Rheuma Facts

A Quarterly Magazine

Serving physicians with interest In Rheumatology

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Current News

Antibiotic use in children linked to Juvenile Idiopathic Arthritis (JIA)

Written by Honor Whiteman

A new study recently presented at the American College of Rheumatology Annual Scientific Meeting in Boston, MA, researchers have linked antibiotic use in children to increased risk of juvenile idiopathic arthritis.

The researchers found that children exposed to antibacterial antibiotics - not antifungals or antivirals - were at higher risk of developing JIA than those who had not been exposed to these antibiotics. This risk was higher for children who had been exposed to multiple courses of antibiotics.

While antibiotics are certainly essential to treating some infections, these drugs are also overprescribed for other infections - frequently respiratory - that will usually resolve without treatment.

If the link between antibiotics and juvenile arthritis can be confirmed, antibiotic avoidance - in the right clinical situation - might be one of the few ways we have to prevent this life-changing disease.

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Viral Arthritis

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Compiled and summarized by:
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Arthralgias are common presentations to general practice. Many cases are self-limiting and are presumed to be due to viral infections. However sometimes systemic inflammatory arthritis may be difficult to differentiate from viral arthritis, yet require early intervention to improve long-term outcomes. Patients presenting with early inflammatory arthritis, the suspicion of RA* is raised, therefore patient should be assessed very carefully on clinical features. These patients benefit from early rheumatologist referral. Some viral infections, such as hepatitis and HIV*, may present with joint symptoms, and it is axiomatic that these conditions should be identified and managed appropriately. Some viral infections may cause more prolonged symptoms and their recognition, and particularly differentiation from early inflammatory arthritis, is important in determining prognosis.

Clinical Presentations

Parvovirus B19

Parvovirus B19 infections in children present as a viral exanthema, and in adults as a cause of arthralgia and arthritis. The incubation period is 7–10 days with non-specific flu-like symptoms in the first week followed by arthralgias or arthritis in up to 60% of patients in the second week. Up to 75% of adults will have a rash, although only 20% will have the typical "slapped cheek" appearance. The hands, feet and knees are commonly affected, usually symmetrically. Pain, rather than swelling, is the dominant feature. A dramatic decrease or absence of reticulocytes is a hallmark laboratory finding. Rarely, joint symptoms persist for months or years, but the arthritis is non-destructive.

Hepatitis A (HAV)

In its prodromal phase, hepatitis A infection in adults usually presents with flu-like symptoms. The infection then progresses to the icteric phase, which may include jaundice, bilirubinuria, pruritus and abdominal pain. Arthralgias and rash occur in 10–14% of patients, but arthritis is extremely rare.

Hepatitis B (HBV)

HBV infection may be asymptomatic, but symptomatic patients will develop constitutional symptoms in the prodromal period. During this period, HBV-infected hosts can develop a sudden-onset, transient polyarthritis (involving the wrists, knees, ankles and small joints of the hands) that may mimic the onset of RA, although typically accompanied by a rash. The arthritis usually subsides at the onset of jaundice.

Hepatitis C (HCV)

HCV infection is usually asymptomatic but can present with acute hepatitis, nausea and abdominal pain. HCV infection becomes chronic in about 80% of patients and is usually asymptomatic or manifests with mild, non-specific symptoms.

*Rheumatoid Arthritis
*Human Immunodeficiency Virus

20% of patients with chronic HCV and an inflammatory oligoarthritis or polyarthritis (mimicking RA but not destructive) occurs in 2–5% of patients. Chronic HCV infection is associated with abnormal immune function, including cryoglobulinemia and positive rheumatoid factor, leading to potential diagnostic confusion. It is important to exclude HCV in RA patients as HCV infection can be exacerbated by immunosuppressive therapy.

Human Immunodeficiency Virus (HIV)

Early HIV infection may be asymptomatic or present with a variety of non-specific symptoms and signs, including constitutional symptoms, adenopathy, pharyngitis and frequently a rash. Arthralgias and arthritis are present in 5.5% of people with HIV. Acute HIV-associated arthritis tends to be self-limiting, lasting less than 6 weeks. It will usually present as oligoarticular or polyarticular, with negative tests for antinuclear antibodies and rheumatoid factor.

Measles, Mumps and Rubella

Rubella classically presents with a maculopapular rash on the face that spreads to involve the trunk, hands and feet, sparing the palms and soles, accompanied by significant head and neck lymphadenopathy. Rubella and rubella vaccine are associated with arthritis, which occurs in 30–50% of females and 6% of males. The arthritis is similar to that in rheumatic fever and the small joints of the hands, wrists and the knees are most commonly involved. Arthralgia is much more common than frank arthritis, and peri-articular involvement is frequently seen. The arthritis typically starts in the week before and after the onset of rash and usually resolves within 2 weeks. Arthritis with mumps is extremely rare, with small or large joint synovitis within 4 weeks of parotitis. Symptoms can persist for up to several weeks.

Epstein-Barr Virus (EBV)

EBV infections are typically asymptomatic, reflected in the high rates (80%) of people with IgG antibodies directed at EBV. However, when acute infections do occur, all will have pharyngitis and 95% will have cervical adenopathy. Arthritis is relatively rare and does not occur in isolation, although widespread myalgias are common. Other herpes viruses, such as Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) are unusual causes of arthritis.

Adenovirus and Enterovirus

Adenovirus rarely causes arthritis and is usually acquired asymptomatically or manifests as respiratory tract or gastrointestinal infection. Similarly, enteroviruses (Coxsackie virus and echoviruses) may have protean manifestations, most typically non-specific febrile illness, aseptic meningitis, pleurodynia or exanthems. They are most unlikely to present with isolated joint manifestations.

A Summary of the Clinical Presentations of Viral Arthritis:

Virus	Frequency of arthritis	Typical presenting features	Likelihood of presenting with arthritis	Duration of arthritis	Comments
EBV	Very low	• Pharyngitis, cervical lymphadenopathy • Fevers	Very low	Days	Often have myalgias with acute infection
Adenovirus and enterovirus	Very low	• Upper respiratory tract infections, gastrointestinal symptoms, conjunctivitis	Very low	N/A	
Parvovirus B19	High	• Viral exanthem in children • Arthritis/arthralgia in adults with preceding febrile illness	High	Days but may be prolonged for months	Diagnosis assisted by concurrent demonstration of IgM and IgG antibodies
Hepatitis A	Low	• Flu-like illness followed by jaundice	Low	Days	Arthralgia more common than frank arthritis
Hepatitis B	Moderate	• Malaise, rash, jaundice	Moderate	Days/weeks	Arthritis is abrupt in onset, in RA distribution preceding icteric phase
Hepatitis C	Moderate	• Malaise, jaundice	Moderate	Weeks, months in chronically infected patients	Chronic arthralgia (20%); true arthritis (2–5%)
HIV	Low	• Acute infectious mononucleosis-like illness at seroconversion in some patients.	Low		Arthritis, arthralgia with acute infection. Increased incidence of several rheumatic diseases in chronic infection
RRV	Very high	• Arthralgia, myalgia, rash, fever	Very high	Weeks to months	Diagnosed by demonstration of seroconversion. Can rarely be associated with prolonged arthritis
Mumps	Very low	• Parotitis and lymphadenopathy	Very low	Weeks	
Rubella	High	• Acute maculopapular rash, sparing soles	High	Weeks	Can occur with rubella vaccine

Features Suggesting Rheumatoid Arthritis

- Symptom duration of longer than 6 weeks
- Early morning stiffness for longer than one hour
- Arthritis in three or more regions
- Bilateral compression tenderness of the metatarsophalangeal joints
- Symmetry of areas affected
- Rheumatoid factor positive
- Anti-cyclic citrullinated peptide (anti-CCP) antibody positive
- Bony erosions evident on X-rays of the hands or feet (uncommon in early disease)
- Family history of inflammatory diseases

Establishing the Diagnosis

Viral arthritis is typically associated with symptoms of a flu-like illness and systemic signs such as a viral exanthema, fever and lymphadenopathy, and these features should be sought on history and examination. Most presentations are with a polyarthritis; a monoarthritis should prompt investigation for other etiologies. The presence or absence of extra-articular features of an autoimmune disease should also be elicited. Confirmation of a recent viral infection requires an appropriate change in paired serology. IgM antibodies do not always represent recent infection as they can persist for up to 2 years. Testing for antinuclear antibodies, rheumatoid factor and anti-citrullinated protein antibodies (ACPA) is useful in evaluating people with typical or persistent presentations of inflammatory arthritis, but are neither sufficiently sensitive nor specific to make diagnosis alone. Viral arthritis can be associated with rheumatoid factor, although this is usually at low titer and transient.

Specific testing for viral arthritis is indicated if treatable diseases are suspected on the basis of the clinical picture (such as HCV or HIV), or when reassurance is important. Routine screening for all potential arthritogenic viruses is not advised.

General Treatment

Viral arthritis that has been evident for less than 6 weeks is treated symptomatically. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment. The potential benefits of NSAIDs should be weighed up against their potential risks. It is essential to provide reassurance to the patient that the symptoms are self-limiting and unlikely to develop into a serious condition, such as RA, or cause joint destruction or disability. The use of corticosteroids is to be discouraged unless there are troublesome symptoms and contraindications to NSAIDs, or where a brief course of low dose (<10mg of prednisone daily) may be reasonable.

When to Refer

Rheumatologist referral for acute viral arthritis is rarely needed. It should be

considered when arthritis persists beyond 6 weeks, where an early inflammatory arthritis such as RA is suspected or where investigation results are ambiguous or inconsistent with the clinical findings. Patients with suspected HIV, HBV or HCV may also benefit from specialist referral.

Key Points

- Viral arthritis is typically self-limiting and requires no specific intervention.
- Arthritis may be a manifestation of an important treatable viral infection, such as hepatitis or HIV.
- Some viruses have a predilection for the joints and result in prolonged symptoms.
- Early systemic inflammatory arthritis can be difficult to differentiate from viral arthritis and should be actively considered in all patients.

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Methotrexate Induced Pancytopenia

In a Patient With Takayasu's Arteritis

A Case Report

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Methotrexate Induced Pancytopenia

Methotrexate is one of the most commonly used Disease Modifying Anti-rheumatic Drugs (DMARD)*. Methotrexate (MTX)* is employed as a gold standard while starting treatment in rheumatoid arthritis as well as in other arthritis and vasculitis. It is prescribed both as a monotherapy and in combination with other DMARDs. The prevalence of methotrexate induced hematological toxicity is around 3-5% and the incidence around 1.4%[1,2]. This includes leucopenia, thrombocytopenia, anemia as well as pancytopenia. Amongst these; pancytopenia in context of MTX remains an under reported yet life threatening issue.

We hereby present a case report of patient who faced severe pancytopenia following methotrexate therapy.

Case Report

A 32 year old lady; teacher by profession came in with history of myalgia , weight loss and intermittent fever along with arm claudication especially while doing overhead activities like writing on board. Examination revealed absence of radial, brachial and carotid pulse on left side along with carotid bruit. Blood pressure was immeasurable in left arm and was 170 systolic in right arm. Computed tomography (CT) angiogram confirmed the diagnosis of Takayasu's Arteritis. Once disease activity status was documented and baseline laboratory profile was done; treatment was initiated with steroids (1mg/kg) along with MTX 10mg/week. Patient was advised monitoring initially fortnightly for one month followed by monthly visits for first three months.

MTX was built up to 15mg/week over next four visits. At next follow-up, patient came in with complaints of pedal edema, puffy face and rash involving upper limbs and back of chest. Patient was admitted at once. On examination, the patient looked weak, pale and had petechial blanching rash present all over the trunk and upper limbs. Chest and abdominal examination was also unremarkable.

Investigations revealed pancytopenia with all three cell line depressed. Follow up of these laboratory findings during hospital stay is as follows:

*Disease Modifying Anti-rheumatic Drugs
*Methotrexate

	DAY 1	DAY 3	DAY 5
Hemoglobin (Hb) gm/dl	9.8	7.9	7.1
Total leucocyte count (TLC) cu.mm	3000	450	345
Platelet count	50,000	19,000	14000
Neutrophils%	21.4	5.5%	4.8%
Lymph%	78.6	-	-
Urea (m.mol/l)	20	30	32.8
Creatinine (m.mol/l)	269	398	457
ALT (iu)	42	35	40

Bone marrow examination revealed depressed erythropoiesis, myelopoiesis with markedly reduced megakaryopoiesis and a hypo cellular bone marrow consistent with features of bone marrow suppression.

Methotrexate was withheld immediately on day 1 of admission. Patient was shifted to isolated unit. Barrier nursing was adopted. Supportive treatment with IV daily transfusion of platelet concentrate was initiated on day 3. Recombinant granulocyte colony stimulating factors (G-CSF) (filgrastim) 300µg subcutaneous injection was given daily for 5 days. Antibiotic coverage with neutropenic regimen started after correcting the dose for renal compromise. Red cell concentrate was given from third day of admission. Renal support was sought from the nephrology department.

Patient became dyspneic on day 5, and had to be shifted to ICU facility. A repeat chest x-ray showed soft patchy infiltrates over bilateral lung fields. Patient was immediately put to inhaled oxygen therapy. On day 6, the counts started to improve in response to aggressive supportive therapy. Total leucocyte count rose to 2500, platelets increased to 4200 and hemoglobin went up to 8.6.Despite this; patient went into respiratory distress and chest findings worsened owing to acute respiratory distress. Patient was put to ventilator support but she succumbed to a cardiac arrest.

Case Discussion

Methotrexate (MTX) may lead to isolated decrements in either red cells, white cells or platelets without affecting other cell lines; but pancytopenia when all lineages are affected is particularly life threatening complication[3]. Profound pancytopenia has been mentioned as early as after a single dose of MTX in a case report[4]. However, it is usually seen later in the

course of MTX therapy resulting from cumulative dose.

The risk of pancytopenia may increase with daily dosing errors, folic acid deficiency, hypoalbumenia, concomitant infections like parvo virus infection, dehydration, renal insufficiency and co-administration of other drugs like cotrimoxazole[5]. For patients with renal impairment dose adjustment should be done with complete avoidance of MTX if creatinine clearance is <30 ml/min[6]. The reason for pancytopenia in our patient was also likely an antecedent viral infection and renal impairment. Therefore American College of Rheumatology suggests that periodic routine peripheral blood count should be performed (every four to eight weeks) [7].

Methotrexate by its action as a folic acid antagonist with an average half-life of 6-8 hours; becoming undetectable in serum by 24 hours. But after take up inside the cell, methotrexate is converted in to polyglutamate derivatives (MTXglu) which prolongs its intracellular stay (median half- life of 3 weeks) [8]. This accounts for the chronic toxicity associated with MTX. Concomitant administration of folic acid (1 to 3mg/day) halts the toxicities.[9]

In a case series, Lim et al[10] describe that prolonged exposures to high dose of MTX is responsible for the toxicity rather than achieving the peak plasma levels at one time. Similarly in another case report patient mistakenly took 20mg MTX daily for two weeks leading to supra threshold concentrations in tissues and hence, mucositis, gastrointestinal and myelotoxicity[11].Hence the cause of such toxicity in individual patient should be determined with a primary focus on management.

The management of MTX induced pancytopenia is mainly supportive with stopping the offending drug at the first instance. Folinic acid (Leucovorin) should be given to all; most effective if administered 24 to 48 hours after the last dose of MTX[1]. Afterwards, Folinic acid might not work as the cellular uptake of the offending drug is already complete. Supportive therapy includes fluid support; blood component replacement, antibiotics and antifungal administration. The availability of Recombinant growth factors like granulocyte colony stimulating factor (G-CSF)[12] also improve outcomes in such patients. In our case both Folinic acid and supportive measures including G-CSF were adopted with complete avoidance of antifungals as our patient had marked renal impairment. The mortality despite all these measures remains high (28%)[10].

Conclusion

Methotrexate induced pancytopenia is a serious and fatal complication that needs timely detection and prevention. Physicians need to be aware of the potential toxicity of MTX. They should follow their patients with regular monitoring with complete blood counts, liver and renal function tests to avoid sequelae of pancytopenia and other related toxicities.

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A Patient with Cough, Fever, Joint pain & Tender Nodules

Compiled and summarized by:
Dr. Ahmad Iqbal Mirza

A 59-year-old woman presented with a 2 months history of dry cough and a 1-month history of low-grade fever, arthralgia and pretibial nodules that were red and painful. Physical examination confirmed a temperature of 38.4°C, severe bilateral ankle periarthritis and prominent erythema nodosum affecting the lower anterior shins and forearms around the elbows. Chest imaging revealed bilateral hilar adenopathy.

Differential Diagnosis?

a. Systemic lupus erythematosus
b. Rheumatoid arthritis
c. Sarcoidosis
d. Lymphoma
e. Lyme disease

(Erythema Nodosum)

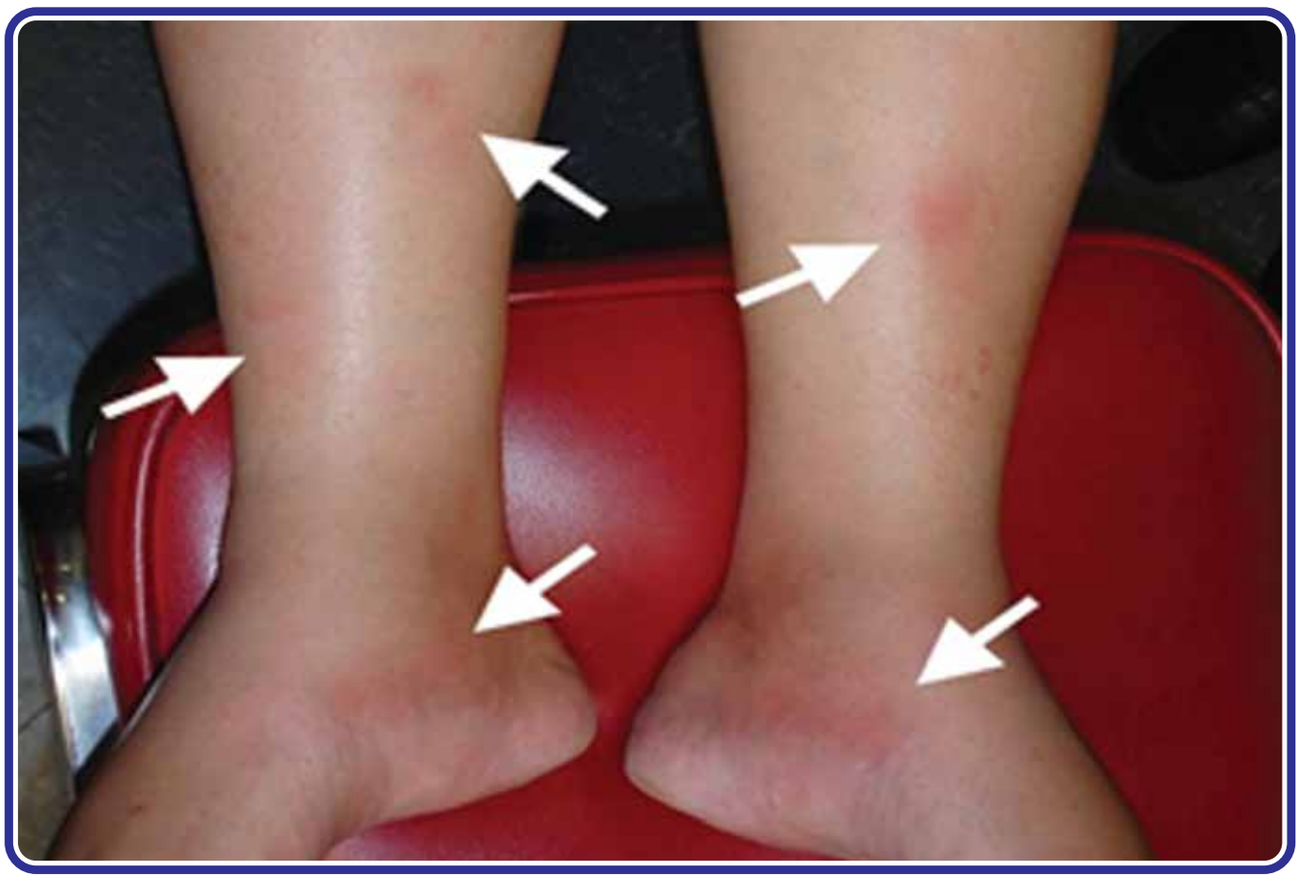

Table 1: Investigation Summary

Investigation	Results
Complete blood count with differential, urinalysis, measurement of creatinine, rheumatoid factor, serum calcium and angiotensin-converting enzyme levels	Within normal limits
Erythrocyte sedimentation rate	Elevated at 34mm/h
Chest radiography and computed tomography	Bilateral hilar adenopathy
Pulmonary function study	Within normal limits
Skin testing for Candida, Streptococcus, Trichophyton and purified protein derivative antigens	Anergy

Discussion

The answer is sarcoidosis. We diagnosed a variant of sarcoidosis known as Löfgren's syndrome based on the patient's history of malaise, low-grade fever, bilateral ankle periarthritis, erythema nodosum and abnormal chest imaging. The patient received a short course of prednisone and colchicine therapy. Her symptoms completely resolved within 6 months and she was still disease-free after 2 years.

Löfgren's syndrome is characterized by a combination of erythema nodosum, fever, hilar adenopathy and migrating polyarthritis mostly affecting the ankle joints. The condition tends to be transient, usually remitting after 3 – 4 months, with or without analgesic, anti-inflammatory therapy.

Table 2: Selected Variants of Sarcoidosis

System Involved	Löfgren's Syndrome	Lupus Pernio	Heerfordt's Syndrome	Darier-Roussy Syndrome
Skin	Erythema nodosum	Acral papulonodules and plaques	—	Subcutaneous nodules
Lung	Hilar adenopathy	Upper respiratory tract involvement	—	—
Musculoskeletal	Ankle polyarthritis	Lytic bone lesions	—	—
Eye	Iritis*	—	Uveitis	—
Central nervous system	—	—	Cranial nerve palsy	—
Other	—	—	Parotid gland enlargement	—

*May or may not present.

Sarcoidosis in General

Sarcoidosis is a multi-system disorder of unknown cause with a variable presentation and clinical course. Any organ system can be affected, most commonly the lungs (90% of cases) and skin (30% of cases). Lung involvement ranges from alveolitis and granulomatous infiltration in early sarcoidosis to fibrosis with bronchiolectasis in a later stage of the disease. Hilar and paratracheal lymphadenopathy occur in 90% of patients.

Sarcoidosis is a diagnosis of exclusion based on clinical suspicion of disease and histological confirmation of non caseating granulomas in at least 1 organ system after elimination of other causes of granulomatous reactions, such as

foreign-body reactions and mycobacterial or fungal infections. The determination of systemic involvement warrants thorough history-taking and physical examination, with an investigation that includes complete blood count, acute phase reactants such as the erythrocyte sedimentation rate or C-reactive protein levels, kidney and liver function tests, thyroid stimulating hormone and chest radiography. Skin anergy is the rule even in benign sarcoidosis. Elevation of the angiotensin- converting enzyme level occurs in about 60% of patients, and is related to the extent of systemic involvement. This test may be suitable for monitoring disease progression but not for establishing the diagnosis. Ocular symptoms warrant an ophthalmologic exam as part of the initial workup and thereafter with disease exacerbations. Although ocular involvement occurs in about 25% of patients with sarcoidosis, it is rare in Löfgren's syndrome. The need for further testing follows specific organ involvement.

Sarcoidosis Involving the Skin

Skin involvement may be the first and only manifestation of the disease. The most common cutaneous presentation of sarcoidosis is red–brown papules and plaques distributed symmetrically on the face, lips, neck, upper trunk and extremities. Erythema nodosum, which consists of bilateral tender nodules on the anterior surface of the legs, is common but not specific to sarcoidosis. It is usually predictive of a milder, transient form of the disease that resolves spontaneously.

Treatment is guided by disease severity and progression. Localized cutaneous disease may be treated with topical or intra-lesional corticosteroid therapy. In cases of generalized or severe cutaneous disease or systemic involvement, prednisone, colchicine, methotrexate, chlorambucil, azathioprine, thalidomide, etanercept and infliximab have been used with success.

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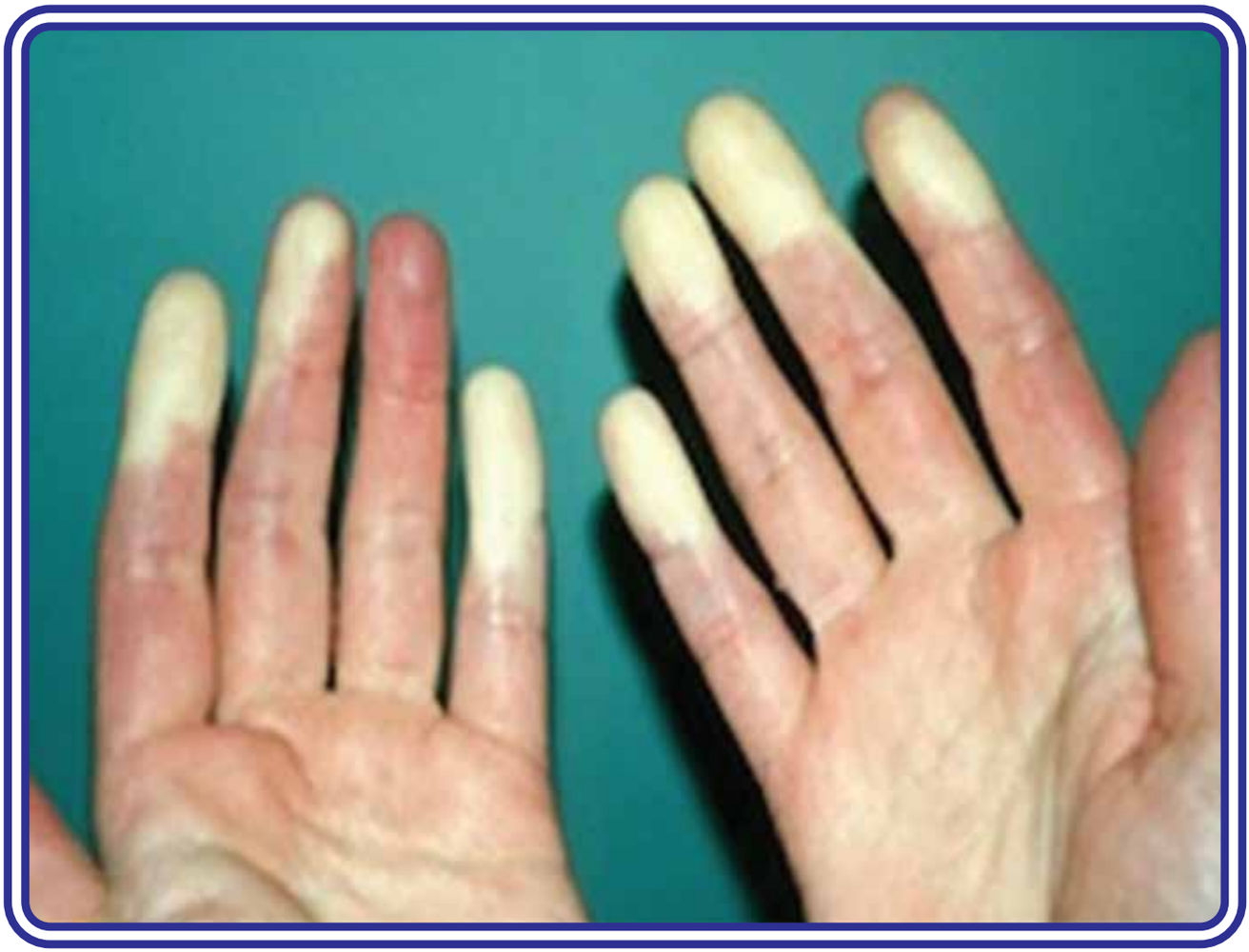
Photo Quiz



Question

What is the diagnosis for the above given picture ?

Answer of last quiz

- Psoriatic Arthritis