Case Report
Common variable immune deficiency associated Hodgkin’s lymphoma complicated with EBV-linked hemophagocytic lymphohistiocytosis: a case report

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Abstract: Hemophagocytic syndrome (HPS) is described by an increase in macrophages accountable for extensive phagocytosis of hematopoietic cells. Secondary HPS arises commonly in the presence of infections, neoplasia, autoimmune disorders and immune disorders. Here, we reported a patient with common variable immune deficiency (CVID) and Hodgkin’s lymphoma (HL) who later developed EBV linked hemophagocytic lymphohistiocytosis. 42 year old men underwent check-up because of back pain in July 2012. He had known CVID disease. In physical examination he had no lymphadenopathies however his spleen was palpable 3 cm under arcus costa. He had hypogammaglobulinemia with IgG levels around 500 mg/dl. In abdominal computed tomography (CT) multiple lymphadenopathies reaching maximum 26×17 cm size were seen so, PET-CT was performed. Involvement in thorax, abdomen, and bone was detected with maximum SUV max 11.5. He had undergone tru-cut biopsy from lymph node in November 2012 which revealed HL. Bone marrow investigation favored with mix cell type. His cytogenetic analysis was reported as 46 XY. He was considered as stage 4 disease and ABVD (Adriamycin, bleomycin, vincristine and dexamethasone) was given. He had undergone six cycles of chemotherapy in May 2013 and complete remission was observed in control CT screening in July 2013. However pancytopenia evolved in August 2013. Bone marrow investigation revealed suspicious lymphohistiocytic infiltration. Treatment was planned to apply autologous stem cell transplantation (SCT) after salvage chemotherapy. Control bone marrow investigation again revealed the lymphohistiocytic aggregates with hemophagocytosis. Our patient showed 5 criteria of hemophagocytic syndrome. He had ferritin elevation (>5000 µg/dl), splenomegaly (13 cm) cytopenia, triglyceride elevation and hemophagocytosis. He had unrelated SCT transplantation however he died from transplant related toxicity. The primary and secondary immune deficiency caused by chemotherapy are the major causes for our patient inability to control his EBV infection which eventually lead to hemophagocytic lymphohistiocytosis. To conclude, rare simultaneous manifestation of primary immune deficiencies (PID), Hodgkin’s lymphoma and EBV-HLH occurred in our patient which have concordant immunological mechanism that eventually lead poor prognosis in our patient.

Keywords: Common variable immune deficiency, Hodgkin’s lymphoma, hemophagocytic lymphohistiocytosis

Introduction
Hemophagocytic syndrome (HPS) is described by an increase in macrophages accountable for extensive phagocytosis of hematopoietic cells [1]. Fever, hepatomegaly, splenomegaly, elevated liver enzymes, increase in ferritin and triglyceride levels could be present in HPS. HPS has a poor prognosis and high mortality rates [2]. Secondary HPS arises commonly in the presence of infections, neoplasia, autoimmune disorders and immune disorders. Viruses especially Epstein-Barr virus (EBV) infections were related with HPS [3]. Common variable immunodeficiency (CVID) is characterized by deficient antibody synthesis. An increase in neoplastic disorders especially lymphomas were observed. Herein, we aimed to report a patient with CVID and Hodgkin’s lymphoma (HL) who later developed EBV linked hemophagocytic lymphohistiocytosis.

Case report
42 year old men underwent check-up because of back pain in July 2012. He had known CVID. He had hypogammaglobulinemia with IgG levels around 500 mg/dl. In blood test liver enzyme
levels (AST 104 u/l, ALT 90 u/l, GGT 326 u/l) were high. USG was performed which revealed cholelithiasis. Cholecystectomy was performed in August 2012. However his complaint of back pain did not resolve. In physical examination he had no lymphadenopathies however his spleen was palpable 3 cm under arcus costa. He had a cachectic appearance. He had no pain except backache which had started from July 2012. He was using pain killers since the beginning of backache. He had no fever, night sweat and weight loss. He was a smoker and his gastric endoscopy was normal. His family anamnesis revealed death of his father from myocardial infarct and cancer history of unknown type in his mothers’ family. In abdominal computed tomography (CT) multiple lymphadenopathies reaching maximum 26×17 cm size were seen so, PET-CT was performed. Involvement in thorax, abdomen, and bone was detected with maximum SUV max 11.5. In PET-CT involvement and thickening of rectum was seen, so rectoscopy was performed which resulted in normal. He had undergone true-cut biopsy from lymph node in November 2012 which revealed HL. Bone marrow investigation favored with mix cell type. His cytogenetic analysis was reported as 46 XY. He was considered as stage 4 disease and ABVD (Adriamycin, bleomycin, vincristine and dexamethasone) chemotherapy regimen was started in November 2012. After 4 cycles of treatment CT investigation performed. In CT investigation only involvement in lomber vertebra and pelvic bone was seen. PET investigation was normal. The ABVD treatment was planned to be given 2 more cycles with a total of 6 cycles. At the same time he was given periodic monthly IVIG treatment because of CVID. He was given the sixth cycle of chemotherapy in May 2013 and complete remission was observed in control CT screening in July 2013. However pancytopenia evolved in August 2013 with a complete blood count test as, hemoglobin 3.7 gr/dl, white blood cell 1700/mm³, platelet 9000/mm³. Bone marrow investigation revealed suspicious lymphohistiocytic infiltration. Therefore CT and PET screenings were performed again. In lung and other regions of body multiple PET positive involvement sites were observed. He was diagnosed as refractory disease. Treatment was planned as to apply autologous stem cell transplantation (SCT) after salvage chemotherapy. He had one brother whose HLA antigens did not match him. He was given 2 cycles of ICE chemotherapy protocol. Response to treatment was evaluated with PET screening. Involvements were seen to disappear almost completely however there was no improvement in cytopenia. More ICE treatment could not be given because of infections and cytopenia. Control bone marrow investigation again revealed the lymphohistiocytic aggregates with hemophagocytosis. Our patient showed 5 criteria of hemophagocytic syndrome. He had ferritin elevation (>5000 µg/dl), splenomegaly (13 cm) cytopenia, triglyceride elevation and hemophagocytosis. Interestingly he had no fever which is one of the most frequent symptoms of Hodgkin lymphoma. At the same time the investigation for donors for unrelated SCT was performed. He was given steroid, cyclosporine and IVIG treatment for EBV induced hemophagocytic lymphohistiocytosis (HLH). In April 2014 HLH-2004 protocol was started. The protocol could not be administrated full dose because of severe neutropenia. Half of Vepesid doses could not be given. During treatment myopathy appeared due to dexamethasone. ALT levels were fall to normal range from 550. Ferritin levels were fall to approximately 10000 µg/dl from 15000 µg/dl. Donor for unrelated SCT was found. He had unrelated SCT transplantation however he died from transplant related toxicity.

Discussion

One of the reasons for HLH is Epstein-Barr virus (EBV) infection. Mainly EBV-HLH cases occur in immunocompetent patients [4]. However sometimes it may develop in chronic active EBV disease, lymphoproliferative neoplasia like peripheral T-cell lymphoma and NK cell leukemia [5-8]. Exitus from EBV-HLH is mainly the consequence of the hypercytokinemia which develops from excessive activation of macrophages and T/NK cells. Because of this, cytokine storm may develop which ends in multiple organ failure. The treatment strategies mainly focus on controlling of cytokine storm, supportive treatment, HLH-94 or etoposide-containing regimens, administration of cyclosporine (CsA), corticosteroids and IVIG [9-13]. It is vital to identify EBV-HLH quickly. First treatment choice may be corticosteroids/IVIG, however if the answer to treatment is poor, treatment should be quickly converted to an etoposide-containing treatment. If the patient is revealed as neu-

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trope, CsA should be added into the etoposide-containing regimen. Intensive supportive care avoid the fatal complications such as opportunistic pulmonary infections and CNS hemorrhage.

CD8+ T lymphocytes are important for the eradication of virus-infected cells and reconnaisance against tumor cells. EBV has a well-known tropism for B cells and the invasion of CD8+ T cells are significant in development of HLH [14]. Excess cytotoxicity avoids effective elimination of infected cells which is the reason of permanent antigenic stimulus for CTLs and NK cells [15, 16]. Triggered CTLs and NK cells release enormous quantities of c interferon (IFN-c) and tumor necrosis factor-a (TNF-a), stimulating the macrophages, that infiltrate numerous organs and produce destructive cytokines [17]. Inherited defects of lymphocyte cytotoxic function, Signalling lymphocytic activation molecule (SLAM)-associated protein (SAP) deficiency, X-linked inhibitor of apoptosis (XIAP) deficiency, Interleukin-2-inducible T-cell kinase (ITK) deficiency, CD27 deficiency, Magnesium transporter 1 (MAGT1) deficiency, Serine-threonine kinase 4 (STK4) deficiency, Coronin-1A deficiency are some new findings on the range of primary immune deficiencies (PID) predisposed to uncontrolled EBV infection and portray their pathogenesis [18].

In the literature there are a few reports of PID associated HL complicated with hemophagocytic lymphohistiocytosis. In a case report, simultaneous manifestation of fulminant infectious mononucleosis with hemophagocytic syndrome and B-cell lymphoma in X-linked lymphoproliferative disease was reported [19]. EBV-Induced B-Cell Proliferative Disorder after Chemotherapy in a Patient with Hemophagocytic Lymphohistiocytosis with Associated EBV-Induced T-cell Proliferation was described [20]. In our case common variable immune deficiency is the main reason for innate immune system which played a major for the development of HL. The primary and secondary immune deficiencies caused by chemotherapy are the major causes for our patient inability to control his EBV infection which eventually lead to hemophagocytic lymphohistiocytosis.

To conclude, rare simultaneous manifestation of PID, HL and EBV-HLH occurred in our patients which have concordant immunological mecha-

nism that eventually lead poor prognosis in our patient.

Disclosure of conflict of interest
None.

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