OLGU SUNUMU

HODGKIN LYMPHOMA DEVELOPMENT AFTER THE DIAGNOSIS OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) AND INFECTIVE ENDOCARDITIS

İDİOPATİK TROMBOSİTOPENİK PURPURA VE ENFEKTİF PERİKARDİT TANISI SONRASI HODGKİN LENFOMA GELİŞMESİ

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ABSTRACT

Hodgkin's lymphoma (HL) represents the most common subtype of malignant lymphoma in young people in the western World. Most patients can be cured with modern treatment strategies, although approximately 20% will die after relapse or progressive disease. Although there are many factors, which are suspected in the pathogenesis of Hodgkin's lymphoma, infectious agents are believed to play more marked roles. We will present in our case report development of Hodgkin's lymphoma after the diagnosis of infective endocarditis, which has been ensued following the corticosteroid treatment given for the previous Idiopathic Thrombocytopenic Purpura diagnosis.

Keywords: Hodgkin's Lymphoma, Idiopathic Thrombocytopenic Purpura, Infective Endocarditis

ÖZET

Hodgkin Lenfoma (HL) batı memleketlerinde genç yaşlarda en sık görülen malign lenfomadır. Çoğu hastada modern tedavi stratejileri ile kür sağlanırken, yaklaşık %20'si relaps veya progressif hastalık nedeniyle ölmektedir. Hodgkin Lenfomanın patogenezinde şüphelenilen birçok factor olmasına karşın, infeksiyöz ajanların daha belirgin rol oynadığına inanılmaktadır. Biz şimdi, daha önce Idiopatik Trombositopenik Purpura tanısı alıp kortikosteroid tedavisi verildikten sonra infektif endokardit gelişen hastada Hodgkin Lenfoma gelişmesini içeren olguyu sunacağız.

Anahtar kelimeler: Hodgkin Lenfoma, İdiopatik Trombositopenik Purpura, infektif endokardit.

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INTRODUCTION

The Hodgkin's lymphoma is a most striking example of close tumor-host relationship. The hallmark of HL is mononuclear Hodgkin's cells and multinuclear Reed-Sternberg cells, which usually account for only about 1% of cells in the tumor tissue. This disease was first described in 1832 by Thomas Hodgkin that was the first report on lymphoma. HL is one of most frequent lymphoma (account for about 30% of all lymphomas) and is extensively studied for more than 150 years (1). Nevertheless, only in the last decade studies of individual HRS cells using molecular biology methods and micro-dissection, as well as studies of antigen expression and signal transduction pathways, revealed the nature of these tumor cells and have provided the major insights in the pathogenesis of Hodgkin's lymphoma. Patients with HL in general have a favorable prognosis, and about 80% are cured with chemo- and radiotherapy. Treatment schemes for HL have considerable risks of short- and long-term toxicity, which may also lead to secondary malignancies. Effective therapeutic approaches are still needed for refractory or relapsed patients, as most carry a high morbidity rate. Thus, novel therapies with improved safety and/or efficacy profiles are still needed to be developed for the group of patients with a poor prognosis. Currently, new therapeutic approaches, which have been developed based on the biology and molecular profile of HRS cells, are on different stages of clinical trials (2).

HL include two disease entities; nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) that account for only 5% of cases and classical Hodgkin's lymphoma (cHL), which is further subdivided into nodular sclerosis (60–70%), mixed cellularity (20–25%), lymphocyte rich (5%) and lymphocyte depleted (< 5%) [1]. Neoplastic lymphocytic and/or histiocytic Reed -Sternberg cells in NLPHL have a monoclonal B cell nature. They express multiple B cell lineage markers, such as CD20, CD79a, Ig, and also markers of germinal center cells — transcription factor Bcl- 6 and activation induced cytidine deaminase (AID). Moreover, these cells have rearranged and somatically mutated Ig V genes, sometimes with ongoing somatic hypermutation (3, 4). Most likely these cells originate from antigen-selected germinal center cells on the intermediate developmental stage between germinal center and memory B cells (4).

The interaction between EBV (Ebstein Barr Virus) +HL cells and the microenvironment is better understood in the context of EBV biology. EBV gains entry into B cells using the major envelope glycoprotein gp350 which binds to the C3d complement receptor CD21 expressed by B cells (5). The MHC class II antigen acts as a cofactor for EBV infection of B cells (6). The binding of viral glycoprotein gp350 to CD21 occurs on the cell surface at which time it is 50nm from the cell membrane (7). Internalization involves a complex of three glycoproteins, gH, gL, and gp42. Glycoprotein gp42 binds to HLA-DR (6). EBV's linear DNA molecule then becomes circular, forming an episome, and persists as a latent infection in memory B cells for years (8). Whereas 94 viral proteins are encoded by the EBV genome and are expressed during viral replication, most are downregulated when the virus assumes its latent form, so that only 10 continue to be expressed in latent infections (9). Therefore, the latently infected B cells are less likely to be cleared by the immune response which during the primary infection includes natural killer (NK) cells and cytotoxic T cells (10). The virus deploys additional strategies to escape immune attack, expressing proteins that mimic various receptors and cytokines. For instance, the BCRF1 gene encodes viral IL-10, which is highly homologous to human IL-10 and is necessary for B cell transformation by EBV (11). IL-10 has several properties that promote cell survival, including upregulation of Bcl-2 and inhibition of cytokine production by macrophages and Th1 cells. Certain single nucleotides polymorphisms in the IL-10 gene are associated with worse outcome.

The iatrogenic lymphoproliferative disorders are lymphoid proliferations or lymphomas that arise in patients treated with immunosuppressive drugs (12). They comprise a spectrum ranging from polymorphic proliferations to cases that fulfill the criteria for large B-cell or T/NK-cell lymphomas or cHL. Methotrexate was the first reported immuno suppressive agent associated with lymphoproliferative disorders. In this setting, EBV is detected more frequently in cHL (80%) than in DLBCL (about 25%). Among iatrogenic lymphoprolife rative disorders, other than PTLD, there is an increase in frequency of cHL and lymphoid proliferations with Hodgkin-like features. Thus, lesions containing RS-like cells but do not fulfill the criteria of cHL, the so-called Hodgkin-like lesions, have been included in this setting. Because cHL has only recently been recognized as an iatrogenic complication, few cases have been reported in the medical literature (12).

We have already mentioned about roles of infectious agents, especially EBV infection and other viral infections, in the pathogenesis of Hodgkin lymphoma. This present case was diagnosed with ITP and received corticosteroid treatment before, later endocarditis was diagnosed and then the patient developed Hodgkin's lymphoma. ITP development in patients diagnosed with Hodgkin's lymphoma has been published in a couple of case reports before. However, there was no previous reporting about Hodgkin's lymphoma development in patients diagnosed with and treated for ITP, which was similar to our case.

CASE

Patient, 39 years old female, applied to the emergency unit for gingival bleeding was hospitalized after determination of low thrombocyte count (3000/L) (Fig.1). In the physical examination, there was gingival bleeding, but no other pathological finding, like lymphadenopathy and organomegaly. Test results were: ANA (-), anti ds DNA <10 IU/ml, CMV IgM (-), anti cardiolipin IgG (-) and anti cardiolipin IgM (-). Pulse steroid (methylprednisolone 1 g/day) was initiated with the preliminary diagnosis of Acute Idiopathic Thrombocytopenic Pur pura. Since the thrombocyte count was determined as 31000/L in the third steroid treatment day, the dose was decreased under control, and as the thrombocyte counts were

168000/l at the seventh and 268000/L at the fourteenth days, steroid treatment was tapered down. Then as thrombocyte counts were not decreased during the follow ups, patient was discharged and scheduled for an outpatient clinic visit at 2 weeks later. Patient did not attend the control visit, but after 1 month, she applied to the emergency unit with the complaint of gingival bleeding, and after determining the thrombocyte count as 3000/L she was hospitalized and received random thrombocyte trans fusion with IVIG (intravenous immuno globulin) of 1 mg/kg for 2 days. Since the patient was unresponsive to the treatment, she received azathiopurine with a dose of 3 mg/kg. Then the thrombocyte count was increased to 440000/L and she was discharged for the outpatient follow up visits. One month later, her thrombocyte count was 6000/L again and she had splenectomy with the diagnosis of refractory Idiopathic Thrombocytopenic Purpura.
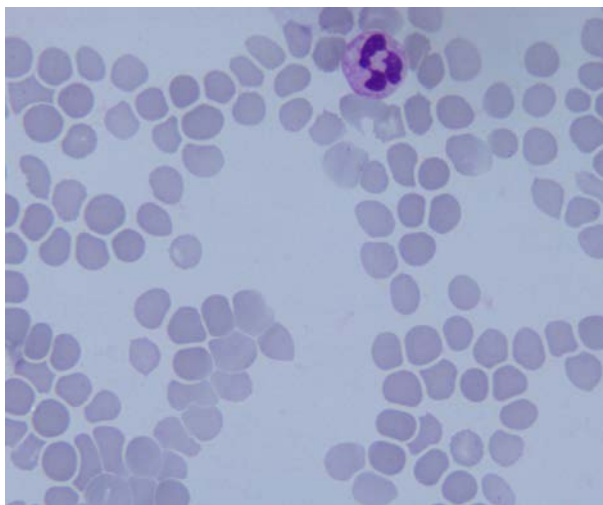

Figure 1. The peripheral blood smear of the patient showing a decreased number of platelets.
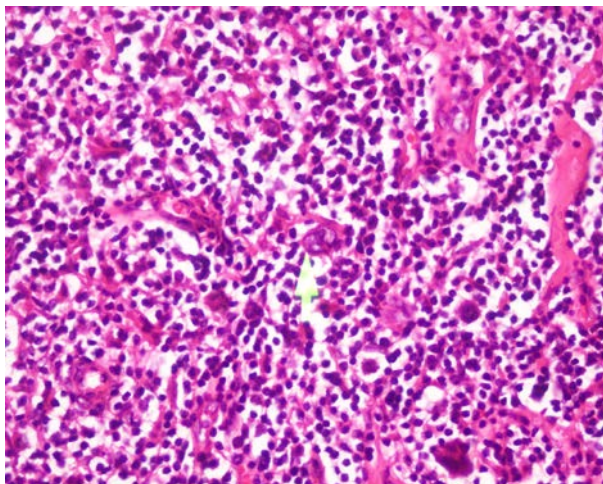

Figure 2. The lymph node biopsy specimen of the patient showing a typical Reed-Sternberg cell. (arrow) (H&E X 400)

After the splenectomy, her thrombocyte count was increased to 680000/L, and then during the follow ups it was 400000/L. Patient was discharged with a scheduled outpatient visit one month later. However, the patient applied to the emergency unit

with recurrent gingival bleeding after 20 days and her thrombocyte count was 7000/L, so she was hospitalized again and immune absorption method was applied to the patient. Her thrombocyte count was increased to 253000/L, but after one day she developed fever of 39.3°C. Since there was no growth in blood, urine, throat and gaita cultures (they were repeated three times) and markers for Brucella, Salmonella and Hepatitis were all negative, piperacilline + tazobactam treatment was initiated. However, since the high fever continued in the patient with leukocytosis and C-reactive protein positivity, sampling for culture studies were repeated, no focus of infection was determined in the physical examination, and serologic marker tests for brucella and salmonella were again negative. No infection focus was determined by abdominal ultrasonography and trans thoracic echocardiogram. In the thorax CT, there were multiple lymphadeno pathies of 35 mm in the right paratracheal region, 15 mm in the perivascular region, and 12 mm in the aortapulmoner localization and approxi mately 10 mm in the precarinal region. The high fever, leukocytosis and C-reactive protein positivity did not respond to high antibiotic treatment. She has transesophageal echocardiogram for the evaluation of infective endocarditis, and after the detection of a mobile mass (vegetation) 1X2 mm diameter just below the coronary cuspid, she was diagnosed with infective endocarditis. Since ESBL (+) E. coli was detected in the blood cultures, antibiotherapy was initiated. Thorax CT examination was evaluated as the lymphadenopathies were secondary to the infection. Patient received antibiotic treatment for 8 weeks, and no vegetation was detected in her control transesophageal echocardiogram. However, since the patient's fever continued; there was no regression in the diameters of lymph adenopathies, on the contrary mild increase in sizes, detected by the thorax CT; weight loss and sweating complaints were detected, the definite diagnosis was suggested to be lymphoma. During the follow up, a lymphadenopathy on the right supraclavicular region developed, and excisional biopsy was performed. Pathological examination revealed that it was nodular sclerosing type of Hodgkin's lymphoma. Neck, thorax, abdominal and pelvic CT scans were performed for staging and bone marrow biopsy was performed (Fig. 2). She was diagnosed with Stage 2B Hodgkin's Lymphoma and ABVD chemotherapy protocol was planned. After 4 courses of ABVD treatment, she got remission and she has been still under the follow up.

DISCUSSION

Although HL is generally a successfully treated disease, treatment failure in a substantial proportion of patients and treatment-related early and late sequelae of chemotherapy and radio therapy underscore the need for novel therapeutic approaches, especially for relapsed HL. No new drugs have been approved for HL in the past two decades; however, many agents are being tested in preclinical studies and currently enrolling active trials (13). The concept that the tumor microenvironment might be a promising therapeutic target has been reinforced by reports

in relapsed HL about the efficacy of the pyrimidine analog gemcitabine, a cytotoxic agent that has been reported to specifically target Treg cells. (14,15). Furthermore, the results of a study combining the anti-CD20 monoclonal antibody rituximab with gemcitabine in relapsed HL are encouraging and suggest that a combined treatment targeting reactive B and T cells in the microenvironment might be an effective approach. Trials targeting CD20+ B cells using radioimmunoconjugates have been initiated. However, it remains contro versial if the efficacy of anti-CD20 immunotherapy results from the direct killing of HRS cells that do occasionally express CD20 or from the depletion of HRS cell supporting reactive B cells in the microenvironment(16). It is note worthy that two gene expression profiling studies have reported correlate ons between increased numbers of background B cells and favorable prognosis, a finding that needs further clarification in the context of rituximab treatment. Support for a direct effect on HRS cells also comes from a recent study suggesting that HRS progenitor cells might express CD20 on their surfaces, and could be eradicated by rituximab [17]. Unequivocally, treatment effects in NLPHL have been attributed to a direct effect on the CD20-expressing LP cells. Other antibodies with a predominant effect on the microenvironment that are currently being tested in clinical trials including patients with HL are represented by alemtuzumab (anti CD52) and galiximab (anti- CD80) (18,19). Furthermore, immunotherapy with EBV-specific cytotoxic effector cells has shown promising results, providing proof of principle for adoptive immuno therapy with ex vivo expanded viral antigen specific T cells (20). Remarkably, in a subsequent study, five of six patients with relapsed HL had a tumor response; of these five, four achieved complete remissions that were sustained for more than 9 months (21). Because of the increased expression of members of the TNF receptor family and the dependence of malignant cells on TNF receptor downstream signaling, these molecules are considered ideal targets for specific agents in HL. CD30 in particular has been the target of a number of preclinical and clinical studies, of which the anti-CD30 compounds SGN-30 and MDX060 can be considered representative but disappointing in phase I/II clinical trials because of limited efficacy in relapsed disease (22). However, using an alternative strategy of conjugating an anti-CD30 antibody with the cytotoxic antimicrotubule agent monomethyl auristatin E (brentuximab vedotin), 195 much higher partial and complete remission rates were achieved. 196 It is noteworthy that in a heavily pretreated patient cohort, tumor reductions were documented in more than 80% of patients. As a result, additional clinical trials with brentuximab vedotin as a single agent and in combination with ABVD are currently recruiting. An anti-CD40 antibody trial and a study of the combination bortezomib with agonistic anti–TNF related apoptosis-inducing ligand receptor 2 compound AMG655197 are enrolling patients with HL; however, results are still pending. A number of novel drugs have downstream receptor signaling as their primary targets, of which everolimus (mammalian target of rapamycin, phosphoinositide 3-kinase pathway), bortezomib (TNFR signaling, NFκB pathway), and vorinostat (STAT6, IL

signaling) have shown promising preclinical results (23,24). Of these, however, bortezomib as a single agent in relapsed HL had low clinical efficacy (25). Combination therapies are now being tested.

In summary, therapies targeting cells in the microenvironment or disrupting microenvironment-dependent signaling in the malignant cells seem to be effective and show promise in patients with relapsed HL. Current clinical trials are also focusing on combination therapies with classical chemotherapy agents. Randomized trials comparing these novel agents with the current standard of care for first and second-line therapies will ultimately determine their significance in the overall landscape of HL treatment.

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