CONNECTIVE TISSUE DISEASES IN CHILDREN

Departament of pediatrics

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DEFINITIONS

- Connective tissue diseases (CTD) result from autoimmune processes that lead to inflammation of target organs- skin, musculoskeletal and cardiovascular systems, digestive tract, lungs, kidneys, SNS.

PATHOGENESIS

- The immune system normally responds to viruses, bacteria and others non-self molecules.
- The reactions are lost in CTD between similarity foreign and self molecules are recognized by immune cells, particularly T lymphocytes.
- T lymphocytes recognize viral, bacterial, vaccines antigens on the surfaces of antigen-presenting cells. Rubella, Epstein-Barr, influenza viruses, Chlamydia, Mycopl. Pneumoniae are identified in ARJ.
- Genetic factors- HLA alleles may influence susceptibility to developing disease.
- HLA-DR8,11, DRw2 in pauciarticular JRA, DR1,4 in systemic JRA; HLA-A1,B8, DR2,3 in SLE. Polymorphic markers on the chromosomes 1,6,19,20 specific in JRA.
- Activated macrophages produce inflammatory cytokines: TNF-a, interleukins IL-1, IL-6, IL12.
- Macrophages and T-cell invasion and cytokines cause tissue damage through direct effects or mediated by B lymphocytes, produce excessive antibody, including autoantibodies.
- Normal cells in target organs can be destroyed by complement-mediated cytolysis C3, C5, TNF-a, natural T-killer.

CLASSIFICATION

New ACR EULAR guidelines propose to include the follow diseases with involving the connective tissue inflammation:

1. Juvenile Idiopathic Arthritis
2. Systemic Lupus Erythematosus
3. Systemic Sclerosis
4. Juvenile Dermatomyositis
5. Undifferentiated connective tissue diseases

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is defined by the International League of Association for Rheumatology (ILAR) as arthritis of unknown etiology that begins before 16th birthday and persists at least 6 weeks with other known conditions excluded. JIA is a common chronic rheumatic disease of childhood, with a prevalence 1 per 1000.

JIA is classified as systemic, pauciarticular, or polyarticular disease according to onset within the first 6 months.Systemic-onset disease occurs with equal frequency in boys and girls.

Pathogenesis of JIA

- The synovitis with villous hypertrophy and hyperplasia, edema, increased of synovial fluid.
- Vascular endothelial hyperplasia with infiltration of mononuclear and plasma cells.
- Pannus formation and progressive erosion of cartilage and contiguous bone.
- All proinflammatory factors resulting in severe artthritis and systemic disease.
- As a result of increased B-cell activity, hyperglobulinemia, circulating immune complexes (CIC), antinuclear antibodies (ANA), and rheumatoid factor are commonly found in patients with JRA.

CRITERIA FOR THE CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS

1. Age of onset <16yr.
2. Arthritis (swelling or effusion, or the presence of 2 or more of the following signs, limitation of range, of motion, tenderness or pain on motion, increased heat in >1 joints.
3. Duration of disease >6wk.
4. Onset type defined by type of articular involvement in the 1st 6mo after onset:

- Polyarthritis >5 inflamed joints.
- Oligoarthritis (Pauciarthritis) 4 or< inflamed joints.
- Systemic disease arthritis with a characteristic high spiking intermittent fever.

Systemic clinical manifestation

Systemic onset of JIA (formerly called Still's disease) occur 10-20% of all cases of JIA.

- The intermittent fever >39o for >2wk in association with the macular not pruritic rash is salmon-colored, may be linear or circular, often distribution on the trunk and extremities.
- Visceral involvement- hepatosplenomegaly, lymphadenopathy, pericarditis, pleural effusion in starting of disease. Some children with this disorder are initially thought to have leukemia because of the high white blood cell counts. Arthritis may not be evident for months following onset, making diagnosis difficult.

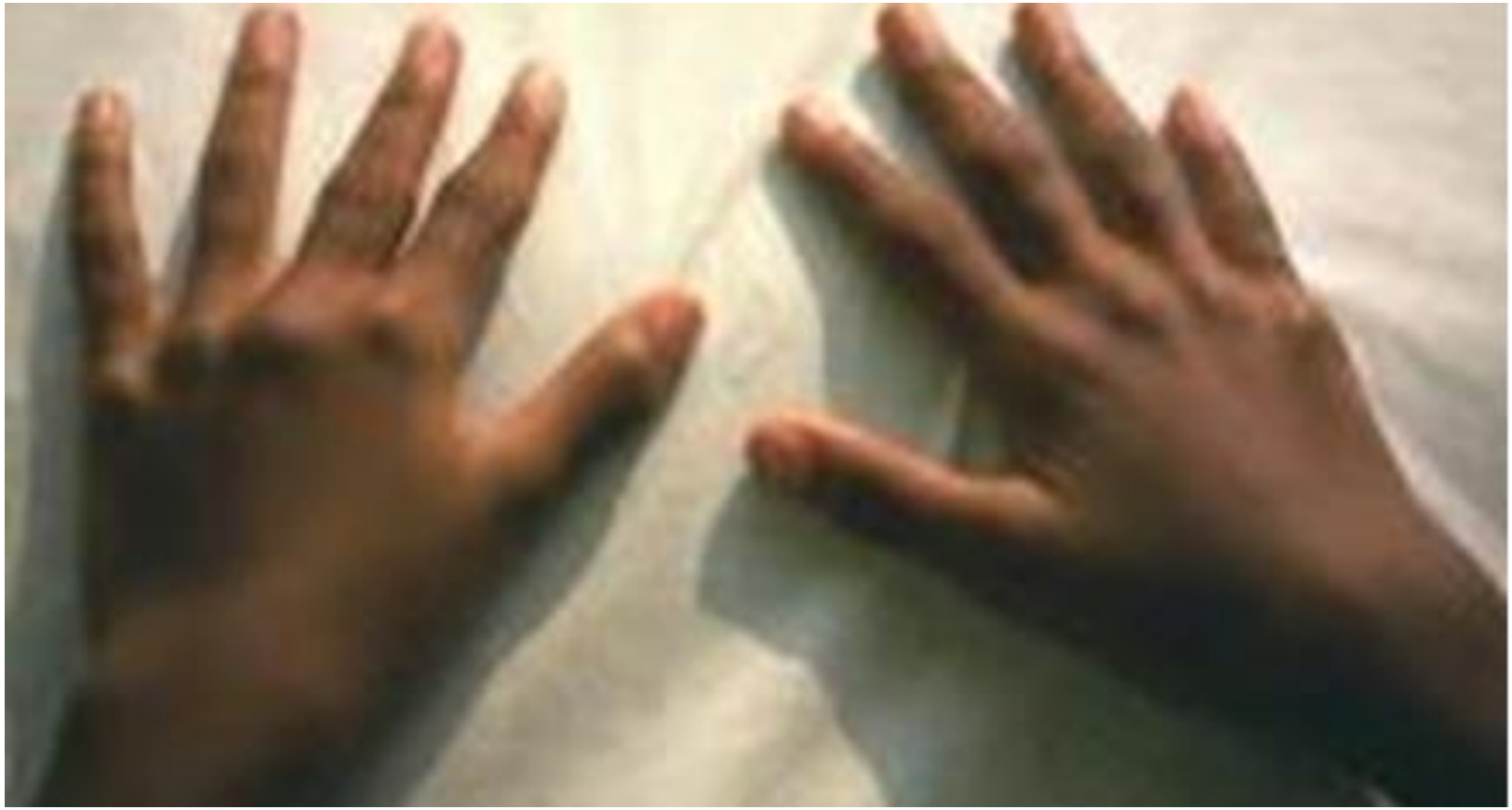
Pauciarticular onset of JIA

- Pauciarticular onset of JIA in patients with involvement less than four joints (50%of cases), during the first six months of disease. The peak incidence of it is in the second and third years, rarely begins after age 10, more often in girls.
- Pauciarticular JIA affects the large joints (knees, ancles, wrists, elbows), but virtually never begins in the hips.

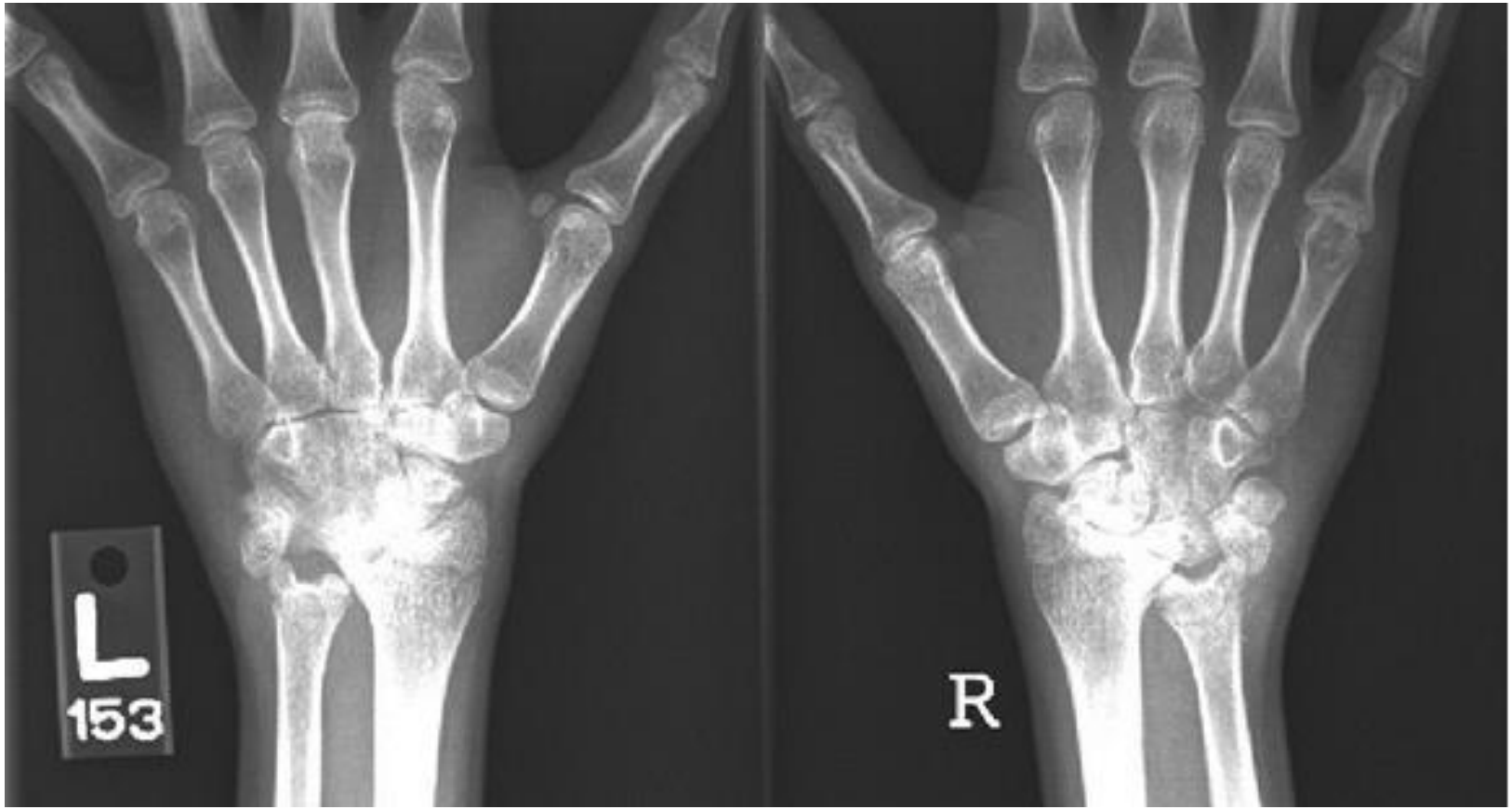
- The complication is uveitis with photophobia, synechiae (irregular iris perimeter resulting from inflammatory adhesions of iris to lens).
- Monoarticular arthritis in a hip is highly unusual. Consider Legg-Calve-Perthes disease; toxic synovitis of the hip; septic arthritis.

Polyarticular JIA

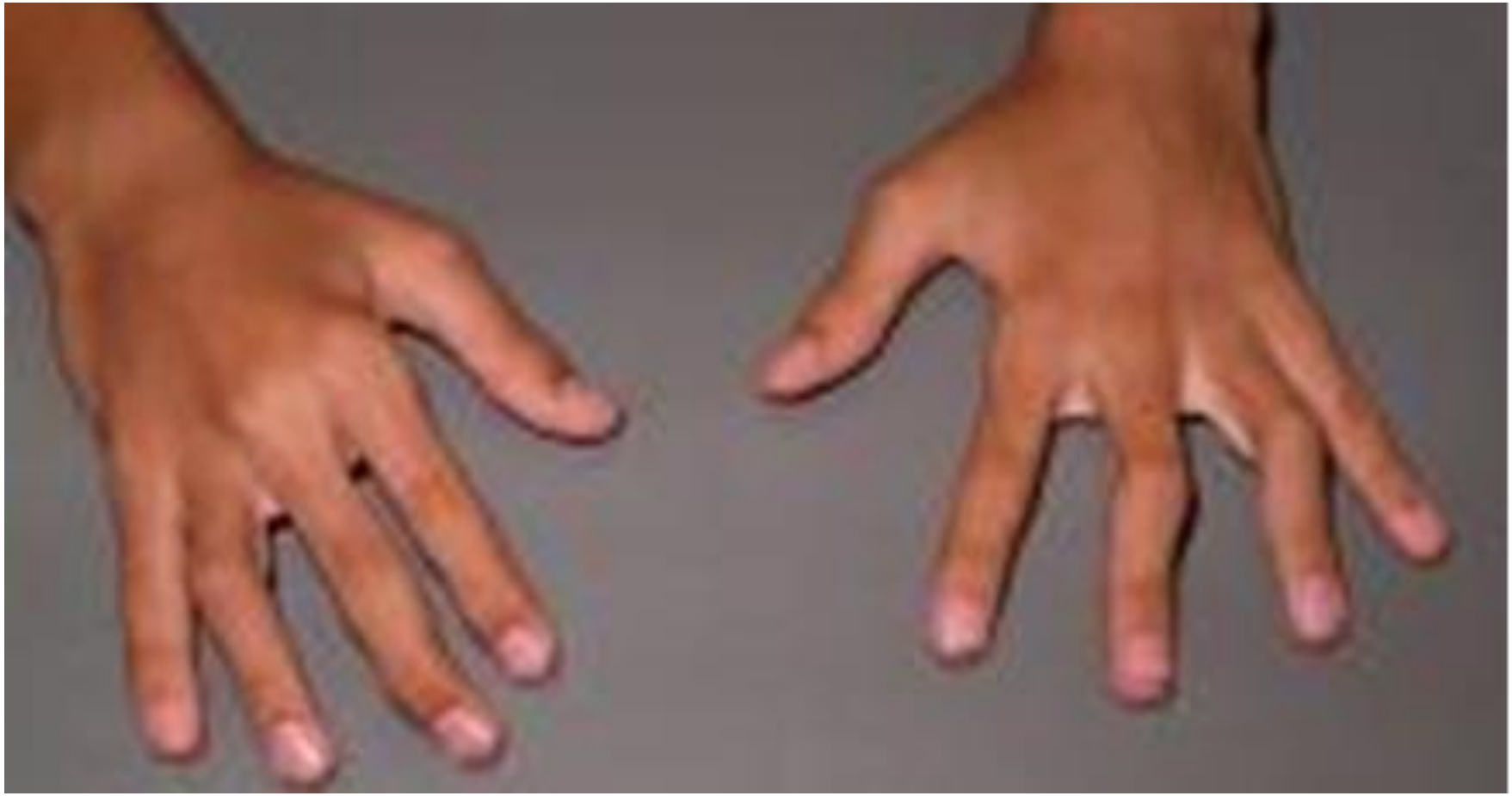
- Is defined by the presence of more than 5 affected joints during the first 6 months of illness.
- Distribution of the age at onset: the first peak in incidence is between the ages of 2-5 years, and the second peak between 10-14 years. It is more common in females than males.
- Typically, larger joints (knees, ankles, wrists), cervical spine are affected with swollen and tenderness. Muscle atrophy often in extensor muscles(vastus lateralis, quadriceps), flexion contractures.
- Rheumatoid nodules on the extensor surfaces of the elbows, and over the Achilles tendons are associated with a more severe course.
- There are no characteristic laboratory findings, although an elevated ESR,≥40mm/hr, anemia Hb ≤11g/dL, and hypergammaglobulinemia may be present.



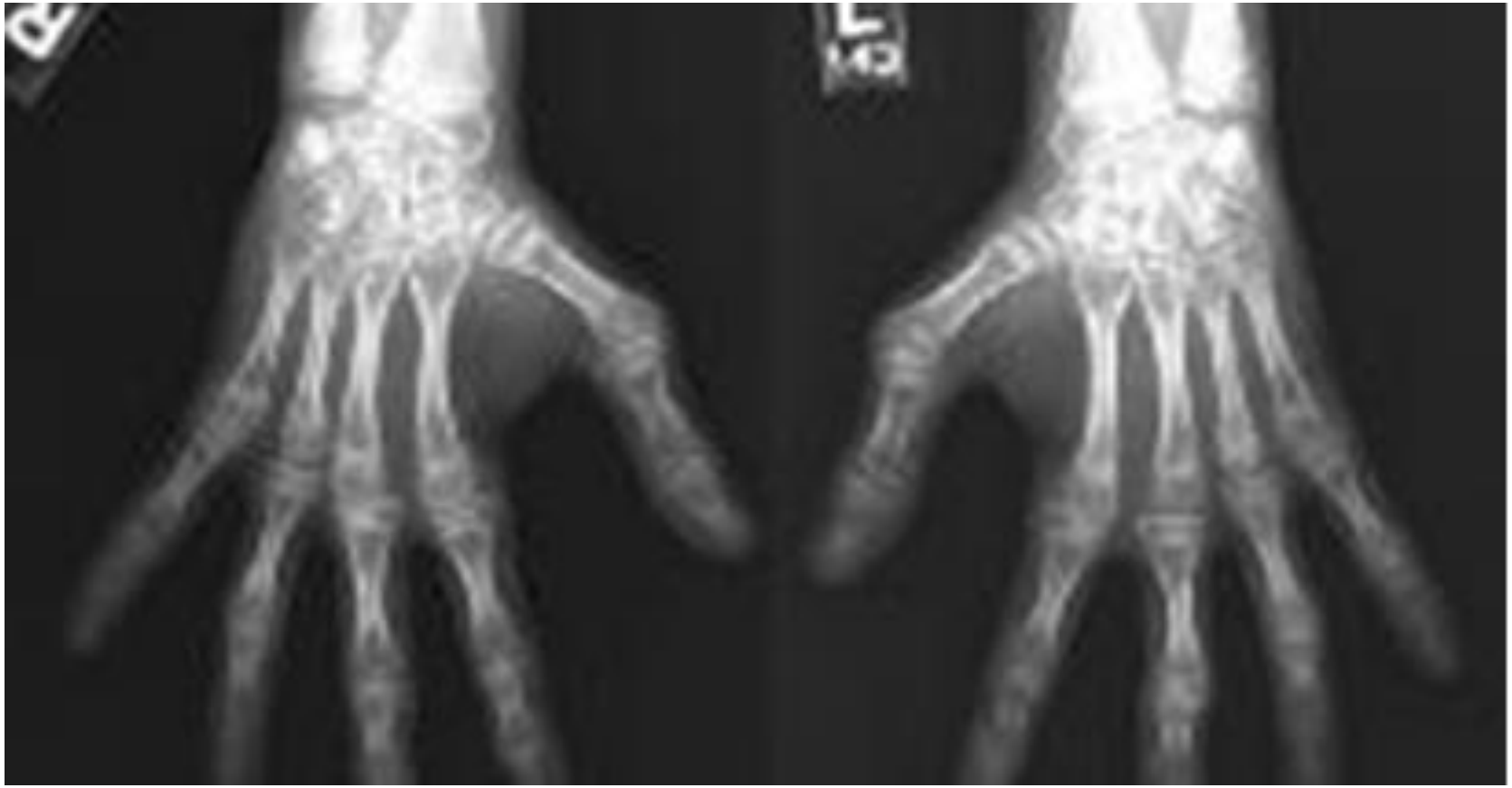
Picture 1. Patient with active polyarticular arthritis. Note swelling (effusions) of all proximal interphalangeal (PIP) joints in addition to boney overgrowth. Also note lack of distal interphalangeal joint (DIP) involvement. The patient has interosseus muscle wasting (observed on the dorsum of the hands), and subluxation and ulnar deviation of the wrists are present



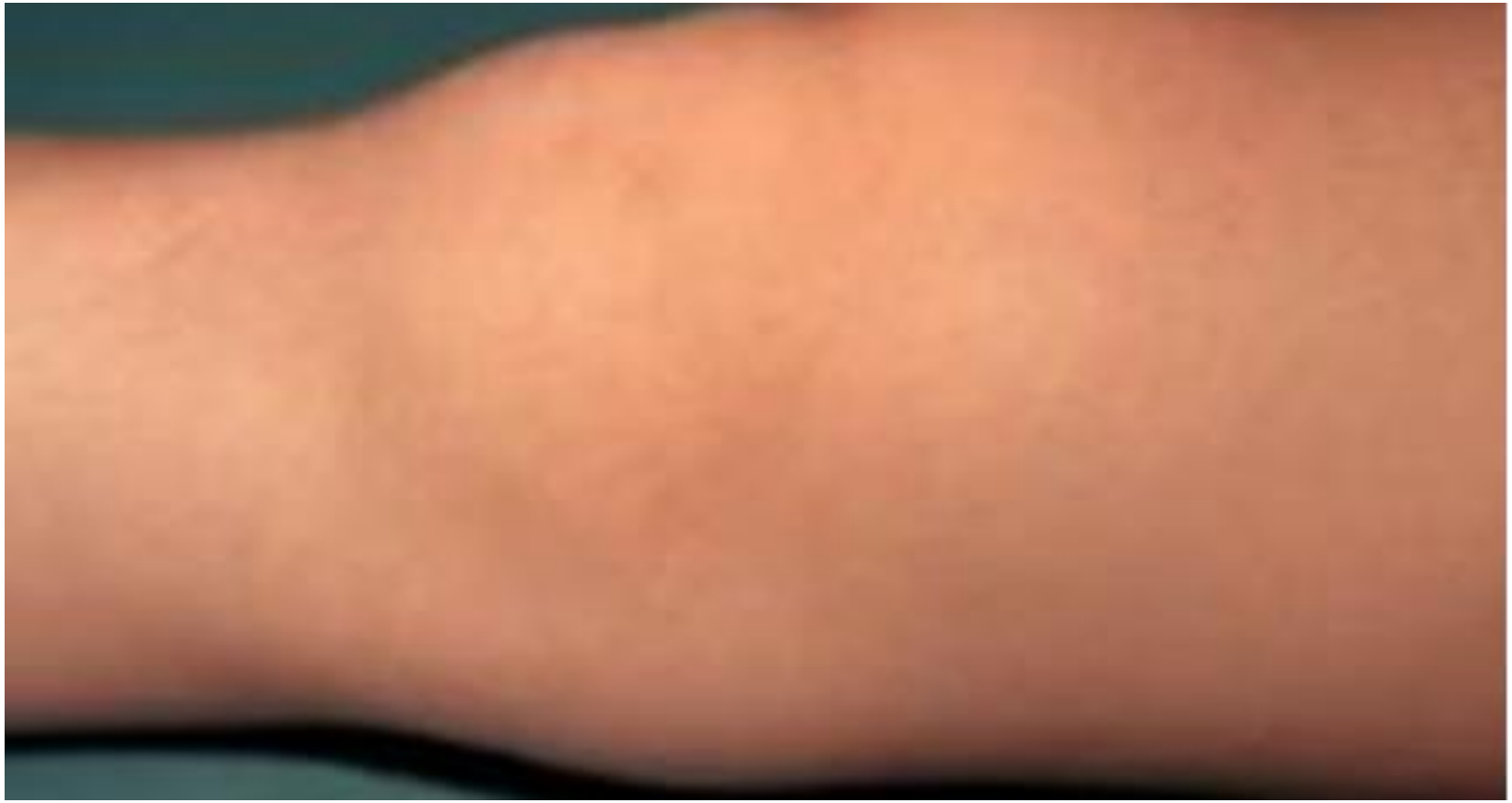
Picture 2. Wrist radiographs of the patient with active polyarticular arthritis shown in Image 2. Note severe loss of cartilage in the intercarpal spaces and the radiocarpal space of the right wrist. A large erosion is present in the articular surface of the ulnar epiphysis. The view of the left wrist shows boney ankylosis involving the lateral 4 carpal bones with sparing of the pisiform. Erosions are present in the distal radius and ulna. Almost a loss of cartilage has occurred between the radius and ulna and the carpus. Narrowing of the carpal/metacarpal joints is present.



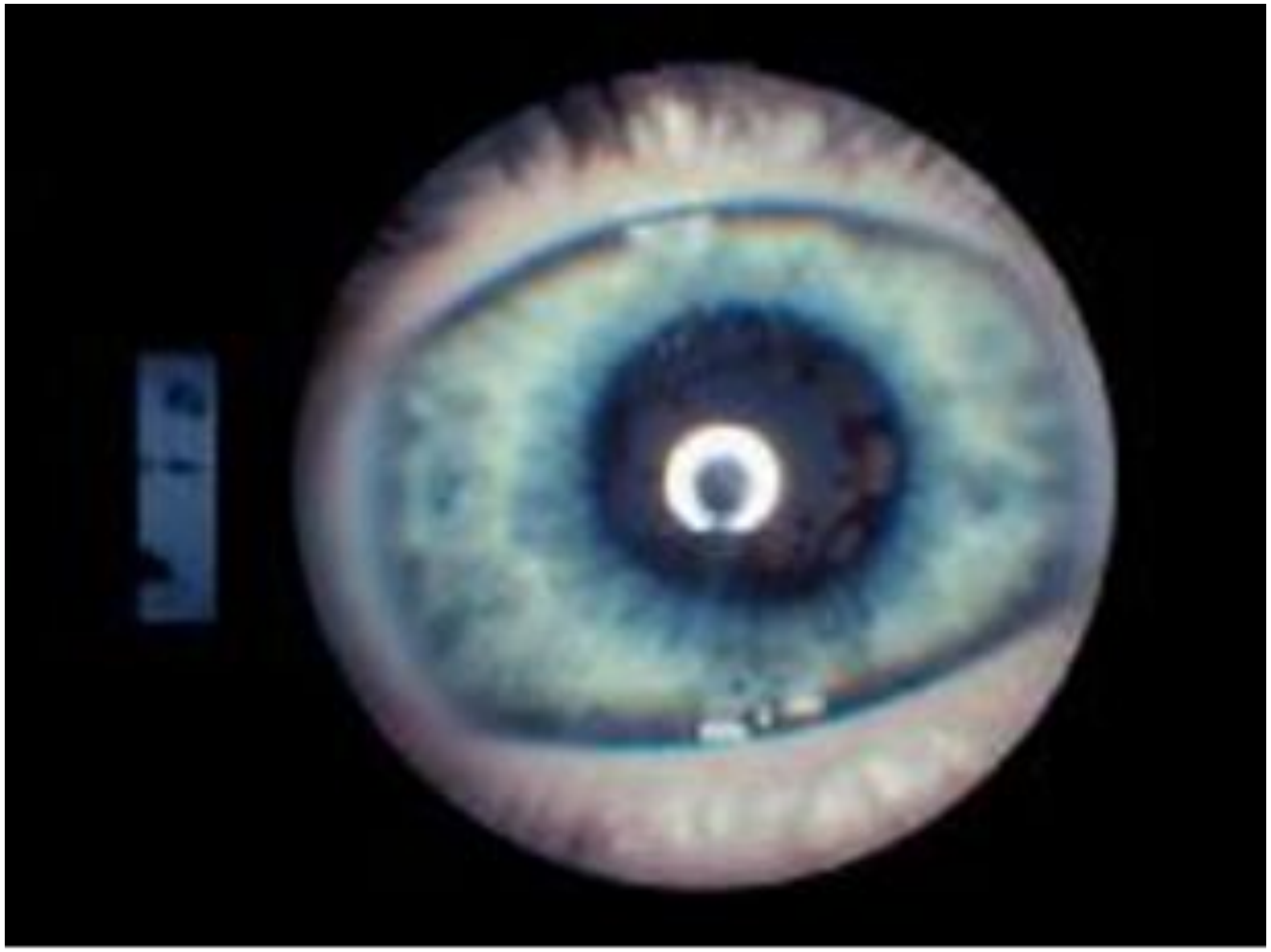
Picture 3. . Patient with inactive polyarticular arthritis. Long-term sequelae of polyarticular disease includes joint subluxation (note both wrists and thumbs), joint contractures (at proximal interphalangeal joints [PIPs] and distal interphalangeal joints [DIPs]), boney overgrowth (at all PIPs), and finger deformities (eg, swan-neck or boutonniere deformities)



Picture 4. Hand and wrist radiographs of the patient with inactive polyarticular arthritis shown in Image 5. Long-term sequelae of polyarticular disease includes periarticular osteopenia, generalized increase in the size of epiphyses, accelerated bone age, narrowed joint spaces (especially at the fourth and fifth proximal interphalangeal joints [PIPs] bilaterally), boutonniere deformities (at left third and fourth interphalangeal joints), and medial subluxation of the first metacarpophalangeal joints (MCPs) bilaterally.



Picture 5. Patient with active pauciarticular disease. Note significant suprapatellar swelling (effusion) as well as loss of natural contour medial to the patella. Image courtesy of Barry L. Myones, MD.



Picture 6. Sequelae of chronic anterior uveitis. Note the posterior synechiae (weblike attachments of the pupillary margin to the anterior lens capsule) of the right eye secondary to chronic anterior uveitis. This patient has a positive antinuclear antibodies (ANAs) and initially had a pauciarticular course of her arthritis. She now has polyarticular involvement but no active uveitis.

DIFFERENTIAL DIAGNOSIS

1.Psoriatic arthritis with limited joint involvement of the hand, ankle and skin manifestation.

2.Isolated hip pain with limited motion raises the possibility of suppurative arthritis.

3.Patients with acute lymphocytic leukemia and expansion of lymphoblasts in bone metaphyses, can present severe joint pain, even the arthritis; neutropenia and lymphocytosis are present. Bone marrow aspiration confirms the diagnosis.

4.Children and adolescent with spondyloarthropathy, characterized by periods of inflammation of tendons and ligaments at the area of insertion into bone (enthuses)may present arthritis. Although enthesitis can be observed in pauciarticular JIA.

LABORATORY STUDIES

- ESR is always elevated in children with systemic and polyarticular JIA, but is often within reference range in pauciarticular disease.
- When elevated, ESR may be used to monitor success of medical treatment.
- CBC with differential and platelet count.

- Lymphopenia is not uncommon because of emigration of activated lymphocytes out of the circulation into synovium.
- Neutropenia particularly with lymphocytosis or thrombocytopenia, raises the possibility of acute lymphocytic leukemia.
-Thrombocytopenia may also be observed in children with SLE presenting with arthritis.
-Microcytic anemia may result from chronic active JIA; usually refractive to treatment with iron.

- Elevated ALT levels need to exclude hepatitis (viral or autoimmune) prior treatment with NSAID, which can cause hepatotoxicity.
- Perform a urinalysis to exclude the possibility of infection (as a trigger of JIA or transient arthritis) and nephritis (more common in SLE).

Serum investigation

- Antinuclear antibody (ANA) observed in >25% of children with pauciarticular JIA.
- Titers of 1:80 or higher are positive; a 1:40 titer or lower is negative.
- When found in young girls a positive ANA is a marker of increased risk of uveitis.
- Very high titers of ANA may be in SLE.
- Rheumatoid factor defined as IgM 19S antiglobulin. Gel filtration at acid pH dissociated IgM from IgG and allows IgM RF. It is considered a marker for persistence of polyarticular JIA.
- Other laboratory tests:

- Total protein and albumin C-reactive protein: levels are often decreased during active disease.
- Fibrinogen and D-dimer: levels are often elevated in patients with active disease.

IMAGING STUDIES

- X-ray of affected joints: is important to exclude other diseases, such as osteomyelitis or septic arthritis.
- Bone scanning as a means of identifying of other abnormality.
- Perform MRI with gadolinium injection to enhance inflamed synovium.
- MRI is helpful when considering trauma in the differential diagnosis.
- Perform CT scanning when considering osteoid osteoma in a child with lower extremity pain, often at night.
- EcoCG in patients with possible systemic JIA and with fevers.
- Perform EcoCG in patients with orthopnea by history to exclude pericarditis; in nonspecific rash, adenopathy to exclude coronary arterial dilation (possibly Kawasaki disease), to exclude valvular disease in other rheumatic diseases.

OTHER PROCEDURES

- Arthrocentesis in a child with monoarticular swelling to exclude septic arthritis.
- Synovial biopsy may be helpful to exclude other diagnoses- villonodular synovitis, granulomatous arthritis; may demonstrate synovial infiltration with plasma cells, mature B lymphocytes, and T lymphocytes, with areas of thickening and fibrosis.
- Pericardiocentesis need to tret severe pericarditis.

TREATMENT OF JIA

NSAID are used to treat all subtypes of JIA, refers to cyclooxygenase 2 inhibitors, all medication regimens may contain NSAID.

Naproxen (7-20 mg/kg/d), Ibuprofen (30-50mg/kg/d not to exceed 2-4g/d), Diclofenac 2-3mg/kg/d, Tolmetin (20mg/kg/d), Indomethacin (1-2mg/kg/d). If NSAIDs are used , careful monitoring of hepatic and renal function is need.

IMMUNOSUPPRESSIVE AGENTS

- Methotrexate was recommended for patients with high and moderate activity of JIA and features of poor prognosis.
- Methotrexate (Rheumatrex): 7.5 mg/wk=> 2.5mg q12h for 3 doses.
- Sulfasalazine (Azulfidine, EN-tabs) in children>6yr 10mg/kg/d initially, increase by 10mg/kg/d qwk. Was recommended in enthesitis-related arthritis category of JIA.
- Cyclosporine has been effective in children with dactylitis who no responded to Sulfasalazine.

CORTICOSTEROIDS

- Are used in systemic onset JIA to minimize toxicity, particularly in patients, who have not responded to a 6-12 week used of NSAIDs; in uveitis and intraarticular joint injections for active arthritis.
- Prednisone dose 0.5-2mg/kg/d; taper over 2wk, as symptoms resolve.
- Methylprednisolone (Solu-Medrol) 15-30mg/kg/d ;IV administered over 30min for 2-3d, used temporarily for JIA until longer-term treatment provides effective relief.
- Intraarticular injections of corticosteroids are effective in polyarticular JIA, but more effective is systemic therapy.
- Uveitis is initially treated with topical corticosteroids, if the inflammatory process is not decrease systemic corticosteroids and/or methotrexate may be helpful. In severe disease , Cyclosporine, Adalimumab or Infliximab have been used.

TUMOR NECROSIS FACTOR (TNF) INHIBITORS

- TNF-a or cachecitin is produced predominantly by macrophages; TNF-beta or lymphotoxin is produced by lymphocytes. Both of them are involved in the inflammatory cascade in JIA.
- Etanercept (Enbrel) are used in children 4-17years: 0.4mg/kg twice/wk; should be used before Methotrexate, more effective, possibly less toxic.
- Adalimumab (Humira), has been effective in children who no responded to Etanercept.
- Infliximab (Remicade) have similar efficacy to that seen of Etanarcept. Adverse effects such macrophage activation, alopecia and double rises DNA antibodies was reported.

PROGNOSIS

- Children with pauciarticular JIA, particularly girls with onset at an age of <6yr, are at risk to develop chronic uveitis, cataracts, blindness.
- Risk in patients with seropositive RF for early development of erosions afection of the cervical spine or hips.
- Prognosis in the systemic-onset disease is dependent on the number of joints involved, duration of active inflammation, and the severity of the arthritis.
- The acute development of a severe anemia, thrombocytopenia or leucopenia with a high, spiking fever, lymphadenopathy, and hepatosplenomegaly occurs with the macrophage activation syndrome, a rare complication of systemic JIA. Emergency treatment with high dose IV pulse Methylprednisolone, Cyclosporine or Etanercept, may be effective.
- Orthopedic complications, medical control of patients with contractures, psychosocial adaptation may be counseling by health professionals.

SYSTEMIC LUPUS ERYTHEMATOSUS

DEFINITION: A chronic multisystem autoimmune connective tissue disorder that manifests with a broad spectrum of clinical phenotypes.

- Prevalence rates of 3.3-8.8/100,000 children. Median age of onset between 11-12 yr.: female predominance varies from 4:1before puberty to 8:1 afterward.

TRIGGERS:

- Chronic viral infections: myxovirus-like particles in endothelial cells. Increased serum titers of antiviral antibodies to rubella, EVB, paramyxovirus.

Criteria for the Classification of SLE

- Malar (butterfly) Rash
- Discoid-Lupus Rash
- Photosensitivity
- Oral or Nasal Ulcerations
- Nonerosive arthritis
- Serositis: Pleuritis or Pericarditis

- Hematological disorder: hemolytic anemia, leucopenia, lymphopena,trobocytopenia.
- Positive Antinuclear Antibody Test
- Renal disorder: persistent proteinuria >0.5g/day, cellular casts
- Neurological disorder: seizures or psychosis in the absence of offending drugs or metabolic derangements.

- Immunological disorder: antibody to native DNA or antibody to Sm protein or antiphospholipid antibodies-either anticardiolipin antibodies, presence of the lupus anticoagulant, or false-positive test for Syphilis
- Antinuclear antibody: presence by immunofluorescence or an equivalent assay
- *** Four of 11 criteria provide a sensitivity of 96% and a specificity of 96%**

Skin Manifestations

- **Malar (Butterfly) Rash-** is seen in 60-85% of children at the onset of SLE, is raised, non-pruritic, and non-scarring, extend over the nasal bridge, affects the chin and ears, but spares the nasolabial folds. Is distributed symmetrically in a butterfly fashion on both malar eminences and occasionally involves the forehead, may be precipitated by exposure to sunlight , does not result in scarring

- **Discoid-Lupus Rash-** is a rare manifestation in childhood SLE, occurs on the scalp or limbs. Scarring of the involved skin and hair loss of the temporal areas of the scalp is common.
- **Oral and Nasal Ulcers.**
- **Hard Palate Lesions-**a shallow, erythematous, painless ulcer with an irregular border, can also get erythematous lesions without ulceration. **M**ucous membrane involvement always indicates active SLE . **Aphthous Ulcers-**involve the mouth and pharynx, develop early in SLE and with exacerbation.

Subacute Cutaneous Lupus

- Distribution- involving the trunk, limbs, and face .**B**egins as papules which evolve into annular lesions with raised edges, may eventually become crusted, hyperpigmented, and atrophic.
- **Livedo Reticularis-** reflects active SLE, involves the lower extremities, associated with anticardiolipin auto-antibodies.
- **Others skin manifestations-** angiitic papules on soles and palms, bullae, chronic leg ulcerations. **E**rythema nodosum, rheumatoid nodules, gangrene, hypo/hyperpigmentation .**P**etechiae, purpura, telangiectases, urticarial or angioneurotic lesions.

Central Nervous System (CNS) Manifestations

- occur in 20-35% of children with SLE, tend to occur later in the course of the disease; a significant cause of morbidity and mortality; psychiatric manifestations are common in SLE

- **Headache-**occur at disease onset in about 10% of children with SLE, are severe, may or may not indicate CNS disease in those with SLE, may recur during exacerbations and disappear with remissions
- **Seizures-**a common manifestation in SLE, may be focal or generalized, may or may not be recurrent ,not related to a poor prognosis.
- **Movement Disorders-** cerebellar ataxia is a rare CNS manifestation of SLE, chorea in children is associated with SLE but is an uncommon complication

Central Nervous System (CNS) Manifestations

- **Others SNS manifestations-** aseptic meningitis, cortical blindness, hypothalamic lesions, intracranial hemorrhage . **P**aralysis, pseudotumor cerebri, transverse myelitis.

Pulmonary Manifestations

- **P**atients may demonstrate moderate to marked functional impairment with normal chest x-ray.
- **Pleural Effusions and Pleuritis -**in 27% of children with SLE
- **Pulmonary Infiltrates/Atelectasis-**in 13% of children with SLE . **"Shrinking" Lung-** in 13% of children with SLE, secondary to diaphragmatic dysfunction; on chest x-ray is seen as a progressive elevation of the level of the diaphragm . **Pleuropulmonary Infections-** a common pulmonary complication of SLE . **Others-** pneumonitis - acute and chronic; pneumothorax; pulmonary hemorrhage.

Cardiovascular (CVS) Manifestations

- **Pericarditis-** occurs in up to 30% of children with acute SLE, may be asymptomatic.
- When symptomatic may be associated with precordial chest pain which worsens with lying down or deep breathing and relieved by sitting up and leaning forward..Complications include constrictive pericarditis and cardiac tamponade but are rare.

Cardiovascular (CVS) Manifestations

- **Myocarditis-** occurs in up to 25% of children with SLE. **A**ssociated with congestive heart failure, arrhythmias, cardiomegaly, and/or narrow pulse pressure, aortic insufficiency may be a complication .
- **Endocarditis-** Libman-Sacks verrucous endocarditis, may develop in acutely ill patients; may be associated with a clinically significant murmur or changing murmur. **A**ssociated with 1-4mm nodes of fibrinoid necrosis of the supporting connective tissue of the valves:
- mitral > aortic > pulmonic > tricuspid valve (in descending order of involvement), lesions are demonstrable on 2D echo

Investigation of SLE

Antinuclear Antibodies (ANA)- a screening test to determine if autoantibodies to cell nuclei are present in more than 95% of SLE patients.

- Double-stranded DNA (dsDNA) antibodies have high specificity. Anti-Smith antibodies with dsDNA are associated with renal involvement and more severe disease.
- Other autoantibodies observed in SLE include anti-ribonuclear protein (anti-RNP), anti-Ro (also known as anti-SSA). Females with anti-Ro antibodies are at risk for Neonatal Lupus Erythemathosus and should be informed of this risk prior to any pregnancy.

Investigation of SLE

- **ANA Test-**is called the immunofluorescent anti-nuclear antibody test (ANA or FANA).
- The patient's blood is mixed with rat or mouse liver cells or HEp-2 cells, exposed to fluorescein-tagged anti-IgG antibodies, and then examined under a microscope , the preparations are assessed in two ways:
- **ANA Titre-** this tells how many times the patient's plasma had to be diluted to get a sample free of the fluorescein-tagged anti-IgG antibodies
- **ANA Pattern-** this looks at the distribution of fluorescein-tagged anti-IgG antibodies on the cells, there are 4 patterns .

Serum investigation of SLE

- **Acute Phase Indicies-** tend to be elevated in children with SLE: ESR, CRP, alpha-2-globulins, polyclonal hypergammaglobulinemia ,the degree of elevation is correlated to disease activity.
- Hypocomplementemia (particularly C3 and C4).
- **Complete Blood Count (CBC)- Anemia-** seen in 50% of children with SLE. **I**n SLE, there are several causes of anemia: anemia of chronic disease (normocytic, hypochromic), hemolytic anemia associated with auto-antibodies directed against erythrocytes (seen in 5% of cases), hypersplenism, microangiopathy.

Serum investigation of SLE

- **Thrombocytopenia-**PLT <150,000 in 30% of children with SLE; PLT <100,000 in 5% of children with SLE, may have normal platelet number despite increased production and destruction of platelets. **M**ay result in menorrhagia or gastrointestinal bleeding, may be severe enough to produce ITP or TTP.
- **Leukopenia-** WBC <4.5 in 40% of children with SLE, WBC <2.0 in 10% of children with SLE.
- Leukopenia (particularly lymphocytopenia) is a hallmark of acute SLE, children with leukopenia (WBC <2.0) may not response to septicemia with leukocytosis.

Treatment of SLE

- NSAIDs are used in SLE patients with arthritis and for serositis
- Anti-malarials drugs used for mild symptoms particularly rash and articular manifestations.
- Cyclophosphamide (trade names Cytoxan and Neosar) is used in lupus nephritis, neuropsychiatric involvement.
- In more severe cases corticosteroids and immunosuppressants are used to control the disease and prevent recurrence of symptoms (known as flares).
- Rituximab, a monoclonal antibody is effective for the treatment of cytopenias and autoimmune anemia.

Complications of SLE

- Patients who require steroids frequently may develop obesity, diabetes mellitus, and osteoporosis. Depending on the dosage, corticosteroids can cause other side effects such as a puffy face, an unusually large appetite and difficulty sleeping.
- Long term use of even low doses can cause elevated blood pressure and cataracts. Due to these side effects, steroids are avoided if possible.
- Worse prognosis are seen in patients with severe lupus nephritis or cerebritis, with risk of chronic disability or progression to renal failure and need renal transplantation.
- Opportunistic infections in patients reseiving immunosuppresive therapy. Osteonecrosis, especialy on the hips and knees.

Prognosis of SLE

- Mortality rates decreased over the with 10 and 15 year survival exceeding 85%.
- Mortality in the first several years of SLE is secondary to infections, lupus nephritis and myocardial infarction in young women.
- Monitoring inflammation and disease activity improved the prognosis.

Prevention of SLE

- Avoid ultraviolet light and sunlight exposure.
- Monitoring BP and serum lipids to prevent CAD of renal progression, myocardial infarction.
- ACE inhibitors and/or angiotensin receptor blockers in chronic renal disease.
- Calcium, vitamin D and prophilactic bisphosphonates may reduce the risk of glucocorticoid-induced osteoporosis.

JUVENILE DERMATOMYOSITIS

DEFINITION: Juvenile dermatomyositis (JDM) is an idiopathic inflammatory myopathy with systemic vasculopathy and skin signs. Incidence: 2-4 cases/million children per year, peak incidence is from 5 to 10 years. Girls are affected twice more than boys.

Pathogenesis of JDM

- TNF-a, TNF-b abnormalities: up regulation of genes controlled.
- Complement-mediated vascular inflammation.
- Cytotoxic effect of CD8, CD56 lymphocytes on muscle.
- T cell invasion of muscle fibers.
- Damage of muscle fibers, fibrosis.
- Edema and vascular inflammation of skin.

CLINICAL MANIFESTATIONS

- Proximal muscle weakness when climbing stairs, walking, rising from a sitting position.
- The heliotrope rash with edema in a symmetrical periorbital skin.
- Gottron papules over bony prominences of metacarpophalangeal and proximal interphalangeal goints.
- The periungual teleangiectases, hypertrophy of the cuticle, small hemorrhagic infarcts in areas.
- Scalp involvement manifested by psoriasiform dermatitis.
- Dysphagia is an urgent prognostic sign for hospitalization and treatment to prevent aspiration.
- Pulmonary function tests for myosytis-specific document decreased vital capacity.
- Gastrointestinal tract involvement associated with constipation, diarrhea, abdominal pain.
- Other signs: hepatosplenomegaly, retinitis, iritis, SNS involvement with seizures, depression.

JDM- DIAGNOSTIC CRTERIA

- Myopathic muscle weakness
- Elevated muscle enzymes.
- Electromyographic evidence of myopathy.
- Muskle biopsy: perifascicular atrophy, in addition to perimysial or perivascular infiltrates.
- Skin rash, calcinosis.

Four of the 5 criteria are related to the muscle disease.

LABORATORY STUDIES

- Elevated serum levels of muscle-derived enzymes: CK, aldolase , AST, LDH.
- ANA, anti-Mi-2, anti-Jo-1 (antihistidyl transfer RNA), antisignal recognition protein (anti-SRP) antibodies.

IMAGING STUDIES

- MRI- may detect myopathy, differentiating, selecting a muscle biopsy site.
- Chest X-ray in pulmonary symptoms.
- A barium swallow in esophageal dysmotility.
- EMG of detecting muscle inflammation.
- CT scans in the evaluation of potential malignancy.

OTHER TESTS

- Pulmonary function studies
- Electrocardiography
- Esophagal manometry in select patients
- Muskle biopsy is useful in differentiating steroid myopathy from active inflammatory myopathy.

Treatment of JDM

- Bed rest in patients with severe muscle inflammation.
- In children with muscle weakness a program of physical therapy to prevent contractures.
- Corticosteroids orally or intravenously: prednisone 1-2mg/kg/d; Methylprednisolone 30mg/kg/d for 3 days.
- Immunosuppresive- Ciclosporin A 3mg/kg/d addition of methotrexate. In decreased levels of IgG <500mg/dl replacement with IV immunoglobulin 0.4g/kg/mo or 1-2mg/kg, 1-2days/month for resistant disease.
- Maximal protection against ultraviolet A and B. Vitamin D to prevent bone fracture.

Prognosis of JDM

- Depend greatly on the extent of muskle disease, onset time and initiation of therapy.
- JDM follows one of three clinical courses: a uniphasic course in which patients are treated and improve without significant sequelae; a chronic recurrent course; and a chronic progressive course, marked by poor response to therapy and loss of function.

Systemic Sclerosis

Department of pediatrics

Definition

- Systemic sclerosis (SS) is a proliferative vasculopathy associated with systemic fibrosis and significant organ damage.
- Skin induration and thickening accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs.

Causes of systemic sclerosis (SS)

- The exact etiology of SS is unclear, the following pathogenic mechanisms are always present: endothelial cell injury, fibroblast activation.
- Immunologic derangement: positive anti-centromere and anti-topoisomerase-1 antibodies. Positive antinuclear antibodies.

ACR EULAR classification for SS

Items	Sub-items	Weight
Skin thickening of both hands extending to the proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (only count the highest score)	Puffy fingers	2
	Whole finger, distal to MCR	4
Finger tip lesions (only count the highest score)	Digital tip ulcer	2
	Pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or intrstitial lung disease		2
Raynaund`s phenomenon		3
Scleroderma related antibodies	(any of anti-centromere, anti-topoisomerase (anti-ScL 70 anti-RNA polymerase III)	3

Patients having a total score of 9 or more ara classified as having definite SS

Pathophysiology of SS

- Systemic sclerosis affects many organ and systems. It is most obvious in the skin; however, the GI tract; the respiratory, renal, cardiovascular, and genitourinary systems; and numerous vascular structures are frequently involved.
- The symptoms result from inflammation and progressive tissue fibrosis and occlusion of small blood vessels by excessive production and deposition of types I and III collagens. The levels of other macromolecules found in the connective tissue (eg, glycosaminoglycans, tenascin, fibronectin) are also increased.

Clinical manifestations

- Skin
  - Diffuse pruritus, pain or prickly sensation , edema, skin tightness and induration, loss ability to make a skin fold, loss of hair, decreased sweating
  - Raynaud phenomenon triggered by cold, smoking or emotional stress, the female-to-male ratio is 4:1
  - Skin hyperpigmentation or hypopigmentation -"salt and pepper" appearance, finger tip lesions .Cutaneous and mucosal telangiectasias on the face, hands and anterior chest
  - Reduced oral aperture (microstomia), poor dentition, decreased salivary production- xerostomia
  - Musculoskeletal system: synovitis, tendon friction rubs, artralgia, myalgia flexion contractures of joints.

Systemic involvement in SS

- Gastrointestinal system: esophageal reflux, severe esophagitis, esophageal strictures, dyspepsia, bloating, and early satiety, constipation, sphincter incompetence, colonic diverticula, malabsorption, liver dysfunction.
- Respiratory system: progressive dyspnea, persistent dry cough, decrease vital capacity, pulmonary artery hypertension.
- Cardiovascular system: dyspnea, pericardial effusion, cardiomyopathy, arrhythmias, heart failure.
- Renal system: hypertension, renal crisis (edema, oliguria, headache, elevate creatinine levels), chronic renal insufficiency.

Laboratory Studies

- Antinuclear antibodies are present in about 95% of the patients, usually with a speckled or homogenous pattern.
- Cell-mediated abnormalities involve lymphocytes, mononuclear phagocytes, and mast cells.
- Topoisomerase I antibodies (anti Scl-70) are present in approximately 30% of patients with SS (absent in limited disease) and are associated with pulmonary fibrosis.
- Anti-centromere antibodies are present in about 60-90% of patients with limited disease and are rare in patients with diffuse disease.

Laboratory Studies

- Anti-Fibrillin antibodies (FBN1) and antibodies to U3 ribonucleoprotein (RNP) may be present mostly in patients with diffuse disease with overlap syndromes, skeletal muscle involvement and pulmonary disease.
- Anti-ThRNP is present mostly in limited disease and is associated with more extensive visceral disease.
- Anti-PM-Scl is present in limited and overlap states and is associated with myositis and renal involvement.
- Current studies report new autoantibodies in systemic sclerosis that may play a role in its pathogenesis; these autoantibodies include anti-endothelial cell (AECA), anti–matrix metalloproteinase (MMP)–1 and anti–MMP-3, and anti–platelet-derived growth factor receptor (PDGFr).

Imaging Studies

- CT scan: may reveal a ground-glass appearance indicate active alveolitis, is the first abnormality during the development of lung fibrosis.CT scanning should be performed every 6 months if active alveolitis or interstitial pulmonary fibrosis is present.
- Radiography: Chest X-ray shows only late findings of pulmonary fibrosis, such as increased interstitial markings. Extremity radiography should be performed to reveal calcinosis and resorption of the distal tufts of the digits.

Imaging Studies

- Echocardiography: Conduct this test to evaluate the patient's pulmonary artery pressure and to assess septal fibrosis or pericardial effusions. Roughly 30% of patients have asymptomatic pericardial effusions.
- Right-heart catheterization for diagnosing pulmonary hypertension is performed after an elevated pulmonary artery pressure is found on echocardiographic screening.
- Esophagraphy: Perform this test to document esophageal dysmotility and incompetence of lower esophageal sphincter.

Other Tests

- Serum N-terminal pro-brain natriuretic peptide (NT-proBNP): Elevation of NT-proBNP levels may correlate with early pulmonary hypertension.
- Cardiac rhythm monitoring: Perform 24-hour a Holter monitoring to evaluate arrhythmias and serious conduction defects.
- Esophagogastroduodenoscopy, esophageal manometry, and pH monitoring studies.
- Bronchoscopy with bronchoalveolar lavage to assess active lung inflamation.

Treatment of skin afections

- Moisturizers, histamine 1 (H1) and histamine 2 (H2) blockers, tricyclic antidepressants, and trazodone in pruritis
- Raynaud phenomenon can be treated with calcium channel blockers, prazosin, prostaglandin E1, dipyridamole, aspirin, and topical nitrates. In the event of thrombosis a tissue plasminogen activator, heparin, and urokinase may be necessary.

- Bosentan, a dual endothelin receptor antagonist, is under investigation and may decrease new digital ulcer formation.
- Sildenafil has also been shown to be effective and tolerated in patients with primary Raynaud and is currently approved to treat pulmonary hypertension.

Treatment of digestive system

- Antacids, H2 blockers, reflux and aspiration precautions, proton pump inhibitors, prokinetic agents, smaller meals, and laxatives.
- Diet- avoid large doses of vitamin C(>1000mg/d) because it stimulates collagen formation and its deposition. Avoid food, that decreased pressure of lower esophageal sphincter: citruses, coffee, tomato.

Treatment of respiratory system

- Pulmonary fibrosing alveolitis may be treated with cyclophosphamide, either orally or in intravenous pulses. Pulmonary hypertension may require supplemental oxygen. Bosentan is effective in treating primary (idiopathic) pulmonary hypertension associated with systemic sclerosis.
- Other endothelin receptor antagonists such as sitaxsentan and ambrisentan; prostaglandin derivatives such as epoprostenol, treprostinil, beraprost and iloprost; and phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil. Preliminary nonrandomized studies have also shown benefit from mycophenolate mofetil.

Treatment of musculoskeletal system

- Myositis may be treated with steroids (first choice), methotrexate, and azathioprine. Doses of prednisone greater than 40 mg/d are associated with a higher incidence of scleroderma renal crisis. Digital ulcers must be kept clean and dry.
- Arthralgia can be treated with acetaminophen and non-steroid anti-inflammatory drugs (NSAIDs).
- Instruct the patient to perform physical and occupational therapy to minimize or delay contractures.

Immunosuppressive agents

- **Methotrexate 5-15mg/M2/wk** + folic acid 1mg/day
- Azathioprine 2-3mg/kg;Cyclosporine A 3-5mg/kg
- Anticytokines - Etanercept 0.4 mg/kg/wk
- Glucocorticosteroids - Prednisone 2.5-5mg/kg, gradually decrease to lower dose
- Chelating agents: Penicillamine 5 - 10mg/kg/d responsible for collagen formation

Treatment of vascular affections

- ***Endothelin Receptor Antagonist – Bosentan***, Ambrisentan for treatment of pulmonary arterial hypertension
- Phosphodiesterase Type 5 inhibitor – Sildenafil, peripheral vasodilator, promotes vasodilation in the pulmonary vascular bed.
- Calcium channel blockers – Nifedipin
- ACE inhibitors in renal crisis episodes

FOLLOW-UP

- Patients may need to be treated by other subspecialists depending on their symptoms (e.g. cardiologist, pulmonologist, gastroenterologist, nephrologist, hand surgeon).
- The value of serology testing is for initial diagnosis and assessment of associated conditions, but it is less use for monitoring disease activity.
- Instruct the patient to stop smoking, to avoid cold exposure, digital or skin trauma, to minimize the risk of Raynaud phenomenon.
- Renal and lung transplantation are performed in specialized centers for patients with end-stage renal or lung involvement.
- Current studies of stem cell transplantation are ongoing and may lead to disease remission.

Prognosis

- For patients with limited involvement, 10-year survival rates are roughly 60-70%. For patients with diffuse disease, 10-year survival rates are 20%.
- Factors that imply a more severe prognosis are as follows:

  - Youth
  - African descent
  - Rapid progression of skin symptoms
  - Extent of skin involvement
  - Anemia
  - Elevated erythrocyte sedimentation rate (ESR)
  - Pulmonary and renal involvement

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