Treatment of One Case with Cryoglobulinaemia Secondary to Connective Tissue Disease with Small Doses of Rituximab
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ABSTRACT

Objective: This study aims to observe the clinical efficacy of low-dose rituximab in patients with cryoglobulinaemia secondary to connective tissue diseases.

Methods: Rituximab (100 mg) was infused in patients once a week for four weeks, combined with prednisone (20 mg) once a day, and reduced regularly. Treatment effect was observed regularly.

Results: Joint pain, fever, rash and fatigue symptoms in patients eased. The serology (globulin, erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase and others) parameters returned to normal.

Conclusion: Low-dose rituximab therapy for cryoglobulinaemia secondary to connective tissue diseases was safe and effective, and can be used as a treatment option in this condition.

Keywords: Connective tissue disease, cryoglobulinaemia, rituximab

CASE REPORT

This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Lanzhou University. Written informed consent was obtained from the participant. A male patient, aged 38 years, was admitted to our hospital in December 2011 mainly because his hands were turning purple in cold weather over 24 years, rash on face and limbs for seven years, which worsened over three months, with intermittent fever for two weeks. The patient narrated that his hands turned purple or red in cold weather. There was no paraesthesia, and the hands returned to normal after being warmed. There was no fever, no mouth ulcers, no hair loss, no light allergy, no joint swelling and pain in 24 years. The above symptoms worsened every winter, and he received no treatment. Seven years before the admission, a dark red rash appeared on his face in the winter; the cheek and forehead, nose tip and ears were especially affected, while the dark red on the dorsum of the hands and both ankles were not...
Additional examinations revealed normal vital signs, the cheeks, forehead and ears were normal; the chest radiograph was normal and likewise the electrocardiogram (ECG), abdominal B and echocardiography.

The patient was diagnosed with cryoglobulinaemia secondary to undifferentiated connective tissue disease after admission. He was prescribed 20 mg qd prednisone (Wuhan Xinxinjiali Bio-Tech Co, LD, Wuhan, China) and 100 mg qw rituximab (Roche/Genentech, USA) for four weeks, while 600 mg bid hydroxychloroquine and 0.6 tid pavlin for four months. The rash on his face and limbs occurred every winter, but no treatment was carried out. Three months before admission, the face and limb rash worsened. Intermittent fever appeared two weeks prior, and his body temperature reached up to 39 °C, while both wrist joints, knees, shoulder joints, and both bilateral ankle pains appeared, with no joint swelling.

At outpatient follow-up, regular urine showed urine protein, no blood. On regular blood examination, WBC was 1.7 × 10^9/L. The patient was admitted for further treatment with a diagnosis of connective tissue disease. Admission examination revealed stable vital signs, the cheeks, forehead and ears had a dark red rash, which was slightly more than the skin, no blanching when pressed, no itching, no desquamation or exudation; both hands dorsally and both ankles laterally had dark red rash but not more than the skin, blanched when pressed and which disappeared after warming. There were significant mandibular lymph nodes of the jaws, with size of 2 × 1 cm, moveable, and which were not tender and not fixed to underlying tissue. The respiratory system, abdomen, and the rest of the physical examination were normal.

Admission laboratory tests were: WBC 1.63 × 10^9/L ↓, haemoglobin (Hb) 10 g/L ↓, red blood cells (RBC) 2.82 × 10^12/L ↓, platelet (PLT) 120 × 10^9/L; urine: urine protein (-) red blood cell (-); shit (-); erythrocyte sedimentation rate (ESR) 53 mm/h ↑; C-reactive protein (CRP) 36.4 mg/L ↑; biochemical examination: IgG 26.1 g/L ↑ (8–16), IgA 3.46 g/L ↑ (0.7–3.3), IgM 0.63 g/L; normal complement C3, C4; phosphorus 1.58 g/L ↑ (0.8–1.45), magnesium 1.25 ↑ (0.7–1.2), lactate dehydrogenase (LDH) 445 U/L ↑ (0–240), hydroxybutyrate dehydrogenase (HBDH) 352 U/L ↑ (0–250); the remaining was normal. Twenty-four hour urine protein quantification: 0.36 g/24 hours; urine Bence Jones protein was negative; serum electrophoresis κ, λ were negative; serum globulin: 42.4 g/L ↑ (0–20); autoantibodies: positive ANA, cytoplasmic granules type was 1:320, negative anti-SM antibody, negative anti-ds-DNA antibody, SSA, negative SSB, negative anti-U-RNP antibody, negative ANCA, negative anti-CCP, negative RF and negative ACA.

The examinations for infectious diseases were all negative; negative anti-tuberculosis antibody and purified protein derivative (PPD); positive cold globulin (5.1 g/L), ophthalmic examination showed no xeroma, bone marrow biopsy showed megaloblastic anaemia. The chest radiograph was normal and likewise the electrocardiogram (ECG), abdominal B and echocardiography.

**DISCUSSION**

Cryoglobulin is a protein that could have reversible precipitation at low temperatures (less than 4 °C) and which dissolves at around 37 °C. The increase of blood cryoglobulin levels (> 250 mg/L; cryoglobulinaemia) can cause a series of symptoms, such as rash, joint pain and weakness, and also involves the kidneys, liver and peripheral nervous system. Cryoglobulinaemia is divided into primary and secondary, and the latter represents the majority (accounting for 60%–75%), which can be secondary to connective tissue diseases such as systemic lupus erythematosus, vasculitis, systemic sclerosis and, Sjogren’s syndrome, can lead to malignancies such as multiple myeloma, lymphoma, liver cancer and chronic
lymphocytic leukaemia, as well as secondary to chronic infectious diseases such as hepatitis, syphilis and leishmaniasis (1). Cryoglobulins are actually immunoglobulins, and can be divided into three types according to the different types of immunoglobulin in precipitation (2): Type I is a monoclonal type, Types II and III are mixed types. Type I is common in multiple myeloma and Waldenstrom macroglobulinaemia. Types II and III cryoglobulinaemia have at least two types of immunoglobulin, and are found in a variety of diseases, such as autoimmune diseases, lymphoproliferative disorders and liver disease [hepatitis B or hepatitis C] (3). The index case has a history of 24 years with repeated rashes and arthritis in cold weather, high globulin, white blood cells and haemoglobin-blast were decreased and urinary protein was mildly elevated; ANA was positive, cytoplasmic granules type was 1:320. On admission at a previous hospital, he had positive U-RNP antibody, with IgM deposition in the dermal layer on skin biopsy. Although he was diagnosed with systemic lupus erythematosus in another hospital, the authors believe that the patient’s long history (24 years), no improvement in the disease with standard treatment for lupus and with no major organ involvement or progression, the diagnosis of systemic lupus erythematosus was questionable. The patient was finally diagnosed with undifferentiated connective tissue disease, which induced secondary cryoglobulinaemia. He had increased IgG and IgA, suggesting Type III cryoglobulinaemia.

Traditional treatment for cryoglobulinaemia is mainly hormones, immunosuppressive agents (such as cyclophosphamide), chlorambucil, interferon and plasmapheresis and other methods (4). Rituximab is a chimeric monoclonal antibody that could bind with B cell surface antigen CD20. The infusion of rituximab can effectively remove B cells and plasma cells from the body to interrupt the synthesis of monoclonal IgM and cold globulin (5, 6). Rituximab can be used for the treatment of connective tissue diseases (7, 8) and cryoglobulinaemia. Zaja et al., in 2003 (9), reported the efficacy and safety of treatment for Type II cryoglobulinaemia by rituximab; subsequently, other authors have also reported on rituximab as treatment for cryoglobulinaemia (10, 11). In 2011, Ferri et al. (11) reported the results of a retrospective study on treatment of mixed cryoglobulinaemia with rituximab. Thirty-nine published reports (n = 279 patients) on rituximab treating mixed cryoglobulinaemia were included in the review. The retrospective study included 87 cases with cryoglobulinaemic vasculitis; hepatitis C occurred in 92%. Regardless of the presence or absence of hepatitis C virus infection, monotherapy for six months resulted in significant clinical and serological remission, and confirmed the safety of the treatment during follow-up in six months (11). The patients in this report had associated connective tissue disease and because they had prolongeated leukopenia and reduced symptoms, cyclosporine and corticosteroids were additionally used. After rituximab, cyclosporine, prednisone and hydroxychloroquine treatment, the symptoms disappeared. There was no recurrence in long-term follow-up and no serious adverse reactions (11).

Rituximab for treatment of cryoglobulinaemia secondary to autoimmune diseases was safe and effective. For relapsed or refractory patients, it can be used as a treatment option, but its exact efficacy and safety issues need to be confirmed by further research and clinical studies.

CONFLICT OF INTEREST
All authors have no conflict of interest regarding this paper.

REFERENCES