REVIEW ARTICLE

Evans Syndrome Associated with Hematological Malignancies: A Literature Review

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Search: selection criteria
The author searched PubMed for articles published in peer-reviewed recent English-literature during the period 1951–2021. The search terms "Evans syndrome," "autoimmune hemolytic anemia," "immune thrombocytopenia," and "hematological malignancies," and the name of the disease of interest as search terms. Although the author tried to cite seminal studies when necessary, representative articles were often selected.

Abstract
Evans syndrome (ES) is a rare disorder in which the immune system produces antibodies that accidentally destroy red blood cells and platelets. The diagnosis of ES is made by the simultaneous presence of autoimmune hemolytic anemia and immune thrombocytopenia. However, the diagnosis of ES associated with hematologic malignancies necessitates a comprehensive evaluation of clinical course, clinical findings, and laboratory test results. Hematological malignancies are the most significant underlying diseases factors impacting ES and the prognosis, but there is no established standard therapy for autoimmune cytopenia associated with hematological malignancies. In ES associated with hematologic malignancies, achieving remission of the underlying disease seems to be the key to long-term remission.

Keywords: Evans syndrome, hematological malignancies, autoimmune hemolytic anemia, immune thrombocytopenia

Content

1. Introduction

Evans syndrome (ES) is a rare disorder in which the immune system produces antibodies that accidentally destroy red blood cells (RBC) and platelets. It was first reported by Robert S. Evans and colleagues in 1951.[1] ES leads to low levels of blood cells (cytopenia). Hemolysis due to autoimmune mechanisms is classified as autoimmune hemolytic anemia (AIHA), and thrombocytopenia due to platelet destruction by autoimmune mechanisms is classified as immune thrombocytopenia (ITP). ES is defined as the association of AIHA along with ITP. Occasionally, autoimmune destruction of these blood cells occurs at the same time (simultaneously). ES is diagnosed by the simultaneous presence of AIHA and ITP.

The symptoms and severity of ES vary greatly, and it can cause severe, life-threatening complications and can be fatal. ES was originally recognized as occurring with AIHA and ITP. However, the disorder is now recognized as a distinct condition characterized by dysregulation of immune system. ES is classified into primary or secondary based on the presence of underlying disease. The distinction between primary and secondary ES is important as it can influence treatment.

A study using Danish health data from 1977–2017 reported the epidemiological features of 242 ES patients. The annual

incidence and prevalence of ES in 2016 were 1.8/million person-years and 21.3/million persons, respectively. The mean age of ES diagnosis was 58.5 years [55.9–61.0, confidence interval (CI)]. Men and women accounted for 48.8% and 51.2% of cases, respectively. The cases were Primary 72.7% and Secondary 27.3%.[2] Another study reported the underlying the primary associated with secondary ES as being systemic lupus erythematosus, primary antiphospholipid syndrome, Sjogren's syndrome, common variable immunodeficiency, Immunoglobulin (Ig) A deficiency, B-cell lymphoma, chronic lymphocytic leukemia, T-cell lymphoma, chronic myelomonocytic leukemia, lymphoproliferative disorder, monoclonal gammopathy of unknown significance, hepatitis C, congenital asplenia, and idiopathic CD4 lymphocytopenia.[3]

There is no standard treatment for ES. However, treatment of ES usually consists of immunosuppressive therapy, including the corticosteroid. Secondary ES may require treatment of the underlying disease in addition to immunosuppressive treatment.[4, 5] As for the ES immunosuppressive treatment, at follow-up of a median 4.8 years from the start of treatment, 32% of patients were in remission and requiring no treatment, while 56% were in remission but still receiving treatment with prednisone and immunosuppressive agents. The remaining 12% of patients still had active disease.[3] Regarding prognosis, the median survival time of patients with ES is 7.2 years. (10.9 years for primary ES and 1.7 years for secondary ES).[2] Patients with ES have a significantly increased risk of death due to bleeding, hematological malignancies, and other causes of death compared to the general population; adjusted sub-distribution hazard ratios of 4.1, 23.9, and 1.7, respectively. Furthermore, in secondary ES, hematological malignancies were the most common cause of death.[2]

Thus, hematological malignancies is the most significant underlying diseases factors impacting ES and the prognosis. This review presents an overview of ES, with a primary focus on ES associated with hematological malignancies in adults.

2. Pathophysiology of Evans syndrome

The pathophysiology of ES remains relatively unknown, although the pathophysiology of AIHA and ITP is comparatively well understood. Subtypes of AIHA and ITP are summarized in Table 1.

Summary of subtype of autoimmune hemolytic anemia

	Associated autoantibodies or tests	Immunoglobin subtype	Optimum temperature	Antigen specificity of autoantibodies	Type of hemolysis	Results of direct antiglobulin test
Warm autoimmune hemolytic anemia	Direct antiglobulin test	IgG	37°C	not specific; panreactive	extravascular	IgG and/or C3 positive
Cold agglutinin disease	Cold agglutinin	IgM-κ	4°C	specific for erythrocyte surface I antigen	intravascular	C3 positive
Paroxysmal cold hemoglobinuria	Donato-Landsteiner antibodies	IgG	biphasic (∗)	specific for erythrocyte surface P antigen	intravascular	C3 positive

(∗) biphasic; the antibody-antigen reaction is low, C1 fixation occurs in normal central body temperature

Immunoglobulin G; IgG, complement 3; C3

Summary of immune thrombocytopenia

	Associated autoantibodies or tests	Immunoglobin subtype	Antibodies to be measured by PAIgG	Platelet destruction
Immune thrombocytopenia	PAIgG	IgG	platelet-bound IgG	extravascular

PAIgG; Platelet associated IgG

2.1. Pathophysiology of autoimmune hemolytic anemia

In AIHA, the CD4-positive T-helper (Th) cell subsets; Th1, Th2, Th17, and the regulatory T cell (Treg) control the humoral immune system and have a critical role in losing self-tolerance.[6] Namely, in AIHA patients, cytokines promote humoral immunity, while Treg is reduced. To be more specific, Th17 cells amplify the pro-inflammatory and autoimmune response through interleukin-17 (IL-17). Th1 promotes cell-mediated immunity through secreting IL-2, IL-12, interferon-γ, and tumor necrosis factor-β. Th2 cells promoting humoral responses thought secreting IL-4, IL-5, IL-6, IL-10, and IL-13.[6] However, Treg cells were found reduced in AIHA patients; the mean (standard deviation) percentage of circulating Tregs in peripheral blood was significantly lower in AIHA patients (4.63%) than in healthy controls (9.76%) (P<.001).[7] Moreover, AIHA is classified into three distinct subtypes according to the autoantibodies involved; warm-AIHA, cold agglutinin disease (CAD), and paroxysmal cold hemoglobinuria (PCH).[6]

2.1.1. Pathophysiology of warm-autoimmune hemolytic anemia

Warm-AIHA accounted for 60% of AIHA patients.[8] The most frequent immunoglobulin subtype of autoantibodies against RBC is IgG, which reacts optimally at 37°C. Typically, the autoantibodies are not specific; the autoantibodies are polyclonal and react with all RBC (pan reactive). The direct antiglobulin test (DAT) detects the autoantibodies and/or complement fragments are on the RBC surface. The hemolysis involved mainly extravascular hemolysis through the antibody-dependent cell-mediated cytotoxicity (ADCC) in the spleen and liver. ADCC mediated by cytotoxic T cells and natural killer cells also contributes to extravascular hemolysis.[6, 9]

2.1.2. Pathophysiology of cold agglutinin disease

CAD accounted for 8% of AIHA patients.[8] The autoantibodies associated with CAD are termed cold agglutinins (CA). CA agglutinates RBC optimally at 4°C and has specificity for erythrocyte surface antigen I. A previous study of 86 CAD patients reported that 94% of them had a monoclonal band in serum electrophoresis with an immunofixation test. The immunoglobulin subclass was IgM class in 90% of the patients, and the light chain restriction was κ in 94% of the patients. Bone marrow biopsy revealed a presence of non-Hodgkin B-cell lymphoma in 76% of the patients.[10] Regarding pathophysiology of CAD, passing through the acral parts of the circulation makes the blood cooled, which results in CA binding to RBC and agglutination of RBC. When the temperature reaches 37°C in the body circulation, CA detaches from RBC, and the aggregated RBCs separate. The hemolysis in CAD is entirely complement-dependent. The antigen-IgM complex binds to complement (C) 1q on the cell surface and initiates the classical complement pathway. However, the cells opsonized with C3b undergo phagocytosis.[11]

2.1.3. Pathophysiology of paroxysmal cold hemoglobinuria

Donato-Landsteiner antibodies are the autoantibodies found in PCH. The antibodies have specificity for erythrocyte surface antigen P, and the optimal temperature for the reaction is biphasic. This means that the optimal temperature for

the antibody-antigen reaction is low, and subsequent C1 fixation occurs at normal central body temperature. The classical and terminal complement pathways are activated, and hemolysis occurs predominantly intravascular.[11]

2.2. Pathophysiology of immune thrombocytopenia

The essence of the pathophysiology of ITP is an abnormal T-cell immune response. In particular, follicular helper T cells play an important role. Follicular helper T cells stimulate the proliferation and differentiation of auto-reactive B cells. As explained in detail, platelets are opsonized and destroyed. Macrophages and phagocytes present a platelet-derived antigen to T cells, resulting in activating autoreactive T cells. Subsequently, auto-reactive B cells differentiate into plasma cells that produce anti-platelet antibodies. However, this abnormal autoimmune response is not counteracted due to the decrease in Treg number and/or function in the blood, the spleen, and the bone marrow. Thus, the anti-platelet autoantibodies facilitate platelet phagocytosis by macrophages, essentially in the spleen. In addition, CD8-positive T cells participate in increasing platelet apoptosis. Besides this peripheral platelet destruction, a decrease in megakaryocyte maturation and in platelet production due to autoimmune response against megakaryocytes and inappropriate levels of thrombopoietin exacerbates thrombocytopenia.[12]

3. Clinical presentation of Evans syndrome

The clinical presentation of ES is a combination of the clinical presentation of AIHA and ITP. The clinical presentation of AIHA includes pallor, fever, fatigue, jaundice, hemoglobinuria. Moreover, splenomegaly is observed in 32% of cases. Especially in CAD patients, cold-mediated vasoocclusive phenomena, including acrocyanosis, can be observed in the fingers, toes, nose, and ears. These symptoms are observed in 91% of CAD.[8, 10, 13] As for the clinical manifestations of ITP, the symptoms are due to thrombocytopenia. The most frequent manifestation was purpura, which is observed in 64.80%, followed by gingival bleeding in 20.27%, epistaxis in 12.49%, hematuria in 6.21%, melena in 6.10%, and intracerebral hemorrhage (ICH) in 1.14%. [14]

4. Laboratory findings of Evans syndrome

The laboratory findings of ES are a combination of the laboratory findings of AIHA and ITP. Laboratory findings of AIHA include positive autoantibodies (DAT, CA, and Donato-Landsteiner antibodies), elevated unconjugated hyperbilirubinemia, decreased hemoglobin (Hb) level, elevated serum lactate dehydrogenase (LDH), increased reticulocytes, reduced haptoglobin, and hemosiderinuria.[6, 15] Peripheral blood smears can reveal polychromasia indicates reticulocytosis. Spherocytes are seen in patients with moderate to severe hemolytic anemia. RBC fragments, nucleated RBCs, and occasionally erythrophagocytosis by monocytes may be seen in severe cases.[13, 16, 17] Laboratory findings of ITP include thrombocytopenia (peripheral blood platelet count $<100 \times 10^9$/L), which is usually not accompanied by a drop in white blood cell count and Hb level.[18]

5. Diagnosis of Evans syndrome

The diagnosis of ES is made by the simultaneous presence of AIHA and ITP.

5.1. Diagnosis of autoimmune hemolytic anemia

The diagnosis of AIHA requires evidence of hemolysis and serologic evidence of an autoantibody to RBC.[19]

5.2. Diagnosis of immune thrombocytopenia

The diagnosis of ITP requires the exclusion of other diseases that cause thrombocytopenia and a presence of thrombocytopenia (peripheral blood platelet count 100 × 10^9/L), which is usually with normal white blood cell count and Hb level.[18]

6. Treatment of Evans syndrome

There is no standard treatment of ES. Data for the management of ES are limited to case reports and retrospective studies with small numbers of patients. However, ES patients are usually treated through interventions to treat AIHA and/or ITP. Secondary ES patients require not only treatment for ES, but also treatment for the underlying disease.[4, 5] The treatment results of 68 ES patients have been reported.[3]

- First line treatment; Corticosteroids

All 68 patients received at least one course of corticosteroids (prednisone or prednisolone) as first-line treatments. Sixty-four patients (94%) were treated with corticosteroids at a dose from 1 to 2 mg/kg per day. The response rate to treatment for hemolytic anemia is 83%. Half of the responders had a complete response (CR), the other half had a partial response (PR), whereas 11 patients (17%) were considered as nonresponders. The response to treatment for thrombocytopenia is 82% (CR in two-thirds, PR in one-third of the cases). Thirty-three patients (48%) were given intravenous immunoglobulin (IVIG), almost for the management of thrombocytopenia, leading to short-term PR or CR in only 20 (60%) of the 33 cases.[3]

- Second line treatment; Rituximab

Eleven ES patients who received rituximab were reported (among whom 5 had previously undergone splenectomy). The main indication for using rituximab was chronic severe and/or refractory thrombocytopenia in 7 cases, severe or relapsing hemolytic anemia in 3 cases, and the need to corticosteroids long-term of in 1 hemolytic anemia and 1 thrombocytopenia. The initial response rate to rituximab was 82% (5 CR and 4 PR). One patient with an lymphoproliferative disease did not respond to rituximab and achieved a CR after a subsequent splenectomy. In addition, one primary ES patient with severe hemolytic anemia did not respond to rituximab. After a mean follow-up of 12 months after the first rituximab, 2 patients out of 9 initial responders had a relapse.[3]

- Second line treatment; Splenectomy

Nineteen ES patients, including 11 primary and 8 secondary ES patients who underwent splenectomy, were reported. The main reason for splenectomy was chronic severe thrombocytopenia in 11 patients, persisting AIHA in 6 patients, and ES in 2 patients. Treatment response at 1 month later of splenectomy was 78% (10 CR and 5 PR). After a mean follow-up ranged 3.1 to 12.9 years after splenectomy, 5 of the initial

responders had relapsed. One patient died of sepsis on day 21 after the procedure, and none of the patients had any documented venous thrombosis after splenectomy.[3]

7. Evans syndrome associated with hematological malignancies

ES associated with hematological malignancies is very rare. ES associated with chronic lymphocytic leukemia (CLL), Hodgkin lymphoma (HL), and angioimmunoblastic T-cell lymphoma (AITL) have been reported relatively frequently, and therefore their epidemiology, clinical features, response to treatment, and prognosis will be reviewed. On the other hand, these are described for multiple myeloma (MM) and other diseases reported in case reports.

7.1. Chronic lymphocytic leukemia

- Overview

CLL is the most common leukemia of adults in western countries and rare in Asian countries. CLL is a neoplasm composed of monomorphic small mature B cells with co-expression CD5 and CD23. Clinically, CLL presented with an increase in monoclonal B-cell count, anemia, thrombocytopenia, lymphadenopathy. The frequency of hypogammaglobulinemia is about 30% at diagnosis and increases over time to as much as 60% among patients with advanced disease. B-cell receptors of CLL cells demonstrate highly selected immunoglobulin heavy chain variable gene usage.[20] CLL can be accompanied by autoimmune disorders.[21] Moreover, CLL is complicated by autoimmune cytopenia (AIC), including AIHA, ITP, pure red cell aplasia (PRCA), and autoimmune granulocytopenia (AIG).[22]

- Epidemiology of autoimmune cytopenia

A previous study reported the epidemiologic features of 70 CLL patients with AIC. The incidence in CLL with AIC, including ES, AIHA, and ITP, was 7.2% (70 out of 960 patients). Furthermore, 49 out of 70 patients had AIHA (42 patients were DAT-positive and 7 patients were DAT-negative), 20 out of 70 had ITP, and one patient presented with ES. Thus, the incidence of ES in CLL patients is 0.1%. Moreover, that of AIHA and ITP are 5.1% and 2.0%, respectively. As for the timing of the AIC diagnosis, 27% of patients were found at the time of diagnosis of CLL. in the same way, 4.2% of patients before diagnosis and 68% of patients during the course of the disease.[23]

- Pathophysiology of autoimmune cytopenia

AIC is usually mediated by IgG autoantibodies,[22] however, CLL is often accompanied by hypogammaglobulinemia. Moreover, CLL clones may rarely secrete auto-antibodies, but in IgM subclass and in small amounts.[24] It is considered that this is because normal B cells are involved in the production of autoreactive antibodies. This is based on the observation that in healthy individuals and CLL patients, the percentage of harboring autoreactive antibodies is the same.[25] Furthermore, in CLL patients with AIC, Treg cell count is increased compared with age-matched healthy volunteers, but the T-cells have an abnormal function. To explain in detail, patients with CLL had a significantly higher absolute Treg cell count compared with age-matched healthy volunteers ($p = 0.0006$).

Forethermore, the mean absolute Treg count in the patients with AIC was significantly higher than those patients with no AIC ($p<0.01$).[26] However, CLL patients have dysregulation of T-cell. The mechanism of T-cell dysregulation includes chronic immune activation with Th2 shift, hyperreactivity, T-cell senescence with propensity to undergo apoptosis, and down-regulation of T-cell receptor signaling and cytokine secretion.[27] Moreover, in vitro studies have shown that somatic hypermutation plays an important role in autoreactivity in CLL. In CLL, Ig heavy-chain variable–unmutated (IgV-unmutated) B cells expressed highly polyreactive antibodies, whereas most IgV-mutated B cells did not.[28] In addition, autoreactive T/NK cytotoxic cells may interfere with megakaryocyte maturation and erythroid precursors, by releasing inhibitory cytokines or with a direct cytotoxic effect.[22]

- Factors associated with autoimmune cytopenia

The factors associated with AIC in CLL patients have been reported. CLL patients with autoimmune disorders, including AIC, comparing those who without, had a statistically significant higher percentage of the presence of the atypical prolymphocytic CLL cells, more than 1000 mg/dL of serum lgG level, more than 20% of CD38 and/or FMC7 antigen expression, and more than 1900 ng/mL of beta-2 microglobulin.[21] Moreover, CLL patients who have AIC including AIHA and ITP have a statistically significant higher percentage of patients harboring positive DAT and splenomegaly compared to those who do not have AIC.[29]

- Diagnosis of autoimmune cytopenia

Diagnosis of AIC with CLL should be made with caution because CLL can present with anemia and thrombocytopenia due to bone marrow failure. In the presence of bone marrow failure, there can be no increase in reticulocyte count even in the presence of AIHA. Moreover, an elevation of serum LDH is observed both in hemolysis and in tumor growth. In the previous study,[23] the diagnosis criteria of AIHA and ITP complicated CLL were as follows. The diagnosis of AIHA in CLL was based on the presence of an unexplained Hb level <10 g/dL or hematocrit < 30% and a positive DAT for either IgG or C3 and the presence of ≥1 indirect marker of hemolysis: high reticulocyte count, low serum haptoglobin levels, increased serum LDH or bilirubin levels. For patients in whom DAT was negative, the diagnosis of AIHA was made if ≥2 of the indirect signs of hemolysis were present. Regarding ITP, ITP was defined as a sudden and unexplained fall in platelet count to $<100 \times 10^9$/L with ≥2 of the following: evidence of normal bone marrow function (normal or increased megakaryocytes in bone marrow, or no reticulocytopenia if bone marrow aspirate was not available), no splenomegaly, no chemotherapy within the last month.[23]

- Treatment of autoimmune cytopenia

There is no standard therapy of CLL with AIC. A previous study reported treatment response of CLL with AIC including ES.[30] Regarding corticosteroid, the corticosteroid treatment of all patients was started with prednisolone at a dose of 1 mg/kg. All CLL patients with ES responded to corticosteroid treatment. Regarding chemotherapy, 2 patients treated by CHOP regimen consisting of cyclophosphamide,

doxorubicin, vincristine, and prednisone, resulted in short-term efficacy. Six patients underwent immunochemotherapy (R-COP consisting of rituximab, cyclophosphamide, vincristine, and prednisone, and R-CHOP consisting of rituximab combined with CHOP regimen). Among the six patients, including 2 patients treated with R-COP and 4 patients treated with R-CHOP, remission in 3 patients continued 9–24 months, and the other 3 patients have also shown response to treatment. However, the remission was short-term, and the patients died in 4, 8, and 24 months after the treatment.[30] A previous study reported ibrutinib treatment among 29 CLL patients with a history of AIC, including 5 ES patients prior to ibrutinib start. Among 12 patients requiring AIC therapy, there was no AIC worsened after starting ibrutinib. 8 patients had discontinued or de-escalated AIC treatment. Eleven patients developed to require AIC treatment after a median of 59 days (range, 6–319) following the initiation of ibrutinib, 7 of the patients could continue ibrutinib treatment.[31] Regarding splenectomy 5 CLL patients with ES underwent splenectomy. All these patients required splenectomy because of the development of thrombocytopenia, warm-AIHA, splenomegaly with an abdominal syndrome, and resistance to corticosteroids and chemotherapy. One patient developed acute cardiovascular failure during the postoperative period, which was successfully cured. The long-term outcomes of splenectomy; the median overall survival (OS) was only 15 months.[30]

- Prognosis of patients with autoimmune cytopenia

A previous study has reported of prognosis of CLL with AIC, including AIHA, ITP, PRCA, and AIG. In the survival period from the time of diagnosis of CLL, patients with AIC had better survival (median 12.4 years) than patients without cytopenia (median 9.7 years). Moreover, in the survival period from the time of diagnosis of cytopenia, patients with AIC had a statistically significantly better survival (median 9.1 years) than patients with cytopenia caused by bone marrow failure (median 4.4 years). Thus, among CLL patients, the presence of AIC did not impact prognosis.[32]

Key messages

- The incidence of ES complicated with CLL is 0.1%.
- The diagnosis of AIC associated with CLL should be made with caution.
- There is no standard therapy of CLL with AIC.
- Immunochemotherapy and ibrutinib seem to result in long-term remission among CLL patients with AIC.
- Among CLL patients, the presence of AIC seems not to impact prognosis.

7.2. Hodgkin Lymphoma

- Overview

HL are lymphoid neoplasms. They are composed of large dysplastic mononuclear and multinucleated cells surrounded by a variable mixture of mature non-neoplastic inflammatory cells. HL has two major subtypes: nodular lymphocyte predominant HL and classic HL. Epstein Barr virus infection plays a significant role in the pathogenesis in some subtypes. Clinical features include lymphadenopathy, mediastinal and splenic involvement. Bone marrow involvement is less common (5%). B symptom consists of fever, drenching night sweats, and significant weight loss is

present in 40% of patients.[33]

- Epidemiology of autoimmune cytopenia

The incidence of AIC (AIHA, ITP, and ES) among HL patients is 2.5% (14 out of 563 patients). Moreover, the incidence of ES is 0.36% (2 out of 563 patients). The incidence of AIHA and ITP is 1.1% (6 out of 563 patients). In patients with AIC, AIC was present at the time of diagnosis of HL in 26% of patients but occurred during follow-up after initial treatment in 74% of patients.[34]

- Characteristics of patients with autoimmune cytopenia

Comparison of baseline characteristics between HL patients with and without AIC at presentation, patients with AIC were significantly older (p=0.01), higher frequency of the mixed cellularity subtype (p=0.002) and absence of peripheral lymphadenopathies (p=0.04), and higher frequency of patients with clinical stage III and IV (p=0.04) and a presence of bone marrow involvement (p=0.02), as well as a marginally higher frequency of B symptom (p=0.08). Furthermore, HL patients with AIC had a significantly higher erythrocyte sedimentation rate (p=0.005), significantly lower lymphocyte count (p=0.02), and lower leukocyte count (p=0.07).[35]

- Treatment of patients with autoimmune cytopenia

Corticosteroids and IVIG were used in the three patients with ITP since patients either failed to respond or initially responded and subsequently relapsed very rapidly.[35] Guidelines on the management of secondary AIHA recommend that first line therapy for AIHA associated with HL is anti-lymphoma therapy, and if the patient achieves complete remission, treatment for AIHA should be given.[4]

- Prognosis of patients with autoimmune cytopenia

HL patients with AIC had an increased short-term (1-year) mortality compared to HL patients without AIC (p<0.022). The 5-year OS of HL patients with concurrent AIC at diagnosis was inferior compared to HL patients developing AIC during follow-up (p=0.005) and to HL patients without AIC (p<0.001).[34]

Key messages

- The incidence of ES is 0.36% among HL patients.
- Treatment of AIC associated with HL should be anti-HL treatment.
- HL patients with AIC seem to shorter survival time compared to those without AIC.

7.3. Angioimmunoblastic T cell lymphoma

- Disease overview

AITL accounts for 18.5% of peripheral T cell lymphoma and more frequent in Europe, followed by Asia and North America. AITL is a neoplasm of mature T follicular helper cells. T follicular helper cells release various factors, including CXCL13, iL21, iL10, TGF-beta, VEGF, angiopoietin, and iL6. A complex network of interactions takes place between the tumor cells and the various cellular components of the reactive microenvironment. The clinical presentation of AITL follows as lymphadenopathies, bone marrow involvement, and skin rash and laboratory

test abnormalities; anemia, positive direct antiglobulin test, thrombocytopenia, hypergammaglobulinemia, and hypereosinophilia. AITL rarely present with plasmacytosis.[36]

- Initial characteristics of autoimmune cytopenia

A previous study reported 28 AITL patients with AIC. Forty-one AIC cases were observed in 28 patients; 7 patients had ES, 21 presented AIHA including warm-AIHA (16 patients) and CAD (5 patients), 12 patients with ITP, 7 patients with PRCA, and 1 patient with AIG. Seventeen patients (61%) had only 1 AIC, 7 patients had ES and 4 patients had PRCA associated with another AIC.[37]

- Epidemiology of patients with autoimmune cytopenia

AITL can be associated with AIC, but the incidence is precisely unknown. As for the timing of the diagnosis of AIC, 82% (23 out of 28 patients) were diagnosed concomitantly with AITL. In 14% (4 out of 28 patients), AIC developed after AITL diagnosis (median 14 months ranged 8–114 months), and 3% (1 out of 28 patient) was diagnosed as ITP 3 years before AITL relapse.[37]

- Characteristics of patients with autoimmune cytopenia

The characteristics of patients with AIC comparing those without AIC at diagnosis of AITL were as follows higher percentage of the presence of spleen and bone marrow involvement (54% vs. 19% and 71% vs. 34%, respectively, $p<0.001$), the detection of Epstein-Barr virus replication in the plasma (89% vs. 39%, $p<0.001$), higher gammaglobulin level (median 23 vs. 15 g/L, $p=0.002$), a higher percentage of DAT positivity rate (93% vs. 59%, <0.001), and a higher percentage of a prognostic index for peripheral T-cell lymphoma[38]≥ 2 (93% vs. 73%, $p= 0.026$). [37]

- Treatment of autoimmune cytopenia

First-line treatments given for AIC included corticosteroids (88%), chemotherapy for AITL (71%), IVIG (27%) and/or other therapies (12%, including cyclosporine, splenectomy, rituximab, and romiplostim). Chemotherapy regimens are used as first-line treatment, mainly CHOP-based regimens. All patients achieved a complete response except for 2 ITP patients. Both had low platelet count and bleeding despite IVIG but showed response to chemotherapy.[37] There is a case report of a patient who maintained remission for 70 months after treatment with chidamide and cyclosporine.[39]

- Relapse of autoimmune cytopenia

Among the 28 AIC patients, 10 patients experienced AIC relapse, including 5 ITP, 4 AIHA, 3 PRCA patients, with a median time to relapse of 4 months (range 1–18). Moreover, all AIC relapses were associated with AITL relapse.[37]

- Relapse of angioimmunoblastic T cell lymphoma

The number of patients with AITL relapse did not differ between AITL patients with AIC and those without AIC (64% vs. 66%). Median OS was 77 and 33 months, and median progression-free survival was 12 and 11 months in the AIC group and in the control group, respectively.[37]

Key messages

- Chemotherapy seems to result in the successful management of AIC complicated with AITL.

7.4. Multiple myeloma

- Disease overview

Most patients with MM have M protein and clinical evidence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB).[40]

- Case reports of multiple myeloma with Evans syndrome

There have been case reports of ES associated with MM.[41-46] All reported cases had IgG subtype. A previous study demonstrated that among AIHA patients associated with MM, the subclass of the antibody binding to RBC was fully linked with that of M protein in all patients.[47] This observation suggests that M protein is associated with AIHA associated with MM. In the above-mentioned case reports, some cases did not have an increase in reticulocyte count. The presence of increased indirect bilirubin and low haptoglobin levels can be useful for the diagnosis of AIHA associated with MM. It should be noted that because MM can complicate with TMA,[48, 49] in diagnosis ES associated with MM, TMA should be considered as differential diagnosis.

Key messages

- All reported cases of ES associated with MM have IgG subtype.
- ES associated with MM can present without an increase in reticulocyte count.
- The presence of increased indirect bilirubin and low haptoglobin levels can be useful in diagnosing AIHA associated with MM.

7.5. Case reports of Evans syndrome complicated by hematological malignancies

- Splenic marginal zone lymphoma

A 60-year-old man presented with lymphadenopathies, splenomegaly, and B symptom. The patient was diagnosed with splenic marginal zone lymphoma and eight cycles of CHOP therapy, resulting in remission. Four months after chemotherapy, the patient experienced a relapse. The patient was complicated with ES. In addition, lupus anticoagulant, prolonged partial thromboplastin time, antinuclear, antineutrophil cytoplasmic, anticardiolipin, antiplatelets, anti-HLA I, and anti-EPCR antibodies were also detected. Chemotherapy consisting of fludarabine, mitoxantrone, dexamethasone, and rituximab was started. After one cycle of this chemotherapy, all the autoimmune tests became negative.[50]

- Lymphoplasmacytic lymphoma

A 77-year-old man presented with ES and was diagnosed as having lymphoplasmacytic lymphoma and amyloidosis. The patient responded well to high-dose steroids and IVIG. Subsequently, dose-reduced cyclophosphamide was administered. The patient developed neutropenic fever, atrial fibrillation and died.[51]

- Hepatosplenic T-cell lymphoma

An unusual case of hepatosplenic T-cell lymphoma was observed in a 61-year-old man who presented with ES, fever, and

hepatosplenomegaly. A spleen biopsy was consistent with T-cell lymphoma. Initial steroid treatment was efficacious in limiting autoimmunity, but constitutional symptoms did not subside. Chemotherapy was successful in obtaining complete clinical remission.[52]

8. Conclusion

Diagnosis of ES associated with hematological malignancies requires careful attention. ES complicated with hematological malignancies may not present typical laboratory findings due to bone marrow infiltration, resulting in anemia, thrombocytopenia, and elevated serum LDH, which is reflected in tumor proliferation. Thus the diagnosis of ES associated with hematologic malignancies necessitates a comprehensive evaluation of clinical course, clinical findings, and laboratory test results. Although the treatment of ES has not been established due to the rarity of the disease, it is usually treated through interventions to treat AIHA and/or ITP. Furthermore, there is no established standard therapy for AIC associated with hematological malignancies. Among AIC associated with hematological malignancies, only AIC treatment seems to provide a temporary response but not long-term remission. In ES associated with hematologic malignancies, achieving remission of the underlying disease seems to be the key to long-term remission of ES. In secondary ES associated with hematological malignancies, treatment of the underlying disease should be considered.

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