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Journal of Cancer Research and Cellular Therapeutics
Richmond Ronald Gomes *

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Case Report

Autoimmune Hemolytic Anemia and Classical Hodgkin Lymphoma: An Often-Overlooked Alliance

Richmond Ronald Gomes

Professor, Medicine Ad-din Women's Medical College Hospital, Dhaka Bangladesh.

***Corresponding Author:** Richmond Ronald Gomes, Professor, Medicine Ad-din Women's Medical College Hospital, Dhaka Bangladesh.

Received Date: October 30, 2023; **Accepted Date:** November 08, 2023; **Published Date:** November 16, 2023

Citation: Richmond R. Gomes, (2023), Autoimmune Hemolytic Anemia and Classical Hodgkin Lymphoma: An Often-Overlooked Alliance, *J. Cancer Research and Cellular Therapeutics*, 7(5); **DOI:10.31579/2640-1053/165**

Abstract

Autoimmune hemolytic anemia (AIHA) is related to an underlying condition in an estimated 50 to 60%, while the remaining is Idiopathic. AIHA is associated with viral infections, autoimmune disorders, immunodeficiencies, lymphoproliferative disorders (LPD), and pregnancy. AIHA has predictive properties and may be a harbinger of future LPD in up to 20% of AIHA cases. AIHA has been associated with LPD particularly chronic lymphocytic leukemia and non-Hodgkin lymphoma. Rarely is it seen in Hodgkin's lymphoma (HL). HL accounts for ten percent of all lymphomas. AIHA is usually detected at the time of diagnosis when it accompanies Hodgkin's and rarely precedes it. It is a warm immune hemolytic anemia. In the following report, we describe the presentation of AIHA, ultimately resulting in the diagnosis of mixed cellularity Hodgkin lymphoma. From the limited reports and reviews available, it is understood that advanced Hodgkin (stage III or IV) of nodular sclerosis (NS) or mixed cellularity (MC) types portend a stronger affiliation to AIHA. The mainstay of AIHA therapy has been corticosteroids; however, this first line regimen appears to be less effective when treating AIHA in the setting of HL. The exact mechanism of AIHA related to HL is unclear, and it may be thought to be that tumor cell produced autoantibodies. Other hypotheses include paraneoplastic phenomena. Through this paper, the authors intend to remind the medical community about the importance of a prompt and deep study of all AIHA cases found in elderly patients, without overlooking possible malignant causes related to this condition such as a LPD. Thus, before diagnosing a hemolytic anemia as idiopathic, the practitioner must be certain that the condition is not a clinical manifestation of an underlying disease.

Keywords: autoimmune hemolytic anemia; lymphoproliferative disorders; hodgkin's lymphoma; mixed cellularity

Introduction:

Autoimmune hemolytic anemia (AIHA) is a relatively rare disease with an annual incidence of 1 per 75 000 to 80 000 people. The etiology of autoimmune hemolytic anemia (AIHA) is related to an underlying condition in an estimated 50 to 60%, while the remaining is idiopathic, as a result of a combination of immune activation, deficiency, or dysregulation [1]. AIHA is associated with viral infections, autoimmune disorders, immunodeficiencies, lymphoproliferative disorders, and pregnancy. For decades, autoimmune entities such as hemolytic anemia, thrombocytopenic purpura, neutropenia and insulin receptor antibodies have been reported as paraneoplastic manifestations of Hodgkin's disease (HD) [2,3,4,5]. Autoimmune hemolytic anemia (AIHA) is rarely seen in Hodgkin lymphoma (HL) patients, with a reported incidence of 0.2–4.2%. [3,6,7]. Sporadic case reports and reviews have shown that when AIHA occurs in HL patients, it happens mostly at stages III and IV nodular sclerosis HL (NSHL) or mixed cellularity HL(MCHL).8 The Hodgkin

lymphoma implies alterations in the immune system, which include abnormalities in the cytokine production and increased sensitivity to regulatory T cells, but with an overall decrease in the number and functional capacity of T cells 9,10,11. Thus, during a decrease of cytotoxic T lymphocytes, an increase in autoantibody production may occur; this is currently the most accepted mechanism to explain the appearance of AIHA in some of these patients [12]. HL is usually manifested as lymphadenopathy typically in the cervical (70%), axillary (25%,), mediastinal areas (60%), and in 16-34 % of the cases presents as nodal disease below the diaphragm. HL presenting as AIHA has been reported in very few case reports in literature. We hereby report a case mixed cellularity type HL who presented as AIHA.

Case Report

A 52 years old Bangladeshi nonsmoker male not known to have diabetes, hypertension, bronchial asthma or ischemic heart disease presented with low grade fever, malaise, night sweats, exertional dyspnoea, generalized weakness and painless lumps over neck and axilla and weight loss of 10 kg of three months duration. On query, he also complained of pruritus especially at night, anorexia and ten kg weight loss during the past 3

months. On examination, his vital parameters were stable but febrile (axillary temperature 101o F). He had conjunctival pallor but non icteric. Multiple anterior and posterior cervical and axillary nodes were palpable. Nodes were rubbery, non tender, mobile, largest lymph node of 2.5 x 2 cm size. There was no overlying sinus. Systemic examination revealed Hepatosplenomegaly.

The CBC revealed normal white cell count, hemoglobin 6.9 gm/dL, hematocrit of 19.6 gm/dL, and platelets of 234,000 gm/dL, MCV 113fL, and MCH 33.5pg. Peripheral blood film showed moderate anisocytosis and poikilocytosis with spherocytes, polychromatic cells (Figure 1). Lactate dehydrogenase was elevated at 624 gm/dL, reticulocytes count 6.6%. Total bilirubin was 4.3 mg/dL with most of it being indirect; the rest of the liver function test was normal. Direct Coomb's test was positive, consistent with the diagnosis of AIHA. ANA was negative. His ultrasound abdomen showed paraaortic lymphnodes with mild hepatosplenomegaly and no abnormalities were seen on his chest radiography. CT scan of the thorax, abdomen, and revealed multiple symmetrically enlarged lymph nodes in the mediastinum and abdomen with hepatosplenomegaly (figure 2).

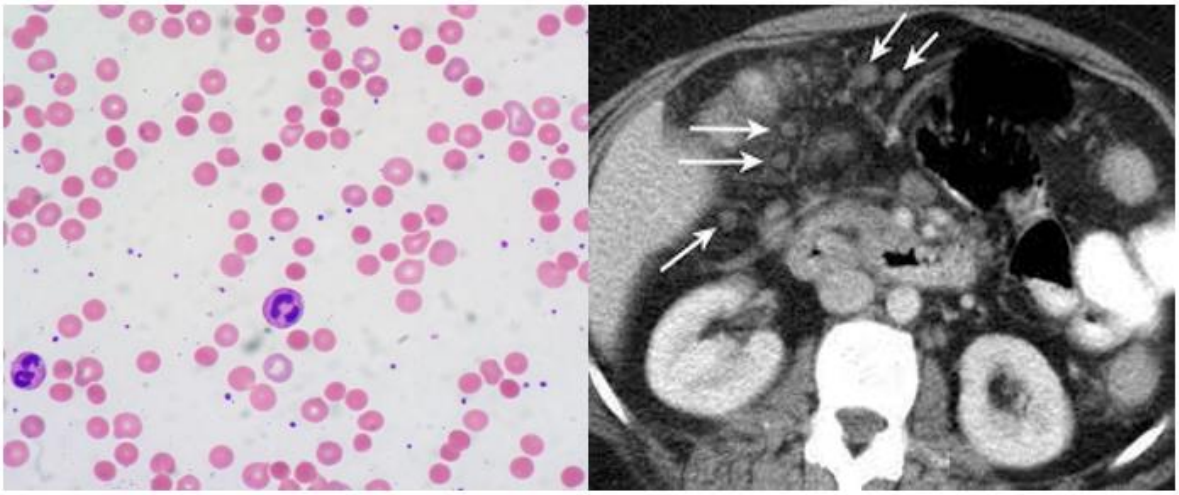

Figure 1 and 2: Peripheral blood film showing spherocytes, polychromatic cells and CT abdomen showing multiple enlarged intra-abdominal lymph nodes respectively.

His lymph node biopsy showed polymorphous population of lymphocytes, plasma cells, eosinophils and scattered mononuclear and binuclear variants of Reed Sternberg (RS) cells (figure 3). The immuno histochemistry on the lymph node biopsy revealed all the RS like cells stained strongly positively with CD 30 (figure 4). Few RS cells stain positively with CD 15. These cells stained negatively for CD45, CD 20 and Oct- 2. Bone marrow examination revealed reactive hyperplasia. A diagnosis of autoimmune hemolytic anemia with Hodgkin's lymphoma was made. Our patient had stage III disease with 'B' symptoms.

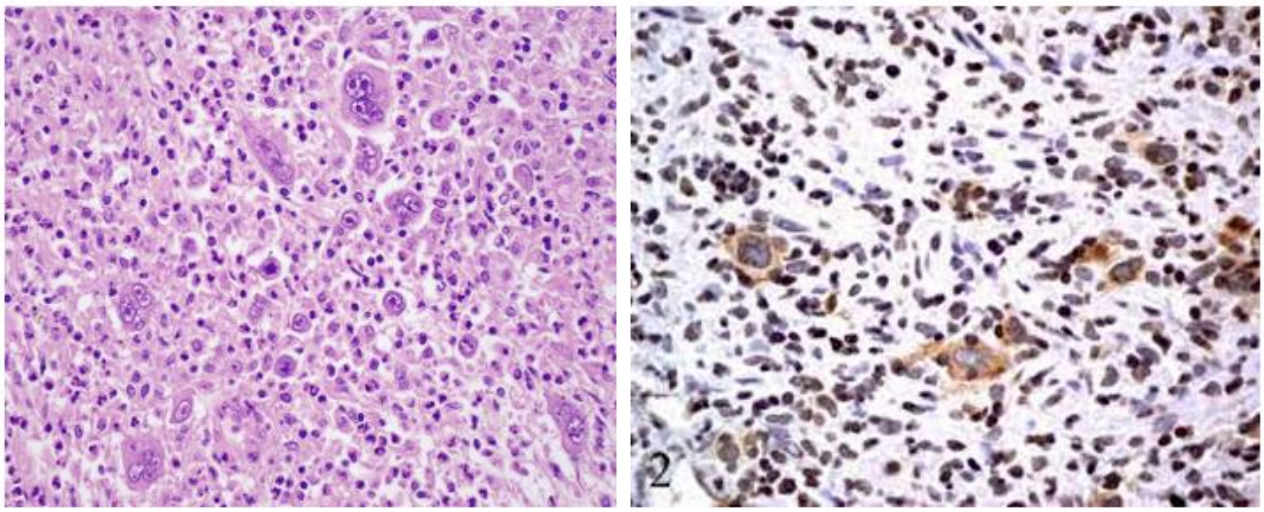

Figure 3 and 4: Photomicrograph of lymph node biopsy showing Reed-Sternberg cells and its cellular environment and Reed-Sternberg cells staining strongly positive for CD 30

Patient improved symptomatically on treatment with oral prednisolone 1 mg/kg/day. Patient was started on chemotherapy cycles with inj Adriamycin, inj Bleomycin, inj Vinblastine, inj Dacarbazine and inj dexamethasone at referral oncology centre. After completing two cycles with ABVD of a planned six cycles, the CT scan of chest and pelvis showed good response to treatment with a marked decrease in lymph node size No new site of disease was seen. With chemotherapy patient's hemolysis resolved, steroids were tapered and discontinued. At this time, the patient has completed six cycles of ABVD. He is planned for ongoing surveillance.

Discussion

Hodgkin's lymphoma (HL) is a solid tumor that arises from B lymphocytes. It was first described in 1832 [13,14]. Since that time, this

neoplasm has been extensively studied; currently, it is classified into classic Hodgkin lymphoma (cHL) and lymphocyte predominant variant. cHL is further divided into four categories-nodular sclerosis, mixed cellularity, lymphocyte rich, and lymphocyte depleted [13,15,16]; other lymphomas, especially primary mediastinal large B-cell lymphoma, show borderline histological features similar cHL.

In the developed countries, HL roughly accounts for ten percent of all diagnosed lymphomas. This neoplasm follows a bimodal age distribution having a peak in early adulthood and then in the seventh decade. It has male predominance. The classical Reed-Sternberg (RS) cells have been identified in every subclass of cHL. They originate from germinal center B cells that have lost their genetic regulation for normal development and maturation; Epstein-Barr virus (EBV) or its remnants have identified in Sternberg-Reed cells. This supports the hypothesis that EBV is associated with HL; however, it is not clear whether its presence is necessary for oncogenesis, since 40%–60% of HL is EBV negative [13,15,16,17].

cHL presents with B symptoms (night sweat, fever, and weight lost) which are encountered in about twenty percent of patients with early stages and as much as in fifty percent of those with advance disease. Unexplained weight loss of more than 10% of body weight is one of the most frequent presenting complaints. Pel-Ebstein fever, although less common, is also associated with this illness. It usually happens at irregular intervals of several days or weeks before it finally disappears. Seldom symptoms such as pruritus, which may precede the diagnosis of cHL for months, cholestatic liver disease, skin lesions such as ichthyosis, acrokeratosis, and hyperpigmentation, neurological symptoms secondary to central nerve system malignant cells infiltration, and nephrotic syndromes resulting from hypersecretion of toxic lymphokines can be observed at onset of clinical disease. Fatigue is almost universally seen at the time of diagnosis; it results from anemia. The mechanism of anemia varies; it could be secondary to chronic disease reflecting the underlying malignant process. In advanced, disease anemia occurs from bone marrow infiltration by malignant cells. It can also be iatrogenic due bone marrow suppression by chemotherapeutic agents. Rarely, it results from hemolysis. Autoimmune hemolytic anemia is known for its link to B-cell non-Hodgkin's lymphoma, suggesting a relationship between the two. Here, we discuss a case of MCHL which presented with AIHA. Typically, the Hodgkin/Reed-Sternberg cells stain positively for CD30 (80-100% of cases), CD15 (75-85% of cases), and B-cell specific activating protein (BSAP), which is the product of the PAX5 gene (>90% of cases). CD20, a generally reliable marker of B-cell lineage, is positive in about 40% of cases of classic Hodgkin's lymphoma but the staining can be weak.

Autoimmune hemolytic anemia occurs when a patient produces pathologic antibodies that attach to and lead to the destruction of red blood cells causing anaemia. Warm antibodies are typically of the IgG variety, may or may not fix complement, and primarily lead to RBC loss by splenic removal of sensitized cells. Acquired AIHA has been described to be associated with an underlying disease in more than fifty percent of cases. The majority of AIHA is related to an underlying etiology that alters immune system activity such infectious, autoimmune disorders, immunodeficiencies, lymphoproliferative disorders, and pregnancy. The lymphoproliferative disorders are comprised of diseases such as autoimmune lymphoproliferative syndrome (ALPS), CLL, non-Hodgkin lymphoma, and Hodgkin lymphoma [12,18,19,20]. While AIHA has well-known associations with non-Hodgkin lymphoma and CLL, its relationship to Hodgkin lymphoma is rarer and potentially less well recognized. The relationship of autoimmune hemolytic anemia with cHL has been recognized for more than forty years. Previously, prevalence of autoimmune hemolytic anemia has been reported in patients with Hodgkin's disease ranging between 0.2% and 2.7% [3,21]. When it occurs, it is usually seen in adults rather than children. Autoimmune hemolytic anemia may be present at any stage of Hodgkin's disease; although it is usually associated with the active or advanced disease, it can precede the diagnosis or be present in a relapse episode [2,7]. A positive Coombs test can be an indicator to suspect possible relapses in patients with a history of HD in remission with or without AHA 7,9. Immune-mediated hemolytic anemia is mostly seen in the nodular sclerosing subtype and in mixed cellularity subtypes, as in this case. It was reported that 90–100% of Hodgkin's disease patients with immune hemolytic anemia were in stages 3 or 4 [22].

In very rare cases, HL-related AIHA may be direct antiglobulin test negative which may be attributed to undetectably low levels of IgG, low-affinity bound IgG antibodies are washed away during pretest processing, or non-IgG antibodies are the cause of the AIHA (e.g., IgA and IgM) [23].

The mainstay of AIHA has been corticosteroids; however, this first-line regimen appears to be less effective when treating AIHA in the setting of HL [10, 16]. In one single center study, the use of rituximab, traditionally a second-line therapy, had significantly improved mortality rates compared to corticosteroids in those with warm AIHA and lymphoproliferative disease [24]. As seen in this case, treatment of the primary disease with combination chemotherapy led to treatment of AIHA. In very rare cases, splenectomy may be advocated as an effective therapy [25].

Currently, there are no studies of sufficient quality to establish appropriate protocols for the management of AIHA, nor a consensus on what complete remission or partial remission of the diseasemeans [8], therefore, the management of hemolytic autoimmune anemia is based on experience and individual clinical decisions. It should be noted that the effectiveness of therapies for AIHA is low when it is secondary to an underlying disease, this being especially true for autoimmune hemolytic anemias secondary to lymphoproliferative syndromes [9,26].

The above statement was evident in the case reported here, in which no adequate response to treatment with corticosteroids was obtained. Definitive therapy for autoimmune hemolytic anemia associated with Hodgkin's disease is the treatment of the underlying disease, through which there is a progressive decrease of antibody titers until reaching the eventual negativization of the Coombs test [27], the recovery of Hb values and the disappearance of hemolysis signs.

Conclusion

AIHA although unusual, can be a paraneoplastic manifestation of a LPD, especially chronic lymphocytic leukemia. HL however is rarely associated with AIHA. Clinicians should consider the differential diagnosis of this malignancy in patients affected by seemingly idiopathic AIHA. Although the initial treatment of AIHA is steroids, immune hemolysis associated with Hodgkin's disease requires definitive treatment with systemic chemotherapy. While there is much to be elucidated about the relationship between AIHA and HL, it is clear that further study must be done into the interactions of lymphoproliferative diseases, their effects on the immune system, and the development of autoimmune disorders. As we continue to develop foundational knowledge of these interactions, greater understanding of best treatments for AIHA in the setting of HL will aid in management of this complication and potentially reveal further mechanisms to research

Conflict of interest: None declared

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DOI:10.31579/2640-1053/165