Autoimmune Hemolytic Anemia and Classical Hodgkin Lymphoma: A Case Report and Literature Review

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Introduction

Autoimmune hemolytic anemia (AIHA) is rarely seen in Hodgkin lymphoma (HL) patients, with a reported incidence of 0.2–4.2%.[1-3] Sporadic case reports and reviews have shown that when AIHA occurs in HL patients, it happens mostly at stages III and IV of nodular sclerosis HL (NSHL) or mixed cellularity HL (MCHL).[4] We present a case of AIHA at the time of diagnosis of classic HL, stage IIIB, with a detailed review of the literature of HL accompanied by AIHA. Our goal is to give clinicians an overview of this complication for better management in the future.

Case Report

A 46-year-old man was admitted to our hospital for constant, nonradiating, bilateral sharp flank pain, which he rated a 6 of 10 in intensity and which was pleuritic in nature. The patient also had chills, sweats, and leg weakness, and he complained of decreased appetite and weight loss of 20 pounds in the past 2 years. His vital signs were stable. Physical examination revealed cachexia, jaundice and icteric conjunctivae, a soft abdomen with normal bowel sounds, normal heart sounds, and no peripheral lymphadenopathy. The bilateral lungs were clear on auscultation. There was no hepatosplenomegaly and no edema of the extremities. Laboratory data showed severe normocytic anemia compared to 2.5 years prior (Table 1). Iron study, folate levels, and vitamin B_{12} levels were normal.

AIHA was diagnosed, with elevated indirect bilirubin, reticulocyte count, decreased haptoglobin, and a positive direct Coombs test of both immunoglobulin (Ig) G and complement 3 (C3). The patient received 2 units of red blood cells for transfusion and oral prednisone (60 mg/daily for 4 days.) Meanwhile, a computed axial tomography (CAT) scan of the abdomen and pelvis showed extensive retroperitoneal, paraaortic lymphadenopathy with a large conglomerate of left paraperitoneal mass (4 x 5.8 cm^2) and possible pelvic lymphadenopathy and hepatomegaly. The patient underwent a computed tomography (CT)-guided biopsy. Pathology confirmed classic HL with Reed-Sternberg cells. A subsequent positron emission tomography (PET) scan showed no mass in the brain or neck but revealed lymphadenopathy in the chest and abdomen. Bone marrow biopsy results were normal. The patient was diagnosed with lymphocyte-rich HL (LRHL), stage IIIB.

One month later, repeat blood work showed improved hemolytic anemia. An Ig test showed increased IgA and IgG (Table 1). Fluorescence in situ hybridization (FISH) did not reveal any chromosomal abnormalities. The patient received rituximab (Rituxan, Genentech) every 21 days for 4 cycles and a chemotherapy regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) every 14 days for a total of 12 cycles. One year later, laboratory tests of the patient were normal (Table 1, column 5). He was in remission when this article was written.

Discussion

Fifty-four percent of AIHA cases in adults are secondary to underlying causes, such as autoimmune diseases and malignancy.[5] We reviewed 39 published cases, including 8 pediatric, of HL with AIHA (Table 2) and summarized the general, clinical, and pathologic characteristics, including our case (Table 3). The Chi-square test, Fisher's exact test, and paired t-test were employed in this study.

Thirty-seven (93%) patients had a positive direct Coombs test, mostly specified as IgG and/or C3 (57%). Of the 3 patients with a negative direct Coombs test, only 1 had positive RBC-IgG. A prior study found a few cases with anti-I^T,[6] an antibody against cord cells. The significance of this finding is still unclear. In 1 case, the antinuclear antibody was positive (1:1,280) without any other data, suggesting autoimmune connective tissue diseases; in this patient, treatment with steroids and chemotherapy lowered the titer.[7] Our patient had a positive direct Coombs test with IgG and C3, and

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Table 1. Laboratory Data for the 46-Year-Old Male Patient

Variable	2.5 Years Before Admission	On Admission	One Month After Steroid Therapy and Transfusion, But Before Chemotherapy	1 Year After Chemotherapy
Hemoglobin (g/dL)	13.4	5.9	9.4	14.8
Hematocrit (%)	41.3	19.1	29.7	45.9
Reticulocyte (%)		5	1.8	
White cell count (x 10^3/mL)	10.8	6.1	11.2	6.8
Neutrophil (%)	66.5	68.7	71.7	55
Lymphocytes (%)	20.8	21.5	19.5	37.1
Monocytes (%)	11.3	7.8	7.6	4.2
Platelet (x 10^3/mL)	373	790	625	300
Total bilirubin (mg/dL)	0.8	1.6	0.5	0.4
Direct bilirubin (mg/dL)	0.3	0.6		
Lactate dehydrogenase (IU/L)	197	403		
Ferritin (ng/mL)		1368		
Haptoglobin (mg/dL)		<13	226.3	
Direct Coombs test		+IgG +C3		
IgA			574 (h)	
IgM			202	
IgG			1,743 (h)	

C3=complement 3; h=high; Ig=immunoglobulin.

increased IgA and IgG, probably due to the decreased cytotoxic T cells in HL, which lead to increased autoantibody production.[7,8]

Among 29 cases with reported pathologic subtypes, 14 (48%) had MCHL, 10 (34%) had NSHL, 3 (10%) had LRHL, 1 (3%) had both MCHL and NSHL, and 1 (3%) fell between NSHL and the lymphocyte-depleted subtypes. The median age of the MCHL group was much older than that of the NSHL group (39 years vs 20 years; $P<.02$). The incidence of each subgroup in the United States and Europe was reported as 70% for NSHL, 20–25% for MCHL, 5% for LRHL, and 1% for lymphocyte-depleted HL (LDHL).[8] Similar results were found in children and adolescents. Ours is the third case of LRHL reported with AIHA. Two other patients with the lymphocyte-dominant subtype developed AIHA at stage II; the anemia was refractory to steroid treatment.[9,10] This observation supports the theory that AIHA can occur in all subtypes of HL. The fact that AIHA was found more often in the MCHL and NSHL subtypes than in the LDHL or LRHL subtypes may be because the first 2 subtypes are more common.[11]

The reviewed data suggested that AIHA might develop in any stage of HL but was more common in late stage III (43%) to IV (30%), especially in patients with constitutional symptoms (38%) (Table 3). Anemia resolved after excisional biopsy of the affected lymph node in 2 of the 5 patients who had AIHA with stage I HL.[12,13] Two stage I cases along with 1 stage II case had only spleen involvement,[10] and AIHA was resolved after splenectomy.[6,14] Although minimal tumor loads in mediastinal lymph nodes could also cause AIHA in HL patients, it was interesting to find that 30% of patients had documented spleen involvement either histologically or radiologically, including 2 cases of stage I and 2 cases of stage II disease.

Diagnosis of HL in patients who primarily present with AIHA is challenging. AIHA was the onset symptom of HL in 16 (40%) patients, but it preceded HL by 8–36 months in 8 (20%) patients (Table 3). In patients previously treated for HL, development of AIHA indicated the relapse of the disease, which was reported in 14 (35%) patients. Therefore, in patients with AIHA refractory to steroid treatment, malignancy should be considered in the differential diagnosis of underlying causes. Some authors suspected that steroid treatment for AIHA altered the HL clinical courses, making it difficult to diagnose.[14] Lack of continuity during follow-up also delayed diagnosis.[15] One

Table 2. Summary of Reported Cases of Hodgkin Lymphoma With AIHA

Year	Author	Age	Sex	Onset of AIHA vs Diagnosis (Months)	Subclass	Stage	Coombs Test	Treatments for AIHA
1966	Bowdler and Glick[28]	18	M	-36		III	+	RT
1967	Eisner et al[12]	16	F	38		III	+	None
		53	F	0.5		III	+	Steroid
		24	M	132		III	+	ABVD, RT
		37	F	94		III	+	RT
		61	M	0		III	+	RT, steroid, splenectomy
		16	M	10		III	+	RT, corticosteroid
		65	M	5		I	+	None
		33	F	13		III	+	RT, steroid
1973	Cazenave et al[29]	64	F	-92	MCHL	IVA	IgG and anti-e	Steroid, splenectomy
1973	Jones[30]	23	M	20	NSHL	IVAs	+	Steroid, splenectomy
		29	M	20	MCHL	IVA	+	Steroid, MOPP
1974	Garratty et al[6]	44	M	14 years		IVA	IgG and C3, anti-I	Steroid, RT
		60	M	9	MCHL	IIIB	IgG and C3, anti-I	Steroid
		33	M	-12	NSHL	IAs	IgG and C3, anti-I	Steroid, splenectomy
1976	May and Bryan[31]	9	M	-2	MCHL	IIA	IgG and C	RT, MOPP
1976	Chu et al[32]	10	F	-2	NSHL	IIIAs	IgG	Prednisone, splenectomy, RT
1978	*NEJM* case record[9]	55	F	-1	LRHL	IIA	IgG and non-IgG	Steroid, splenectomy
1980	Levine et al[3]	32	M	Relapse of HL	MCHL	IVB	IgG	Steroid, vincristine
		29	M	0	MCHL	IVB	+	Splenectomy, MOPP
		11	M	2 relapses of HL	NSHL	IIIB	-	MOPP
1982	Chu[13]	10[32]	F	-2	NSHL	IIIAs	+IgG	Prednisone, splenectomy, RT
		13	M	0	MCHL	IA	+	Splenectomy, RT
		3.5	M	84	NSHL		+	Steroid, RT, MOPP
1982	Björkholm et al[10]	41	F	96	LRHL	IIAs	+IgG, C3b	Steroid, splenectomy
1982	Carpentieri et al[33]	8	M	-24	NSHL MCHL	IIIA	+	Steroid, splenectomy, MOPP
1988	Xiros et al[1]	27	M	-8	MCHL	IIIAs	+	Steroid, MOPP/ ABVD

Table 2. Summary of Reported Cases of Hodgkin Lymphoma With AIHA

Year	Author	Age	Sex	Onset of AIHA vs Diagnosis (Months)	Subclass	Stage	Coombs Test	Treatments for AIHA
1991	Sierra[16]	55	M	6 days post-operative	NSHL	IIAs	+ IgG and C3	Steroid, cyclophosphamide, MOPP/ABV
1992	Kalmanti and Polychronopoulou[34]	9	M	0	NSHL	IIIBs	+ IgG Anti-D, E	RT, ABVD
1992	Pasini et al[35]	24	M	-3		IVB	-	MOPP/ABVD
1995	Majumdar[14]	39	M	-12 Refractory	NSHL	IAs	+ IgG and C3	Steroid, IV IgG, splenectomy, ChlOPP
		75	F	-24 Refractory	MCHL	IA	+ IgG and C3	Steroid, cyclophosphamide, azathioprine
1996	Costello et al[36]	24	F	0	Between NSHL and LDHL	IVBs	+ IgG	Steroid, plasmapheresis, splenectomy, MOPP
1996	Shah et al[7]	4	M	0	NSHL*	IIIBs	+ IgG and C3	Methylprednisolone, APE/OPPA
1997	Brady-West et al[37]	17	F	0	NSHL	IVB	+	Steroid, ABVD
1997	*NEJM* case record[11]	32	M	0	MCHL	IVBs	+ IgG	Splenectomy
2001	Kondo et al[38]	52	M	0	MCHL	IIB	+RBC-IgG	ABVD
2005	Ozdemir et al[17]	47	M	3 days after chemotherapy	MCHL	IVBs	+ IgG	Steroid
2009	Siddiqui et al[15]	32	M	-12	MCHL	IVBs	IgG + C3	Steroid, ABVD
		44	M	-12	MCHL	IIIB	IgG + C3	Steroid, ABVD

*Direct antiglobulin test (-). The patient also presented with idiopathic thrombocytopenia purpura.
ABVD=doxorubicin, bleomycin, vinblastine, and dacarbazine; AIHA=autoimmune hemolytic anemia; APE=doxorubicin, cisplatin, and etoposide; C=complement; ChlOPP=cyclophosphamide, vincristine, procarbazine, prednisone; F=female; HL=Hodgkin lymphoma; Ig=immunoglobulin; IV=intravenous; LDHL=lymphocyte-depleted Hodgkin lymphoma; LRHL=lymphocyte-rich Hodgkin lymphoma; M=male; MCHL=mixed cellularity Hodgkin lymphoma; MOPP=mechlorethamine, oncovin, procarbazine, prednisone; *NEJM=New England Journal of Medicine*; NSHL=nodular sclerosis Hodgkin lymphoma; OPPA=oncovin, procarbazine, prednisone, doxorubicin; RBC=red blood cell; RT=radiation therapy.

case of AIHA occurred 6 days after chemotherapy administration, and the other developed 3 days after lymph node biopsy and was complicated by pneumonia.[16,17] Whether these 2 cases represent coincident findings or a causal relation to biopsy or chemotherapy remains unclear.

The incidence of HL peaks at 2 age spans: between 15–35 years and older than 55 years. Among the 40 reported cases, the ages ranged from 3.5 years to 75 years, with a median age of 32 years, which is slightly younger than the median age of 38 years reported by the Surveillance Epidemiology and End Results (SEER) study from 2002–2006.[18] We found that 31% of patients were younger than 20 years at diagnosis. In contrast, in the SEER data, 11.9% were younger than 20 years at diagnosis (P<.001). The incidences in the other age groups were close to the SEER statistics fact sheet (P=.20–.58).[18] Taken together, the incidence of patients diagnosed with AIHA and HL follows the incidence trend of HL in the general population, with a male predominance, but shows an increased prevalence in the under 20 age group.

Among the 40 reported cases, AIHA was predominantly treated with combined steroids, radiation, and chemotherapy, albeit a few cases of anemia recovered spontaneously or responded to steroid treatment. Anemia recurs if the underlying cause is not treated. In the 1970s to

Table 3. General, Clinical, and Pathologic Characteristics of 40 Cases of HL With AIHA, Including Our Case

Characteristics	Patients (n)	Percentage
Age (years)		
Range	3.5–75	
Median	32	
<20	12	30*
20–34	10	25
35–44	5	13
45–54	4	10
55–64	5	13
65–74	1	3
75–84	1	3
Male:Female	29:11	2.6:1
Time of AIHA in relation to time of HL diagnosis		
Onset	16	40
Proceeding	8	20
Post-HL/relapse	14	35
Other (postoperative and postchemotherapy)	2	5
Stage (n=39)		
I	5	13
II	5	13
III	17	43
IV	12	30
Constitutional B symptoms	15	38
Subtype of HL (n=29)		
MCHL	14	48
NSHL	10	28
LRHL	3	10
Between LDHL and NSHL	1	3
MCHL and NSHL	1	3
Unclassified	11	28
Coombs test		
Positive (IgG and/or C3)	37 (21)	93 (57)
Negative	3	8
RBC-IgG	1	
Alive at the time of the report		
>5 years	17	43
Died from HL	1	
Died from other causes	2	
1–5 years	14	35
Died from HL	4	
Died from other causes	2	
<1 year	6	15
Died from HL	1	
Died from other causes	1	
Unreported survival	3	8
Total death from HL	6	15
Median age of death (years)	24 (16–53)	
Total death from other causes	5	13
Median age of death (years)	61 (60–75)	

*P=.001 compared to 11.9% reported incidence in the same age range between the years 2002–2006 as reported by the Surveillance Epidemiology and End Results (SEER) Stat Fact Sheet: Hodgkin Lymphoma.[18]

AIHA=autoimmune hemolytic anemia; C3=complement 3; HL=Hodgkin lymphoma; Ig=immunoglobulin; LDHL=lymphocyte-depleted Hodgkin lymphoma; LRHL=lymphocyte-rich Hodgkin lymphoma; MCHL=mixed cellularity Hodgkin lymphoma; NSHL=nodular sclerosis Hodgkin lymphoma; RBC=red blood cell.

1980s, in cases that involved only local organs, nodal zones, or the spleen, surgical excisional biopsy/staging or local radiation caused remission. Recently, rituximab, a monoclonal antibody against CD20, showed promising results in the treatment of autoimmune diseases, such as AIHA,[19-21] and hematogenic malignancies, such as non-Hodgkin lymphoma and lymphocyte-predominant HL.[22-24] In 2 studies,[23,25] 26 cases of recurrent, classic HL were treated with rituximab after other treatments failed; rituximab has been reported to resolve B symptoms and result in clinical remission. Although our patient did not have recurrent HL (but did have severe AIHA and stage IIIB HL), he was treated with rituximab plus ABVD. Although some might consider this overtreatment, in this rare entity, the data are limited in evaluating the survival benefit of rituximab. The patient's hemoglobin remained above 14 mg/dL 1 year after chemotherapy, indicating a positive clinical course. More studies in the treatment of HL with rituximab are in progress.[26] To our knowledge, this is the first case of LRHL with AIHA treated with rituximab and ABVD.

At the time this article was submitted, 11 deaths had been reported (Table 3). Six patients died directly from HL, with a median age of 24 years, which is much younger than the other 5 patients (median age, 61 years) who died of various causes, including congestive heart failure secondary to long-standing AIHA with HL stage IA,[14] metastatic carcinoma of the biliary duct with HL stage I,[12] and brain toxoplasmosis after months of steroid treatment[6] (P=.004). This finding indicates that even though AIHA occurs frequently in the late stage of HL, it does not necessarily worsen the outcome of the HL. Age, serum albumin, leukocytosis, lymphocytopenia, and other comorbidities of the patients play important roles in overall HL outcome.[27] Note that 9 of the 11 patients died before 1974, and 2 died in 1995–1996, suggesting that more effective chemotherapy, such as ABVD, might have improved survival rates.

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Review

Hodgkin Lymphoma and Autoimmunity: A Two-Way Street

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Introduction

Feng and colleagues present an interesting case and comprehensive review of Hodgkin lymphoma (HL) associated with autoimmune hemolytic anemia (AIHA).[1] As noted by the authors, HL may be accompanied by AIHA in up to 4% of cases, making it one of the more common of the unusual paraneoplastic manifestations of this disorder.[2] However, AIHA is not the only autoimmune hematologic abnormality associated with HL, or, for that matter, other non-Hodgkin lymphomas (NHL). Other described autoimmune hematologic abnormalities include autoimmune thrombocytopenia and autoimmune neutropenia, the latter a manifestation that is believed to be unique to the Hodgkin variant of lymphomas.[3]

Additional autoimmune paraneoplastic manifestations in HL may include the production of autoantibodies as well as the development of classic autoimmune diseases. Autoantibodies may be those usually associated with autoimmune rheumatic diseases[4] or directed against other autoantigens, including oncoproteins.[5] Other autoimmune manifestations may include the development of neurologic disorders, including neuropathies, glomerulonephritis, vasculitis, and, rarely, arthritis.[6] Taken together, these manifestations highlight the prominent relationship between immune dysfunction and HL.

Autoimmunity and Lymphomagenesis

The relationship between HL and autoimmunity is not a one-way street. An increased incidence of malignant lymphocytic disease is present in a number of autoimmune rheumatic diseases, suggesting a bidirectional relationship between the immune system and lymphoproliferative disorders.[6] Although most clearly described with NHL, an increased incidence of HL has also been reported with several systemic autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, Sjögren's syndrome, and scleroderma.[7-10]

In a recent large, population-based, case-controlled study in Denmark and Sweden, Landgren and colleagues evaluated the historical association between 7,476 case subjects with HL against more than 18,000 matched control subjects and more than 86,000 first-degree relatives of case and control subjects.[11] According to their analysis, a statistically significant increased risk of HL was associated with personal histories of several autoimmune conditions, primarily those characterized by systemic involvement. These included RA, systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, and immune thrombocytopenic purpura. A weaker association was found with autoimmune diseases in which more organ-specific involvement is characteristic, including primary biliary cirrhosis and Wegener's granulomatosis. In addition, a statistically significant increased risk of HL was also associated with *family histories* of sarcoidosis and ulcerative colitis, further suggesting a shared susceptibility for these conditions.[11]

Data from the US Surveillance Epidemiology and End Results (SEER)-Medicare database incorporating 44,350 lymphoid malignancy cases in subjects ages 67 years and older and 122,531 population-based controls also demonstrated an association between HL and both systemic and discoid lupus erythematosus as well as RA.[12] This study was perhaps more limited than the Scandinavian study due to the older age of the individuals and the relatively smaller number of HL versus NHL patients.[13]

The possible mechanism by which autoimmunity could be related to the risk of developing lymphoma has been the subject of investigation for more than 50 years. Initial theories focused on the similar proliferative processes of lymphocytes that characterize both autoimmunity and hematologic malignancies.[14] Goodnow in a recent review described the pathways and genes likely to be involved in both autoimmune diseases and lymphomas.[15] According to his analysis, both disease types are the consequence of multistep processes that eliminate the checkpoints that inhibit uncontrolled B-cell growth, including uncontrolled growth of autoimmune lymphocytes. These processes

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are likely to involve both inherited and somatic mutations of the genes involved in these pathways. The most prominent example is the finding that somatic and germline *Fas* mutations are associated with both autoimmune diseases and lymphomas in mice and in humans. These mutations presumably interfere with apoptosis, thus influencing both the autoimmune and lymphoproliferative processes.[15]

Hansen and colleagues summarized the possible mechanisms for progression of autoimmune diseases to lymphomas, including how specific dysregulation and hyperactivity of B cells associated with autoimmune diseases and impaired T-cell function may lead to lymphomagenesis. They emphasize that the more intense disease activity and/or longer duration of disease might indicate a higher risk of lymphoma development.[16]

A comprehensive picture of the major immune-related factors thought to contribute to lymphomagenesis is presented by Goldin and Landgren.[17] In their model, autoimmunity may lead to both overstimulation and defective apoptosis of B cells. Secondary inflammation due to autoimmune stimulation can also promote these processes. Several infections have been associated with lymphoma development, including hepatitis C and Epstein-Barr virus. In addition, certain bacteria are likely to operate through some of these same pathways. Genetic factors predisposing to both autoimmune diseases and lymphomas may also play a substantial role.

Immunosuppressive Therapy and Lymphoma

An association between immunosuppressive therapies used in the treatment of autoimmune diseases has long been suspected to play a role in the development of lymphomas in these individuals. Mostly studied in RA, development of lymphoma is increased by the use of cyclophosphamide and equivocal with respect to azathioprine. Although methotrexate has been associated with certain cases of "reversible lymphoma," which disappear with drug discontinuation, epidemiologic studies have failed to demonstrate an increased risk beyond what is expected in RA alone.[18]

Of more recent interest is the possible association of newer biologic agents, particularly those directed against tumor necrosis factor (TNF), and the onset of malignancies, including lymphomas. Although some studies have detected a possible increased lymphoma risk with the use of biologic agents,[19,20] large population-based studies have failed to demonstrate an increased risk with use of anti-TNF drugs.[18,21-23] Therefore, the prevailing opinion is that immunomodulatory biologic agents do not appear to increase the risk of lymphoma development.

Summary

Although HL and other hematologic malignancies may present with autoimmune paraneoplastic manifestations, the relationship between these disorders is a two-way street, with similar pathogenic mechanisms predisposing to the development of both autoimmune and lymphoproliferative disorders. Epidemiologic studies and basic immune and genetic investigations are needed to further clarify this complex bidirectional process.

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