Chapter 4

Aches and Pains in SLE

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ABSTRACT

Musculoskeletal (MSK) involvement in systemic lupus erythematosus (SLE) causing aches and pains are common. They have been described in 53% to 95% of patients. MSK manifestations can affect joint, muscle, bone and supporting structures. These include arthritis and arthralgia, tenosynovitis, myositis, osteoporosis, fibromyalgia and osteonecrosis. Fibromyalgia (FM) can be seen in up to 25% of patients with lupus and adverse impact on quality of life. It is important FM is identified and treated appropriately to minimize its effects on quality of life. The involvement ranges from active disease (arthralgia/arthritis, myalgia/myositis) to conditions associated progressive organ damage (joint deformities, muscle atrophy, osteoporosis and osteonecrosis) as a consequence of long-term disease or as a complication of treatment. It is associated with significant morbidity, has adverse impact on quality of life and increased the risk of work loss and workplace impairment. MSK damage is a poor prognostic factor and associated with increased risk of mortality. Early recognition and adequate control of lupus disease activity are essential in prevention of the long-term sequelae associated with these conditions. Glucocorticoids (GCs) are associated with damage accrual in the MSK system. Adequate bone protection measures, minimizing exposure to GCs whenever possible are essential to reduce long term risks associated with GCs usage. There is a need for treatment regimens wherein exposure to GCs can be avoided or minimized.

INTRODUCTION

Aches and pains are one of the most common manifestations in SLE. They have been described in 53% to 95% of patients and in majority these symptoms are present at presentation.[1-6] Musculoskeletal (MSK) involvement can have a significant impact on quality of life and are associated with work disability.[7,8] Active disease affecting the MSK system is frequent and constitutes 58% of disease flares.[2] Damage accrual in the MSK system was found about 24% of Hopkins lupus cohort.[2] MSK damage is a poor prognostic marker and is associated with increased mortality rates.[9] MSK manifestations can affect joint, muscle, bone and supporting structures.[10] These include arthritis and arthralgia, tenosynovitis, myositis, osteoporosis, fibromyalgia and osteonecrosis.[10] In addition, infection of MSK systems can occur in SLE due to immunosuppressive drugs.[11]

A 25-year female presented with1 year history of intermittent symmetrical joint pain and swelling associated with morning stiffness involving both hands, wrist, shoulder and knee joints. She required help for activities of daily living. She also had complaints of fever, oral ulcer and fatigue. However, she denied history of Raynaud's phenomenon or sicca symptoms.

On examination she had active polyarthritis and palatal ulcer. Labs revealed anemia and elevated ESR of 56 mm and CRP of 2.36 mg/dl. Urine analysis, liver function and renal function tests were normal. Direct Coomb's test and ANA was positive. In addition, she had rheumatoid factor, anti-dsDNA, anti-nucleosome and anti ribosomal antibodies. Complement were low. Rheumatoid factor (RF) was positive. Anti-cyclic citrullinated peptide antibody (Anti CCP) was negative. She was treated with steroids, hydroxychloroquine sulfate (HCQs) and Azathioprine (AZA) with which she had good response.

Though this patient has polyarthritis and RF was positive, the patient was diagnosed to have SLE as she had extra-articular features (fever, oral ulcers) and lab results (ANA, ENA screen, complement levels) supporting the diagnosis of SLE. Thus every patient with polyarthritis need to have a detailed system review as well as review of investigations.

JOINT MANIFESTATIONS

Joint involvement at presentation is common in SLE and can occur in 60 to 95% of patients during the disease course.[6,10] In 30 to 50 %, of patients with SLE, articular involvement is the initial symptom.[1-3] They can precede the diagnosis of SLE by months to years and are associated with increased risk of work loss and workplace impairment.[3,12,13] The symptoms of articular involvement may include joint pain, swelling and stiffness. Morning stiffness is a frequent complaint but it usually lasts few minutes and is not as prolonged as in RA. In about 33% of patients morning stiffness may be absent.[3]

Arthralgias are the most common manifestations of lupus joint involvement both at the onset and during the course of the disease.[2,14] Pain due to arthralgia is often extremely intense and disproportionate to the finding at the physical examination. Tumulty et al initially described this paradox in 1954 as characteristic of lupus joint involvement.[15] In the Hopkins lupus cohort, arthralgia and arthritis were observed in 90% and 80% of patients with SLE respectively.[2] Another feature described as characteristic of lupus arthritis is marked soft tissue swelling which is often present in the hands. Unlike rheumatoid arthritis (RA), the swelling may not be localized to joints alone. The swelling is diffusely present over the entire dorsum of wrist, hands and finger.[5] Arthritis in SLE can be polyarticular or oligoarticular. Mono-articular involvement is rare.[1,3] The typical pattern is symmetrical similar to that seen in rheumatoid arthritis. However, asymmetric patterns can also be seen.[3] All major and minor joints may be affected. Commonly affected joints include the wrists, knees, ankles, elbows, and shoulders, in that order of prevalence.[1,3] Arthritis in the course of the disease can be migratory, episodic or persistent.[3] Chronic or persistent arthritis as defined as persistent arthritis for at least 6 weeks is rare and seen in <5% of patients with SLE.[16]

There is variability with regards to severity of arthritis ranging from arthralgia or mild arthritis to severe erosive and/or deforming arthritis with functional disability.

Traditionally, three types of arthritis have been described in SLE:[10] Non-deforming and non-erosive arthritis, Jaccoud's arthropathy and Rhupus.

A. Non-deforming and Non-erosive Arthritis

This is the most common form of arthritis seen in SLE. This description was based on absence of deformities on clinical examination and absence of erosions on conventional radiology. However, recent studies using either high-resolution ultrasonography (HRUS) or magnetic resonance imaging (MRI) have shown the presence of erosions in this subset of lupus patients.[7]

B. Jaccoud's Arthropathy

Jaccoud's arthropathy (JA) is a deforming, non-erosive arthropathy which was initially described in association with rheumatic fever but has been seen in other rheumatological disorders including SLE. Its prevalence in SLE is about 3–5%.[14,20] It mainly affects the hands, but has been described in the feet, knee and shoulder.[17-20] Deformities affecting the hand include ulnar deviation, swan neck, 'z'-thumb, 'boutonniere' (Figs 4.1a and 1b). Deformities of the feet ("lupus feet") include hallux valgus, hammer toes and/or subluxation of metatarsophalangeal joint.[14,19] These deformities result from joint capsule laxity with subsequent fibrosis, muscle atrophy, and tendon contracture.[17-20]

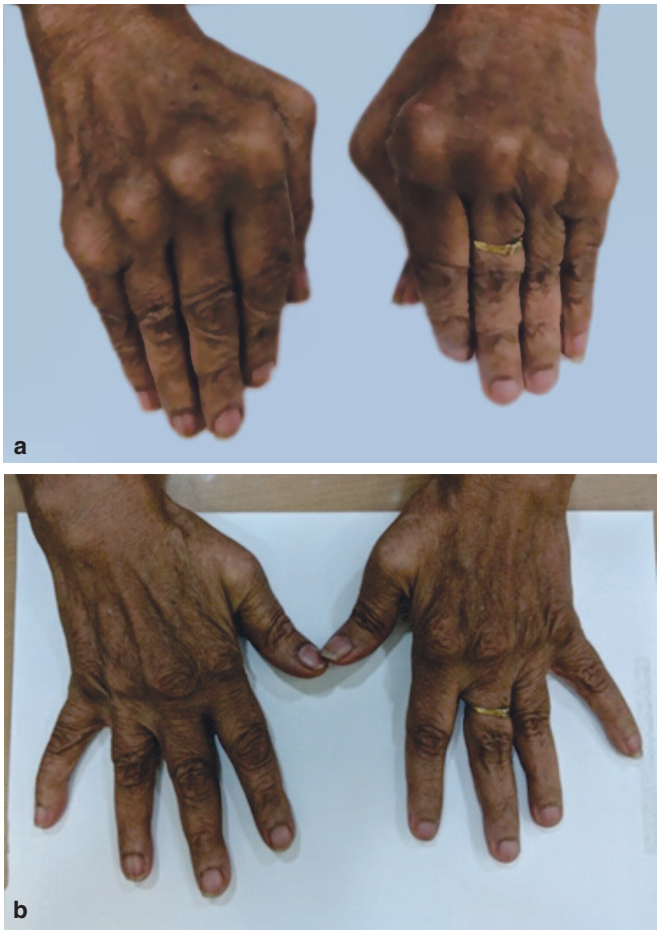

Fig. 4.1a and b: Jaccoud's arthropathy: Reversible deformity affecting the hands

A classical radiographic feature of JA is the hook lesion observed on the palmar-radial surface of the metacarpal heads seen in plain radiograph of the hands.[17] However, these lesions are not pathognomonic for JA and can be seen in conditions like RA, gout, pseudogout and osteoarthritis.[17] Though X-rays donot show erosions HRUS and MRI have shown erosive changes in JA.[17]

C. Rhupus

Rhupus is an erosive arthritis seen in SLE. In 1971, Peter Schur coined the term "Rhupus" to describe SLE patients with arthritis who also fulfill the classification criteria for RA. It is rare and seen in <5% of SLE patients.[14]

RHEUMATOID FACTOR AND ANTI CCP ANTIBODIES

Rheumatoid factor (RF) though seen more often in rheumatoid arthritis (RA) can be seen in 40–50% of patients with SLE. In SLE, presence of RF is not associated with joint involvement, but with sicca syndrome and a lower prevalence of nephropathy.[21]

Anti-CCP antibody, a more specific antibody for RA is reported in 4.4–27.3% of patients with SLE. However in SLE patients with arthritis, anti-CCP antibodies may be present in upto 50% of patients and is associated with erosive arthritis.[21,22]

TREATMENT

In the absence of clinical trials for treatment of lupus arthritis, the treatment is based on lines of RA and case series of lupus arthritis.[10] The treatment includes hydroxychloroquine sulfate (HCQs) as a background agent.[10,21] The dose of oral glucocorticoids (GCs) is usually dictated by underlying lupus activity.[10] Intra-articular GCs may be indicated especially when arthritis is limited to one or few joints or in tenosynovitis. Disease modifying antirheumatic drugs (DMARDs) and immunosuppressive agents (IS) can be used in lupus arthritis, which is refractory to HCQs and background glucocorticoids. Methotrexate is a reasonable option in these cases.[10] Other agents like leflunomide (LEF), azathioprine (AZA) and cyclosporine (CSA) can be considered in cases refractory to MTX.[10,23]

Biologics can be considered in lupus arthritis which is refractory to DMARDs/IS agents. Rituximab (RTX) has shown efficacy in RA.[10] There are no trials in lupus arthritis. There are some reports, which have shown efficacy of RTX in lupus arthritis.[24] Though anti-TNF agents have been shown to induce autoantibodies and lupus-like syndromes, case series have shown that treatment with anti-TNF agents is beneficial in lupus arthritis.[10] Belimumab is a newly approved biologic agent for SLE, having demonstrated benefit across organ systems including the musculoskeletal system.[10] Other biologic agents, such as abatacept and tocilizumab have shown benefit in case series.[10,25,26] There is a need for further evaluation of the role of biologic agents in treatment of lupus arthritis.

Tendon Involvement

There is a lack of clinical description of tenosynovitis in most of the lupus series. Studies using HRUS have shown that tenosynovitis occurs in 28–65% of the SLE patients.[14,27] The extensor and flexor tendons of the wrists are mainly affected.

Tendon rupture has been well documented.[1,28] The risk factors for tendon rupture include trauma, male gender, long-term oral steroid administration, intra-articular injections,

Jaccoud's arthritis, and/or long disease duration.[1,28] Almost all occur in weight-bearing areas, especially in tendons about the knee (65%; most are infra-patellar) and ankle (Achilles tendon; 27%).[1]

Subcutaneous nodules near tendons can be found in SLE in 3–13% of patients.[4,5,28] They are mainly found on the flexor tendons of the hand. Histologically, the appearance is similar to rheumatoid nodules.[28]

A 24-year-old female presented with intermittent fever; photosensitive malar rash; polyarthritis and Raynaud's phenomenon. In addition, she had progressive difficulty in stepping up and down the staircase, standing from sitting position, combing hair and cleaning shelves. On examination she had an erythematous malar rash but no Heliotrope rash or gottron's papules, active synovitis of small joints of handand proximal muscle weakness (Grade IV/V). Lab results showed coombs positive hemolytic anemia, ANA positivity, low complement levels, and elevated CPK of 1140 IU/l, ESR of 55 mm/hr and CRP of 2.3 mg/dl. Urine analysis was normal. ENA screen showed antibodies to Smith, nRNP, Ro and nucleosomes. A diagnosis of SLE with inflammatory myositis was made and she was treated with Prednisolone 1 mg/kg along with HCQs and Azathioprine.

Muscle Involvement

Muscle involvement can occur in the form of myalgias and weakness and is seen in up to 40 to 80% of patients with SLE.[1] Myalgias can occur during disease exacerbations and may reflect overall disease activity.[10] Muscle involvement in SLE is usually mild it is usually present at onset along with other systemic manifestations. Treatment of myalgias is symptomatic and is dictated by overall lupus disease activity levels and exclusion of other causes like drugs, infections

Inflammatory myopathy is rare and seen in about 5–10% of lupus patients.[10] It is similar to idiopathic inflammatory myopathy (IIM) in terms of clinical presentation, elevation of muscle enzymes and muscle biopsy findings[10] as well as severity.[29] Most of the patients have a relapsing and remitting course.[29] In clinical practice, muscle biopsy is not needed and may be done in refractory cases or when other causes, such as drugs, need to be excluded.[10] Muscle biopsy shows evidence of myositis like inflammatory infiltrate in perivascular, perimysial distribution and in some cases extending to endomysium.[30]

Lupus with myositis can be differentiated from dermatomyositis based on characteristics of skin rash.[31,32] Lupus rash spares the nasolabial folds, whereas the rash of dermatomyositis involves nasolabial folds.[31,32] Examination of the hands can provide additional clues—lupus rash involves the inter-joint spaces and spares the joints; Dermatomyositis rash involves the joints and spares the inter-joint spaces (Gottron's papules).[31,32] The scalp involvement in dermatomyositis tends to have diffuse scalp involvement and is pruritic.[31] Heliotrope rash, shawl sign, V sign and poikiloderma are characteristics of dermatomyositis.[31] Lower extremity involvement is more commonly seen with dermatomyositis.[31]

Treatment of Myositis is similar to IIM. It may include high dose GCs (including high dose pulse therapy) and use of immunosuppressive agents (Methotrexate, Azathioprine, MMF).[10, 23] Intravenous cyclophosphamide and biologics may be considered in refractory myositis.[10,23]

In lupus patients with muscle weakness other conditions like drug-induced myopathy (e.g., GCs, antimalarials, statins), endocrinopathies, and neuropathies also need to be considered.

Drug-induced myopathy is usually reversible upon discontinuation of the offending drug (statins, antimalarials).[10]

A 32-year-old female was diagnosed as SLE with lupus nephritis and treated with pulse methylprednisolone (1gm/day x 3 days) followed by oral glucocorticoids.In, addition, Mycophenolate mofetil (MMF) and HCQs were also started. Steroids were gradually tapered to 5 mg/day.

Two years later she developed autoimmune hemolytic anemia which required pulses of methylprednisolone (1 gm/day × 3 days) followed by prednisolone 1 mg/kg tapering 5 mg every week. In between she has mild flares of arthritis and skin disease requiring escalation of glucocorticoid dosages.

Following a trivial fall, she presented with acute onset localized low back pain without motor, sensory, or bladder bowel involvement. X-ray showed osteoporosis with multiple vertebral fracture. DEXA Scan revealed lumbar spine T score of 4.8. Her complete hemogram, ESR, CRP, renal function, liver function, serum calcium, phosphorus, PTH and vitamin D3 level were normal. Serum protein electrophoresis did not show any evidence of monoclonal gammopathy.

She was started on Teriparatide 20 mcg subcutaneously once daily.

OSTEOPOROSIS

Osteoporosis is characterized by reduced bone mass and microarchitecture deterioration of bone tissue that leads to an increased risk for bone fragility and fracture.[33] In SLE, osteoporotic fracture and resultant damage accrual forms a major part of musculoskeletal damage.[2,9] Approximately 40% of patients with musculoskeletal damage have osteoporotic fractures.[9] The prevalence of osteoporosis ranges from 4.0% to 48.8%.[10] In women with SLE, fracture risk is nearly 5-fold compared with healthy women of a similar age.[34] Symptomatic osteoporotic fractures occur in 6–12.5% of patients.[34] Frequent sites for fractures are the hip/femur, vertebra, rib, foot, ankle, and arm.[34]

In SLE, apart from the traditional risk factors GCs use is well known risk factor.[10] Higher daily dose as well as cumulative dose are associated with increased risk of fracture.[35] Other risk factors include chronic inflammation and active disease (low C4); serological factors (anti-Sm, anti-Ro); low androgenic state; ovarian failure; concomitant thyroid disease; metabolic factors (low vitamin D, hyper-homocystinemia); renal dysfunction and ovarian failure.[10,34]

Prevention and Treatment

Recent guidelines are available from various societies on how to manage these patients.[10, 33–36] Briefly, important elements in management include lifestyle modification like avoiding smoking, limiting alcohol intake, maintaining a normal body weight, preventing falls, and performing regular weight-bearing exercise.

GCs should be used in the lowest possible dose for the shortest period of time. Administration of calcium and vitamin D in adequate doses is must. Pharmacological agents used in treatment of osteoporosis include bisphosphonates, teriparatide and denosumab.[10,30–36]

A 28-year-old female was diagnosed with SLEand was started on low dose prednisolone, HCQs for symptoms of polyarthritis, rash and fever. During routine review, she complained of diffuse aches and pains, polyarthralgia, non-refreshing sleep. The pain increased on activities and was better at rest. She didn't have any early morning stiffness. On clinical examination there were no features of active arthritis. She had multiple tender points. All lab investigations including inflammatory markers (ESR—16 mm, CRP—1.9 mg/L) were normal. She was diagnosed as Fibromyalgia associated with SLE.

FIBROMYALGIA

All pains in SLE are not due to active arthritis or active SLE. In patients presenting with nonspecific aches/pain, absence of active arthritis, presence of tender points in an otherwise well controlled disease activity it should raise a suspicion of fibromyalgia.

Fibromyalgia (FM) is a disorder characterized by chronic, widespread musculoskeletal pain.[37] The prevalence rates of fibromyalgia in patients with SLE range from 5 to 25 %.[4,38–41] Fibromyalgia has an adverse impact on quality of life and is associated with significant disability.[42,43] Therefore, it is important that in patients with SLE, FM is identified and treated appropriately to minimize its effects on quality of life.

Treatment of FM requires both a pharmacological and a non-pharmacological approach.[37] The non-pharmacological measures include patient education and self-management, exercises and cognitive behavioral therapy.[37] The drugs include anti-depressants, particularly those with mixed reuptake inhibitors of serotonin and norepinephrine, such as duloxetine and milnacipran, and other agents useful for neuropathic pain, such as gabapentin and pregabalin.[37]

A 27 year old female had a long history of SLE of 4 years with class III lupus nephritis at onset requiring pulse methylprednisolone and prednisolone along with MMF and HCQs. After 4 years while she was on maintenance treatment with prednisolone 5 mg per day. MMF 2 g/ day and HCQs 200 mg/day she had a relapse with macrophage activation syndrome which again required high dose dexamethasone.

Now she presented with 2 months history of dull aching persistent pain over both groin which increased on walking or climbing stairs and was relieved on resting.On examination movement of both hip joints were restricted. X-ray of the pelvis was normal, while MRI showed osteonecrosis of both hip joints (Stage 2 Ficat and Arlet classification). She was referred to orthopedic surgeons and underwent core decompression of the both hip joints.

OSTEONECROSIS

Osteonecrosis (ON) is also known as aseptic vascular necrosis, or ischemic necrosis of bone. ON is caused by death of bone marrow and trabecular bone due to compromised arterial blood supply.[45] In patients with SLE undergoing joint replacement ON is the major underlying cause.[46] The prevalence of ON in SLE varies from 2.1– 44%.[10,47] Hip joints are the most commonly affected (Fig. 4.2). However, other joint areas including the knees, shoulders, wrists, and ankles can also be affected. In SLE ON can also be multifocal.[10, 48,49]

In patients with SLE, glucocorticoid (GCs) use has been consistently identified as a risk. Important risk factors with GCs use include cumulative dose, peak daily dose, mean daily dose, duration of use of high doses and use of methylprednisolone pulses.[10,45,47] The time interval between steroid use and the development of ON varies ranging from 1 to 16 months.[10] When compared to other diseases, the incidence of GCs related ON is much higher in SLE suggesting other factors intrinsic to SLE may be contributing this increased risk.[50]

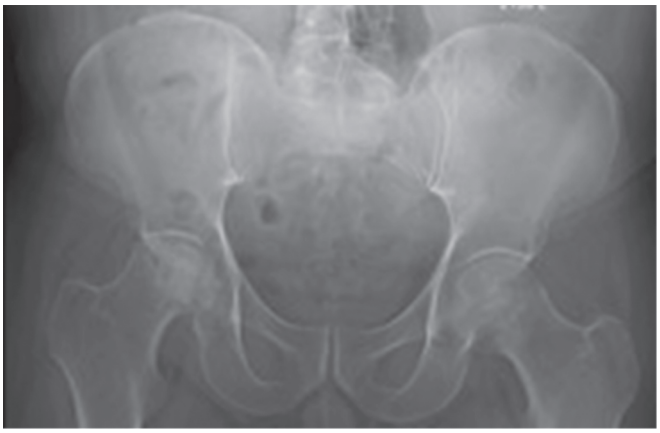

Fig. 4.2: AVN hip: Radiograph showing AVN affecting the right hip joint

These risk factors include vasculitis, Raynaud phenomenon, cytotoxic treatment, high disease activity, production of inflammatory mediators, defects in fibrinolysis, gene polymorphisms, antiphospholipid syndrome/antibody, and other hypercoagulable states.[10,45,47]

ON should be suspected in any patient with SLE who presents with persistent joint pains, especially if GCs have been used as treatment. The onset of pain is insidious and aggravated by weight bearing and ambulation.[10] Imaging studies are required to confirm the diagnosis. In early stages plain radiographs can be normal. MRI is imaging modality of choice especially in early disease[44]

Early diagnosis is crucial to the successful treatment of ON. Nonsurgical treatment of osteonecrosis includes avoiding weight bearing on the affected joint, use of analgesic medications, and physiotherapy.[44] These measures are effective only in the early stages.[10,44] They provide symptomatic relief and do not seem to alter the natural course of the disease.[10,44]

Surgical management of ON includes joint preserving procedures (core decompression, structural bone grafting, vascularized fibula grafting), osteotomy, resurfacing arthroplasty, hemiarthroplasty, and total joint replacement.[10,44] The timing and type of surgical intervention depends on the involved site and the stage of ON.[10,44,47] In the pre-collapse stage, the contour of the joint surfaces is maintained and joint-preserving procedures are indicated for these types of lesions.[10,44,47] The rationale of joint-preserving procedures is to reduce intraosseous pressure and intramedullary pressure; increase blood flow to the necrotic subchondral bone; and provide structural support to overlying subchondral bone.[44,47] For post-collapse lesions joint-preserving procedures are not indicated due to high failure rates. In such cases joint arthroplasty and other surgical procedures are indicated.[44,47]

CONCLUSION

MSK involvement in SLE is common. The involvement ranges from active disease (arthralgia/arthritis, myalgia/myositis) to conditions associated with damage (joint deformities, muscle atrophy, osteoporosis, and osteonecrosis) as a consequence of long-term disease or as a complication of treatment (GCs). MSK involvement is associated with significant morbidity, has adverse impact on quality of life and increases the risk of work loss and workplace impairment. Early recognition and adequate control of lupus disease

activity are essential in prevention of the long-term sequelae associated with these conditions. GCs are associated with damage accrual in the MSK system. There is a need for treatment regimens wherein exposure to GCs can be avoided or minimized. Fibromyalgia has an adverse impact on quality of life. Therefore it is important that in patients with SLE, FM is identified and treated appropriately to minimize its effects on quality of life.

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