Evaluation of Connective Tissue Diseases

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Introduction

- **Connective tissue diseases** are a broad category of disorders that primarily affect the body's **connective tissues**, which provide **structural support** and help bind different parts of the body together.
- - Rheumatic diseases are diagnosed based on a combination of **physical examination, autoimmune marker** and other **serologic tests, tissue pathology,** and **imaging**.
- - **Clinical patterns** are important for diagnosis since there is **no single diagnostic test** and **positive results** can occur in the **absence** of disease.
- - Children may present with **evolving criteria** or features of **more than one** rheumatic disease (overlap syndromes).

Classification

- Connective tissue diseases can be broadly classified into two groups:
- 1. Heritable, which includes conditions with hereditary defects in the structure of collagen and elastin, with no specific tendency to cause inflammatory changes in the joints.
- 2. Rheumatic diseases: mostly autoimmune conditions with special predilection for joint inflammation.

- This presentation will focus on the latter.

Examples of Connective Tissue Diseases (I)

- Heritable connective tissue disorders
  - Marfan syndrome
  - Ehlers–Danlos syndromes
  - Hypermobility spectrum disorder
  - Osteogenesis imperfecta
  - Stickler syndrome
  - Alport syndrome
  - Congenital contractural arachnodactyly
  - Loeys–Dietz syndrome
  - Congenital contractural arachnodactyly

Examples of Connective Tissue Diseases (II)

- Rheumatic diseases
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Scleroderma
  - Sjögren's syndrome
  - Mixed connective tissue disease
  - Undifferentiated connective tissue disease

Criteria

- - Most rheumatic diseases have **defined diagnostic criteria**.

For example, below are the criteria for Juvenile Rheumatoid Arthritis

- **Age at onset:** <16 yr
- **Arthritis** (swelling or effusion, or the presence of ≥2 of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint
- **Duration of disease**: ≥6 wk
- **Onset type** defined by type of articular involvement in the 1st 6 mo after
  - Polyarthritis: ≥5 inflamed joints
  - Oligoarthritis: ≤4 inflamed joints
- **Exclusion** of other forms of juvenile arthritis

Introduction

- **Infection** and **malignancy** are the primary mimics of rheumatic diseases
- Other conditions such as **metabolic disorders, orthopedic conditions, immune deficiencies, autoinflammatory diseases**, and **chronic pain conditions** can also mimic rheumatic disease symptoms.
- Exclusion of possible mimicking disorders is crucial before starting treatment, especially with corticosteroids.
- Referral to a **pediatric rheumatologist** should be considered after careful evaluation has ruled out nonrheumatic causes, for confirmation of diagnosis and treatment.

Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and postinfectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile idiopathic arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis-related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

Arthritis

- - Arthralgia can also be a presenting symptom of pediatric **systemic lupus erythematosus (SLE)** and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA).**
- - Symptoms more suggestive of **arthritis** include **morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever,** and **fatigue** or **stiffness after physical inactivity** (gelling phenomenon).
- - A diagnosis of JIA requires the finding of **arthritis** on physical examination.
- - **No laboratory test is diagnostic of JIA** or **any other chronic inflammatory arthritis** in childhood.

Fatigue

- - **Fatigue** is a nonspecific symptom that may indicate the presence of a rheumatic disease but can also occur in nonrheumatic causes such as **viral infections, pain syndromes, depression**, and **malignancy.**
- - In juvenile dermatomyositis (JDM), fatigue is a **common presenting complaint** rather than specific complaints of muscle weakness.
- - Fatigue is also frequently present in **SLE, vasculitis**, and the **chronic childhood arthritides.**
- - **Overwhelming fatigue** with inability to attend school is more suggestive of **chronic fatigue syndrome, pediatric fibromyalgia**, or other **amplified pain syndrome**.

Signs Suggestive of Rheumatic Disease

- - A **complete physical examination** is necessary for children with suspected rheumatic disease to identify subtle physical findings and determine the extent of organ system involvement.
- - **Photosensitive malar rash** that **spares** the **nasolabial folds**, especially in an **adolescent girl**, suggests **SLE.**
- - **Diffuse facial rash** is indicative of **JDM**.
- - **Hyperkeratotic rash** on the face or around the ears in a **black** adolescent girl may indicate **discoid lupus**.
- - Palpable **purpuric rash** on the **extensor surfaces** of the lower extremities suggests **Henoch-Schönlein purpura.**

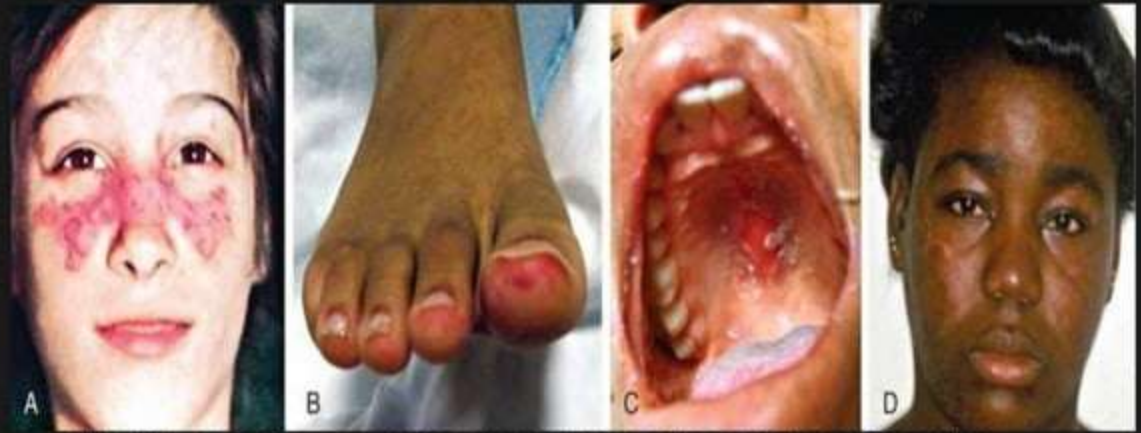


FIG. 183.1 Mucocutaneous manifestations of SLE. A, Malar rash; B, vasculitic rash on toes; C, oral mucosal ulcers; D, discoid rash in malar distribution.

A boy with Henoch-Schonlein Purpura

Signs Suggestive of Rheumatic Disease

- - **Nonblanching erythematous papules** on the **palms** can be seen in **vasculitis, SLE**, and **endocarditis**.
- - **Gottron papules** and **heliotrope rashes**, along with erythematous rashes on the **elbows** and **knees**, are pathognomonic of JDM.
- - **Dilated capillary loops** in the **nail beds** (periungual telangiectasias) are common in **JDM, scleroderma**, and **secondary Raynaud phenomenon**.
- - **Evanescent macular rash** with fever is part of the diagnostic criteria for **systemic-onset arthritis**.
- - **Sun sensitivity or photosensitive rashes** can indicate SLE or JDM but may also be caused by **antibiotics.**

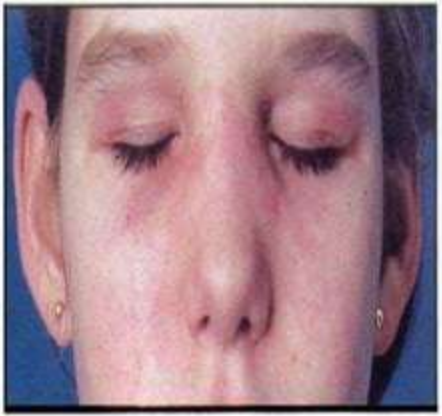
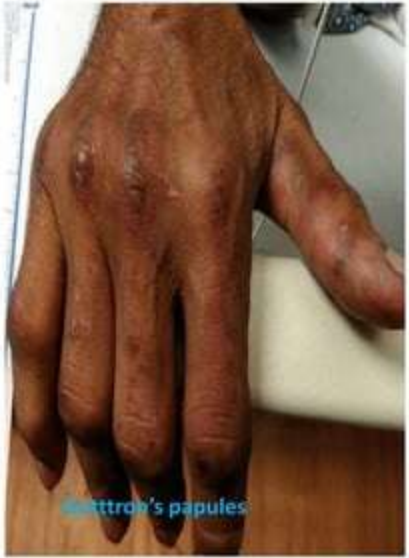


Figure 6. Heliotrope rash involving the upper eyelid and the area between the upper eyelid and the eyebrow. There is also a malar rash that extends over the bridge of the nose.



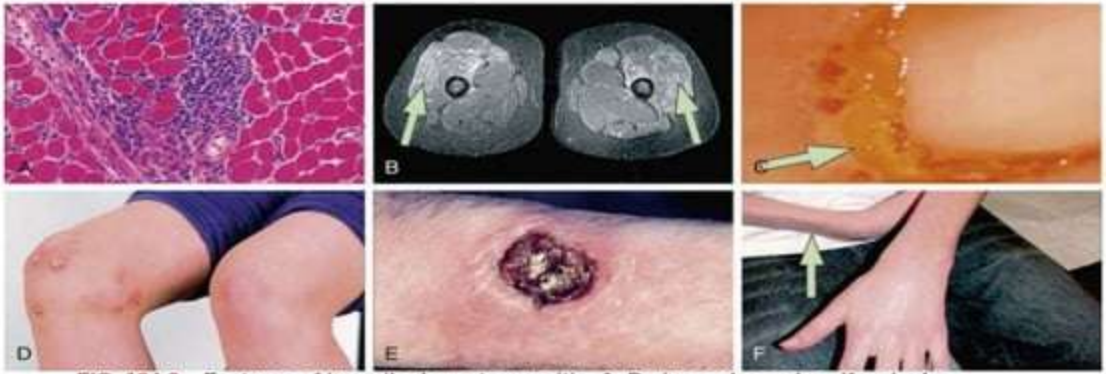


FIG. 184.3 **Features of juvenile dermatomyositis. A, Perivascular and perifascicular inflammatory infiltrates with necrotic fibers, perifascicular atrophy, and regeneration in a muscle biopsy. B, MRI is a sensitive indicator of myositis. Inflamed areas appear bright on short-tau inversion recovery–weighted images *(arrows)*. C, Capillaries are most often abnormal when viewed at the nail fold. Typical changes of dilation with adjacent dropout *(arrow)* is seen. D, About 30% of juvenile dermatomyositis (JDM) patients have dystrophic calcinosis. E, Cutaneous ulceration with central necrosis, crust, and surrounding erythema at the elbow of 10-year-old boy with severe JDM. F, Lipoatrophy of the forearm *(arrow)* in a boy with JDM. (From Feldman BM, Rider LG, Reed AM, Pachman LM: Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood, *Lancet* 371:2201–2212, 2008, Fig 3, p 2205.)**

Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically **spares nasolabial folds**	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with **genital ulcers**	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis, e.g., ANCA-associated vasculitis, HSP	HSP typically starts as small lesions on **lower extremities and buttocks** that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated **heliotrope rash,** periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	**Chronic joint swelling (>6 wk)** required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and adenitis

Signs Suggestive of Rheumatic Disease

- - **Mouth ulcers** are part of the diagnostic criteria for **SLE** and **Behçet's disease.**
- - **Painless nasal ulcers** and erythematous macules on the **hard palate** are common in **SLE**.
- - **Cartilage loss** in the nose, leading to a **saddle nose deformity**, is seen in **granulomatosis with polyangiitis, relapsing polychondritis**, and **syphilis**.
- - **Alopecia** can be associated with **SLE, localized scleroderma**, and **JDM**.

Signs Suggestive of Rheumatic Disease

- - **Raynaud phenomenon** may be a **primary** benign idiopathic disorder or can be associated with **scleroderma, lupus, MCTD**, or an **overlap syndrome.**
- - **Diffuse lymphadenopathy** is present in **many** rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA.
- - **Irregular pupils** may indicate the onset of **uveitis** associated with JIA.
- - **Erythematous conjunctivae** may result from uveitis or episcleritis associated with JIA, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

Signs Suggestive of Rheumatic Disease

- - **Pericardial rub** and **orthopnea** are suggestive **of pericarditis**, often seen in systemic JIA, SLE, and sarcoidosis.
- - **Coronary artery dilation** is strongly suggestive of Kawasaki disease but may also be found in **systemic arthritis** and other forms of systemic vasculitis.
- - **Interstitial lung disease**, indicated by dyspnea on exertion or basilar rales with decreased carbon monoxide diffusion capacity, occurs in **SLE, MCTD, and systemic sclerosis**.
- - **Pulmonary hemorrhage** suggests **granulomatosis with polyangiitis**, microscopic angiitis, or SLE.
- - **Pulmonary vascular aneurysms** are indicative of **Behçet's disease**.

Signs Suggestive of Rheumatic Disease

- - **Arthritis** is defined by **intraarticular swelling** or the presence of **two or more findings** on joint examination (pain on motion, loss of motion, erythema, heat).
- It is present in various conditions, including **all chronic childhood arthritis syndromes, SLE, JDM, vasculitis, Behçet's disease, sarcoidosis, Kawasaki disease**, and **Henoch-Schönlein purpura**.
- - **Nonrheumatic causes** of arthritis include **malignancy, septic arthritis, Lyme disease, osteomyelitis, viral infections** (e.g., rubella, hepatitis B, parvovirus B19, chikungunya), and postinfectious etiologies such as **EBV, ARF, and reactive arthritis**.

Signs Suggestive of Rheumatic Disease

- - Acute Rheumatic Fever typically involves migratory (lasting hours to days) and painful arthritis.
- - **Pain on palpation of long bones** suggests malignancy.
- - Muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, as these symptoms may indicate muscle inflammation.

Laboratory Testing

- - There are **no specific screening tests** for rheumatologic diseases.
- - Testing is performed based on the determined **differential diagnosis**.
- - **Initial laboratory studies** are typically performed in **standard local laboratories**, while screening for **specific autoantibodies** may require confirmation in a **tertiary care center** immunology laboratory.
- - The **complete blood count** (CBC) is an essential test for rheumatic disease assessment because it can provide diagnostic clues.
- - **Elevated white blood cell (WBC) count** can be seen in **malignancy, infection, systemic JIA**, and **vasculitis**, while **leukopenia** can be **postinfectious**, or caused **by SLE** or **malignancy.**

Laboratory Testing

- - **Lymphopenia** is more specific **for SLE** than leukopenia.
- - **Platelet levels** are elevated with **inflammatory markers**, except in certain conditions such as **bone marrow-occupying malignancy, SLE**, and early **Kawasaki disease**.
- - **Anemia** is nonspecific and can be caused by any chronic illness, while **hemolytic anemia** (positive Coombs test) may suggest **SLE or MCTD.**
- - **Rheumatoid factor (RF)** has **poor sensitivity** as a diagnostic tool for **JIA** but may be elevated in **various infections, primary biliary cirrhosis**, and **malignancies**.
- In **chronic arthritis**, RF serves as a **prognostic indicator.**

Laboratory Testing

- - **Inflammatory markers** (**erythrocyte sedimentation rate, C-reactive protein**) are **nonspecific** and can be elevated in **infections, malignancies, and rheumatic diseases**.
- -Their levels can also be **normal** in certain rheumatic diseases.
- - Inflammatory marker measurements are **more useful** in rheumatic diseases for **following response to treatment** than as diagnostic tests.
- - **Muscle enzymes** (AST, ALT, CPK, aldolase, LDH) can be elevated in **JDM** and other conditions causing muscle breakdown.

Laboratory Testing

- **Muscle-building supplements, medications**, and **extreme physical activity** can also cause enzyme elevations.
- - **AST, ALT, and aldolase** can be elevated in both muscle breakdown and liver disease, and measuring **γ-glutamyltransferase (GGT)** can help differentiate the source.
- - The use of antinuclear antibody (ANA) measurement as a screening test is not recommended due to its low specificity.
- - A **positive ANA test** result can be induced by various infections, such as **EBV, endocarditis**, and **parvovirus B19 infection**.
- - **Up to 30% of normal children may have a positive ANA test result**, and ANA levels are increased in those with a first-degree relative with a known rheumatic disease.

Laboratory Testing

- - In the **majority** of children with a positive ANA test result but **no signs of a rheumatic disease** on initial evaluation, **autoimmune disease does not develop over time**, so referral to a pediatric rheumatologist is not necessary.
- - A **positive ANA test** result is found in many rheumatic diseases, including JIA, where it serves as a predictor of the risk for **inflammatory eye disease.**
- - **Specific autoantibody testing** is directed by the **presence of clinical signs and symptoms** once a positive ANA test result is discovered.

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
Systemic lupus erythematosus (SLE) Mixed connective tissue disease (MCTD)	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If **ANA test result is positive**: anti-SSA (Ro), anti-SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2 -glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
Juvenile dermatomyositis (JDM)	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
Juvenile idiopathic arthritis (JIA)	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti- CCP	MRI

Evaluation Based on Suspected Diagnosis of Rheumatic Disease

Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants; HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum IgG, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper GI radiography series

Evaluation Based on Suspected Diagnosis of Rheumatic Disease

Imaging studies

- - **Plain radiographs (PR)** are useful in evaluating arthralgias and arthritis, providing reassurance in benign pain syndromes.
- - PR can also detect abnormalities in conditions such as **malignancies, osteomyelitis,** and **chronic juvenile arthritis.**
- - **Radionucleotide bone scans** help localize areas of abnormality in patients with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis.
- **- MRI** is valuable in assessing inflammatory myositis, guiding biopsy site selection, detecting early erosive arthritis, demonstrating joint fluid increase, synovial enhancement, and internal joint derangement due to trauma

Imaging studies

- - MRI is also helpful in ruling out infection or malignancy.
- - **Cardiopulmonary evaluation** is recommended for diseases that commonly affect the **heart and lungs**, including **SLE, systemic scleroderma, MCTD, JDM**, and **sarcoidosis**, as clinical manifestations may be subtle.
- - Evaluation may include **echocardiogram, pulmonary function tests, high-resolution CT of the lungs**, and consideration of **bronchoalveolar lavage.**

References

- 1. Kliegman R, St Game J, Blum N, Shah S. Nelson Textbook of Pediatrics. Ed 21, Canada. 2020;

THANK YOU