Med. J. Kagoshima Univ., Vol. 47, Suppl. 2. 57~59, November, 1995

Inveted Paper

Characteristics of Extranodal Lymphomas in Japan

Koji NANBA

Department of Health Science, Faculty of Integrated Art & Science
Hiroshima University, Hiroshima, Japan

1. Limitation of epidemiological study and value of geopathologic study in hematology :

It was known for the epidemilologists that the incidence of various major diseases of hematopoietic malignancies significantly varied among different ethnic groups. For example, the incidence rates of lymphatic leukemia, malignant lymphoma and multiple myeloma were very low in Japan compared to other countries[1]. Epidemiologists had to use the secondary information for their study, however, since Cancer Registry Data of some was their main source.

The author has been working on this problem from the viewpoint of histopathologist before the introduction of the Working Formulation. By reviewing the registered tissue slide of malignant lymphomas in Hiroshima Prefecture, the author was able to calculate the annual incidence rate of malignant lymphomas in Japan was 5.1 per 100, 000 population, less than a half of that in U. S. A. that is 12.1.

When viewed from histopathologic subtypes, follicular lymphomas and Hodgkin's disease were very low in contrast to American data.

As far the primary site of lymphomas, it was well known that about 80% cases belong to nodal lymphomas in American and European countries. However, in Japan, only 50% of lymphomas were nodal in origin. In other words, nodal/extranodal ratio of lymphoma was 1:1 in Japan in contrast to 4:1 in U. S. A. Among the nodal lymphomas, Hodgkin's disease and follicular lymphomas were very popular in western countries.

Address for Correspondence: Koji NANBA,
Department of Health Science, Faculty of Integratend Arts & Science, Hiroshima University, Kagami-yama 1-7-1, Higashi-Hiroshima 724, Japan

The author had already delivered a lecture titled 'Why B-cell lymphomas are rare in Asia?' at the 5th International lymphoma Conference held in Lugano, Switzerland, 1993, June.
This work became possible owing to the Working Formulation.

2. Why T-cell lymphomas were erroneously reported to be frequent in Asia?

At the time when the author first reported these geopathologic differences in the Seattle meeting[2], he was not aware of the excess of T-cell lymphomas in Japan. Later Dr. Tajima[3] of Aichi Cancer Center collected the cases for which T and B-phenotyped data were available nationwidely, and reported that ratio of T and B-cell lymphomas was widely differed in different areas of Japan with Kyushu island having the highest incidence of T-cell lymphoma (about 75%). Even in other areas, about 50% of lymphomas were of T-cell and B-cell lymphoma was less than 25%. Similar reports were published thereafter, and by these reports it was generally agreed upon that not only in Japan but also in Asia general T-cell lymphomas were more frequent than B-cell lymphomas in contrast to the Western lymphomas in which B-cell lymphomas are more common.

Since the introduction of immunohistochemistry based on paraffin sections, by which detailed immunophenotyping of surgically excised extranodal lymphomas became possible, the author had been in questioning if B-cell lymphomas were really rare in Japan. Because most of the extranodal lymphomas the author had examined were B-cell lymphomas and by knowing that 50% of Japanese lymphomas were of extranodal in origin, it seemed worthy of doubt that we still had excess of T-cell lymphomas in Japan, even if all lymphomas were combined.

Just before the Lugano confevence, the author had studied consecutive 100 cases of biopsied or surgically removed lymphomas regardless of the site of origin. These were all immunophenotyped with a battery of monoclonal antibodies specific to several differentiation antigens of T, B and H cells.

The result clearly demonstrated that, when all sites are combined, 75% was B-cell, 20% T cell and 5% were unclassifiable with the method used. Surprisingly these data were very similar to the results reported for Western lymphomas.

If it is so, how we can explain the previous reports stated the excess of T-cell lymphomas in Japan and in other areas of eastern Asia? The author's explanations

were as followings.

First, in early 80th immunophenotyping was mostly done using free cells obtained through the biopsy, therefore most cases studied were peripheral blood or lymph nodes. This was a bias in selecting the cases and the free cell method tended to pick up more T cells than sticky B-cells.

The second reason was that a large number of HTLV-1-positive cases were included in the nationwide survey. Even though HTLV-1-positive ATLL occurs in certain populations in unique geographic distributions, the incidence rate among the virus-infected people was so high and the detection rate due to heightened medical curiosity was so high also at that time, many cases were reported to the survey.

Thus, national data in Japan was heavily biased as if to have excess of T-cell lymphomas. If these biases were removed, local data even at that time did not show much difference from American data, e.g., Hiroshima data in which ATLL was not popular and phenotyping was performed mostly by pathologists was one of such example.

However, once "many Ts in Asia" theory was widely propagated and believed by many scientists of the world, it is not easy to correct the misunderstandings.

3. Japanese lymphomas are characterized by the low incidence of nodal lymphomas and relatively high ratio of extranodal lymphomas:

Overall low incidence rate of Iymphomas in Japan was now a well-established fact. Moreover, this low rate seems to be primarily determined by low incidence of nodal lymphomas not by the low incidence of extranodal ones. Was this related to either environmental factors or genetic factors, or both?

One of the best way to investigate this problem was to study the lymphoma among Japanese immigrants to U.S.A. Hawaii is one of such place, and through the Hawaii Cancer Registry and Dr. Yanagihara at Kuwakini Hospital, the author was able to review the tissue slides of lymphoma cases of Japanese American[4].

Interestingly, the incidence rate was slightly increased compared to Japanese in Japan, and this was ascribed to increase of nodal lymphoma (mostly follicular lymphomas). As for the primary site, nodal was 52% and extranodal was 48%. Eighty percent of the cases were diffuse non-Hodgkin's lymphomas and Hodgkin's disease was found only in 4%. This data strongly suggested that although environmental factors such as food, clothing or aging might influence the incidence of certain types of lymphomas, major factors were genetically connected.

If it is so, artificially induced immuno-suppressed state should influence the incidence rate of secondary lymphomas among different ethnic groups. Only comparable data were those of renal transplantation that is the only organ transplantation widely practiced in Japan. To prevent graft rejection, azathiopurine was widely used as the immunosuppressant in the past in both countries. It turned out that the incidence of Iymphomas among American lymphomas were high grade immunoblastic or Burkitt-like lymphomas, according to the case report and the author's experience, so there seemed to be no difference in the type of lymphoma complicating the renal transplantation or artificially immuno-suppressed state.

4. Structure of extranodal lymphomas as viewed from geopathological points:

As described above, the overall incidence rate of extranodal lymphomas among Japanese is similar to the data reported for other ethnic groups. This does not, however, mean that the incidence rates at all extranodal sites are similar. In order to investigate this problem, we have to use tissue registry data of some kinds, since the data from single institute might be heavily biased regarding the case distribution.

There are several cancer centers in Japan. Because of poor development of medical oncology divisions, some institutes do not treat ophthalmologic and/or dermatologic cases at all. On the same reason, so-called national data that is compiled of the reports from major university hospitals (mostly from the departments of internal medicine) and cancer centers is also biased.

Table 1 demonstrates three representative data from either national survey or cancer registry system. If it is permitted to regard American white and Norwegian belong to the same ethnic group, we will be much surprised to know that how Japanese data did not change much. Perhaps, only difference noted in the table may be the relatively high ratio of thyroid lymphomas in Japan. This point will be discussed later.

These data, however, do not necessarily mean that variations within the same system do not exist. For example, the digestive tract that covers, in this table, from the esophagus to the rectum is such a long canal that differences of the lymphoma ratio between the upper and lower digestive tracts might have been rounded up.

In order to scrutinize these problems, we have to use the data collected for specific system or organs with reasonable denominators such as all the gastrointestinal (GI) tract malignancy or all the gastric malignancy, etc.

Actually as regard to GI-lymphomas gastric primary comprises 58% among Japanese in contrast to 33% in American whites, among whom the small intestinal lymphoma (46%) comes to the first. However, when gastric lymphoma was viewed within the spectrum of the entire gastric malignancy, relative incidence rates do not reveal significant differences between two ethnic groups, simply because the incidence of gastric carcinoma is much higher in Japan than in U.S.A.

Recently, it has been discussed much that Helicobacter pyrolii infection might have some etiologic relationship with chronic gastritis and gastric malignancies. Etiologic role of this bacteria was also discussed with

Table 1, Frequency (%) of extranodal lymphomas in organs in each people and contry

Site	Whites in U.S.A.	Norwegian	Hiroshima	Tokyo Univ Hosp.	Aichi Cancer Hosp.	Korea	China
GI tract	38.0	22.8	35.5	20.0	33.0	24.4	28.7
Waldeyer	14.0	24.6	19.5	39.0	37.0	28.7	20.8
Nose/Oral cavity	2.0	10.1	7.6	11.0	7.0	23.2	
Skin/Soft tissue	13.0	13.9	13.7	15.0	5.0	11.0	15.7
Thyroid	2.0	0.6	5.0	4.0	4.0	-	
Mediastinum	2.0	5.3	-	-	4.0	-	
Orbita	2.0	-	3.0	5.0	1.0	-	
C.N.S	1.6	1.5	3.8	1.0	0.3	1.8	
Breast	2.0	2.4	1.5	-	2.0	1.2	
Bone	5.0	3.8	1.9	1.0	2.0	0.6	
Others	18.0	20.4	8.4	4.0	4.0	9.1	47.6
No.of cases	1.467	379	262	440	322	164	731

regard to lymphomagenesis in the stomach.

These findings are of course valuable, but should be interpreted carefully together with the pre-existing clinicopathologic as well as geopathologic data.

5. Lymphoid cell subpopulation and pathogenesis of the extranodal lymphomas:

Pathologists as well as clinicians have been long aware of the differences in clinical behavior of the extranodal lymphomas arising in different primary sites. For example, lymphomas of the GI-tract seldom involving the skin and vice versa. These specific behaviors are now going to be interpreted due to the differences in the adhesion receptors expressed on the surface of lymphoma cells with different homing patterns.

Modern immunology is demonstrating that there are major lymphocyte subpopulations' compartment in the body. They are lymph node, mucosal system (MALT), skin, spleen and bone marrow at least for the moment.

Since immunologic system works based on the specific molecule to molecule interaction, it is only natural, with the advent of our knowledge, that the fact will be made clear that lymphocytes residing in different sites are equipped with different receptors for specific homing. No one would be surprised to know that orbital lymphocytes differed in the homing receptor from those of intestinal lymphocytes even though they belonged to the so-called MALT system in the present-day terminology.

Traditionally lymphomas have been classified and diagnosed with the combination of two parameters: i.e. cytohistology and primary site. This system of nomenclature of tumors were widely used in other tumors except lymphomas. Thus, menigioma means, scientifically, tumor of meningio-epithelial cells regardless of its origin.

Suppose, if this axiom was abandoned for lymphomas, and they started to be classified according to their homing receptors, which the author thinks not-easy-a work thinking about the availability of the techniques and the current stage of the development of immunology, it will not only cost tremendous amonut of money and time for the pathologists responsible for the diagnosis but it will contribute little to the current therapeutics, as they were not prepared for such versity of treatment modalities.

Based on these facts, the author would like to propose to keep the procedure to classify the lymphomas whether nodal and extranodal in origin until the other site classifications were in the future proved to be of great advantage.

Key words : Extranodal lymphoma, epidemiology, geopathology, immunology

References

1) Segi.M., Tominaga S., Aoki K. and Fujimoto I. (eds.) Cancer motality and morbidity statistics-:Japan and world. GANN Monogr. Cancer Res. 26. Japan Sci. Soc. Press, Tokyo, 1981
2) Kadin M., Berard C.W., Nanba K. and Wakasa H. Lymphoproliferative diseases in Japan and western countries: Proceedings of the United States-Japan Seminar, September 6 and 7, 1982 in Seattle, Washington. Hum Pathol. 1983;14:745-72.
3) Tajima K., Tominaga S., Kuroishi T., Shimizu H., and Suchi T. Geographical features and epidemiological approach to endemic T-cell leukemia/lymphoma in Japan. Jpn. J. Clin. Oncol. 9 (Suppl.): 1979;495-504.
4) Nanba K. and Wakasa H. Geographical pathology of malignant lymphoma. in 18b, lymph nodes, spleen reticuloendothelial system and thymus, Current Encyclopedia of Pathology, Nakayama-Shoten, 1987, pp.153-70. (in Japanese)