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RESEARCH ARTICLE

PARANEOPLASTIC MANIFESTATIONS OF LYMPHOMA

Anvesh Rathore., AP Dubey., SK Rai and Abhishek Pathak

Army Hospital (R&R), New Delhi, India, PIN110010

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ABSTRACT

Introduction- Paraneoplastic syndromes (PNS) are a group of clinical disorders associated with an underlying malignant disease that are not directly related to the physical effects of the primary or metastatic tumor but caused by systemic effects occurring remotely from the cancer primary site or metastasis. **Aims & Objectives-** The aim of study is to study various types of paraneoplastic manifestations associated with the patients of Hodgkin's and non-Hodgkin's lymphoma. **Material And Methods-** All the patients presented to this center and freshly diagnosed with Hodgkin and Non Hodgkin Lymphoma were assessed for associated Paraneoplastic manifestations. **Results-** A total of 175 patients of Hodgkin or non Hodgkin lymphoma reported to this center out of which 67 (38.2%) were having Hodgkin lymphoma and 108 (63.8%) had Non Hodgkin Lymphoma. Out of 67 patients presented with hodgkin lymphoma six patients (8.9%) were detected to have paraneoplastic manifestaions. Most common age group affected was identified as those between 6th to 7th decade. Females were more commonly affected and anemia was noticed as the most common. Out of 108 patients detected to have Non hodgkin lymphoma, 22 (20.37%) patients were detected to have paraneoplastic manifestation which was higher as compared to patients with Hodgkin lymphoma (8.9%). **Conclusion-** This study was conducted to define various paraneoplastic manifestations associated with lymphoma.

INTRODUCTION

Lymphoma is a heterogeneous group of biologically and clinically distinct neoplasms that originate from cells in the lymphoid organs and have been historically divided into two distinct categories: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL).

Hodgkin's lymphoma which was earlier known as Hodgkin's disease makes up 8.2% of lymphoid malignancy and Non-Hodgkin's lymphoma makes up 62.4% of lymphoid malignancies.

Paraneoplastic syndromes (PNS) are a group of clinical disorders associated with an underlying malignant disease that are not directly related to the physical effects of the primary or metastatic tumor but caused by systemic effects occurring remotely from the cancer primary site or metastasis. They are estimated to affect up to 8% of patients with cancer (1). The most commonly involved systems in paraneoplastic syndromes are the neurologic, endocrine, hematologic, dermatologic, and rheumatologic.

The frequency of PNS is low; they occur in <1% of patients with solid tumors, particularly small-cell lung carcinoma (SCLC), breast, and ovarian cancers. The frequency is probably lower in Hodgkin lymphoma (HL) and other lymphomas. However, the correct diagnosis of PNS is important because an early recognition of a neurological syndrome as paraneoplastic often leads to the discovery and treatment of the underlying tumor, which is a crucial step in the management of the PNS (2)

We conducted a descriptive study to find out the incidence of paraneoplastic manifestations in patients of Hodgkin's and non-Hodgkin's lymphoma, the characteristics of the various systemic involvement and to assess the response of the symptoms after standard treatment protocol.

AIMS AND OBJECTIVES

Aims: The aim of study is to find out the incidence of paraneoplastic manifestations in the patients of Hodgkin's and non-Hodgkin's lymphoma and this study was carried out at a tertiary care oncology centre.

Objective

1. To find out the incidence of paraneoplastic manifestations in patients of Hodgkin's and non-Hodgkin's lymphoma.
2. To characterize the various systemic involvement.

MATERIAL AND METHODS

This study group will comprise of all the freshly detected patients of Hodgkin and Non Hodgkin Lymphoma. All the

patients diagnosed to have any type lymphoma will be subjected to complete clinical examination, lymph node biopsy or tissue biopsy for the diagnosis, staging workup which include hematological and biochemical parameters including erythrocytes sedimentation rates and lactate dehydrogenase, CT scan chest, abdomen and pelvis, whole body PET scan and bone marrow examination. All the patients were treated as per existent guidelines.

Before starting the treatment all patients will be assessed for associated Paraneoplastic manifestations which include detailed clinical examination of central nervous system, peripheral nervous system and respiratory and dermal system. The final outcome will be assessed by response to therapy which can be complete response, partial response or no response.

Inclusion Criteria-

All new and old cases of confirmed Hodgkin's and Non-Hodgkin's lymphoma between age group of 5-70years.

Exclusion Criteria

1. Patients having co-existent tuberculosis .
2. Patients suffering from autoimmune disease .
3. Patients with known connective tissues disorder.
4. HIV associated lymphoma.

RESULTS AND OBSERVATION

Patients

A total of 175 patients of Hodgkin or non Hodgkin lymphoma reported to this centre over a period of 2 years and they were analyzed to find out the various Paraneoplastic manifestations.

Age Distribution of Patients

Out of total 175 patients 67 (38.2%) were having Hodgkin lymphoma and 108 (63.8%) had Non Hodgkin Lymphoma. In Hodgkin disease patients maximum incidence was noted between the age group of 10-20 (19 out of 67 i.e. 28.3% patients) and 50-60 years (21 out of 67 i.e. 31.3% patients). While for non Hodgkin lymphoma maximum incidence was noted for the age group 20-30 (20 out of 108 i.e. 18.5%) and 50-60 years (24 out of 108 i.e. 22.2%). (Table no-1)

Table 1 Age wise distribution

Age group (Year)	Hodgkin's lymphoma	Non-Hodgkin's lymphoma	No of Patients
0-10	05	04	09
10-20	19	09	28
20-30	07	20	27
30-40	03	19	22
40-50	15	14	29
50-60	21	24	45
60-70	07	08	15
Total	67	108	175

Sex distribution

Out of the 175 cases studied 116(66.2%) were male and 59(34.8%) were female. Amongst pt with Hodgkins Lymphoma 47 (70.14%) out of 67 patients were males while 20 (29.86%) were female with an overall ratio of male to female being 2.35:1. while patient with Non Hodgkin Lymphoma 69 (63.8%) out of 108 were males with female being 39 (36.2%). (Table no-2).

Table 2 Sex wise distribution

Sex	Hodgkin Lymphoma	Non- Hodgkin Lymphoma	No of Patients	Percentage
Male	47	69	116	66.2 %
Female	20	39	59	34.8%

Paraneoplastic Presentation in Hodgkin's Lymphoma

Out of 67 patients presented with hodgkin lymphoma six patients (8.9%) were detected to have paraneoplastic manifestaions. Most common age group affected was identified as those between 6^{th} to 7^{th} decade.

In our study Anemia was noticed as the most common manifestation with all six patients having anemia. While only two had severe anemia (Hb<8gm%) rest of ther patients had only mild to moderate anemia.

Eosinophillia which has been documented as a common manifestation associated with Hodgkin Lymphoma. In our study we only had one pt with eosinophillia with AEC 1200/cu mm.

Other common presentation noticed in our study were dermatological manifestation with three patients showing skin lesion (two had panniculitis while one patient had acanthosis nigricans). Two patients also showed neurological manifestation with one having Paraneoplastic Cerebellar Degeneration with features of peripheral neuropathy also while the other patient had only features of peripheral neuropathy. One patient had features of nephrotic syndrome alongwith panniculitis. (Table no-3)

Table-3 Distribution of various Paraneoplastic manifestations in Hodgkin Lymphoma

System	No of Patient	Percentage
Anemia	06	8.9%
Eosinophillia	01	1.4%
Dermatological:		
Acanthosis Nigricans	01	1.4%
Sweet Syndrome	0	0
Erythema Multiforme	0	0
Pemphigus Vulgaris	0	0
Granuloma Annulare	0	0
Panniculits	02	2.8%
Neurological:		
Peripheral Neuropathy	02	2.8%
Paraneoplastic Cerebellar Degeneration	02	2.8%
Gait Imbalance	0	0
Motor Neuron Disease	0	
Nephrotic Syndrome	1	1.4%

In our study we observed that most of the patient with paraneoplastic manifestations were female (four out of six) and most of them had advanced disease ie beyond stage IIb. None of our patient presented with features of tumor lysis syndrome, rheumatological disease.

Most of the patient after standard therapy as per current days recommendations had shown good response to the therapy (82%). four out of six patients (75%) with paraneoplastic manifestation had more chances of having residual disease.
Out of total six patients with paraneoplastic manifestation one had a fatal outcome.

Paraneoplastic Presentation in Non- Hodgkin's Lymphoma

In our study out of 108 patients detected to have Non hodgkin lymphoma, 22 (20.37%) patients were detected to have

paraneoplastic manifestation which was higher as compared to patients with Hodgkin lymphoma (8.9%).

Most common age group was identified 50-60 years. In our study we observed that most of the patient with paraneoplastic manifestations were female (13 out of 22; 59.09%).

Commonest presentation noticed in our study were hematological disorders. Out of 22 patients 16 (72.7%) had at least one abnormal blood count at diagnosis. Anemia was present in 10 patients (62.5%), both thrombocytopenia and thrombocytosis in 20% with leucopenia in 5%.

Autoimmune hemolytic(AIHA) was seen in 02 patients with B cell NHL.

Second most common presentation noticed in our study was hypercalcemia (10 out of 22 patients; 45%). while most of the patient had mild to moderate hypercalcemia. Only two pateints had severe hypercalcemia (>15 mg/dl), both of them required dialysis support and both of them presented with altered sensorium. Out of these two patient one had succumbed due to renal failure.

Other common manifestations noted were neurological manifestations. Out of total 22 patients eight were detected to have neurological involvement in some form. Three patients had features of peripheral sensory neuropathy. Only two patients had presented with altered sensorium who later diagnosed to have hypercalcemia. One patient had presented with progressive limbic encephalitis who had partial regression of symptoms following treatment. Other neurological disablities noted were acute demyelinating polyneuropathy and CIDP.

Dermatological manifestation were seen in 07 (31.8%) patients showing skin lesion. Commonest lesion noted was panniculitis (03) while one patient had acanthosis nigricans).

Two patients also showed neurological manifestation with one having Paraneoplastic Cerebellar Degeneration with features of peripheral neuropathy also while the other patient had only features of peripheral neuropathy. One patient had features of nephrotic syndrome alongwith panniculitis. Only two patient were detected to have polyarthritis but without any features of joint deformity. None of the patient had reported features of polymyositis or dermatomyositis. (Table no-4)

Table no-4 Distribution of various Paraneoplastic manifestations in Non Hodgkin Lymphoma

System	No of Patient	Percentage
Hematological	16	72.7%
Anemia	10	45.4%
Thrombocytosis/ thrombocytopenia	05	20%
Leucopenia	01	05%
Hypercalcemia	10	45.4%
Dermatological:	07	31.8%
Acanthosis Nigricans	01	14.2%
Sweet Syndrome	01	14.2%
Erythema Multiforme	01	14.2%
Pemphigus Vulgaris	01	14.2%
Panniculits	03	42.8%
Neurological:	02	9%
Peripheral Neuropathy	01	50%
Paraneoplastic Cerebellar Degeneration	01	50%
CIDP	01	50%
Rheumatological:	02	9%
Polymyositis	0	0
Dermatomyositis	0	0
Arthritis	02	100%

DISCUSSION

Paraneoplastic manifestations are signs and symptoms of malignancy that are not physically related to tumor itself. The etiology of most paraneoplastic syndromes remains obscure, although the most common underlying mechanism are thought to be secretion of cytokines by tumors cells, and induction of immune response against normal tissues. Paraneoplastic phenomena, which are primarily endocrinological, neurological, hematological, renal or dermatological, could be first or early manifestations of malignancy.

The most common paraneoplastic endocrinopathy in patients with lymphoma is hypercalcemia. In our study we reported an incidence of 1.4% of Hypercalcemia in Hodgkins Lymphoma and 5.5% for Non Hodgkin Lymhoma.

The study carried by Canellos GP, reported hypercalcemia to occur in approximately in 1% of patients with Hodgkin's and 4% of patients with non –Hodgkin's lymphoma(3).The incidence of hypercalcemia in high grade NHLs may approach to 30% while in low grade it is only about 1 to 2%. B cell lymphoma is more commonly implicated as compare to adult T cell lymphoma although hypercalcemia has been reported in peripheral T –cell lymphoma and angioimmunoblastic Lymphadenopathy(4).

Hypoglycemia is rare but has been a documented paraneoplastic manifestation in lymphoma. In our study we reported only one case of hypoglycemia with Non Hodgkin Lymphoma. The study done by Braund WJ, Williamson DH, Clark *et al* showed the hypoglycemia in Hodgkin's disease due to formation of autoantibody which may have stimulated the insulin receptors and produced hypoglycemia(5).

Neurological involvement in Hodgkins Lymphoma is a rare event, occurring at a frequency between 0.02 and 0.5 percent (6-9). Several rare paraneoplastic neurologic syndromes have been described in patients with Hodgkin Lymphoma. These include paraneoplastic cerebellar degeneration, chorea, neuromyotonia, limbic encephalitis, subacute sensory neuronopathy, subacute lower motor neuronopathy, and the stiff person syndrome (10-14).

The etiology of neurological symptoms in patients with lymphoma, including direct spread to central nervous system or peripheral nervous system , toxicity of specific therapies, neurological manifestations of CNS infection. The most common mechanism is immunologic, malignancy induced formation of antibodies that attack normal neural tissues.

Paraneoplastic cerebellar degeneration (PCD) is one of the most common neurological syndrome reported in Hodgkin's lymphoma. Hodgkin's lymphoma is one of the more common cause of PCD, after lung , ovarian and breast cancer .PCD has also reported in non- Hodgkin's lymphoma.

The study carried by Grauss F,Dalmau J, Valldeoriola F,et al showed the immunological characterization of neuronal antibody (Anti-Tr) associated with Paraneoplastic cerebellar degeneration and Hodgkin's disease in serum and CSF of patients with PCD and HD but not alone. These anterior Purkinje cells antibody is different from those seen in Gynaecological cancer (anti-Yo) or small cell lung cancer.

Hematological

In one large series study carried by Conlan MG, Armitage JO, *et al* of 317 Patients with Non-Hodgkin's lymphoma, 63% had at least one abnormal blood count at diagnosis, regardless of whether the disease involved the bone marrow. Anemia was present in 42% both thrombocytopenia and thrombocytosis in 26% with leucopenia in 6%. Thrombocytopenia and Leucopenia were more common in patients with bone marrow disease (15).

Autoimmune hemolytic(AIHA) due to warm – reacting antibodies occurs mainly in T or B- cell lymphoproliferative disorders, although it has been reported in HD. AIHA due to cold reacting autoantibody is commonly associated with B cell NHL of many cases, according to Crisp D and Pruzanski *et al* (16).

The study carried by Evans RS, Takahasi K, Daune RT,*et al*, showed immune mediated thrombocytopenia and autoimmune hemolytic anemia as Evans syndrome or in isolation.The mechanism for the development of these syndromes include tumor production of autoantibodies, tumor induction of novel antigens that lead to auto antibody production. The effective treatment of disease will often induce remission (17).

Eosinophilia occurs in about 20% cases of Hodgkin lymphoma, 21% of Patients with acute T cell leukemia/lymphoma,11% of patients with T cell lymphoma, and 10% of patients with B – cell lymphoma. According to Von Wasielewski R, Seth S, Franklin J, *et al*- tumor infiltration by more than 5% of eosinophils has been shown to predict decreased survival in Hodgkin Lymphoma, but did not correlate with peripheral eosinophila (18)

Nephrotic syndrome is most common paraneoplastic manifestations in lymphoma, approximately 10% of patients with newly diagnosed Idiopathic nephrotic syndrome, are found to have malignancy, usually a carcinoma.

According to Dabbs DJ, Striker L, *et al*, Renal involvement as part of systemic lymphoma is quite frequent, however, primary extranodal renal non-Hodgkin's lymphoma (NHL) is extremely rare, and only about 65 cases have been reported in the world literature (19).

The most common (80%) glomerular lesion of nephrotic syndrome is lipoid nephrosis, minimal change disease. The remaining 20% of cases show typical membranous glomerulonephritis, focal sclerosis or membranoproliferative glomerulonephritis.

Dermatological

A variety of skin lesions have been associated with HL. These include ichthyosis, acrokeratosis (Bazex syndrome), urticaria, erythema multiforme, erythema nodosum, necrotizing lesions, hyperpigmentation, and skin infiltration (20, 21).

Malignancies have been associated with greater number of paraneoplastic skin lesions. Acanthosis nigricans, characterized by symmetrical brown areas of hyperpigmentation and hyperkeratosis especially in the axilla, neck flexor and anogenital areas is usually associated with abdominal malignancy but occasionally associated with lymphoma also, according to Curth HO *et al* (22).

Cohen PR,Talpaz M, and Kurzrock R *et al*, Sweet's syndrome is an acute febrile neutrophilic dermatosis in which approximately 20% of the reported patients have an associated cancer. They review the 79 patients with malignancy-associated Sweet's syndrome documented in the world literature. The most common underlying neoplasm was acute myelogenous leukemia (AML). Lymphomas, chronic leukemias, myelomas, myelodysplastic syndromes, and a variety of solid tumors have also been observed (23).

According to Fullerton SH, Woodley DT, Smoller RS, *et al* Paraneoplastic pemphigus is a recently described disease in which patients have polymorphous skin lesions suggestive of both erythema multiforme major and pemphigus vulgaris in association with internal neoplasms, especially non-Hodgkin's lymphoma(24). These patients have characteristic autoantibodies that bind specific epidermal proteins.

Bullous lesions have been reported in patients with Hodgkin's lymphoma and NHL. Paraneoplastic pamphigus is rare and distinct autoimmune disease characterized by extensive and painful mucosal ulcerations and skin lesions. The mucocutaneous eruptions resembles both erythema multiform major (Stevons-Johnson syndrome) and pemphigus vulgaris. The disease is most commonly associated with NHL and CLL, and most patients die in several months regardless of the course of the underlying malignancy.

Rheumatological

Rheumatoid arthritis, asymmetric polyarthritis, and systemic lupus erythematous (SLE) have all been associated with lymphoma, but this relationship may be due to known increased risk of lymphoma in patients previously diagnosed with connective tissue disease. Palmar fasciitis and arthritis are characterized by complete loss of upper extremity function and contracture.

The study carried by Pfingsgraff J,Buckingham RB, Killian PJ,*et al* shown the association of Palmar fasciitis and arthritis with HD47. Polymyositis and dermatomyositis are inflammatory myopathies that can occur in age all groups.

The inflammatory myopathies are a heterogeneous group of chronic, subacute, or acute acquired diseases of skeletal muscle. Their common features are moderate to severe muscle weakness and inflammation in the skeletal muscles .An analysis of 153 cases by Carl Pearson's group in 1977 forms the basis of current clinical knowledge of the muscular involvement in PM and DM.

PM has been reported in a child with an occult immunoblastic lymphoma, study done by Sherry DD,Haas JE,and Milstein JM *et al* they showed that, approximately 33% of adult patients with dermatomyositis develop malignancy with up to 42% presenting after the diagnosis has been made; careful evaluation for malignancy is often undertaken at the time of dermatomyositis diagnosis. This phenomenon has rarely been noted in pediatric patients and extensive workup for malignancy is not indicated in pediatric patients (25).

DM patients develop progressive muscle weakness affecting the proximal muscles around the shoulders and hips (limb-girdle muscles), or neck muscles (often in juvenile DM). The weakness is usually symmetric. In general, the onset is gradual and the disease develops relatively slowly, occurring over weeks to even months, and rarely appear acute. In their series of 153 patients Bohan *et al*. (1977) reported that, on initial

presentation, muscle strength was normal in 48 cases (31%).However, on occasions, the onset can be acute, with rapid development of weakness. The muscle involvement is the second most common presenting feature of DM, which varied between 53% and 96% of patients with skin rash). Almost all patients presented proximal muscle weakness in some studies(26).

Primary angiitis of the CNS has been reported in 12 patients with HD. The study done by Rosen CL,DePalma L, and Morita L *et al*. Granulomatous angiitis of the central nervous system is a rare cause of neurological deterioration. It is often diagnosed posthumously, and a high index of suspicion is necessary to make the correct diagnosis on a timely basis. Patients presented with nonspecific symptoms including headache nausea, vomiting. A review of the literature revealed a total of 12 patients with central nervous system angiitis and Hodgkin's disease. As a group, these patients had very poor outcomes. However, of six patients who presented with central nervous system angiitis and concurrent Hodgkin's disease and who underwent aggressive treatment for both conditions, three had a full recovery, two had a partial recovery, and one died (27).

Fulminant hepatic failure-Neoplasm frequently present with hepatic involvement, without significantly affecting hepatocellular unction, at least not at initial stages of the disease. Spyros P, Dourakis, Eftichios Tzemanakis *et al*. They presented an usual cases of Hodgkin's disease, presenting as a fulminant hepatic failure in form of Jaundice, ascites, encephalopathy and bleeding diathesis in a 34 year male56. Chemotherapy was initiated, resulting in dramatic improvement not only in patients level of consciousness but also in prothrombin time. Unfortunately, he succumbed shortly after to disseminated candidiasis.A post-mortem needle liver sample revealed massive hepatocellular necrosis , but no liver infiltration by neoplastic disease.They conclude that in Hodgkin's disease ,liver involvement can be manifestation of paraneoplastic fulminant hepatic failure.

CONCLUSION

This study was conducted to define various paraneoplastic manifestations associated with lymphoma. Though these are not very common but an astute and good clinician should not miss it. Treatment of the disease usually leads to the complete resolution of these manifestations.

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