T-cell Non-Hodgkin lymphoma associated with myelodysplasia: A case report in a child

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Abstract
Myelodysplastic syndrome (MDS) is a clonal bone marrow disease characterized by ineffective erythropoiesis. MDS patients have also cytopenia. The risk of acute leukemia, and particularly of acute myeloblastic leukemia (AML), is the most important characteristic of the disease.

Myelodysplasia associated with Non Hodgkin’s lymphomas (NHL) has been rarely described in the literature. This is suggested to be due to the defect in the immune system, an up-regulation of some cytokines, and a common molecular origin.

In this article, we reported a 7-year-old pediatric NHL case with a normal karyotype and myelodysplasia in the bone marrow and discussed the pathogenesis of the association of NHL and myelodysplasia.

Keywords: Lymphoma, myelodysplasia, relation

Introduction
Myelodysplastic syndrome (MDS) is a clonal bone marrow disease characterized by ineffective erythropoiesis. MDS patients have also cytopenia. The risk of acute leukemia, and particularly of acute myeloblastic leukemia (AML), is the most important characteristic of the disease (1).

MDS is defined as primary of de novo MDS if it develops in a child who has no other diseases, and who has not received chemotherapy or radiotherapy for any other reason, while it is considered as secondary MDS if there is a factor which promotes the development of myelodysplasia, especially a history of chemotherapy or radiotherapy (2).

Genetic factors, ionized radiation, chemotherapy, benzene, smoking, alcohol, hair dyes and over-consumption of foods especially rich in phenol are risk factors for the development MDS (2).

In primary MDS cases, cytogenetic abnormalities are found in 50-70% of the patients, while this rate rises over 85% in cases with treatment-related secondary MDS (2).

Non-Hodgkin’s lymphomas (NHL) are a group of malignant diseases originating in the organs and cells of the immune system. Childhood NHL exhibits diffuse and extranodal involvement. Childhood NHL generally arises from lymphoid precursors and B-cell type is found in 80% of the cases (3).

Non-Hodgkin’s lymphomas typically metastasize early and the risk of leukemic presentation and central nervous system relapse is high in NHLs (4).

Myelodysplasia associated with NHL has been rarely described in the literature. This is suggested to be due to the defect in the immune system, an up-regulation of some cytokines, and a common molecular origin (5-10).

In this article, we reported a 7-year-old pediatric NHL case with a normal karyotype and myelodysplasia in the bone marrow and discussed the pathogenesis of the association of NHL and myelodysplasia.

Case
A 7-year-old female patient admitted with a swelling on the right side of the neck which had been noted 5 days ago. She had had no complaints such as fever, weight loss, or night sweating. The past medical history and family history of the patient revealed no significant findings. The physical examination of the patient revealed multiple lymphadenopathies in both cervical chains in the submandibular region, with the largest on the left measuring 2.5x1.5 cm and the largest on the right measuring 3.5x1.5 cm, and a 2x2 cm lymphadenopathy in the right inguinal region.
The laboratory examinations revealed a hemoglobin value of 10.1 g/dl, a WBC count of 1.2x10^9/l, and a platelet count of 159x10^9/l. Peripheral blood smear revealed no blasts. The lactate dehydrogenase 705 U/l and B 12 levels and the other biochemical test results were considered as normal. The immunoglobulin A 133.0 mg/dl, G 955.0 mg/dl, M 44.0 mg/dl and E 49.25 IU/ml levels were consistent with the age of the patient.

The results of the direct Coombs’s test and the ELISA-based Parvovirus PCR, EBV, and CMV assays were negative.

Abdominal ultrasonography revealed multiple ovoid and round lymphadenopathies with loss of echogenic hilus in the para-aortic, para-iliac and mesenteric regions, with the largest measuring 21x13 mm and neck ultrasonography revealed multiple reactive lymphadenopathies with echogenic hilus and hilar blood flow in both cervical chains in the submandibular region, with the largest one on the left measuring 23x10 mm and the largest one on the right measuring 32x14 mm.

The bicytopenia of the patient continued for 4 days in the clinical follow-up and bone marrow aspiration was performed. The bone marrow aspiration smear revealed 4% monocytes, 35% normoblasts, 30% lymphocytes, 15% myelocytes, 6% metamyelocytes, 6% neutrophils, and 4% blasts. Dysplasia was found in bone marrow cells. Diffuse hypogranular myeloid cells, dysplastic megakaryocytes and erythroblastic cells were observed (Figure 1a,1b,1c). The cervical lymph node biopsy result was consistent with diffuse NHL with a high-grade malignancy (Figure 2).

Immunohistochemical examination of cervical lymph node was consistent with T-cell. Analyses of 17p13.1, p53, 20q12, 5q31, 7q31 gene deletions and monosomy/trisomy 7, and monosomy/trisomy 8 chromosomes were performed with bone marrow cytogenetic and FISH (fluorescence in situ hybridization) studies. The results were accepted as normal. The patient left our hospital to continue her diagnostic studies and treatment in another institution.

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Discussion

MDS is known to be related to a process in tumor differentiation. A high incidence of MDS was reported in relation with solid tumors, such as lung, colon, prostate and liver cancers (11). The same relationship was described between MDS and lymphoid neoplasms, such as acute lymphoblastic leukemia, chronic lymphocytic leukemia, and NHL (12-15). In 1996, a group of Spanish investigators studied the association of lymphoid malignancy in patients with primary MDS and found an association rate of only 1% and concluded that this association could be a coincidence (14).

The association of MDS and lymphoma was described in 21 cases in the literature. However, in 9 of these 21 cases MDS and NHL were diagnosed simultaneously.

In 12 cases, MDS diagnosis was made primarily before the onset of lymphoma and the time between the two diseases ranged between 5 months and 4 years (5,13,16-27).

The mechanisms responsible for the development of NHL in MDS patients have not been cleared yet. MDS is generally considered as a clone disorder with pluripotent stem cell origin and with a potential to differentiate into lymphoid and myeloid cells. Some authors suggest that the two diseases are caused by the same neoplastic process or a common origin (6).

Another opinion is that MDS plays a predisposing role in the development of lymphoid neoplasms. (5). MDS is associated with abnormal immunological functions. Abnormal lymphocyte count and function (especially natural killer cells) induce growth of neoplastic cells. The immune system defect underlying the development of myelodysplasia is also present in NHL (8,9).

Shimanoto et al. related the association of MDS and NHL to the up-regulation of particular cytokines, such as IL-6 and vascular endothelial growth factor (VEGF) and reported a case of anaplastic large-cell lymphoma with presence of high IL-6 and VEGF levels and bone marrow myelodysplasia at the time of diagnosis (10).

Chromosomal anomalies are common in both MDS and lymphomas. The questions, whether there are other...
cytogenetic abnormalities not known yet, and whether the association of MDS with NHL is caused by these common cytogenetic anomalies, still remain to be answered.

In 1998, Mori A et al. found bone marrow dysplasia simultaneously with the diagnosis of angiocentric lymphoma in a 46-year-old male patient. They thought that the association might be caused by cytokines, such as interleukin-2, -4, and -6 (28).

Huang HH et al. also reported a case with the association of bone marrow dysplasia and lymphoma in 2009. They suggested that this association might be caused by a common chromosomal anomaly (del (20q)) based on the fact that the patient had 20q deletion in both myeloid and lymphoid cell lines (29).

Conclusion

In conclusion, the association of MDS and lymphoma is very rare. Only 21 cases have been reported to date. However, de novo MDS and lymphoma were simultaneously identified in 8 of these cases. We think that this association may be caused by a common molecular origin, common chromosomal anomalies and cytokines. Large scale studies including many cases are needed on this subject.

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