

**INTRODUCTION**

Polyarthritis is a cardinal manifestation in rheumatology. It is essential to recognize and find the most correct cause for polyarthritis in an individual patient. The diagnosis of the cause of inflammatory polyarthritis relies heavily on good history taking and physical examination. Rheumatology as a speciality is unique in that inflammatory rheumatic diseases evolve over time. Hence one rheumatologist may label a patient of polyarthritis as undifferentiated arthritis which over a few months or years may manifest signs of rheumatoid arthritis (RA) or psoriatic arthritis (PsA). This is also true for connective tissue diseases such as undifferentiated connective tissue disease (UCTD) which may evolve in to systemic lupus erythematosus (SLE).

**GENERAL APPROACH TO A PATIENT WITH MUSCULOSKELETAL (JOINT) PAIN**

Does the patient have arthritis? - A patient is said to have arthritis if one has joint pain and swelling, and the origin of "joint pain" (true arthritis) is from the joint (articular) structures, in contrast to pain arising from peri-articular structures.<sup>1</sup> Articular structures include synovium, synovial fluid, cartilage, intra-articular ligaments, the joint capsule, and adjacent bone.<sup>2</sup> RA a disease of synovium, is a classic example of polyarthritis. Osteoarthritis (OA) of hands a disease of articular cartilage, presents with joint pain is also polyarthritis.

Joint pain also arises from involvement of peri-articular structures: ligaments, tendons, bursae, muscle, fascia, bone and nerve.<sup>2</sup> Examples of peri-articular (non-articular) origin of joint pain include Baker's cyst (bursitis) producing knee pain, Achilles tendinitis can produce ankle pain, carpal tunnel syndrome can produce wrist pain. In arthritis the pain is deep or diffuse, with limited and painful range of motion on both passive and active movement of the involved joint, there is palpable swelling due to synovial proliferation (synovitis), joint space effusion, crepitation, and deformity. By contrast non-articular disorders tend to be painful on active (but not passive assisted) range of motion, example is peri-arthritis of shoulder (frozen shoulder). Also there is no swelling, deformity, crepitus or instability.<sup>2</sup> Local tenderness is present in regions away from the joint line. Patients with arthritis tend to hold the joint in partial flexion, hence contractures may develop. Therefore the finding of contracture is a sign of inflamed joint.<sup>3</sup>

How many joints are involved? - Single joint arthritis is monoarthritis. A person with 2-3 joint involvement is

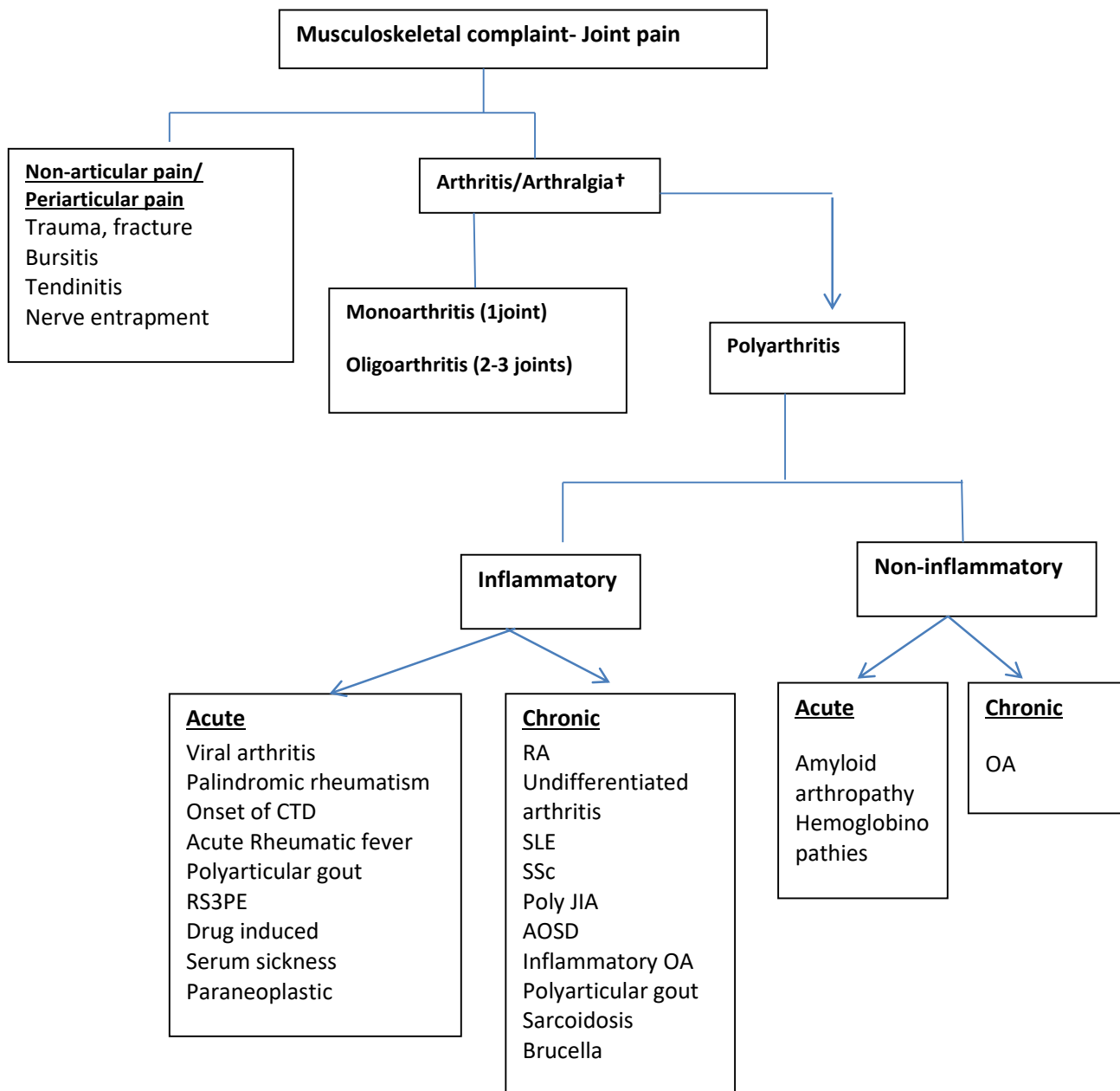
oligoarthritis, while polyarthritis is defined as pain (and swelling) involving 4 or more joints.

What is the duration of arthritis? Conventionally if the duration of arthritis is less than 6 weeks it is acute arthritis, and more than 6 weeks it is chronic arthritis.<sup>1</sup>

Inflammatory versus non-inflammatory arthritis - Probably most important is to decide whether it is inflammatory or non-inflammatory.<sup>1,3</sup> This is so because inflammatory arthritis especially RA if not diagnosed and treated early will cause bony erosion, deformity to the joints and impair the patient's quality of life. SLE can have life threatening major organ involvement.

The classical signs of inflammation are pain, warmth, swelling, and erythema.<sup>2,3</sup> All patients may not have all these signs. Inflammatory arthritis is characterized by presence of prolonged morning stiffness. Morning stiffness is defined as the time to maximal improvement after an extended period of inactivity, and typically improves with movement. In inflammatory arthritis early morning stiffness (after waking up in the morning) is prolonged and is present at least for 30 min, some patients may have morning stiffness lasting for hours. The pain and stiffness of inflammatory arthritis often improve on gentle use of joints and activity. An example is the low back pain, or buttock pain of ankylosing spondylosis which worsens with rest and improves with activity. By contrast non-inflammatory conditions such as OA is characterized by pain which is precipitated by brief periods of rest (gel phenomenon), exacerbated by use of the joint (activity) and stiffness is brief. Inflammatory arthritis is characterised by spontaneous "flares".<sup>1</sup> In clinical practice we often see inflammatory arthritis patients (prototype RA) whose disease appears well controlled but then they present with arthritis flare. So a spontaneous up and down course is indicative of inflammatory disease. Most inflammatory arthritis is accompanied by constitutional symptoms especially fatigue, low-grade fever, weight loss. Fatigue is an important symptom of RA, SLE, polymyalgia rheumatica.

On investigations a patient with inflammatory arthritis may have one or more of the following;<sup>1</sup> High erythrocyte sedimentation rate (ESR), high C-reactive protein (CRP) levels. There may be normocytic normochromic anaemia. Thrombocytosis i.e. platelet count of more than 400,000/cumm is also a sign of inflammation. The total leukocyte count (TLC) may be high. A reversal of albumin /



†See text on how to differentiate arthritis from peri-articular/non-articular pain

**Abbreviations-** CTD, connective tissue disease; RS3PE, remitting seronegative symmetrical synovitis with pedal edema; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; Poly JIA, Polyarticular juvenile idiopathic arthritis; AOSD, adult onset still's disease; OA, osteoarthritis;

**Fig. 1: Approach to the patient with joint pain and differential diagnosis of polyarthritis**

globulin ratio and moderate elevations of serum alkaline phosphatase are all seen in inflammatory arthritis.

### APPROACH TO POLYARTHRITIS

Polyarthritis is arthritis of 4 joint or more. Using the broad principles outlined above we have the following 4 diagnostic categories in polyarthritis (Figure 1).<sup>1,4</sup>

- Acute inflammatory polyarthritis
- Chronic inflammatory polyarthritis
- Acute non-

inflammatory polyarthritis and c) Chronic non-inflammatory polyarthritis.

### Point to consider while taking the history of a patient presenting with polyarthritis

Investigations cannot replace the diagnostic clue one can get from detail history and physical examination.<sup>3</sup> Demographic parameters are important. Some types of arthritis are seen more commonly in young people while some are more common in older people. A young woman

**Box 1: Conditions that mimic polyarthritis****Acute polyarthritis mimics**

Fibromyalgia

Neuropathies

Carpal tunnel syndrome

Tarsal tunnel syndrome

Bone secondaries

Myeloma

Leprosy

Multiple sclerosis

Parkinson's disease

Tendonitis

Polymyalgia rheumatic

Chronic recurrent multifocal osteomyelitis

Multifocal osteonecrosis

with painful swelling of the joints of her hands and history of Raynaud's phenomenon suggest a connective tissue disease. Whereas an older man who has diabetes and hypertension with history of polyarthritis of large suggest crystal induced arthritis.

Apart from musculoskeletal history the respiratory, cardiovascular, gastrointestinal, central nervous system, has to be reviewed.<sup>4</sup> In addition involvement of the airways, lungs, eye, skin, mucous membranes, and renal system involvement is closely linked to rheumatology. A past or present history of psoriasis suggests psoriatic arthritis. Eye involvement (uveitis, scleritis, conjunctivitis) is very common in the SpA family of diseases. History of nasal or ear discharge or hemoptysis helps to point toward a systemic necrotizing vasculitis. History of oral ulcers especially on the hard palate suggests SLE, while recurrent oral aphthous ulcers and scrotal ulcer suggest Behcets syndrome. Presence of diarrhoea, abdominal pain may indicate mesenteric ischemia. History of urethritis or diarrhoea preceding the arthritis helps to diagnose reactive arthritis (ReA). History of edema feet and other features of renal disease like cola coloured urine, frothy urine can suggest glomerulonephritis of SLE.

The CTDs and systemic vasculitis can present with fever of unknown origin (FUO). History of dry cough and presence of bibasal rales on lung auscultation is diagnostic of interstitial lung disease (ILD). ILD is particularly common in systemic sclerosis (SSc). A patient may present only with polyarthralgias, raynaud's phenomenon and evidence of synovitis on physical examination. If lung auscultation on such a patient reveals bibasal rales we are almost sure of dealing with SSc or a mixed connective tissue disease (MCTD) as the cause of polyarthritis.

**Pattern of joint involvement<sup>3</sup>**

During physical examination one can know the extent and pattern of joint involvement.<sup>3</sup> A pattern of inflammatory polyarthritis involving large and small joints including

hands and feet, (with sparing of the DIP joints) in a bilateral symmetrical fashion is almost diagnostic of RA.

A pattern of asymmetrical polyarthritis predominantly lower limb oligoarthritis (2-3 joint involvement), with or without root joint involvement (either hip or shoulder), presence of inflammatory back pain, alternating buttock pain in a young male strongly suggest SpA. Peripheral arthritis can be the first manifestation of ankylosing spondylitis in India.

A gout patient will give history of attacks of great toe arthritis (podagra). Subsequent attacks can be polyarticular and involve the hands also. Therefore when a middle aged, maybe obese man with hypertension and/or diabetes presents with polyarthritis one should not forget to enquire for past history of podagra.

DIP joint involvement without inflammation is characteristic of primary nodal OA. Involvement of the first carpometacarpal joint is also very common in OA. The pattern of DIP joint involvement with nail findings is typical of PsA.

The pattern of bilateral ankle arthritis, and ankle edema, with erythema nodosum is almost diagnostic of sarcoidosis or tuberculosis. Further distinctions between these two conditions depend on tuberculin test, findings of chest radiographs, and computed tomography (CT) of chest.

Cause of Acute Inflammatory Polyarthritis- In acute inflammatory polyarthritis there is involvement of 4 or more joints, and the duration is less than 6 weeks. This category often poses a diagnostic challenge because the causes for acute inflammatory polyarthritis could either be a self-limiting viral arthritis or it could be the onset of a chronic illness such as RA.<sup>3,4</sup> There are several conditions which can mimic acute polyarthritis.<sup>4</sup> In the authors experience the conditions listed in box 1 can mimic acute polyarthritis. The causes for acute inflammatory polyarthritis are viral arthritis, acute rheumatic fever, infective endocarditis, onset of RA, onset of CTDs (SLE, SSc, MCTD), ReA. It could also be due to palindromic rheumatism, which is characterized by attacks of arthritis of short duration. Some patients with palindromic rheumatism can develop RA. Another possibility is a syndrome called RS<sub>3</sub>PE the acronym for remitting seronegative symmetrical synovitis with pedal edema.<sup>5</sup> This condition which is seen mainly in older individuals is characterised by a remitting symmetrical synovitis of the upper limbs with pitting edema of dorsum of hands. Patients respond very well to steroids and can be associated with polymyalgia rheumatica, other CTDs, and neoplasia.

Presence of high grade fever at onset could be a pointer to a viral illness such as Chikungunya arthritis.<sup>6</sup> Viral arthritis could be related to HBV or HCV infection. Presence of features of heart failure and heart murmurs in a young individual with arthritis suggest acute rheumatic fever or infective endocarditis, where an echocardiogram may reveal valvular regurgitation and vegetations. Reactive

172 arthritis (ReA) although classically is oligoarticular often have explosive acute onset, predominant lower limb involvement and there is preceding history of urethritis or diarrhoeal illness.

Drugs like hydralazine, isoniazid, pyrazinamide can produce a lupus like syndrome with the clinical presentation of myalgia, arthralgia, arthritis, and ANA positivity.<sup>7</sup> Therefore drug history is important.

But many times such clues are not forthcoming and we may have to wait and watch while the disease evolves. For many such patients we may initially give an open label of "undifferentiated arthritis" or "early inflammatory arthritis", the diagnosis of which may evolve in to RA or it may go in to spontaneous remission.<sup>8</sup> However these labels can be applied after ruling out conditions like septic polyarthritis or infective endocarditis.

Acute non-inflammatory polyarthritis- Acute polyarthritis (less than 6 weeks duration), without any signs or symptoms of inflammation (i.e. no palpable synovitis, no prolonged morning stiffness, normal ESR, CRP, and platelet counts etc.) is probably due to fibromyalgia, pain amplification syndromes, or rarely psychogenic/malingering. Fibromyalgia is an important clinical condition which accounts for many rheumatology consultations.<sup>9</sup> Although it is not life threatening the condition can impair the patients' quality of life. It can occur on its own or it secondary to RA or SLE. Patients with fibromyalgia present with widespread pain including both joint and muscle, accompanied by fatigue, headaches and un-refreshed sleep. It is often accompanied by irritable bowel syndrome, headache, and migraine. Clinical examination reveals widespread tender points, but there will be no synovitis.

Chronic inflammatory polyarthritis which is arthritis of more than 4 joints and present for more than 6 weeks is probably the most important among these 4 categories because of the implications of long term treatment. The patient with chronic inflammatory polyarthritis can have predominant articular involvement the most common cause of which is RA.<sup>4</sup>

Chronic inflammatory polyarthritis with prominent extra-articular manifestations are discussed.<sup>4</sup> In SLE polyarthritis is an important manifestation but more prominent are mucosal, dermatological, haematological, renal, and CNS manifestation.

Patients with early Sjögren's syndrome may not only have arthralgia/arthritis without sicca symptoms. They often times are mistaken for RA. However with progression of disease there are prominent symptoms of dryness (sicca) due to lacrimal, salivary and parotid gland involvement. Another clue for diagnosis is presence of purpura.

In SSc the first manifestation is Raynauds's phenomenon. At the same time many patients will have history of swelling of the joints, examination of which confirms presence of inflammatory polyarthritis. Detail examination will show

sclerodactyly, ulcerations of finger tips, digital pits, and ILD.

Psoriatic arthritis (PsA) can have a polyarthritis pattern very similar to RA. The clue for diagnosis is skin psoriasis, pitting of the nails, other nail changes with distal phalangeal (DIP) joint involvement. Skin involvement may not be obvious. One should examine the scalp, behind the ears, the natal cleft, and the navel for any evidence of psoriasis.

Behcets syndrome is a disease characterised by recurrent genital and recurrent aphthous oral ulcers. ReA arthritis can have an explosive onset of inflammatory polyarthritis predominantly in lower limbs, with preceding diarrhoea or urethritis and conjunctivitis. Dermatomyositis is an inflammatory condition where apart from arthralgias/arthritis the patient has prominent proximal muscle weakness and characteristic skin changes specific to dermatomyositis (Gottron's sign, Gottron's papules, shawl sign, V sign, heliotrope rash etc).

Sarcoidosis where the patient has tender nodules on the lower limbs (erythema nodosum), chest radiograph will show bilateral hilar lymphadenopathy. Multicentric reticulohistiocytosis is a rare condition characterized by destructive arthritis involving hands including DIP joints. The clue for diagnosis is presence of nodules on the skin, the arthritis involves the DIP joint, and patient can have underlying malignancy.

Systemic necrotizing vasculitides are a group of multisystem disease where renal failure manifested by hypertension and presence of active sediments on urine examination is prominent. Other manifestations of vasculitis are involvement of upper and lower airway, parenchymal lung involvement, mononeuropathy multiplex, and mesenteric ischemia. Adult-onset Still's disease is a differential when there polyarthritis and PUO along with skin rash, serositis, hepato-splenomegaly and lymphadenopathy.

Chronic tophaceous gout often presents with polyarthritis. The clue to diagnosis is history of involvement of the great toe (podagra) in the past, presence of tophaceous deposits, and demonstration of monosodium urate crystal in synovial fluid analysis.

Carcinomatous polyarthritis is another unique situation where a patient presents with polyarthritis which is actually the expression of a malignancy.<sup>10</sup> Carcinomatous polyarthritis is suspected when the arthritis has is of short duration, rapidly progressing, disproportionate weight loss, hepatosplenomegaly, or poor response to steroids and disease modifying agents. Polyarthritis similar to RA has been reported to occur in association with cancer of lung, stomach, colon, ovary and leukemia. The arthritis generally predates the cancer by few months.

### CHRONIC NON-INFLAMMATORY POLYARTHRITIS

The classic example of a chronic non-inflammatory polyarthritis is primary OA of the hands.<sup>2,3,4</sup> The patient is typically an elderly person, with predominant

involvement of the DIP and PIP joints of the hands in a symmetrical fashion.<sup>3</sup> On examination bony enlargement (nodules) are present over the DIP (Heberden's nodules) and over the PIP joints (Bouchard's nodules) with sparing of the MCP joints. Primary OA of the hands is often mistaken for seronegative RA. The differentiating point is patient have no systemic symptoms and all inflammatory markers are negative. Other causes of chronic non-inflammatory polyarthritis are rare conditions such as hemochromatosis, where there is characteristic involvement of both hand MCPs. The other causes are ochronosis, hypothyroidism, and amyloidosis.

### INVESTIGATIONS

Once a clinical diagnosis is achieved based on history and examination one can go for relevant investigations. If the clinical suspicion is RA we can ask for rheumatoid factor (RF), and anti-citrullinated peptide antibodies (ACPA), plus plain radiographs of the both hands and feet to look for bony erosions. The presence of ACPA in high titres is predicts erosive disease. Presence of RF, ACPA are considered poor prognostic markers in RA.

In suspected connective tissue disease such as SLE one should ask for ANA by indirect immunofluorescence technique. ANA is a very good screening test for SLE and but is also present in SSc, dermatomyositis, ILD etc. ANA may also be present in low titre in up to 15% normal individuals or elderly population.<sup>2,3</sup> It can also be present in chronic liver disease and chronic infections. Hence the practice of asking for ANA routinely for all arthritis should be avoided.

When the clinical suspicion for vasculitis is high, i.e. patient has arthritis, proteinuria, and active sediments in urine, suspicious nodules on the chest radiograph, anti-neutrophil cytoplasmic antibody (ANCA) test can be ordered. Over 90% of patients with active granulomatosis with polyangiitis (Wegener's granulomatosis) have a positive c-ANCA.<sup>12</sup> However the presence of ANCA should be to support the diagnosis, and should not replace tissue diagnosis. Other routine (but relevant) investigations should also include complete hemogram to look for cytopenias which can be a sign of active SLE. Blood counts are also useful to monitor for drug toxicities. All patients with chronic inflammatory polyarthritis should also have baseline liver function tests, renal function tests, examination of urine for proteinuria and active sediments, plain chest radiograph, ECG and echocardiogram.

Imaging by plain radiographs during acute inflammatory polyarthritis is often normal. Plain radiographs are useful if there is history of trauma and one suspects fracture.<sup>3</sup> However in a situation of chronic inflammatory polyarthritis plain radiographs of hands and feet are indicated to look for soft tissue swelling, juxta articular osteopenia, and bone erosions. In gout bony erosions are typically present on the first metatarsophalangeal joint with

overhanging margins. Plain radiographs of hands and feet are particularly useful in follow up of RA to assess joint damage in the longterm.<sup>11</sup>

### CONCLUSION

Evaluation of inflammatory polyarthritis is a challenge because of the wide differential diagnosis. The cornerstone in achieving a diagnosis is good history, review of all systems, recognizing the pattern of arthritis, and followed by relevant investigations. This approach of trying to achieve a clinical diagnosis first will reduce the number of investigations ordered and benefit most to both patient and treating physician.

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