We describe a case of a young female with lupus that complained about suprapubic pain, dysuria, fever and vomits, symptoms first interpreted as pyelonephritis, despite negative cultures and imaging studies showing hydroureteronephrosis with inflammatory changes. When she developed malar rash, anasarca and nephrotic syndrome, the diagnosis of lupus cystitis with stage IV nephropathy was made, and she started immunosuppressive induction treatment with three pulses of methylprednisolone followed by oral prednisolone (60 mg/d) and mycophenolate (1.5 g/d). One month later she was admitted again with blood exams compatible with thrombotic microangiopathy, requiring aggressive immunosuppression and plasma exchange. After overcoming multiple complications, the patient gradually improved, and was discharged with close surveillance. This case poses the question: if the urogenital involvement had been recognized and treated in time, would it prevent the onset of lupus nephritis and other complications?

Keywords: Systemic lupus erythematosus;

INTRODUCTION

Lupus cystitis is a manifestation of systemic lupus erythematosus (SLE) mainly reported in the Asian literature and in Asian patients living in Western countries. It was first described by Nitze in 1907, and the concept of “lupus cystitis”, defining interstitial cystitis complicated with SLE, was first used by Orth et al. The incidence has been estimated as 0.01% with female predominance of 92%. It is characterized by bladder irradiation symptoms with few abnormal urinalysis results, hydroureteronephrosis and reduced bladder capacity, associated with gastrointestinal involvement. The delay on diagnosis and prompt corticosteroid therapy can lead to irreversible damage, such as progressive bladder fibrosis and obstructive uropathy resulting in renal failure.

Thrombotic microangiopathy (TMA) is also a rare, life-threatening disease, rarely reported in SLE. According to a cohort study by Ming-Han et al, there are only 129 cases in the English literature, most of them being sporadic case reports. Kwok et al estimated an incidence rate of approximately 2.2%. Microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, renal impairment, fever and neurologic manifestations are the main features of this condition. SLE complicated by two rare disorders, and the exhaustive immunosuppressive treatment used based on case reports led to a favorable outcome.

CASE REPORT

We describe a 27-year-old female diagnosed with SLE in 2007, with malar rash, photosensitivity and arthritis, responsive to prednisolone (PDN) 10 mg/day (d) and hydroxychloroquine (HCQ) 400 mg/d. In 2010 she had a disease flare during pregnancy, resolved by a transitory increase of corticosteroid therapy and pre-term birth. In October 2011 she developed malar rash and presented low complements, so azathioprine was started in increasing doses up to 2 mg/Kg/d.

In December/2011 the patient went three times to the hospital emergency room (ER) with dysuria, lumbar and suprapubic pain interpreted as a renal colic. During the assessments an ultrasonography and subsequently a pelvic tomography were done, both showing right hydroureteronephrosis and ureteral wall thickening with inflammatory changes without obs-
truction. The blood tests had no leukocytosis, the C reactive protein (CRP) was of 9.9 mg/L (NR 5.0 mg/L) and the urinalysis was normal. She was treated with analgesics and antibiotics.

In the following three months she was admitted several times with the same complaints associated with fever (38°C) and persistent vomits, diagnosed as pyelonephritis, but always with negative cultures. By this time she presented bilateral hydronephrosis (15.5 mm left; 8.8 mm right), and persistent inflammatory changes, in the pelvic tomodography (Figure 1). Renal function and urinalysis were normal. Permanent urinary catheterization was needed as a result of an hypotonic bladder.

She returned to the ER with anasarca and malar rash (Figure 2). Laboratory tests showed worsening of renal function and nephrotic range proteinuria, with casts and erythrocytes. She was hospitalized in the Rheumatology department (RhD). Blood tests confirmed: hemoglobin (Hb) 8.9 g/dl, ESR 129 mm/1st hour, CRP 1.2 mg/L, creatinine 2.5 mg/dl, hypocomplementemia and elevated anti-dsDNA antibodies (Ab) (498UL/ml). Renal biopsy was consistent with lupus nephropathy class IV (WHO), with an activity index of 9 and a chronicity index of 2. It also showed some hya line thrombi.

Diagnosis of Lupus enteritis was assumed because the patient presented persistent vomiting, nausea and marked weight loss associated with generalized edema of the gastrointestinal mucosa (Figure 3) in the upper endoscopy, unfortunately biopsy couldn’t be performed because the mucosa was very fragile.

She was diagnosed with lupus cystitis with stage IV nephropathy and started induction treatment with three intravenous pulses of methylprednisolone (MTP) 500mg and mycophenolate mofetil (MMF) 1.5 g/d. She was discharged also with HCQ 400mg/d, prednisolone 60 mg/d, furosemide 160 mg/d, lisinopril 2.5 mg/d, calcium and vitamin D supplementation, tansulosine 0.4 mg/d, omeprazol 20 mg/d, cotrimoxazole (CTX) prophylaxis, nystatine (for oral candidiasis) and urinary perm cath.

One month later, the patient presented anasarca associated with pancytopenia: normocytic normochromic anemia (hemoglobin 6.8 g/dL), leucopenia (3.81x10⁹/L) and thrombocytopenia (99x10⁹/mL). Her renal function had improved, but maintained hypoalbuminemia (24.4 g/L), nephrotic range proteinuria (4.0 g/L). MMF and CTX were suspended for the possibility of bone marrow toxicity and three intravenous pulses of MTP 500mg were given without hematologic response. Further laboratory tests were compatible with microangiopathic hemolytic anemia (blood smear with schistocytes, elevated lactate dehydrogenase (LDH) and low haptoglobin). Coombs’test, anticardiolipin antibodies and lupus anticoagulant were negative. Blood cultures were negative and urine culture was positive for multisensible E. coli, treated
with ceftriaxone. Her SLE Disease Activity Index was 10.

The case was discussed in a multidisciplinary meeting. Assuming the diagnosis of TMA the patient was admitted in an intermediate care unit. She began daily sessions of plasmapheresis and immunosuppressive treatment, based on a similar case report: intravenous cyclophosphamide (CYC) 750 mg once per month, rituximab (RTX) 375 mg/m² weekly for a total of 4 administrations and PDN 80 mg/d with progressive dose tapering. Analytic stability was achieved but multiple complications arose that hampered the prognosis: neutropenic fever needing granulocyte colony stimulating factors treatment; opportunistic infections (cellulitis, catheter associated infections, oral candidiasis and candiduria); serous chorioretinitis associated to corticosteroids (with improvement after dose reduction); acute pulmonary edema and electrolyte imbalance, which contributed to a depressive syndrome. At this time patient infectious risk was too high to allow another CYC cycle.

One month later, she had clinical worsening, sustained thrombocytopenia and increasing LDH so she started plasmapheresis twice a day and ultrafiltration. A cycle of two days with intravenous immunoglobulin (IVIG) (a total of 80 g) was also administered. Within a week the patient improved significantly, plasma exchange was suspended and PDN decreased from 60 to 30 mg/d. She initiated physical rehabilitation care and training for intermittent urinary catheterization and was finally discharged two weeks later with close surveillance, medicated with HCQ 400 mg/d, PDN 20 mg/d, losartan 50 mg/d, prophylactic CTX, aspirin 100 mg/d, rosvastatin 10 mg/d, pantoprazole 40 mg/d, calcium and vitamin D supplementation with weekly alendronic acid and sertraline.

Her analytical parameters stabilized and she went on remission with resolution of the ureteropelvic dilatation. She evolved from urinary catheterization each six hours to spontaneous voiding without residual urine. MMF 1 g/d was restarted with PDN 15 mg/d two weeks after discharge.

One year later she is on remission and regained autonomous bladder function, with MMF 1 g/d and HCQ 400 mg/d, without PDN and no need to repeat RTX.

**DISCUSSION**

Interstitial cystitis should be suspected in the presence of bladder irritation symptoms with few abnormal urinalysis results, associated with gastrointestinal manifestations, like enteritis. The diagnosis is reinforced by the observation of hydronephrosis or gastrointestinal wall edema in ultrasonography or tomography, by the presence of reduced bladder capacity or by edema and inflammatory infiltration on bladder biopsy. Our patient exhibited dysuria, suprapubic pain, bilateral hydronephrosis, norm al urinalysis, bladder dysfunction, weight loss, persistent nausea and vomiting with gastric wall edema, supporting the diagnosis of lupus cystitis with associated lupus enteritis.

Interstitial cystitis is associated not only with SLE, but also with other connective tissue diseases as Sjögren’s syndrome and Rheumatoid arthritis. Its physiopathology remains unclear, but immune complex mediated vasculitis, anti-bladder and anti-intermediate filament Abs and elevation of interleukin-8, monocyte chemotactic activating factor and urinary chemokines have been implicated in the pathogenesis of this process. In our patient, SLE was diagnosed 4 years before the onset of lupus cystitis. In a study describing bladder changes in 413 patients with SLE, 10 had urinary complaints, and of these, 5 had lupus cystitis. All presented gastrointestinal symptoms, bilateral hydronephrosis and bladder wall thickening on computerized tomography. Bladder irritation symptoms, previously described in our patient, are also documented by several case reports.
The relationship between interstitial cystitis and hydroureteronephrosis reveals a possible common smooth muscle dysmortality. The association between cystitis, enteritis and renal involvement has been consistently described. A study by Yuji et al. reported on a total of 78 patients with lupus cystitis, concurrent or subsequent development of lupus enteritis (81.7%) and renal involvement (61.3%)1. They also stated that lupus enteritis, female gender and positivity of anti-ds-DNA were risk factors for lupus cystitis. Furthermore early diagnosis and corticosteroid therapy are essential for a good prognosis4. A delay of six months on starting corticosteroid was related to poor urinary bladder function1. In our case we had a five month delay, crucial for the sustained inflammatory state that allowed the evolution of the disease with subsequent lupus nephropathy (LN).

Lupus cystitis responds well to corticosteroid pulse therapy and other immunosuppressive agents, such as cyclosporine and cyclophosphamide. Based on age and prognostic factors, we decided to treat the patient with pulses of MTP and MMF, with good response. Some studies also report the efficacy of cetirizine hydrochloride for lupus cystitis refractory to corticosteroid1.

The association of TMA and SLE is also rare, about 1.0% in a cohort study by Ming-Han Chen et al. Active SLE disease has been considered an independent risk factor for TMA development, but the pathogenesis seems to be multifactorial, including low ADAMTS13 levels, SLE disease activity, infection, drugs, etc5.

The incidence of class IV LN and TMA was reportedly up to 8.3%6. Also the incidence of anemia, leukopenia and thrombocytopenia is very high in patients with this association8. Our patient had a previous renal biopsy confirming class IV LN and microangiopathic haemolytic anemia (presence of schistocytes, elevated LDH and low haptoglobin), leukopenia and thrombocytopenia. There were some hyaline thrombi on the renal biopsy without evidence of a concomitant antiphospholipid syndrome or renal artery thrombosis.

The lack of randomized control trial due to the rarity of these disorders made it necessary to search the literature for the description of similar cases, and also the close cooperation with other medical specialties to define a treatment path. Based on the results described by Gharbi et al., we decided to use a similar scheme, adapted to our patient's clinical complications. Addition of plasma exchange enhances the prognosis compared to immunosuppressive therapy alone8. The initial response was not as good as expected, but after intensifying plasmapheresis concomitantly with a pulse of immunoglobulin, a sustained increase in platelets occurred, schistocytes disappeared and LDH and haptoglobin level normalized.

It has been advised to perform plasma exchange continuously in refractory cases, until haemoglobin, platelet count and creatinine return to normal levels8. Rituximab and IVIG are also alternative options in such cases8. TMA mortality improved after the introduction of plasma exchange, but in the coexistence of SLE mortality is still high (31.9%-52%), especially if the patient presents four or more TMA features8, and even higher when infection is present (72.2%)3. Fortunately our patient survived, is now in remission and without sequelae of the disease.

CONCLUSION

This case stands out for the rarity of its clinical manifestations, especially the urogenital involvement in SLE. We believe that the delayed diagnosis had a negative impact on the disease evolution and on the appearance of cumulative complications. Nevertheless the subsequent aggressive immunosuppressive treatment and plasmapheresis used to treat TMA were crucial, and despite all the intrinsic risks, the final outcome confirmed that the right choices were made.

Finally, the description of rare cases regarding clinical presentation, treatment and outcome is essential for the guidance of patients with similar manifestations. It also provides data that might be used to gather information from which data and epidemiological characteristics of these diseases could be derived.

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