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An Overview of Evans Syndrome–A Rare Disease

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Abstract: Evans syndrome is characterized by the simultaneous or consecutive occurrence of immune thrombocytopenia, warm autoimmune hemolytic anemia, and, less frequently, autoimmune neutropenia. It is linked to non-cross-reacting autoantibodies that target antigens unique to neutrophils, platelets, or red blood cells.Corticosteroids or immunoglobulins are the first-line treatment for Evans syndrome. For patients who are not responsive to steroids, rituximab or splenectomy are the second-line treatments. Deficits of CTLA-4, LRBA, TPP2, and a reduced CD4/CD8 ratio are among the recent molecular ideas that explain the physiopathology of ES .Rituximab, mofetil mycophenolate, cyclosporine, vincristine, azathioprine, sirolimus, and thrombopoietin receptor agonists are among the second-line treatments for refractory ES. Hematopoietic stem cell transplantation has been effective in situations where immunosuppressive medications have failed to work. Since ES is chronic and has a high recurrence rate despite improvements, timely diagnosis, cautious treatment, and close patient monitoring are necessary to improve quality of life and achieve the best results. Prospective clinical trials are required for possible targeted therapy in order to improve ES.

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I. INTRODUCTION

Warm autoimmune hemolytic anemia (AIHA) is associated concurrently or sequentially with immune thrombocytopenia (ITP) and, less commonly, autoimmune neutropenia in Evans syndrome (ES), a rare eponymous illness initially reported by Robert Evans et al. in 1951 [1,23].Evans syndrome (ES) is an uncommon autoimmune disease with an unclear cause that affects a tiny percentage of people who have been diagnosed with either autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP), either consecutively or concurrently there is sometimes neutropenia. [25].

Reticulocytosis, elevated blood bilirubin and fecal urobilinogen, no family history of hemolytic diseases, antibodies against erythrocytes at 37°C, hemolysis of transfused erythrocytes, purpura, prolonged bleeding time, bone marrow aspiration with normal or increased numbers of megakaryocytes, and the lack of exogenous toxic agents or a baseline disease are among the first diagnostic criteria for ES,[3].Although autoimmune hemolytic anemia and immune thrombocytopenia are both present in patients with Evans syndrome, little is known about the epidemiology of this uncommon condition.[20]. The autoimmune disease known as immune thrombocytopenia (ITP) is typified by low platelet counts of less than 100 x 109[12]. An absolute neutrophil count <1.0 109/L for six months following the exclusion of other reasons (such as medications, infections, or known genetic mutations) was considered AIN , Based on recent research, immuno-rheumatological diseases were diagnosed in secondary ES cases[15]. Primary autoimmune neutropenia, also known as autoimmune neutropenia of infancy (AIN), is a condition in which antibodies target neutrophil membrane antigens, primarily found on immunoglobulin G (IgG) Fc receptor type 3b (FcγIIIb receptor), resulting in the peripheral death of the cells[16].

The precise pathophysiology of ES is yet understood, however it is likely caused by immunological dysfunction followed by the development of antibodies that target platelets and erythrocytes[2].Research on ES in AIHA is available in certain cohorts that report an incidence of roughly 37% to 73% in this scenario, while its global frequency is unknown. It has been observed that between 60 and 70 percent of ES patients are female[3].Unknown etiology of rare clinical syndrome involving thrombocytopenia [autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) coexistence] and autoimmune hemolytic anemia (immediate Coombs positive). It is also uncertain how common the syndrome is[5]. An yearly incidence of 1.8/million person-years and an annual prevalence of 21.3/million persons verified the

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disease's rarity. ES accounts for 0.3–7% of AIHA and 2–2.7% of ITP when isolated AIC is taken into account[6].

Although it is more prevalent in boys than girls (1.4:1) in youngsters, women appear to be the ones that suffer the most in adulthood[5].Another component of ES is autoimmune neutropenia (AIN), which affects 15% of adults and 20% of children [6] According to Lyall et al. (1992), the historical incidence is 1 out of 100,000 children under the age of ten. However, because the condition progresses in a benign manner, there is ample evidence of underreporting, as evidenced by the frequent fortuitous finds (8–27% of all cases)[16]. A situation when the number of circulating neutrophils is less than 1500/µl is called "neutropenia." According to the method of induction, neutropenias can be categorized into three types: those caused by decreased neutrophil production, neutrophil sequestration from endothelium or tissue pools, and enhanced neutrophil destruction in the periphery[17]. ES has a significant mortality rate and accounts for 5% to 10% of all wAIHA and 2% to 5% of all adult ITP cases. It is necessary to rule out other potential diagnosis when ITP and wAIHA occur simultaneously[21]. Warm AIHA, as opposed to cold AIHA, is the form of AIHA that manifests in Evans syndrome, where IgG antibodies react with RBC surface antigens at body temperature. ITP involves the immune system attacking platelets that have GPIIb/IIIa.[26]. Treating these conditions can be difficult, and there is little information available comparing second-line treatments[22] ES can be a potentially fatal illness that can coexist with other autoimmune or lymphoproliferative diseases[24]. When Evans syndrome is linked to a disease, it is crucial to identify it as secondary because cytopenias have been found to be more severe when Evans syndrome is present than when AIHA or ITP are the only symptoms. Additionally, the classification affects the available therapy options[26].

II. TYPES

ES can be either main or secondary. Secondary ES happens when other autoimmune disorders are present, but primary ES is frequently idiopathic. Medication-induced ES has been linked to medications including ramipril and diclofenac[25]. Seven different forms of AIHA have been identified, primarily by serological results .The following are the seven categories of AIHA: Paroxysmal cold hemoglobinuria (PCH), also known as Donath–Landsteiner antibody test-positive AIHA; direct antiglobulin test-negative AIHA (DAT-negative AIHA); drug-induced autoimmune hemolytic anemia (DIAIHA); warm-antibody autoimmune hemolytic anemia (wAIHA); cold-antibody AIHA (including cold agglutinin syndrome (CAS) and cold agglutinin disease (CAD); mixed AIHA (also known as combined cold and warm AIHA); and passenger lymphocyte syndrome (PLS) (associated with transplantation, and manifesting as AIHA with a specificity)[10].The principal ITP Platelet count <100 × 109/L, or isolated thrombocytopenia, that happens without the presence of another illness that is known to be linked to thrombocytopenia is primary ITP of evans syndrome.All immune-mediated thrombocytopenia types other than main ITP are referred to as secondary ITP[4]. When there is another pathology, usually rheumatological (especially Felty's syndrome and systemic lupus erythematosus [SLE]) or haematological (large granular lymphocyte [LGL] syndrome), the AINs are categorized as primary (i.e., not associated with other detectable pathology) or secondary when there is another pathology, usually rheumatological (especially Felty's syndrome and systemic lupus erythematosus [SLE]) or haematological (large granular lymphocyte [LGL] syndrome)[17].

III. SYMPTOMS

Clinically, AIHA can manifest as rapid, potentially fatal hemolysis that compromises hemodynamics or as mild hemolysis with compensatory reticulocytosis. The risk of thrombotic events is higher in patients with active hemolysis[9]. Depending on the type, AIHA has different symptoms. Dyspnea, exhaustion, headaches, muscle weakness, pallor, and/or jaundice are some possible symptoms[10]. concurrent constitutional signs, such as hepatosplenomegaly, increased fever, and more weight loss compared to adults[9]. There is considerable individual heterogeneity in the bleeding risk of ITP presentations, ranging from thrombocytopenia without additional clinical symptoms to severe visceral bleeding, cutaneous mucosal bleeding, and deadly cerebral hemorrhage[11]. Hematological malignancies, infections, and bleeding were the leading reasons of death among Evans syndrome patients[20].

IV. BIOMARKERS

TNFα and interleukin 10 (IL-10) were shown to be the most raised in wAIHA, although IL-8/CXCL8 and IP10/CXCL10 were also found to be up and may therefore be suitable as biomarkers. When combined, the four potential cytokine/chemokine biomarkers for wAIHA patients are TNFα, IL-10, IL-8/CXCL8 and IP10/CXCL10, and maybe IL-6[10].

V. DIAGNOSIS

It is challenging to recognize and quickly identify ES because of the small number of cases reported in both adult and pediatric populations, as well as the lack of specificity in the diagnostic tools currently in use[25]. The concurrent or sequential diagnosis of AIC is necessary for the diagnosis of ES; however, the interval between AIC occurrences is not a limiting factor. When reticulocytosis and indicators of hemolysis, such as elevated lactate dehydrogenase, low haptoglobin, and elevated indirect bilirubin, are present along with a positive direct antiglobulin test (DAT) for IgG with or without complement (C3d), AIHA is suspected in cases of anemia (haemoglobin <11 g/dL for females and <12 g/dL for males), as cold agglutinins are not present in ES[6] .Evans' syndrome diagnosis include, complete blood count, and reticulocyte count:

- Indirect/free bilirubin, LDH, and hemoglobin
- Antiglobulin Direct Test

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- The non-systematic Monoclonal Antibody Immobilization Platelet Assay (MAIPA) may be useful if antiplatelet antibody determination is necessary.

The CD16/FcγRIII, CD11b, CD35/CR1, and CD32/FcγRII antineutrophil antibodies [6,15] ΛDNT: CD3+CD4-CD8-alfa/beta+, hemolysis markers: LDH, haptoglobin, bilirubin, T and B maturation and activation: CD4/CD8 T naïve (CD45RA+), CD4/CD8 T memory (CD45RO), B naive (CD27–), B memory (CD27+), BCD21loCD38lo, Treg (CD4+CD25+CD127(low/–)[15]. Antineutrophil antibody evidence serves as the basis for the diagnosis of AIN. The optimum antibody screening method has been found to be a combination of immunofluorescence and agglutination testing due to the challenges in detecting neutrophil autoantibodies[17].

VI. MECHANISM AND PATHOGENESIS

The precise pathophysiology of ES is yet understood, however it is likely caused by immunological dysfunction followed by the development of antibodies that target platelets and erythrocytes[2].

Clinically , AIHA is a diverse illness that can range from completely compensated to potentially fatal. Autoantibodies against red blood cells (RBCs), with or without complement activation, are the reason. Generally speaking, AIHA may be primary (idiopathic, 50%) or due to an underlying illness, such as cancer, immunodeficiency, infections, or lymphoproliferative disease(20%)[7]. the development of AIHA is associated with dysregulation of the central and peripheral self-tolerance and the presence of autoreactive T and B cells .Naturally occurring CD4+ and CD25+ Tregs contribute to immunologic self-tolerance by suppressing potentially autoreactive T cells[8]. Naturally produced CD4+ and CD25+ Tregs block potentially autoreactive T cells, which helps promote immunologic self-tolerance. Defective CD4+ and CD25+ Treg suppressive activity may be crucial for the development of autoantibodies against RBC and the maintenance of AIHA, according to a study on a murine model of the disease[8]. Warm or cold antibodies are assumed to be the mechanism responsible for the death of red blood cells[9]. MΦ phagocytosis of antibody- and/or complement-opsonized autologous red blood cells is the traditional extravascular is the pathophsioloy of hemolysis in wAIHA . However, in certain instances of wAIHA, antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer cells may also be active[10]. Thrombocytopenia's precise mechanism is unknown, however it is now understood to be linked to accelerated platelet destruction through a complicated immune-mediated process[13]. The pathophysiology of autoimmune thrombocytopenia and AIHA are not well known and are probably complex. Recent research has shown the significance of cytokines in the underlying pathologic process, despite the fact that the generation of auto-antibodies is essential to the illness process.[14]. ES may be regarded as an immune system imbalance. There are various processes behind immune-mediated cytopenias, including humoral and cellular immunity[15]. Even though the mechanisms of cell depletion in some cases are still unclear and cannot be directly linked to autoimmunity, neutropenia can exacerbate other autoimmune disorders like systemic lupus erythematosus. Evans syndrome and autoimmune thrombocytopenia are the most commonly associated diseases in children[16]. During the course of the disease, antibody specificity in AIN can shift from FcγRIIIb reactivity to anti-HNA-1a specificity. This finding could indicate that the disease is triggered by another autoantigen and that the anti-HNA-1a specificity is sometimes due to epitope spreading[18]. Both allo- and autoimmune neutropenia and acute lung damage associated with transfusions have been linked to antibodies to human neutrophil antigens (HNAs)[19].

When Boxer and colleagues reported five instances where antineutrophil antibodies changed certain neutrophil functional characteristics and made it easier for splenic macrophages to phagocytose opsonized neutrophils[17]. The primary antigens linked to autoimmune neutropenia of infancy (AIN) include HNA-1 (FcγRIIIb), the most immunogenic glycoprotein on the granulocyte membrane, and its at least four alleles, FCGR3B*01 (HNA-1a), FCGR3B*02 (HNA-1b,1d), and FCGR3B*03 (HNA-1c)[18]. The collapse of central and/or peripheral tolerance, followed by the generation of autoantibodies by tissue and circulating self-reactive B lymphocytes with assistance from T helper cells, is a key factor in the development of this disease[23].

VII. TREATMENT

While prednisone and rituximab are used to treat SLE patients alone, romiplostim should be added to the treatment of SLE with Evan syndrome[27]. The majority of patients with these conditions will benefit from first-line steroid therapy, but others will show signs of resistance or intolerance to several regimens. Autologous or allogeneic hematopoietic stem cell transplantation (HCT) may be the final treatment for these individuals (and perhaps even a few chosen patients who are not refractory)[28]. Autoimmune illnesses are frequently treated with immunosuppressive treatment. Given that marrow-derived lymphocytes seem to be crucial in many disorders, autologous or allogeneic stem cell replenishment after lymphoid ablation might be a treatment option[29]. A decreased relapse-free survival rate was linked to glucocorticoid medication. This implies that sirolimus may be a viable therapy option for refractory or relapsed warm AIHA as well as ES[1]. Despite the absence of controlled trials demonstrating their effectiveness, corticosteroids continue to be the mainstay of treatment for acute symptomatic cytopenias, with encouraging first findings. Prednisolone at a daily dosage of 1-2 mg/kg was reported to induce remission. Acute viral infections and/or dose reduction did not, however, result in remission[30].Therapies (particularly splenectomy, corticosteroids, and intravenous immunoglobulin, or IVIG), the disease's progression, with a focus on recurrences, and the patient's condition at the most recent follow-up[31]. Different therapeutic modalities were employed, with varying degrees of success. Two patients had splenectomy; four patients recovered well; and four patients died from sepsis and

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hemorrhage. These results demonstrate the heterogeneity and substantial morbidity and mortality of Evans' condition[32]. cite three individuals with Evans syndrome (immune hemolytic anemia and immune thrombocytopenia) who did not respond to standard treatment, which included splenectomy and steroids for all three, vincristine for two, and cyclophosphamide for one. Modified intravenous gamma globulin at a dose of 0.4 g/kg/day was administered to the patients for five days in a row,two of them failed to respond[33].

VIII. CONCLUSION

To sum up, ES is a disease with a varied course that continues to present difficulties for both patients and doctors. The illness has a chronic relapsing course and is ultimately compounded by catastrophic clinical episodes that might result in mortality. The results of currently available therapy modalities are inadequate. Prospective clinical trials are required to investigate possible targeted therapy in order to improve long-term response or possibly cure the condition. Although novel approaches to treating the most severe instances have been made possible by the discovery of biological treatment, further clinical studies are required and Since ES is still chronic and has a high recurrence rate despite improvements, timely diagnosis, cautious treatment, and close patient monitoring are necessary to improve quality of life and achieve the best results.

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