Review Article

Arthropathy in Dermatology: A Comprehensive Review

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Abstract

Dermatology and rheumatology are two specialties that deal with significant overlap. In this context, it is important that the dermatologists acquaint themselves with conditions presenting with arthropathy. As the first step, it is essential to know whether the origin of musculoskeletal symptom is articular or extra-articular; inflammatory or noninflammatory; acute or chronic; oligo- or poly-articular. This will help in narrowing down the differential diagnoses as well as in better correlation with the cutaneous symptoms. In this review, we discuss the skin and articular manifestations of common inflammatory and noninflammatory arthropathies including rheumatoid arthritis, spondyloarthropathies, connective tissue disorders, vasculitis, crystal arthropathies, infective arthritis, arthritis associated with degenerative, endocrine and metabolic conditions, etc. We have also added a section on the common cutaneous features associated with the treatment of rheumatologic diseases. A basic understanding of the joint pathologies and associated skin changes will help a long way in the better management of these conditions.

Keywords: *Arthropathy, dermatology, rheumatology, rheumaderm, rheumatology-dermatology*

Introduction

Dermatology is a branch of medicine that often deals closely with other specialties and has overlap with many; among these, rheumatology is a specialty with significant overlap. Whether in the area of inflammatory arthropathies such as rheumatoid and psoriatic arthritis; connective tissue disorders such as systemic lupus erythematosus, scleroderma, or dermatomyositis; infective conditions such as leprosy, Lyme disease and the like; or the various vasculitis and vasculopathies, skin and joints often go hand in hand. The presence of a skin rash and arthritis often presents an intriguing diagnostic challenge too. With the advent of newer drugs such as biologics, the overlap has attained therapeutic implications, as the involvement of either system would influence the choice of the drug. It is imperative, therefore, that in view of the expanding horizons of the specialty, dermatologists acquaint themselves better with the conditions presenting with arthropathy.

In this article, we outline the common conditions presenting with skin and joint involvement, discuss the clinical manifestations, and later present an algorithmic approach based on the pattern of joint involvement.

A glossary of the common clinical and radiographic terms used in this context is given in Table 1.

Approach to Joint Diseases and Classification

The first and foremost step in the approach to a patient with joint pain is to distinguish between articular and nonarticular pain. In articular pain, virtually all movements of the joint will be painful, as opposed to selective pain found in periarticular lesions. Further, in articular lesions, the pain has a similar intensity with both active and passive mobilization and both can be limited in range. This is in contrast to periarticular lesions, where active movements will be more painful than passive.[1]

As the second step, four fundamental features of the articular pattern should be defined:

1. "Inflammatory" or "noninflammatory" nature of the disorder
2. The temporal pattern of the disorder, especially acute versus chronic
3. The spatial pattern: Primarily, mono-, oligo-, or polyarticular arthritis, and the presence of axial involvement
4. The existence of extra-articular and/or systemic manifestations.

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The inflammatory nature of the arthritis can be differentiated from noninflammatory arthritis by virtue of early morning stiffness lasting for more than 30 minutes, presence of joint swelling, and raised acute phase reactants. Once we have differentiated inflammatory arthritis from noninflammatory arthritis, it is the pattern of joint involvement which helps us in pinpointing the diagnosis [Figure 1]. The presence of axial involvement as indicated by the presence of inflammatory low back pain will point towards a diagnosis of spondyloarthropathy; whereas systemic symptoms such as fever, skin rash, and major organ involvement will point towards a diagnosis of connective tissue disease (CTDs).[1]

For ease of understanding, we will discuss arthritis presenting with dermatological manifestations in 5 broad subheadings.

1. Autoimmune rheumatic diseases e.g., rheumatoid arthritis, spondyloarthropathies, connective tissues diseases, and vasculitis
2. Crystal arthropathies
3. Arthritis associated with infections
4. Arthritis associated with degenerative, metabolic, and endocrine disorders
5. Miscellaneous.

Autoimmune Rheumatic Diseases

Rheumatoid arthritis

One of the most common conditions presenting with features of both articular and cutaneous involvement is rheumatoid arthritis (RA). RA is a systemic inflammatory disorder which has an insidious onset and has significant extra-articular manifestations.[2]

It is the prototype of inflammatory arthritis and usually manifests with signs of inflammation, which include joint swelling, pain, erythema, effusion, stiffness, and weakness. These features are more evident or aggravated in the morning or after prolonged inactivity or rest. The disease progresses in a symmetric manner and preferentially involves the small joints of the hands and feet; the proximal interphalangeal, metacarpophalangeal,

Table 1: Glossary of the key clinical and radiographic features of arthropathies

Dactylitis	Diffuse swelling of an entire digit (finger or toe), taking the shape of a sausage, often painful.
Enthesitis	Inflammation occurring at the entheses, i.e., the site of insertion of a tendon, ligament, joint capsule, or fascia to bone.
Erosions	Loss of mineralized tissue at juxta-articular sites, associated with a break in the cortical lining.
Syndesmophytes	Calcifications or heterotopic ossifications seen usually within the spinal ligaments or annulus fibrosis.
Osteophytes	Bony spurs or projections arising from the joint margins

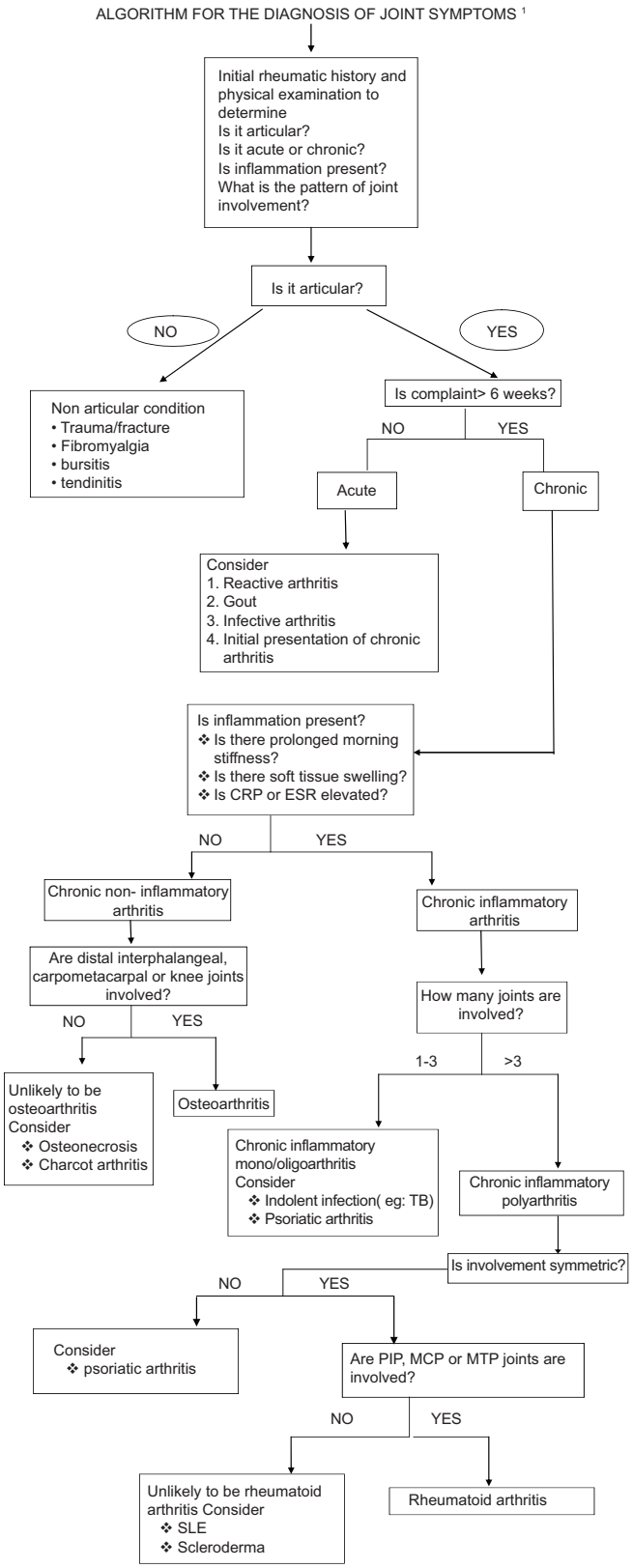

Figure 1: Algorithm for the diagnosis of joint symptoms (Modified from reference 1)

and metatarsophalangeal joints, with sparing of the distal interphalangeal joints and IP joints of the thumb. The wrist and ankle joints are also involved. Cervical spine is also involved, however characteristically, the lumbar spine is spared, which is a differentiating feature from other inflammatory arthropathies. Other joint findings include synovial thickening, decreased range of motion, deformities, ankylosis, and subluxation.[3,4] Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface. Some of the specific hand deformities (which can also occur in osteoarthritis) include ulnar deviation, swan neck deformity [Figure 2b], boutonniere deformity [Figure 2c], and Z-thumb deformity and notably, these are fixed deformities, unlike in other arthropathies.[4,5] The common articular features of RA are summarized in Table 2.

Cutaneous involvement is well described in RA and is considered a part of the extra-articular manifestations of RA. Several nonspecific general findings, as well as more specific cutaneous manifestations can occur in RA.

Nonspecific cutaneous features in rheumatoid arthritis

The skin becomes atrophic, leading to fragility and easily bruisability. The skin overlying the dorsum of the hands may become pale or even translucent.[5] Raynauds phenomenon is uncommonly seen. The nails may become brittle and longitudinal ridging and clubbing are observed. The other nail changes include periungual erythema with telangiectasia, onycholysis, and red lunula.[6-8]

Specific cutaneous features in rheumatoid arthritis

Rheumatoid nodules

Rheumatoid nodules are the most common extra-articular manifestations of RA and are seen in approximately 25% of the patients with RA.[9] They are more common in white males and are seen exclusively in those with a positive rheumatoid factor (RF).[10] They appear as solitary or multiple skin-colored nodules ranging in size from a few millimeters to several centimeters and are usually situated on areas of repetitive trauma such as the olecranon [Figure 3], extensor forearms, occiput, fingers, and heel.[10] They are typically situated within the deep subcutaneous tissue, and rarely, they may also involve the internal organs.[1,11]

Histologically, three distinct zones have been described – an inner central necrotic zone, a surrounding cellular palisading zone, and the outer zone composed of perivascular infiltrates of chronic inflammatory cells.[12-14] These nodules are usually asymptomatic and do not require treatment unless they ulcerate, become infected, or compresses adjacent nerves.[15]

Accelerated nodulosis

Accelerated rheumatoid nodulosis was first described in patients on long-term treatment with methotrexate. This entity is more common in males and may be seen in patients with no pretreatment history of rheumatoid nodules.[16] The lesions are more commonly found on the hands, especially on the metacarpophalangeal and proximal interphalangeal joints.[17] They have been found to regress on discontinuation of methotrexate treatment

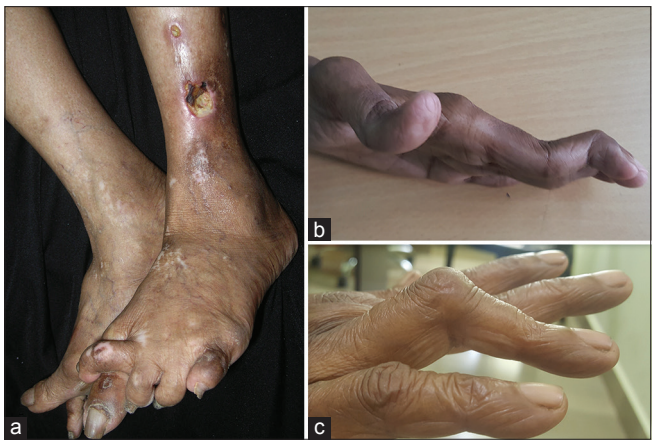

Figure 2: (a) Leg ulceration in a patient with rheumatoid vasculitis, rheumatoid arthritis, and deformities of the toes seen in the image. (b) Swan neck deformity of the hand in rheumatoid arthritis (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal joint). (c) Boutonniere deformity of the hand in rheumatoid arthritis (flexion of proximal interphalangeal joint and extension of distal interphalangeal joint)

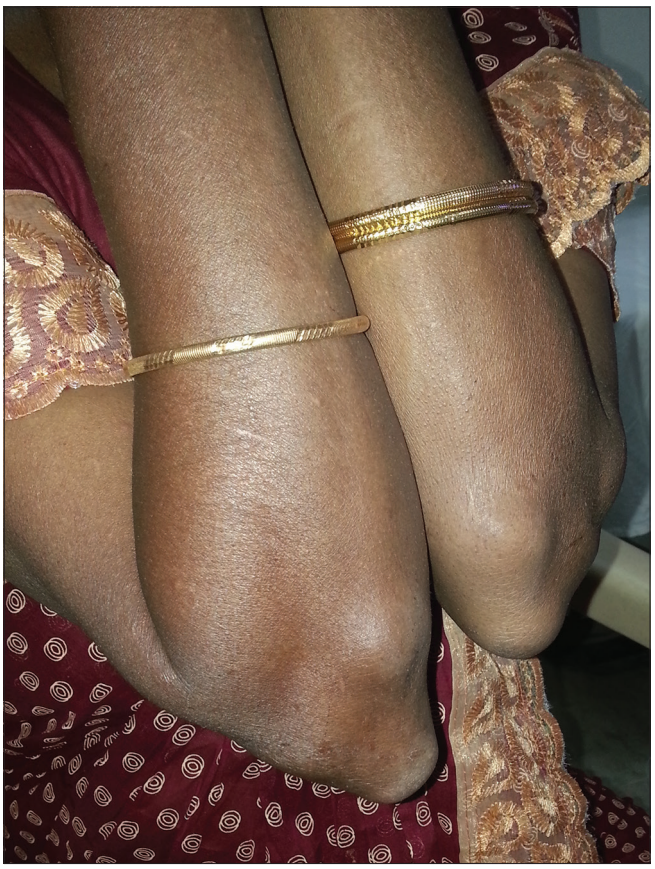

Figure 3: Rheumatoid nodules near the elbow joints

Table 2: Summary of articular and cutaneous features of RA

Articular features of RA	Dermatological manifestations in RA
Symmetrical small joint arthritis involving the proximal interphalangeal, metacarpophalangeal, wrist, metatarsophalangeal, ankle, knee, and cervical spine joints. Distal interphalangeal joints are spared	Rheumatoid nodules
Morning stiffness lasting for at least 1 hour before improvement	Accelerated nodulosis
Hand deformities including Swan neck, Boutonneire's, and Z deformity of the thumbs, fixed deformities	Rheumatoid vasculitis
Erosions in radiographs	Felty syndrome
Absence of involvement of lumbar spine	Pyoderma gangrenosum
	Interstitial granulomatous dermatitis with arthritis
	Palisaded neutrophilic and granulomatous dermatitis
	Rheumatoid neutrophilic dermatitis
	Sweet's syndrome
	Nonspecific cutaneous features

and reappear on restarting methotrexate. However, because the condition is associated with minimum discomfort and morbidity, methotrexate can be allowed to be continued in the majority of the patients.[17,18] Etanercept has also been implicated in the development of accelerated rheumatoid nodulosis.[19]

Rheumatoid vasculitis

Rheumatoid vasculitis (RV) is an important though uncommon manifestation of RA seen in less than 1% of the patients.[20] It is preferentially seen in seropositive RA patients with long standing disease and those with rheumatoid nodules, joint erosions, etc.[21]

Skin manifestations are the common presenting features of RV and include skin ulceration, digital infarcts, petechiae, palpable purpura, peripheral gangrene and bowel ulcers, or perforation. RV may cause acute, painful, punched-out leg ulcers to appear along the lateral malleolus or the pretibial region [Figure 2a].[22,23] The ulcers are usually multifactorial and can be attributed to vasculitis, accelerated atherosclerosis, venous insufficiency, and poor wound healing due to immunosuppressants. Bywaters first described the transient, painless, purpuric, or pigmented lesions in the nail edges, folds, and finger pulps in 1956.[24] They are thought to be benign lesions and entail low risk of progression.

Felty syndrome

The triad of splenomegaly, leucopenia, and arthritis was first described by Felty in 1924.[25] It affects less than 1% of the patients with RA, usually those who have long standing, seropositive, destructive RA. Skin manifestations include leg ulcers, rheumatoid nodules, and hyperpigmentation around the shins and ankles.[26]

Granulomatous dermatitis

Palisaded neutrophilic and granulomatous dermatitis is seen in patients with RA and other connective tissue diseases. It presents with symmetric erythematous to violaceous plaques, papules, and nodules on multiple body sites. On histologic examination, a spectrum of changes is observed ranging from urticaria-like infiltrates to leukocytoclastic vasculitis and granuloma annulare with neutrophils.[27,28]

Interstitial granulomatous dermatitis with arthritis is an uncommon condition, seen in middle-aged women with severe RA and rheumatoid factor positivity. Clinically, the lesions present symmetrically on the axilla, trunk, and inner portions of the thighs as erythematous to violaceous papules, nodules, and plaques, which may be tender or associated with a burning sensation. Erythematous to violaceous indurated linear cords (the rope sign) are characteristic. The pathologic feature is the presence of interstitial histiocytic granulomas.[29-33]

Neutrophilic dermatitis

The neutrophilic dermatoses associated with RA include rheumatoid neutrophilic dermatosis, palisaded neutrophilic granulomatous dermatitis, pyoderma gangrenosum and sweet's syndrome. Rheumatoid neutrophilic dermatosis (RND) classically presents with asymptomatic papulo-nodules or plaques distributed on the extensor surfaces of extremities, particularly over the hands, forearms, as well as the neck and trunk. Histologically, a dense neutrophilic infiltrate is seen without vasculitis. The lesions tend to resolve spontaneously with improvement in RA.[34-36]

Pyoderma gangrenosum (PG) is a painful, recurring, chronic neutrophilic disease of the skin, which presents frequently as four clinical variants – ulcerative, bullous, pustular and superficial granulomatous, out of which the ulcerative variant [Figure 4] is most commonly associated with RA.[37]

Sweet's syndrome is also known to be associated with RA. Here, the lesions present as erythematous, raised plaques, which are often tender and sharply demarcated and associated with fever. The cutaneous and articular features of RA are summarized in Table 2.

Childhood rheumatic diseases

Usually encompasses a diverse group of disorders. The most common of these is juvenile idiopathic arthritis (JIA). For the diagnosis of JIA, the arthritis must begin before the

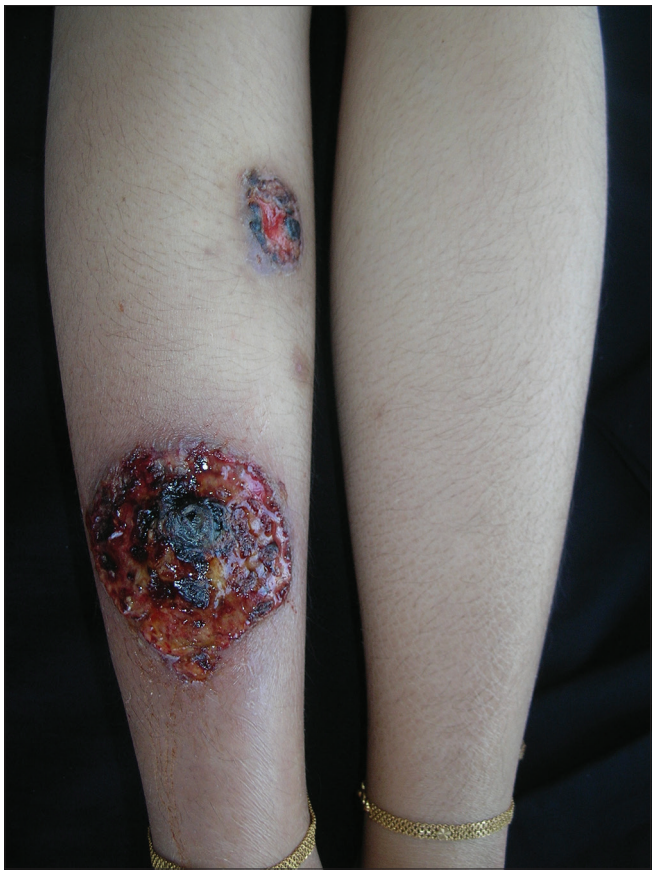

Figure 4: Pyoderma gangrenosum in a patient with rheumatoid arthritis

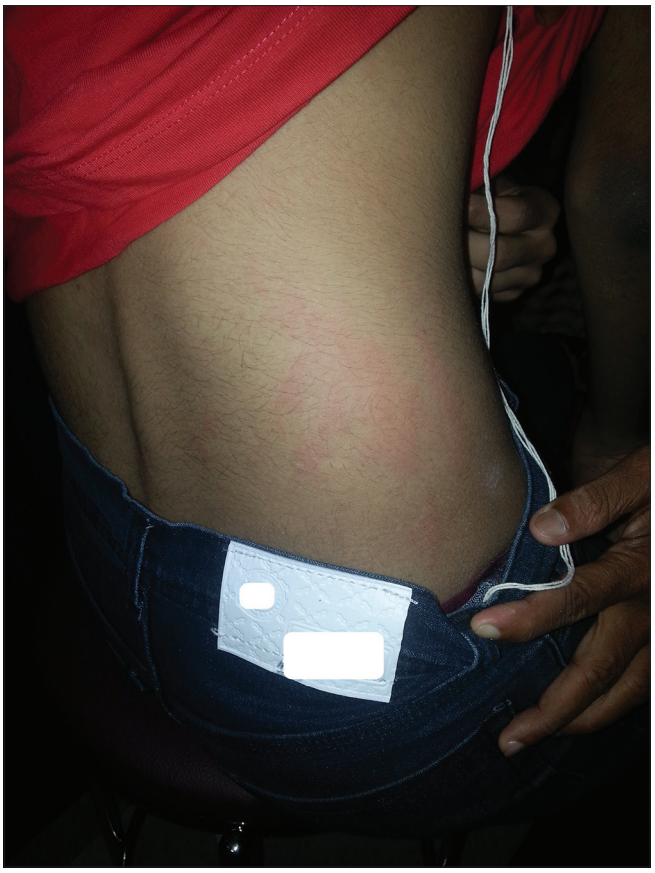

Figure 5: Salmon-colored maculopapular rash in systemic-onset juvenile idiopathic arthritis

age of 16 years and must last for more than 6 weeks in at least one joint. JIA has 4 subtypes – systemic, polyarticular, pauciarticular, and enthestis related.[38]

In pauciarticular-onset JIA, 1–4 joints are involved, whereas polyarticular-onset JIA (40% of cases) involves 5 or more joints and is similar to adult RA. Systemic-onset JIA, also called Still's disease, is defined as arthritis with daily fever, lasting for at least 2 weeks that is quotidian in nature for 3 or more days and is usually accompanied by an evanescent rash, which is typically nonpruritic, salmon-colored, papular or macular with slightly irregular margins, on the trunk [Figure 5] and extremities.[2] The rash occurs during the fever spikes. Histologically, there is a scanty infiltrate, sometimes of neutrophils, in the dermis. These patients also have arthritis, usually polyarticular, along with lymphadenopathy and hepatosplenomegaly. Very high ferritin levels (>1000) are one of the clues to the diagnosis along with leucocytosis and raised inflammatory markers. Subcutaneous nodules may also be seen in some cases.[2]

There is a subset where, adult onset (adult onset Still's disease) is described. However, the clinical features are more or less the same.

Spondyloarthropathies

Spondyloarthropathies (SpA) are a group of disorders that include ankylosing spondylitis (AS), psoriatic arthritis (related to cutaneous psoriasis), enteropathic arthritis (related to inflammatory bowel disease), and reactive arthritis (post-infection SpA). These diseases are grouped into one because they share similar clinical features as well as have an association with *HLA-B27* gene. As the name implies, spinal involvement is the hallmark of these group of diseases and is characterized by inflammatory back pain (back pain with early morning stiffness lasting more than 1 hour) along with sacroiliitis. Sacroiliitis presents with buttock pain and can be diagnosed using magnetic resonance imaging (MRI) at an early stage itself.

Arthritis in SpA is usually asymmetric and lower limb predominant although upper limbs also can be involved, especially in psoriatic arthritis. Dactylitis is a characteristic feature of SpA. Another important feature seen here is enthesitis, such as tendoachillitis [Figure 6] and plantar fasciitis. Eye involvement in the form of uveitis and bowel involvement in the form of inflammatory bowel disease (IBD) are also common in this group of arthropathies. Cutaneous manifestations in SpA include oral ulcers, erythema nodosum, pyoderma gangrenosum, keratoderma blennorrhagicum, and psoriasis. The first three are commonly associated with enteropathy.[39]

We will discuss psoriatic arthritis and reactive arthritis, the most common SpA that may present to the dermatologist.

Psoriatic arthritis

Psoriatic arthritis (PsA) is a seronegative (negative rheumatoid factor and negative anti-CCP), predominantly peripheral spondyloarthropathy, which occurs in up to 40% of the patients with moderate to severe psoriasis. It can be destructive to the joints and adds considerably to the impairment of the quality of life suffered by patients with psoriasis.[40]

The diagnosis of PsA is important and an enquiry regarding joint symptoms should be made at every consultation inpatients with psoriasis. A practical approach would be to examine the joints of the hands and feet for evidence of joint swelling or tenderness and dactylitis. In rheumatology practice, psoriatic arthritis can be differentiated from the other forms of arthritis according to Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, with 99% sensitivity and 91% specificity [Table 3].[40,41]

The arthropathy in psoriasis is heterogeneous; and according to the Moll and Wright classification, is classified as peripheral mono or asymmetric oligoarthritis, symmetric oligoarthritis mimicking RA, arthritis mutilans, as well as as an axial disease predominantly affecting the spine. The symmetrical type is especially difficult to differentiate from RA, however, the distal interphalangeal joint involvement, presence of dactylitis and enthesitis [Figure 7a-c and 8] helps to diagnose PsA. Moreover, involvement of the lumbar spine, though can occur in PsA, is not seen in RA.[42]

Usually, skin lesions precede joint involvement in 70–80% of the cases by approximately 10 years. However, in 15% of the patients, arthritis and psoriasis begin simultaneously, and in an additional 15%, arthritis precedes psoriasis by as long as 15 years.[43] In a study reported from Kashmir, chronic plaque psoriasis was the most common type of psoriasis seen in PsA (81% patients). Nail involvement is more frequent in psoriatic patients with associated PsA and has been seen in 60–80% of the patients.[44] In a large North Indian series by Kumar *et al*., among 1149 patients with psoriasis, 8.7% patients had PsA; the most common pattern was symmetrical polyarthritis (58%), followed by spondyloarthropathy, asymmetric oligoarthritis, isolated spondyloarthropathy, predominant distal interphalangeal arthritis, and arthritis mutilans. Enthesitis and dactylitis were present in 67% and 26% of the cases, respectively, and nail involvement was seen in 87% of the cases.[45] Pitting, onycholysis, subungual hyperkeratosis, and nail fragmentation are some of the common nail changes observed along with PsA. Therefore, nail changes in a patient with psoriasis should prompt a search for joint disease. Definite correlation between the severity of nail disease and articular involvement has not been established.

Table 3: CASPAR criteria for psoriatic arthritis

A diagnosis of PsA is made if a patient with inflammatory articular disease (joint, spine or enthesis) has some or all of the following criteria (-diagnosis requires 3 or more points*):

1. Evidence of psoriasis
   a. Current psoriasis (2 points),
   b. Personal history of psoriasis (1 point) or
   c. Family history of psoriasis in a first or second-degree relative (1 point)
2. Typical psoriatic nail involvement including onycholysis, pitting, and subungual hyperkeratosis on current physical examination (1 point)
3. Dactylitis
   a. Current
   b. History
4. Absence of serum rheumatoid factor
5. Radiographic evidence of juxta-articular new bone formation in the hands or feet

*All items carry one point, except current psoriasis, which carries 2 points.

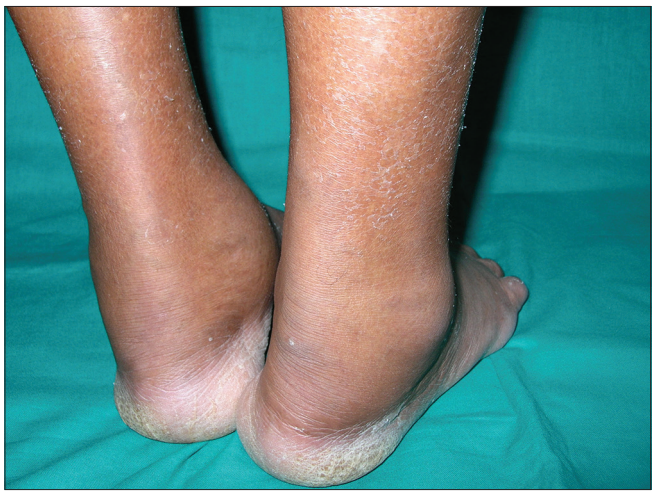

Figure 6: Enthesitis at the insertion of the Achilles' tendon

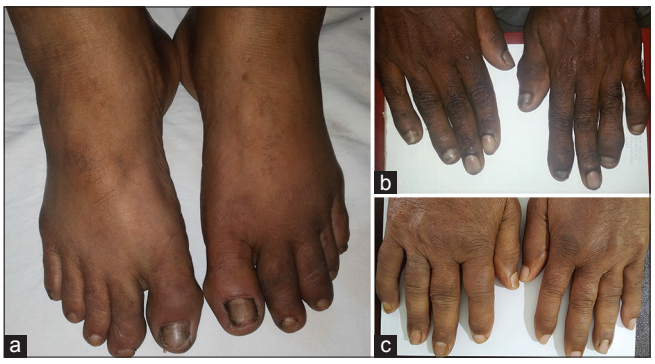

Figure 7: (a) Sausage toes (dactylitis) in psoriatic arthropathy. (b) Distal interphalangeal joint arthritis with nail changes in psoriatic arthropathy. (c) Dactylitis with swelling of the digits of the hands in psoriatic arthropathy

Reactive arthritis

Reactive arthritis, previously known as Reiter's syndrome, presents usually in a young male, with the symptomatic triad of arthritis, urethritis, and conjunctivitis. The exposure to an infectious agent (usually *Chlamydia*, *Shigella*, *Yersinia*, *Salmonella*, and *Campylobacte*r species) leads to the development of an inflammatory arthritis and other characteristic clinical findings. An acute onset asymmetrical oligoarthritis, predominantly involving the lower extremities, is the major presenting symptom, often associated with constitutional symptoms such as fever.[46]

Skin and mucocutaneous lesions are commonly observed. Keratoderma blennorhagicum is one of the characteristic findings, which is described as a papulosquamous rash, that begins as clear vesicles on erythematous bases and progresses to macules, papules, and nodules. These lesions are found on the soles of the feet, palms, scrotum, trunk, or scalp and eventually coalesce to form hyperkeratotic erythematous lesions resembling pustular psoriasis. Mucosal lesions include serpiginous annular lesions on the glans penis, termed circinate balanitis. Oral ulcers (typically painless) and geographic tongue are also described. Nail dystrophy is also often associated.[46] The differentiating features of common SpAs are listed in Table 4.[39,40,44,46]

Connective tissue diseases

This is a key area of overlap between the skin and joints. The major diseases pertaining to this include systemic lupus erythematosus, scleroderma, dermatomyositis, Sjogrens syndrome, and mixed connective tissue diseases.

It will be beyond the scope of this article to discuss the detailed cutaneous manifestations of the connective tissue diseases [Figure 9], which we believe are familiar to

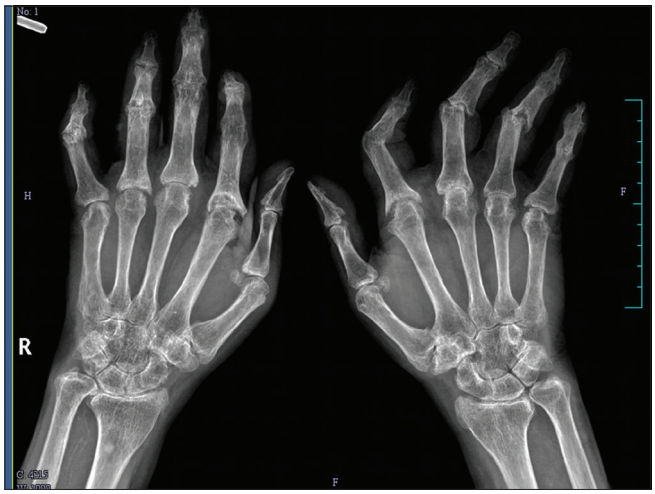

Figure 8: Radiograph of hands in psoriatic arthropathy: Showing erosions, joint space narrowing, with "pencil in cup" deformities in interphalangeal joints

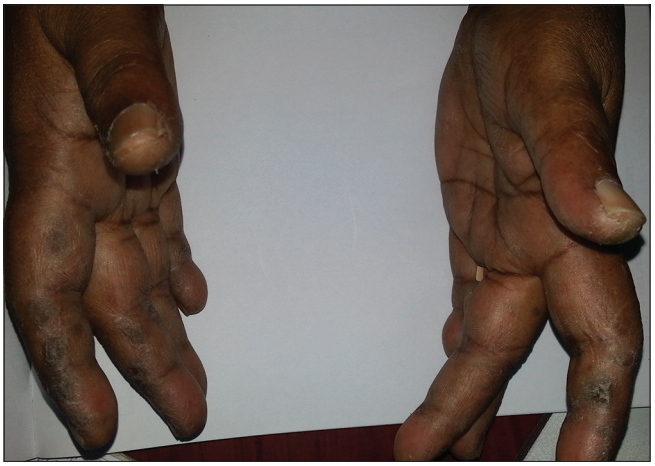

Figure 9: Mechanic's hand in dermatomyositis showing hyperkeratosis of the ulnar aspect of the thumb and the radial aspect of the index fingers with fissuring

Table 4: Features of different spondyloarthropathies

	Ankylosing spondylitis	Reactive arthritis	Enteropathic arthritis	Psoriatic arthritis
General feature	Most common subtype	Develops 1-3 months after gastrointestinal or genitourinary infections	Develops in 5-29% patients with inflammatory bowel disease	10-40% patients with psoriasis develop arthropathy. In 70%, psoriasis precedes arthritis
HLA B27 (in white population)	90%	40-80%	35-75%	40-50%
Dactylitis	Uncommon	Common	Uncommon	Most common
Enthesitis	Common	Common	Uncommon	Common
Sacroilitis	Symmetrical	Symmetrical/Asymmetrical	Symmetrical	Asymmetrical
Skin manifestations	Uncommon	Keratoderma blenorrhagicum, circinate balanitis, papulopustular/papulosquamous lesions	Oral ulcers, erythema nodosum, pyoderma gangrenosum	Psoriasis lesions
Other extra-articular features	Uveitis, aortic insufficiency	Uveitis, conjunctivitis, urethritis, aortic insufficiency	Inflammatory bowel disease, uveitis,	Uveitis, conjunctivitis, urethritis

most dermatologists. However, connective tissue disorders constitute a very important differential diagnosis of skin rash presenting with arthropathy. Articular involvement in connective tissue disorders is relatively similar, presenting as inflammatory polyarthritis involving the peripheral joints, which are usually nonerosive.

In patients with SLE, arthralgia is more frequent than arthritis and arthritis is classically described as nonerosive, involving mainly the wrists, knees, shoulders, and hands. However, 5% cases of SLE may be associated with a correctable nonerosive deformity of the hand joints known as *Jaccoud arthritis*. The clinical aspect may be misleading and suggestive of RA. The hand deformities such as the ulnar drift at the metacarpophalangeal joints, swan neck, and boutonniere deformities and hyperextension at the interphalangeal joints of the thumb closely mimic RA, however, the absence of erosions on the radiographs and their reducibility distinguishes this condition from the deforming arthritis of RA.[47] In rare cases, erosive arthritis similar to RA can also occur in SLE. Resorption of the bones of the digits is a feature seen in scleroderma.

The cutaneous involvement in connective tissue disorders often helps in pinpointing the diagnosis, which can usually be proven histologically. However, nonspecific skin lesions such as vasculits or vasculopathic changes and a myriad other skin lesions may also occur in these diseases. Moreover, internal organ involvement should be specifically examined, both from a diagnostic and therapeutic point of view. Serological tests are often required to confirm or rule out the diagnosis.

Vasculitis

Vasculitis constitutes a highly heterogeneous group of conditions, involving inflammation of the vessel wall and are difficult to classify. They frequently present with cutaneous manifestations because of the abundant vascular supply in the dermis and the subcutaneous tissue and many of them also present with joint involvement.

Cutaneous signs of vasculitis may vary depending on the size of the affected blood vessels. The hallmark of small vessel vasculitis is palpable purpura. The inflammation here involves the capillaries, post-capillary venules, and nonmuscular arterioles that reside in the superficial dermis and the purpura results from extravasation of erythrocytes from the vessel lumen into the dermis. It does not blanch under pressure and is seen in the dependent regions such as the legs or back. Petechiae, vesicles, pustules, urticaria, and splinter hemorrhages are other findings seen associated with small vessel vasculitis.[48,49] The common vasculitides that come under this group include Henoch–Schönlein purpura (HSP), urticarial vasculitis, cryoglobulinemic vasculitis, and cutaneous small vessel vasculitis.

In cases of medium vessel vasculitis, the skin manifestations that are common include nodules, ulcers, livedo reticularis, and digital infarctions. The vessels affected here are the arterioles with muscular walls, located at the junction of the dermis and the subcutaneous tissue (the deep reticular dermis).[50] Nodules are typically erythematous and painful and tend to ulcerate; there are certain similarities with erythema nodosum, however, can be differentiated by the fact that erythema nodosum does not ulcerate and commonly occurs on the extensor surfaces of the legs, whereas vasculitic nodules are more commonly seen on the malleoli or flexor surfaces of the legs.

The ANCA-associated vasculitides (AAV) include microscopic polyangiitis (MPA), Wegener granulomatosis, and Churg–Strauss syndrome, and are now classified as small vessel vasculitis. They may present with more diverse skin manifestations. Granulomatosis with polyangiitis (GPA) is the new term for Wegener granulomatosis and eosinophilic granulomatosis with polyangiitis (EGPA) for Churg Strauss syndrome. In addition to the the other skin lesions described with small vessel vasculitis, papulonecrotic lesions are the hallmark lesions seen in GPA and EGPA. They are seen on the extensor aspects of the limbs, such as rheumatoid nodules, and hence, these lesions may be confused with rheumatoid nodules; however, the papulonecrotic lesions eventually ulcerate.[48,51] Further, papulonecrotic lesions are more freely mobile as the pathology is in the dermis.

Although large vessel vasculitis do not present with cutaneous manifestations, erythema nodosum can be seen in the initial stages of Takayasu arteritis, and Behcet's disease is a variable vessel vasculitis that can involve large vessels. Behcet's disease usually presents with prominent mucosal involvement including recurrent oral aphthous ulceration, genital erosions that may heal with scarring, uveitis, and other eye changes. Skin lesions include papulopustular lesions, pseudo-folliculitis, acneiform eruptions, and erythema nodosum-like lesions.

As far as the joint involvement in vasculitis is concerned, in AAV, arthralgias are more common than frank arthritis, but true synovitis does occur. The typical pattern of joint involvement is migratory and oligoarticular, often involving large joints, but polyarthritis is also observed.[52] Patients with arthritis in Behcet's disease predominantly present with recurrent, self-limited, nondeforming, and nonerosive, inflammatory asymmetric mono-oligoarthritis, affecting the larger joints, mainly of the lower limbs.[53] Patients with overlapping features of both relapsing polychondritis and Behcet's disease have been described, and the term MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) has been used for this overlap syndrome. In HSP (now termed IgA vaculitis), ankle and knee joints are most commonly involved and the arthritis is usually nondeforming and self-limiting.

In addition to cutaneous and joint manifestations, the associated symptoms that suggest systemic involvement include hemoptysis, recurrent sinusitis, wheezing, abdominal pain, diarrhea, melena, hematuria, paresthesias, etc.[48]

Crystal Arthropathies

Gout

Gout is a disease characterized by deposition of monosodium urate crystals in the joints or synovial fluid with or without hyperuricemia, renal insufficiency, or nephrocalcinosis. It is described to occur in 4 stages:

a. Asymptomatic hyperuricemia
b. Acute gouty arthritis – usually affects the first metatarsophalangeal joint most commonly (podagra). Typically, monoarticular, but other joints may be involved later or in rapid succession.
c. Intercritical gout – there may be intervals lasting from 6 months to 2 years between attacks and as the duration increases.
d. Chronic tophaceous gout – crystals are found in skin, cartilages, and tendons of various sites, and the disease is rarely asymptomatic at this stage [Figure 10a-d].
e. The tophi may be confused with rheumatoid nodules and aspiration or biopsy might prove helpful in differentiating them.[54]

Elevated uric acid levels are a clue to diagnosis, but are not seen in all cases, especially in acute arthritis. Raised total counts and ESR can be seen during acute attacks. Polarized microscopy of the synovial fluid reveals negatively birefringent, needle-shaped crystals, and is diagnostic. Histopathologic examination demonstrates granulomatous "fluffy" infiltrates surrounding yellow- brown urate crystals or radially arranged needle-like spaces.[54]

Pseudogout

Caused by calcium pyrophosphate crystals and termed calcium pyrophosphate dehydrate crystal deposition (CPPD). The presentation may be diverse and may be asymptomatic; acute crystal arthritis mimicking gout, chronic crystal inflammatory arthritis mimicking RA, joint degeneration mimicking osteoarthritis which is superimposed with acute arthritic attacks; or as joint degeneration mimicking neuropathic joints have been described.[55,56] Unlike gout, most common joints affected are the knee and the wrist joints. The presence of positively birefringent calcium pyrophosphate (CPP) crystals, demonstrated by compensated polarized light microscopy is diagnostic. The CPP crystals differ from the urate crystals of gouty arthritis by the facts that they are smaller, more difficult to detect, are weakly positively birefringent, and are more polymorphic with rod-shaped and cuboidal crystals in addition to the usual rhomboid forms.[57]

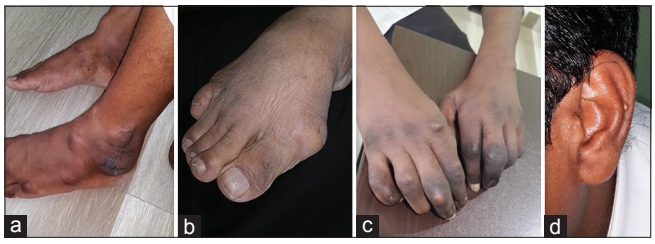

Figure 10: Gouty tophi in the (a) feet, (b) first metatarsophalangeal joint, (c) hands, and (d) ears

Arthritis Associated with Infections

Hansen's disease

After skin and neurological symptoms, articular symptoms are the third most common in leprosy. However, it is often under diagnosed. The dermatologist and the rheumatologist need to have a high level of awareness regarding the common articular presentations of Hansen's disease.

Acute arthritis in leprosy is more commonly associated with lepra reaction (both types 1 and 2), whereas chronic, as a result of direct infiltration of the lepra bacilli into the synovium. Acute and chronic symmetric polyarthritis, mimicking RA, involving hand joints have been described with or without lepra reaction. It may also manifest in the form of Charcot's arthropathy or as isolated tenosynovitis or tenosynovitis associated with arthritis or neuropathy. At times, articular involvement may be the sole presenting manifestation even without cutaneous lesions. Other rheumatological manifestations occasionally reported are enthesitis, sacroiliitis, vasculitis, etc.[58,59] Often, in lepromatous leprosy, antinuclear antibodies may also be weakly positive and may complicate the clinical picture. The authors have encountered Hansen's disease presenting with different clinical manifestations mimicking vasculitis, lupus, sarcoidosis, etc. A high index of suspicion is necessary to clinch the diagnosis in predominant articular presentations of Hansen's disease, especially in nonendemic countries.

Arthritis associated with sexually transmitted diseases

Sexually transmitted infections may provoke a wide variety of rheumatic lesions. The arthritic manifestations of gonococcal infections maybe diverse – as localized septic arthritis, or as a part of bacteremia, seen in disseminated gonococcal infections. The dermatitis–arthritis syndrome seen in bacteremia refers to the triad of skin rash, tenosynovitis, and polyarthritis. It responds promptly to appropriate antibiotic therapy.[60,61]

Rheumatic syndromes, including arthralgia, inflammatory arthritis, and neuropathic arthritis, may occur during any stage of congenital or acquired syphilis. Syphilitic synovitis responds well to antibiotic therapy, however, neuropathic lesions cannot be treated effectively.[60,62]

Hepatitis B infections are also characterized by joint symptoms, which may be in the form of arthralgia and arthritis that occur as a part of the viral prodromal manifestations. Joint symptoms may be accompanied by urticarial or cutaneous vasculitic lesions, especially on the legs. One also has to rule out hepatitis B infections in

the setting of the skin and articular features suggestive of necrotizing vasculitis.[63]

HIV infection may be associated with joint manifestations including that of seronegative arthritis, a Sjögren's-like syndrome, vasculitis, and myopathies. Synovitis is also described with HIV infections.[64]

Septic arthritis has rarely been described as a complication of disseminated mycoplasma or Urea-plasma infections. Moreover, joint involvement, sometimes associated with erythema nodosum, have been reported in lymphogranuloma venereum and granuloma inguinale.[60]

Tuberculous arthritis

Tuberculous arthritis is characteristically monoarticular and most commonly affects the spine and weight-bearing joints such as the knee, hip, and ankle. It commonly presents with chronic joint pain and only minimum signs of inflammation. In this type of arthritis, *Mycobacterium tuberculosis* may be isolated from the affected joints (tuberculous septic monoarthritis). However, active TB may be complicated by a lesser known reactive type of arthritis, which is termed Poncet's disease. It presents as an aseptic polyarthritis, similar to reactive arthritis (though sacroiliitis is rare), and the presence of erythema nodosum is often a diagnostic clue. A new set of diagnostic criteria have been proposed by Sharma *et al*. for this entity.[65]

Lyme disease and other rickettsial infections

Infection with B. burgdorferi results in a multisystem disorder. It may manifest as early as a week following the infection, and in some, can progress to a chronic form. The cutaneous hallmark of Lyme disease is erythema migrans (EM), a slowly enlarging annular lesion at the site of the tick bite [Figure 11]. In the disseminated stage, smaller, annular lesions may be found in a polycyclic pattern.[66,67] The late cutaneous manifestation is acrodermatitis chronic atrophicans, where small papules progress to large plaques with central atrophy, induration, and ulceration. Lyme disease is also characterized by neurological abnormalities and episodes of arthritis. Some of these clinical features, especially arthritis, subside and recur throughout the course of infection. Intermittent episodes of arthritis develop several weeks or months after the infection, and despite adequate antimicrobial therapy, symptoms persist in 10% of the patients with arthritis. In severe cases, the highly inflammatory aspects of Lyme arthritis can lead to cartilage and bone erosion with permanent joint dysfunction.[68,69]

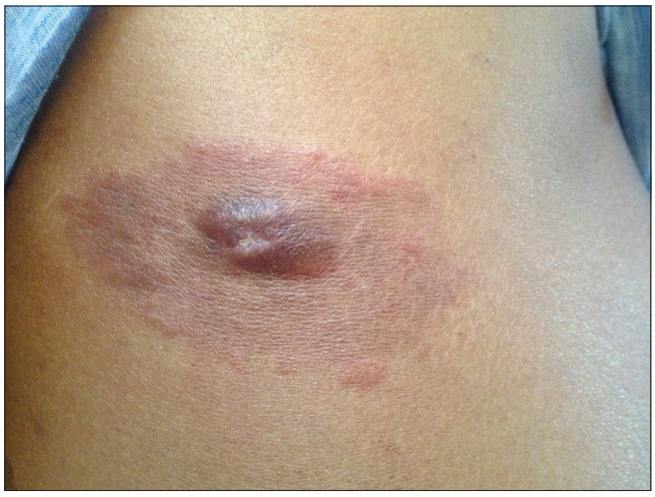

Figure 11: Erythema migrans in Lyme disease

Rheumatic fever

Typically, the first manifestation of acute rheumatic fever is a very painful migratory polyarthritis. This is seen in approximately 80% of the patients. Large joints such as knees, ankles, elbows, or shoulders are typically affected. Often, associated fever and constitutional symptoms may be present.[54,70] A history of pharyngitis (streptococcal) may be evident 1–5 weeks prior to the onset of symptoms. Signs of carditis must be looked for at the time of presentation. Sydenham's chorea is rare and even if present is usually a late manifestation.

Erythema marginatum is the characteristic rash of rheumatic fever; though it is rarer and is seen in 10–25% of cases only. It is asymptomatic and appears as evanescent, superficial semicircles and rings, which disappears completely in a few days. Histologically, neutrophils are seen perivascularly in the papillary dermis and may help in the diagnosis if it precedes other manifestations. Erythema marginatum is seen in approximately 25% cases of rheumatic fever; the other manifestations include petechial spots, erythema multiforme-like lesions, urticarial, and livido reticularis. Subcutaneous nodules, which are more transient than RA may also be seen, particularly on the occiput, wrists, and forearms.[54,70]

Viral arthritis

Arthropathy is seen in many viral infections such as Parvo virus B19, *Rubella*, hepatitis-associated viruses, and Chikungunya viruses. The clinical presentation may be diverse depending on the age of the patient, type of virus, etc. Arthritis or arthralgia is usually seen in the prodromal phase of the viral infection, though it can become chronic in some cases. However, in most cases, it is nondestructive. The dermatologists may find a variety of cutaneous lesions such as maculopapular rash, purpuric lesions, or slapped-cheek appearance in Parvo virus infections, urticarial lesions or periarteritis nodosa-like lesions in hepatitis B infections, vasculitic lesions with cryoglobulinemia, or Sjogren syndrome in Hepatitis C infections. In Chikungunya fever, a bewildering array of cutaneous findings have been reported including maculopapular rash, pigmentary changes, especially around the centrofacial area [Figure 12], aphthae like ulcers,

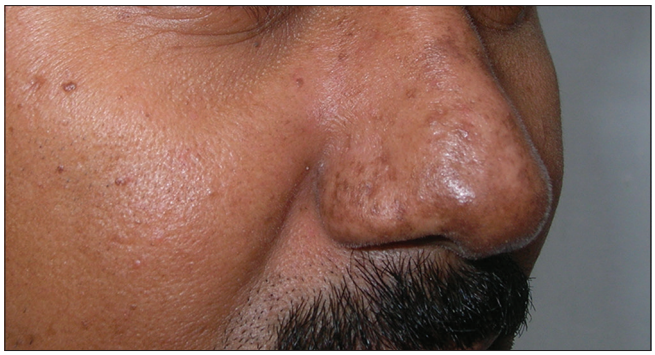

Figure 12: The typical nose pigmentation in Chikungunya fever (chik sign)

desquamation, exacerbation of existing dermatoses, and other miscellaneous findings.[71,72]

Arthritis Associated with Degenerative, Metabolic, and Endocrine Disorders

Osteoarthritis

Osteoarthritis (OA), the most common arthropathy, targets the knees, hips, finger interphalangeal joints, thumb bases, first metatarsophalangeal joints, and spinal facet joints. Frequent symptoms and signs include usage-related joint pain, morning stiffness of short duration, locomotor restriction, coarse crepitus, bony enlargement, and joint-line tenderness. To differentiate from RA, features such as distal interphalangeal joint involvement, first metatarsophalangeal involvement, and first carpometacarpal involvement would be helpful. Furthermore, it can be broadly differentiated from all other inflammatory arthropathies (including PsA) by the shorter duration of morning stiffness, the phenomenon of "gelling," and the pain that is induced by movement and relieved by rest. Though osteoarthritis is not associated with many skin changes, it is important to differentiate it from other arthropathies that present with skin manifestations.[73] Heberden nodes are posterolateral bony outgrowths affecting one or more distal interphalangeal joints, and Bouchard nodes are similar outgrowths affecting the proximal interphalangeal joints.[74]

Hemochromatosis

Hemochromatosis is a rare disorder characterized by tissue damage caused by iron deposition. The clinical manifestations depend on the site of abnormal iron accumulation, whether in the liver, pancreas, heart, or skin.

Hyperpigmentation is common and more commonly seen in the sun-exposed areas, especially the face. The color may vary from frank brown to metallic gray. Pigmentation may be also seen around the genitalia, nipple-areola complex, scars, and other flexural areas. Skin biopsy can be helpful in confirming the iron deposits.

The arthropathy is usually noninflammatory and initially involves the small joints of the hands, particularly the second and third metacarpophalangeal joints (peculiar hook like osteophytes may be seen), and eventually the large ones such as the knees, hips, and shoulders. It may be associated with multiple cysts in the subchondral bone. The arthropathy superficially resembles degenerative joint disease, with joint-space narrowing, sclerosis, and osteophytosis; however, the symmetric loss of articular space is an unusual finding in a degenerative joint disease.[75,76]

Diabetes

Diabetic hand syndrome or cheiroarthropathy is associated with insidious development of flexion contractures in hands resulting in restricted joint mobility. Charcot arthropathy and rocker bottom feet due to midtarsal collapse may also be seen in diabetic patients. Osteolysis characterized by osteoporosis and variable degrees of resorption of distal metatarsal bones and proximal phalanges in the feet are also seen. These joint symptoms may be associated with the various cutaneous manifestations of diabetes.[77]

Ochronosis, amyloidosis and scleromyxedema are also known to present with arthralgia and arthritis. Thyroid diseases can also present with arthropathies. Other metabolic disorders that may have skin and bony or jointsymptoms include Fabry's disease, Gaucher's disease, and Farber's disease.

Miscellaneous

Sarcoidosis

The classical constellation of features in acute sarcoidosis includes erythema nodosum, arthralgia of medium-sized joints, and hilar lymphadenopathy. Less recognized, but common, is an acute periarticular ankle inflammation, which may occur alone or with erythema nodosum and is more common in men. Chronic sarcoid dactylitis typically affects young adults; the fingers and toes become sausage-shaped with spindling. Chronic sarcoid oligo- or polyarthritis is rare; the so-called early-onset sarcoidosis associated with chronic granulomatous polyarthritis is recognized to be a variant of Blau syndrome.[74]

Fibroblastic rheumatism

This rare condition affecting predominantly white people, presenting with an acute onset symmetrical polyarthritis associated with multiple skin-coloured papules and nodules on the limbs. Some may also give a history of Raynaud phenomenon, and there maybe sclerodactyly and palmar thickening, suggesting a forme fruste of a connective tissue disease such as systemic sclerosis.[74,78]

Autoinflammatory syndromes

Autoimmune inflammatory syndromes are an important differential diagnosis to consider in a patient suffering

from repeated episodes of skin rash, joint inflammation, and constitutional symptoms from a young age onwards. These diseases are usually genetically mediated and characterized by recurrent attacks of systemic inflammation with primary physical manifestations of fever, rash, serositis, lymphadenopathy, and musculoskeletal symptoms. Newer conditions are increasingly being included under this umbrella of diseases, as the molecular and genetic mechanisms are being elucidated.[79] The major autoinflammatory syndromes with their skin and musculoskeletal features are listed in Table 5.

Several variants of inflammatory acne and hidradenitis suppurativa are also associated with joint symptoms and arthritis.

Bowel-associated dermatitis arthritis syndrome

Bowel-associated dermatitis arthritis syndrome (BADAS), originally referred to as bowel bypass syndrome, because of its association with bariatric surgery, is a recurrent neutrophilic dermatosis characterized by an episodic flu-like illness associated with vesiculopustular eruptions, nonerosive tenosynovitis, and polyarthralgias.[80] The skin lesions are seen on the trunk and extremities and begin as erythematous macules, and then become papules and vesiculopustules. Joint symptoms are described as episodic, migratory, and polyarticular, with involvement of the fingers and associated tenosynovitis; however, there is usually no long-term damage or deformity. Each flare usually settles in 1 week, followed by relapses every 4–6 weeks.

Originally postulated to result from bacterial overgrowth from the creation of a blind loop during bariatric surgery, BADAS has also been described in other intestinal diseases such as inflammatory bowel disease. Histologically, the lesions are identical to Sweet's syndrome.[80,81]

Skin lesions secondary to treatment of rheumatologic diseases

When we discuss conditions presenting with skin rash and joint involvement, it is also essential that dermatologists are aware of the common drugs used in rheumatological conditions and their dermatological adverse effects.

Lichenoid eruptions and rashes secondary to hydroxychloroquine are often seen in practice and cause

Table 5: The common autoinflammatory syndromes with skin and musculoskeletal features

Acronym	Meaning	Cutaneous features	Musculoskeletal features
Hereditary periodic fever syndromes			
CAPS (Cryopyrin-associated periodic syndromes)			
CINCA	Chronic infantile neurologic cutaneous and articular syndrome (same as NOMID)	Chronic urticarial-like skin rash	Arthralgia, arthritis, bony overgrowth of epiphysis, bony hypertrophy/ deformity, frontal bossing
FCAS	Familial cold autoinflammatory syndrome	Urticaria	Arthralgias
FMF	Familial Mediterranean fever	Erysipelas-like rash	Recurrent monarthritis, tenosynovitis, arthralgias, myalgia
MWS	Muckle-Wells syndrome	Erythematous rash, chronic or cold- induced urticaria	Myalgias, arthralgias, arthritis
HIDS	Hyperimmunoglobulinemia D syndrome	Palmar/plantar rash, aphthous ulcers	Arthralgia, arthritis
TRAPS	TNF receptor-associated periodic syndrome	Erythematous migratory rash or plaques on extremities	Arthralgia, myalgia
Autoinflammatory syndromes with pustulosis			
DIRA	Deficiency of the IL-1Ra	Pustular lesions, mucosal lesions	Periostitis, osteomyelitis,
DITRA	Deficiency of the IL-36R antagonist	Chronic pustular psoriasis	-
PAPA	Pyogenic arthritis, pyoderma gangrenosum, and acne	Recurrent pustular skin lesions (pyoderma gangrenosum) with acne	Recurrent pyogenic, sterile arthritis (inflammatory arthritis, usually non-erosive)
PASH	Pyoderma gangrenosum, acne, suppurative hidradenitis	Same as PAPA without the pyogenic arthritis	-
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy	Aphthous ulcerations	-

diagnostic dilemma, especially in patients on treatment for SLE.[82] Lichenoid eruptions have also been reported secondary to use of TNF-alpha inhibitors such as Infliximab, Adalimumab and Etanercept.[83] The authors have also seen lichenoid eruptions occurring secondary to rituximab and leflunamide.

Accelerated nodulosis seen with methotrexate has been discussed above and should be differentiated from rheumatoid nodules and subcutaneous nodules seen in vasculitis. NSAIDs are a group of drugs, commonly used in rheumatologic diseases. They can cause photosensitivity, pseudoporphyria-like lesions, photo-onycholysis, and some drug reactions such as fixed drug eruptions. Sulfasalazine is another common drug used by the rheumatologists that can cause Steven–Johnson syndrome or drug hypersensitivity syndrome.[84] It is a photosensitizer and can also induce or exacerbate lupus. Azathioprine and other cytotoxic drugs may be associated with hair loss.[85] Nail changes have also been described with many of these drugs. Eruptive melanocytic nevi, lentigenes, and increased incidence of nonmelanoma skin cancers are also noted with the use of these immunomodulators.[74] Increased skin infections are also often associated with the use of immunomodulators.

Paradoxical worsening of psoriasis has been reported with the use of TNF alpha inhibitors and would necessitate stopping the biologic and doing a class-switch.[86] The use of cyclosporine, tacrolimus, and systemic steroids is also associated with hypertrichosis. Long-term use of systemic steroids will also result in many changes in the skin, including atrophy, striae, telengiectasia, dyspigmentation, acneform eruptions, etc., which most dermatologists are familiar with.

Conclusion

The diseases that present with skin and joint manifestations form an important part of practice of the dermatologist and rheumatologist. In most conditions, the dermatologist and the rheumatologist have to work in tandem. However, from a dermatologist's perspective, a basic understanding of the joint pathologies and associated skin changes will help to go a long way in the better diagnosis and management of these conditions.

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Conflicts of interest

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