CASE REPORTS

Wegener’s granulomatosis effectively treated with rituximab: a case study

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Abstract: Wegener’s granulomatosis (WG) is a granulomatous disorder associated with systemic necrotizing vasculitis. Wegener’s granulomatosis predominantly involves the upper airways, lung and kidneys. The disease is often associated with cytoplasmic antineutrophil cytoplasmic antibodies (cANCA). B lymphocytes are potential cANCA producers and there is an evident correlation between cANCA titre, severity of the disease and response to treatment. Wegener’s granulomatosis usually begins with symptoms limited mostly to the upper and/or lower respiratory tracts and may transform into the generalized phase, characterized by systemic necrotizing vasculitis. If left untreated, it can turn fulminant with poor prognosis. The severe form of the disease is usually treated with a combination of cyclophosphamide and corticosteroids. In refractory cases, rituximab that binds to CD20 expressed on B-cells should be considered. We presented a case of a 38-year-old woman with severe form of WG, refractory to standard therapy. Despite the standard treatment with cyclophosphamide and corticosteroids and the addition of infliximab with methotrexate, progression of the disease was observed. Exacerbation affected mainly the lungs and caused the gradual destruction of pulmonary tissue and development of respiratory insufficiency. Rituximab (500 mg) was given intravenously every week in four infusions, causing a partial remission of WG and the arrest of lung deterioration. The following administration of 500 mg was given every two weeks, which induced the remission of WG and enabled the patient to return to her normal activity and work. Such treatment appeared to be successful and prevented severe pulmonary involvement.

Key words: anti-CD20 antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, rituximab, Wegener’s granulomatosis

INTRODUCTION

Wegener’s granulomatosis (WG) is a necrotizing inflammation of small and medium-sized vessels, upper and lower airways and kidneys, characterized by granulomas formation and presence of cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) [1].

In 95–99% patients with active and in 65% of patients with inactive forms of this disease, the presence of cANCA antibodies has been observed. Their titre correlates with the severity of the disease and response to treatment [2].

Besides the classic triad of the involved organs specified in the definition, otitis with progressive hearing loss [3], involvement of the eyeballs, frequently their protrusion [4], skin, nervous system, joints or mucous membranes are also observed.

Diagnosing limited or generalised (severe) forms of WG is crucial for proper therapeutic management. In the limited form, life-threatening symptoms or severe damage of life-sustaining organs are not present, while in the severe form a significant impairment of the functioning of many vital organs is observed.

In the limited form, combined treatment with glucocorticosteroids (GS) with trimethoprim + sulphamethoxazole or GS with methotrexate is used. The severe form of WG is conventionally treated with cyclophosphamide and corticosteroids. In refractory cases, rituximab that binds to CD20 expressed on B-cells should be considered. We presented a case of a 38-year-old woman with severe form of WG, refractory to standard therapy. Despite the standard treatment with cyclophosphamide and corticosteroids and the addition of infliximab with methotrexate, progression of the disease was observed. Exacerbation affected mainly the lungs and caused the gradual destruction of pulmonary tissue and development of respiratory insufficiency. Rituximab (500 mg) was given intravenously every week in four infusions, causing a partial remission of WG and the arrest of lung deterioration. The following administration of 500 mg was given every two weeks, which induced the remission of WG and enabled the patient to return to her normal activity and work. Such treatment appeared to be successful and prevented severe pulmonary involvement.

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served. The patient was unsuccessfully treated with numerous antibiotics.

In March 2004 she was admitted to the Clinic of Rheumatology of the Medical Academy in Wrocław, where a diagnosis of Wegener’s granulomatosis was made on the basis of the above clinical symptoms, purulent necrotizing lesions on the mucous membrane of the nasopharynx, sinusitis, otitis media of the left ear, lesions in the lungs and the following abnormalities in laboratory tests such as high activity of inflammatory parameters: erythrocyte sedimentation rate (ESR) – 86 mm/h, C-reactive protein (CRP) – 5.8 mg%, fibrinogen 526 mg%, significant increase of the cANCA antibodies levels (PR3: 196.4 RU/ml; norm to 15 RU/ml), anemia (Hb value – 10.4 g%), secondary thrombocytosis (platelet count of 704 G/l), presence of protein in the urine.

Treatment with trimethoprim + sulphamethoxazole, glucocorticosteroids and cyclophosphamide was implemented. From March to November 2004, the patient received 9 infusions of cyclophosphamide for 800 mg every 3–4 weeks and prednisone orally in doses of 20–40 mg/24 h. After this therapy only a transient clinical improvement with normalization of inflammatory parameters: erythrocyte sedimentation rate (ESR) – 86 mm/h, C-reactive protein (CRP) – 5.8 mg%, fibrinogen 526 mg%, significant increase of the cANCA antibodies levels (PR3: 196.4 RU/ml; norm to 15 RU/ml), anemia (Hb value – 10.4 g%), secondary thromboctysis (platelet count of 704 G/l), presence of protein in the urine.

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Since September 2004, an exacerbation of clinical symptoms and increase in activity of inflammatory parameters have been observed, and on computed tomography of the chest the presence of 5 tumors, 2.4 cm in diameter with visible air space, have been found.

**CASE REPORT**

The first symptoms in this 38-year-old woman appeared at the beginning of January 2004 – putrid purulent rhinitis, progressive loss of body mass (loss of about 18 kg within 3 months), progressive hearing loss in the left ear, a high fever, hoarseness, and generalized joint pain, especially in the elbow, knee and iliac joints were observed. In the chest X-ray examination non-specific infiltrations in the lungs were observed. The patient was unsuccessfully treated with numerous antibiotics.

Rituximab is a chimeric human-mouse monoclonal antibody directed against CD20 surface marker, localised on pre-B lymphocytes, normal and neoplastically transformed mature B lymphocytes. Rituximab was registered for the first time in the United States in 1997 for the therapy of malignant non-Hodgkin’s lymphomas, and in Europe in 1998. The medication is also successfully used in patients with rheumatoid arthritis, idiopathic thrombocytopenic purpura, hemolytic anemia, and in patients with vasculitis.

The following is the case of female patient with a severe, recurrent form of WG with cANCA antibodies, refractory to standard therapy with cyclophosphamide and prednisone, with no response to therapy by infliximab and methotrexate. Rituximab appeared to be successful.

**Fig. 1. Lung lesions on chest X-ray (October 2005)**

**Fig. 2. Regression of lung abnormalities after the completion of the first cycle of rituximab therapy (January 2006)**
Wegener’s granulomatosis effectively treated with rituximab: a case study

In the face of the exacerbation of the disease, in December 2004 the decision was made for implementation of therapy with infliximab.

Until September 2005, 200 mg of infliximab (altogether 6 infusions) were coadministered with methotrexate at a dose of 15 mg/week and methylprednisolone in oral doses of 12 mg/24 h, without significant improvement.

Due to the symptoms exacerbation in form of fever, exacerbation of purulent lesions in the nasopharynx, appearance of purulent necrotizing lesions on toes of both feet, increasing dyspnea connected with significant progression of tuberous changes in the lungs (Fig. 1), increase of activity of inflammatory the parameters (ESR – 80 mm/h, CRP – 17.2 mg%) and cANCA antibodies (PR3 – 39.3 RU/ml), the decision to use rituximab was made.

In the period between November and December 2005, 4 infusions of rituximab in doses of 500 mg each were administered every week in 4-hour infusions. Each rituximab administration was preceded by a methylprednisolone infusion in doses of 500 mg. In the period between the infusions, methylprednisolone was administered in doses of 24 mg/24 h.

In January 2006 – one month after the completion of the treatment – an evaluation of treatment was carried out; significant subjective improvement, normalization of inflammatory parameters (ESR – 16 mm/h, CRP – 0.9 mg%) and blood morphology parameters (Hb – 14.2 g%, leukocytes – 13,900, platelets 257 G/l), improvement of lung functions in spirometry and normalization of ANCA value (PR3: 5.634 RU/ml), significant regression of changes in both lungs (Fig. 2) and partial regression of lesions in sinuses were observed.

The complete remission of disease at 8 mg of methylprednisolone only was maintained by the end of September 2006 (10 months after the rituximab infusion).

The patient’s condition was stable by October 2006, when hemoptysis, periodic fever, joint pain and malaise occurred. An increase of the ESR value to 56 mm/h and cANCA value to 43.7 RU/ml was observed. It was decided to implement the subsequent therapy with rituximab; the medication was administered in December 2006 (two administrations of medicine, 500 mg each at interval of 14 days).

The next administration of medication took place in June 2007 (2 administrations for 500 mg). Since then patient’s general state was good, she returned to work and used only 8 mg/24 h of methylprednisolone. In the beginning of February 2008 the patient underwent check-ups, which revealed clinical and laboratory remission (ESR – 11 mm/h, cANCA –

Fig. 3. Charts of erythrocyte sedimentation rate (ESR) and cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) values during the treatment of resistant Wegener’s granulomatosis. Abbreviations: GS – glucocorticosteroids, RTX – rituximab
CASE REPORTS

10.9 RU/ml) and further reduction of pulmonary lesions on computed tomography. To maintain the remission, 2 more rituximab infusions of 500 mg each with 14-day intervals were administered.

Figure 3 presents charts of ESR and cANCA values over the course of disease and the medications used.

DISCUSSION

This case of a female patient with WG with cANCA antibodies is characterized by an unusually strong activity of disease and resistance to a 9-month therapy with cyclophosphamide. This cytostatic agent is still the most effective medication used in therapy of vasculitis with ANCA antibodies. The mechanism of its action depends on selective suppression of immunoglobulin production by lymphocytes B. Ten percent of WG patients show resistance to conventional therapy with cyclophosphamide, and these patients require intensive treatment with new generation drugs that are monoclonal antibodies.

The lack of response to therapy with infliximab in combination with methotrexate suggests that proinflammatory cytokines, such as tumor necrozing factor, do not play an important role in patomechanism of WG. An analysis of literature [8] shows, that lymphocytes B and their product – cANCA – play a more important role in the mechanisms of this disease, as the level of these antibodies visibly correlates with the disease’s activity.

Taking into consideration data from the literature and the severe, life-threatening course of the disease in the case of our patient, the decision was made to implement rituximab. The first administration of the medication was performed according to the scheme presented by Kallenbach et al. [9], in the form of 4 infusions of 500 mg of the medication in combined therapy with weekly glucocorticosteroids.

The full remission of the disease confirmed the effectiveness of this therapy, which has been described by other authors [7-10].

The remission lasted 10 months, which can be explained by the regeneration of lymphocytes B in this period.

The number of peripheral lymphocytes B directly after the rituximab administration is practically indeterminable, after 6 months it gradually increases, and after an average of 11 months it obtains a normal value.

Taking into consideration that each exacerbation of the disease in our patient caused further gradual destruction of pulmonary tissue and development of respiratory insufficiency, the decision to administrate rituximab every 6 months in half doses (2 × 500 mg) was made. Consequently, doses of medication were administered every 6 months according to the pattern for rheumatoid arthritis patients treated with rituximab in clinical trials, i.e. 2 infusions for 500 mg in 14-day intervals [11].

The therapy appeared to be effective, and after 3 therapeutic courses clinical and laboratory remission and reduction of pulmonary changes were achieved.

Rituximab appears to be very effective medication in resistant, severe forms of WG. Taking into consideration that the medication does not cause severe side effects or infectious complications, its usefulness in therapy for severe forms of WG may be greater than cyclophosphamide, which causes multiple side effects.

REFERENCES