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

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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 microlithiasic 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.

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-β2-glicoprotein-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. 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.

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 prednison 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.

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

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-β2-glicoprotein-1, and antiphospholipid 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 fragmentated 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. Gallbladder disease is no more common in patients with systemic lupus erythematosus than in the general population. 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.

Symptomatic gallbladder vasculitis requiring treatment by cholecystectomy is rare. Chen 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. described the first case of acute acaulocysitis (ACC) in SLE. Since then, only a few SLE cases have been reported in the literature. Newbold et al. have reported two cases of gallbladder involvement in patients with SLE; histologically there was acute arteritis with periartherial 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. have reported a case of acaulocysitis 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 treatment with corticosteroids alone has also been reported. It is of note that, rarely, the symptoms of serositis can mimic those of acute cholecystitis.

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 β2-glicoprotein-1, 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. Dessailloud et al. reported a fatal case of a 29-year-old woman with acaulocysitis secondary to catastrophic APS. The patient developed mesenteric ischemia, left limb ischemia and acute renal failure. In another report, Nolen et al. have described a 26-year-old female with primary APS who was treated successfully with medical management. Rhoton et al. described a 22-year-old woman with SLE who developed hemobilia, and also had high titers of antiphospholipid 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 perivascularitis. Although microthiasis could have contributed to the inflammatory process located in the gallbladder and pancreas, the presence of vasculitis reflects an autoimmune process.
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.

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**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                    | ANA                       |
| Newbold et al (1987)        | F      | 28      | SLE             | Acalculous Cholecystitis | ANA                       |
| Newbold et al (1987)        | F      | 38      | SLE             | Small vessel vasculitis| ANA                       |
| Kamimura et al (1998)       | F      | 27      | SLE             | ACC                    | ANA                       |
| Rhoton et al (1993)         | F      | 22      | SLE             | Hemobilia              | Not specified             |
| Raijman et al (1989)        | F      | 34      | SLE             | Hemorrhagic            | ANA                       |
| Shin et al (2002)           | F      | 39      | SLE             | Acalculus Cholecystitis| Not reported              |
| Swanepoel et al (1983)      | F      | 22      | SLE             | AAC                    | ANA                       |
| Bando et al (2003)          | F      | 43      | SLE             | AAC                    | Not reported              |
| Nolen et al (1999)          | F      | 26      | SLE             | AAC                    | ANA                       |
| Kara et al (2004)           | M      | 65      | APS             | AAC                    | ANA                       |
| Dessailoud et al (1998)     | F      | 29      | APS             | Acalculous             | ANA                       |
|                            |        |         |                 | Ischemic               | $\beta$-glycoprotein-1    |
|                            |        |         |                 | Gallbladder Necrosis   | Antiphosphatidylserine    |
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S-Editor Wang J  L-Editor Wang XL  E-Editor Lu W