The Categorization of Pain in Systemic Lupus Erythematosus

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KEYWORDS

• Systemic lupus erythematosus • Autoimmunity • Pain • Arthritis • Fibromyalgia • Quality of life • Depression • Immunosuppression

KEY POINTS

- Lupus is a systemic autoimmune disease characterized by multiple sources of pain.
- Arthritis is the most common form of musculoskeletal pain in lupus.
- Symptoms in lupus can be divided into 2 categories called type 1 and type 2.
- Type 1 and type 2 symptoms can differ in response to immunosuppressive agents.
- Fibromyalgia can cause widespread pain in lupus.

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by immunologic disturbances and diverse symptoms that vary in pattern and severity among patients.[1,2] These disturbances are highly interconnected and underlie many of the clinical and laboratory findings of SLE, including the prominent expression of antinuclear antibodies.[3] In view of the unequivocal evidence of immune cell disturbance in SLE, investigators have tended to view disease pathogenesis as well as disease manifestations primarily in terms of immunology. Because current technologies are providing a more detailed picture of cellular abnormalities than ever before possible, investigative interest in this area has surged.[4]

Although characterizing immune abnormalities is eminently appropriate for an autoimmune disease, such a focus may not adequately incorporate the patient perspective and the wide range of symptoms of SLE that can impact quality of life. SLE is a disease of tissue inflammation and injury. It is also a very painful disease in which pain can dominate the lived experience of the patient.[5] Furthermore, pain in SLE can occur in

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the context of other symptoms such as fatigue, which can impair quality of life beyond the consequences of inflammatory injury of the tissues.[6–9]

For the patient, pain is often the symptom that brings them to the physician, with pain relief the proximate goal of therapy. For the physician or other provider evaluating such a patient, the challenge is to understand the origin of the pain, assess its relationship to inflammation, and develop a treatment plan to decrease its impact. In the treatment of SLE, pain management is a particular challenge because the relationship of pain to inflammation is often obscure, with immunomodulatory therapy frequently unsuccessful. As a result, patients may experience inadequate symptom relief, leading to dissatisfaction with the medical encounter. Discordancy between patients and providers in the assessment of the basis of symptoms can, unfortunately, complicate communication and prevent the establishment of an effective therapeutic relationship.[10–12]

In our unit, we have been exploring a new approach to the management of pain in SLE that we hope will improve overall patient care. This approach is based on the division of signs and symptoms of SLE into 2 broad categories that are termed type 1 and type 2; in view of their temporal variation, both types can be assessed at the time of each medical visit.[13,14] Type 1 manifestations are the classic signs and symptoms of SLE that are, in general, immunologically mediated. These manifestations include nephritis, inflammatory arthritis, rash and serositis. Type 2 manifestations include pain (especially fibromyalgia), fatigue, depression, sleep disturbance, and perceived cognitive dysfunction.

In this article, we review the manifestations of SLE that are painful and then discuss in greater detail the application of the type 1 and type 2 categorization to patient care. As this discussion proceeds, it is important to note that we consider both type 1 and type 2 symptoms as manifestations of the underlying disease pathogenesis in SLE, even if the link between certain symptoms and immune cell abnormalities may be obscure at the present time.

MUSCULOSKELETAL PAIN

Table 1 lists the cause of pain attributable to the musculoskeletal system. These manifestations encompass both inflammation and damage as well as symptoms that would be categorized as type 2 symptoms.

Arthritis

The importance of arthritis as a manifestation of SLE has grown, especially in the setting of clinical trials for new agents to treat this disease. In the development path, the usual first step is the assessment of the ensemble of manifestations known

Table 1
Sources of musculoskeletal pain

Condition	Mechanism
Arthritis	Activity
Myositis	Activity
Avascular necrosis	Damage
Fracture	Damage
Osteoarthritis	?
Fibromyalgia	Type 2

as nonrenal SLE, which primarily involve musculoskeletal and mucocutaneous manifestations.[15] Unlike nephritis, which has been extensively investigated in animal models of disease and has a well-validated disease mechanism (ie, immune complex deposition), arthritis and related musculoskeletal manifestations have lacked a clear model or experimental framework to elucidate mechanisms.

According to classical concepts of arthritis in SLE, patients can display 3 distinct patterns of joint involvement: (1) a symmetric polyarthritis involving primarily the small joints, with prominent involvement of the fingers and wrists, (2) a nonerosive deforming arthritis, termed Jaccoud's arthropathy, characterized by reducible ulnar deviation and swan neck deformities owing to ligamentous and joint capsule laxity, and (3) an overlap between SLE and rheumatoid arthritis (RA) that is characterized by serologic disturbances similar to those of RA (ie, anti–cyclic citrullinated peptide and rheumatoid factor).[16,17] This overlap condition has sometimes been called "rhupus." **Box 1** presents definitions of joint involvement in SLE used to measure for assessing classification or disease activity.[18–20]

According to the older literature, the small joint form of arthritis is marked by pain out of proportion to the findings on physical examination and, although joint tenderness can be elicited, swelling has been considered to be mild. Because plain radiographs do not show evidence of erosion, patient reports of pain and tenderness have represented the most substantial evidence of synovitis.

More recent studies are redefining the nature of arthritis in SLE, positing greater similarity to RA than historically thought. One possibility for the changing perspective relates to changes in the nature of synovitis in RA, which is the prime example of an inflammatory arthritis with which others are compared. As many clinicians can attest, RA now seems to be a less severe condition than before; this situation perhaps reflects earlier recognition and treatment with more effective disease-modifying antirheumatic drugs.[21] In RA at present, synovitis seems to be less prominent and both erosion and deformity are markedly attenuated. In the care of patients with RA, clinicians have adapted to a picture of a much less severe disease, interpreting lesser degrees of synovitis as, nevertheless, clinically significant.

Now that clinicians are accustomed to assessing more limited joint findings as evidence of active RA, they are perhaps paying more attention to synovitis in SLE. As such, the same metrics used to assess disease activity in RA (eg, DAS28) are being applied to SLE.[22–24] Indeed, studies have demonstrated that, in SLE, both joint tenderness and swelling can involve numerous joints in seeming contradiction to previous ideas that arthritis in SLE is characterized by tenderness out of proportion to swelling.

Along with a change in the findings noted on the physical examination, new approaches to imaging have documented more objective findings of lupus arthritis.[25–28]

Box 1
Definitions of Arthritis or Joint Involvement in SLE

Systemic Lupus International Collaborating Clinics Criteria for Disease Classification
Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness of 2 more joints and 30 minutes of morning stiffness

2019 American College of Rheumatology–European League Against Rheumatism Criteria for Disease Classification
EITHER (1) synovitis involving 2 or more joints characterized by swelling or effusion OR (2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Systemic Lupus Erythematosus Disease Activity Index
More than 2 joints with pain and signs of inflammation (ie, tenderness, swelling, or effusion)

Ultrasound imaging of joints in patients with SLE can demonstrate synovitis, with most studies concentrating on the fingers and wrists. In addition, ultrasound examination can show a prominent tenosynovitis, a finding that may be relevant to the development of deformity.

Even though SLE arthritis has been considered nonerosive (with the exception of the rhupus overlap), imaging by both ultrasound examination and MRI can show bone marrow changes. Changes of this kind are common in studies of RA and are thought to represent an early stage in the erosive process; nevertheless, it is possible that these changes indicate inflammation or edema in the bone marrow, which may not progress to actual cortical breaks demonstrable on plain films.

The advances in imaging raise important questions concerning the best approach to assessing pain in arthritis in the clinical setting and developing a treatment strategy analogous to treat-to-target strategies in RA.[29] Whereas in RA the goal of treatment is to decrease pain and retard erosion and deformity, the goal in SLE is primarily to decrease pain because erosion seems uncommon or at least different in kind from that in RA. In view of recent studies showing that measures such as the DAS28 are applicable to RA, it seems to be reasonable to base treatment decisions on a tender and swollen joint count, although symptoms and imaging may not be directly related. In SLE, the effects of certain cytokines may decrease levels of C-reactive protein, however, making it less reliable as a measure of inflammation.[30]

Once a framework for assessing inflammatory arthritis in SLE is established in the routine care setting, then the usual agents to treat this condition include hydroxychloroquine, methotrexate, nonsteroidal anti-inflammatory drugs, and glucocorticoids. Because a drug like belimumab is approved for nonrenal manifestations of active, autoantibody-positive SLE, it is often used for the treatment of arthritis because studies have indicated an effect on musculoskeletal manifestations as a part of conventional measures of disease activity.[31]

Myositis

Whereas myalgia is not an uncommon source of pain in SLE, some patients develop signs and symptoms of an inflammatory myopathy.[32,33] In these patients, muscle pain and tenderness can accompany weakness. The frequency of myositis in SLE varies widely depending on the case definition and, for example, the requirement for elevation of creatinine phosphokinase for diagnosis. One study suggested that myositis in SLE is marked by elevation of levels of aldolase rather than creatinine phosphokinase.[32] An evaluation for myositis would depend on findings of weakness, although this assessment can be complicated by the presence of a steroid myopathy or deconditioning.

Avascular Necrosis

In contrast with inflammatory arthritis, which is a sign of disease activity, avascular necrosis (AVN) is a sign of damage and a source of intense pain.[34–36] This condition can affect multiple joints, although large joints such as the knees and the hips are the most common. The etiology of AVN in SLE seems to be complex, with contributions from underlying immunologic and hematologic disturbances as well as the effects of glucocorticoids. Whatever the exact interplay of these disturbances are, AVN results from ischemia to bone with subsequent death and collapse.

Clotting disturbances, including the antiphospholipid antibody syndrome, are among the potential factors contributing to the development of AVN in SLE, but are difficult to assess because of the concurrent use of glucocorticoids.

Among its many actions that lead to damage in SLE, glucocorticoids are clearly associated with the development of AVN. Given the diverse manner in which glucocorticoids are prescribed in SLE, determining the relationship of dose to the development of AVN is difficult. Thus, it is not clear whether the major determinant of AVN is total glucocorticoid dose, average glucocorticoid dose, or highest glucocorticoid dose.

In general, the diagnosis of AVN is made on the basis of symptoms of pain, with plain films demonstrating various stages of radiographic progression. MRI is also a useful modality in evaluating pain in patients suspected of AVN; furthermore, it can show changes in regions that may not be symptomatic. As in the case of AVN in patients with other conditions, therapy includes surgery with core decompression and bone grafting as well as total joint replacement.[37] AVN is one of the most frequent reasons for total joint replacement for patients and is one setting when more pain relief can be achieved decisively.

Fracture

Osteoporotic fracture is another source of musculoskeletal pain in SLE that seems to be complex in etiology.[38–40] The most common locations are the hips, vertebrae and humerus. Although glucocorticoid-induced osteoporosis is a main etiology, other factors can lead to bone loss. These factors include vitamin D deficiency from sun avoidance, immobility, lack of weight-bearing exercise, lupus nephritis, disease duration, prior history of fracture, and generalized disease activity. Bone loss is a feature of a proinflammatory state, with agents that can decrease inflammation potentially able to retard bone loss. Glucocorticoids, however, have their own direct effects on bone, leading to glucocorticoid-induced osteoporosis.

As in the case of AVN, the occurrence of fracture provides a strong impetus to limit glucocorticoid use by substitution of other agents without this complication. The prevention of glucocorticoid-induced osteoporosis by antiresorptive therapy can be an important strategy to decrease fracture risk. In SLE, however, the use of agents such as bisphosphonates must take into account patient age and child-bearing potential because bisphosphonates are in pregnancy class C.

Osteoarthritis

With better therapy for SLE, the overall outcomes of patients with SLE have improved. Patients are living longer and, not surprisingly, osteoarthritis can occur, providing another source of pain in those patients with longstanding disease.[41] Although precise data on the frequency of osteoarthritis are difficult to obtain, the frequency of total joint replacement in patients with SLE allows inference on the development of this condition.[37] Unlike other musculoskeletal manifestations of SLE, osteoarthritis is difficult to categorize as either activity or damage.

Fibromyalgia

Of the various sources of musculoskeletal pain in SLE, fibromyalgia is among the most common.[42,43] Fibromyalgia is a chronic, painful condition in which disturbances in neuropsychological function and sensitization lead to pain amplification.[44–46] Widespread body pain is the hallmark, with tender points providing support for a role of pain amplification. Rather than calling fibromyalgia a disease or state, “fibromyalgianess” can be conceptualized as a trait that can also condition the perception of other painful conditions.

Despite causing significant distress, fibromyalgia does not fit well as either activity or damage; as such, fibromyalgia, along with other symptoms, may not receive the same efforts at treatment and prevention as those disease manifestations that are

more clearly immunologically mediated. As many studies show, fibromyalgia is frequent in SLE and, although the assessment of fibromyalgia can be difficult, the occurrence of this condition in SLE is far greater than the general population.[42,43] The coexistence of fibromyalgia and arthritis occurs with other inflammatory diseases, such as spondyloarthritis, raising the possibility that it may be a consequence of localized pain, inflammation, or stress.[47]

In the context of other sources of musculoskeletal pain, awareness of fibromyalgia is important because it can allow for an interpretation of the findings of tenderness in the absence of swelling or high pain reports in patients with peripheral arthritis whose joint examination shows little or no evidence of synovitis.

NEUROPSYCHOLOGICAL SOURCES OF PAIN

Headache

Among the sources of pain in SLE, headache is notable because it is a criterion for disease activity in the Systemic Lupus Erythematosus Disease Activity Index.[18] Despite this standing, the nature of headache in SLE is unclear.[48–51] Furthermore, it is unclear whether the frequency of headache in SLE is any greater than the general population, recognizing that the frequency of headache in the population depends on age and sex. One of the reasons for uncertainty about headache as a manifestation of SLE relates to the definition of headache by various organizations. For example, in the Systemic Lupus Erythematosus Disease Activity Index, lupus headache is defined as "severe persistent headache, may be migrainous, but must be nonresponsive to narcotic analgesia." In contrast, the International Headache Society provides a different categorization of headaches, in general, denoting tension headache as well as migraine headache with or without aura as common forms of headache in the population. Using the International Headache Society criteria, most headaches in SLE can be readily characterized in the usual symptom categories. Although such considerations do not exclude the existence of a distinct headache associated with disease activity, it seems reasonable to manage headache according to the usual approach for the general population.

Small Fiber Neuropathy

As a systemic disease, SLE has protean manifestations that occur with widely varying frequency. Although not included in the 19 neuropsychiatric syndromes as defined by the American College of Rheumatology,[52] small fiber neuropathy can lead to diffuse pain, burning, tingling, numbness, and changes in thermal sensation. Diagnosis is confirmed by skin biopsy, demonstrating a decreased intraepidermal nerve fiber density.[53,54] Treatment involves the usual medications for neuropathic pain; there are data supporting the use of intravenous IgG.[55]

SEROSITIS

Pericarditis and pleuritis can both present with sudden and severe pain along with signs of inflammation and demonstration of effusions by either chest radiographs or ultrasound examination.[56,57] In contrast with other sources of pain that have been discussed, serositis represents an acute situation that demands prompt diagnosis and treatment, including the exclusion of infection. Depending on the severity of these conditions, therapy may involve nonsteroidal anti-inflammatory drugs, colchicine, or glucocorticoids.

For some patients with SLE, chest pain may occur in the absence of other evidence of pleuritis or pericarditis. These patients are often treated with anti-inflammatory

agents, even if the evidence for inflammation is scant. In this setting, there is concern about overtreatment with glucocorticoids.

Peritonitis can also present a diagnostic challenge, because abdominal pain can signal a wide variety of serious visceral ailments, including emergent problems such as a perforation or bowel infarction. Therefore, the diagnostic workup must be detailed, with concern for conditions that need surgical attention.

OTHER CONDITIONS

Patients with SLE can develop other sources of pain that may arise from immunologic disturbances (eg, vasculitis leading to infarction), the effects of drugs (eg, pancreatitis or esophagitis from glucocorticoids or nonsteroidal anti-inflammatory drugs), or coincidence. Not everything that occurs in patients with SLE need be attributed to that disease. For the more acute painful conditions, the workup has to be sufficient to exclude problems that would demand therapies other than anti-inflammatory or immunosuppressive agents.

SYMPTOM CATEGORIZATION

The Type 1–Type 2 Paradigm

According to current thinking about SLE pathogenesis, clinical manifestations can, in general, be divided into 2 broad categories: activity and damage.[18,58–60] This categorization suffices for manifestations such as nephritis, where biopsies can show signs of inflammation (activity) or scarring and fibrosis (damage). Among the main complaints of patients with SLE are a series of symptoms that can be difficult to bin into these 2 categories. These symptoms include fatigue, pain, depression, sleep disturbance, and perceived cognitive dysfunction. The origin of these symptoms is often obscure and seemingly lacks a relationship to conventional measures of disease activity. It is perhaps surprising that one of the main complaints of patients (ie, fatigue) does not signify disease activity; it also does not signify damage.

Our clinic has proposed a different scheme for symptom categorization in SLE that does not rely on the simple dichotomy of activity and damage. Rather, we have proposed that symptoms of SLE activity can be divided into 2 main categories or bins that are simply called type 1 and type 2 symptoms. As noted elsewhere in this article, type 1 symptoms are the classical signs and symptoms of SLE that can be clearly ascribed to inflammation and autoreactivity. Nephritis is at the top of the list. There are excellent biomarkers for nephritis in terms of renal function, tissue pathology, and serology. Rash is another example of type 1 manifestation where an immune mechanism can be established. Importantly, some type 1 manifestations are asymptomatic and patients may be unaware of serious renal disease.

In contrast with the type 1 manifestations, type 2 manifestations are all symptomatic, with the magnitude, persistence, and pervasiveness of these symptoms often dominating the patient experience of this illness. For type 2 symptoms, it can be difficult to establish a link between the symptoms, on the one hand, and inflammation and autoreactivity, on the other hand. Furthermore, by their nature, some of these symptoms can be multifactorial in origin. For example, depression can result from the burden of chronic illness, unrelenting pain, loss of employment and, disability.

Although type 2 symptoms may not show obvious links to inflammation, they may, nevertheless, result from immune activity. Thus, cytokines can act as mediators in the central and peripheral nervous system and there is substantial evidence that proinflammatory cytokines contribute to symptoms of pain, fatigue, and depression. Clinical trials have shown efficacy of tumor necrosis factor-α blockers in ordinary depression although

the benefits may be greatest in those with elevation of C-reactive protein.[61] Similarly, tumor necrosis factor-α blockers have ameliorated depression in patients with psoriasis.[62]

As a group, pain, fatigue, depression, and cognitive dysfunction often track together, especially in patients with chronic inflammatory disease. In this setting, the array of symptoms is analogous to so-called sickness behavior that describes the symptoms that accompany acute inflammatory and infectious illnesses.[63] These symptoms are part of an overall host response that can influence energy metabolism to shift nutrients to fuel an immune response to overcome infection. The infected (or inflamed) person becomes tired and sedentary, showing weakness, lassitude, and pain to deter more strenuous activities that would be energetically demanding. Although this program may have evolved for acute host defense and be physiologic or protective in the acute setting, it can be replayed in the setting of a chronic inflammatory disease and become pathologic.[64,65]

The division of symptoms into type 1 and type 2 categories does not mean that type 2 symptoms are totally or substantially independent of inflammatory mediators. Rather, the division signifies that the 2 types of symptoms can occur independently, with type 2 symptoms often dissociated from flares of SLE and increases in measures of disease. Importantly, the division indicates that therapies necessary to decrease type 1 and type 2 symptoms may be different and that immunosuppressive agents for type 1 symptoms may not attenuate type 2 symptoms. As manifestations of SLE, type 2 symptoms demand their own therapies as part of a more comprehensive treatment program, even if these therapies are seemingly unrelated to the immune system. In contrast, data from clinical trials indicate an effect of belimumab on fatigue.[66] Importantly, patients can have both type 1 and type 2 manifestations in varying extents (**Fig. 1**).

The Rationale of the Type 1–Type 2 System for the Management of Pain

The type 1–type 2 categorization is a theoretic construct whose goal is to elucidate better the origin of symptoms, including pain, in patients with SLE, to enhance patient–provider communication, and to improve patient quality of life by addressing the full gamut of patient symptoms. In this construct, the totality of symptoms that the patient reports constitute their "lupus" because that is how patients understand their disease. Unlike investigators or practitioners, patients do not engage in attribution because they want relief from the full range of symptoms.

As shown by many studies, there is frequent discordance between patients and providers in the assessment of disease activity or severity, contributing to problems in communication and patient dissatisfaction.[10–12] We believe that this discordance relates in part to the relative weight that patients and providers place on different disease manifestations. Whereas providers may focus on type 1 manifestations to form an assessment of disease activity, patients may focus on type 2 manifestations because these manifestations, by their nature, are very symptomatic. In terms of pain, the provider may perform a joint examination and find minimal tenderness, concluding that

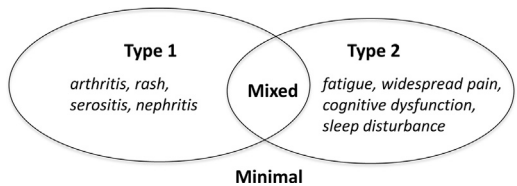

Fig. 1. The figure illustrates the relationship between type 1 and type 2 manifestations, demonstrating the overlap between the 2 categories. Some patients may report neither type 1 nor type 2 symptoms and can be considered to have minimal SLE.

arthritis is inactive. In contrast, the patient may be experiencing widespread pain, with fibromyalgia underlying the patient assessment that the disease is very active.

Regarding that both type 1 and type 2 symptoms are essential elements in disease has important implications for therapy. First, patient–provider communication can be enhanced by validating the symptoms that patients report (eg, fibromyalgia) are, indeed, a part of their condition, requiring evaluation and treatment. Second, by recognizing that type 1 and type 2 symptoms may have distinct origins, even in the same patient, the provider can choose therapy more appropriately, expanding beyond the base of immunosuppressive agents. A more thoughtful approach to therapy based on the type 1–type 2 categorization can limit the use of corticosteroids for problems that are not primarily inflammatory in origin.

Just as the categorization of symptoms into type 1 and type 2 bins may decrease the use of immunosuppressive agents, it may also increase the use of other classes of drugs related to fibromyalgia or depression. As a study from our clinic has found, depression in SLE is frequently undertreated because it is not clearly a manifestation of neuropsychologic lupus and can be complex in its etiology.[67] By incorporating depression in the type 1–type 2 paradigm, the issue of attribution becomes less pressing and a more satisfactory treatment plan can be developed to include exercise and stress reduction, for example.

The Application of the Type 1–Type 2 Paradigm to Treatment

In our clinic, we have begun more formal application of the type 1–type 2 system in routine care and are constructing a research platform to investigate many issues that flow from this type of a more holistic patient approach.

At present, there are a variety of measures for type 1 disease that range from patient reports and surveys for disease activity to laboratory testing to sophisticated molecular analyses to interrogate immune response. The measures for type 2 disease are also many but, in general, these are patient reports that have been developed for other settings (eg, depression, fatigue) not necessarily related to lupus. The use of measures for type 2 manifestation at this time must be borrowed from other conditions, pending the development of measures that are more specific for SLE.

For our initial operationalization of care according to the type 1–type 2 system, we have used the Systemic Lupus Erythematosus Disease Activity Index for type 1 disease activity. For type 2 symptoms, we have used the 2011 American College of Rheumatology fibromyalgia criteria, considering a widespread index score of 7 or higher and a symptom severity score 5 or higher, or a widespread pain index of 3 or higher and a symptom severity score of 9 or higher as indicative of type 2 disease. We chose this measure because it does relate to pain, a major type 2 symptom, and is consistent with studies indicating the frequency of fibromyalgia in SLE.[42,43] In using this scale, we are considering fibromyalgia as a trait that can be of varying intensity or severity. In our use, the total fibromyalgia severity score (a sum of the widespread pain index and the symptom severity score) can provide a measure of "fibromyalgianess" that can lead to symptoms itself (ie, widespread body pain) or color or condition the reporting of other symptoms (eg, hair loss, chest pain).

Our first study showed how the incorporation of assessment for both type 1 and type 2 can lead to a new and hopefully more informative categorization of patients that goes beyond the more classic activity–damage dichotomy.[14] The use of 2 measures allows the delineation of 4 patient groups as indicated in **Box 2**, although more subdivisions are possible.

Using the type 1 and type 2 categorization, we found that 20% of patients can be categorized as having high type 2 SLE activity. As a group, patients with type 2 SLE

Box 2
Categorization of symptoms in SLE

Type 1 SLE: Active SLE without meeting fibromyalgia or polysymptomatic distress criteria

Type 2 SLE: Inactive SLE meeting fibromyalgia or polysymptomatic distress criteria

Mixed SLE: Active SLE meeting fibromyalgia or polysymptomatic distress criteria

Minimal SLE: Inactive SLE without meeting fibromyalgia of polysymptomatic distress criteria.

In our studies, we have identified type 2 SLE using either criteria for fibromyalgia or polysymptomatic distress.

activity had more severe self-reported lupus activity and higher rates of lupus flares than those without type 2 activity. Moreover, we found that patients with type 2 SLE reported a higher frequency of many symptoms, including fatigue, muscle pain, forgetfulness, and headache; they also reported symptoms that are potentially inflammatory in origin. Although synovitis was not documented on examination in patients with type 2 SLE, the frequency of self-reported joint swelling was similar between patients with type 1 and type 2 SLE.

Our understanding and application of the type 1 and type 2 SLE model are in evolution with, for example, a preliminary cluster analysis indicating there may be more than 4 categories of type 1 and type 2 SLE symptoms including those with fatigue predominant type 2. Moreover, we have found that the severity of type 1 and type 2 activity can fluctuate between visits, even resulting in a change in category.[68]

SUMMARY

Pain in SLE is a major symptom of patients and can result from a wide variety of processes. Although some types of pain may result from immunologic mechanisms associated with inflammation and autoreactivity, other types of pain seem to reflect central mechanisms. To understand and treat pain more effectively, we have proposed a new system to divide symptoms of lupus into 2 broad categories, both of which are intrinsic features of disease. Hopefully, this categorization will promote better communication between patients and providers as well as represent a more effective framework for treating one of the most persistent, severe, and disabling manifestations of SLE.

CLINICS CARE POINTS

- The approach to therapy of patients with SLE can be based on division of the manifestations into 2 categories.
- Inflammatory manifestations (type 1) are related to disease activity and include arthritis and nephritis. These manifestations can respond to immunomodulatory agents.
- Noninflammatory manifestations (type 2) include widespread pain, fatigue, depression, and sleep disturbance. These manifestations do not generally respond to immunomodulatory agents and need other treatments.
- Type 2 manifestations represent some of the common and persistent symptoms of SLE and can impact quality of life.
- Type 1 manifestations can be assessed by the Systemic Lupus Erythematosus Disease Activity Index while type 2 manifestations can be assessed by instruments for fibromyalgia and fatigue.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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