Serum Immunoglobulin Level Derangements in Chronic Lymphocytic Leukemia, Hodgkin's Disease and Non-Hodgkin's Lymphoma

Dr. Talib H. Kammona, M.B.Ch.B.-C.A.B.M. - DM

Iraq / Najaf / Kufa University / College Of Medicine / Department of Medicine

Abstract

Objective: to compare the degree of immunoglobulin derangement "hypo or hypergammaglobulinaemia" among patients with cll, nhl, and hd.
Design: forty three patients with hematologic malignancies attended hematology and oncology unit in al-sadr teaching hospital in najaf city between february and august 2007, were evaluated for their serum igg, igm, and iga level with a comparable number of healthy adult controls. Sixteen patients with cll, thirteen patients with nhl, and fourteen patients with hd were included in this study.
Results: there is a significant alteration in the level of immunoglobulin among patients with hematologic malignancies, with a reduced level seen in patients with cll and nhl, and an elevated level is seen in patients with hd.
Conclusion: immunoglobulin derangement is a common problem in patients with cll, nhl and hd.
Recommondations: larger number of patients, with extension of the study to include igg subsets is needed for good outcome and better results.

Introduction

Immunoglobulins are the product of differentiated B cells and mediate the humoral arm of the immune response. Their primary functions as antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or other foreign substances from the body. [1] They are Y shaped proteins consisting of two identical heavy polypeptide chains and two identical light chains- kappa or lambda, which are functionally identical. In contrast, there are five types of heavy chains, for which each class of immunoglobulin is named: alpha, found in immunoglobulin IgA, gamma in IgG, delta in IgD, epsilon in IgE, and mu in IgM. [2]

Immunoglobulin and antibody deficiency states can be divided into two major categories: primary disease, usually arising in childhood, and secondary immune deficiency syndrome related to the acquisition of major diseases. [3]

The primary hypogammaglobulinaemia by definition is without a known cause. In adults the two most common forms are common variable immune deficiency and selective IgA deficiency, while secondary hypogammaglobulinaemia can be due to a variety of conditions, which can be divided into disease of immunoglobulin loss, disease of immunoglobulin production, drug induced states, and high stress states.[2] A number of malignancies, including chronic lymphocytic leukemia (CLL),[4] multiple myeloma,[5] Hodgkin's lymphoma,[6] and Non Hodgkin's lymphoma (including Epstein – Barr related post– transplantation lymphoproliferative disease) – all malignancies involving the B cells.[3]

Malignancies of lymphoid cells range from the most indolent to the most aggressive human malignancies. These cancers arise from cells of the immune system at different stages of differentiation, resulting in a wide range of

morphologic, immunologic, and clinical finding.[7]

CLL is a monoclonal hematopoietic disorder characterized by a progressive expansion of lymphocytes of B cell lineage in 95% of cases. These small mature appearing lymphocytes accumulate in the blood, bone marrow, lymph nodes, and spleen. [8] Hypogammaglobulinaemia is one of the two routinely measured immune defects associated with CLL (the other being neutropenia), and its association with infection in CLL patients is well known.[9-10] The pathogenesis of hypogammaglobulinaemia probably reflect the dysfunction of non clonal CD5 B cells in CLL [11] and carries a poor prognosis. [12] Additionally, the incidence of hypogammaglobulinaemia depends on the duration of CLL. [13] During the course of their illness, most CLL patients will ultimately have severe, permanent hypogammaglobulinaemia [14-15] that cannot be reversed using antileukemic therapy, even if a complete remission is achieved. [16]

Hodgkin's disease (HD) has been traditionally defined as hematopoietic neoplasm composed of diagnostic Reed – Sternberg cells within a reactive inflammatory cell background. [17] Reed-Sternberg cell can be rare or absent in nodular lymphocyte predominant and nodular sclerosis HD. [17] The humoral-mediated immunity may be affected in addition to the cellular immunity [18] and the changes in the immunoglobulin concentration were found to be dependent on clinical stage and histological subtype. [18, 19] Some studies demonstrate that impairment of immunoglobulin synthesis by cultured lymphocytes may be, at least in part, the result of a pre existing in vivo activation of lymphocytes in HD patients. [20]

There are at least 3 different entities referred to as Non Hodgkin's lymphoma (NHL). Although not apart of the current classification system for NHL, it is clinically useful to divide NHL into indolent, aggressive, and highly aggressive tumor. [21] Lymphoma is an immune cancer and they may directly affect immunoglobulin production through immune suppression; thus Ig level may not accurately reflect the immune environment in which the lymphoma developed. [22]

Patients and Methods

The Patients:

The samples under study consist of forty three patients, were grouped into sixteen patients with CLL, fourteen patients with NHL, and thirteen patients with HD, attending to the oncology and hematology unit, in AL-Sadr teaching hospital from February 1st 2007 to August 30th 2007.

Patients with CLL underwent diagnostic workup depending on the history, clinical examination, hemoglobin, white blood cells count, platelets count, and bone marrow study. The diagnosis of CLL relies upon the International workshop on CLL (IW-CLL), and staged according to Binet's system. Samples of blood were taken for measuring IgG, IgM, and IgA concentration.

Patients with NHL were diagnosed depending on the information obtained from history, clinical examination, hemoglobin, white blood cells count, platelets count, and Histopathologic examination of tissue biopsy. The patients staged according to Ann Arbor System. Samples of blood were taken for measuring IgG, IgM, and IgA concentration.

Patients with HD were diagnosed depending on the information's obtained from history, clinical examination, hemoglobin, white blood cell count, platelet count, and tissue biopsy. The patients staged according to Ann-Arbor System. Samples of blood were taken for measuring IgG, IgM, and IgA concentration.

The Control:

The control group consist of healthy forty three persons "age and sex matched ", they represent paramedical staff, and some relatives of the patients in the hospital. None of them had history of immunologic, connective tissue, or malignant diseases, and all of them were in good health for their age

as a rapid survey was taken for each one to exclude important diseases by detailed history and careful examination. The samples of blood were taken for measuring IgG, IgM, and IgA concentration.

Technique:

Immunoglobulin measurements were done by RID technique, using Biomaghreb RID plate product. The procedure consists of an immunoprecipitation in agarose between an antigen and its homologous antibody. It is performed by incorporating one of the two immune reactants (usually antibody) uniformly throughout a layer of agarose gel, and then introducing the other reactants (usually antigen) into well duly punched in the gel. Antigen diffuses radially out of the well into the surrounding gel-antibody mixture, and a visible ring of precipitation forms where the antigen and antibody reacted.

Statistical Analysis

Data were collected and analyzed by using SPSS "Statistical Package of Social Science". Chi-squire test was used to compare among frequency variables. P value of < 0.05 was regarded as significant.

Results

PART (I)

The demographic data for the patients with CLL and their control were shown in table1 and figure 1. Then the serum concentration of IgG, IgM, and IgA from each CLL patient and control were measured
and the results were shown in table 2 and figure 2.

Table 1. Showing the demographic data for the CLL patients and their control

CHARACTER		CLL	CONTROL
MEAN AGE (Years)		64.3	61.25
SEX	MALE	10	10
	FEMALE	6	6
STAGE	A	0	0
	B	8	0
	C	8	0

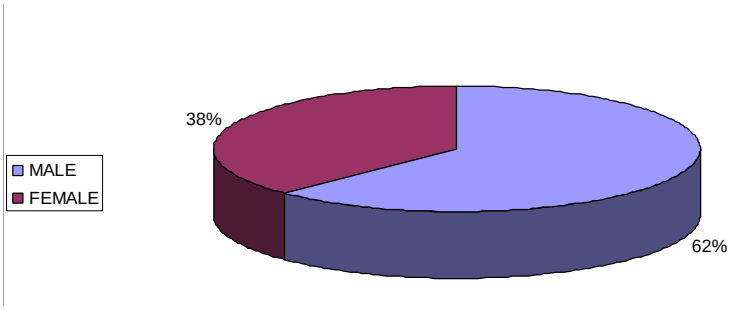


Fig 1. showing the sex distribution of CLL patients

Table 2. showing the Ig level among CLL patients and their control

PATIENT & CONTROL No.	CLL IgG mg/dl	CLL IgM mg/dl	CLL IgA mg/DL
1	510	62	15
2	405	362	37
3	402	25	97
4	635	47	113
5	750	21	95
6	1080	113	112
7	104	10	9
8	84	11	15
9	843	488	103
10	66	86	12
11	157	368	10
12	103	373	14
13	137	118	48
14	360	42	38
15	1340	639	102
16	502	51	11

P = 0.037
Pearson Chi – square = 160.173
dF = 130

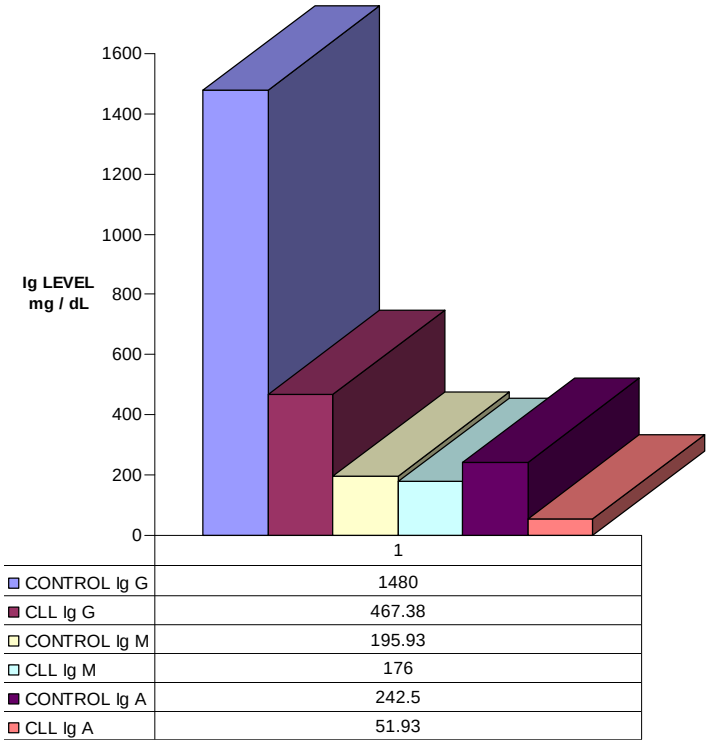


Fig 2. Showing a comparison on mean level of each IG in CLL patients & their control

From table (2), the IgG level was reduced in 11 patients (68.75%) normal in 5 patients (31.75%), and the IgM level was low in 7 patients (43.75%) normal in 7 patients (43.75%) and elevated in 2 patients (12.5%), while the IgA level was reduced in 10

patients (62.5%) and within the normal range in 6 patients (37.5%). These results were statistically significant (P. value < 0.05).

Then the mean levels of IgG, IgM, and IgA from CLL group were compared with that of control group and the result was shown in figure (2). In this figure the mean level of each Ig was low in comparison to that of control group.

PART (II)

The demographic data for the patients with NHL and their control were shown in table (3) and figure (3). Then the serum concentration of IgG, IgM, and IgA from each NHL patient were measured and the results were shown in table (4).

Table 3. Showing the demographic data for the NHL patients and their control

CHARACTRE		NHL	CONTROL
AGE MEAN (Years)		37.30	34.76
SEX	MALE	5	5
	FEMALE	8	8
STAGE	I	0	0
	II	3	0
	III	3	0
	IV	7	0

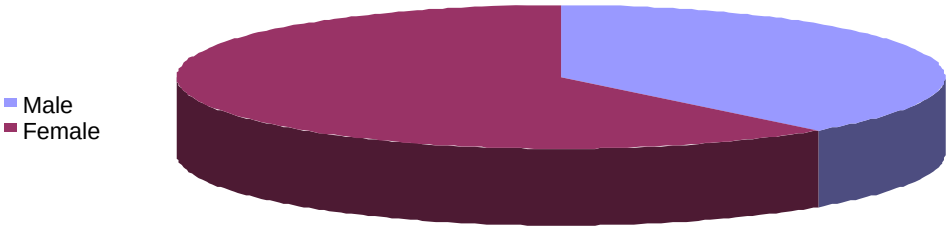


Fig 3. Showing sex distribution of NHL patients

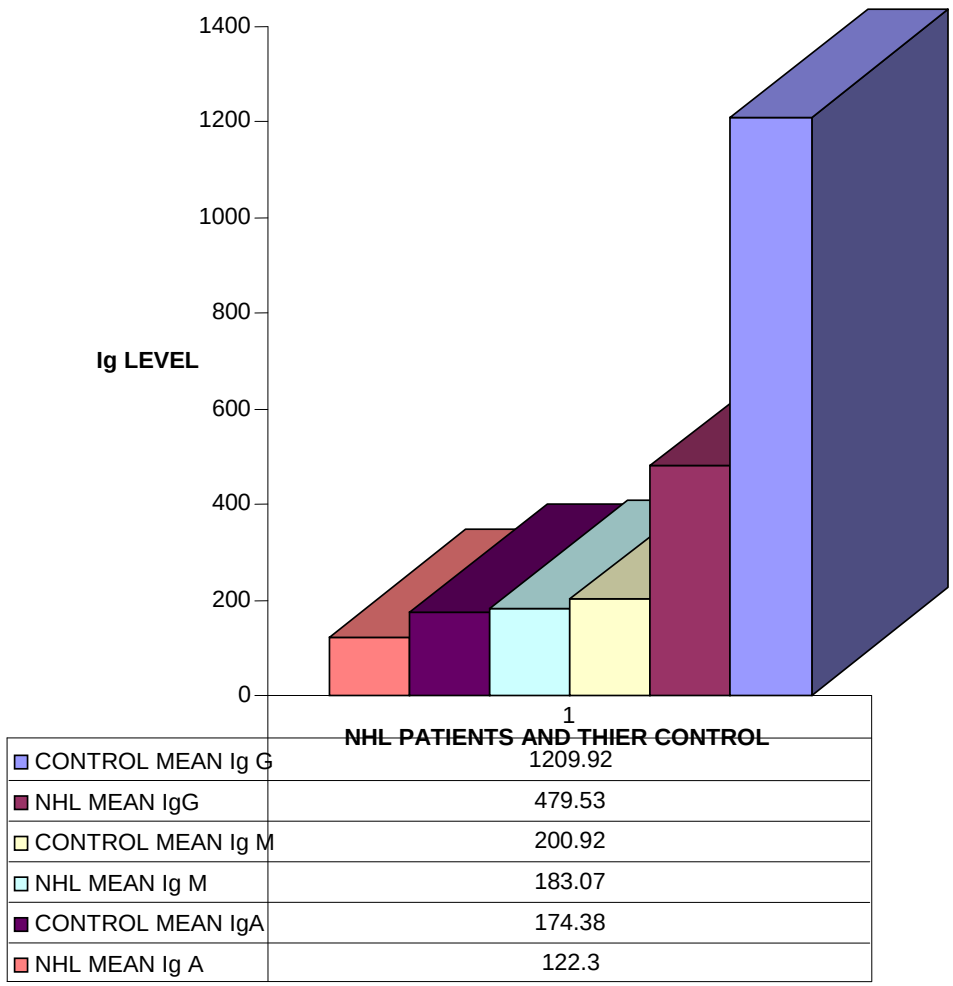
Table (4) showing Ig level among NHL patients and their control

PATIENT & CONTROL No.	NHL IgG mg/dl	NHL IgM mg/dl	NHL IgA mg/dl
1	325	213	84
2	316	164	350
3	119	293	223
4	387	76	29
5	140	42	31
6	839	332	367
7	463	302	68
8	268	98	54
9	624	187	18
10	736	297	76
11	1408	180	188
12	192	149	40
13	417	47	36

From table (3) IgG level were reduced in 9 patients (69.23%) normal level in 4 patients (30.77%), the level of IgM shown to be reduced in 2 patients (15.38%) and were normal in 11 patients (84.62%), while the level of IgA were reduced in 8 patients (61.53%) and normal level in 5 patients (38.47%) . These results were statistically significant (P. value < 0.05).

The mean levels of IgG, IgM, and IgA from NHL group were compared with that of control group and the result was shown in figure (4). This figure shows the low level of the mean Ig levels among NHL group in comparison to their control group.

FIGURE (4) COMPARING THE MEAN Ig LEVEL OF NHL PATIENTS AND THEIR CONTROL



CONTROL MEAN Ig G	1209.92
NHL MEAN IgG	479.53
CONTROL MEAN Ig M	200.92
NHL MEAN Ig M	183.07
CONTROL MEAN IgA	174.38
NHL MEAN Ig A	122.3

PART (III)

The demographic data for the patients with HD and their control were shown in table (5) and figure (5). Then the serum concentration of IgG, IgM, and IgA from each patient with HD were measured and the results are shown in table (6).

Table 5 Showing the demographic data for the HD patients and their control

CHARACTRE		HD	CONTROL
AGE MEAN (Years)		36.92	38.21
SEX	MALE	7	7
	FEMALE	7	7
STAGE	I	0	0
	II	6	0
	III	4	0
	IV	4	0

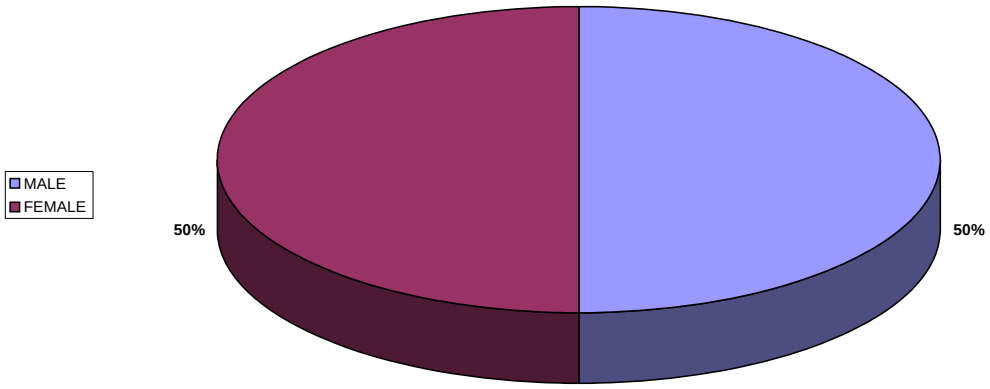


Fig 5. Showing sex distribution of HD patients

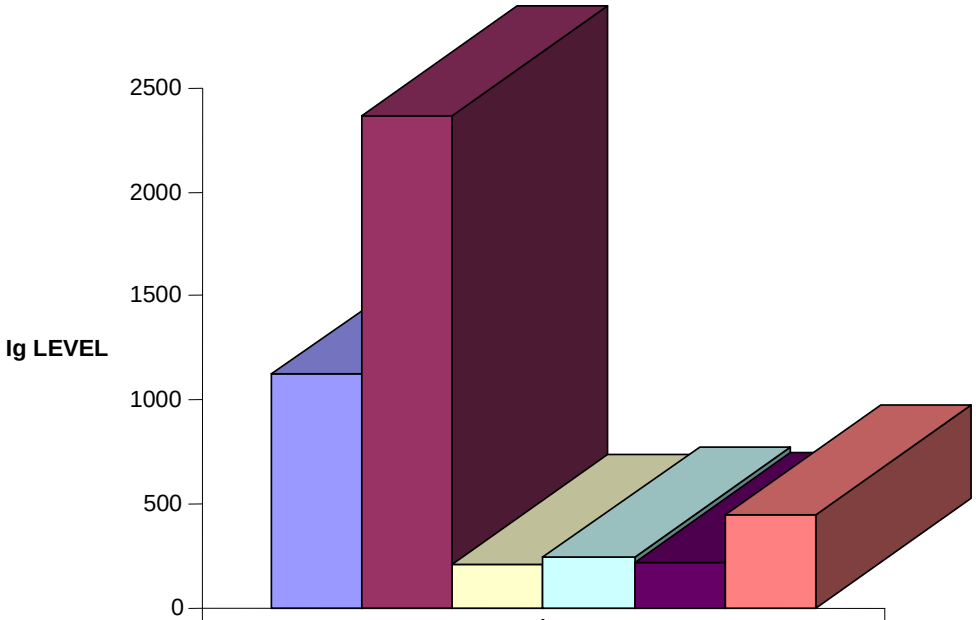
Table 6. Showing the demographic data for HD patients and their control

PATIENT & CONTROL No.	HD IgG mg/dl		HD IgM mg/dl		HD IgA mg/dl	
1	**1625**		**210**		**616**	
2	**2160**		**224**		**314**	
3	**1910**		**330**		**725**	
4	**3750**		**155**		**436**	
5	**1800**		**316**		**527**	
6	**1432**		**167**		**260**	
7	**2166**		**417**		**350**	
8	**4260**		**320**		**1236**	
9	**2310**		**280**		**457**	
10	**910**		**346**		**480**	
11	**3124**		**306**		**420**	
12	**1504**		**89**		**154**	
13	**2460**		**252**		**216**	
14	**3710**		**97**		**92**	

P =0.027
Pearson Chi – square = 12.59
dF = 5

From table (5) the IgG level were elevated in 10 patients (71.42%) and normal level in 4 patients (28.58%), and the IgM elevated in 1 patient (7.1%) and normal in 13 patients (92.9%), while the IgA level were elevated in 8 patients (57.14%) and were normal in 6 patients (42.86%) . These results were statistically significant (P. value < 0.05).
Thereafter the mean level of each Ig from HD group was compared with that of their control group, and the result shown in figure (6). This figure shows higher level for disease group in comparison to the control group.

FIGURE (6) COMPARING THE MEAN Ig LEVEL AMONG HD PATIENTS AND THEIR CONTROL



CONTROL MEAN Ig G	1122.85
HL Ig G MEAN Ig G	2367.07
CONTROL MEAN Ig M	208.57
HL MEAN Ig M	250.64
CONTROL MEAN Ig A	223.21
HL MEAN Ig A	448.78

PART (IV)
The mean value of each Ig from CLL, NHL, and HD were taken and a comparison among them were done and shown in table (6), and figure (16). Both shows elevated levels of mean Ig in HD group and reduced in CLL and NHL group.

Table 7. showing the mean level of each Ig among patients with CLL, NHL, and HD.

CHARACTER	CLL	NHL	HD
Ig G (mg/dl)	467.38	479.53	2367.07
Ig M (mg/dl)	176	183.07	250.64
Ig A (mg/dl)	51.93	120	223.21

P value = 0.037
Pearson Chi – square = 160.17
dF = 130

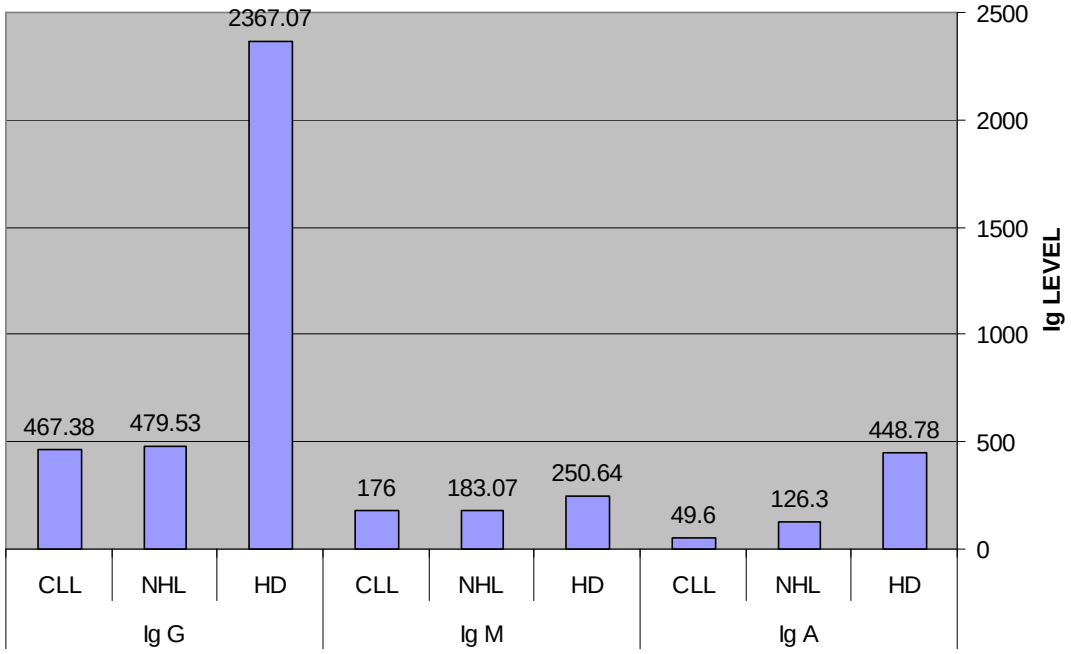


Fig 16. Comparing the level ov mean Ig among disease groups

Discussion

In this study, among patients with CLL the IgG level were reduced in 11 patients (68%) of 16, normal level were seen in 5 patients (32%). Other studies showed that the hypo-IgG had been reported in 19% of 47 CLL patients "Videbaek A ",[23] 36% of 50 CLL patients "Jim",[23] and 68% of 40 CLL patients " Hudson and Wilson ".[23]

While IgM in the present study were reduced in 7 CLL patients (44%) normal in 7 patients (44%) and increased in 2 patients (12%). Other studies showed depressed IgM levels were seen in 63% of 52 CLL patients " Robert Foa et al ".[24] However " Razuddin S et al " [25] detected hyper IgM in 1 of 2 T-Cell CLL, while " Rundles et al " [23] and " Teitelbaum et al " [23] reported an abnormally localized bands similar to those found in myelomatosis. The IgA level is reduced in 10 patients (62%) and within the normal range in 6 patients (38%). Other studies by "Robert Foa et al" [24] reported depressed IgA level in 75% of 52 CLL patients.

In this study, among patients with NHL the IgG level was reduced in 9 patients (69%) of 13, normal level was seen in 4 patients (31%). Other studies demonstrated that the serum concentration of IgG was reduced among patients with NHL.[26] In the present study there is reduction in the level of IgM in

2 patients (15%), normal in 11 patients (85%), and no elevation detected . Other studies performed by " Stein H et al " [27] and "Lis Ellison-Loschmann et al" [28] detect either normal or reduced level of IgM among NHL patients, but "Solanki RL et al " [29] detected high IgM level in 3 of 17 NHL patients. Also in this study the level of IgA were reduced In 8 patients (61%), normal in 5 patients (39%), and no elevated level detected among NHL group. Other studies also demonstrate significant reduction in the level of IgA among NHL patients, [27] and more sever with disease dissemination. [28]

In the present study, among patients with HD the level of IgG was elevated in 10 patients (71%) of 14, normal in 4 patients (29%), and no reduction in it's level were detected. Other studies performed by "Loginskii VE, Peretiatko DS", [30] and "Dienstbier Z et al" [31] showed an elevation in the level of IgG. In this study the level of IgM was elevated in 1 patient (7%), normal in 13 patients (93%), and no reduction in it's level seen. Other study performed by "Alsabti Ea, Shaheen A" [18] showed normal IgM level in active HD, but lowered with achieving remission, while other study by "Stiedie C et al" [32] showed decline of IgM level with disease dissemination. The level of IgA in the present study is elevated in 8 patients (57%), normal in 6 patients (43%), and no reduction in IgA level detected. Other studies by " Dienstbier Z et al ", [31] and "Alsabti Ea, Shaheen A" [18] showed a significant elevation in the level of IgA in untreated HD patients, haw ever a decline in the level of IgA demonstrated by "Stiedie C et al" [32] with disease dissemination.

In regard to the table (7) when comparing the mean level of IgG, IgM, and IgA among different disease groups, we found a lowest level of means among CLL group followed by NHL group then HD group , which mean CLL<NHL<HD.

Conclusion

1- In patients with CLL, there is a substantial reduction in the level of IgG, IgM, and IgA.

2- In patients with NHL, there is a marked reduction in the level of IgG, and IgA, with mild reduction in the level of IgM.

3- In patients with HD there is marked increase in the level of IgG, IgA, and mild increase in the level of IgM

4- Alteration in the level of IgG, IgM, and IgA alone is insufficient to explain the increasing risk of infections among these hematological malignancies.

Recommendations

1- Larger number of patients with CLL, NHL, and HD will provide us with better insight about immunoglobulin derangement.

2- Extension of the study to include patients with other hematologic malignancies such as multiple myeloma, and acute leukemia also helpful.

3- Measurement of Ig G subset G2 and G3 will give an important knowledge about the immunological status of each disease group.

Refrences

1. Braunwold et al. Harrison's Principles of Internal Medicine. Sixteenth edition, Chapter XIII, page 1921.
2. David M. Lange Hypogammaglobulinaemia. Cleveland clinic journal. Volume 23, number 2, February 2006, 135-144.
3. Goldman Ausiello et al. Cecil Textbook of Medicine. Twenty second edition, Chapter 298, page 1743.
4. Aitoniemi J et al. opsonising immunoglobulins and mannan-binding lectin in chronic lymphocytic leukemia. Leuk Lymphoma J 1999; 34:381-385.
5. Perri RT, Oken MM, Kay NE. Enhanced T cell suppression is directed toward sensitive circulating B cells in multiple myeloma J Lab Clin Med 1982; 99:512-519.
6. Castellano G et al. Malignant lymphoma of jejunum with common variable

hypogammaglobulinaemia and diffuse nodular hyperplasia of the small intestine. A case study and literature review. J Clin Gastroenterology 1992; 15:128-135.
7. Braunwold et al. Harrison's Principles of Internal Medicine. Sixteenth edition, Part V, page 641.
8. Vincent T. De vita et al. Cancer Principles and practice of Oncology. Seventh edition, part III, Chapter 43, page 3475.
9. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N Engl J Med. 1995; 333: 1052-1057.
10. Dighiero G. Hypogammaglobulinaemia and disordered immunity in CLL. In: Cheson BD, ed. chronic lymphocytic leukemia: Scientific Advances and Clinical Developments. New York, NY: Marcel Dekker; 1993: 147-166.
11. Chapel HM. Hypogammaglobulinaemia and chronic lymphocytic leukemia. In: Gale RP, Rai KR, eds. Chronic Lymphocytic Leukemia: Recent Progress, Future Direction. New York, NY: Liss; 1987: 383-389.
12. Miller DG, Budinger JM, Karnofsky DA. A clinical and pathological study of resistance to infection in chronic lymphocytic leukemia. Cancer. 1962; 15:307-329.
13. Rai KR, Montserrat E. Prognostic factors in chronic lymphocytic leukemia. Semin Haematol. 1987; 24:252-256.
14. Griffiths H et al. Predictors of infection in chronic lymphocytic leukemia (CLL). Clin Exp Immunology. 1992; 89:374-377.
15. Foa R. Pathogenesis of the immunodeficiency in chronic lymphocytic leukemia. In: Cheson BD, ed.Chronic Lymphocytic Leukemia: Scientific Advances and Clinical Development. New York, NY: Marcel Dekker; 1993: 147-166.
16. Miller DG, Karnofsky DA. Immunologic factors and resistance to infection in chronic lymphocytic leukemia. Am J Med. 1961; 31:748-757.
17. Hagop M et al. MD Anderson Manual of Medical Oncology. Sixth edition. Part II, Chapter 7, page 258.
18. Alsabti Ea, Shaheen A. The prognostic value of serum immunoglobulin levels in Hodgkin's disease. Neoplasm. 1979; 26(3): 329-333.
19. Anuradha S, Gopalakrishna V. Role of immunoglobulin estimation in lymphomas. Indian J Pathol Microbiol. 1989 Oct; 32(4): 297-300.
20. Romagnani S et al. Abnormalities of in vitro immunoglobulin synthesis by peripheral blood lymphocytes from untreated patients with Hodgkin's disease. J Clin Invest. 1983 May; 71(5): 1375-82.
21. National cancer institute sponsored study of classification of NHL. Cancer. 1982; 29: 2112-2135.
22. Hansen DA, et al. Identification of monoclonal immunoglobulins and quantitative immunoglobulin abnormalities in hairy cell leukemia and chronic lymphocytic leukemia. Am J Clin Pathol 1994; 102: 580-5.
23. G. Hamilton Fairley. Hypogammaglobulinaemia in chronic lymphocytic leukemia. Br. Med J. 1961 Oct; 7: 920-924.
24. Robert Foa et al. Clinical staging and immunological findings in chronic lymphocytic leukemia. Cancer. 1979 Aug; 44:383-387.
25. Raziuddin S, Sheiikha A, Teklu B. Humoral immunodeficiency in T-cell chronic lymphocytic leukemia. An immunologic assessment. Cancer. 1991 May 15; 67(10): 2518-22.
26. Gajl-Peczalska KJ et al. B lymphocytes in untreated patients with malignant lymphoma and Hodgkin's disease. J Clin Invest. 1973 Dec; 52(12):3064073.
27. Stein H et al. Demonstration of immunoglobulin production by tumor cells in non-Hodgkin's and Hodgkin's malignant lymphomas and its significance for their classification. Recent Result Cancer Res. 1978; 64: 158-75.
28. Ellison-Loschmann L et al. Immunoglobulin E levels and risk of lymphoma in a case- control study in Spain. Cancer Epidemiology Biomarkers Prev. 2007 Jul; 16(7): 1492-98.
29. Solanki RL, Anand VK, Arora HL. Serum immunoglobulins in leukemia and malignant lymphoma. J Indian Med Assoc. 1990 Nov; 88(11): 305-7.
30. Loginskii VE, Peretiatko DS. Blood serum immunoglobulin in lymphogranulomatosis and other malignant lymphomas. Vopr Onkol. 1979; 25(11): 7-11.
31. Dienstbier Z et al. Immunoglobulin levels in patients with Hodgkin's disease. Neoplasm. 1978;25(6): 723-31.
32. Steidle C et al. Immunoglobulin G, A, M, and E in lymphogranulomatosis. MMW Munch Med Wochenschr. 1976 Apr 16; 118(16): 50