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REVIEW

GASTROINTESTINAL AND NEUROLOGICAL MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with unknown etiology and incompletely elucidated pathogenesis. It implies the loss of tolerance to the inner self, which leads to perturbations in the immune system, with production of autoantibodies. SLE is characterized by multisystem involvement, the evolution of these patients being directly influenced by the severity of organ complications. The most common pattern seen in patients with SLE is a combination of musculoskeletal, skin, renal, central nervous system, cardiovascular, hematologic and gastrointestinal manifestations. The gastrointestinal symptoms are commonly seen in patients with SLE, the main pathological mechanisms involved being mesenteric vasculitis, intestinal pseudo-obstruction and protein losing enteropathy. Neurological manifestations are also frequent among these patients and they correlate with a high rate of morbidity and mortality. This review aims to analyze the correlation between gastrointestinal and neurological manifestations in SLE and their impact on the quality of life.

Résumé

Manifestations gastro-intestinales et neurologiques dans le lupus érythémateux systémique

Le lupus érythémateux systémique (LES) est une maladie auto-immune chronique d'étiologie inconnue et de pathogenèse incomplètement élucidée. Cela implique la perte de tolérance envers soi-même,ce qui entraîne des perturbations du système immunitaire, avec la production d'autoanticorps. Le LES est caractérisé par une implication multisystémique, l'évolution de ces patients étant directement influencée par la gravité des complications organiques. Le schéma le plus courant observé chez les patients atteints de LES est une combinaison de manifestations musculosquelettiques, cutanées, rénales, du système nerveux central, cardiovasculaires, hématologiques et gastro-intestinales. Des symptômes gastro-intestinaux sont fréquemment observés chez les patients atteints de LES, les principaux mécanismes pathologiques impliqués étant une vascularite mésentérique, une pseudo-obstruction intestinale et une entéropathie avec perte de protéines.

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Keywords: systemic lupus erythematosus, autoantibodies, gastrointestinal manifestations, neurological manifestations.

Les manifestations neurologiques sont également courantes chez ces patients et elles sont corrélées à un taux élevé de morbidité et de mortalité. Cette revue a pour objectif d'analyser la corrélation entre les manifestations gastro-intestinales et neurologiques dans le LES et leur impact sur la qualité de vie.

Mots-clés: lupus érythémateux systémique, autoanticorps, manifestations gastro-intestinales, manifestations neurologiques.

Introduction

SLE is a chronic inflammatory disease characterized by multiple autoimmune anomalies which are responsible for the production of a broad range of autoantibodies, in particular antinuclear antibodies (ANA)[1-3]. Epidemiological research on the prevalence of SLE shows that it varies depending on geographical location, race, age and gender[4]. In the United States, the prevalence rates vary from 20 and 150 cases per 100,000[5], outnumbering the prevalence rates found in African populations[6]. When it comes to race, the prevalence is higher among African Americans (406 cases per 100,000) compared with Caucasians (164 cases per 100,000)[5]. Furthermore, recent studies have reported a threefold increase in SLE incidence in the last 40 years, which most certainly is not attributed only to the perfection of the diagnostic tools[4,5]. The frequency of SLE is ten times higher among women; multiple mechanisms have so far been incriminated: estrogen hormonal effects, pregnancy, gene variants located on X chromosome, chronobiologic differences and menstruation[5]. On the other hand, SLE that occurs in men is slightly different from that in women, being reported that men usually have worse outcomes[5]. The predilection of SLE for young women is well documented; 65% of patients have disease onset between the ages of 16 and 55, median ages at diagnosis ranging from 37 to 50 years[5].

Table 1. SLICC Classification Criteria for Systemic Lupus Erythematosus

Clinical Criteria	*Immunologic criteria*
1. Acute cutaneous lupus	1. ANA
2. Chronic cutaneous lupus	2. Anti-DNA antibodies
3. Oral or nasal ulcers	3. Anti-Sm antibodies
4. Non-scarring alopecia	4. Antiphospholipid antibody
5. Arthritis	5. Low complement (C3, C4, CH50)
6. Serositis	6. Direct Coombs' test (do not count in the presence of hemolytic anemia)
7. Renal	
8. Neurologic	
9. Hemolytic anemia	
10. Leukopenia	
11. Thrombocytopenia (<100.000/mmc)	

Legend: ANA=anti-nuclear antibodies; Anti-DNA Antibodies = Anti-deoxyribonucleic acid Antibodies; Anti-Sm Antibodies =Anti-Smith Antibodies.

Table 2. Associations between clinical manifestations and the presence of specific antibodies seen in patients with SLE.

Antibodies	*Clinical manifestations*
Anti-DNA	Nephritis
Anti-histones	Drug-induced SLE
Anti-Ro (SS-A) Anti-La (SS-B)	Cutaneous manifestations Neonatal lupus
Anti-Sm	Nephritis
Anti-U1RNP	Arthritis, Raynaud's phenomenon
Anti-ribosomal P protein	Psychosis
Anti-phospholipids	Thrombosis, miscarriage

Despite numerous research studies aiming to elucidate the etiology of SLE, it continues to remain unclear. Genetic, immunologic, hormonaland environmental factors have been considered to have an important role in setting the stage of the disease[4,5].

Clinical and biological manifestations of SLE are the result of cellular destruction triggered by autoantibodies, either by cytotoxic reactions or by participating in the formation of immune complexes. The clinical heterogeneity of SLE as well as the absence of pathognomonic elements pose a challenge in the diagnosis of the disease[7]. When making the diagnosis of SLE, clinicians refer to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria revised in 2012 (Table 1)[8].

The positive diagnosis is based on the presence of at least 4 criteria (at least one clinical and one laboratory criteria) or biopsy-proven lupus nephritis with positive ANA or Anti-DNA[8].

Serological anomalies include multiple autoantibodies with associations being identified between clinical manifestations and the presence of specific antibodies (Table 2)[4].

Clinical manifestations in SLE

The clinical manifestations of SLE (Table 3) vary significantly due to multiple organ affected[4,9,10]. As a result of chronic inflammation, patients with SLE can present general symptoms such as fever, anorexia, asthenia and weight loss.

Gastrointestinal manifestations in SLE

Gastrointestinal symptoms are common among patients with SLE, being first described by Sir William Osler in 1895[15]. Pathogenically speaking, they are rarely a result of the direct damage to the gastrointestinal tract caused by the chronic inflammatory processes characteristic to SLE[2]. Thus, in more than half of the cases, digestive symptoms are secondary to adverse drug reactions, viral infections, bacterial infections and other intercurrent processes, such as uremia[16,17]. So far, no specific antibodies were identified in lupus-induced gastroenteropathy[16].

These symptoms can occur at any age, but are most commonly found in women of childbearing age, in-between puberty and menopause[18].

Table 3. Clinical manifestations of SLE.

Skin and mucous membrane involvement[9]	Facial eruption (butterfly rash), maculopapular lesions, discoid lesions, photosensitivity, Raynaud's phenomenon, generalized or focal alopecia, and others.
Musculoskeletal involvement[10]	arthralgias, arthritis, Jaccoud's syndrome, spontaneous tendon rupture, crystalline arthropathies, subcutaneous calcifications, inflammatory myopathy
Cardiopulmonary involvement[11]	Pericardial effusion, pericarditis, heart failure, myocarditis, endocarditis (infectious and non-infectious), atrioventricular block, sinus tachycardia, stable angina, acute coronary syndrome
Renal involvement[12]	Lupus nephritis: • Minimal mesangial lupus nephritis (class I) • Mesangial proliferative lupus nephritis (class II) • Focal lupus nephritis (class III) • Diffuse lupus nephritis (class IV) • Lupus membranous nephropathy (class V) • Advanced sclerosing lupus nephritis (class VI) tubulointerstitial nephritis, vascular disease, thrombotic microangiopathy, glomerular podocytopathy (lupus podocytopathy), collapsing glomerulosclerosis
Obstetric involvement[4]	recurrent miscarriages
Pulmonary involvement[13]	Pleural effusions, acute lupus pneumonitis, pulmonary hemorrhage, various idiopathic interstitial pneumonias, thromboembolic disease, pulmonary hypertension, shrinking lung syndrome, lung infection, chest wall pain
Ocular involvement[14]	Discoid lupus-type rash over the eyelids, conjunctivitis, dry eye syndrome, scleritis, anterior uveitis, lupus retinopathy (cotton wool spots, intraretinal hemorrhages, and vascular tortuosity), central serous chorioretinopathy, optic nerve involvement
Gastrointestinal involvement[17]	esophageal motility disorders, gastroesophageal reflux disease, esophagitis, gastric ulcer, intestinal pseudo-obstruction, protein-losing enteropathy, hepatomegaly, elevated liver enzymes, alkaline phosphatase, jaundice, splenomegaly, acute pancreatitis, mesenteric vasculitis, peritonitis and ascites
Neurological involvement[4]	Cognitive dysfunction, strokes, seizures, headache, peripheral neuropathy, and others
Generalized adenopathy[4]	

SLE can affect any segment of the digestive system, from the oral cavity and the esophagus to the colon, liver or pancreas:

- *Damage to the oral cavity* can occur through oral ulcers that are typically painless and involve the upper palate[2].
- *Damage to the esophagus* can manifest itself by dysphagia, which is the most common digestive complaint of patients with SLE. Patients may also associate retro-sternal chest pain, heartburn, acid regurgitation or a sore throat. The implied mechanisms are: esophageal motility disorders, gastroesophageal reflux disease, infections (such as Candida, Cytomegalovirus) or drug esophagitis[17,19].
- *Damage to the stomach* may result in gastric ulcer when patients can accuse epigastric pain, a feeling of plenitude, early satiety or nausea. They may also be asymptomatic or can go as far as gastrointestinal complications such as bleeding, obstruction, perforation, penetration or fistulization[17]. It is well-known that SLE is a risk factor for stomach ulcers, independent of other causes such as non-steroidal anti-inflammatory treatment or an infection with Helicobacter pylori.
- *Damage to the small intestine and colon* may be manifested by intestinal pseudo-obstruction, or protein-losing enteropathy. Intestinal pseudo-obstruction is a rare complication of SLE, which usually occurs during disease activity. It is characterized by the presence of signs and symptoms of mechanical bowel obstruction, such as abdominal pain, flatulence or vomiting in the absence of anatomical lesions[17]. The responsible mechanisms are the deposits of immune complexes in the smooth muscle cells and chronic ischemia or vasculitis and hypomotility[17,20]. Protein-losing enteropathy is characterized by the occurrence of hypoalbuminemia and edema in the absence of nephrotic proteinuria. Also, about 50% of patients have severe diarrhea[21].
- *Damage to the liver and spleen*, although considered rare, has been shown in recent studies to be much more common than previously thought[4]. Possible causes include: steatosis, drug toxicity, hepatitis, vascular thrombosis[22] and coexistence with primary biliary cirrhosis or autoimmune hepatitis[23]. Patients may have hepatomegaly, elevated liver enzymes, alkaline phosphatase, or jaundice[17]. They might also present splenomegaly following a periarterial fibrosis or splenic infarction[4].
- *Damage to the pancreas*: Acute pancreatitis occurs in 2-8% of patients with SLE[24]. Some of the responsible mechanisms include vasculitis, antiphospholipid antibodies-associated thrombosis, deposits of immune complexes and intimal thickening by side effects of azathioprine[24,25]. Some studies suggest a possible correlation between the presence of anti-La antibodies and the risk of pancreatitis[2].
- *Other gastrointestinal disorders: mesenteric vasculitis, peritonitis and ascites.*

Mesenteric vasculitis is a serious complication that can be life-threatening. Chronic ischemia can occur insidiously with postprandial abdominal pain, nausea, vomiting or diarrhea. In the case of thrombosis due to mesenteric infarction, the patient can present an acute abdomen, to which there is a risk of perforation and peritonitis[17]. Primary peritonitis secondary to SLE can also be chronic or acute. The acute form can occur in an exacerbation of disease activity, presenting the clinical picture of a surgical acute abdomen, or may be masked by the concurrent use of immunosuppressive drugs. In contrast, chronic peritonitis develops insidiously and may go unnoticed for a long time[17,26]. Ascites is rare among patients with SLE. Its other possible causes may be congestive heart failure, nephrotic syndrome, hypoalbuminemia, or enteropathy secondary to loss of protein[27-29].

From a therapeutic point of view, most of these gastrointestinal complications have good responses to steroids or immunosuppressive therapy. Also, supportive measures, such as fasting and nutritional support, antibiotics or prokinetics are useful to facilitate functional recovery[16].

Neurological manifestations in SLE

Nervous system involvement causes one of the severe manifestations in SLE; it is seen in 10-80% of patients either prior to the diagnosis or during the course of the disease[4,30]. SLE may affect the nervous system at multiple levels, leading to various neurologic and psychiatric syndromes[31]; they may be classified as primary neurologic and psychiatric disease or secondary disease[30]. The latter is a more common cause of neuropsychiatric symptoms and can be produced by various mechanisms such as active central nervous system (CNS) lupus, sequelae of lupus that is now inactive, complications of chronic LES, complications of other organ system involvement and complications of treatment[30].

The neuropsychiatric syndromes are the result of the interaction of multiple factors: vasculitis, autoantibodies (anti-neuronal antibodies, antiphospholipid antibodies, lymphocyte toxic antibodies) and accelerated atherosclerosis[4]. Vasculitis was initially thought to be responsible for the neurological manifestations in SLE but investigators found that true vasculitis was a rare finding in these patients[31,32]. However, vasculopathy is seen in many patients and it may cause direct injury, thus affecting the blood-brain barrier and allowing antibodies to enter the nervous system[30].

Secondary factors such as infections associated with immunosuppressive therapy, metabolic complications of other organ system failure, hypertension and toxic effects of therapy (particularly corticosteroids) have been considered to play an important role in causing neurologic episodes[33].

The most common neurologic manifestations of SLE are cognitive dysfunction, stroke, seizures, headaches, and peripheral neuropathy[30].

- Cognitive dysfunction is frequently seen in patients with SLE and it implies affecting mental activities such as memory, abstract thinking and judgment. Deficits in the cognitive function may be present in 20 to 80 percent of patients[30].
- Stroke: 19% of patients with SLE can develop a stroke during the course of the disease, baseline disease activity, hyperlipidemia, and hypertension being identified as risk factors for stroke[34]. Increased risk of stroke was demonstrated among patients of younger age[35] and patients with persistent elevated antiphospholipid antibodies of different specificities[36,37].
- Seizures may be the first manifestation of lupus and they may be present in up to 20% of patients with SLE[2]. Patients can present with both generalized and partial seizures (complex or simple); various contributing factors have been identified: metabolic disturbances, hypertension, infections, tumors, head trauma, stroke, medication withdrawal[38,39].
- Headache is a frequent symptom in patients with SLE, migraine and tension headache being the most common. Regarding the mechanism of headache, none was identified and no correlation between headache and the disease status has been established.
- Peripheral neuropathy is also a common manifestation in SLE, seen in 15% of patients[40]. Most of the times it is asymmetric, sensory nerves are affected more than motor nerves and more than one nerve may be damaged[40]. In a few case reports, patients presented with inflammatory polyradiculoneuropathy, including the acute form resembling Guillain-Barré syndrome and the chronic form resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIPD)[40,41].

The correlation between neurological and gastrointestinal damage in SLE

A 2017 study, conducted on 32 patients, two males and 30 females, revealed a correlation between the presence of neurological and gastrointestinal complications in patients with SLE[15]. Thus, of the 32 patients with SLE, 7 had neurological manifestations in association with all the digestive symptoms. One possible explanation for this correlation could be common pathogenic mechanisms of damage to the two systems or vasculitis. On the other hand, the same study identifies a possible correlation between impaired endocrine function and gastrointestinal lupus. Thus, 9 of the 32 patients had hypothyroidism in association to all digestive symptoms[15]. Further studies are needed to deal with this correlation and thus contribute to elucidate the etiology of this debilitating disease.

Conclusions

Despite great impact on morbidity and mortality worldwide, as well as the significant costs involved, the etiology of SLE remains uncertain. Even though it is not as frequent as other events, such as the lupus nephritis, gastrointestinal involvement is very important because it can be life-threatening in the absence of appropriate treatment. Damage to the nervous system is also one of the severe manifestations of lupus. If in the case of gastrointestinal damage of SLE specific antibodies have not yet been identified, for psychosis a link with a ribosomal P-protein antibody has been found[4]. Recent studies suggest a possible correlation between neurological and gastrointestinal damage from lupus, association that could be the basis for future studies to elucidate the pathogenesis of autoimmune diseases.

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