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Autoimmune Cytopenias in Children with Hodgkin's Lymphoma

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Abstract

This study aims at discussing autoimmune cytopenias (AIC) in Hodgkin's Lymphoma (HL) by reporting three cases which were diagnosed and treated in the Department of Pediatric Hematology and Oncology at Ankara University School of Medicine. HL is known to have rarely AIC including autoimmune hemolytic anemia (AIHA), autoimmune thrombocytopenia and autoimmune neutropenia. Nodular sclerosis and mixed cellularity are considered as the most frequent subtypes in patients with AIC. In various articles, it is concluded that AIC in HL are paraneoplastic autoimmune syndromes. Herein three patients with HL associated with AIC are reported. Autoimmune thrombocytopenia was observed at remission in one case at stage IV-B HL with mixed cellularity subtype while AIHA developed concomitantly with diagnosis in another patient at stage IV B with nodular sclerosis subtype. It is interesting that autoimmune thrombocytopenic purpura (ITP) and AIHA were seen as presenting manifestations of HL in one case at stage 1-B with mixed cellularity subtype.

Keywords: Hemolytic anemia; Autoimmune; Hodgkin; Thrombocytopenia; Paraneoplastic syndrome.

Introduction

Immune neutropenia, AIHA and ITP were reported in patients with HL [1-3]. Some researchers suggest that AIC are likely autoimmune paraneoplastic syndromes of the patients with HL [4,6,7]. Paraneoplastic autoimmune syndromes may be observed preceding lymphoma and/or concomitantly with diagnosis. It is also possible to say that they may be seen after treatment as a sign of relapse [5,6]. The sporadic case reports and reviews showed that HL with autoimmune cytopenia is more commonly seen in males and is more likely to have mixed cellularity and nodular sclerosis histopathology [6,7]. Herein three patients associated with immune thrombocytopenia and/or immune hemolytic anemia which were published separately, are evaluated together.

Case presentations

Case 1

A 13-year-old boy was admitted with complaints of lymphadenopathy. In physical examination, he had enlarged right supraclavicular (4 cm in diameter) and axillary (2 cm in diameter) lymph nodes, hepatosplenomegaly, weight loss and intermittent fever without infection. Biopsy of the cervical mass revealed HL with mixed cellularity histopathologic subtype. Abdominal and thoracic computed tomographic scan and abdominal ultrasonography demonstrated enlarged periaortic, mesenteric lymph nodes and hepatosplenomegaly. The patient was at stage IV-B HL and received two cycles of OPPA (vincristine, prednisone, procarbazine and adriamycin) chemotherapy. Subsequently, four cycles

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of C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisone) chemotherapy was given. The patient achieved complete remission. One year later, he was presented with epistaxis, bruising and petechial spots. His thrombocyte count was 20000/µL. Bone marrow aspiration revealed erythroid hyperplasia and a marked increase in megakaryocyte. Abdominal and thoracic computed tomographic scan were normal. His diagnosis was ITP and the patient was treated with prednisone totally twelve weeks. He responded to prednisone treatment and his thrombocyte count became normal. Two years after the diagnosis of ITP, he was readmitted with abdominal pain, weight loss and splenomegaly. Enlarged retroperitoneal lymph nodes and massive splenomegaly were determined in abdominal ultrasonography. The patient was relapsed and he received three cycles of CEM (CCNU, VP16-213 and methotrexate) combination chemotherapy. After obtained partial remission with CEM treatment, the patient could not be followed up.

Case 2

A 8-year-old boy was admitted with complaints of enlarged left cervical lymph node (5 cm in diameter). On admission, the case had left cervical lymphadenopathy, hepatosplenomegaly, weight loss and fever without any infection. Biopsy of cervical lymph node revealed HL with nodular sclerosis subtype. An abdominal ultrasonography exhibited enlarged periaortic and celiac lymph nodes and hepatosplenomegaly. The patient was diagnosed with clinical stage IV-B HL and received two cycles of C-MOPP chemotherapy. During the second course of therapy, jaundice developed and the diagnosis of AIHA was found on a strongly positive (4+positive) direct Coombs test, elevated reticulocyte count, indirect bilirubin and LDH levels. The dose of prednisone was given 2 mg/kg/ day and good response was obtained within two weeks. Direct Coombs test became negative, reticulocyte count and bilirubin level improved. However, the patient passed away after the second course of chemotherapy due to lymphoma progression.

Case 3

A 6,5-year-old boy presented complaining of pallor, epistaxis and petechial spots. The patient had marked pallor and scattered petechial spots without significant lymphadenopathy and splenomegaly. Blood count showed a hemoglobin level of 5,2 g/dL, hematocrit of 15,4%, thrombocyte count of 3000/µL and the reticulocyte count was 7,4%. Direct Coombs test was (4+) positive. Bone marrow aspiration revealed significant increase in megakaryocytes. A diagnosis of Evans syndrome was made and the patient was treated with high-dose methylprednisolone. His platelet count increased to normal level. However, the hemoglobin level slightly increased to maximum 9,1 g/dL and Coombs test was still positive. A partial response to steroid therapy was obtained but his left posterior cervical small lymph nodes grew in size rapidly up to 5 centimeters in diameter. The biopsy revealed HL with mixed cellularity subtype. All the other staging procedures were normal. The patient was at stage1-B and OPPA chemotherapy was started. After the first cycle of chemotherapy, his hemoglobin level normalized, reticulocyte count decreased and direct Coombs test became negative. The patient was treated 2 cycles of OPPA plus 2500 cGy involved field radiotherapy. He achieved complete remission and he is presently alive with no symptoms.

Discussion

Immune thrombocytopenia, AIHA and autoimmune neutropenia are uncommon in HL. In some series of patients with HL, the occurrence of immune thrombocytopenia was noted in only between 0,6% - 2% of the cases and the association of AIHA with HL was reported to be 0,2% - 4,2% [1,2,10]. One hundred ninety one children with newly diagnosed HL were treated and followed up in our institution between 1964 and 2000. The median age in 144 males and 47 females was ten years with an age range 3-15 years. Majority of the patients were in stage III and IV with a predominance of mixed cellularity subtype. Immune thrombocytopenia and/or AIHA were observed in 3/191 patients (1,5%) in our institution [8].

Mixed cellularity and nodular sclerosis subtypes of HL are reported as the most frequent subtypes in patients with AIHA whereas autoimmune thrombocytopenia is observed with all histologic subtypes both with limited and extensive disease [2,6,9]. In our patients, the subtypes were mixed cellularity in one patient with immune thrombocytopenia and nodular sclerosis with AIHA in another case. In the third case having mixed cellularity subtype, autoimmune thrombocytopenia and AIHA were observed as presenting manifestations of HL.

The patients have got severe immunosuppression because of interaction between tumor cells and the immune system. Another unusual feature of Hodgkin and diagnostic Reed-Sternberg cells comprise less than 1% of HL. The majority of the tumor bulk is constituted by reactive or inflammatory cells in varying compositions which depend on the subtypes. Hodgkin and Reed-Sternberg cells are capable of modulating their environment by producing several cytokines. Several studies demonstrated that cell-mediated immunity was defective in HL. Patients exhibit a persistent defect in T-cell function at presentation and in remission. Impairment of delayed cutaneous hypersensitivity, high levels of circulating immune complexes, decreased natural killer cell cytotoxicity, enhanced sensitivity to suppressor monocytes and suppressor T cells, decreased E-rosette formation, decreased mitogen induced and mixed lymphocyte proliferation, abnormal interleukin-2 production, decreased serum, erythrocyte and hair zinc levels were published [11,12].

Immune thrombocytopenic purpura by documented destruction of platelets and the presence of increased number of megakaryocytes in the bone marrow. Anti-platelet antibodies and autoimmune thrombocytopenia were detected in HL. Possible mechanism include cross-reaction between tumor associated antigens and platelet antigens or immune complex adherence to platelet membranes [13]. The appearance of immune thrombocytopenia was documented prior to diagnosis, subsequent to diagnosis or in remission of HL. In the treatment of ITP in lymphomas, conventional therapeutic modalities may be employed: Corticosteroids, splenectomy and perhaps immunosuppressive treatment [2,7]. In the first patient, ITP was observed in remission of HL and responded well to the steroid therapy [8]. In the third patient, ITP and AIHA preceded the diagnosis of HL and the patient was treated with high-dose methylprednisolone therapy which led to a complete recovery of thrombocyte count but his hemoglobin level slightly increased [9].

Although the mechanism of AIHA is unknown, researchers sug-

gested that tumor associated antigens induce antibodies cross-reacting with erythrocytes antigens and the production of autoantibodies were the causes of AIHA [13]. Unlike autoimmune thrombocytopenia, AIHA is related to the activity of HL and usually occurs in cases with wide spread involvement and systemic symptoms. It usually precedes the diagnosis or a recurrence of the disease. AIHA developed during the chemotherapy in the second patient at stage IV-B with nodular sclerosis subtype and responded to the steroid therapy even when HL was active but the patient passed away due to lymphoma progression. Interestingly, immune thrombocytopenia and hemolytic anemia were seen as presenting manifestations in the third patient. High-dose steroid therapy was not completely effective for AIHA while it was effective in autoimmune thrombocytopenia. After the first cycle of OPPA, his hemoglobin level increased with and reticulocyte count decreased and direct Coombs test became negative. Definitive therapy for the underlying HL appears to be necessary to successfully treat AIHA associated with lymphoma.

Conclusion

Autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia may occur prior to, concurrent with and at the time of recurrence of HL or incomplete remission. The authors conclude that autoimmune cytopenias were likely an autoimmune paraneoplastic syndromes of the patients with Hodgkin disease. Autoimmune hemolytic anemia in Hodgkin's Lymphoma responds better to anti-lymphoma treatment than to steroids.

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