Undifferentiated Connective Tissue Disease and Overlap Syndromes

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Overlap Syndromes

- As many as 25% of patients with rheumatic diseases with systemic symptoms cannot be definitely diagnosed based on strict textbook criteria for disease. Our bodies don't always read textbook and generally the connective tissue or systemic rheumatic diseases are diagnosed clinically.
- Overlap syndrome or undifferentiated connective tissue disease is the term often applied to patient in this category. Patients in some cases fail to meet adequate criteria (ie only 3 lupus criteria) or have symptoms and signs of several diseases.

Overlap Syndromes

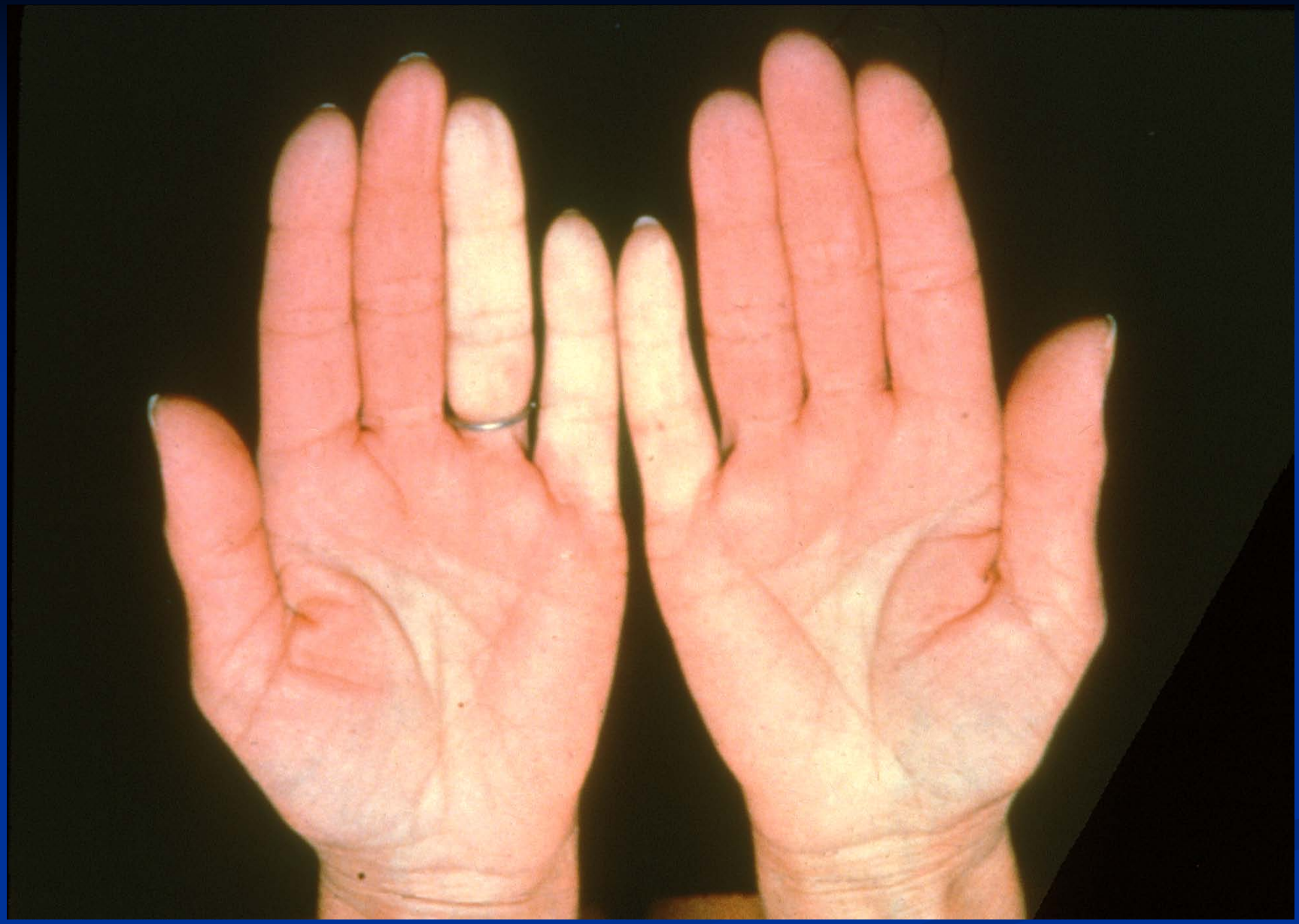
- Rheumatoid arthritis, myositis, scleroderma and Sjogren's syndrome all have some symptoms in common and can coexist with lupus or a lupus-like syndrome.
- With time some patients can evolve to develop more classical disease processes and become a "textbook" case, other continue in a overlap state forever.
- The common factor in these disorders is systemic inflammation and autoimmune activation.

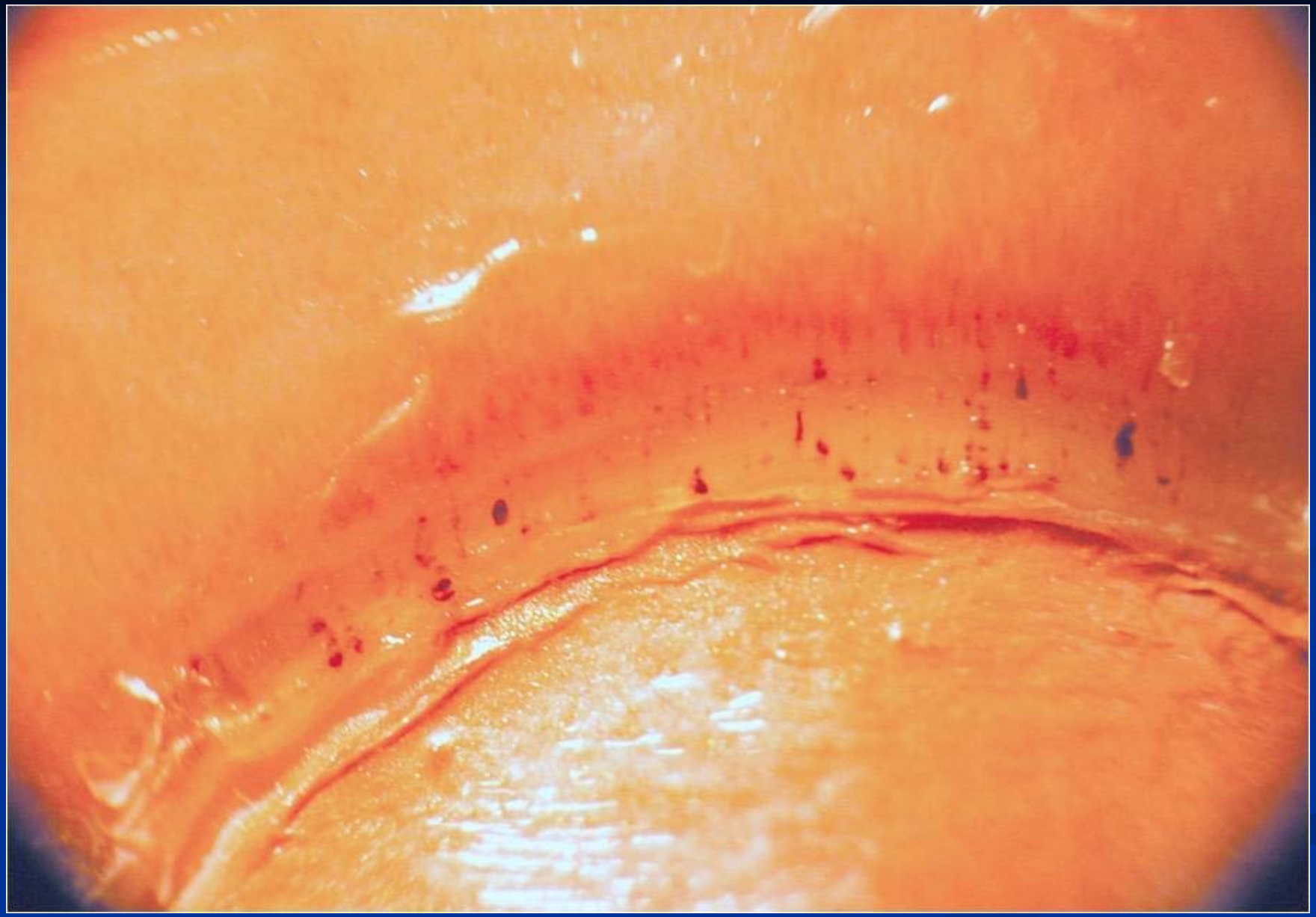
Raynaud's Phenomena

- Raynaud's phenomena (RP) is a common symptom of early rheumatic disease (ERD).
- It can be seen in individuals without other systemic disease but a work up of patients is warranted.
- One study showed 36 % of patients with RP went on to develop a rheumatic disease.
- Nailfold capillaroscopy is an exam finding that be more suggestive of rheumatic disease.

Nailfold Capillary

- Patients with nailfold capillary abnormalities are more likely to develop scleroderma or CREST syndrome. In one study 109 of 133 patient with Raynaud's and nailfold capillary abnormalities developed PSS or CREST.



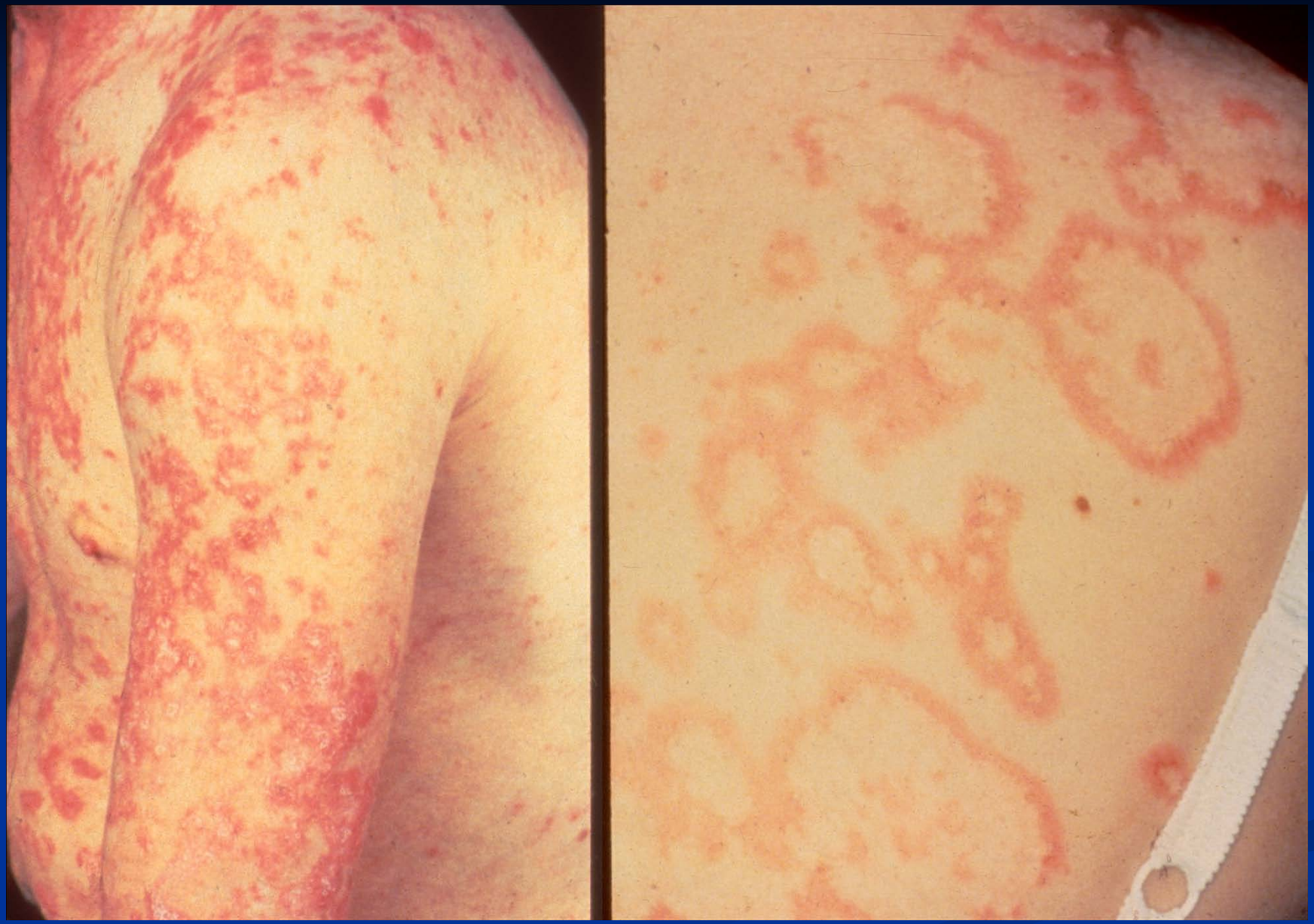


Polyarthritis

- Arthritis is one of the most common symptoms. Early in the course of arthritis it is often difficult to determine if it is rheumatoid arthritis (RA) vs a undifferentiated arthritis.
- Symmetrical inflammatory arthritis frequently will evolve to RA. Based on studies 40 to 60 % of patients go on to RA. In the presences of other symptoms such as rash or myositis it is more like to be part of overlap. By definition this type of arthritis should be nonerosive.
- Rhupus is a term used to indicate a true overlap between RA and lupus. Patients meet full criteria of both diseases.
- An RF or anti-CCP antibody tend to be associated with development of classic RA

Rash

- Rashes are a common symptom but should not be the classic rashes of lupus (malar or discoid). The rash tends to be more characteristic of subacute cutaneous lupus with a more diffuse maculopapular rash.
- Those with classic type of rashes are more likely to develop SLE.
- Photosensitivity is another symptom seen in overlap syndrome.



Sjogren's Syndrome

- Secondary Sjogren's (SS) is very common in longstanding rheumatic diseases. Many patients with lupus, RA, or scleroderma may develop Sjogren's.
- Dry eyes and mouth are hallmark symptoms. Perhaps 60% of patients with SLE for more than 10 years develop SS.
- Often it is difficult to absolutely distinguish SS and SLE since they are many overlapping symptoms but in Patients with objective sicca and + SSA/SSB antibodies are usually called Sjogren's.

Myositis

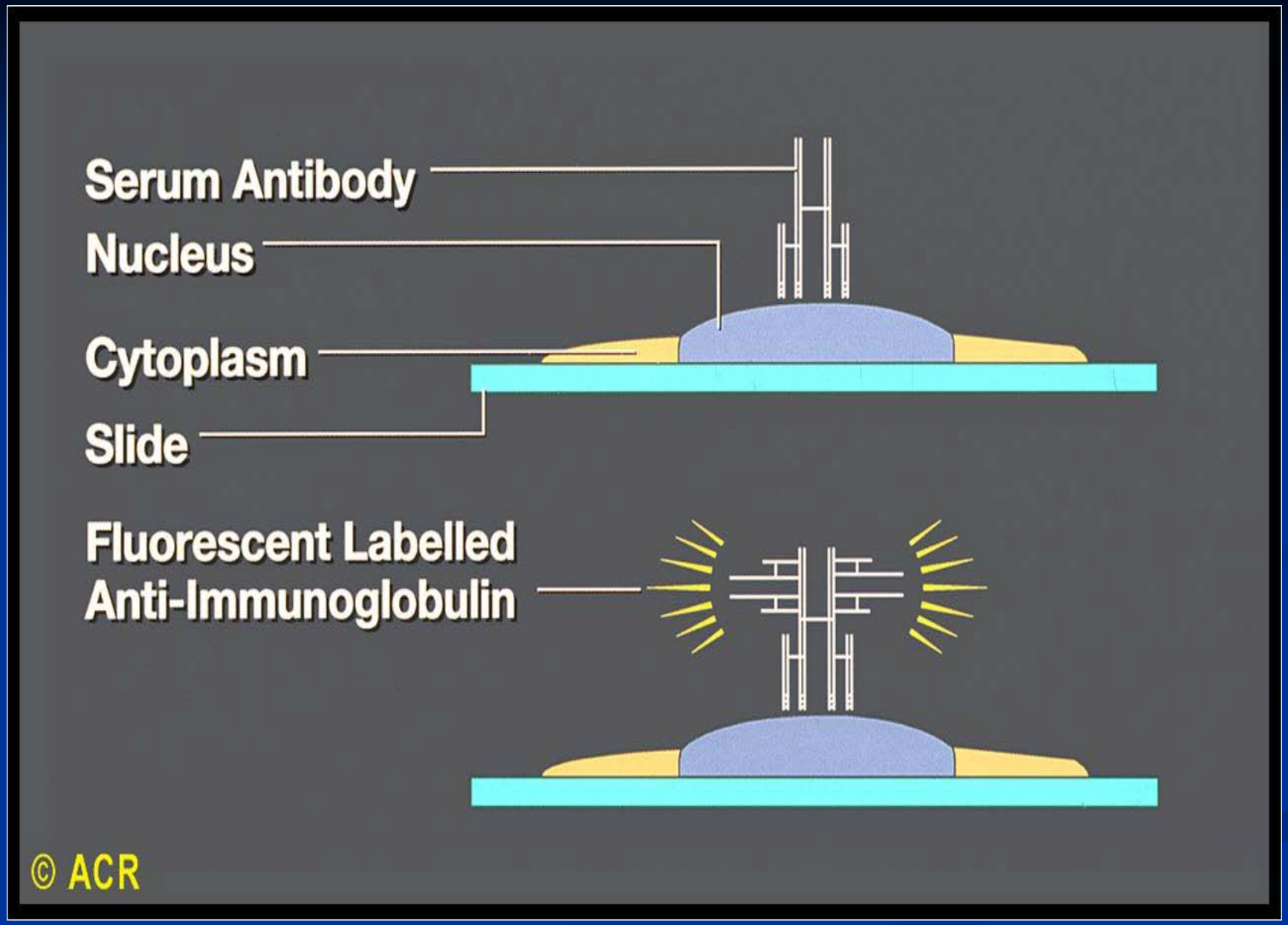
- Inflammation of the muscle is the hallmark symptom of poly/dermatomyositis. In patients with overlap syndromes myositis can be a finding. Lupus and scleroderma can have associated myositis. Often this is overlooked as it is in some cases subtle. Some patients get work ups for liver abnormalities. SGOT and SGPT (ALT and AST) are classically thought of as liver function tests but are also seen elevated in myositis. Elevated CPK with a muscle biopsy showing inflammation of the muscle is the precise method of diagnosis.

Labs

- Evidence of inflammation and autoimmunity are considered hallmark lab findings.
- Inflammation is usually demonstrated by elevated ESR (sed rate) and CRP. Anemia (anemia of chronic disease) and low proteins (ALB and TP) can also indicate inflammation.
- Autoimmunity is usually manifest through autoantibodies-ANA, RF, Anti-CCP, and ANCA.

Labs

- An ANA is common in overlap. The ANA has a high rate of false positive. This increases with age. Our classic studies regarding ANA and its disease association are based on "gold standard" method immunofluorescence. Most labs use ELISA and each lab uses a different type that leads to more confusion. Many PCPs confuse a positive ANA with SLE. Specific autoantibodies (dsDNA, SSA, SSB, Scl-70) have specific disease associations.


Serum Antibody
Nucleus
Cytoplasm
Slide
Fluorescent Labelled
Anti-Immunoglobulin
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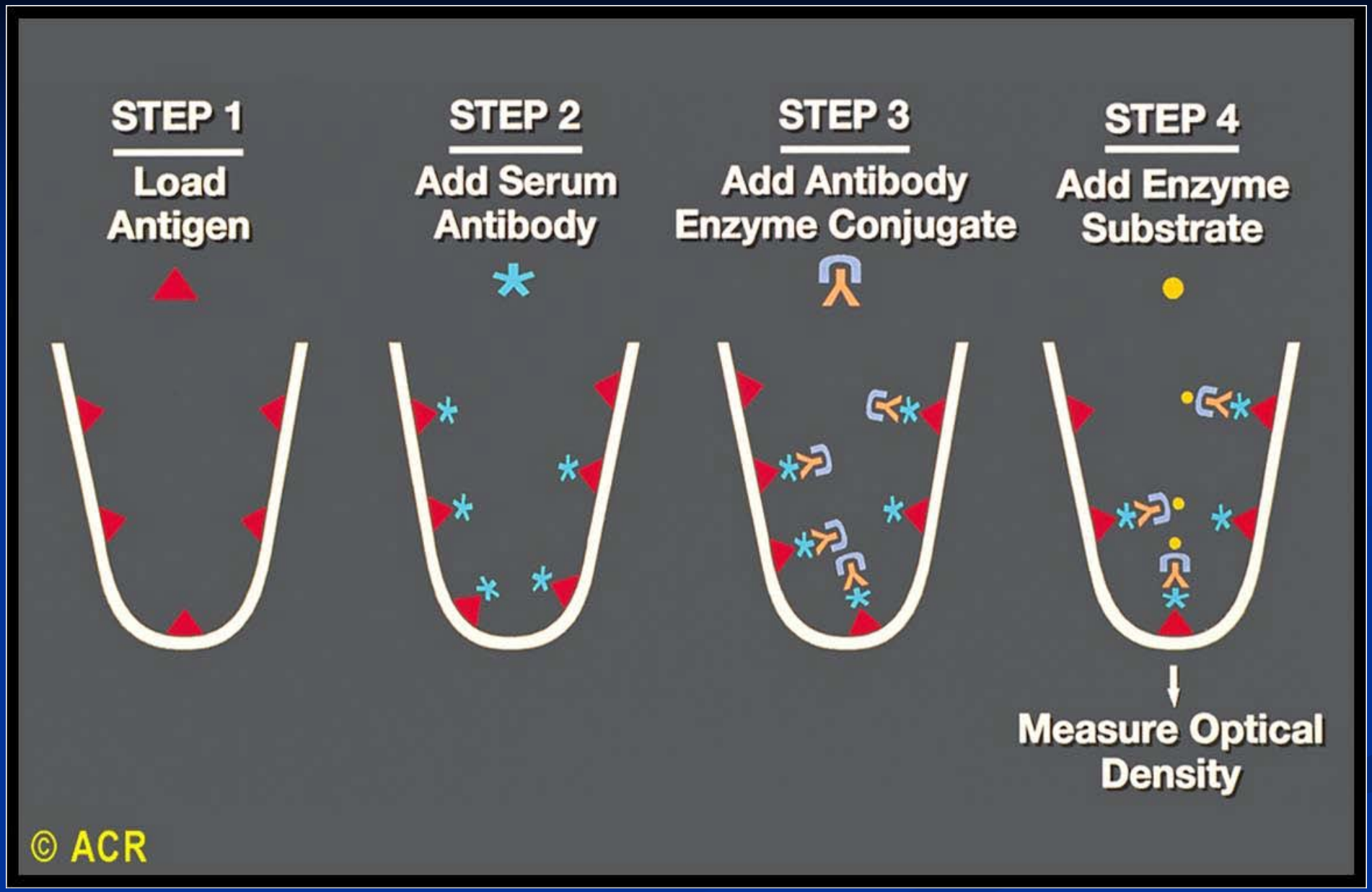
STEP 1
Load Antigen
STEP 2
Add Serum Antibody
STEP 3
Add Antibody Enzyme Conjugate
STEP 4
Add Enzyme Substrate
Measure Optical Density
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Labs

- Patient with anti-CCP antibodies are very likely to develop RA.
- Other tests that are evaluated include CPK (for myositis), urinalysis (for hematuria and proteinuria, uric acid (for possible gout).

Mixed Connective Tissue Disease

- This may be a unique entity or another form of overlap. A group of patients at the University of Missouri were identified with symptoms of lupus and scleroderma often with myositis and were found to have positive RNP antibodies on ANA profile without other specific antibodies. There is some controversy whether this is a separate syndrome vs an overlap syndrome.

Treatment

- In general treatment is directed at specific symptoms. NSAIDs are used arthritis. Steroids can be used for acute inflammation or vasculitis. DMARDs are used based on severity of symptoms and need to taper steroids.
- DMARD (disease modifying antirheumatic drugs) are used when symptoms warrant. Plaquenil (hydroxychloroquine) and methotrexate (MTX) are two the most commonly used drugs.

Plaquenil

- Plaquenil has been approved for lupus since the early 1960s and even longer for RA. It is used frequently in early rheumatic diseases. Several studies have supported that it can prevent progression of early disease. It is shown to prevent complications of autoimmune diseases in general. Yearly eye exams are necessary.

Methotrexate

- MTX is most commonly used in inflammatory arthritis. There are studies that support its early use in undifferentiated arthritis. In a controlled comparison study, the use of MTX early prevented progression to classic RA as compared to those treated with placebo. Liver tests and CBC need to be followed.

Other Medications

- Imuran, Cellcept, Minocycline are all used in specific cases based on symptom and findings.

Overlap Syndromes

- Overlap syndrome encompasses a large group of patients with symptoms of inflammation and autoimmunity. It does not mean the doctor doesn't know what is going on, but indicates failure to meet specific disease criteria. It is appropriate not to over diagnosis patients as there can be long term insurance implications and a number of patients with overlap will resolve with time.
- However, the is a need for close follow up and regular evaluations to rule out progression and change to classic diseases.

Thank You