

## IMMUNOGLOBULIN LEVELS IN MALIGNANT LYMPHOMA

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### ABSTRACT

Immunoglobulin levels (IgA, IgG and IgM) were examined in 41 cases of malignant lymphoma, consisting of 14 cases of Hodgkin's disease, 23 cases of reticulum cell sarcoma, and 4 cases of lymphosarcoma. Data were summarized as follows.

- 1) Levels of the 3 classes of immunoglobulins tend to divert from the normal with aggravation of the clinical course. An improvement of the clinical course, on the other hand, tends to bring the immunoglobulin values to the normal range.
- 2) Low level of IgA in Hodgkin's disease and sarcoma group may be closely related to improvement in the lymphatic tissues, rather than due to treatment.
- 3) Statistically correlated IgA or IgG levels to peripheral lymphocyte counts lower than 1,500/cmm were also observed.

### INTRODUCTION

In the course of the recent advances in immunology, the characterizations of humoral antibody and related immunoglobulins have been explored extensively. Malignant lymphoma, as a malignant disorder of lympho-reticular tissues, has been found to show various immunological aberrations, including immunoglobulin abnormalities<sup>1-8)</sup>.

Biosynthesized immunoglobulins from their producing cells are distributed in metabolic pools and are gradually catabolized. There are two methods of quantitative estimation of immunoglobulins in malignant lymphoma i.e., either by those in the metabolic pools or by those in the serum. The former involves isotope-labelling and intravenous administration of the isolated immunoglobulins, followed by tracing of the clearance curve<sup>9,10)</sup>. Because of the clinical difficulties of this method, we investigated the concentrations of serum immunoglobulins in Hodgkin's disease and sarcoma group of lympho-reticular malignancies.

### MATERIALS AND METHODS

Fourteen cases of Hodgkin's disease, 23 of reticulum cell sarcoma, and 4 of lymphosarcoma were investigated. All cases were diagnosed histologically and hematologically. All cases of Hodgkin's disease were of the granuloma type, and

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excluded cases suggestive of reactive reticulosis. Out of the total of 41 cases, 20 cases died and 15 were autopsied.

Reticulum cell sarcoma and lymphosarcoma were tentatively summarized as "sarcoma group", because there were several cases histologically difficult to differentiate from each other, and clinically almost similar therapy was instituted to both. Thus in this study, cases were divided into two diagnostic categories: (1) Hodgkin's disease; 14 cases (18 to 72 year-old, male 12, female 2). (2) sarcoma group; 27 cases (3 to 74 year-old, male 22, female 5).

Concentrations of immunoglobulins in human serum were measured by Mancini's method<sup>11</sup>. Plates for quantitations were made by using 1% special agar-Noble (Difco Inc. Detroit) with veronal buffer (ionic strength 0.025, pH 8.6) containing specific anti  $\gamma$ -chain, anti  $\alpha$ -chain, and anti  $\mu$ -chain antisera, respectively. All antisera were made in the laboratory by immunizing rabbits with fractionated immunoglobulins and by absorptions with both kappa and lambda typed Bence Jones proteins.

#### RESULTS

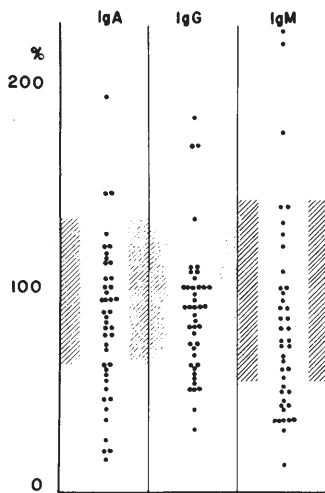


Fig. 1. Immunoglobulin Levels in Malignant Lymphoma.

Figure 1 shows immunoglobulin levels of all the cases. Shaded areas in each column represent the normal values. Levels of immunoglobulin of each case are expressed as percentages of the mean value of normal, and show some with abnormal levels, either high or low. There were no cases with monoclonal immunoglobulins in this study. In the figure, 15 cases were already under treatment at the time of study.

Figure 2 shows a comparison of 3 classes of immunoglobulins "before and after aggravation" or "before and after improvement" in some cases with clinical follow-up studies.

Indices representing clinical activities in lymphoma consisted of enlargement of lymph nodes or spleen and extensive involvement of lymph nodes. Aggravation of the clinical course seems to be correlated with a tendency to divert from the normal values. Improvement of the clinical course, on the other hand, also seems to show a tendency to improve the immunoglobulin values to the normal range.

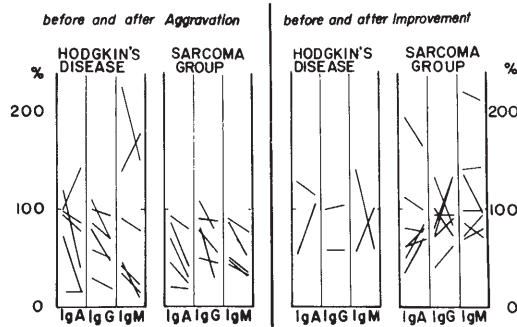


Fig. 2. Comparison of 3 classes of Immunoglobulins.

Figure 3 shows the clinical course of 4 cases of the sarcoma group. The distribution of lymphadenopathy is classified as stage I, II and III according to Peters' classification. It must be emphasized that the classification of stage I or II has to be decided with the result of lymphangiography. In all cases in Figure 3, lymphangiographies were performed. The numbers in the panel of splenomegaly represent the enlargement of the spleens (3 means 3 figures' breadth below the costal margin). In cases A. I. and H. M., the levels of immunoglobulin tended to be in the normal range with improvement of the clinical course. In case K. I., the IgA level was low at the onset, with no improvement until the patient's death 9 months later. In case J. Y., immunoglobulins became higher than normal, with aggravation of the clinical course. It was noteworthy that, among 3 classes of immunoglobulin, IgA seemed to be more proportionally correlated to clinical activity i.e. stage or splenomegaly in these 4 cases.

Figure 4 shows the relationship of clinical stages and immunoglobulins. As

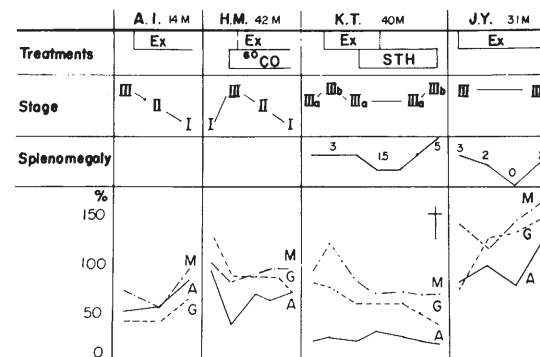


Fig. 3. Clinical Stages and Immunoglobulins (I).

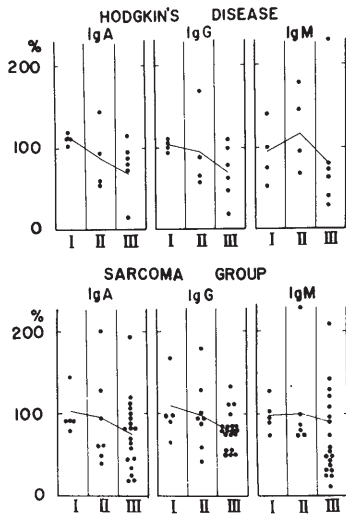


Fig. 4.

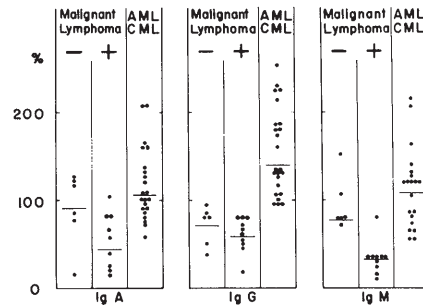


Fig. 5.

Fig. 4. Clinical Stages and Immunoglobulins (I).

Fig. 5. Immunoglobulin Levels in Malignant Lymphoma with or without Bone Marrow Infiltration, as Compared with Those in Myeloid Leukemias.

the stage progressed, levels of both IgA and IgG decreased. There seemed to be no such relationship in the IgM level.

Figure 5 shows immunoglobulin levels with or without bone marrow infiltration, as compared with those in myeloid leukemia. Fifteen autopsied cases were divided into 2 groups, i.e., one with bone marrow infiltration (expressed as plus) and another without infiltration (as minus) according to the presence or absence of marrow infiltration by malignant cells. Immunoglobulin levels of 22 aggravated cases with myeloid leukemia, either acute or chronic, were compared as a control group of marrow infiltration. Cases with marrow infiltration appeared to have lower levels of immunoglobulins than cases without marrow infiltration. However, levels with myeloid leukemia ranged rather higher than those of lymphoma, demonstrating that the marrow infiltration *per se* is not closely related to the low levels of immunoglobulins.

Figure 6 shows the relationship between absolute lymphocyte counts in the peripheral blood and serum immunoglobulins. The lowest panel of the figure represents data from a control group consisting of 27 cases of non-reticular neoplasia with peripheral lymphopenia due to disease processes, chemotherapies or radiation-therapies.

Application of the "t" test to IgA and IgG levels in Hodgkin's disease yielded coefficients of correlation of 0.69 ( $p < 0.05$ ) and 0.73 ( $p < 0.05$ ) respectively, and showed significant correlation with peripheral lymphocyte counts. There was no correlation in the sarcoma and control groups.

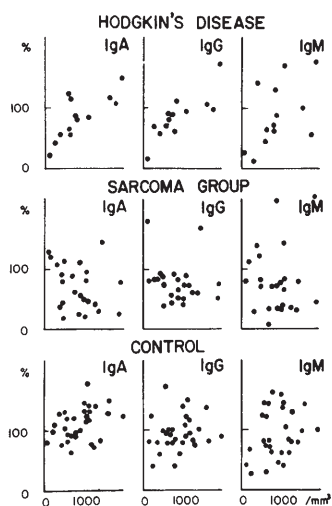


Fig. 6.

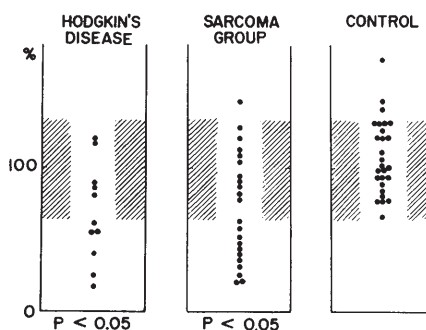


Fig. 7.

Fig. 6. Absolute Lymphocyte Counts and Immunoglobulins.

Fig. 7. IgA Levels in Cases with Lymphopenia (< 1,500/cmm).

Another finding noted in Figure 6 was the low level of IgA in the lymphoma groups, but not in the control group. Therefore, as shown in Figure 7, IgA levels were compared among groups of cases with peripheral lymphocyte counts of less than 1,500/cmm, demonstrating that IgA levels in Hodgkin's and sarcoma groups were significantly lower ( $p < 0.05$ ).

DISCUSSIONS

The concentrations of serum immunoglobulins are maintained at certain levels by the balance between synthesis and catabolism. However, pathological disorders and possibly subsequent treatments can influence the balance of metabolic pools, occasionally causing the immunoglobulin concentrations to be out of the normal range.

In this paper, we attempted to elucidate one of the clinico-pathological features of lymphoma by measurement of serum immunoglobulins.

Since lymphoma is a disorder of lymphatic tissues, the indices representing clinical activities in lymphoma were studied by the following:

- 1) Enlargement of lymph nodes of spleen (Fig. 2 & 3).
- 2) Clinical stages i.e., distributions of involved lymphatic tissues (Fig. 4).
- 3) Involvement of bone marrow (Fig. 5).
- 4) Peripheral lymphocyte counts, as a result of systemic involvements of lymphatic tissues (Fig. 6 & 7).

From figures 2 to 7, several interesting points were noted. First, there were

cases which had low IgA levels from the onset of the diseases (see Fig. 3, K. T. and A. I.). Secondly, immunoglobulin levels tend to increase i.e., recover to the normal ranges in the course of clinical improvement by treatment. Thirdly, among cases with peripheral lymphocyte counts of lower than 1,500/cmm, IgA levels are lower in the lymphoma group than in the non-lymphoreticular malignancies. Thus, it seemed to be that the low level of IgA in Hodgkin's disease and sarcoma group might be closely related to the involvement of lymphatic tissues, rather than the result of treatment.

It is also interesting that a correlation exists between IgA or IgG levels and peripheral lymphocyte counts (Fig. 6). However, more detailed analyses regarding the T cell-B cell subpopulations of the peripheral lymphocytes should be carried out. In various malignancies of the lymphoreticular system there reported many abnormalities in the immunoglobulin levels. Among these abnormalities, there was no case with monoclonal immunoglobulin in this study, although these have been reported. Hypoimmunoglobulinemia has also been noted in various lymphomas, such as lymphosarcoma or chronic lymphatic leukemia. Regarding reticulum cell sarcoma, Miller pointed out that IgG and IgM are lower than IgA levels, as in lymphosarcome.

We have already reported on low levels of serum immunoglobulins in reticulum cell sarcoma as contrasted with the high levels in reticulosis<sup>5</sup>. Hodgkin's disease has been frequently reported as being associated with hyperimmunoglobulinemia<sup>1-3</sup>. However, as in our previous paper<sup>5</sup> or the paper by Poe et al.<sup>4</sup>, there were certain cases with hypoimmunoglobulinemia. In general, in consideration of the clinical activities of diseases, it is important to analyse the immunoglobulin values as one of the clinico-pathological features.

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