Common Pediatric Rheumatologic Diseases

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- Juvenile Idiopathic Arthritis
- SLE
- HSP
- JDM

Juvenile idiopathic arthritis (JIA)

Juvenile Rheumatoid Arthritis
Juvenile Chronic Arthritis

Arthritis: swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks, is observed by a physician, and is not due to primarily mechanical disorders or other identifiable causes.

- JIA is a group of disorders characterized by chronic arthritis.
- It is the most common chronic rheumatic illness in children.
- It is a clinical diagnosis made in a child less than 16 years of age with arthritis.
- The incidence of JIA ranges from 1 to 22 per 100,000.

Pathophysiology:

The pathogenesis of JIA is not understood well.

Substantial evidence suggests that JIA is an autoimmune process.

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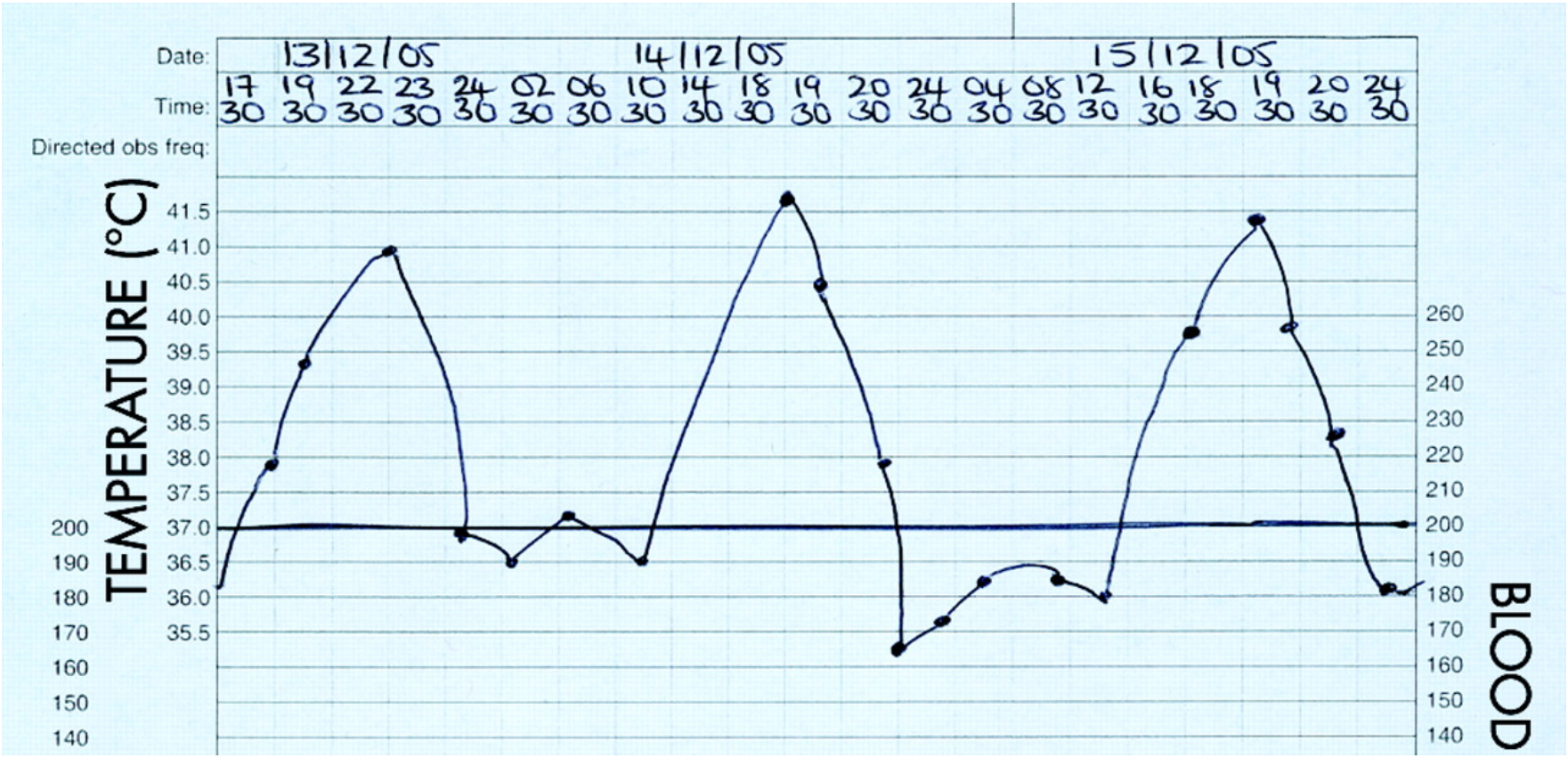
- Classification of JIA:
  - Oligoarticular JIA.
  - Polyarticular rheumatoid factor positive JIA.
  - Polyarticular rheumatoid factor negative JIA.
  - Systemic JIA.
  - Psoriatic JIA.
  - Enthesitis related arthritis(ERA).
  - Undifferentiated.

- Oligoarticular JIA
  - <5 joints during the first 6 months of disease.
  - At high risk for developing uveitis especially ANA-positive girls.
  - Persistent & extended oligoarticular JIA.


EyeRounds.org

- Polyarticular JIA
  - RF-negative disease (20% to 30% of JIA patients)
  - RF-positive disease (5% to 10% of JIA patients).
  - Both types affect girls more frequently than boys.
  - RF-negative patients often develop polyarthritis in early childhood.

- Systemic onset juvenile idiopathic arthritis:
  - No specific age and gender.
  - At onset, extra-articular manifestations including rash, fever, lymphadenopathy, hepatosplenomegaly, and serositis predominate.
  - The classic rash is evanescent .
  - Stress or a warm bath may exacerbate the rash.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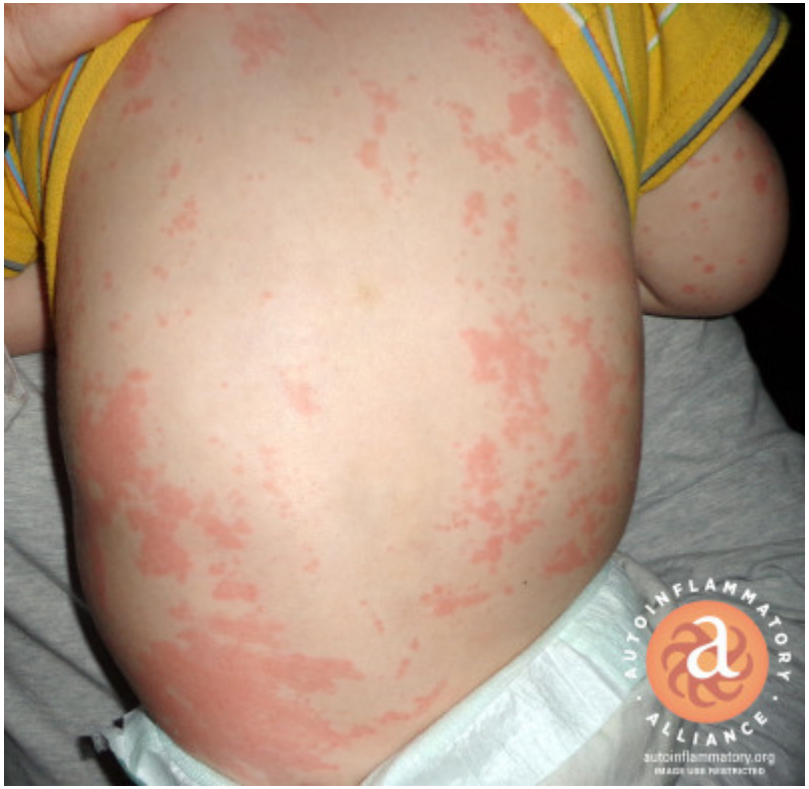
BLOOD

- Evancent rash



Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis

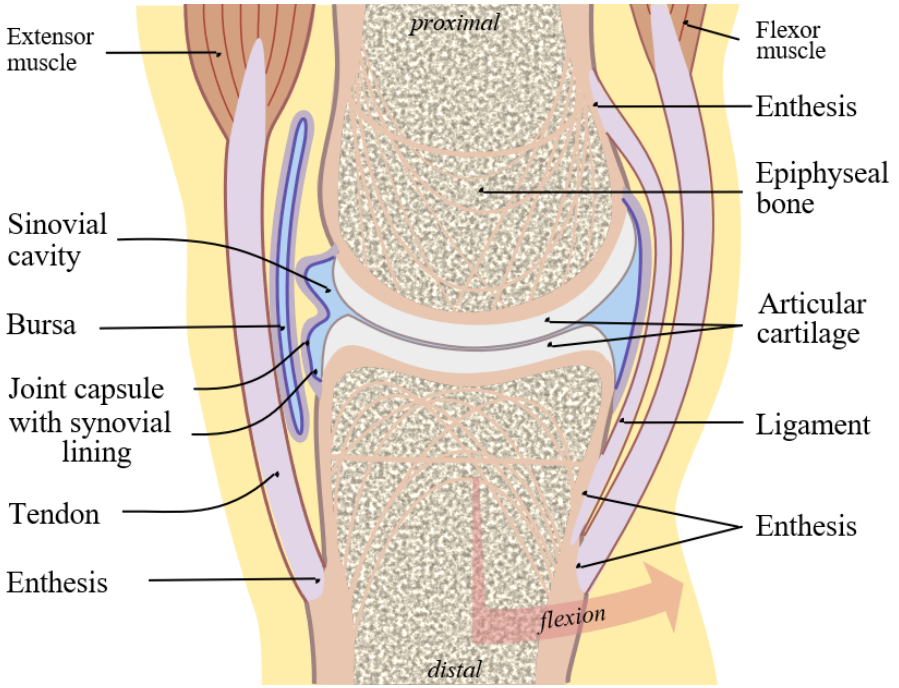
A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin >684 ng/ml
and any 2 of the following:
Platelet count ≤181 x 10^9/liter
Aspartate aminotransferase >48 units/liter
Triglycerides >156 mg/dl
Fibrinogen ≤360 mg/dl

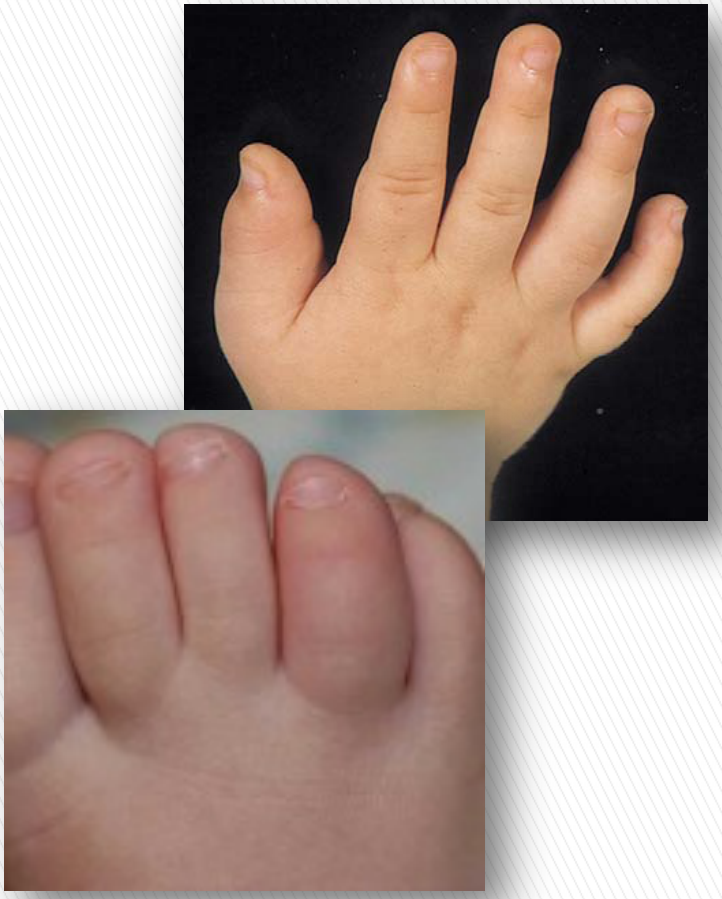
Figure 2. Criteria for the classification of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidemia.

- Enthesitis-related arthritis:
  - Most common in boys older than 8 years of age.
  - It has a strong genetic predisposition.
  - The hallmarks of the disease are pain, stiffness, and eventual loss of mobility of the back.

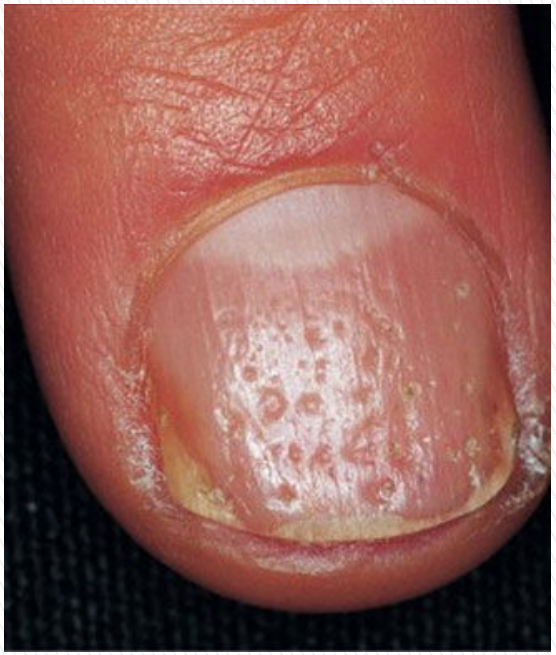
- Enthesis


proximal
Extensor muscle
Flexor muscle
Enthesis
Epiphyseal bone
Sinovial cavity
Articular cartilage
Bursa
Joint capsule with synovial lining
Ligament
Tendon
Enthesis
Enthesis
flexion
distal

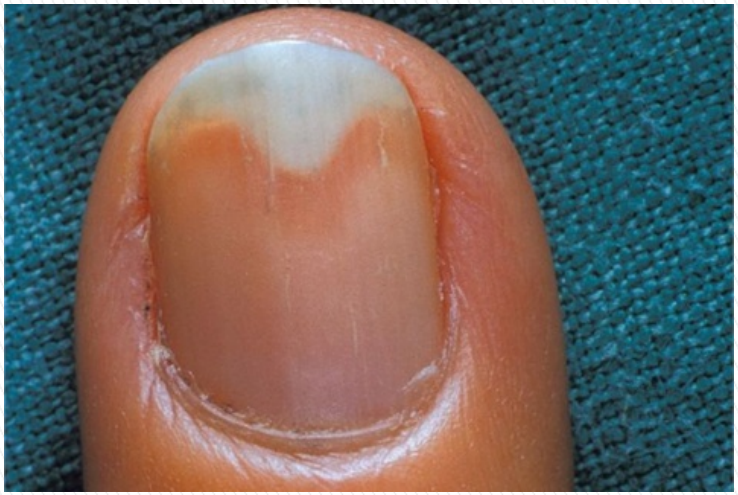
- Psoriatic arthritis:
  - A peak age of onset in mid childhood.
  - Extra-articular manifestations include rash, nail changes (including pitting, onycholysis) and uveitis.



- Nail pitting



- onycholysis



Differential diagnosis of arthritis:

- **Reactive**:
  - Post-enteric.
  - Rheumatic fever.
  - Post-streptococcal.
- **Inflammatory**:
  - Juvenile idiopathic arthritis.
  - Inflammatory bowel disease.
  - Sarcoidosis.
- **Systemic**:
  - Kawasaki disease.
  - Behcet's disease.
  - Henoch-Schonlein purpura.
  - Serum sickness.
  - Systemic lupus erythematosus.
  - Dermatomyositis.
- **Malignancy**:
  - Leukemia.
  - Neuroblastoma.
  - Malignant bone tumors.
- **Infection**:
  - Septic.
  - Osteomyelitis.
  - Viral.
  - Bacterial sacroilitis.
- **Benign bone tumors.**
- **Trauma.**

- Laboratory :
  - No specific lab. can confirm the diagnosis
  - Lab. can be used to :
    - Provide evidence of inflammation.
    - Support the clinical diagnosis.
    - Monitor treatment toxicity.

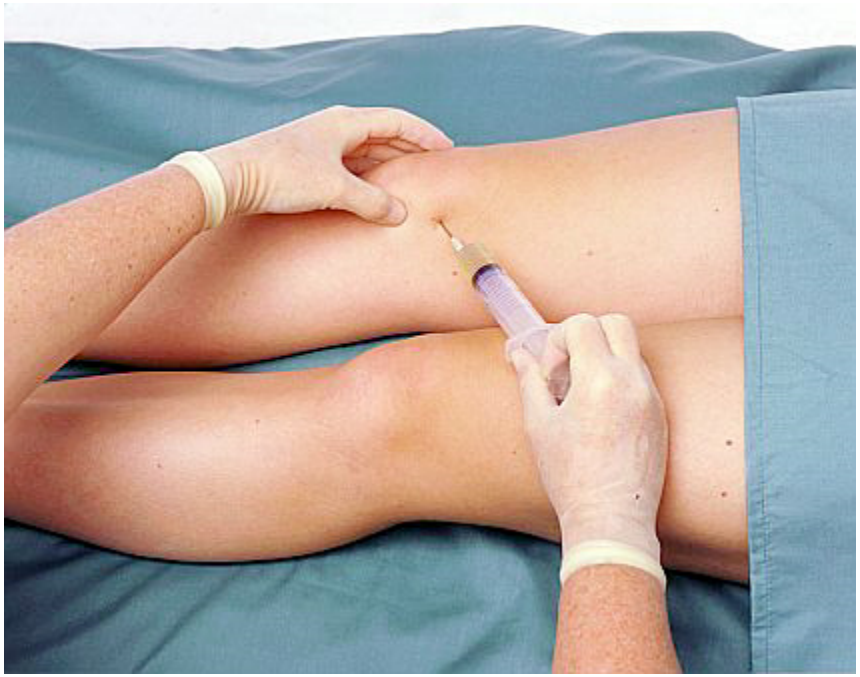
- Limited joint disease:
  - Mild anemia.
- Moderate –extensive arthritis:
  - Normocystic hypochromic anemia or severe anemia.
  - Iron deficiency anemia.
  - High WBC count.
  - High platelets.

- ESR (erythrocyte sedimentation rate):
  - Useful but not totally reliable measure of active disease.
  - Helpful in monitoring the therapeutic efficacy of the medications.

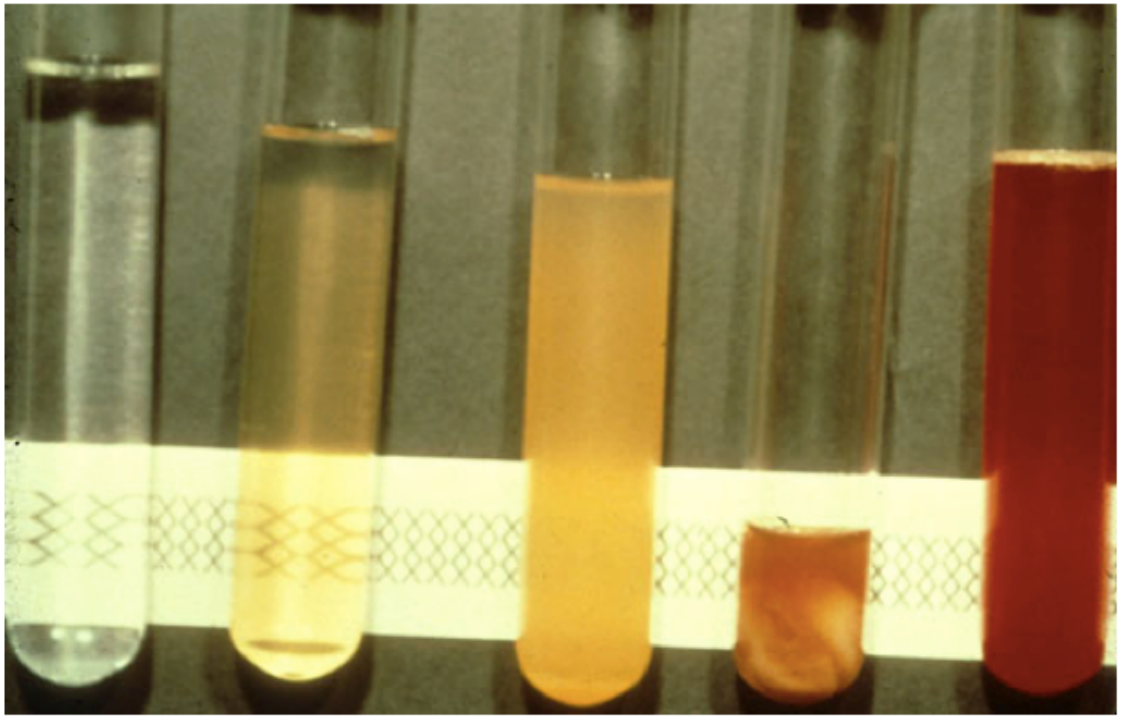
- CRP (c –reactive protein):
  - More reliable monitor of inflammation response.

- Rheumatoid factor:
  - IgM anti IgG
  - RF positive in:
    - Later childhood poly arthritis
    - Subcutaneous nodules
    - Articular erosions.

- ANA (antinuclear antibody):
  - More frequent in young girls with oligo JIA.
  - Less frequent in older boys with systemic arthritis.



Synovial Fluid Color and Clarity



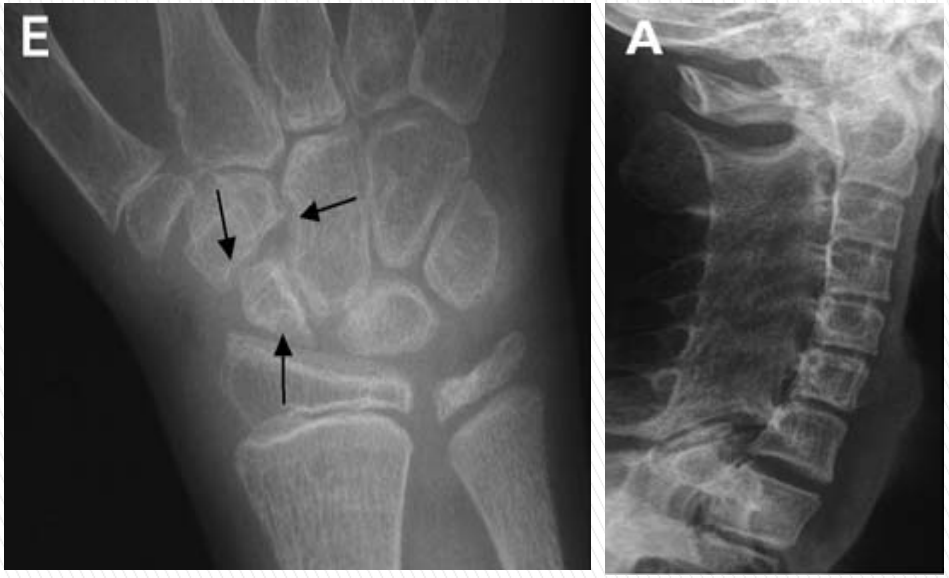
Normal | Non-inflammatory | Inflammatory | Septic | Hemorrhage

- Radiology:

Plain x-ray

  - Early radiological changes:
    - Periosteal soft tissue swelling.
    - Widening of the joint space.
    - Juxta articular osteoporosis.

- Later changes:
  - Joint space narrowing
  - Erosions.
  - Subluxation.
  - Ankylosis.
  - Fracture.



Management:

- Multidisciplinary approach.
- The aim of management of JIA include:
  - Controlling pain.
  - Controlling inflammation.
  - Preserving function.
  - Promoting normal growth.
  - Promoting overall development.
  - Manage systemic complication.

- Medications:
  - NSAIDS:
    - Naproxen.
  - Methotrexate.
  - Steroids:
    - Systemic.
    - Intra-articular.
  - Biologics (relatively new).

Systemic Lupus Erythematosus

- SLE is a multisystem autoimmune disease with a great variability in disease presentation and course.

- The diagnosis of SLE is based on the clinical and laboratory features consistent with this illness.

- The etiology of systemic lupus erythematosus (SLE) remains unknown and it is multifactorial.

- **Genetic factors** :

  There is a high concordance rate (14 to 57 percent) of SLE in monozygotic twins.

  - Children of mothers with lupus may have a positive test for anti-nuclear antibodies

- **Hormonal factors** :
  - The use of estrogen-containing contraceptive agents is associated with a 50 percent increase in risk of developing SLE

- **Immune abnormalities:**
  - SLE is primarily a disease with abnormalities in immune regulation

- **Environmental factors** :
  - Viruses
  - Ultraviolet (UV) light
  - Allergies to medications

Criteria for classification of systemic lupus erythematosus:

Old criteria

RheumTutor.com

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

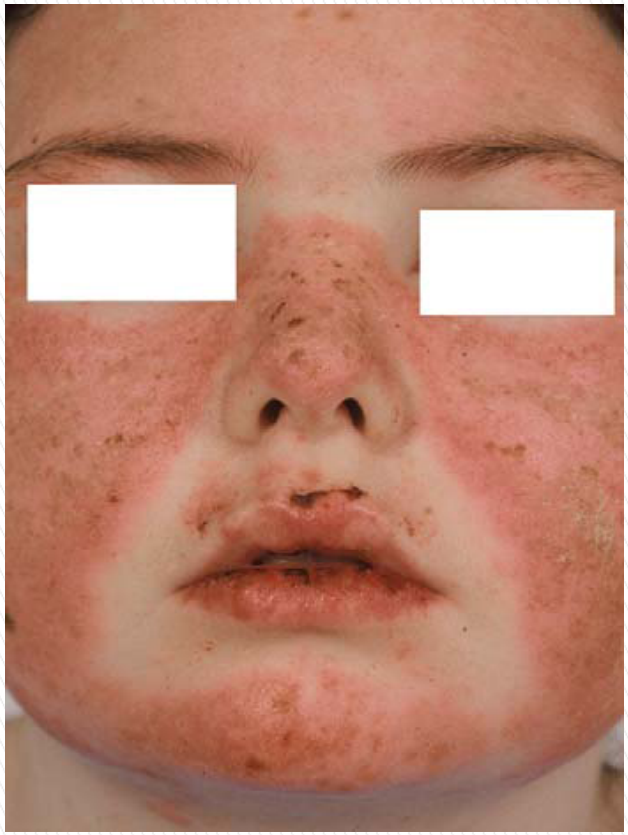
Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure 2 Classification criteria for systemic lupus erythematosus.
§Additional criteria items within the same domain will not be counted.
*Note: In an assay with at least 90% specificity against relevant disease

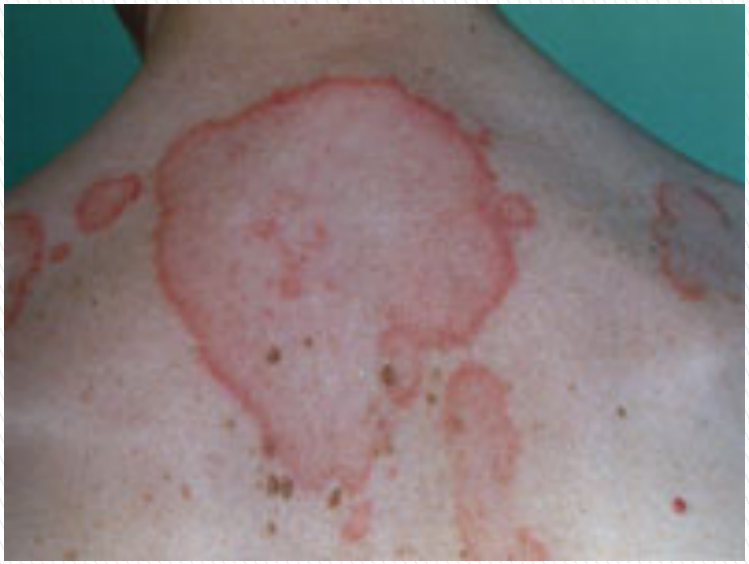
CLINICAL CRITERIA

Acute Cutaneous Lupus :

malar rash

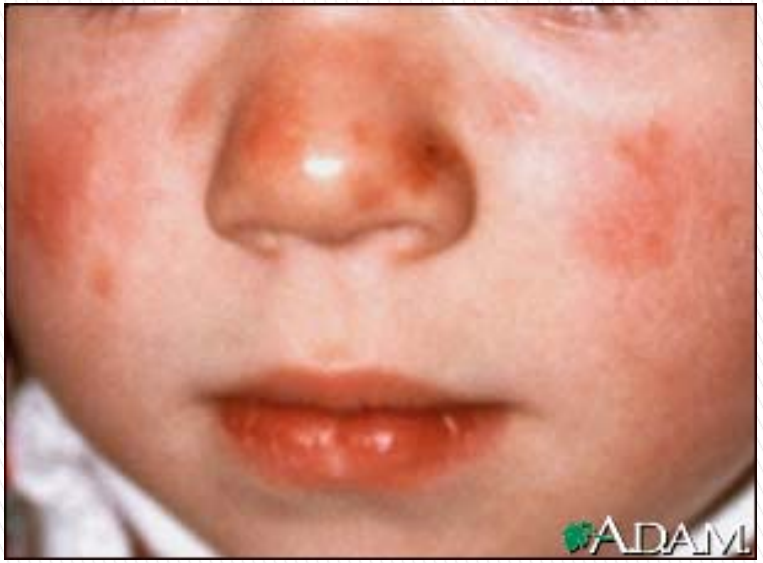


Subacute cutaneous lupus:



Chronic Cutaneous Lupus

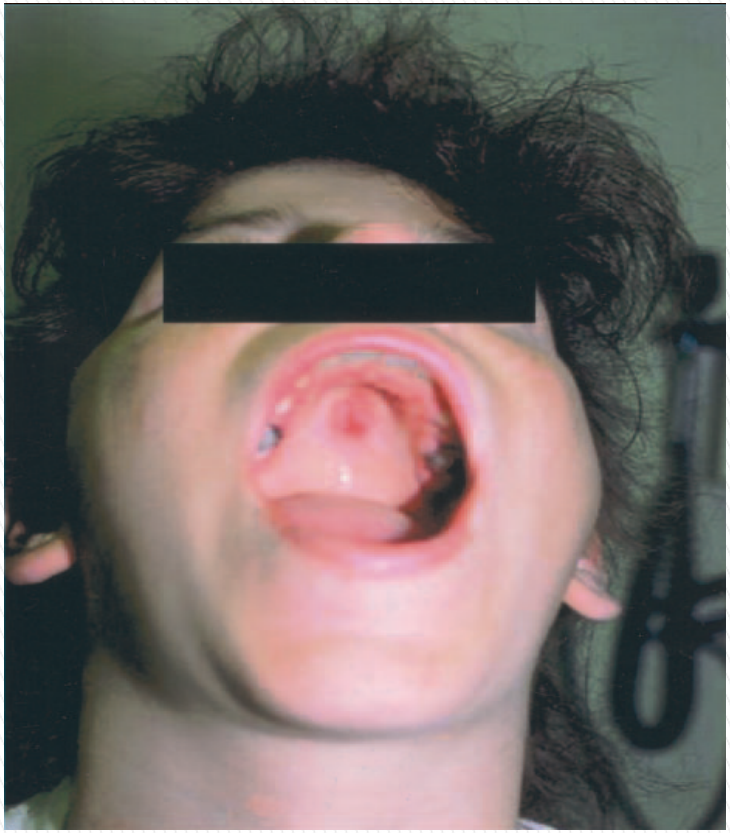
discoid rash



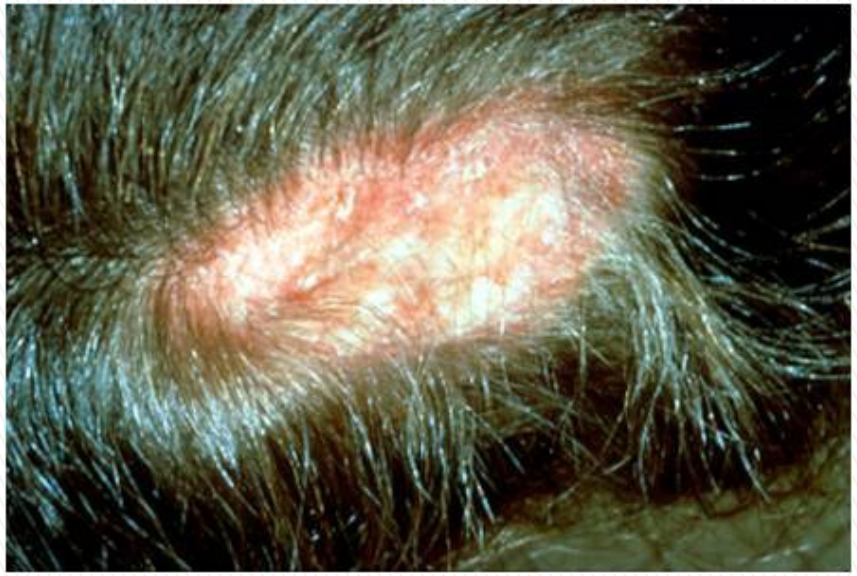
Oral Ulcers

OR

Nasal Ulcers



Non-scarring alopecia



Arthritis involving 2 or more joints

Serositis

pleural effusions

pericardial effusion

pericarditis by electrocardiography

In the absence of other causes, such as infection, uremia.

Renal

Urine protein–to–creatinine ratio (or 24–hour urine protein) representing 500 mg protein/24 hours

OR

red blood cell casts

Neurologic

- Seizures
- Psychosis
- Mononeuritis multiplex(in the absence of other known causes)
- Myelitis
- Peripheral or cranial neuropathy (in the absence of other known causes)
- Acute confusional state (in the absence of other causes).

Hemolytic anemia

Leukopenia (<4000/mm3)

OR

Lymphopenia (<1000/mm3)

Thrombocytopenia (<100,000/mm3)

At least once in the absence of other known causes.

IMMUNOLOGIY

(1) **ANA** level above laboratory reference range.
(2) **Anti-dsDNA** antibody level above laboratory reference range .
(3) **Anti-Smith**

(4) Antiphospholipid antibody

(5) **Low complement** (C3, C4, or CH50)

(6) **Direct Coombs' test** (in the absence of hemolytic anemia)

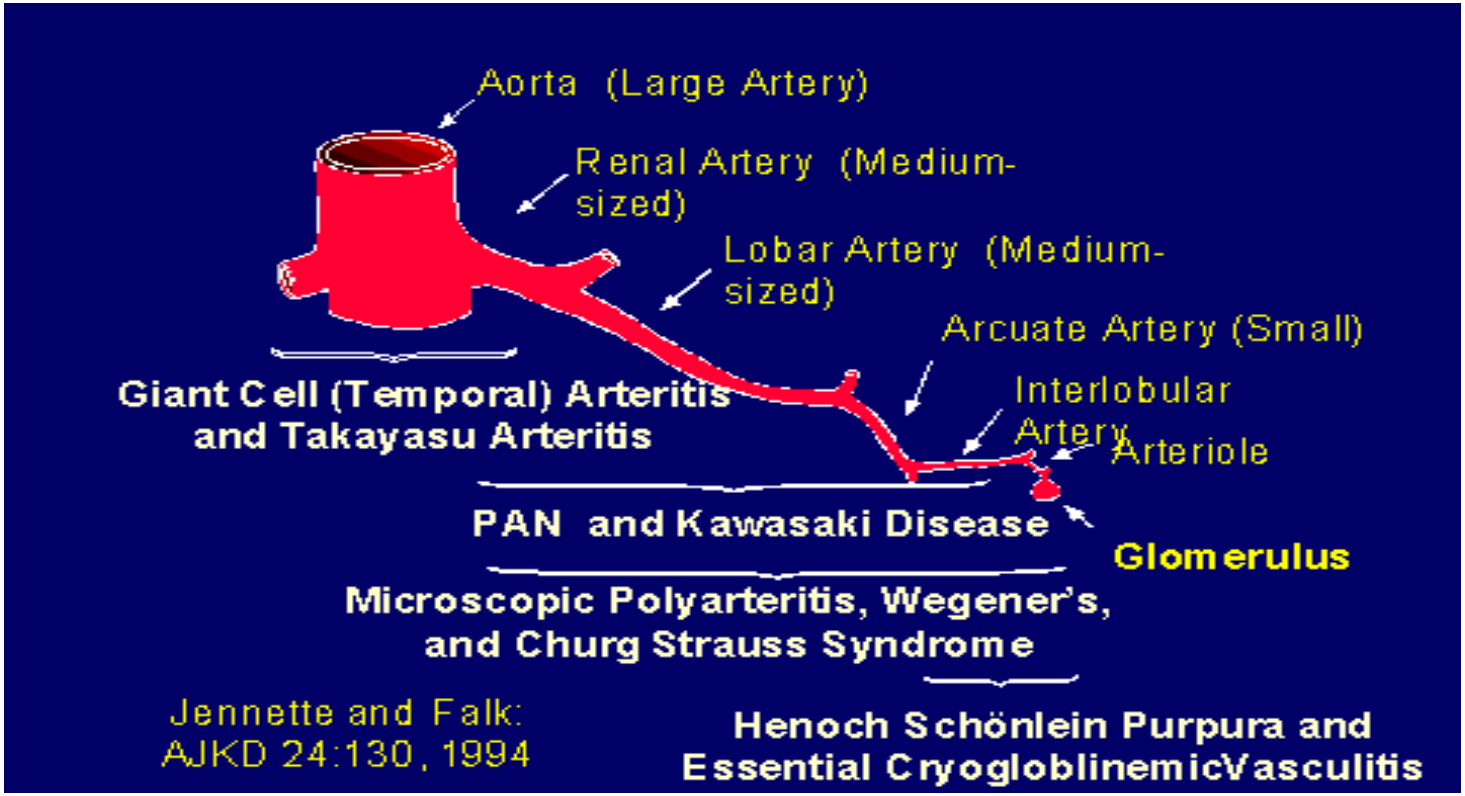
- Treatment:

  General :

  Team approach.
  - Counseling.
  - Education.
  - Appropriate nutrition.
  - Use of sun protection.
  - Immunization.
  - Prompt management of infection.

- Nonsteroidal Anti-inflammatory.
- Hydroxychloroquine.
- Glucocorticoids.
- Immunosuppressives.

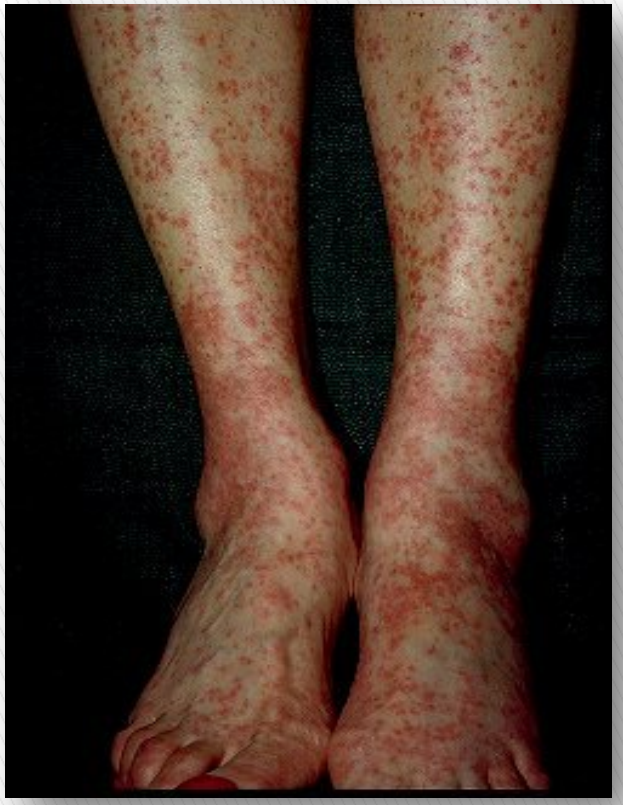
Henoch-Schonlein purpura



Henoch-Schonlein purpura

- HSP is the most common pediatric vasculitis.

- Classically presents with the triad of:
  - Non-thrombocytopenic palpable purpura.
  - Colicky abdominal pain.
  - Arthritis.



- **Pathophysiology**
  - Immunoglobulin A (IgA) immune complexes deposition.

- The major cause of morbidity is renal involvement.
- 3-15 years.
- A wide variety of infections may trigger HSP.

- Skin involvement (100%) in HSP may begin as urticaria, but in most cases it progresses to dramatic purple, non-blanching lesions .
- Gastrointestinal involvement (75%)ranges from colicky abdominal pain to profuse bleeding, intussusception.
- The arthritis of HSP (50%) is usually transient, and it does not cause chronic joint changes.

- **Renal Disease**
- The most serious sequela of Henoch-Schonlein purpura is renal involvement.
- This complication occurs in about 25 percent of children .

Diagnosis:

Purpura (mandatory criterion)

- 1. Abdominal pain.
- 2. Histopathology; vasculitis with predominant IgA deposit.
- 3. Arthritis or arthralgia.
- 4. Renal involvement.

- Therapy of HSP is primarily supportive, aiming for symptomatic relief of arthritis and abdominal pain.

- Use of steroids in children who do not respond to NSAIDs or in those thought to be at highest risk of developing renal compromise continues to be controversial.

Juvenile Dermatomyositis

- Idiopathic inflammatory myopathies (IIMs), collectively known as myositis, are heterogeneous disorders characterized by muscle weakness and muscle inflammation.

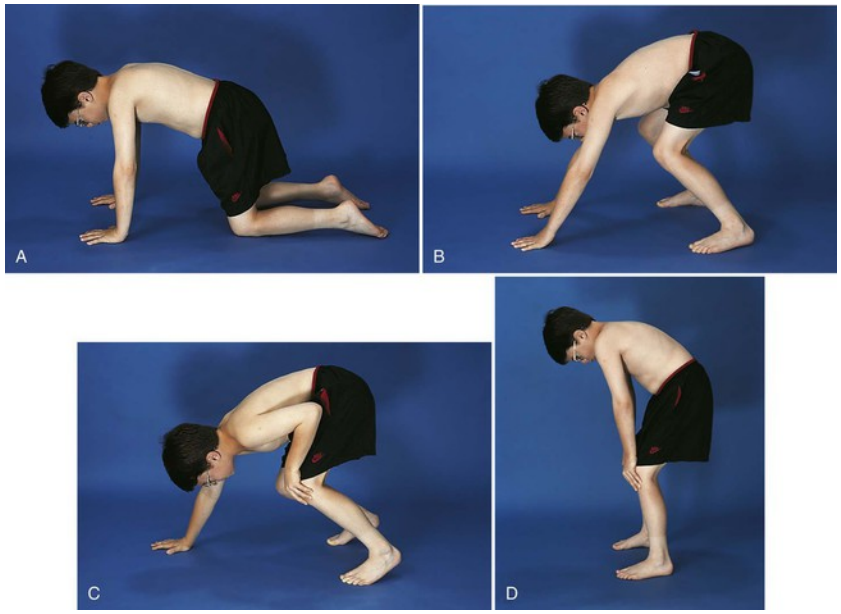
- The most common subgroups in children, juvenile DM (JDM).

Incidence:

- In population-based studies, JDM has a reported annual incidence that ranges from two to four cases per one million children.
- The peak incidence is from 5 to 10 years of age.

JDM - Etiology & Pathogenesis

- Cause unknown
- Likely autoimmune angiopathy
- Environmental and genetic factors implicated
  - A history of infection prior to onset is common
    - 65- 70% of patients have a history of a significant infection during the three months prior to first onset of symptoms
  - Proposed triggers include various infectious agents, vaccines, medications, UV light
- Cellular and humoral immunity implicated
- Complement-mediated injury important
- Innate immune response: type I interferons and dendritic cells

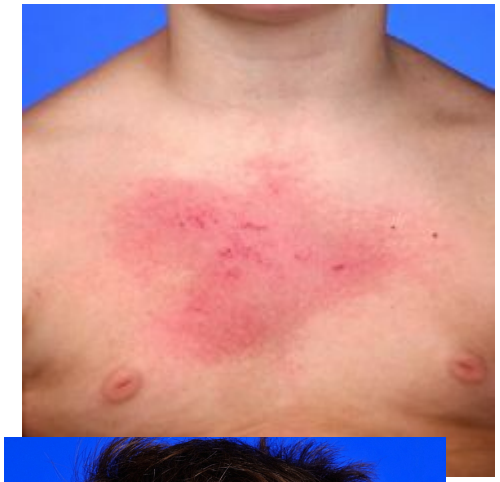

A
B
C
D

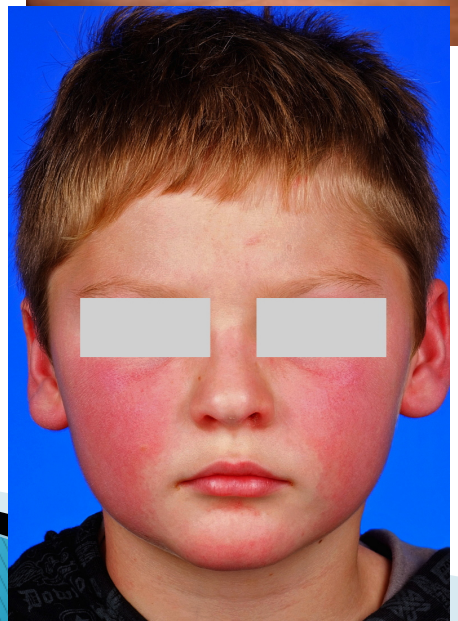
Differential Diagnosis of Juvenile Idiopathic Inflammatory Myopathies

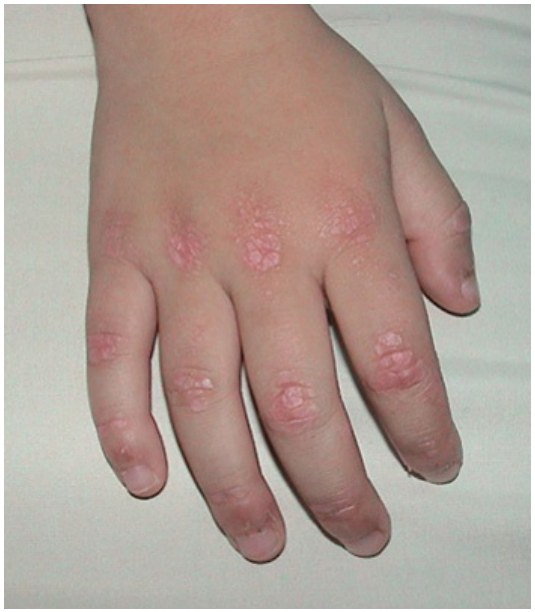
	Condition
Weakness alone	
Muscular dystrophies	Limb-girdle dystrophies, dystrophinopathies, facioscapulohumeral dystrophy, other dystrophies
Metabolic myopathies	Muscle glycogenoses (glycogen-storage diseases), lipid-storage disorders, mitochondrial myopathies
Endocrine myopathies	Hypothyroidism, hyperthyroidism, Cushing's syndrome or exogenous steroid myopathy, diabetes mellitus
Drug-induced myopathy	Consider for patients taking any of the following drugs or biological treatments: statins, interferon α, glucocorticoids, hydroxychloroquine, diuretics, amphotericin b, caine anaesthetics, growth hormone, cimetidine, and vincristine
Neuromuscular transmission disorders	Myasthenia gravis
Motor neuron disorder	Spinal muscular atrophy
Weakness with or without rash	
Viral	Enterovirus, influenza, coxsackievirus, echovirus, parvovirus, poliovirus, hepatitis B, human T-lymphotropic virus 1
Bacterial and parasitic organisms	Staphylococcus, streptococcus, toxoplasmosis, trichinosis, *Lyme borreliosis*
Other rheumatic conditions	Systemic lupus erythematosus, scleroderma, juvenile idiopathic arthritis, mixed connective-tissue disease, idiopathic vasculitis
Other inflammatory conditions	Inflammatory bowel disease, coeliac disease
Rash without weakness	Psoriasis, eczema, allergy

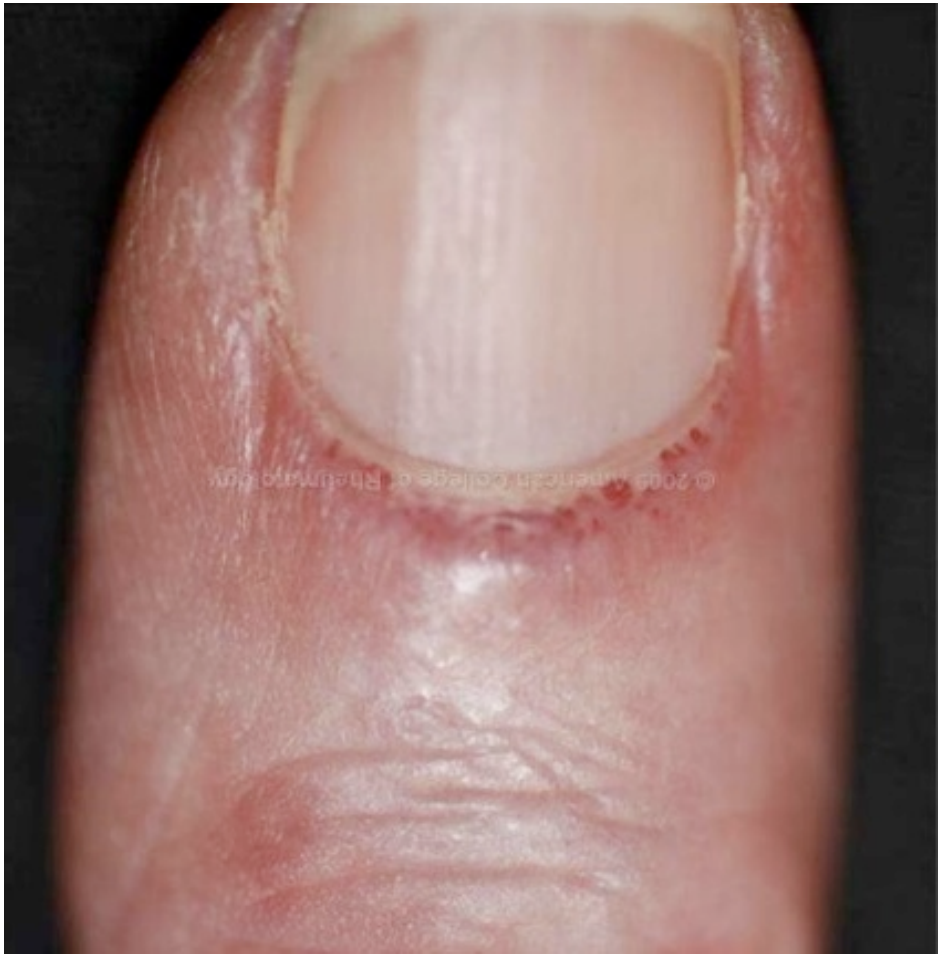
In many of these conditions, diagnosis is facilitated by muscle biopsy; muscle biopsy should be strongly considered in the absence of rashes of typical juvenile dermatomyositis.

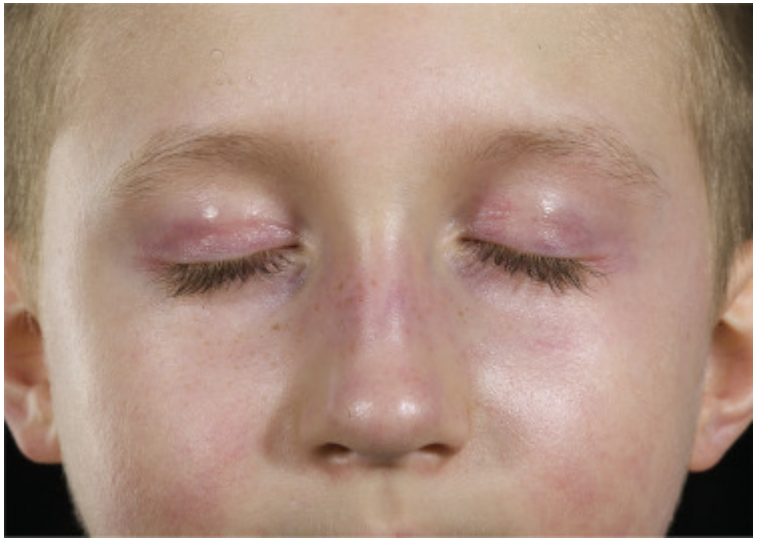
Feldman et al, Lancet 2008; 371, 2201-12

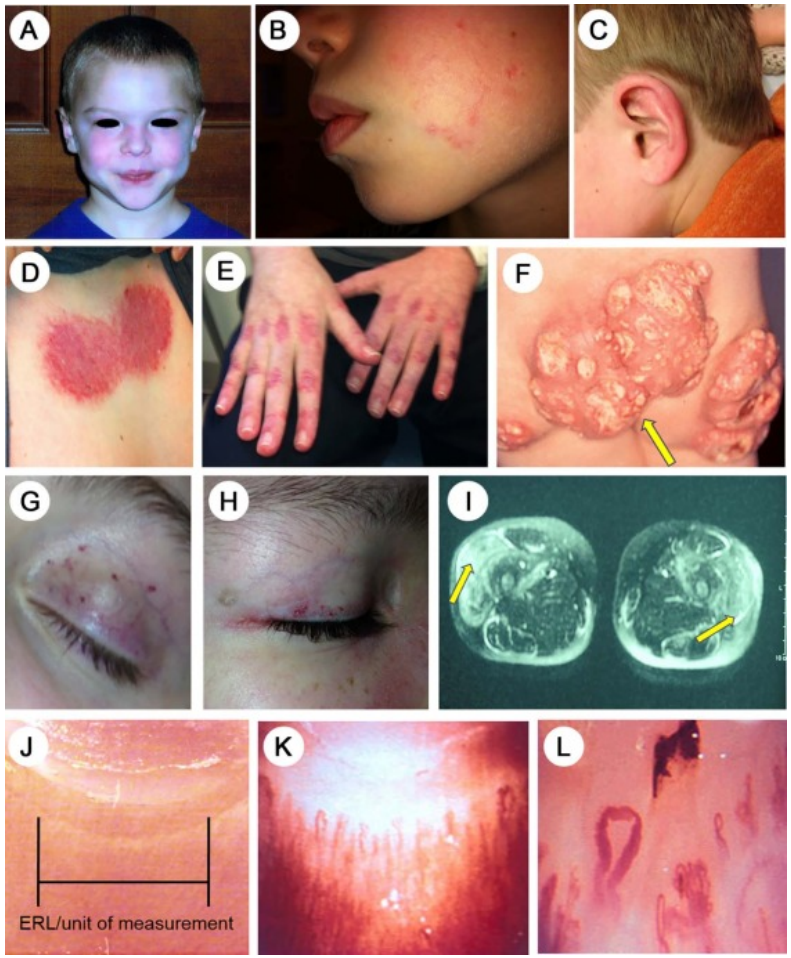








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L
ERL/unit of measurement

Table 1

Bohan and Peter Diagnostic Criteria[21,22]

A	Proximal and symmetrical muscle weakness of the pelvic and scapular girdle, anterior flexors of the neck, progressing for weeks to months, with or without dysphagia or involvement of reparatory muscles.
B	Elevation of the serum levels of skeletal muscle enzymes: creatine phosphokinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase.
C	Electromyography characteristic of myopathy (short and small motor units, fibrillations, positive pointy waves, insertional irritability and repetitive high-frequency firing).
D	Muscle biopsy showing necrosis, phagocytosis, regeneration, perifascicular atrophy, perivascular inflammatory exudate.
E	Typical cutaneous changes: • heliotrope with periorbital edema and violaceous erythema; • Gottron's sign: vasculitis in the elbow, metacarpophalangeal, and proximal iterphalangeal joints.

Criteria for DM	
Definitive	Three criteria (A, B, C or D) + E
Probable	Two criteria (A, B, C or D) + E
Possible	One criterion (A, B, C or D) + E

Table 2. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs)

When no better explanation for the symptoms and signs exists, these classification criteria can be used

Variable	Score points: Without muscle biopsy	Score points: With muscle biopsy	Definition
Age of onset			
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5	18 ≤ age (years) at onset of first symptom assumed to be related to the disease <40
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2	Age (years) at onset of first symptom assumed to be related to the disease ≥40
Muscle weakness			
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7	Weakness of proximal upper extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5	Weakness of proximal lower extremities as defined by manual muscle testing or other objective strength testing, which is present on both sides and is usually progressive over time
Neck flexors are relatively weaker than neck extensors	1.9	1.6	Muscle grades for neck flexors are relatively lower than neck extensors as defined by manual muscle testing or other objective strength testing
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2	Muscle grades for proximal muscles in the legs are relatively lower than distal muscles in the legs as defined by manual muscle testing or other objective strength testing
Skin manifestations			
Heliotrope rash	3.1	3.2	Purple, lilac-colored, or erythematous patches over the eyelids or in a periorbital distribution, often associated with periorbital edema
Gottron's papules	2.1	2.7	Erythematous to violaceous papules over the extensor surfaces of joints, which are sometimes scaly. May occur over the finger joints, elbows, knees, malleoli, and toes
Gottron's sign	3.3	3.7	Erythematous to violaceous macules over the extensor surfaces of joints, which are not palpable
Other clinical manifestations			
Dysphagia or esophageal dysmotility	0.7	0.6	Difficulty in swallowing or objective evidence of abnormal motility of the esophagus
Laboratory measurements			
Anti–Jo-1 (anti–histidyl–transfer RNA synthetase) autoantibody present	3.9	3.8	Autoantibody testing in serum performed with standardized and validated test, showing positive result
Elevated serum levels of creatine kinase (CK)* *or* lactate dehydrogenase (LDH)* *or* aspartate aminotransferase (ASAT/AST/SGOT)* *or* alanine aminotransferase (ALAT/ALT/SGPT)*	1.3	1.4	The most abnormal test values during the disease course (highest absolute level of enzyme) above the relevant upper limit of normal
Muscle biopsy features—presence of:			
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7	Muscle biopsy reveals endomysial mononuclear cells abutting the sarcolemma of otherwise healthy, non-necrotic muscle fibers, but there is no clear invasion of the muscle fibers
Perimysial and/or perivascular infiltration of mononuclear cells		1.2	Mononuclear cells are located in the perimysium and/or located around blood vessels (in either perimysial or endomysial vessels)
Perifascicular atrophy		1.9	Muscle biopsy reveals several rows of muscle fibers, which are smaller in the perifascicular region than fibers more centrally located
Rimmed vacuoles		3.1	Rimmed vacuoles are bluish by hematoxylin and eosin staining and reddish by modified Gomori trichrome stain

* Serum levels above the upper limit of normal.

- Patients with pathognomonic skin rashes (heliotrope rash, Gottron's papules, and/or Gottron's sign) of JDM or DM are accurately classified with the EULAR/ACR classification criteria without including muscle biopsy data.

- For patients without these skin manifestations, muscle biopsy is recommended.

- For DM patients without muscle involvement, a skin biopsy is recommended.

- The EULAR/ACR classification criteria provide a score and a corresponding probability of having IIM.

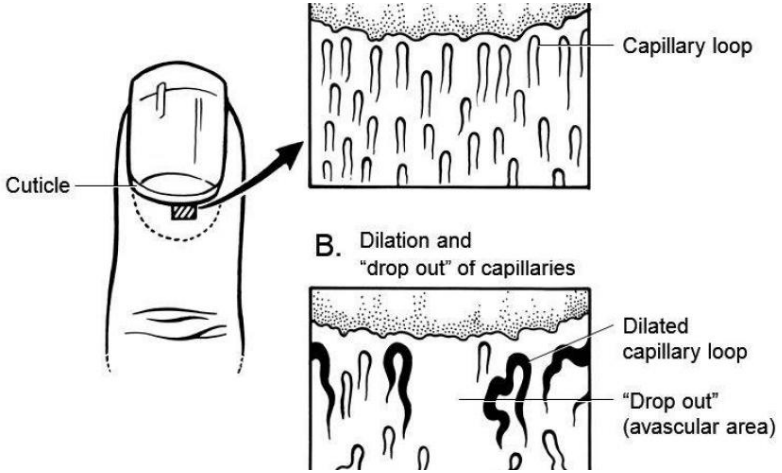
- A probable IIM :
  - For a total score of $\geq$5.5 and $\leq$5.7) for the criteria not including muscle biopsy data, and a score $\geq$6.7 and $\leq$7.6 when including muscle biopsies.

- Definite IIM :
  - For a total aggregate score of 7.5 or more without muscle biopsy and 8.7 with muscle biopsy.

Investigations:

- Muscle enzymes—including creatinine phosphokinase (CPK), LDH, AST (SGOT), ALT (SGPT), adolase (if available)
- Full blood count and blood film
- ESR and CRP
- Myositis-specific and myositis-associated antibodies
- Renal function and liver function tests
- Infection screen (for differential diagnosis)
- Investigations for alternative systemic causes of myopathy including endocrine disorders (especially thyroid function), electrolyte disturbances, vitamin D deficiency

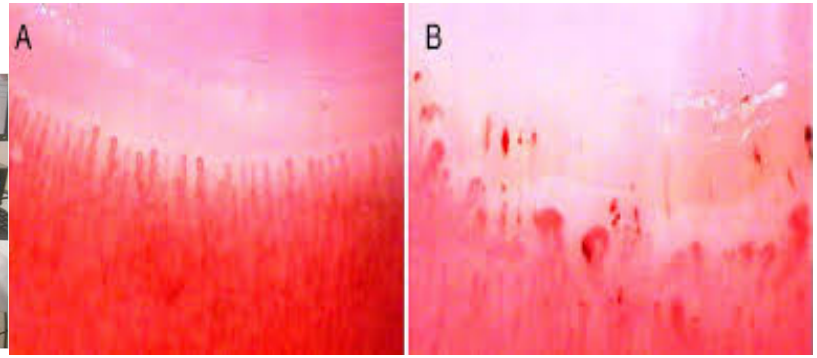
- Further tests for metabolic/mitochondrial myopathies (especially in the absence of rash/atypical presentation)
- Urine dipstick (with further evaluation if positive for protein)
- Nailfold capillaroscopy
- Echocardiogram and ECG
- Pulmonary function tests (chest X-ray and HRCT if concern)
- MRI of muscles.
- EMG (particularly if suspicion of neuropathy/disorder of neuromuscular junction)
- Muscle biopsy (especially in the absence of rash/atypical presentation)
- MRI brain if neurological involvement suspected.

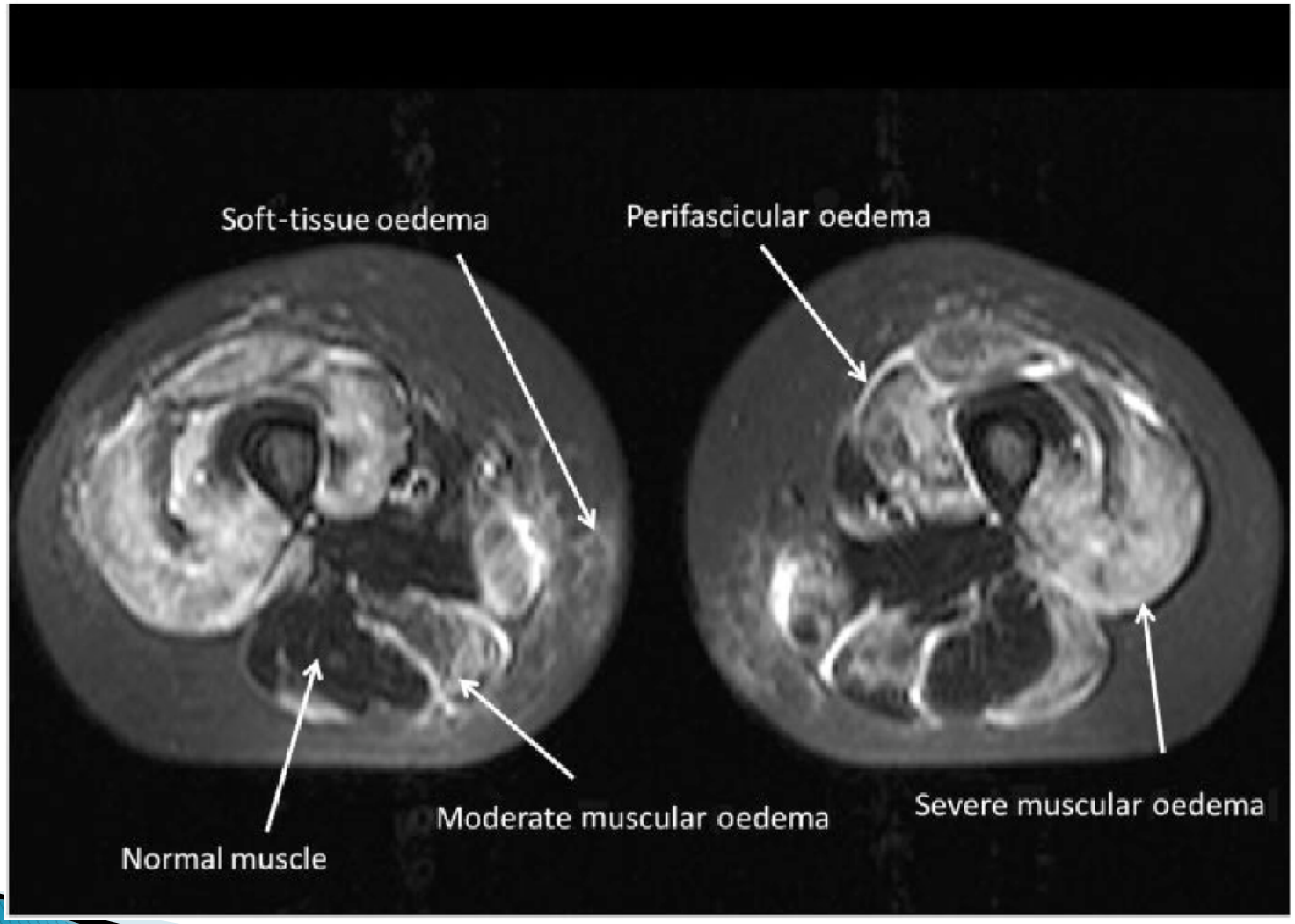

Capillary loop
Cuticle
B.
Dilation and
"drop out" of capillaries
Dilated
capillary loop
"Drop out"
(avascular area)


A


B
dermLite


C


A
B


Soft-tissue oedema
Perifascicular oedema
Normal muscle
Moderate muscular oedema
Severe muscular oedema

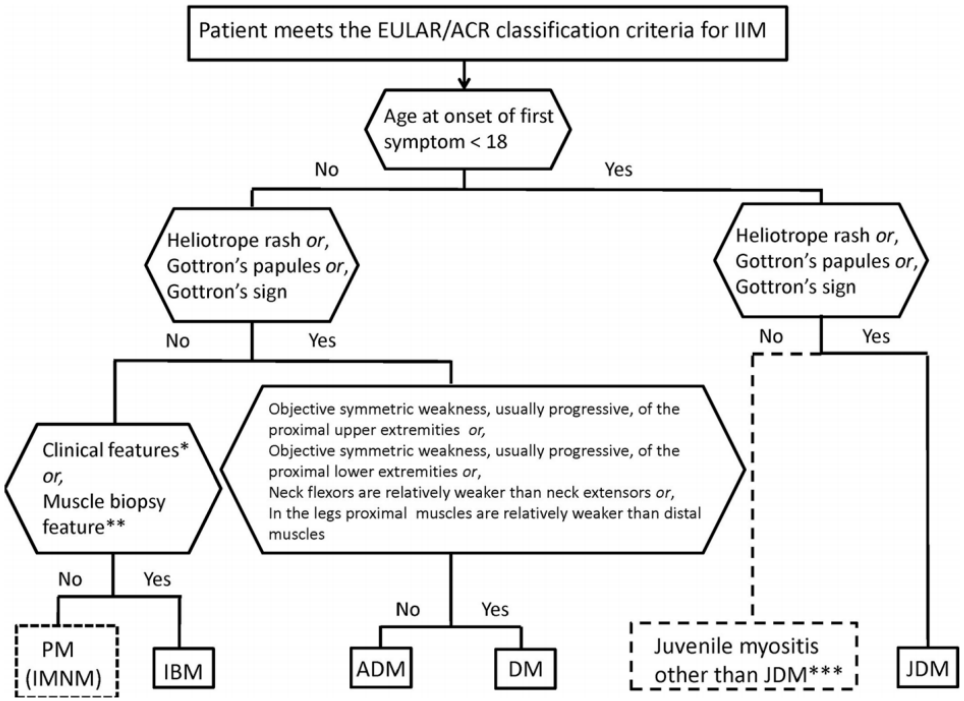


Figure 2. Classification tree for subgroups of idiopathic inflammatory myopathies (IIMs). A patient must first meet the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIM (probability of IIM ≥55%). The patient can then be subclassified using the classification tree. The subgroup of polymyositis (PM) patients includes patients with immune-mediated necrotizing myopathy (IMNM). For inclusion body myositis (IBM) classification, one of the following is required for classification: finger flexor weakness and response to treatment: not improved (*), or muscle biopsy: rimmed vacuoles (**). *** = Juvenile myositis other than juvenile dermatomyositis (JDM) was developed based on expert opinion. IMNM and hypomyopathic dermatomyositis were too few to allow subclassification. ADM = amyopathic dermatomyositis; DM = dermatomyositis.

Dermatomyositis – other organ involvement

- Gastrointestinal vasculitis- gut wall perforation
- Arthritis - common but usually early and mild, non-erosive
- Cardiac - inflammation, fibrosis, conduction defects
- Renal - glomerular hypercellularity
- Pulmonary - fibrosis, pneumothorax
- Central nervous system - behavior changes, seizures
- Alopecia
- Eyes - exudative vasculitis of retina
- Derm – calcinosis, subcutaneous nodules, ulcerations
- Lipodystrophy

Treatment:

- Steroid.
- Methotrexate (subcutaneous).