

CASE REPORT

Thrombotic microangiopathy involving the gallbladder as an unusual manifestation of systemic lupus erythematosus and antiphospholipid syndrome: Case report and review of the literature

Beatriz De-Leon-Bojorge, Samuel Zaltzman-Girsevich, Arturo Ortega-Salgado, Adelina Prieto-Patron, Ruth Córdoba-Córdoba, Marco Yamazaki-Nakashimada

Beatriz De-Leon-Bojorge, Department of Pathology, Instituto Nacional de Pediatría Mexico City, Mexico
Samuel Zaltzman-Girsevich, Department of Nephrology, Instituto Nacional de Pediatría Mexico City, Mexico
Arturo Ortega-Salgado, Department of Surgery, Instituto Nacional de Pediatría Mexico City, Mexico
Adelina Prieto-Patron, Ruth Córdoba-Córdoba, Yamazaki-Marco Nakashimada, Department of Clinical Immunology, Instituto Nacional de Pediatría Mexico City, Mexico
Correspondence to: Marco Yamazaki-Nakashimada, MD, Department of Clinical Immunology, Instituto Nacional de Pediatría, Insurgentes Sur 3700-C, Col. Insurgentes Cuicuilco, C.P. 04350, Mexico City, Mexico. yzki71@yahoo.com.mx
Telephone: +52-55595526
Received: 2006-04-16 Accepted: 2006-05-25

<http://www.wjgnet.com/1007-9327/12/7206.asp>

INTRODUCTION

Gallbladder disease is no more common in patients with systemic lupus erythematosus (SLE) than in the general population^[1]. Scarce reports on acalculous cholecystitis (ACC) in SLE or in antiphospholipid syndrome (APS) have been described in the literature^[2-12]. We describe a patient with SLE, nephritis, pancreatitis and microlithiatic cholecystitis. Open cholecystectomy was performed and the histopathological findings revealed vasculitis and thrombotic microangiopathy in the gallbladder. She was diagnosed with secondary APS and started on anticoagulation therapy. Coincidentally, her lupus nephritis also improved. This case illustrates that calculous or acalculous cholecystitis should be considered as a manifestation of SLE and APS.

Abstract

Gallbladder disease is no more common in patients with systemic lupus erythematosus (SLE) than in the general population. We describe a 17-year-old patient with SLE, who developed nephritis that was well controlled with medications. Initial treatment consisted of azathioprine, aspirin and prednisone with stable control of her symptoms. Two years later she developed a right quadrant abdominal pain, and an abdominal ultrasound revealed microlithiasic cholecystitis. Open cholecystectomy was performed and the histopathological findings revealed vasculitis with thrombotic microangiopathy in the gallbladder. This case presentation illustrates that calculous or acalculous cholecystitis should be considered as a manifestation of active SLE and APS.

© 2006 The WJG Press. All rights reserved.

Key words: Gallbladder; Cholecystitis; Systemic lupus erythematosus; Antiphospholipid syndrome

De-Leon-Bojorge B, Zaltzman-Girsevich S, Ortega-Salgado A, Prieto-Patron A, Córdoba-Córdoba R, Yamazaki-Nakashimada M. Thrombotic microangiopathy involving the gallbladder as an unusual manifestation of systemic lupus erythematosus and antiphospholipid syndrome: Case report and review of the literature. *World J Gastroenterol* 2006; 12(44): 7206-7209

CASE REPORT

In 2002, a 17-year-old female with arthritis and oral ulcers was referred to the Instituto Nacional de Pediatría in Mexico City. Laboratory results showed autoimmune hemolytic anemia, leucopenia, lymphopenia, hypocomplementemia. She also had positive anti-nuclear antibodies (ANA), anti-dsDNA, anti- β_2 -glycoprotein-I, and anti-cardiolipin antibodies. Based on her clinical presentation and laboratory studies, she was diagnosed with SLE. Initial treatment consisted of azathioprine, aspirin and prednisone with stabilization of symptoms. In 2003 she presented with renal complication including proteinuria and hematuria. Oral cyclophosphamide was started with improvement in her renal function. In 2004 she developed right quadrant abdominal pain, and an abdominal ultrasound revealed microlithiasic cholecystitis. The abdominal pain spontaneously resolved and dietary modifications were initiated. She was clinically well until July 2005 when she presented with a flare consisting of hypertension, autoimmune hemolytic anemia and marked proteinuria.

On admission the physical examination was unremarkable. Laboratory tests showed proteinuria: 7.2

g/d, serum Cr: 1.6 g/dL, Coombs: +, Hb: 9.3 g/dL, leucocyte count: 3300/mm³, total lymphocyte count: 369, platelets: 218 000/mm³. Immunological tests were positive for anti-dsDNA, anti- β_2 -glycoprotein- I, and anticardiolipin antibodies, CH50: 49 IU/mL (normal 150-250 IU/mL), C3: 21 mg/dL (normal 86-184 mg/dL), C4: 5.3 mg/dL (normal 19-58 mg/dL). She was started on methylprednisolone and cyclophosphamide.

A renal biopsy showed a global, diffuse, proliferative and membranous glomerulonephritis (class IV-V) without thrombosis. During her admission she developed acute abdominal pain, including a positive Murphy sign on exam. Liver and pancreatic function tests were elevated: gamma-glutamyltranspeptidase was 210 mU/mL (30-60 mU/mL), AST 339 mU/mL (11-33 mU/mL) ALT 154 mU/mL (4-30 mU/mL), total bilirubin 1.1 mg/dL (0.2-1.0 mg/dL) with direct bilirubin, 0.6 mg/dL, amylase 932 mU/mL (68-215 mU/mL) and lipase 649. Abdominal ultrasound revealed lithiasic cholecystitis and pancreatitis. The patient underwent open cholecystectomy and histopathological findings of the gallbladder showed segmental necrotizing vasculitis and vascular occlusion with fragmented erythrocytes (Figures 1A and 1B). Anticoagulation therapy was started with subsequent resolution of the proteinuria and normalization of the laboratory values including the creatinine level.

DISCUSSION

A variety of gastrointestinal complications have been reported in association with systemic lupus erythematosus (SLE), including mesenteric arteritis, intestinal perforation, and peritonitis^[9]. Gallbladder disease is no more common in patients with systemic lupus erythematosus than in the general population^[1]. Gallstone disease is a common condition in Western populations, and its etiology is multifactorial, including genetic and environmental factors. Hemolysis, obesity, aging, estrogen treatment, pregnancy and diabetes are consistently associated with a higher risk of developing gallstones^[10].

Symptomatic gallbladder vasculitis requiring treatment by cholecystectomy is rare. Chen^[13] has divided the gallbladder vasculitis into three groups: gallbladder vasculitis as a manifestation of polyarteritis nodosa (group 1), gallbladder vasculitis occurring in diseases known to be associated with vasculitis as in our SLE case (group 2) and isolated gallbladder vasculitis (group 3). In 1983, Swanepoel *et al*^[5] described the first case of acute acalculous cholecystitis (ACC) in SLE. Since then, only a few SLE cases have been reported in the literature. Newbold *et al*^[9] have reported two cases of gallbladder involvement in patients with SLE; histologically there was acute arteritis with periarterial fibrosis, changes similar to those found in polyarteritis nodosa. In fact, the development of gallbladder disease appears to be more common in polyarteritis nodosa than in SLE. Recently, Bando *et al*^[12] have reported a case of acalculous cholecystitis induced by mesenteric inflammatory veno-occlusive disease in SLE. Although surgical removal of the gallbladder is the generally accepted treatment for SLE patients who develop acute cholecystitis successful

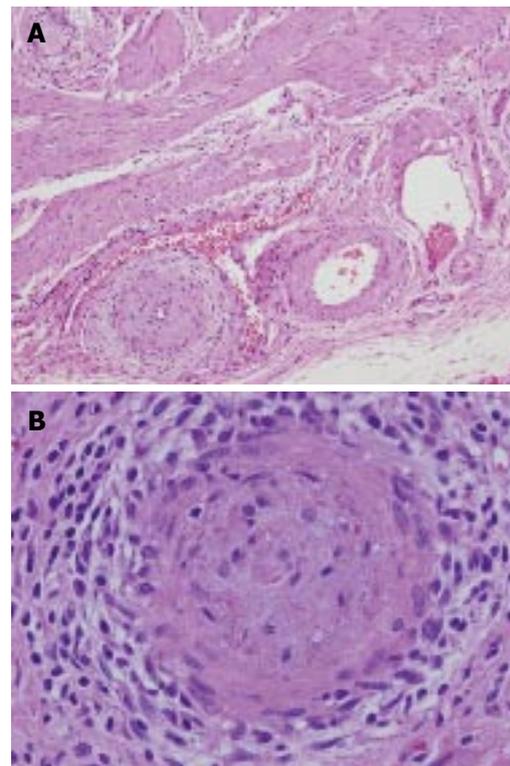


Figure 1 Occlusion with fibrosis in a gallbladder artery (HE x 1) (A); Total artery occlusion, fragmented erythrocytes and perivascular inflammation with mononuclear infiltration (B).

treatment with corticosteroids alone has also been reported^[11]. It is of note that, rarely, the symptoms of serositis can mimic those of acute cholecystitis^[13,14].

Antiphospholipid syndrome (APS) was first described in patients who suffered from recurrent fetal loss and thromboses. Since then the spectrum of associated symptoms in APS has broadened considerably. The clinical criteria for diagnosis of APS include arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis has to be confirmed by imaging, Doppler studies or histopathology. For laboratory diagnosis of APS, affected patients have antibodies to β_2 -glycoprotein- I, cardiolipins or positive lupus anticoagulant in two separate occasions at least 6 wk apart. Gallbladder involvement secondary to APS has rarely been described in the literature. Dessailoud *et al*^[2] reported a fatal case of a 29-year-old woman with acalculous cholecystitis secondary to catastrophic APS. The patient developed mesenteric ischemia, left limb ischemia and acute renal failure. In another report, Nolen *et al*^[3] have described a 26-year-old female with primary APS who was treated successfully with medical management. Rhoton *et al*^[8] described a 22-year-old woman with SLE who developed hemobilia, and also had high titers of anticardiolipin antibodies.

Our case presented with thrombotic and inflammatory complications involving the gallbladder, likely secondary to both SLE and APS. The vasculopathy showed thrombotic microangiopathy (TMA) and perivasculitis. Although microlithiasis could have contributed to the inflammatory process located in the gallbladder and pancreas, the presence of vasculitis reflects an autoimmune process.

Table 1 SLE and APS cases reported in the literature with gallbladder involvement

Author	Gender	Age(yr)	Diagnosis	Gallbladder pathology	Serology
Present report (2006)	F	17	SLE/APS	TMA Vasculitis	ANA Anti-DNA Anticardiolipin
Newbold <i>et al</i> (1987)	F	28	SLE	Acalculous Cholecystitis vasculitis and thrombosis	ANA
Newbold <i>et al</i> (1987)	F	38	SLE	Small vessel vasculitis	ANA Anti-DNA
Kamimura <i>et al</i> (1998)	F	27	SLE	ACC	ANA Anti-DNA Anti-Sm
Rhoton <i>et al</i> (1993)	F	22	SLE	Hemobilia	Not specified
Rajjman <i>et al</i> (1989)	F	34	SLE	Hemorrhagic Acalculous Cholecystitis	ANA Anti-DNA Anticardiolipin Anti-platelet antibodies
Swanepoel <i>et al</i> (1983)	F	22	SLE	AAC	ANA
Bando <i>et al</i> (2003)	F	43	SLE	AAC	ANA Anti-DNA
Shin <i>et al</i> (2002)	F	39	SLE Sjogren syndrome	AAC	ANA Anti-dsDNA Anti-Ro
Nolen <i>et al</i> (1999)	F	26	APS	AAC	Anticardiolipin Lupus antcoagulant
Kara <i>et al</i> (2004)	M	65	APS	AAC	Not reported
Dessailloud <i>et al</i> (1998)	F	29	APS	Acalculous Ischemic Gallbladder Necrosis	ANA β -glycoprotein- I Antiphosphatidylserine

Eventually the histopathological findings helped us diagnose the APS and initiate anticoagulation therapy, which led to improvement of our patient's renal disease. Although presence of small gallstones is associated with increased risk of acute pancreatitis, our patient's pancreatitis could also be a manifestation of APS^[15]. All the SLE and APS cases reported in the literature with gallbladder involvement are summarized in Table 1. Of note is that our patient is the youngest patient described to date, reflecting the rarity of this complication in the pediatric age group.

Renal thrombotic manifestations have been reported since the initial description of APS. TMA is the best known characteristic lesion of APS nephropathy, leading to hypertension, proteinuria and renal impairment. Recently, consideration of the APS nephropathy in every SLE case has been emphasized because successful treatment requires both anticoagulation in addition to immunosuppression^[16].

In summary, although rare, gallbladder involvement in patients with SLE should raise the suspicion of vasculitis or APS. We believe that both gallbladder vasculitis and thrombosis contributed in the clinical picture of our patients. Sometimes surgical cholecystectomy is needed for both therapeutic and diagnostic purposes. If thrombotic manifestations of APS are documented, anticoagulation therapy should be started.

ACKNOWLEDGMENTS

The authors thank Dr. Joann Lin for technical assistance and invaluable discussions.

REFERENCES

- 1 **Hallegrua DS**, Wallace DJ. Gastrointestinal and hepatic manifestations. In: Wallace DJ Hahn BH (eds) *Dubois Lupus Erythematosus*. 6th ed. Baltimore: Williams and Wilkin, 2000: 843-886
- 2 **Desailloud R**, Papo T, Vaneecloo S, Gamblin C, Vanhille P, Piette JC. Acalculous ischemic gallbladder necrosis in the catastrophic antiphospholipid syndrome. *Arthritis Rheum* 1998; **41**: 1318-1320
- 3 **Nolen N**, Bellaiche G, Warmberg C, Nouts A, Ley G, Slama JL. [Acute acalculous cholecystitis associated with primary antiphospholipid antibody syndrome. Cure with low-molecular-weight heparin and antivitamin K]. *Gastroenterol Clin Biol* 1999; **23**: 144-146
- 4 **Kara E**, Ayden H. Antiphospholipid antibody syndrome (APS) presenting as splenic thrombosis and acute acalculous cholecystitis. *Acta Chir Belg* 2004; **104**: 733-735
- 5 **Swanepoel CR**, Floyd A, Allison H, Learmonth GM, Cassidy MJ, Pascoe MD. Acute acalculous cholecystitis complicating systemic lupus erythematosus: case report and review. *Br Med J (Clin Res Ed)* 1983; **286**: 251-252
- 6 **Suwa A**, Hama N, Kawai S, Ishiyama K, Tanabe M, Yamada T, Goto M, Nakajima A, Kashiwazaki S, Inada S. [A case of Sjogren's syndrome and systemic lupus erythematosus complicated with necrotizing angitis of the gallbladder]. *Ryumachi* 1995; **35**: 904-909
- 7 **Shin SJ**, Na KS, Jung SS, Bae SC, Yoo DH, Kim SY, Kim TH. Acute acalculous cholecystitis associated with systemic lupus erythematosus with Sjogren's syndrome. *Korean J Intern Med* 2002; **17**: 61-64
- 8 **Rhoton AJ**, Gilliam JH, Geisinger KR. Hemobilia in systemic lupus erythematosus. *South Med J* 1993; **86**: 1049-1051
- 9 **Newbold KM**, Allum WH, Downing R, Symmons DP, Oates GD. Vasculitis of the gall bladder in rheumatoid arthritis and systemic lupus erythematosus. *Clin Rheumatol* 1987; **6**: 287-289
- 10 **Rajjman I**, Schragar M. Hemorrhagic acalculous cholecystitis

- in systemic lupus erythematosus. *Am J Gastroenterol* 1989; **84**: 445-447
- 11 **Kamimura T**, Mimori A, Takeda A, Masuyama J, Yoshio T, Okazaki H, Kano S, Minota S. Acute acalculous cholecystitis in systemic lupus erythematosus: a case report and review of the literature. *Lupus* 1998; **7**: 361-363
- 12 **Bando H**, Kobayashi S, Matsumoto T, Tamura N, Yamanaka K, Yamaji C, Takasaki C, Takasaki Y, Hashimoto H. Acute acalculous cholecystitis induced by mesenteric inflammatory veno-occlusive disease (MIVOD) in systemic lupus erythematosus. *Clin Rheumatol* 2003; **22**: 447-449
- 13 **Chen KT**. Gallbladder vasculitis. *J Clin Gastroenterol* 1989; **11**: 537-540
- 14 **Martinez D**, Lowe R. Case report: systemic lupus erythematosus (SLE) serositis mimicking acute cholecystitis. *Clin Radiol* 1991; **44**: 434-435
- 15 **Venneman NG**, Buskens E, Besselink MG, Stads S, Go PM, Bosscha K, van Berge-Henegouwen GP, van Erpecum KJ. Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy? *Am J Gastroenterol* 2005; **100**: 2540-2550
- 16 **D'Cruz DP**. Renal manifestations of the antiphospholipid syndrome. *Lupus* 2005; **14**: 45-48

S- Editor Wang J L- Editor Wang XL E- Editor Lu W