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Successful Treatment of Splenomegaly and Pancytopenia with Rituximab in a Patient with Nijmegen Breakage Syndrome

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Abstract

Nijmegen breakage syndrome is a rare autosomal recessive congenital disorder causing chromosomal instability, characterized by short stature, microcephaly, distinctive facial features, recurrent respiratory tract infections, an increased risk of cancer, intellectual disability, and other health problems. People with Nijmegen breakage syndrome have immunodeficiency. Some patients with ataxia telangiectasia-like syndromes (about 10%) have decreased serum IgA and IgG levels with normal or raised IgM level, a phenotype reminiscent of hyper IgM syndrome, which is due to class switch recombination defect. The case presented in this report was an eight-year-old female with related parents, who had been admitted to the hospital several times with recurrent infections (pneumonia and sinusitis). In immunological workups, she had high IgM, low IgG, and IgA levels. According to high α-fetoprotein level and her microcephaly, Nijmegen breakage syndrome was suggested. She was receiving IVIg monthly for two years, when she developed hypersplenism and pancytopenia. Her bone marrow aspiration and biopsy was reported normal twice. The patient underwent Rituximab therapy (375mg/m^2) weekly for four weeks, with good response and improvement of splenomegaly and pancytopenia. Class switch recombination defects should be considered in patients with ataxia telangiectasia variants, especially when they have hyper IgM phenotype, and if they present lymphoproliferation, Rituximab therapy could be an effective treatment.

Keywords: Nijmegen Breakage Syndrome, Rituximab

1. Introduction

Nijmegen breakage syndrome (NBS, an ataxia telangiectasia variant) is a rare autosomal recessive congenital disorder, causing chromosomal instability, probably as a result of a defect in the double stranded DNA repair mechanism and hypersensitivity to ionizing radiation (1). This syndrome is characterized by a very high predisposition to lymphoid malignancies, short stature, an unusually small head size (microcephaly), distinctive facial features, recurrent respiratory tract infections, increased risk of cancers, intellectual disability and other health problems (2). Some patients with ataxia telangiectasia-like syndromes, like patients with NBS, have immunodeficiency with decreased serum IgA and IgG and increased IgM levels, due to class switch recombination defects, which can be associated with more severe infections (3, 4).

In this report, we present for the first time, a patient with NBS with initial diagnosis of hyper IgM syndrome, who developed splenomegaly and pancytopenia in follow up visits. He was treated with Rituximab, because of the probability of class switch recombination defects, with very good response to treatment.

2. Case Presentation

An eight-year-old female was admitted to the hospital because of recurrent infections and failure to thrive. She had microcephaly (head circumference = 42 cm) and typical bird-like facial appearance (Figure 1).

She had a history of several flues and recurrent infections (pneumonia and sinusitis) from the age of four years. Immunologic investigations showed high IgM and low IgA and IgG levels (Table 1). Percentage of T and B lymphocytes and NK cells, evaluated by flow cytometry, are shown in Table 2. According to her special phenotype (microcephaly, bird like face, etc.), her failure to thrive, low IgA and IgG and

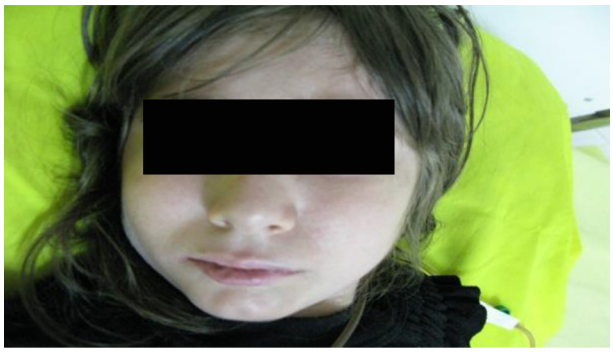

Figure 1. The Patient's Facial Characteristics

high IgM levels and exclusion of other primary immunodeficiencies, the patient was diagnosed with Nijmegen breakage syndrome. Genetic counseling also confirmed this diagnosis, according to its inheritance pattern and the patient's family tree. The patient underwent IVIg therapy monthly and received prophylactic antibiotics. She was doing well for 18 months, when she developed pancytopenia (Table 3) and huge splenomegaly. Fanconi anemia was ruled out. Autoimmune and virological (Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) polymerase chain reaction (PCR)) assessments showed normal results. As NBS patients are predisposed to malignancies, bone marrow aspiration and biopsy was done twice that had a normal pattern, and hematologic malignancies were ruled out. According to hyper IgM pattern and splenomegaly, the probability of class switching recombinant defects was proposed. The patient was treated with Rituximab (Anti CD20 mAb), 375 mg/m^2 weekly for four weeks. Cytopenia was improved after four weeks of therapy with Rituximab (Table 3). The spleen size shrunk to normal and the patient underwent monthly IVIg therapy and prophylactic antibiotic. She was symptom free in her two years follow up.

Table 1. Serum Immunoglobulin Levels

Immunoglobulins	Value	Normal Range
IgM, mg/dL	1200	40 - 150
IgA, mg/dL	7	40 - 300
IgG, mg/dL	18	600 - 1300
IgE, IU/mL	1	Up to 115

Table 2. Flowcytometric Analysis of the Patient's Lymphocytes

CD Markers, %	Value	Normal Range
CD 3	82	49 - 80
CD 4	60.7	20 - 60
CD 8	22.2	10- 37
CD 19	2.9	3 - 14
CD 16	16	5 - 19

Table 3. Complete Blood Count Before and After Rituximab Therapy

	Before Rituximab Therapy	After Rituximab Therapy
White blood cells	1700 (Neutrophils: 26%, lymphocytes: 74%)	5300 (Neutrophils: 53%, lymphocytes: 41%)
Lymphocytes, cell/μL	1258	2173
Neutrophils, cell/μL	442	2809
Hemoglobin (Hb), g/dL	7.6	15.3
Platelets, cell/μL	82000	205000

3. Discussion

Nijmegen breakage syndrome (NBS) (OMIM251260) is a rare autosomal recessive condition. The major manifestations include microcephaly, a distinct facial appearance, growth retardation, recurrent infections due to combined immunodeficiency, spontaneous chromosomal instability, hypersensitivity to ionizing radiation, and a very high predisposition to lymphoid malignancies. The immunological, cytogenetic, and cell biological findings are very similar to those in ataxia telangiectasia (5-7). Defects of class switching are typically associated with low serum IgG and IgA, and normal to increased serum IgM levels, a phenotype reminiscent of hyper IgM syndrome, which may be associated with more severe infections (2).

In this patient with NBS, the presence of hyper IgM phenotype and its associated class-switching defect had resulted in lymphoproliferation (huge splenomegaly) and pancytopenia. Rituximab therapy was started because of its good effect in treatment of hyper IgM syndrome complications. Her splenomegaly and cytopenia disappeared and she was controlled well with Rituximab therapy for four weeks.

Hennig et al. reported two patients with intrinsic B-cell class switch defects (subclass of hyper IgM syndromes), with lymphoproliferation and autoimmunity (such as autoimmune hemolytic anemia, autoimmune thrombocytopenia and lymphoproliferative disorders), that had improved by Rituximab therapy and remained well-controlled during the follow-up period (three to four years) (8).

The patient was diagnosed to have an intrinsic B-cell

class switch defect, when lymphoproliferation and cytopenia were detected and responded well to Rituximab therapy.

This case report suggests that class-switching defects should be considered in patients with ataxia telangiectasia variants, especially when they have hyper IgM phenotype, and if they present lymphoproliferation, Rituximab therapy could be an effective treatment.

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