모세관확장실조 환자에서 발생한 호지킨림프종

임주연 • 전민아 • 김효선 • 한정우 • 유철주 • 한승민

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A Case of Hodgkin Lymphoma Developed in an Ataxia-telangiectasia Patient

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Ataxia-telangiectasia (AT) is characterized by cerebellar ataxia, progressive immunodeficiency, radiation sensitivity, telangiectasia, and predisposition to malignancy. AT patients have a 100-fold increased risk for the development of lymphoid malignancies. It is important to consider AT in a child with pre-existing ataxia, or lymphoid malignancy that was diagnosed at a younger age than expected. This consideration avoids the confusion between ataxia development and toxicity from chemotherapy. Hodgkin's lymphoma (HL) is usually treated with chemotherapy and/or radiotherapy. Unfortunately, when treated with conventional doses of radiotherapy, AT patients invariably experience devastating necrosis of their normal tissues. Therefore, a new treatment protocol for patients with HL in AT must be established. In this paper, we report the case of an 8-year-old female patient with HL in AT who was treated with chemotherapy. This patient was also treated with brentuximab (which targets CD30) for salvage therapy after the disease progressed.

Key Words: Ataxia-telangiectasia, Hodgkin lymphoma, Chemotherapy, Brentuximab

pISSN 2233-5250 / eISSN 2233-4580
https://doi.org/10.15264/cpho.2016.23.2.184
Clin Pediatr Hematol Oncol 2016;23:184～187

Received on June 14, 2016
Revised on July 16, 2016
Accepted on August 19, 2016

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Introduction

Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder characterized by progressive cerebellar ataxia, telangiectasia, and immunodeficiency. It is caused by mutations in the ataxia-telangiectasia mutation (ATM) gene on chromosome 11. Mutations in the ATM gene cause the complete absence or impaired function of the ATM protein kinase [1]. One of the most important features of AT is that it increases patients' susceptibility to cancer, and to lymphoid malignancies in particular [2].

Approximately 10% of patients with AT develop cancer. The most common forms of malignancy in AT are non-Hodgkin lymphomas, followed by acute lymphoblastic leukemia and Hodgkin Lymphoma (HL) [3]. Therefore, approximately 5±10% of AT patients develop HL. HL is usually treated with chemotherapy and/or radiotherapy. Unfortunately, AT patients are extremely sensitive to chemotherapeutic agent and ionizing radiation [4]. Significant toxicity was recorded for 70% of patients after conventional chemotherapy [5]. Therefore, conventional HL treatment is not appropriate for AT patients.

At least 70% of patients with AT develop immuno-

deficiency [6]. Therefore, severe pulmonary infections are the most frequent cause of death in AT patients, followed by the combination of pulmonary infection and malignancy [3]. These facts ought to be considered in the treatment of HL in AT, because chemotherapy-induced toxicity can be very severe in these patients.

Case Report

An 8-year-old girl diagnosed as AT from Kazakhstan was referred to our hospital due to multiple lymphadenopathy. Her development was normal until 18 months of age, at which time she began showing ataxia. After this, the patient could no longer stand or walk. Brain magnetic resonance imaging (MRI) when the patient was 2 years old revealed isolated cerebellar atrophy. The patient also experienced recurrent respiratory infections. At the age of 7 years, the patient had fever of unknown origin for several months, which was unresponsive to intravenous antibiotics. The patient's cervical lymph nodes began to enlarge and that progressed for a month. A biopsy was performed in Kazakhstan, and the patient was diagnosed with HL.

Pathology review was performed at our hospital and consistently revealed nodular sclerosis HL. Immunohistochemical analysis revealed that the tumor was positive for CD30. On physical examination, the patient had multiple enlarged cervical lymph nodes and telangiectasia of the bulbar conjunctiva. Neurologic examination revealed decreased tendon reflexes, and ataxic gait. Laboratory investigations identified a normal complete blood count. Biochemistry tests revealed aspartate aminotransferase of 77 IU/L, alanine aminotransferase of 43 IU/L, and lactate dehydrogenase of 233 IU/L. The alpha-fetoprotein level was high (39.9 ng/mL). The patient had hyperbilirubinemia with a total bilirubin of 6.2 mg/dL, and direct bilirubin 5.5 mg/dL. There were decreased levels of immunoglobulin (Ig) A (26 mg/dL), Ig G (426 mg/dL), Ig M (19 mg/dL) and Ig E (<2.0 kU/dL).

Positron emission tomography-computed tomography (PET-CT) demonstrated lymphoma involvement of lymph nodes in the left neck, upper mediastinum, hilum, anterior diaphragm, retroperitoneum, liver, spleen, and lung at multiple sites. Analysis of the ATM gene revealed a compound heterozygous mutation (exon 61; c.8753 T>G.p.M2918R and exon 51 c.7438 delC) that confirmed AT. There was no evidence of disease in either the bone marrow or cerebrospinal examinations. Therefore, the patient was diagnosed with HL Ann Arbor stage IV.

After HL was confirmed at our hospital, the patient received chemotherapy according to the COPP/ABV protocol with a reduced dose. The COPP/ABV chemotherapy regimen consists of vincristine (1.4 mg/m^2 day 1), cyclophosphamide (600 mg/m^2, day 2), procarbazine (100 mg/m^2, day 1 to 7), prednisolone (40 mg/m^2, day 1 to 14), vinblastine (6 mg/m^2, day 8), bleomycin (10 U/m^2, day 8), and doxorubicin (35 mg/m^2, day 8). However, in order to minimize alkylating agent toxicity and pulmonary complications, we omitted bleomycin, and reduced the cyclophosphamide dose to 50% (cycle 1, 2) or 66% (cycle 3, 4). In addition, vincristine was omitted during the 1st cycle, and procarbazine was substituted with dacarbazine (80 mg/m^2, day 2 to 4) because of elevated bilirubin. Doxorubicin and vinblastine were administered at 50% normal doses.

During chemotherapy, the patient was also treated with intravenous gamma globulin (400 mg/kg) replacement therapy every 3 weeks because of severe humoral immunodeficiency.

After two cycles of chemotherapy, PET-CT revealed a partial response. We continued chemotherapy every 3 weeks. The treatment was well tolerated, despite grade 4 neutropenia, grade 3 mucositis, and neutropenic fever. However, after the fourth chemotherapy cycle, the patient experienced grade 3 neutropenic fever and serum CMV real-time PCR assay revealed a positive viral load of 2,475,000 copies/mL. Therefore, the patient was treated with intravenous ganciclovir for 2 weeks.

A PET-CT was performed at the end of the sixth cycle of modified COPP/ABV chemotherapy. Unfortunately, the scan demonstrated disease progression in right axilla lymph node and liver. Therefore, we changed the regimen to ICE chemotherapy which consists of ifosfamide, carboplatin, and etoposide. We decreased the dose of ifosfamide (60% of conventional dose, 1.8 mg/m^2, day 1 to 3) to prevent toxicity of the alkylating agents.

However, disease progression was observed again after second cycle of ICE chemotherapy. At this point, we chose brentuximab (1.5 mg/kg) for salvage therapy. After the first cycle of brentuximab therapy, the patient developed left hemiparesis and motor aphasia. A brain MRI suggested the possibility of either infection (such as tuberculosis) or lymphoma involvement. We added tuberculosis treatment and steroids to the second cycle of brentuximab. The patient's neurologic symptoms improved slightly, although not completely. A follow-up MRI revealed stable disease. Another PET-CT scan was performed one month after the second brentuximab infusion. Disease progression was observed, with an increase in the size of known hepatic, lung and soft tissue metastases. In addition, there was new metastasis in axillary and mesenteric lymph nodes. We discontinued the brentuximab therapy. Instead, we began palliative care with COPP chemotherapy every 3 weeks. After the second course of COPP chemotherapy, the patient returned to Kazakhstan to continue therapy with her family. Unfortunately, she died two weeks after returning home, which was one year of receiving the diagnosis of HL.

Discussion

This case describes an AT patient with advanced stage HL who was treated by chemotherapy alone.

In the general population, more than 90% of HL patients survive after treatment [7]. Standard treatment regimens are available for HL, including chemotherapy with or without adjuvant radiotherapy. With such a combined modality approach, excellent event-free survival rate can be reached with acceptable toxicity [3,4,8-10]. However, there are no recommendations regarding HL in AT. Previous studies have demonstrated poor outcomes, with toxicities being the most common cause of death. Sandoval et al. [3] reported 11 patients with HL in AT, all of whom died with a median survival of 3 months. Eight patients died due to pneumonia, and three died from multisystem organ failure. One of the patients developed sudden respiratory distress after receiving the second dose of bleomycin (total cumulative dose 20 U/m^2) [3]. Tamminga et al. [4] reviewed a patient treated with one half to one third the normal dose of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) who later suffered from pulmonary fibrosis; another patient treated with one fourth to one third the normal dose of COPP/ABV was diagnosed with secondary leukemia. Therefore, it has been suggested that excess toxicity may be avoided by removing bleomycin or reducing the doses of alkylating agents. However, the dose reduction of chemotherapy can also increase the risk of treatment failure.

Patients with AT have a more difficult time repairing DNA damage caused by chemotherapy agents in normal cells; therefore, this may increase their sensitivity to toxic side effects [4]. AT also increases the risk of infection due to inherent immunodeficiencies. Therefore, the omission of a drug or the radical reduction of chemotherapy intensity was recommended. However, these changes may also lead to the treatment failure, as in our case. This indicates that we need to further optimize the therapy for HL in AT patients.

We introduced brentuximab after progression. Unfortunately, however, it was unable to bring the disease under control. The delayed start of a drug in the case of deteriorating disease might affect its result. Meister et al. reported [11] a patient with HL in AT treated with brentuximab vedotin and reduced COPP plus rituximab. The patient was diagnosed with nodular sclerosing HL, with high expression levels of CD30. They initiated monotherapy consisting of six courses of brentuximab (50 mg, 1.8 mg/kg) every 3 weeks in phase I and continued the drug for six courses with COPP plus rituximab in phase II. MRI scans after the first five courses revealed complete clinical remission [11]. There are limited data regarding brentuximab-based combination regimens in patients with both HL in AT. However, this combination may help patients with HL in AT if their lymphoma cells exhibit CD30 expression.

In conclusion, treatment-related mortality was observed with full administration of chemotherapy in some cases. This suggests a requirement of reduced intensity chemotherapy in HL developed in AT patients, and addition of brentuximab is likely to compensate for dose reduction of conventional chemotherapy. Reduced dose chemotherapy combined with a molecular targeting agent may improve the outcome of HL in AT.

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