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GASTROINTESTINAL INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW

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Abstract: Gastrointestinal manifestations in Systemic Lupus Erythematosus (SLE) are common, with a prevalence of between 40% and 60%, ranging from mild symptoms such as nausea and abdominal discomfort to serious complications such as intestinal vasculitis and perforations. These symptoms are often underdiagnosed, but directly reflect disease activity, especially in patients with autoantibodies such as anti-DNA double helix and anti-Sm. Such complications can mimic other conditions, making diagnosis and clinical management difficult. Serious complications include vasculitis and thrombosis, which can cause ischemia, perforation and intestinal infarction. Pancreatitis, although rare, has a higher prevalence in SLE patients and is associated with disease activity and sometimes with antiphospholipid antibodies. Early diagnosis, based on imaging tests, biopsies and inflammatory markers, is essential to prevent fatal outcomes. Management depends on severity, ranging from corticosteroids in mild cases to immunosuppressants, such as Cyclophosphamide and Rituximab, in more severe cases. A multidisciplinary approach is fundamental to improving prognosis, reducing morbidity and improving patients' quality of life. Early recognition and personalization of treatment are essential to mitigate complications and achieve better clinical results, reinforcing the need for patient education and access to specialist care.

Keywords: "Systemic Lupus Erythematosus", "Gastrointestinal Manifestations", "Vasculitis", and "Autoimmune Diseases".

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory autoimmune disease that can affect various organs and systems in the human body [1,2,3]. It is characterized by the production of autoantibodies, the most relevant of which are antinuclear antibodies (ANA), present in almost all cases of SLE, double helix anti-DNA antibodies (anti--dsDNA), associated with disease activity and kidney involvement, and anti-Sm antibodies, highly specific for SLE, although less frequent [1,2,3,4]. These autoantibodies play a central role in the pathogenesis of the disease, contributing to the inflammation and tissue damage that characterize SLE [1,2,3,4].

Although the exact cause of SLE is not fully understood, it is believed that several factors contribute to its development [1,2,3,4]. Genetic factors include alterations in HLA genes (such as HLA-DR2 and HLA-DR3), genes related to immune signaling (such as IRF5 and STAT4) and family predisposition [3,4]. From a hormonal point of view, estrogen and prolactin play significant roles, as evidenced by the higher prevalence of the disease in women of reproductive age and the exacerbation of symptoms during pregnancy [3,4,5]. Among environmental factors, exposure to ultraviolet radiation, viral infections such as Epstein-Barr virus, chemicals such as silica, and physical or emotional stress are recognized as potential triggers [3,4,5]. Finally, immunological factors include excessive production of type I interferon, defects in cell apoptosis, an imbalance in the regulation of T and B cells and the presence of autoantibodies such as anti-dsDNA and anti-Sm, which promote inflammation and tissue damage. These factors interact in a complex way, contributing to the onset and progression of the disease [4,5,6].

The disease is characterized by a wide range of clinical manifestations, which can vary from mild symptoms, such as fatigue and joint pain, to more serious conditions, such as kidney failure and neurological involvement [4,5,6]. One of the challenging aspects of SLE is its unpredictable nature, with periods of exacerbation, known as flares, followed by remissions, where symptoms can improve [5,6]. This requires continuous and adapted management, as well as a multidisciplinary approach involving different medical specialties [5,6,7].

Although there is no definitive cure for SLE, it is possible to control the disease through treatments aimed at reducing inflammation, controlling excessive immune activity and preventing organ damage [5,6,7]. Treatment usually involves the use of drugs such as corticosteroids, immunosuppressants and antimalarials, which help to moderate the immune response and control symptoms [5,6,7]. In addition, self-care measures are essential to improve patients' quality of life. These include avoiding excessive exposure to the sun, eating a balanced diet and practicing regular physical activity [5,6,7,8]. Regular medical follow-up is also essential to monitor possible complications and adjust treatment as necessary [5,6,7,8].

In SLE, the gastrointestinal tract is often affected by the chronic inflammation associated with the disease [5,6,7,8]. The deregulated immune response results in the production of autoantibodies that can attack cells in the digestive tract, generating a series of symptoms gastrointestinal [6,7,8]. These symptoms can vary widely between patients and include abdominal pain, nausea, diarrhea and changes in intestinal transit [6,7,8]. In some cases, the inflammation can affect everything from the mouth to the intestines, resulting in generalized digestive discomfort [6,7,8]. The diffuse and vague nature of these symptoms makes clinical diagnosis more challenging, as these signs can also be observed in various other medical conditions [6,7,8,9].

In addition to direct inflammation in the gastrointestinal tract, SLE can cause more serious complications such as vasculitis and thrombosis [7,8,9]. Vasculitis, which is inflammation of the blood vessels, can compromise blood flow to the digestive tract, leading to ischemia, i.e. a reduction in the supply of oxygen and nutrients to the tissues [7,8,9]. In more severe cases, thrombosis can occur, resulting in the formation of clots that block blood flow [7,8,9,10]. This can lead to infarction of the intestinal tissue, causing cell death, or even perforation of the intestine, a serious condition that can lead to peritonitis, inflammation of the abdominal cavity, requiring urgent medical intervention [8,9,10].

The gastrointestinal symptoms of SLE are often underestimated or misinterpreted due to their non-specific nature [8,9,10]. Symptoms such as abdominal pain, diarrhea and nausea are common in several other conditions, which makes early diagnosis difficult [8,9,10]. It is estimated that between 40% and 60% of patients with SLE have some degree of gastrointestinal involvement, but only a small percentage, between 8% and 10%, develop more obvious symptoms [8,9,10]. Post-mortem studies indicate that gastrointestinal involvement is more frequent than previously thought, suggesting that many complications may go unnoticed during the patient's lifetime [9,10].

Given this complexity, regular monitoring and early detection of gastrointestinal complications are essential for the management of SLE [9,10,11]. Identifying early signs can help with intervention before complications become more serious, improving patients' quality of life [9,10,11]. In addition, treatment aimed at the gastrointestinal manifestations of SLE should be individualized, taking into account the variability of symptoms and the patient's response to treatment [9,10,11]. An interdisciplinary approach, including rheumatologists, gastroenterologists and other specialists, is essential to ensure comprehensive and effective care [10,11].

OBJECTIVES

To identify and analyze the prevalence and clinical characteristics of gastrointestinal manifestations in patients with systemic lupus erythematosus (SLE), with an emphasis on their correlation with disease activity and the presence of specific autoantibodies, such as anti-DNA double helix and anti-Sm [11,12]. This study also seeks to explore the main gastrointestinal complications associated with SLE, including intestinal vasculitis, perforations and pancreatitis, highlighting the diagnostic and therapeutic challenges that these conditions present in clinical practice [11,12].

To evaluate the importance of an early and careful diagnostic approach to gastrointestinal manifestations in SLE, considering the use of laboratory tests, imaging and inflammatory markers as tools to improve the identification and management of these complications [11,12]. It also aims to discuss the clinical impact of these manifestations on patients' morbidity and quality of life, proposing strategies for multidisciplinary management that integrates prevention, diagnosis and effective therapy [12].

METHODOLOGY

The systematic review was conducted using the PUBMED, VHL, and MEDLINE databases, focusing on studies published between 2019 and 2024. Specific search criteria were applied, with keywords such as "Systemic Lupus Erythematosus", "Gastrointestinal Manifestations", "Vasculitis", and "Autoimmune Diseases", combined by Boolean operators (AND, OR) to maximize the relevance of the results [12]. Additional filters were applied to limit the studies to the English language and peer-reviewed publications, ensuring high quality and up-to-date evidence [12].

The inclusion criteria covered studies that discussed gastrointestinal manifestations associated with Systemic Lupus Erythematosus (SLE), including intestinal vasculitis, thrombosis, ischemia and general symptoms such as abdominal pain and diarrhea [12,13]. Only articles that presented detailed clinical data and clear diagnostic methods were considered [12,13]. Studies addressing gastrointestinal manifestations in other autoimmune diseases were excluded [12,13].

The selection process was carried out in two stages: initially, titles and abstracts were analyzed to identify relevant studies in 294 articles [12,13]. Next, the full texts of the selected articles were evaluated, extracting data such as patient characteristics, prevalence of gastrointestinal manifestations, diagnostic and therapeutic strategies, and clinical outcomes [12,13]. This standardized approach ensured a thorough analysis of the relevant information from 46 full articles [13].

RESULTS

PREVALENCE AND CLINICAL IMPORTANCE

The prevalence of gastrointestinal manifestations in patients with systemic lupus erythematosus (SLE) varies between 40% and 60%, ranging from mild symptoms such as nausea and abdominal discomfort to serious complications such as intestinal vasculitis and perforations [13,14,15,16]. These conditions are often underestimated in clinical practice, despite being important indicators of disease activity [13,14,15,16]. Studies show that the frequency of gastrointestinal symptoms tends to be higher in patients with greater lupus activity, suggesting a direct association with the presence of specific autoantibodies [13,14,15,16,17].

Among the autoantibodies related to SLE, anti-DNA double helix and anti-Sm stand out due to their strong correlation with more severe manifestations, including gastrointestinal complications [13,14,15,16,17]. These manifestations not only increase patient morbidity, but also pose diagnostic and therapeutic challenges, since they can mimic other conditions, such as inflammatory bowel diseases [13,14,15,16,17]. For this reason, it is crucial that gastrointestinal symptoms are recognized and properly valued by healthcare professionals [14,15,16,17].

Comparing clinical studies with autopsy findings, it is observed that the frequency of gastrointestinal manifestations may be even higher than reported, suggesting that some cases remain underdiagnosed during the patient's lifetime [14,15,16,17]. This discrepancy reinforces the need for a more careful approach to assessing gastrointestinal symptoms in patients with SLE, especially in contexts of high disease activity [14,15,16,17].

Therefore, recognizing and treating gastrointestinal manifestations in SLE is fundamental to improving patients' quality of life and reducing serious complications [14,15,16,17]. The inclusion of specific clinical criteria and more sensitive diagnostic tools can help to identify these symptoms early and provide a more effective therapeutic approach [14,15,16,17].

CLINICAL MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Gastrointestinal manifestations in patients with systemic lupus erythematosus (SLE) are varied and range from mild symptoms, such as abdominal pain, nausea, vomiting and diarrhea, to more serious complications [14,15,16,17]. Weight loss is also a common finding, often related to chronic inflammation and increased disease activity [14,15,16,17,18]. These symptoms can occur in isolation or together, making differential diagnosis with other gastrointestinal conditions difficult [14,15,16,17,18].

Serious complications include vasculitis and thrombosis associated with SLE, which can lead to conditions such as ischemia, perforation and intestinal infarction [14,15,16,17,18]. Although rare, these conditions have a high morbidity and require early diagnosis to avoid fatal outcomes [16,17,18,19]. Other critical findings include pancreatitis, which can occur mainly in the first year after the diagnosis of SLE and presents with severe abdominal pain, nausea, vomiting and elevation of markers such as amylase and lipase [16,17,18,19].

The diagnosis of gastrointestinal manifestations in SLE involves a comprehensive approach that includes imaging tests, such as computed tomography and ultrasound, which are useful for identifying complications such as vasculitis and intestinal perforation [17,18,19]. In some cases, biopsies are essential to confirm vasculitis [17,18,19]. Inflammatory markers, such as elevated CRP and ESR, and the presence of specific autoantibodies, such as antiphospholipid antibodies, are frequently observed in these patients, reinforcing the relationship between disease activity and gastrointestinal manifestations [17,18,19,20].

The association between gastrointestinal involvement and risk factors such as the presence of antiphospholipid antibodies and secondary conditions such as Sjögren's syndrome is well established [17,18,19,20]. In addition, socioeconomic factors, such as limited access to healthcare, and lifestyle habits, such as smoking, can aggravate gastrointestinal manifestations in SLE [18,19,20]. These associations highlight the importance of a multidisciplinary and individualized approach in the management of these patients [18,19,20].

Finally, early recognition and appropriate treatment of gastrointestinal manifestations in SLE are fundamental to preventing serious complications and improving prognosis [18,19,20]. Investing in sensitive diagnostic tools and a detailed clinical approach can facilitate early identification of these conditions, ensuring effective therapeutic interventions and a better quality of life for patients [19,20,21].

TREATMENT AND RESOLUTION

The management of gastrointestinal manifestations in SLE depends on the severity of the condition and the presence of specific complications [19,20,21]. In mild cases, controlling inflammation with corticosteroids, such as prednisone, may be sufficient [20,21,22]. In more severe cases, the use of immunosuppressants, such as Cyclophosphamide, Azathioprine or Rituximab, is often necessary [20,21,22]. These medications work by suppressing the deregulated immune response, reducing inflammation and the risk of fatal complications [21,22].

Despite therapeutic advances, some gastrointestinal complications, such as severe intestinal vasculitis, have a high morbidity and mortality rate [21,22]. The success rate of treatment depends on early diagnosis and an appropriate approach, but persistent or fatal cases are still reported, highlighting the need for ongoing research to improve the therapeutic options available [22,23,24,25,26].

CLINICAL IMPLICATIONS

Early diagnosis of gastrointestinal manifestations in SLE is essential to prevent serious complications and reduce mortality [22,23,24,25,26]. Detailed clinical assessment, combined with laboratory and imaging tests, allows early identification of signs of inflammation or vascular involvement in the gastrointestinal tract [22,23,24,25,26]. The use of specific markers, such as autoantibodies, is also fundamental for directing management [25,26,27,28,29].

Managing these complications requires multidisciplinary monitoring involving rheumatologists, gastroenterologists and other specialists, allowing for an integrated approach [30,31,32,33,34]. In addition, educating patients about the warning signs and the importance of regular follow-up can improve clinical outcomes [32,33,34,35,36].

Finally, a proactive and personalized approach is essential to address the challenges associated with gastrointestinal manifestations in SLE [36,37,38,39,40]. Investing in preventive strategies, early diagnosis and effective treatment can not only reduce morbidity, but also significantly improve patients' quality of life [41,42,43,44,45,46].

DISCUSSION

PANCREATITIS IN SLE PATIENTS: FREQUENCY AND CLINICAL MANIFESTATIONS

Although rare, pancreatitis is a significant complication of systemic lupus erythematosus (SLE) [22,23,32,33,34]. Its prevalence is estimated at approximately 0.8% among patients evaluated for pancreatitis and around 8% among those with abdominal pain [22,23,32,33,34]. Typical symptoms include nausea, vomiting, fever, abdominal distension and absence of bowel sounds, characteristics that can mimic other abdominal conditions, making early diagnosis difficult [32,33,34].

The etiology of pancreatitis in SLE is often related to the activity of the disease [17,18,19,20]. SLE-induced vasculitis is considered to be one of the main underlying mechanisms, as evidenced by the clinical response to treatment with corticosteroids and immunosuppressants [17,18,19,20]. Additionally, in some cases, an association between pancreatitis and antiphospholipid antibodies has been observed, suggesting that thrombosis may contribute to the development of this condition [18,19,20,44,45].

Before attributing pancreatitis exclusively to SLE, it is essential to rule out other possible causes [16,19,20,44,45]. Viral infections, such as cytomegalovirus (CMV), mechanical factors and adverse effects of medications, such as corticosteroids and Azathioprine, are potential causes that need to be considered [17,18,20,21,30]. This detailed diagnostic process is crucial for determining appropriate management and preventing complications [20,21,30,44,45].

SLE-associated pancreatitis is associated with a significant mortality rate, estimated at around 30%, especially in patients with additional complications such as hypocalcemia, central nervous system manifestations and macrophage activation syndrome [16,17,18,26,27,45]. This highlights the need for rapid and effective therapeutic interventions, as well as multidisciplinary monitoring to mitigate the risks [18,19,26,27,45].

Pancreatitis in childhood SLE has a higher prevalence compared to adult SLE, as well as greater disease activity and high rates of complications and mortality [17,26,27,45]. These data reinforce the importance of early recognition and an intensive therapeutic approach in children with SLE who present with pancreatic manifestations [18,19,23,26,40]. The seriousness of this complication in the pediatric context underscores the need for treatment protocols adapted for this population [15,19,23,26,40].

EXUDATIVE ENTEROPATHY: DEFINITION AND CLINICAL CHARACTERISTICS

Exudative enteropathy is a clinical syndrome characterized mainly by hypoalbuminemia, without significant proteinuria or severe liver disease [24,25,27,40]. The condition can also be associated with malabsorption of nutrients or inadequate food intake [26,27,29,41]. Although hypoalbuminemia is the main laboratory finding, other common symptoms include edema, diarrhea and abdominal pain, with edema often standing out as the most prominent symptom [26,27,29,41,44]. This clinical condition can be debilitating, especially due to abdominal discomfort and fluid retention, which negatively affects patients' quality of life [14,15,26,27,29,41,44].

The main laboratory characteristic of exudative enteropathy is hypoalbuminemia, which occurs due to excessive protein loss through the gastrointestinal tract [15,16,21,22,29,41,44]. In addition, patients may present with hypercholesterolemia, hypoglobulinemia, lymphopenia and steatorrhea, which indicate disorders associated with lipid absorption [22,29,41,44]. The diagnosis of exudative enteropathy involves the dosage of fecal alpha-1 antitrypsin, a simple and reliable test, although it cannot precisely identify the site of protein loss [22,24,29,41,44]. Scintigraphy with Tc-99m-labeled albumin is a more specific and sensitive alternative for locating the source of protein loss [22,24,29,41,44].

The pathogenesis of exudative enteropathy involves a combination of factors, including intravascular complement activation, non-necrotizing vasculitis, acquired lymphangiectasia and increased microvascular and endothelial permeability [24,29,41,44]. In the context of systemic lupus erythematosus (SLE), the altered immune system can significantly contribute to increased intestinal permeability, facilitating the loss of proteins into the extracellular space [17,18,20,41,44]. These immunological alterations can aggravate exudative enteropathy, making it an additional challenge in the management of SLE [17,18,20,41,44].

The treatment of exudative enteropathy is predominantly based on corticosteroids, which help to reduce inflammation and improve intestinal absorption [17,18,19,20]. In addition, immunosuppressants such as Azathioprine, Cyclophosphamide, Mycophenolate Mofetil and Rituximab can be used to control immune activity and prevent further damage to the gastrointestinal tract [26,27,29,41,44,46]. The use of additional therapies, such as Octreotide, has shown benefits by reducing intestinal blood flow and exerting an immunomodulatory action [17,28,40,44,46]. A medium-chain triglyceride (MCT) diet is also recommended, as it facilitates the absorption of lipids in patients with malabsorption problems.

The prognosis of exudative enteropathy depends on the response to immunosuppressive treatment and the control of SLE manifestations [22,23,25,34,35,36]. In some cases, the disease can lead to serious complications, such as malnutrition and electrolyte imbalances, due to the continuous loss of proteins and nutrients [17,18,32,34,35]. Strict control of inflammation and careful monitoring of intestinal function are essential to avoid these complications [32,33,39,44,45]. Early detection and appropriate treatment can significantly improve patients' quality of life, although the management of exudative enteropathy remains a challenge in clinical practice [45,46].

ACALCULOUS CHOLECYSTITIS IN SLE PATIENTS: FREQUENCY AND CLINICAL CHARACTERISTICS

Acalculous cholecystitis is a rare manifestation in the context of systemic lupus erythematosus (SLE), but its occurrence, although infrequent, should be considered due to its potential complications [21,22,24,34,35,36]. Patients with SLE who develop this condition usually report pain in the right upper quadrant of the abdomen, often associated with vomiting, which are typical symptoms of cholecystitis [21,22,24,34,35,36]. Severe abdominal pain and the presence of clinical signs indicative of liver dysfunction may suggest the need for detailed investigation, including imaging and laboratory tests, to confirm the diagnosis [21,22,27,34,35,36].

The histopathology of acalculous cholecystitis in SLE can range from medium-caliber vasculitis to thrombotic microangiopathy, especially associated with antiphospholipid antibodies (aPL) [20,24,28,34,35,36]. The presence of these autoantibodies, which are common in patients with SLE, can facilitate the formation of thrombi in the small arteries and biliary vessels, contributing to the development of cholecystitis without the presence of stones [20,24,28,34,35,36]. The complex interaction between immune dysfunction and endothelial thrombosis is a crucial factor in the manifestation of this condition, which can be difficult to diagnose due to its rare nature and similarities to other abdominal pathologies [34,35,36].

The treatment of acalculous cholecystitis in patients with SLE involves the use of corticosteroids, which are the basis of therapy, to reduce inflammation and control the activity of the underlying disease [34,35,36]. In some cases, immunosuppressants such as cyclophosphamide and azathioprine can be used to inhibit the immune activity that is contributing to inflammation and vascular damage [34,35,36]. The main aim of treatment is to control inflammation of the gallbladder and prevent serious complications such as necrosis or perforation of the gallbladder, which can occur if treatment is not effective [34,35,36].

NEED FOR CHOLECYSTECTOMY AND PROGNOSIS

In more severe cases, cholecystectomy may be necessary, especially when conservative treatments are not enough to control the inflammation or when complications arise, such as infection or the risk of gallbladder rupture [21,22,24,34,35,36]. The decision to remove the gallbladder should be carefully assessed by a multidisciplinary team, taking into account the severity of the condition and the response to conservative treatment. In well-treated cases, the prognosis can be favorable, but continuous monitoring is essential to avoid recurrences or further complications [21,22,34,35,36].

DIAGNOSTIC CHALLENGES AND THE NEED FOR FURTHER STUDIES

Although acalculous cholecystitis is rare in patients with SLE, its importance should not be underestimated [22,42,43,44,45,46]. The gastrointestinal manifestations associated with SLE, including cholecystitis, are often underdiagnosed or misinterpreted in clinical practice, leading to inadequate treatment [41,42,43,44,45,46]. The lack of large, robust studies on this condition limits a complete understanding of its pathogenesis, diagnosis and best treatment strategies [21,22,33,44,45,46]. Most of the available data comes from isolated case reports, which highlights the need for more research to develop more precise clinical guidelines and improve the management of this rare and potentially serious condition [41,42,43,44,45,46].

CONCLUSION

The involvement of the gastrointestinal system in patients with SLE is often underestimated and its manifestations correlate directly with the presentations of the disease, which can be potentially fatal. Therefore, awareness of these implications in clinical practice is essential for early diagnosis in order to reduce mortality.

Effective diagnosis involves the use of sensitive tools such as imaging tests, biopsies and inflammatory markers, which are essential for identifying the severity of the case and its complications, as well as preventing underdiagnosis since there is a large discrepancy between clinical studies and autopsy findings, emphasizing the importance of not neglecting the involvement of the gastrointestinal system in SLE.

In addition, the association of gastrointestinal manifestations with the presence of autoantibodies such as anti-DNA double helix, anti-Sm and anti-phospholipids, as well as with vasculitis, thrombosis and secondary conditions such as Sjögren's syndrome, highlights the complexity of the disease. Socioeconomic and behavioral factors, such as smoking, also play an important role.

Vasculitis, intestinal perforation, pancreatitis and exudative enteropathy are serious complications of SLE that require immediate medical intervention and their presence contributes significantly to the morbidity and mortality of cases. Effective control of the disease involves the use of corticosteroids and immunosuppressants, especially in severe cases, helping to reduce the immune response and control symptoms, requiring an individualized approach in the management of these patients.

This approach should be carried out in an interdisciplinary way, including rheumatologists, gastroenterologists and other specialists, in order to guarantee comprehensive care according to the needs of each case. This collaboration not only improves the quality of life of individuals, but also reduces morbidity rates associated with gastrointestinal manifestations and favors more effective control of the progression of the disease.

Finally, the implementation of specific criteria for gastrointestinal manifestations in SLE diagnostic protocols, together with the use of more sensitive tools and the development of innovative therapeutic strategies, are fundamental for identifying symptoms early, reducing serious complications and increasing the success rate of treatment with a view to improving quality of life and better outcomes.

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