

Case Report

Successful Treatment of Recurrent Pancreatitis Secondary to Systemic Lupus Erythematosus with B-cell Depletion Therapy

Zakiya S. Al-Musawi MD¹, Umesh J. Nabar MD²

Abstract

Recurrent pancreatitis secondary to systemic lupus erythematosus is a rare entity of unknown etiology. We report an adolescent with systemic lupus erythematosus and recurrent attacks of acute pancreatitis, which were poorly controlled with conventional therapy for approximately four years. Rituximab, a chimeric anti-CD20 monoclonal antibody therapy resulted in remission of symptoms for more than two years without major toxicity of treatment. Based on tolerability and high efficiency of rituximab therapy, we would suggest using B-cell depletion therapy as an alternative therapy for refractory pancreatitis secondary to systemic lupus erythematosus.

Keywords: pancreatitis, rituximab, systemic lupus erythematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease characterized by a broad range of clinical and serological manifestations. Acute pancreatitis (AP) was reported as an initial manifestation of SLE or it may complicate the clinical course of SLE.¹

The association between SLE and pancreatitis was first documented in 1939 and since then many cases have been reported.^{2,3} Subclinical pancreatitis with elevations of serum amylase occurs more frequently in SLE during flare-up and inactive disease than symptomatic pancreatitis.⁴ Moreover, SLE pancreatitis can be acute, chronic, or fulminant.^{5,6}

Rituximab (RTX) is a chimeric mouse-human monoclonal antibody against a transmembrane protein, the CD20 antigen, present on B lymphocytes. RTX has been used as an adjuvant therapy in childhood-onset SLE or as an alternative therapy after failure of conventional immunosuppressive drugs. Furthermore B-cell depletion therapy has been used in life-threatening conditions in SLE.⁷⁻⁹ Based on the satisfactory results of cases reported, we have proposed an alternative treatment for pancreatitis in SLE.

Here, we report an adolescent boy with SLE who developed recurrent attacks of AP for four years. In spite of clinical and laboratory response to steroid therapy he was unable to tolerate its side effects. B-cell depletion agent was used as an alternative therapy for his recurrent pancreatitis.

Authors' affiliations: ¹Department of Pediatrics, Salmaniya Medical Complex, Manama, Kingdom of Bahrain, ²Department of Radiology, Salmaniya Medical Complex, Manama, Kingdom of Bahrain.

Corresponding author and reprints: Zakiya Al Mosawi MD, Tel: +973-17-279234, Fax: +973-17-279738,

E-mail: zakee08@hotmail.co.uk

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Following RTX therapy, no episodes of AP have been reported. This case illustrated the safety and effectiveness of B-cell depletion therapy for patients who develop recurrent pancreatitis secondary to SLE.

Case Report

A seventeen-year-old Bahraini boy presented at the age of 12 years with a history of intermittent epigastric pain and vomiting of five months duration. Apart from tender epigastrium, his vital signs and systemic examination were unremarkable. His laboratory results showed: Hb 10.9 g/dL, Hct 0.32, wbc 6.7 10⁹/L and platelets 271 10⁹/L, serum amylase 801 U/L (N: 23 – 85), and urine amylase of 8845 u/L (N<400). Cholesterol, triglycerides, calcium, phosphorus, LDH, and liver function tests were normal. Viral and bacterial serology was negative as was *H.pylori*.

Abdominal sonography showed diffuse enlargement of the pancreas, particularly the body and tail. Abdominal CT-scan revealed diffuse enlargement of the pancreas with rather low density and some irregularity of the margins (Figure 1). SA was conservatively treated and five days later the serum amylase levels dropped to 256 u/L, urine amylase to 997 u/L and he was clinically well.

Six months later, the patient was re-admitted for epigastric pain, fever, facial rash, swollen wrists, and photosensitivity. On examination, he was febrile and noticed to have a butterfly rash, vasculitic rashes in the upper extremities, swelling in both wrists, and metacarpophalangeal joints bilaterally, with effusion and mild epigastric tenderness. The family history revealed that his mother died three years prior due to renal failure secondary to SLE and his father

had hypertension. Therefore, the patient was worked-up for a possible diagnosis of SLE. His laboratory results revealed a normal CBC, ESR: 93 mm/hr, ANA: 1/640, and anti-ds DNA antibody 30 IU/mL (N<10 IU/mL). Extractable nuclear antigen antibody (ENA) results were as follows: Sjögren's syndrome antigen A (SSA) and antigen B (SSB) antibodies were positive; anti-smith (Sm) antibody and anti-small nuclear ribonucleoprotein (sn RNP) antibody were equivocal, decreased C3: 65 mg/dL (N:90 – 180) and undetectable C4 (N:10 – 40 mg/dL). During this admission the serum amylase was slightly elevated (257u/L). Urine analysis showed traces of protein, RBC: 8 – 10, WBC: 10 – 15, granular cast and 24 hour urine protein was 0.17gr/day (N: 0.05 – 0.1). Serum IgA, IgM, IgG, and IgG subclasses were within normal ranges. He fulfilled the criteria of SLE and accordingly was treated with the following drugs: hydroxychloroquine (HCQ), nonsteroidal anti-inflammatory drug (NSAID), captopril and prednisolone (1.2 mg/kg).

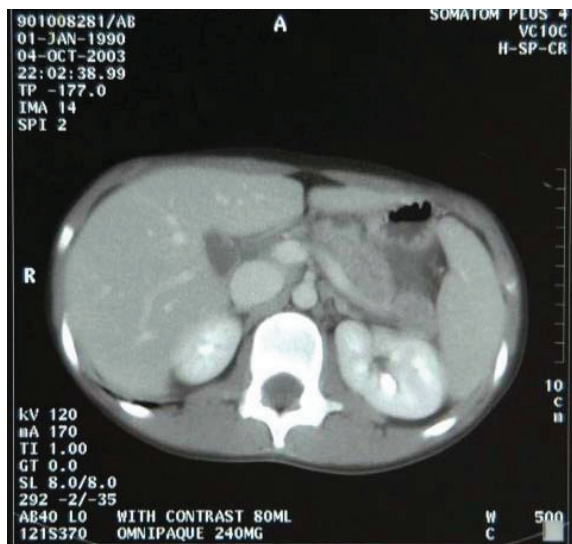


Figure 1. CT-scan of abdomen. Diffuse enlargement of the pancreas with rather low density and same irregularity of the margins (long arrow). There is fluid collection in the lesser sac and the anterior peri renal space; however the pancreatic duct appears of normal caliber (short arrow). No evidence of calcification in the pancreas is seen

The patient's condition improved, including his urine analysis. C3 and C4 increased to normal levels. His renal status remained stable and no renal biopsy was done for him at this stage. Later, the prednisolone dose was gradually tapered by 5 mg/month.

The patient developed recurrent attacks of AP (five attacks) over the subsequent two years associated with flaring of his SLE activity while he was on small doses of prednisolone (5 mg, once daily). He was managed with pulses of methylprednisolone (MP) in addition to azathioprine.

Three years after being diagnosed with SLE, SA de-

veloped back pain and osteoporotic changes in the thoracolumbar spine, L2-L4, on MRI (Figure 2). He had an episode of pancreatitis while on treatment for osteoporosis. Cyclophosphamide (CYC) was given, which made the attacks quiescent for four months. The prednisolone dose was further reduced to 5 mg every other day (EOD). Intravenous immunoglobulin (IVIG) and another CYC pulse therapy were given a few months later for new episodes of AP (Figure 3). However, this adolescent and his family refused more doses of CYC therapy. Mucophenolate Mofetil (MMF) was suggested but the patient was unable to tolerate it because of gastrointestinal upset. Azathioprine was discontinued because of high liver enzymes.

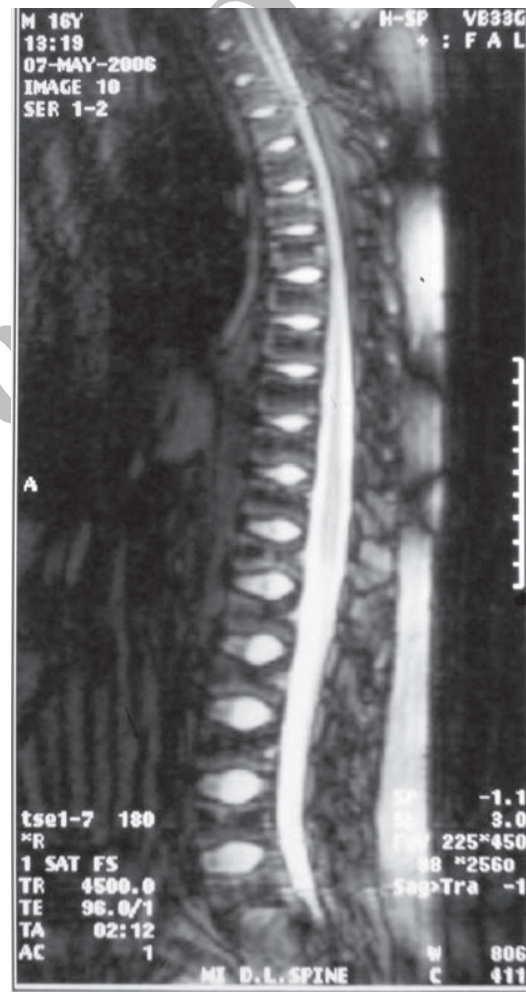


Figure 2. MRI of thoracolumbar spines. The vertebral bodies have biconcave configuration due to infractions of the endplates. It was also noted bright signal intensity of the vertebral bodies on T1 sequences indicative of fatty replacement of the marrow

Five months after CYC pulse therapy, SA had two attacks of AP at short intervals, which were treated with pulses of

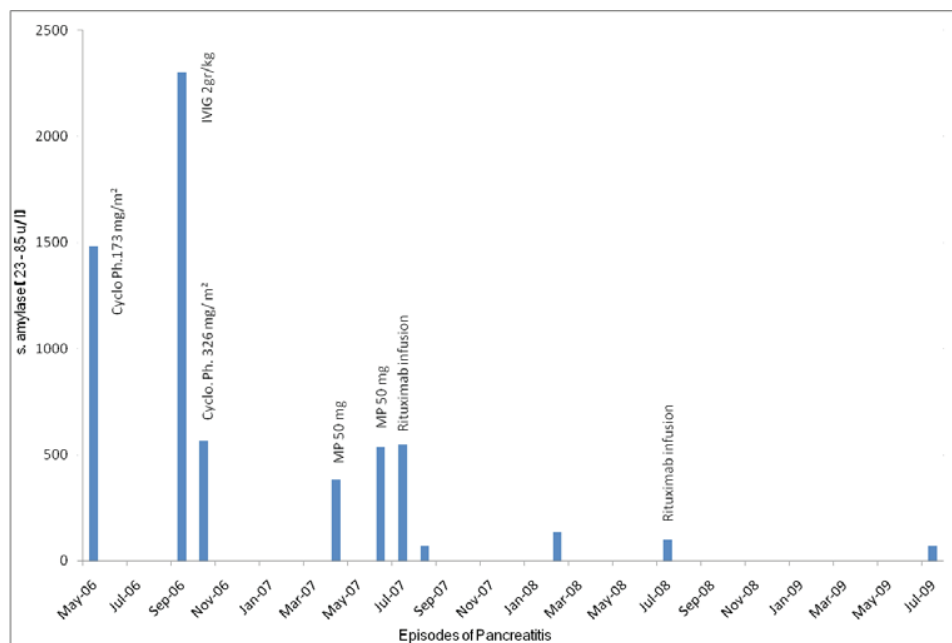


Figure 3. Paecreatitis episodes and the treatment. Cyclo Ph=cyclophosphamide, MP=methylprednisolone

Table 1. Laboratory results before, 2 weeks and 6 months after rituximab infusion

Lab data	Day 0	2 Weeks	6 months
ESR (mm/hr)	5	8	2
WBC (10 ⁹ /L)	4.4	3.7	10.0
HB (gr/dL)	14.2	13.1	15.9
Platelets (10 ⁹ /L)	305	284	311
Amylase (u/L)	550	69	135
C3 (N: 90 – 180 mg/dL)	107	97	135
C4 (N: 10 – 40 mg/dL)	16	14	22.3
IgA (g/L)	2.2	2.09	2.11
IgG (g/L)	13.8	NA	14.6
IgM (g/L)	0.3	0.332	0.291
CD19 (11 – 16%)	14%	0%	2%
CD20 (11 – 16%)	14%	0%	2%

MP 1 mg/kg. At this stage we suggested B-cell depletion therapy as an alternative therapy for recurrent pancreatitis. After discussing this treatment with the patient and his family, they agreed and he commenced RTX infusions, which were given as two doses (375 mg/m²), two weeks apart. These infusions were preceded immediately by acetaminophen, chlorpheniramine, and 50 mg of IV MP.

Laboratory results before RTX therapy, two weeks and six months post infusion are shown (Table 1). The results revealed depletion in CD19 and CD20 along with a decrease in serum amylase, however, there was no change in C3, C4, and immunoglobulin. Six months later, our patient's condition and laboratory results remained stable while CD19 was only 2% (N: 11 – 16%) (Table 1). ANA and Anti-ds DNA were negative before and after RTX therapy.

After reducing the prednisolone dose to less than 5 mg/

day, SA developed nausea, vomiting, headache, fever, and fatigability. Serum amylase was slightly elevated (135 mmol/L). After receiving two pulses of MP (2 mg/kg OD×2 days), symptoms improved. However, one year after B-cell depletion therapy, CD19 was 7% (N: 11 – 16%) and the patient received another infusion of RTX. No further attacks of AP were noticed and he was maintained on prednisolone 5 mg/day and HCQ 200 mg BD.

Fifteen months after the second RTX infusion, the B-cell quantity was 61% cells/UL (N: 200 – 400 U/L) and CD19 was 4% (N: 11 – 16%), therefore no more RTX infusions were given and HCQ was reduced to 200 mg OD. One year later SA was reassessed and found to be clinically stable with normal serum amylase and normal pancreatic size on ultrasound findings. Moreover no episodes of infection were reported since the introduction of RTX therapy.

Discussion

SLE is an autoimmune chronic disease with protean manifestations. The American Rheumatism Association recommends 4 of the following 11 revised criteria for the diagnosis of SLE: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder on serologic testing and antinuclear antibodies.¹⁰ Our patient had more than four criteria for diagnosing SLE that was manifested in his second presentation.

AP was reported as first presentation of SLE in numerous articles.¹¹ The diagnostic criteria for AP in Japan recommends two of the following three presentations: acute abdominal pain and tenderness in the upper abdomen, elevated level of pancreatic enzyme in the blood, urine, or ascitic fluid, and abnormal imaging findings in the pancreas associated with AP.¹² Based on the above criteria our case was diagnosed to have AP. The cause of AP in SLE was attributed primarily to lupus, with the possibility that drugs used to treat SLE might play a role. The mechanism of AP was believed to be vasculitis, microthrombi, and intimal thickening.¹³

Corticosteroids were the main treatment for AP with SLE in spite of being implicated as causes of pancreatitis.¹ Our patient developed recurrent attacks of AP on several occasions once the prednisolone dose decreased below 5mg OD. Furthermore, resolution of AP after treatment with pulses of MP in our case makes steroid as unlikely cause for pancreatitis.

CYC was reported as a successful treatment for gastrointestinal vasculitis including pancreatitis in patients with SLE.¹⁴ In our case we used pulses of CYC, which gave remission for around five months. However, the patient and his family refused to continue further doses of CYC because of its long-term toxicity.^{15,16}

Osteopenia and osteoporosis are common in children with SLE. A cumulative dose of corticosteroid was shown to increase the risk of fractures. Since our patient was taking 2 – 3 times/year MP pulses in addition to more than 7.5 mg/day of oral prednisolone, which was considered as high dose and a risk factor for fractures,¹⁷ he developed osteoporotic changes at L2-L4 that precluded administration of further doses of MP in the acute condition.

The role of B lymphocyte in SLE pathogenesis has been demonstrated in an animal model of SLE, formation of autoantibodies by B cells resulting in immune complex and complement activation leading to tissue damage. Therefore a therapeutic trial against B-cells prevents formation of autoantibodies and an immune complex, thereby leading to disease suppression.¹⁸

Preliminary results of treatment with RTX in adults with SLE and other systemic autoimmune diseases have confirmed its efficacy and safety.¹⁹ In the majority of cases

where B-cell depletion therapy has been used, the period of B-lymphocyte depletion ranged from three to eight months whether RTX was given as four weekly doses or two doses every other week.⁹ Our patient had a generalized flare-up of SLE when the prednisolone dose decreased below 5 mg/day, however, there was no definite picture of AP and the attack was easily controlled with a small dose of methylprednisolone. Moreover, for more than two years no further attack of AP was reported after the second dose of RTX.

Since no optimal doses have been standardized yet for RTX therapy, we chose a two dose regimen fortnightly to deplete B-lymphocyte. No immunosuppressive drug was added during the infusion of RTX.

The limitation in our treatment was the absence of guidelines for the use of RTX in SLE, since the second dose could be deferred because no episode of AP had been reported after the first dose. Also, measuring B-cell quantities rather than B-cell markers before the RTX infusion could add a realistic estimation of B-cell depletion in such cases.

Long-term follow-up is lacking in our study, however, to our knowledge this is the first case of SLE and pancreatitis that has been treated with B-cell depletion therapy. Superiority of RTX over the standard treatment (corticosteroid, CYC and MMF) in our case makes us consider B-cell depletion therapy as an alternative for treating refractory pancreatitis in SLE in the future.

B-cell depletion therapy is safe and effective for the treatment of recurrent pancreatitis secondary to SLE. We would suggest using such therapy in treating pancreatitis as an alternative therapy in refractory pancreatitis secondary to SLE.

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Autumn in Eshkavarat Region, Gilan Province, northern Iran (photo by M. H. Azizi MD)