Adult Still's Disease

16

1. The clinical features of adult Still's disease resemble the systemic form of JRA
   a. Seronegative chronic polyarthritis associated with a systemic inflammatory illness
   b. Initially described in 1897 by George F. Still (pathologist)
   c. Subsequently detailed in adults in 1971 by Eric Bywaters
2. Epidemiology
   a. Rare
   b. Affects both genders equally
   c. Exists worldwide
   d. Majority present at age 16–35 years
      i. 75% before age 35
3. Pathogenesis
   a. Etiology unknown
   b. Principal hypothesis implicates a virus or other infectious agent
   c. Linkage to HLA antigens inconclusive
   d. Immune complexes may play a pathogenic role (not confirmed)
   e. **NO** association with pregnancy and use of hormones
   f. Stress may play a role as inducer (not confirmed)
   g. Circadian release of proinflammatory cytokines
      i. Accounts for many clinical features
      ii. IL-6
      iii. IL-18
         1. Elevated
         2. Stimulates ferritin synthesis in monocytes/macrophages
4. Clinical Findings
   a. Preceded by a prolonged course of nonspecific signs and symptoms
   b. A prodromal sore throat occurs days to weeks before other symptoms
      i. Occurs in 70% (50–92%)
   c. The most striking manifestations
      i. Severe arthralgia (98–100%) and myalgia (84–98%)
      ii. Malaise

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iii. Weight loss (19–76%)
iv. Fever (83–100%)

d. Less common clinical manifestations
i. Lymphadenopathy (48–74%)
ii. Splenomegaly (45–55%)
iii. Pleuritis (23–53%)
iv. Abdominal pain (9–48%)
v. Hepatomegaly (29–44%)
vi. Pericarditis (24–37%)
vii. Pneumonitis (9–31%)

e. Unusual manifestation (numerous)
i. Alopecia
ii. Sjogren's
iii. Subcutaneous nodules
iv. Necrotizing lymphadenitis
v. Acute liver failure
vi. Pulmonary fibrosis
vii. Cardiac tamponade
viii. Aseptic meningitis
ix. Peripheral neuropathy
x. Proteinuria
xi. Microscopic hematuria
xii. Amyloidosis
xiii. Hemolytic anemia
xiv. DIC
xv. TTP
xvi. Orbital pseudotumor
xvii. Cataracts
xviii. Sensorineural hearing loss
xix. Hemophagocytic syndrome

f. Patients appear severely ill
i. Often receive numerous courses of antibiotics
ii. Presumed septic with negative cultures

g. Fever
i. Initial symptom
ii. Usually sudden onset high and spiking
iii. Spikes once daily (rarely twice daily)
1. Usually early morning and/or late afternoon/evening
2. Quotidian or diquotidian pattern
iv. Lasts 2–4 h
v. Temperature elevation marked
1. 66% with fever >40°C
vi. Returns to normal in 80% of untreated patients
1. Can return below normal

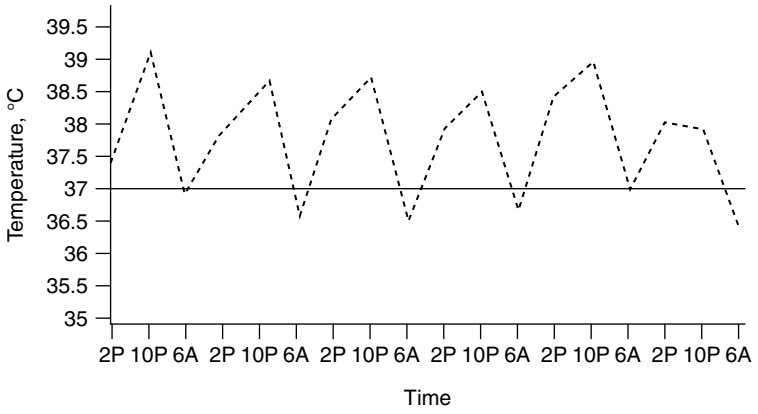

Fig. 16.1 Fever pattern in adult-onset Still's disease (Reproduced with permission from Rheumatoid arthritis, juvenile rheumatoid arthritis, and related conditions. *Atlas of Rheumatology*. ImagesMD; 2002-03-07)

vii. Very ill when febrile
    1. Feels well with normal body temp
viii. Pattern contrasts with that seen with infection
    1. Baseline elevation in body temperature
    2. Episodic fever spikes
ix. Patients evaluated for FUO
    1. 5% eventually diagnosed with Still's

h. Arthritis (88–84%)
    i. Initially affects only a few joints
    ii. Evolves to polyarticular disease
    iii. Most commonly affected joints
        1. Knee (84%)
        2. Wrist (74%)
        3. Ankle, shoulder, elbow, and PIP joints (50%)
        4. MCP (33%)
        5. DIP (20%)
    iv. Other joints affected
        1. MTPs
        2. Hips
        3. Tempromandibular joint (TMJ)
    v. Neck pain (50%)
    vi. Arthrocentesis yields
        1. Class II inflammatory synovial fluid
        2. Neutrophil predominance
    vii. Destructive arthritis (20–25%)

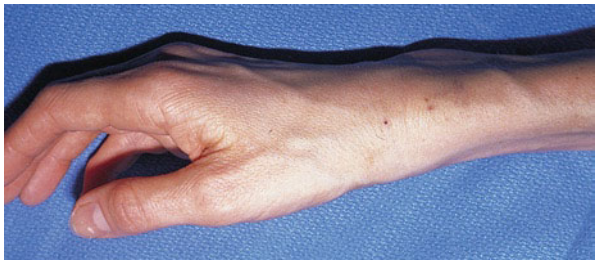

Fig. 16.2 Wrist involvement in adult-onset Still's disease (Reproduced with permission Rheumatoid arthritis, juvenile rheumatoid arthritis, and related conditions. *Atlas of Rheumatology.* ImagesMD; 2005-01-18)

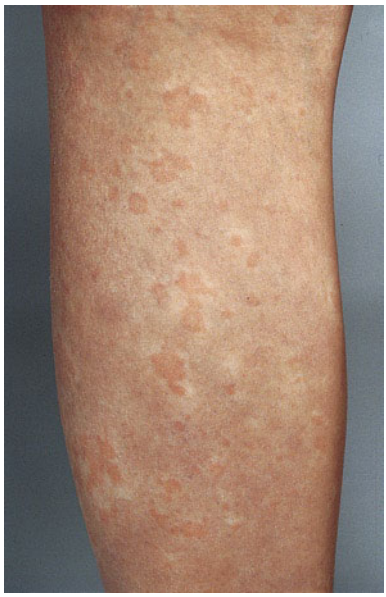

Fig. 16.3 Rash in adult-onset Still's disease (Reproduced with permission from Rheumatoid arthritis, juvenile rheumatoid arthritis, and related conditions. *Atlas of Rheumatology.* ImagesMD; 2002-03-07)

i. Still's rash
    i. Present in more than 85% of patients
    ii. Almost pathognomonic
    iii. Salmon pink
    iv. Macular or maculopapular
    v. Frequently evanescent
    vi. Often occurs with the evening fever spike
        1. Evening rounds may detect this near-diagnostic finding
    vii. More common on the trunk and proximal extremities
    viii. Precipitated by
        1. Mechanical irritation
            a. Clothing
            b. Rubbing
            c. Koebner's phenomenon (up to 40%)

2. Heat
    a. Hot bath
    b. Applying a hot towel
ix. May be mildly pruritic
x. Skin biopsies and immunofluorescent studies
    1. Neurivascular mononuclear cell infiltrate
    2. Nondiagnostic

5. Laboratory Findings
    a. **No** diagnostic tests
    b. Serum ferritin
        i. An acute-phase reactant that reflects inflammation
        ii. An extremely elevated level suggest the diagnosis
        iii. A value of ≥1,000 mg/dl in the proper clinical setting
            1. Confirmatory
            2. Especially associated with a low glycosylated ferritin
        iv. Values >4,000 mg/dl seen in <50%
        v. Reason for such elevations unknown
    c. CRP
        i. Frequently greater than 10 times upper limit of normal
    d. ESR
        i. Universally elevated >50 (96–100%)
    e. Leukocytosis
        i. Range 12–40,000/mm^3 present in 90% (71–97%)
        ii. 80% have WBC count > 15,000/mm^3
        iii. Neutrophils ≥ 80% (55–88%)
    f. LFT
        i. Elevated in up to three-quarters of patients (35–85%)
    g. Anemia
        i. Common (59–92%)
        ii. Sometimes profound
    h. Thrombocytosis (52–62%)
    i. Hypoalbuminemia (44–88%)
    j. RF and ANA
        i. Generally negative or low titer
    k. Synovial and serosal fluids
        i. Inflammatory
        ii. Predominance of neutrophils
6. Radiographic Findings
    a. Early
        i. Soft-tissue swelling
        ii. Effusions
        iii. Periarticular osteoporosis (occasionally)

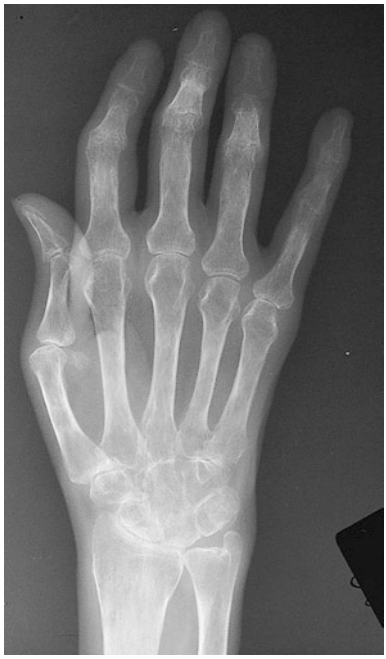

Fig. 16.4 Radiographic changes in adult-onset Still's disease include periarticular osteopenia and loss of joint space (Reproduced with permission from Rheumatoid arthritis, juvenile rheumatoid arthritis, and related conditions. *Atlas of Rheumatology*. ImagesMD; 2002-03-07)

   b. Late
      i. Joint erosions
      ii. Fusions
         1. Carpal bones (50%)
         2. Tarsal bones (20%)
         3. Cervical spine (10%)
   c. Characteristic radiographic findings
      i. Typically found in the wrist
      ii. Nonerosive narrowing of carpometacarpal and intercarpal joints
      iii. Progresses to bony ankylosis
7. Diagnosis
   a. Diagnosis one of exclusion
      i. With the proper clinical and laboratory abnormalities
      ii. With the absence of another explanation (infection or malignancy)
   b. Criteria of Cush (practical guide)
      i. Diagnosis requires the presence of all of the following
         1. Fever >39°C (102.2°F)
         2. Arthralgia or arthritis
         3. RF < 1:80
         4. ANA < 1:100

   ii. In addition, any two of the following
      1. WBC count ≥ 15,000 cells/mm^3
      2. Still's rash
      3. Pleuritis or pericarditis
      4. Hepatomegaly or splenomegaly or generalized lymphadenopathy
c. Most do not present with the full-blown syndrome
d. Typical presentation for adult Still's disease
   i. High, daily fever spikes
   ii. Severe myalgia, arthralgia, and arthritis
   iii. Still's rash
   iv. Leukocytosis
e. Markedly elevated serum ferritin highly suggestive

8. Differential Diagnosis
a. Granulomatous disorders
   i. Sarcoidosis
   ii. Idiopathic granulomatosis hepatitis
   iii. Crohn's disease
b. Vasculitis
   i. Serum sickness
   ii. PAN
   iii. Wegener's
   iv. TTP
   v. Takayasu's
c. Infection
   i. Viral
      1. Hepatitis B
      2. Rubella
      3. Parvovirus
      4. Coxsackie
      5. EBV
      6. CMV
      7. HIV
   ii. Subacute bacterial endocarditis
   iii. Chronic meningococcemia
   iv. Gonococcemia
   v. TB
   vi. Lyme
   vii. Syphilis
   viii. Rheumatic fever
d. Malignancy
   i. Leukemia
   ii. Lymphoma
   iii. Angioblastic lymphadenopathy

e. Connective tissue disease
   i. SLE
   ii. Mixed connective tissue disease
9. Disease Course and Outcome
   a. Median time to achieve clinical and laboratory remission
      i. 10 months while receiving therapy
      ii. 32 months requiring no therapy
   b. Can remit years after onset
   c. Course generally follows one of three patterns (one-third of patients each)
      i. Self-limited disease
         1. Remission within 6–9 months
         2. One-fifth to one-third
      ii. Intermittent flares
         1. One recurrence
            a. Two-thirds
            b. 10–36 months from the original illness
         2. Multiple flares
            a. Up to ten flares reported
            b. Intervals of 3–48 months
            c. Recurrent episodes generally milder than the original
            d. Respond to lower doses of meds
            e. Timing of relapse unpredictable
      iii. Chronic Still's disease
         1. Chronic arthritis is the principle problem
         2. Severe involvement of the knees and hips
            a. Require total joint replacement
         3. Most common in the hip
   d. Markers of chronic disease or poor prognosis
      i. Presence of polyarthritis (four or more joints involved)
      ii. Root joint involvement (shoulders or hips)
      iii. A childhood episode
         1. Occurs in about one of six patients
      iv. More than 2 years of therapy with systemic corticosteroids
   e. A controlled study of patients 10 years after the diagnosis of Still's
      i. Significant higher levels of pain, physical disability, and psychologic disability than unaffected siblings
      ii. Levels of pain and disability lower than other chronic rheumatic disease
      iii. No difference in Still's patients and controls in overcoming handicaps
         1. Educational attainment
         2. Occupational prestige
         3. Social functioning
         4. Family income
   f. 5 year survival rate 90–95%
      i. Similar to the survival rate for lupus
      ii. Vast majority lead remarkably full lives after disease onset

g. Premature death may be slightly increased
h. Causes of mortality
    i. Hepatic failure
    ii. DIC
    iii. Amyloidosis
    iv. Sepsis
    v. Acute respiratory distress syndrome (ARDS)
    vi. Heart failure
    vii. Carcinoma of the lung
    viii. Status epilepticus

10. Acute Treatment
    a. NSAIDs
        i. About one-fourth respond (20–40%)
        ii. A commonly used regimen
            1. High dose enteric-coated aspirin
            2. Achieve a serum salicylate level of 15–25 mg/dl
            3. Sometimes combined with indomethacin (150 mg/day)
        iii. Side effects
            1. Hepatotoxicity
                a. Elevated LFTs usually return to normal
                b. Despite continued NSAID therapy
            2. Increased risk of DIC
    b. Systemic corticosteroids
        i. Patients who fail to respond to NSAIDs
        ii. For severe disease
            1. Pericardial tamponade
            2. Myocarditis
            3. Severe pneumonitis
            4. DIC
            5. Rising LFTs during NSAID treatment
        iii. Prednisone in a dose of 0.5–1.0 mg/kg/day
        iv. About one-third require at least 60 mg of prednisone daily
        v. Relapses occur during tapering
            1. Add one of the slow-acting antirheumatic drugs
                a. Methotrexate
        vi. IV pulse methylprednisolone used for life-threatening disease

11. Chronic Treatment
    a. Medications used to treat arthritis (the most common cause of chronicity)
        i. IM gold
        ii. Hydroxychloroquine
            1. Mild chronic systemic disease may respond as well
                a. Fatigue
                b. Fever
                c. Rash
                d. Serositis

iii. Sulfasalazine
    1. Increased toxicity may occur
iv. Penicillamine
v. Methotrexate
    1. Low doses (similar to those used in RA)
    2. Used in both chronic arthritis and chronic systemic disease

b. Immunosuppressive agents
    i. Used in resistant cases
    ii. Azathioprine
    iii. Cyclophosphamide
    iv. Cyclosporine
    v. IVIG (controversial)
    vi. Mycophenolate mofetil
    vii. Leflunomide

c. Biologics
    i. TNF-α elevated in Still's disease
    ii. Etanercept and infliximab beneficial
        1. Especially articular manifestations
    iii. Anakinra
        1. Successful in refractory disease

d. Therapy after a decade of disease
    i. About one-half of patients will require second-line agents
    ii. One-third will require low-dose corticosteroids

e. Multidisciplinary approach
    i. Physiotherapists
    ii. Occupational therapists
    iii. Psychologists
    iv. Arthritis support groups