T-cell lymphoblastic leukemia/lymphoma in Nijmegen breakage syndrome

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Nijmegen breakage syndrome (NBS) is a rare autosomal-recessive disorder characterized by microcephaly, immunodeficiency and predisposition to cancer.[1] Immunodeficiency and the chromosomal instability may predispose to tumor development at a young age.[2]

We report here a pediatric patient with NBS who was successfully treated for T-cell lymphoblastic leukemia/lymphoma (TLBL/ALL).

Case report

This 17-years-old girl of Slavic origin is a daughter of unrelated, healthy parents. During the pre-school period she suffered from recurrent lung infections. At the age of seven years she underwent lobectomy because of bronchiectasis in the lower left lobe. One year later she was admitted to our institution. On admission we saw 8-years-old girl with severe microcephaly (head circumference = 44 cm) and typical, bird-like facial appearance. Her past medical history of recurrent infections and microcephaly with normal intelligence raised suspicion of an immunodeficiency syndrome. Laboratory investigations at admission were as follows: ESR 43 mm/hr, hemoglobin 147 g/L, WBC count 7.7×10^9/L with 64% neutrophils, 32% lymphocytes and 4% monocytes; platelets were 320×10^9/L. Serum alpha-fetoprotein was not elevated. Immunologic investigations revealed low serum IgA, 0.22 g/l, increased serum IgM, 3.10 g/L and decreased serum IgG,1.7 g/L; serum IgE was undetectable; specific antibody responses to immunizations were absent (tetanus, polio); the phenotypic analysis of peripheral blood lymphocytes was normal; lymphocyte proliferative responses in vitro to mitogens were normal; The diagnosis of NBS was confirmed by mutation analysis of NBS1 gene that revealed homozygousity for a typical 5 base-pair deletion (657del5). Intravenous immunoglobulin (IVIG) replacement therapy was commenced.

She was doing well until the age of 10 years when she developed fever, generalized lymph node enlargement, hepatosplenomegaly and mediastinal mass. Total WBC count was $103{,}000\times10^9$/L and at the evaluation of peripheral blood smear more than 90% of WBC were lymphoblasts. Peripheral blood and bone marrow lymphocyte phenotyping revealed that malignant cells were CD3, CD5 and CD7 positive. The diagnosis of TLBL/ALL was established. We started treatment (Berlin-Frankfurth-Münster, BFM'90 protocol) for standard risk ALL consisting of induction, consolidation, re-induction, and maintenance therapy as previously described.[3] We omitted cranial radiotherapy because of profound immunodeficiency. During treatment no significant side effects of chemotherapy were observed.

Our patient was lost from regular follow-up after treatment of TLBL/ALL and for that reason substitution with IVIG was not continued. Investigations performed at the age of 15 years revealed low serum IgA, 0.23 g/L but normal IgM, 2.16 g/L and IgG, 7.70 g/L concentrations; serum IgG subclasses (IgG1 6.061 g/L, IgG2 1.984 g/L, IgG3 0.386 g/L, IgG4 0.186 g/L) were within normal range for given age. Five years after cessation of chemotherapy she is doing well, without significant infections. She was immunized with three doses of tetanus toxoid, hepatitis B vaccine and pneumococcal polysaccharide vaccine. However, protective titers of anti-tetanus, HBs antibodies or pneumococcal antibodies were not detected. At last follow-up visit an increase of serum IgM (5.17 g/L) was detected.

Discussion

NBS has been so far reported in different populations, but most of the patients are of Slavic origin and carry a typical mutation (657del5) in the NBS1 gene, encoding for nibrin, a protein involved in DNA repair.[2,4] B-cell lymphomas are the most frequently encountered malignancies in NBS, but cases of precursor T-cell, B-cell leukemia or myeloid leukemia also have been reported.[4, 5, 6, 9] NBS study group reported that 40% of 55 patients in Nijmegen registry developed cancer before the age of 21 years.[4] The majority of lymphomas in NBS were diagnosed under 15 years of age and lymphoma was the leading cause of death.[2,4] Our patient developed TLBL/ALL at the age of ten years.

In our patient complete and sustained remission of T-LBL/ALL was achieved. Also, two previously reported NBS patients of Polish origin with diagnosis of TLBL/ALL were alive at the time of NBS registry report.[4] The data in the literature both in regard to type of treatment and survival of NBS patients with malignancy are limited. Recently, Seideman et al. reported complete remission of B-cell lymphoma in two of four NBS patients using BFM '90 protocol.[7] The same patients were treated with reduced doses of methotrexate (20-50%) while alkylating drugs and epipodophyllotoxines were omitted or reduced by 20-50%. Treatment was intensified during following courses if the first doses were well tolerated.[7] Also, Michellet *et al.* reported the use of pentostatin in an attempt to avoid significant immunosupression in NBS patient who developed T-cell prolymphocytic leukemia associated with autoimmune manifestations.[5] In patients who suffer from chromosomal instability syndromes (such as NBS) chemotherapy and radiotherapy must be modified because of potentially serious toxic complications. In our patient we used standard chemotherapy but we omitted cranial irradiation. In pediatric patient with unrecognized NBS, Baskshi et al. reported lethal outcome due to severe dermatitis and gastroesophagitis after craniospinal irradiation for medulloblastoma.[8] The use of standard doses of chemotherapy in NBS should be also avoided because it increases the risk of life-threatening infections.[7,9] Barth *et al.* reported recently NBS patient who developed disseminated Bartonella henselae infection during treatment of myeloid leukemia.[9]

Immunodeficiency in NBS is significant affecting both humoral and cellular immune system.[2] Severe lung infections are the most frequent and if not treated appropriately may lead to chronic lung disease.[4] Immunodeficiency in NBS is highly variable, with a tendency to progress over time.[10] Nearly one-half of 40 Polish patients had significantly decreased level of serum IgG at the time of diagnosis and, like our patient, were given regular IVIG therapy.[10] Surprisingly, our patient after treatment of TLBL/ALL remained free of major infections without IVIG substitution. Three years after the last infusion of IVIG normal concentrations of serum immunoglobulins were detected. However, significant humoral immunodeficiency in our patient remains because specific antibody responses after immunizations could not be detected.

Nibrin has been shown to be involved in the process of immunoglobulin class switch recombination (CSR).[11] Defects of CSR are typically associated with low serum IgG and IgA, and normal to increased IgM serum levels. In our patient dysgammaglobulinemia with increased

serum IgM was detected at the time of diagnosis but with the use of IVIG serum IgM gradually decreased. Also, in nearly one-half of 56 patients with X-linked hyper-IgM syndrome serum IgM decreased with the use of IVIG.[12] This phenomenon may result from a feedback mechanism, which decreases the natural stimulus for IgM production.[13] In immunodeficiencies characterized by immunoglobulin gene switch abnormalities, progressive elevation of serum IgM may reflect the presence of chronic, poorly controlled infection.[12] However, in 16 Polish patients with NBS who were not on IVIG substitution, sudden increase of mono/oligoclonal serum IgM was recorded and in ten patients it predicted development of B-cell lymphoma.[10] In our patient, five years after IVIG was stopped, sudden increase of oligoclonal IgM was detected. Whether the use of IVIG may partially control or suppress Epstein-Barr virus (EBV) driven B-cell proliferation in NBS patients remains to be answered. NBS patients are not generally prone to opportunistic infections.[4] However, an impact of EBV in development of lymphoid malignancies in NBS is likely.[10,14]

In conclusion, we report on a NBS patient with long-term survival after treatment for TLBL/ALL. Careful prevention of infections, including the use of intravenous immunoglobulin and adopted chemotherapy are both essential for successful treatment of lymphoid malignancies in NBS. Monitoring of serum IgM concentration may be a useful indicator for early detection of lymphomas in NBS.

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