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Case Report HEMATOLOGY

A rare paraneoplastic condition in Hodgkin lymphoma: Evans syndrome and literature review

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ABSTRACT

Evans syndrome (ES) is a spectrum of diseases in which the combination of autoimmune hemolytic anemia and immune thrombocytopenia or sometimes neutropenia. ES has been accepted usually as an idiopathic condition, but it may be secondary. The coexistence of autoimmune cytopenias and Hodgkin lymphoma (HL) is rarely observed and the rate of ES in HL patients is not clear. Here we describe a 56-year-old male patient who presented with ES and was diagnosed with HL. After corticosteroids, intravenous immunoglobulin (IVIG) and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) treatment, immune cytopenias were completely resolved. The literature is also reviewed and we found 16 cases in which HL and ES coexist. Although AIHA and immune thrombocytopenia usually develop simultaneously, they rarely occur at different times. Many aspects of the pathogenesis are unknown, but it is thought to be a complex immunological background. Corticosteroids and/or IVIG are the most commonly used first-choice drugs in the initial treatment of ES. Response rates to treatment are variable and response to treatment may be poor, particularly with underlying conditions. If detected, the underlying lymphoma should be treated.

Keywords: Autoimmune hemolytic anemia; Evans syndrome; Hodgkin lymphoma; immune thrombocytopenia

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The relationship between lymphoma and autoimmune diseases is known, and this relationship has mostly been shown in non-Hodgkin lymphoma (NHL) patients [1]. The coexistence of Hodgkin lymphoma (HL) and autoimmune diseases has been less discussed than with NH. HL coexistence is seen with many autoimmune cytopenias and diseases such as sarcoidosis, systemic lupus erythematosus, immune thrombocytopenic purpura, polyarteritis nodosa, and polymyositis/dermatomyositis, particularly autoimmune hemolytic anemia [2].

Evans syndrome (ES) is a spectrum of diseases in which the combination of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia occurs simultaneously or sequentially and is sometimes accompanied by neutropenia. ES was first described in 1951 by Robert S. Evans and his colleagues [3]. In a recent study, the annual incidence of ES between 2000 and 2016 was 1.84/1000000. In the same study, it was reported that 27% of cases were attributed to secondary causes, with 77% of them being secondary to an underlying hematological malignancy [4]. Although it has been accepted as an idiopathic condition and a diagnosis of exclusion since its first description, ES may be secondary to autoimmune diseases such as systemic lupus erythematosus, lymphoproliferative diseases, immunoglobulin A deficiency and primary immunodeficiency and infectious diseases such as Epstein–Barr virus and hepatitis C virus infections [5].

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The coexistence of autoimmune cytopenias and HL is rarely observed, and according to previous reports, it is encountered in approximately 0.5–4.2% of HL patients [6–8]. In contrast, the rate of ES in HL patients is not clear; to our knowledge, 16 patients have been reported in the literature, and it is thus considerably rare [8–16]. In this article, we describe a patient who presented with ES and was diagnosed with HL, and immune cytopenias were completely resolved with treatment. The literature is also reviewed.

CASE REPORT

A 56-year-old male patient presented with fatigue, lower back pain, loss of appetite, and eruption, particularly in the abdominal region. The patient, who experienced weight loss as a B symptom, had no history of recent infection. Upon physical examination, lymphadenopathies of approximately 2 cm were detected in the bilateral axillary and right inguinal regions, with diffuse petechiae and purpura throughout the body. According to laboratory tests, hemoglobin was 6.5 g/dL, platelets were $11x10^3/mm^3$, reticulocytes were 9.9%, lactate dehydrogenase was 518 U/L (normal range <248), sedimentation was >140 mm/hour, and C-reactive protein was 105.3 mg/L (normal range: 0–5). Some increases in spherocytes and vthrombocytopenia were observed in peripheral smears. Immunoglobulin (Ig) G +3 was detected by the direct anti-human globulin test (DAT) and +2 positivity with AHG and +4 positivity with enzyme by the indirect anti-human globulin test. There was no monoclonal gammopathy based on immunofixation electrophoresis, and other autoimmune and viral tests were negative. A diagnosis of ES was made for the patient who had autoimmune hemolytic anemia and concomitant immune thrombocytopenia. In fluorodeoxyglucose positron-emission-tomography/computed-tomography involvement with high SUVmax values in the pathological size was observed in the mediastinal, axillary, intra-abdominal, and inguinal regions and in the form of diffuse lymph nodes and the spleen. The patient was diagnosed with classical-type nodular sclerosing HL by excisional lymph node biopsy of the right inguinal region. The patient who had no bone marrow involvement was evaluated as having stage 3B HL. Methylprednisolone treatment was started 1 day later, as treatment response might be delayed in a patient for whom the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) protocol was started. Following administration of 250 mg/day for the first 3 days, continuation of 1 mg/kg/day methylprednisolone treatment was planned. However, the patient had a platelet count of $3x10^3/mm^3$ and mucosal bleeding, and intravenous immunoglobulin (IVIG) treatment at 1 g/kg/day for 2 days was given 5 days after ABVD. The platelet value increased to $67x10^3/mm^3$ at 4 days after IVIG. Steroid treatment was discontinued for this patient, who was given 10 days of steroids, and ABVD treatment response was awaited. His hemoglobin level to 9.5 g/dL and his platelet level to $101x10^3/mm^3$ before the first course on the 15th day of ABVD treatment; his skin lesions resolved completely, and hemolysis parameters regressed during follow-up. Hemolysis status and thrombocytopenia did not recur after ABVD treatment.

DISCUSSION

In this article, after obtaining written informed consent, the patient presenting with ES, whose association with HL is very rare and has been reported, and the treatment process are discussed. Lechner and Chen [8] searched PubMed between 1951 and 2009 for HL-associated reports and found 34 on AIHA, 48 on autoimmune thrombocytopenia, 6 on ES, and 4 on autoimmune neutropenia. The clinical characteristics of reported ES cases were not specified. In addition, based on our PubMed search up to March 2022, we performed a review in terms of both the pre-2009 period, which was not covered in this study, and studies and case reports published after 2009. A total of 5 patients with ES have been reported in three studies: two patients in each of two different studies in which 563 and 84 adult HL patients were examined, respectively, and one patient in a study in which 11 pediatric patients were examined [9–11]. Moreover, there are case reports involving 5 patients with ES, one adult and four children, among HL patients [12–16]. It was determined that ES was detected during disease presentation in 7 of 16 cases found in the literature and during relapse in 6, but the information for 3 cases could not be obtained [8–16]. Although AIHA and immune thrombocytopenia usually develop simultaneously, they rarely occur at different times [8, 17]. DAT test positivity supporting autoimmune hemolysis occurs in most cases [9, 17]. Most of the cases have warm-type antibodies, but cold-type antibodies have also been reported, albeit rarely [8]. Furthermore, Dimou et al. [7] indicated that a mixed cellular subtype and advanced disease characteristics (stage III/IV, bone marrow involvement, B symptoms) are prominent among HL patients presenting with immune cytopenia.

Although many aspects of the pathogenesis are unknown, ES is thought to occur in a complex immunological background. Autoantibodies directed against erythrocyte, thrombocyte and granulocyte-specific antigens seem to be the most important mechanism that causes this clinical condition [18]. It was also shown that abnormalities in cellular immunity play a role in ES in addition to humoral immunity. In one study, the number of CD4 (T-helper) cells decreased and that of CD8 (T-suppressor) cells increased in some patients with ES. In the same study, it was reported that unlike patients with immune thrombocytopenia, IgG and IgM synthesis are low in these patients, which may be associated with a decreased CD4/CD8 ratio [19]. It has been shown that in addition to antibody production, B cells are involved in autoimmune diseases by presenting autoantigens to T helper cells as antigen-presenting cells [20, 21]. Although autoimmune cytopenias developing in B-cell NHL patients can be explained primarily by these mechanisms, there is no study revealing the main mechanism in cases of ES developing secondary to HL Reed-Stenberg cells, which are the original malignant cells in HL, are present in small numbers, and the majority of the tissue comprises benign immune system cells, primarily T-lymphocytes [22]. The question of whether the autoimmune cytopenia and ES syndrome developing in HL patients result from the T-lymphocyte ratio or whether they are due to antibodies that develop after the immune reaction has yet to be addressed. In addition to all these controversial cellular approaches, a potential genetic abnormality was reported in at least 65% of the patients as a result of genetic studies carried out on 80 pediatric ES patients without HL and that 40% of these patients carry mutation in 1 of 9 genes known to play a role in primary immunodeficiencies [23].

Corticosteroids and/or IVIG are the most commonly used first-choice drugs in the initial treatment of ES [24, 25]. Response rates to treatment are variable [25]; response to treatment and clinical progress may be poor, particularly with underlying conditions [26]. According to the literature, steroids are started during the diagnosis process for patients who present with ES and chemotherapy is started for HL after diagnosis. As in our case, it has been reported that erythrocyte and thrombocyte evaluations of patients improve during the first course after chemotherapy [8, 13–15]. It should be noted that ES may be a manifestation of lymphoproliferative disease. When the diagnosis is made, steroid±IVIG therapy for ES can be started, and if detected, the underlying lymphoma should be treated. Steroid±IVIG can also be used for ES observed during relapse, but HL treatment appropriate for the relapse stage is needed.

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