Joint Involvement in SLE: the Controversy of RHUPUS

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Abstract— Systemic lupus erythematosus (SLE) is an autoimmune and inflammatory disease with multiple clinical manifestations including arthropathy. The severity of the articular involvement may range from minor arthralgias without erosions or deformity to an erosive deforming arthropathy (DA) with severe functional disability. Three different forms of joint involvement have been identified: mild deforming arthropathy, Jaccoud’s arthropathy and erosive arthropathy. In rare cases a severe, erosive and deforming arthropathy, clinically indistinguishable from rheumatoid arthritis (RA) can be observed; this clinical entity is traditionally known as “Rhupus” and describes patients with coexistence of SLE and RA. It remains controversial whether Rhupus is a distinct entity, an overlap between SLE and RA or a serious articular involvement of SLE.

Keywords — Systemic lupus erythematosus, SLE, Rhupus, lupus arthropathy.

INTRODUCTION

SYSTEMIC lupus erythematosus (SLE) is an autoimmune and chronic inflammatory disease of unknown cause, with multiple clinical manifestations, affecting the skin, joints, kidneys, lungs, nervous system, serous membranes and virtually all organs of the body. The clinical course of SLE is variable and may be characterized by periods of remission and acute relapses.[1] Joints are affected in 90% of the patients with SLE.[2] The severity of the articular involvement may range from minor arthralgias without erosions or deformity to an erosive deforming arthropathy with severe functional disability.[3] Generally, arthritis in SLE is transitory, migratory, reversible and very often short in duration, lasting 24 to 48 hours.[4,5] Most patients with SLE have intermittent non erosive asymmetric polyarthritis, characterized by soft tissue swelling and tenderness in joints, most commonly in the hands (metacarpophalangeal (MCP) and proximal interphalangeal (PIP)), wrists and knees.[6] Occasionally, lupus arthritis takes a more chronic course with deforming arthritis affecting principally the hands and feet, which in extreme cases may resemble those of rheumatoid arthritis (RA). [7]

HISTORY OF JOINT INVOLVEMENT IN SLE

Articular involvement in SLE has been long recognized and regarded as a minor clinical manifestation of the disease. In 1872, Kaposi identified arthritis as a manifestation of SLE and suggested that articular disease might portend more serious manifestations of lupus. However, most authors of that time (late nineteenth century and early twentieth century) ignored articular involvement in SLE. In fact, mention of articular involvement in lupus remained confined to arthritis in a few articles until 1932, without a clear distinction between arthralgias and arthritis. Tremaine was the first to provide a histopathological study of the synovial membrane in lupus, describing articular and periarticular inflammatory synovial villous hypertrophy and the “swan-neck fingers”. [8]

In 1936, Friedberg et al. published the first description of deforming arthritis in lupus. [9] In 1937, Keil in New York reported that most patients with lupus have arthralgias and remarked on the difficulty of distinguishing it from RA. [10] The first review and analysis of the articular manifestations in lupus was by Slocumb at the Mayo Clinic in 1940 but an erosive arthropathy as a manifestation of lupus was not recognized until it was described by Armas-Cruz et al. in 1958. [11]

LUPUS ARTHROPATHY

Involvement of the joints in SLE (lupus arthropathy) is one of the earliest and most common manifestations of this multisystemic disease, which affects 60-90% of patients during their clinical history [12] and constitutes one of the original 11 American College of Rheumatology (ACR) criteria and one of the 17 Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of the disease. [13] The arthropathy of SLE has considerable clinical variability. It is usually asymmetric, migratory, with morning stiffness of short duration, involving more commonly proximal interphalangeal (PIP) joints compared to metacarpophalangeal (MCP) joints, wrist and knee joints and has variable expressions with different severity, from arthralgia or transient arthritis to a severe deforming arthritis. [14] Arthritis generally appears early during the disease course without

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significant functional consequences, but it can have rarely a significant impact on the quality of life.[11] In 1998, Vugt et al conducted a study on 176 SLE patients to clarify the various forms of joint involvement. These patients were evaluated according to a standard protocol that covered all known characteristics of arthropathy and by means of the “Jaccoud’s arthropathy index” (Fig 1), three different forms were identified.[4] In particular, on the basis of the obtained score, distinction was made between an erosive and non-erosive arthropathy (Fig 2). The patients of the non-erosive group were then classified as having mild deformity arthropathy or Jaccoud’s arthropathy.

Non erosive arthropathy:

Non-erosive arthropathy is the most frequent form of lupus joint disease and it is characterized by chronic non erosive deformities, which have been described in up to 35% of SLE patients.[7] Usually this form of arthropathy mostly occurs in patients who had been receiving corticosteroids, those who have anti-Ro and/or anti-La antibodies or longstanding disease.[3] Non erosive arthropathy can be divided into two forms: Jaccoud’s arthritis and mild deforming arthropathy.

JACCoud’s ARTHropathy (JA)

Jaccoud's arthropathy (JA) form of arthropathy present in 10-35% of patients with SLE which is characterized by reducible and non erosive articular deformities (Fig.3, 4). Deformities in JA seem to be due to lax joint capsules, tendons and ligaments that cause joint instability [15] in combination with the compressive forces of the muscles acting across the hand rather than the destructive effect of synovitis. Ligaments laxity results from capsular periarticular fibrosis or synovial vasculitis. Spronk et al. hypothesized that patients with SLE and JA may have a persisting inflammatory reaction of the synovium with infiltration of inflammatory cells, resulting in the production of cytokines, such as interleukin 1 (IL-1) and IL-6.[16] Based on the histological findings, such as mild but typical fibrous synovitis with little or no round cell infiltration and microvascular changes, Bywaters et al. proposed a prolonged or recurrent low grade inflammatory activity in both the synovial membrane and the capsule as the underlying mechanism.[17] This can be reflected by the fact that SLE patients with JA have high serum levels of C-reactive protein. Furthermore, another local inducer of the inflammatory reaction in JA seems to be the high occurrence of IgM Rheumatoid Factor (RF) in patients with JA.[18] Often, there is the coexistence of Jaccoud’s and the antiphospholipid syndrome, although we cannot explain the pathogenetic link.[19] It is possible that a small vessel vasculopathy plays a part in the genesis of the periarticular fibrosis.[20] Although it can affect all the joints, the hands and feet are mostly affected. Deformities of the hands (“lupus hands”) include ulnar deviation and at a later stage swan-neck deformities, and “zed” deformity of the thumb. Deformities of the feet (“lupus feet”) include hallux valgus, hammer toes and/or subluxation of metatarsophalangeal joints.[2] Studies of hand radiographs in JA show only mild signs of bony pathology, without evidence of erosions, while luxations and deformities are dominant, while magnetic resonance imaging (MRI) detects capsular swelling edematous and proliferative tenosynovitis, which verifies the findings that deformities in JA are the result of inflammation leading to pericapsular and tendon fibrosis.
MILD DEFORMING ARTHROPATHY

Mild deforming arthropathy is a form of arthropathy which is characterized by functional impairment of hands, finger synovitis, swan-neck deformity and ulnar deviation of 1–4 fingers and in a minority of cases, hypermobility of hands and pain at pressure. Patients with this arthopathy do not seem to differ in any respect from SLE patients without arthropathy.[1]

Erosive arthropathy:

Erosive arthropathy in SLE is unusual and may be present in about 5% of patients.[21] This form of arthropathy was analyzed in a study of Alarcon-Segovia et al which examined the arthropathy of the hand in 858 patients with lupus, describing 41 patients with deforming arthropathy and another 6 patients with arthritis. The characteristics of the deforming arthropathy in these patients with lupus were: collapse of the carpal joints without erosions, rarely erosion of the ulnar styloid apophysis, Z deformity of the thumb, non-erosive cubital deviation with subluxation of the MCP joints, hook- or sickle-shaped erosions of the metacarpophalangeal (MCP) joints, asymmetrical articular erosions and swan-neck deformities of the fingers.[22] In rare cases (up to 1-3%) a severe, erosive and deforming arthropathy, clinically indistinguishable from RA can be observed; this clinical entity is traditionally known as “rhupus” to describe patients with coexistence of SLE and RA.[12] (Fig.5)

RHPUS

Rhupus can be defined as a symmetric deforming polyarthritis of the small and large joints which is erosive on radiography and accompanied by clinical signs and symptoms of SLE and by the presence of specific autoantibodies with high specificity (anti-dsDNA antibody or anti-Sm for SLE and anti-Ra33 or anti-citrullinated peptides antibodies-ACPA for RA).[23] It is also characterized by certain HLA phenotypes (HLA-DR1, DR2).[24]

The first reports of the coexistence of SLE and RA were made in 1963 by Toone [25], who described the presence of LE cells in the serum of 15 patients with RA. Until then, LE cells had been considered to be an exclusive finding in SLE. Panush first used the term “rhupus syndrome” in 1988 to describe patients with overlapping signs and symptoms of RA and SLE.[26] In 1971, Schur coined the term “Rhupus” to describe patients satisfying the criteria for both SLE and RA without establishing whether this coexistence was a distinct clinical and perhaps immunological entity or only the coincident presence of both conditions in the same patient.[11]

In the following years, lines of thought are divided in two because it remained controversial whether rhupus was a distinct entity, an overlap between SLE and RA or a serious articular involvement of SLE. Indeed, some authors, like Fernandez et al [11], supported the idea that “Rhupus” arthropathy was another variant of arthropathy of systemic lupus erythematosus rather than
a separate disease entity. However, other authors, like Amezcua Gyerra et al. [23], support the possibility that Rhupus is an overlap between RA and SLE, because highly specific autoantibodies for RA (ACPA antibodies) and for SLE (anti-dsDNA and anti-Sm antibodies) are detected in coexistence, while other authors, like Iglesias-Gamarra, have proposed that Rhupus is a subset of lupus arthropathy.[27] Some authors, instead, simply provided a description of erosive arthropathy, like Hoffman and colleagues who described three patients with erosive arthritis, included in a cohort of 235 patients with SLE, were positive for ACPA antibodies. These authors suggest that the presence of ACPA antibodies can predispose to a chronic RA-like arthritis in patients with SLE.[28] Additionally, Weissman and colleagues demonstrated that patients with SLE can display radiographic abnormalities similar to those of RA, although the presence of marginal erosions is a rare finding.[27] In Rhupus, the erosions are a result of destructive synovitis associated with RA.[24] Moreover, the irregularity of bone is thought to be attributable to friction rub caused by overlying inflamed tendons or capsule. This may explain the high prevalence of erosive damage to the extensor carpi ulnaris tendon.

Epidemiology

The prevalence of Rhupus varies from 0.01% to 2% in the literature; this variation is likely due to the different classification and patient selection criteria. Different studies indicate that patients with “Rhupus” usually present with a condition and then develop the other over a period of years ranging from 4.6 to 9.2 years.[29] In 2009, Icen and colleagues explored the frequency of SLE in a cohort of 603 patients with RA followed for 25 years. They showed that only 9 of 603 patients had a clinical diagnosis of SLE (1.5%), while 93 patients (15.5%) had at least 4 criteria for the diagnosis of SLE.[30]

Clinical aspects

Rhupus patients have a very particular clinical behavior. Simon et al. [24] demonstrated that patients with Rhupus showed a disease onset characteristic for RA, but on average 4 years later they presented signs and symptoms including laboratory abnormalities, that allowed the diagnosis of SLE. Predominant RA symptoms are erosive arthropathy and rheumatoid nodules, while manifestations of SLE are generally minor, such as photosensitivity, skin disease and haematological abnormalities.[29] However, Fernandez et al. have also observed classic manifestations of shrinking lung syndrome, lupoid sclerosis, vasculitis and glomerulonephritis.[31]

Pathogenesis

The pathogenesis of erosive arthropathy in SLE patients has not been yet elucidated. Mawson postulated that RA and SLE are diseases with an inverse pathophysiological relationship, with a different HLA polymorphism, a different response to hormonal stimuli and with T-helper 1 effect in RA instead of Helper 2 effect in SLE.[32]

Although the pathogenesis is not yet known, it seems to be clear that autoantibodies play a key role in the pathogenesis of Rhupus, as well as in SLE. In particular, SLE is a complex autoimmune disease characterized by the production of specific autoantibodies linked to distinct clinical manifestations. For example, anti-dsDNA antibodies are associated with lupus glomerulonephritis, anticardiolipin antibodies are related to venous thrombosis and anti-Ro/SSA antibodies are associated with subacute cutaneous lupus, neonatal lupus and congenital heart block.[33] However, no antibodies were found to be related to SLE arthritis until ACPA antibodies appeared. Some studies have suggested an association between ACPA antibodies and this pattern of erosive arthritis, but their exact significance in SLE patients remains unclear.

Mediwake et al. first suggested in 2001 that ACPA could be a useful marker to distinguish SLE patients with erosive disease, as these antibodies were prevalent (20%) in this type of arthritis and very rare in other forms (0-2%).[34]

ACPA as serological marker for RA are fully recognized as a diagnostic and prognostic marker with a high sensitivity and specificity for RA [35], but up to 10%-15% of patients with SLE are also positive.[36] In 2009, Kakumanu Prasanthi et al demonstrated that while ACPA in RA is citrulline-dependent, ACPA in some other diseases is citrulline-independent and reacts with both CCP and the unmodified (arginine-containing) cyclic arginine peptide (CAP). Citrulline dependence or high levels (> 10 IU/ml –nv: 0-5 IU/ml) of ACPA were common in SLE patients with deforming/erosive arthritis, while most ACPA in SLE patients was citrulline independent.[36] This may be useful in identifying a subset of SLE patients with high risk for development of deforming/erosive arthritis. At last, they showed this subset of SLE patients with deforming arthritis appeared to have high levels of ACPA and high ACPA/anti-CAP ratios, consistent with their citrulline dependence, and similar to RA; thus it has been proposed the definition of “SLE-RA overlap”. In these patients there is often the positivity of Rheumatoid Factor (RF) which has been shown to act as a protective element in renal damage, explaining partially for the low prevalence of lupus nephritis observed in Rhupus patients.[31] In 1998, Cohen et al. [21] concluded that the presence of anti-RA33 and RF could be a marker of erosive articular disease in patients with SLE and then, in 2006, Wright et al [37] stated that SLE patients with erosive arthropathy presented high titers of anti-Ra33 antibody, which recognizes a 33 KDa nuclear antigen, present in the 40S hnRNP complex and is indistinguishable from the A2 hnRNP core protein. Anti-RA33 antibodies were initially considered as a good specific marker for RA [35], until they were found to be present in patients with SLE. Moreover, anti-RA33 antibodies were suggested to be associated with erosive disease in SLE patients, mainly in non-white women.[38]
Some studies have also suggested that an increase in RF and CRP could be an additional instrument to identify patients at risk of the poorest prognosis[39] as high levels of ESR and CRP have been demonstrated to be a clinical hallmark of rhupus patients with respect to the entire SLE patients.[38]

**Radiological findings**

In the case of Rhupus, hand conventional radiography reveals an erosive form of deforming arthropathy such as that seen in RA with localization of erosions primarily in the second and third MCP joints, but without signs of carpal collapse. Radiologically, plain radiograph may discover scart, asymmetric joint erosions, non-erosive carpal collapse in patients with SLE, while patients with RA are much more likely to have pseudocysts, erosions, joint space narrowing and para-MCP hook formation. Both RA and SLE may present juxtaarticular osteopenia.[1] Hand joint erosions may be not noted on plain radiographs in Rhupus patients, therefore more sensitive methods such as magnetic resonance imaging (MRI) and ultrasonography (US) with power Doppler (PD) have now entered into common clinical practice to distinguish different types of lupus arthritis/Jaccoud’s arthropathy/rhupus.[3] In particular, a recent study showed that these new imaging techniques underlined an unexpected high prevalence of subclinical lupus joint involvement.[40] In fact, Mosca et al evaluated the prevalence and characteristics of joint involvement in 102 consecutive SLE patients, showing physicians’s tendency to underestimate the severity of joint involvement. They proved also that US assessment demonstrates a high prevalence of joint and tendon involvement also in patients without clinical signs and MRI showed a high prevalence of damage, suggesting that joint involvement in SLE is more severe than expected.

**Therapy**

The aim of any treatment of arthritis and arthralgia is to decrease inflammation and pain and to improve the quality of life in SLE patients. Intermittent nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for the episodic and limited lupus arthropathy.[41] Trials of NSAIDs in SLE are very limited and there are not recommendations in favour of one specific NSAID in SLE. If NSAIDs are insufficient, the treatment of articular involvement is based on the use of antimalarial drugs (hydroxychloroquine or chloroquine) which improve joint symptoms and prevent disease flares.[42] Low doses of glucocorticoids (prednisone <0.25 mg/kg/day) may be required to treat the arthritis resistant to NSAIDs and antimalarial drugs, together with infiltrations of corticosteroids.[43] Immunosuppressive therapy or disease-modifying antirheumatic drugs (DMARDs) is often added for refractory arthritis or steroid-sparing effects.[44] Methotrexate, a folate antagonist, has both immunosuppressive and anti-inflammatory effects [45], which was associated, at the dosage of 15-20 mg weekly, with a significant reduction in disease activity and in dose of glucocorticoids used in SLE patients with predominantly mucocutaneous or arthritis features.[46] Leflunomide may be used as an alternative in patients that are intolerant to methotrexate.[47] Azathioprine has been shown to decrease the activity of nonrenal manifestations, including arthritis in SLE and may be used in patients with persistent arthritis unresponsive to methotrexate or leflunomide after three to six months of therapy.[48] Finally, if the antiinflammatory or immunosuppressive therapy is not sufficient to obtain a good control of joint disease, biotechnological drugs could be used. The anti-TNF treatments may induce autoantibodies and may cause rare cases of drug-induced lupus, thus their use is rare and only in cases of Rhupus with symptoms resistant to the classical treatments.[44] Rituximab an anti-CD20 blocking antibody has proven to be effective in the control of patients with Rhupus.[49,50] Abatacept, a fully human, soluble fusion protein which selectively modulates costimulatory signals and interactions between activated T cells and antigen presenting cells (APCs), has proven effective not only in inducing remission of arthritis but also in reducing the production of autoantibodies in SLE.[51] Belimumab, a human immunoglobulin monoclonal antibody that binds and inhibits soluble human B lymphocyte stimulator (BLys), appears to be effective in achieving remission in cutaneous and articular involvement and to reduce the production of autoantibody.[52]

**CONCLUSIONS**

Currently, Rhupus remains an entity not perfectly known, but the pathogenesis, the autoantibody positivity, the radiological manifestations and therapy all support the idea that it is really an overlap syndrome between SLE and RA, although its pathogenesis still remains to be fully understood.

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