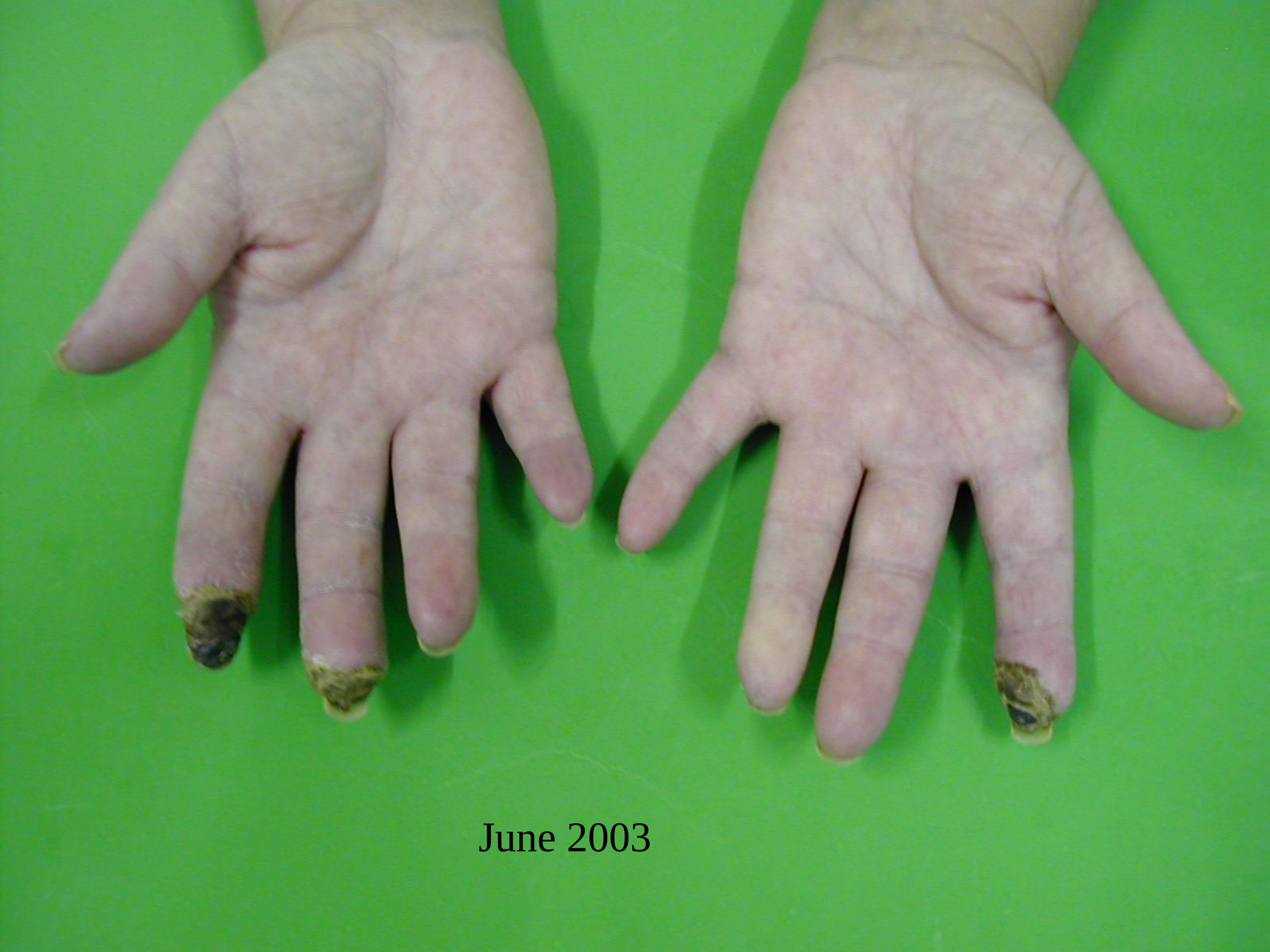








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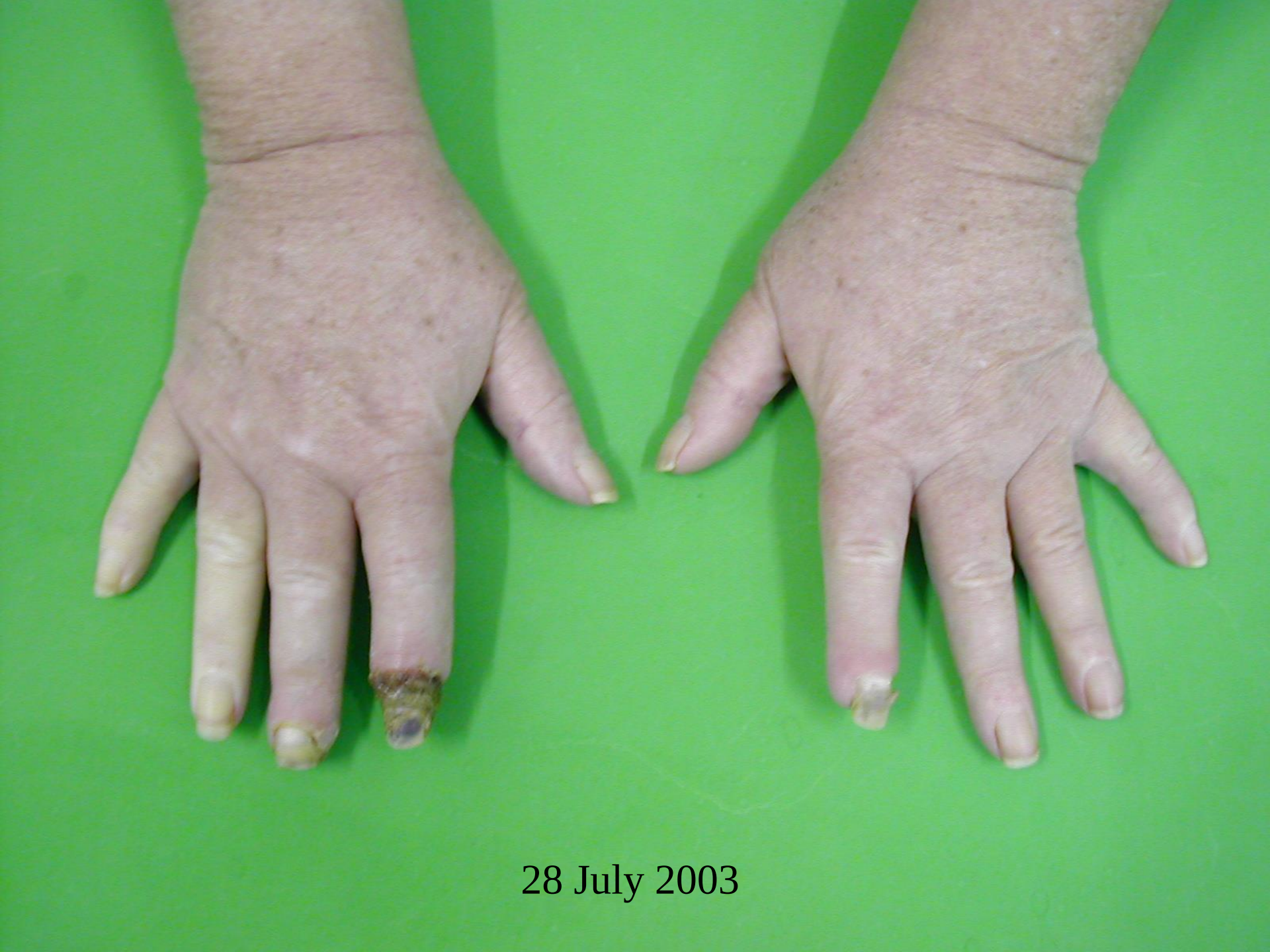

28 July 2003

October 2004