

Juvenile Systemic Lupus Erythematosus and cholecystitis: Case reports and review of literature

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ABSTRACT

Juvenile Systemic Lupus Erythematosus (JSLE) is an autoimmune, multi-systemic disease with a wide range of clinical manifestations; however, the gallbladder disease is not well documented in the pediatric patients, there are few cases of cholecystitis in patients with JSLE in the world literature. We present three JSLE patients from the Immunology Service of the Instituto Nacional de Pediatría who developed cholecystitis during their evolution. We emphasize the awareness of this complication in these patients.

Key words: Juvenile Systemic Lupus Erythematosus, cholecystitis, abdominal pain.

RESUMEN

El lupus eritematoso sistémico juvenil (JSLE) es una enfermedad autoinmune, multisistémica, con una gran variedad de manifestaciones clínicas. Sin embargo, la enfermedad de la vesícula biliar no está bien documentada en los pacientes pediátricos; existen pocos casos de colecistitis en pacientes con lupus juvenil en la literatura mundial. Presentamos tres pacientes con lupus del Servicio de Inmunología del Instituto Nacional de Pediatría quienes desarrollaron colecistitis durante su evolución. Enfatizamos la importancia de sospechar esta complicación en estos pacientes.

Palabras clave: Lupus eritematoso sistémico juvenil, colecistitis, dolor abdominal.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune, multi-systemic disease with an unpredictable course and a wide range of clinical manifestations.¹ It is known that

the incidence of abdominal manifestations in adults is from 8 to 40% and acute cholecystitis represents 15% of them.² There are few reports of gastrointestinal manifestations in children, Richer and cols., evaluated the frequency of gastrointestinal manifestations in French chil-

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Abbreviations

SLE: Systemic Lupus Erythematosus

JSLE: Juvenile Systemic Lupus Erythematosus

APS: Antiphospholipid Antibody Syndrome

AAC: Acute Acalculous Cholecystitis

OVMII: Occlusive Venous Mesenteric inflammatory illness

US: Ultrasound

ALC: Acute Lithiasic Cholecystitis

AMLC: Acute Microlithiasic Cholecystitis

ANA: Anti Nuclear Antibodies

ACA: Anticardiolipin Antibodies

AntiB2GP: Anti-B2 Glycoprotein

Anti-PS: Anti- Phosphatidylserine

dren with SLE (JSLE) and found an incidence of 19%, reporting only one case of cholecystitis in 201 evaluated patients.³ Vesicular pathology is an unusual complication in patients with SLE, even though there are diverse risk factors for developing it in this disease.

We present three JSLE patients from the Immunology Service of the Instituto Nacional de Pediatría who developed cholecystitis during their evolution.

CASE PRESENTATION

CASE 1

A ten year-old female became ill 8 months prior to her hospitalization with malar rash, arthralgia, photosensitivity and muscular weakness. Diagnostic approach was initiated and met criteria for SLE (photosensitivity, discoid lupus, oral ulcers, proteinuria 5.4 g, ANA diffuse pattern 1:320, positive anti-DNAN, anti-SM > 100 U). She had hypocomplementemia C3 29.6 mg/dL, C4 < 6.18 mg/dL and dyslipidemia, 1,964 mg/dL triglycerides, 418 mg/dL cholesterol, negative serology for Antiphospholipid Antibody Syndrome (APS), which was treated with pulse methylprednisolone. During her hospitalization, she had acute abdominal pain associated to the ingestion of **cholecystokinetic food, which was accompanied by nausea and biliary vomiting**. Initial evaluation was normal, but because of persistence of pain in the right hypochondrium, an abdominal US was performed, showing thickening of the vesicular wall with biliary sludge, she had a conservative treatment and because of lupus was initiated with methylprednisolone and cyclophosphamide pulses, with good lupus evolution and remission of the abdominal symptoms.

As the result of recurrent cholecystitis the patient required laparoscopic cholecystectomy, the histopathology showed slight edema and inflammatory infiltrate composed of lymphocytes and plasma cells at the muscle layer, there was no evidence of lithiasis or vasculitis. The patient is currently under treatment with cyclophosphamide pulses for nephritis, and has remained stable.

CASE 2

A thirteen year-old male was initiated with asthenia, weight and hair loss, facial erythema, photosensitivity and intense generalized cephalgia accompanied by nausea and conduct disorders. The patient met SLE criteria (malar erythema, oral ulcers, photosensitivity, arthritis, ANA 1:160, positive anti-DNAN, lymphopenia, hemolytic anemia, and 0.9 g proteinuria) and also had hypocomplementemia and hypergammaglobulinemia (IgG 2,009 mg/dL). The patient needed methylprednisolone pulses because of the activity and also received prednisone,

azathioprine and hydroxychloroquine, and showed satisfactory progress.

Three years later, he presented to the emergency room for abdominal pain in the right hypochondrium. Initial laboratory showed: triglycerides 465 mg/dL, cholesterol 214 mg/dL, HDL 22.3 mg/dL, LDL 144 mg/dL, VLDL 47.2 mg/dL. During inpatient evolution proteinuria, hematuria, hypocomplementemia and positive anti-DNAN were observed. An infectious process was discarded and an abdominal ultrasound was performed, in which free liquid was seen in the right iliac fossa and a 7 mm thickening of the gallbladder wall with no evidence of lithogenesis. The decision was made to initiate methylprednisolone pulses as a result of the activity data, with notable improvement of lupus activity and the cholecystitis, with no need for surgery. The patient continues to receive cyclophosphamide pulses due to neurolupus and nephritis. He has not had cholecystitis episodes and maintains a normal lipid profile.

CASE 3

A fourteen year-old female began ill with arthritis, 5 kg weight loss and purpuric lesions in the lower extremities. Pleural effusion was detected and the patient was diagnosed with SLE (lymphopenia, hemolytic anemia, pleural effusion, oral ulcers, ANA 1:320 and proteinuria). She was treated initially with azathioprine, cyclophosphamide and methylprednisolone pulses. However, since the proteinuria persisted, the decision was made to change to mycophenolate mofetil 60 mg/kg/d. Two years later a thyroid dysfunction was detected, triglycerides 859 mg/dL, cholesterol 434 mg/dL, HDL 40.3 mg/dL, LDL 241 mg/dL, VLDL 171 mg/dL and positive Anti B2 glycoprotein were documented for which treatment with levothyroxine and levastatin was initiated.

After 6 months the patient entered with 2 days of abdominal pain in the epigastric region accompanied by alimentary vomiting, and positive Murphy's sign. Normal pancreatic enzymes were reported and her cholesterol was 387 mg/dL, triglycerides 358 mg/dL. The abdominal US showed a cholelith in the gallbladder. She had lymphopenia and proteinuria of 4.6 g during her stay, for which it was decided to administer methylprednisolone pulses, and she showed improvement of the activity of the illness and cholecystitis symptoms. She is currently receiving 65 mg/kg/d of **mycophenolate mofetil**, is asymptomatic and on a cholecystokinetic-free diet.

DISCUSSION

The ubiquitous gastrointestinal manifestations in patients with SLE consist of oral ulcers, abdominal pain, gastroesophageal reflux, peritonitis, pancreatitis and hepatitis.

Among less frequent manifestations are dysphagia and cholecystitis.^{4,5}

Abdominal pain is a diagnostic and therapeutic challenge in these patients because it could have an autoimmune source secondary to concomitant illnesses, the side effects of the immunosuppressant treatment,^{4,5} and less common due to serositis.¹⁵

Patients with SLE are prone to the formation of biliary sludge and lithiasis because of the presence of biliary dyskinesia caused by ischemia of the gallbladder.⁷ Reshetnyak et al., also found in patients with SLE the relationship between the use of corticosteroids and a metabolic lipid disorder, which predisposes the formation of biliary calculi.⁸

Acute acalculous cholecystitis (AAC), which is non-distinguishable from lithiasic cholecystitis, is present in 5-10% of the patients with acute cholecystitis. It has been reported in patients with burns, severe trauma, infectious processes, prolonged parenteral nutrition, diabetes mellitus, APS and vasculitis. In vasculitis, patients with polyarteritis nodosa are at greater risk of presenting CAA. Echographic criteria proposed for diagnosing CAA include thickening of the gallbladder wall, edema around the gallbladder and the absence of liths.⁸⁻¹⁰

There are two main causes for gallbladder ischemia in SLE: vasculitis and thrombosis. Gallbladder vasculitis is characterized by the presence of acute periarterial fibrotic arteritis.^{9,10} Chen et al., separate gallbladder vasculitis into 3 groups: 1) vasculitis with manifestations of polyarteritis nodosa, 2) vasculitis occurring in ailments associated to vasculitis, such as systemic **lupus erythematosus** and 3) **idiopathic vasculitis**.¹¹ Thrombosis is more characteristic of SLE patients and is presented more frequently in patients with antiphospholipid antibodies. Histologically, multiple thrombi are appreciated in the veins of the gallbladder with no evidence of vasculitis.⁹⁻¹¹

Occlusive venous mesenteric inflammatory illness (OVII) is an infrequent cause of ACC in SLE with unknown etiology. Lie et al., reported that OVII belonged to a new category of vasculitis, in which inflammation is limited and affects intestinal veins and venules, specifically the mesenteric vein and its branches. Histologically, lymphocytic inflammatory with a necrotizing, granulomatous or mixed infiltrates and thrombosis are observed.^{12,13}

In 2006, we reported the case of a 17 year-old patient with SLE who reentered one year later for intense cramping abdominal pain, hemolytic anemia, proteinuria and lymphopenia. Elevated hepatic and pancreatic enzymes were also reported. The abdominal US (ultrasound) showed microlithiasic cholecystitis and pancreatitis. An open cholecystectomy was performed and the histopathology reports showed **segmental necrotizing vasculitis**. Treatment was started with pulse methylprednisolone and cyclophosphamide and the patient

showed improvement. Because of the histopathological findings and data regarding clinical activity, it was considered that the cholecystitis was part of the damage caused by the disease's activity.¹⁴

In 1983, Swanepoel¹⁷ was the first to describe the association between CAA and SLE, since then different reports have been issued.¹⁸⁻²² In *table 1* summarizes the main alterations our patients share with cases reported previously. It attracts our attention that the 3 cases reported here and the one reported previously¹⁴ by our Institute have lupus nephritis and hypertriglyceridemia, in comparison to only two of the rest of the reports. On the other hand, the presence of hemolytic anemia in two of the patients associated to other activity data on the disease, as could be the increase in proteinuria, leads to conclude that: 1. Patients with juvenile SLE go through a more aggressive illness, with greater multi-organ affliction, 2. In patients with disease activity that present abdominal pain, cholecystitis should be suspected. As mentioned by Mendoca et al., it is possible that acalculous cholecystitis is under diagnosed since the abdominal ultrasound is not part of the routine examination for patients with SLE. It is also important to comment that it is possible that data on vasculitis could not appear in the histopathological report of the first case because the patient received immunosuppressant treatment and was surgically intervened during a sub-acute stage.

CONCLUSIONS

Cholecystitis causes unsuspected and rather unrecognized abdominal pain in SLE patients. In the Institute's Lupus Clinic, we treat 119 patients, and only 4 of them have shown this entity. It attracts attention that in patients we reported and in 1 of the pediatric patients reported in the literature (*Table 1*), developed cholecystitis and lupus nephritis, for which more studies should be done to conclude that a direct relationship does exist.

Despite the multiple risks factors known in the SLE patients to develop cholecystitis, the fact is this entity is very uncommon in JSLE patients in large series, this is why it is a remarkable finding that three patients presented with activity of their illness, hypertriglyceridemia and hypercholesterolemia developed cholecystitis, more studies are need to determine if the activity illness and/or dyslipidemia could be the trigger, and permit identify this patients as high risk of complications.

To our knowledge this is the first cases reported in Mexican children with JSLE and cholecystitis.

We believe that acute cholecystitis, especially acalculous, should be suspected in SLE patients with abdominal pain, particularly those showing activity of the illness, and an abdominal US should be ordered as soon as possible.

Table I. Summary of SLE patients with cholecystitis.

Author	Gender	Age	Diagnosis	Morbidity	Histopathology	Serology +
Case 1	F	10	SLE AAC	Lupus nephritis Hypertriglyceridemia	AAC	ANA Anti-Sm Anti-DNA
Case 2	M	13	SLE AAC	Lupus nephritis Hypertriglyceridemia Hemolytic anemia Neuro LES		ANA Anti-DNA
Case 3	F	14	SLE ALC	Lupus nephritis Hemolytic anemia Hypertriglyceridemia		ANA AB2GP
De Leon et al. (2006)	F	17	SLE AMLC	Lupus nephritis Hypertriglyceridemia	Segmental necrotizing vasculitis and vascular occlusion	ANA Anti-Sm
Swanepoel et al. (1983)	F	22	SLE	Lupus nephritis	AAC	ANA
Newbold et al. (1987)	F	28	SLE APS		Vasculitis and thrombotic AAC	ANA
Newbold et al. (1987)	F	38	SLE		Vasculitis of small vessels	ANA Anti-DNA
Kamikura et al. (1998)	F	27	SLE		AAC	ANA Anti-DNA Anti-Sm
Rhoton et al. (1993)	F	22	SLE		Hemobilia	-----
Raijman et al. (1989)	F	34	SLE		Hemorrhagic AAC	ANA Anti-DNA ACA
Nolen et al. (1994)	F	22	SLE		CCA	ACA AL
Desailloud et al. (1998)	F	29	SLE		Ischemic cholecystitis and necrosis	ANA AL AB2GP
Shin et al. (2002)	F	39	SLE Sjögren APS		AAC	ANA Anti-DNA
Bando et al. (2003)	F	43	SLE		AAC	ANA Anti-DNA
Kara et al. (2004)	M	65	APS		AAC	-----
Baristaina et al. (2006)	M	10	SLE	Lupus nephritis	Perivascular mononuclear infiltrated AAC	Anti-PS ANA
Mendoça et al. (2009)	F	12	SLE		AAC	ANA Anti-Sm

SLE: Systemic Lupus Erythematosus, APS: Anti Phospholipid Syndrome, AAC: Acute Acalculous Cholecystitis, ALC: Acute Lithiasic Cholecystitis, AMLC: Acute Microlithiasic Cholecystitis. ANA: Anti Nuclear Antibodies, ACA: Anticardiolipin Antibodies, AntiB2GP: Anti-B2 Glycoprotein, Anti-PS: Anti- Phosphatidylserine.

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