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CASE REPORT

Prompt remission of severe SLE with only three doses of rituximab infusion and low dose steroid: the first case report from Indonesia

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Abstract A 31-year-old Chinese lady presented with severe SLE with nephrotic syndrome, anemia, leucopenia and thrombocytopenia, skin lesions, and joint inflammation after failing previous standard therapy. After treatment with three infusions of rituximab she showed immediate improvements regarding clinical and laboratory parameters. She received no cytotoxic drugs and remained well for at least 7 months, despite stopping prednisolone.

Keywords Rituximab · Severe systemic lupus erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a serious disease; half of the SLE patients have, at some stage, complications that threaten life, organ function or an important bodily function [1]. Renal and hematological involvements are among the most frequently observed and potentially dangerous complications in SLE patients, occurring in 40–75% and approximately 30% of the cases respectively either prior to the diagnosis of SLE or during the course of illness [2].

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SLE is characterized by the formation of auto-antibodies produced by B lymphocytes. It was hypothesized that depletion of pre-B and B cell lymphocytes, which express the CD20 molecule on their cell surface, would prevent generation and/or expansion of antibody-secreting auto-reactive cells [3]. We report the efficacy of treatment with rituximab in a case of severe SLE with lupus nephritis, cutaneous and arthritis symptoms, and hematologic abnormalities, not responding adequately to standard therapy.

Case report

A 31-year-old Chinese female was admitted to our hospital in February 2008 with severe SLE She had a 10-year history of arthralgia without clear diagnosis, treated with symptomatic therapy. Since 2004, she had cutaneous symptoms of photosensitivity and malar rash and increased arthralgia and she was treated with methyl prednisolone by her dermatologist and with Chinese drugs.

At the end of 2007, her condition worsened with arthritis, amenorrhea, anemia, thrombocytopenia, and leucopenia not responding to 3×4 mg of methyl prednisolone daily for 2 weeks, tapered-off after 2 months due to moon face. In January 2008, she received mycophenolate mofetil 2×500 mg/day for 2 weeks which she also stopped herself. As these treatments had no effect, she came to our clinic.

At admission, we saw a very ill emaciated lady with generalized edema, arthritis in the wrists, hands, and knees. She had malar rash and could hardly talk due to a painful rash around her mouth, besides that, she had rashes in her arms, legs, and around the ankles. She also complained of headache.

Laboratory results: Hb 6.2 g/dL, leucocyte 2,100, platelet 69,000, ESR 86 mm/h; serum albumen 2.3 g/dL

and globulin 5.0 g/dL. At urinalysis hematuria (15–18/HPF), cylinder casts (2–3/LPF) and protein 2+. The anti dsDNA was 623 IU (normal <400) and ANA 37.46 IU (strongly positive). Complement C3 was 14 mg/dL and C4 was 2 mg/dL. Liver and kidney function tests were normal. The SLEDAI score was 35. Her plain chest X-ray and electrocardiogram were normal.

She fulfilled the revised classification criteria of the American College of Rheumatology for SLE [4], with nephrotic syndrome and cachexia.

As the patient had wished to bear children, we decided not to give cytotoxic drugs and the patient was given three doses of 500 mg rituximab infusion, 2 weeks apart and low dose oral prednisolone 4 mg once daily. One albumin infusion 100 ml (25% solution) was given prior to the first rituximab infusion due to low albumin level and generalized edema.

The patient showed a prompt regression of the generalized edema, cutaneous and arthritis symptoms, and hematologic disorders. The cutaneous and arthritis symptoms subsided within 2 weeks after the first rituximab infusion. The hemoglobin level increased to 9.3 g/dL and the platelet count to 256,000/U/L without blood transfusion. The Erythrocyte Sedimentation Rate (ESR) decreased to 55 mm/h. The CRP was positive, however no quantification value available.

After the third infusion, no cylinder casts were found anymore at microscopic urine examination. The complement (C3) increased from 14 to 38 mg/dL in 1 month. The hematuria and proteinuria normalized within one month. The serum albumin increased from 2.3 to 3.5 mg/dL the Anti dsDNA became negative The SLEDAI score improved from 35 to 8 points. She gained weight, the menstruation periods returned and she could resume her job as a teacher.

After 7 months, she is still in full remission the CRP was negative, ESR<10 mm serum albumen 3.4 without proteinuria, also, her blood tests remained normal. Her weight is stable at 45 kg and she has good appetite, her menstruation is regular. She had no joint pains or skin abnormalities and she is full time at work.

Rituximab was well-tolerated and the patient experienced no adverse events. After 5 months, she stopped taking 5 mg prednisolone without problems. The follow-up is now up to 7 months and the patient is still in remission. Her menstruation periods resumed and became regular. Her appetite is normal and she could return to her daily activities and to her job as a teacher.

Discussion

We describe a patient with severe SLE with nephrotic syndrome, anemia, leucopenia, and thrombocytopenia, skin lesions and joint inflammation who failed previous standard therapy and was treated with rituximab followed by immediate improvements regarding clinical and laboratory parameters. She received no cytotoxic drugs and remained well for at least 7 months, despite stopping prednisolone.

Rituximab is a chimeric mouse–human monoclonal antibody against the CD 20 antigen, present on B lymphocytes. Treatment with rituximab results in inhibition of B cell proliferation, and their apoptosis and lysis through complement-dependent and -independent mechanisms [5].

Previous studies have shown good results in SLE patients treated with rituximab. A series of seven patients with lupus nephritis was treated with a combination of rituximab and cyclophosphamide. All patients improved after 6 months regarding: albuminuria 4 g dropped to 0.6 g/day; SLEDAI (25 dropped to 3), dsDNA 274 to 56; Anti C2q ab 35–22. An important finding was that the renal biopsy improved in most cases regarding WHO class and all improved regarding activity [6].

A report from Gottenberg et al. also showed the result of two out of four SLE patients with nephritis and seven out of nine without nephritis showed significant reduction in SLEDAI score and 70.4% reduction in steroid dosage following treatment with rituximab [5]. Recently, a complete remission was described of lupus nephritis [7].

In 23 of 24 cases of refractory SLE, rituximab had a good effect [8]. Even treatments repeated two to three times of refractory cases appear safe (seven cases) [9]. In a review of more than 200 cases, 80% showed marked and rapid improvements [10]. In an open study in 26 cases with severe refractory SLE, a combination was given of rituximab with cyclophosphamide. At 6 months, there was a clinical improvement in 23 cases and the SLEDAI dropped from 22.2 to 4.7; there was a remission in nine of 26 cases [11].

Skin involvement is one of the characteristic and most observed in SLE patients. There are many case reports of SLE skin disease treated with rituximab showing generally good results and sometimes long lasting effects. Two cases were described with severe resistant skin disease; a 52-year-old woman had severe skin SLE; after rituximab, the skin lesions disappeared and prednisolone could be tapered. Another case, a 44-year-old woman with MCTD and later SLE, developed severe skin lesions. After rituximab, the lesions disappeared and prednisolone could be tapered [12].

Rituximab also showed positive result in hematologic involvements frequently observed in SLE, such as autoimmune thrombocytopenia and hemolytic anemia. A case was described of a 32-year-old woman with immune thrombocytopenia and SLE for 20 years and also multisystem tuberculosis. Then, she developed severe ITP with platelets of less than 4 g/l; she was treated with IV gamma globulin

without effect; as she had a contraindication for conventional therapy she was put on rituximab and after three infusions, thrombocytes and anti dsDNA had normalized [13].

Another case of immune thrombocytopenia was reported by Mo et al. of a 42-year-old patient with refractory ITP despite of splenectomy. She developed acute cardiac failure and mononeuritis multiplex with cerebral and renal infarcts and was resistant to all treatments. After rituximab treatment, there was a dramatic improvement and normal platelets [14]. In a more recent study, rituximab appeared highly effective in patients with autoimmune thrombocytopenia and in refractory nephritis [15].

A total of 26 severe cases of autoimmune hemolytic anemia (AHA) had been treated with all kinds of therapies, with often insufficient effect. One resistant case received rituximab with long term benefit [16]. Another case of therapy resistant AHA was described: a 28-year-old girl, who, after RTX, improved after a few days and still was disease-free after 7 months [17].

Side effects of rituximab

The most frequent adverse events are infusion reactions, which can be reduced by giving concomitant glucocorticosteroid infusions. These reactions are usually mild. The incidence of infections is slightly higher, but there were no opportunistic infections including tuberculosis in the trials [18].

A recent adverse event reported related with rituximab administration is Progressive Multifocal Leukoencephalopathy (PML): two cases with PML were described in SLE, both had been treated with many immunosuppressant drugs, this was the reason the company was told to warn for this type of complication. PML has often been described in cases of SLE treated with cytotoxic drugs, without rituximab. A relationship with B cell depletion and activation of the JC virus is unlikely [18, 19]. Until 2007, a total of 20 cases with lymphoid malignancies were seen treated with rituximab; until now, no cases are described in rheumatoid arthritis so a relationship with the drug seems unlikely.

Conclusions

The fact that our patient responded positively after treatment with rituximab, regarding clinical and laboratory parameters after failing previous immunosuppressant therapy, demonstrates that it improved the course of the disease. In this case, it is shown that renal and hematological symptoms improved in 1 month's time, while cutaneous and arthritis symptoms subsided within 2 weeks after the first dose of rituximab was given.

The treatment of severe SLE depends mostly on the standard therapy schemes. In exceptional cases, a combination with rituximab can be considered. Ongoing studies will give an answer whether rituximab will have better effects than current schemes.

One of the great advantages of rituximab treatment is the tolerability and safety profile of the drug. This report suggests that rituximab may be a new therapeutic option in patients with SLE, especially for patients who do not respond or tolerate standard immunosuppressant and/or cytotoxic agents.

This is the first case of treatment with rituximab reported in the Indonesia. In this case report, treatment with rituximab showed beneficial effect in a patient with severe SLE and systemic involvement unresponsive to standard therapy. It demonstrated a prompt remission of symptoms and a steroid-sparing effect in this patient. Rituximab in this patient also avoided the need for cytotoxic agents, which may have numerous side effects, concerning that the patient was a female in reproductive age with a wish bear children.

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References

1. Rahman A, Isenberg DA (2008) Systemic lupus erythematosus, mechanisms of disease. New Engl J Med 358:929–939
2. Golbus J, McCune WJ (1994) Lupus nephritis. Classification, prognosis, immunopathogenesis, and treatment. Rheum Dis Clin North Am 20:223–242
3. Tieng AT, Peeva E (2008) B-cell directed therapies in systemic lupus erythematosus. Semin Arhritis Rheum 38:218–227
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arhtritis Rheum 25:1271–1277
5. Gottenberg J-E, Guillevin L, Lambotte O et al (2005) Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 64:923–920
6. Gunnarsson I, Sundelin B, Jonsdottir T, Jacobson SH, Henriksson EW, van Vollenhoven RF (2007) Histopathologic and clinical outcome of Rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum 56:2263–2272
7. Camous L, Melander C, Vallet M, Squalli T, Knebelmann B, Noël LH, Fakhouri F (2008) Complete remission of lupus nephritis with rituximab and steroids for induction and rituximab alone for maintenance therapy. Am J Kidney Dis 52:346–352
8. Leandro MJ, Cambridge G, Edward JC, Ehrenstein MR, Isenberg DA (2005) B cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford) 44:2542–2545
9. Ng KP, Leandro MJ, Edwards JC, Ehrenstein MR, Cambridge G, Isenberg DA (2006) Repeated B cell depletion in treatment of refractory systemic lupus erythematosus. Ann Rheum Dis 65:942–945

10. Sfikakis PP, Boletis JN, Tsokos GC (2005) Rituximab anti-B-cell therapy in systemic lupus Erythematosus: pointing to the future. Curr Opin Rheumatol 27:550–557
11. Jonsdottir T, Gunnarsson I, Risselada A, Henriksson W, Klareskog L, van Vollenhoven RF (2008) Treatment of refractory SLE with rituximab plus cyclophosphamide: clinical effects, serological changes and predictors of response. Ann Rheum Dis 67:330–334
12. Risselada AP, Kallenberg CGM (2006) Therapy resistant lupus skin disease successfully treated with rituximab. Rheumatology 45:925–926 features in systemic lupus erythematosus: Analysis of 600 patients from a single center. Semin Arthritis Rheum 2004; 33:227–230
13. Lehembre S, Macario-Barrel A, Musette P, Carvalho P, Loly P (2006) Rituximab treatment for immune thrombocytopenia associated with systemic lupus erythematosus. Ann Dermatol Venereol 233:53–55
14. Mo N, Collins P, Rayment P, Nash J (2007) The use of rituximab in a case of SLE complicated by TTP and refractory ITP. l EULAR : AB 0434
15. Lindholm C, Börjesson-Asp K, Zendjanchi K, Sundquist AC, Tarkowski A, Bokarewa M (2008) Longterm clinical and immunological effects of anti-CD20 treatment in patients with refractory systemic lupus erythematosus. J Rheumatol 35:826–833
16. Gomard-Mennesson E, Ruivard M, Koenig M, Woods A, Magy N, Ninet J, Rousset H, Salles G, Broussolle C, Seve P (2006) Treatment of isolated severe immune hemolytic anemia associated with systemic lupus erythematosus: 26 cases. Lupus 25:223–232
17. Perrotta S, Locatelli F, La Manna A, Cennamo L, de Stefano P, Nobili B (2002) Anti-CD20 monoclonal antibody (rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. Brit J Haematol 226:465–467
18. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P (2007) New therapies for treatment of rheumatoid arthritis. Lancet 370:2862–2875
19. Calabrese LH, Molloy ES, Huang DR, Ransohoff RM (2007) Progressive multifocal leukoencephalopathy in rheumatic diseases. Arthritis Rheum 56:2226–2228