Successful Treatment of Refractory Idiopathic Thrombocytopenic Purpura and Neutropenia with the Monoclonal Antibody, Rituximab

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Abstract We describe a 22-year-old male with idiopathic autoimmune thrombocytopenia whose diagnosis was made at age of eight. He underwent splenectomy at age ten and ITP recurred at age 21 with episodes of infection and severe neutropenia (absolute count around $170/\mu\text{l}$). He showed no response to immunoglobulin, corticosteroids, danazol, cyclosporine and azathioprine. Anti-CD20 antibody was administered at a dose of 375 mg/m^2 once a week for 2 weeks. After the second infusion of rituximab, the platelet count increased from 4,000 to $516,000/\text{mm}^3$ and neutrophils count raised from 180 to $545/\text{mm}^3$. The response improvement persisted during follow up for 9 months (neutrophil count $4,390/\text{mm}^3$). This observation indicates that B-cells may play a central role in the pathogenesis of ITN. Anti-CD20 antibody therapy may be an efficient treatment for the patients with chronic or recurrent ITN.

Keywords Idiopathic thrombocytopenic purpura · Neutropenia · Anti CD20 antibody · Rituximab

Introduction

Idiopathic autoimmune thrombocytopenia and neutropenia is a concurrent idiopathic thrombocytopenia (ITP) and neutropenia (ITN) with platelet count $<150 \times 10^9/\text{l}$ and absolute neutrophil count $<1.5 \times 10^9/\text{l}$ [1]. ITP is an immune-mediated accelerated destruction of platelets [2]

with approximately 50% response to primary treatments including corticosteroids, IVIG, anti-RhD-immunoglobulins, and splenectomy [3]. Rituximab is a genetically engineered human anti-CD20 monoclonal antibody that is approved for the treatment of low-grade non-Hodgkin's lymphoma. Recent clinical reports suggest that rituximab may be useful in the treatment of patients with chronic refractory ITP [4–11], ITN [12] and ITP with autoimmune hemolytic anemia [13, 14].

Case Presentation

A 22-year-old male admitted to hospital because of fever and septicemia. On admission, his temperature was 38.2°C and his blood pressure was 120/80 mmHg. Physical examination showed petechial rashes on extremities and phlegmons—in the perianal area without splenomegaly or other abnormalities. Complete blood count (CBC) revealed a hemoglobin value of 12.3 g/dl, white blood cell (WBC) count of $9,390/\text{mm}^3$ (97% lymphocyte and 3% neutrophil) and platelet (Plt) count of $8,000/\text{mm}^3$. Peripheral blood smear showed severe thrombocytopenia and severe neutropenia with lymphocytosis. The patient was a known case of idiopathic autoimmune thrombocytopenia since the age of 8 years. He had undergone splenectomy at age 10 due to steroid resistant ITP. He was doing well until age 21 when he noticed some skin lesions and spontaneous mucosal bleedings. Low platelet count was found in his CBC. At age 21, he had tuberculosis pleurisy treated with isoniazid for 6 months. He was also being treated with prednisolone, danazol, and immunoglobulin without any response. Coombs' test, serologic markers for HIV, hepatitis B and C viruses, and also antinuclear antibody were negative. His chest X-ray and abdominal ultrasonography

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revealed no pathologic findings. A bone marrow aspiration showed decreased cellularity with increased megakaryocytes and active myeloid with maturation and shift to the left. Neutrophil agglutination with his serum, in comparison to normal control serums, was positive. His neutropenia did not improve with G-CSF 300 microgram/day for 10 days. His fever and phlegmons improved after administration of antibiotics. He was treated with cyclosporine for a month, but discontinued because of gum hypertrophy and no improvement based on neutrophil and platelet count. Azathioprine also was not effective.

During this period he had sinusitis twice. Rituximab, an anti-CD20 monoclonal antibody, was administered in a dose of 375 mg/m² weekly for 2 weeks. On the 9th day of treatment the platelet count increased to 516,000/mm³ and the neutrophil count to 545/mm³. This response improvement persisted so that in his 19th month of treatment, hemoglobin level was 15.8 g/dl, with WBC 8,420/mm³, neutrophil 6,474/mm³, lymphocyte 1,136 and Plt 328,000/mm³ (Table 1).

Discussion

ITP is an immune-mediated accelerated destruction of platelets by the reticulo-endothelial system [2]. Approximately 50% of cases respond to primary treatments including corticosteroid, IVIG, anti-RhD immunoglobulin, and splenectomy [3]. Chronic and refractory patients who fail primary modalities are difficult to manage. Treatments include danazol, cytotoxic/immunosuppressive chemotherapy agents (cyclophosphamide, vincristine, azathioprine), and the new anti-CD20 monoclonal antibody [3, 4].

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Autoimmune neutropenias (AIN) are rare disorders in which autoantibodies against membrane antigens of neutrophils cause their peripheral destruction. The AINs are classified as primary (i.e. not associated with other detectable pathology) or secondary in which there is another pathology usually rheumatological (particularly Felty's syndrome) and systemic lupus erythematosus or hematological (large granular lymphocyte syndrome). The first-line therapy for secondary AIN is the therapy of underlying causes as Methotrexate for Felty's syndrome in rheumatoid arthritis. G-CSF is the first-line therapy for primary AIN, and severe or unresponsive secondary AIN [15]. Other therapeutic approaches for patients with severe neutropenia have been reported in very small series or even single patient, they include plasmapheresis, splenectomy, cytotoxic drugs and Campath-1H [16–18]. The platelet deficiency of ITN, as reported, tends to be chronic and difficult to treat [1], and neutropenia tends to be much more therapy-resistant [14]. Heavily treated patients (more than three different previous treatments, including any corticosteroid) and those with longer ITP duration (>10 years from diagnosis) had a worse response. Non-splenectomized patients had a better early response rate than those splenectomized [7]. In our case, the patient was refractory to all medications and had all of the poor prognostic characteristics. But when he received rituximab, he experienced a complete remission for more than 19 months, with minimal side effects of the treatment.

In conclusion, Anti-CD20 antibody therapy, considering also the results of other studies, may be a safe and efficient treatment for the ITN patients. More studies and a longer follow up of patients will be useful.

Table 1 Blood cells improvement in a patient with Idiopathic autoimmune thrombocytopenia and neutropenia after treatment with rituximab

	Hb	PLT	WBC	Neutrophil	Lymphocyte	MCV
1st week	14	5,000	3,370	180	–	–
3rd week	12.8	15,000	5,840	391	4,467	100.6
1st month	12	59,000	8,710	653	6,959	98.9
2nd month	12.3	15,000	3,210	224	1,945	95.8
4th month	14.6	420,000	8,480	3,544	4,070	105.1
5th month	15.3	488,000	7,370	2,911	3,640	103.3
6th month	16.0	466,000	8,060	3,304	3,707	103.4
8th month	15.0	368,000	6,240	2,826	2,664	104.8
9th month	16.0	449,000	8,930	4,795	3,348	103.4
11th month	15	399,000	6,100	2,820	2,600	103
13th month	15.1	402,000	6,600	3,260	2,600	107.1
16th month	14.4	307,000	6,250	2,825	2,668	108.7
19th month	15.8	328,000	8,420	6,474	1,136	106.0

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