Virchows Arch. A Path. Anat. and Histol. 388, 213–219 (1980)

Virchows Archiv A

Malignant Lymphoma Reference Centre – Hungary, 1978

G. Kelényi and Maria Várbiró
Department of Pathology, Medical University of Pécs, Hungary

Summary. In the first year of its existence the Malignant Lymphoma Reference Centre in Hungary diagnosed 383 new cases, which may represent about half the cases occurring in this country. The distribution of the cases was as follows: Hodgkin's disease 69 (18%); non-Hodgkin's malignant lymphoma 290 (75.7%), unclassifiable 12 (3.2%), hairy cell leukaemia 4 (1%), Lennert's lymphoma 8 cases (2.1%). Some features of the distribution of malignant lymphomas are discussed.

Key words: Hodgkin's disease – non-Hodkin's malignant lymphoma – Tumor registry – Frequency of malignant lymphomas.

Introduction

The pathohistological diagnosis of malignant lymphomas (ML) and their differential diagnosis from reactive conditions and metastatic tumours is one of the most difficult tasks of histopathology. Pathohistological diagnosis of a ML,

In 1978 the Malignant Lymphoma Reference Centre received cases from the following Departments of Pathology of universities and county, district and city hospitals: The Hospitals of Ajka, Baja, Békéscsaba, Bajcsy-Zsilinszky Hospital of Budapest, Central Hospital of the Hungarian People's Army, János Hospital, Postgraduate Medical School, Péterfy Street Hospital, Budapest, 1st and 2nd Departments of Pathology, Semmelweis Medical University of Budapest, Weil Hospital, Budapest, Medical University of Debrecen, Hospitals of Debrecen, Dombóvár, Dunaujváros, Eger, Esztergom, Györ, Gyula, Hatvan, Hódmezövásárhely, Kaposvár, Karcag, Kazincbarcika, Kecskemét, Keszthely, Kiskunhalas, Marcali, City and County Hospitals of Miskolc, Hospitals of Mosonmagyaróvár, Nagyatád, Nagykanizsa, Orosháza, Ózd, Pápa, Salgótarján, Siófok, Medical University of Szeged, Hospitals of Székesfehérvár, Szekszárd, Szentes, Szombathely, Tatabánya, Veszprém and Zalaegerszeg

This work was in part supported by the Scientific Research Council, Ministry of Health, No. 3-07-0304-06-1/K

Offprint requests to: Prof. Dr. G. Kelényi, Department of Pathology, Medical University of Pécs, Szigeti út 12, 7643 Pécs, Hungary

0340-1227/80/0388/0213/$01.40

and the results of the staging procedures are important factors in establishing a prognosis. Despite the fact that the life expectancy of patients with ML has increased and their way of life has also improved greatly, cure, especially of adult non-Hodkin's ML is still infrequent. In addition, for the patient the diagnosis of ML involves the burden of therapy with a number of possibly dangerous complications.

In the pathohistological diagnosis of Hodkin's disease, the classification of Lukes and Butler (1966), although descriptive in nature, has found world-wide acceptance owing to its reproducibility and clinical relevance. In the field of non-Hodkin's ML the past 10 years have brought very important developments with functional/immunological concepts altering our earlier views. The descriptive morphological classifications of non-Hodkin's ML going back to Virchow (1863) and to Roulet (1930) and more recently to Rappaport (1966) have now been replaced by more functional terms (Gérard-Marchant et al. 1974; Lukes and Collins 1974; Lennert et al. 1975; Lennert 1976, 1978), based on the view that non-Hodkin's ML represent various blocked phases of lymphocyte differentiation and transformation.

The relative imfrequency of ML and the large number of different methods required for their exact typing, have led to the formation of special centres all over the world with the aim of introducing uniform pathohistological diagnoses, developing new methods, and new criteria for postgraduate teaching (Rüdiger et al. 1979). This trend has resulted in more and more ML being referred to the Department of Pathology, Medical University of Pécs, which is working closely together with the 1st Medical Department of the University and with the Haematological Department of the County Hospital of Szombathely, institutions particularly interested in the clinical management of ML patients.

In 1977 a Malignant Lymphoma Group was organised on behalf of a CMEA study entitled "Pathohistology of Malignant Tumours", and the formation of national Reference Centres with the task of collecting larger numbers of uniformly diagnosed ML cases and providing counselling services was agreed. In Hungary the Department of Pathology, Medical University of Pécs, was entrusted with the organization of such a Centre. This paper describes the experience gained in the first year (1978) of our Reference Centre.

Material and Methods

In our work with non-Hodgkin's ML we have been using the terms suggested by the European Lymphoma Club ("Kiel Classification", Gérard-Marchant et al. 1974). Although the Kiel Classification does not mention multiple myeloma in malignant lymphomas, we have been influenced by the remark of Lennert (1978), that every plasmocytoma is derived from B-lymphocytes and is thus strictly speaking a "lymphoma". We have thus included the few multiple myeloma cases in the group of immunoglobulin secreting tumours. In the case of Hodgkin's disease the types described by Lukes and Butler (1966) were used with some modifications (Lennert and Mohri 1974). In 1978 we received the biopsies together with a printed form listing the most important clinical features, historical data, localisation, extent of the disease, blood and bone marrow cytological findings, protein values for serum and urine. In about one third of the cases native material was available, in another third formol-paraffin blocks, unfixed lymph node imprints, blood and bone marrow smears were sent in. In the remaining cases we received only formol-paraffin blocks.

A number of Departments of Pathology of the City Hospitals of Miskolc, Kiskunhalas and Orosháza provided us with plastic embedded material for electron microscopy. This enabled electron microscopic investigations to be performed in about one third of the cases. In a limited number of cases a co-worker of the Reference Centre was present at the re-biopsy and provided material for immunological and electron microscopic studies.

Imprints, blood and bone marrow smears were stained by May-Grünwald-Giemsa, periodic acid-Schiff and peroxidase stains, and when neccessary, acid phosphatase without and with tartrate, non-specific and acid naphthyl acetate esterase, naphthol-AS-D-chloroacetate esterase and alkaline phosphatase reactions were performed. The following staining methods were used on formol-paraffin sections: haematoxylin-eosin, Giemsa after short methylation of the sections, periodic acid-Schiff haematoxylin, reticulin, naphthol-AS-D-chloroacetate esterase. Intracellular immunoglobulins were demonstrated by the immunoperoxidase technique or by immunofluorescence in both cases the sera were obtained from Dakopatts, Copenhagen. If native material was available the E- and EAC-rosette tests and typing of the surface immunoglobulins were performed on cell suspensions. The Departments referring their cases to the Centre received written reports.

Results

In 1978 the Reference Centre made 2029 various cytological, histological, cytochemical and immunocytological examinations on 1,158 patients and diagnosed a total of 383 new ML cases pathohistologically. The distribution of these cases according to diagnosis, age and sex in given in Tables 1–4 and Figs. 1

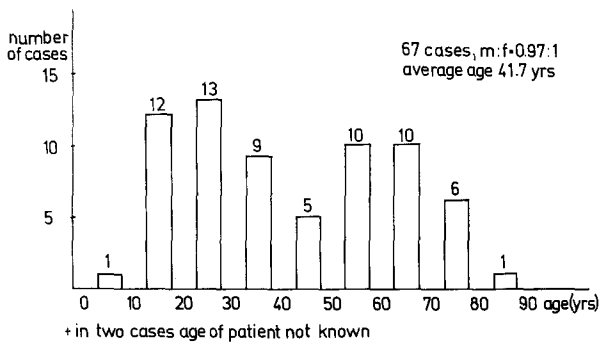

Fig. 1. Age distribution in Hodgkin's disease. In two cases age of patient not known

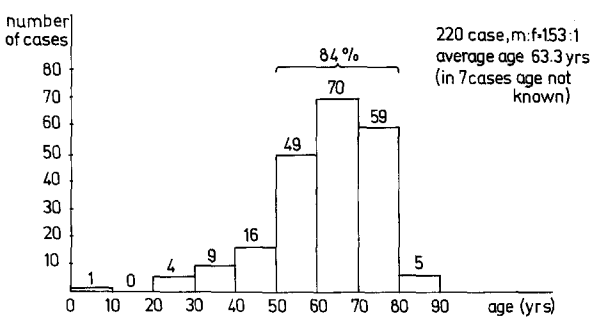

Fig. 2. Non-Hodgkin's ML, low grade malignancy, age distribution

Table 1. Malignant lymphomas (ML)

	Number of cases (%)	Average age	Male:Female
Non-Hodgkin's ML	290 (75.7)	59.4	1.48:1
Non-Hodkin's ML unclassifiable	12 (3.2)	49.8	2 :1
Hodgkin's disease	69 (18.0)	41.7	0.97:1
Lennert-lymphoma	8 (2.1)	53.2	0.6 :1
Hairy cell leukaemia	4 (1.0)	52.7	3 :1
Total	383 (10.0)	55.7	1.36:1

Table 2. Frequency of types in Hodgkin's disease

Pathohistological type	Number of cases (%)	Average age	Male:Female
Lymphocyte predominance	5 (7.2)	28.2	4 :1
Nodular sclerosis	18 (26.1)	35.9	0.28:1
Mixed cellularity	31 (45.0)	45.9	1.21:1
Lymphocyte depletion	7 (10.1)	51.3	1.33:1
Unclassifiable	8 (11.6)	41.1	1.67:1
Total	69	41.7	0.97:1

Table 3. Non-Hodgkin's malignant lymphomas, low grade malignancy

	Number of cases (%)[a]	Average age	Male: Female
CLL (pseudofollicular 29, diffuse 11, unclassified 3, T-cell 1)	44 (15.2)	64.1	2.38:1
ML-s of follicular origin (ML, centroblastic-centrocytic 47 and ML, centrocytic 7)	54 (18.6)	64.1	1.7 :1
ML, immunocytic (lymphoplasmocytoid 36, lymphoplasmocytic 28, polymorphic 31, unclassifiable 9, myeloma m.10)	114 (39.3)	62.3	1.28:1
Unclassifiable	8 (2.8)	59.4	1 :1
Total	220 (75.9)	63.3	1.53:1

[a] percentage of all non-Hodgkin's ML-s

and 2. In 23 of the 383 cases (6%) ML was diagnosed only at autopsy, and 18 of the 23 cases were of low grade malignancy. However, 12 of the 18 proved to be polymorphic immunocytomas, ML representing an intermediate type between low and high grade. Apart from these new cases in 1978, we studied the autopsy tissues of 78 cases of known ml (not included in the above series). In only 7 of them was there no sign of infiltration by ML cells.

Table 4. Non-Hodgkin's malignant lymphomas, high grade malignancy

	Number of cases (%)[a]	Avarage age	Male:Female
ML, centroblastic	28 (9.6)	60.8	0.87:1
ML, lymphoblastic, Burkitt-type	5 (1.7)	16.4	4 :1
ML, immunoblastic	17 (5.9)	65.7	1.43:1
ML, lymphoblastic, convoluted-cell type	16 (5.5)	27.6	1.3 :1
ML, lymphoblastic, unclassified	4 (1.4)	24.3	4 :1
Total	70 (24.1)	48.9	1.33:1

[a] in percentage of all non-Hodgkin's ML-s

Discussion

In recent years the rapid development of medical science has resulted in re-evaluation of a number of diseases. New types and subtypes have been distinguished in certain diseases previously thought to represent a uniform group of disorders. In pathohistology a similar process is taking place, and for the proposed new classifications of disease evidence in support of clinical relevance is needed. This may account for the trend to collect and evaluate as many uniformly diagnosed cases as possible. A large number of patients with a consistently diagnosed disease might also enable new diagnostic and therapeutic procedures to be tried out.

In malignant tumours, in which diagnosis is generally the result of a pathohistologic examination (95%, Kayser et al. 1978) – registers, reference or tumour centres have been organized all over the world. Their aims are to secure uniformity of pathohistological diagnosis, to provide counselling services, postgraduate training, new methods and clinicopathological experience. A large number of cases studied collectively may serve as a basis for oncological, epidemiological or statistical studies (Grundmann 1975, 1978, 1979, Remagen 1979; Tulinius 1977). These factors, on the one hand, and the introduction of the new classifications of ML on the other, neccessitated the formation of ML study groups, registries or reference centres. In Hungary this work has been done by the Department of Pathology, Medical University of Pécs since January 1978.

In 1978 we studied 383 new pathohistologically diagnosed cases of ML. Compared with the yearly total of newly diagnosed ML in Hungary, this figure seems to be high. In a previous study (Angyal et al. 1979) we recorded all cases of ML diagnosed in 1976 in a part of Hungary with a population of 4.1 million. The frequency of these tumours was 5.65 (100,000 inhabitants) year, which means that in 1978 the Reference Centre saw about one half of the pathohistologically diagnosed new cases in Hungary. If this number is compared with Lennert's (1969) study of Schleswig-Holstein with a population of 2.43 million, with 3.76 cases (100,000 inhabitants) year, or with the data of Tokunaga et al. (1978) of the Kagoshima prefecture where the population between 1965–1976 was 1.70 to 1.86 million, with 3.02 cases (100,000 inhabitants) year, the

number of new cases seen in 1976 seems to be high. At the same time the real number of ML is certainly even higher, which may be due to the fact that a number of cases are diagnosed from blood and bone marrow smears (myelomatosis, acute lymphoblastic leukaemia). In addition the clinical diagnosis of chronic lymphocytic leukaemia is sometimes based on blood and bone marrow smears, and a lymph node biopsy is not done.

According to our observation on autopsy material, about 30 of 60 cases of clinically diagnosed CLL (without biopsy) were what we consider today to be CLL, others were ML of follicular origin (ml, centroblastic-centrocytic, centrocytoma) and immunocytomas. It should be mentioned in this context that the study of blood and bone marrow smears is not always reliable in differentiating various forms of lowgrade non-Hodgkin lymphomata especially the two prognostically different subtypes of CLL (diffuse and pseudofollicular, Lennert 1978).

The cases referred to our Reference Centre represent selected material, although some Departments sent in all their lymphoma cases. Thus the distribution of various types can hardly be evaluated. Nevertheless, the low frequency of Hodgkin's disease should be mentioned, the more so because in a previous study (Angyal et al. 1979) in which *all lymphoma cases* were collected from an area with a population of 4.1 million the small number of cases with Hodgkin's disease (18% of all ML) when compared with the frequency in other countries (Devesa et al. 1973, Doll 1970, Stalsberg 1973) was apparent. This cannot be explained by the fact that some conditions previously diagnosed as Hodgkin's disease, are now excluded from this group, (angioimmunoblastic lymphadenopathy or lymphogranulomatosis X, T-zone lymphoma).

The low number of CLL and follicular tumours and the high number of immunocytomas among the low-grade non-Hodgkin ML calls for comment. As described above, CLL may represent about half of these cases in which lymph node biopsy was not done, i.e., if these patients were included the frequency of CLL would increase more than that of the follicular tumours and immunocytomas. Furthermore, it is now clear that the frequency of follicular tumours in different countries or geographic regions shows surprising variations (Lennert 1978).

Some individual variation in pathohistological diagnosis should also be taken into account (Fischer et al. 1979).

By providing clinicians with uniform pathohistological diagnoses our Reference Centre has made possible the formation of Clinical Study Groups. These are neccessary not only for a more appropriate clinical management of the patients, but also for assessing the clinical relevance of new types or subtypes of ML and for a wider application of newer diagnostic and therapeutical methods.

References

Angyal F, Balogh J, Bujalka R, Ferenczy S, Horváth F, Horváth L, Kasza Gy, Kádas I, Kádas L, Kelényi G, Kerekes K, Kindler M, Kövecs Gy, Krutsay M, László M, Lusztig G, Mórocz

J, Orbán I, Péró Cs, Rajkovits K, Rohonyi B, Szabó Zs, Szabolcsi I, Timár K, Tóth P, Wallacher L, Weiland O (1979) The incidence of Hodgkin's disease and non-Hodgkin's malignant lymphomas. (Hung.) Orv Hetil 102:2161–2164

Devesa SS, Silverman DT (1978) Cancer incidence and mortality trends in the United States: 1935–74. J Natl Canc Inst 60:545–571

Doll R, Muir C, Waterhouse J (1970) Cancer incidence in five continents, Springer, Berlin Heidelberg New York

Fischer R, Georgii A, Hübner K (1979) Vergleichende Beurteilung von Non-Hodgkin-Lymphomen (Kiel-Klassifikation) durch verschiedene Untersucher. In: Stacher A, Höcker P (eds) Lymphknotentumoren, Urban and Schwarzenberg, München Wien Baltimore, p 60

Gérard-Marchant R, Hamlin T, Lennert K, Rilke F, Stansfeld AG, van Unnik JAM (1974) Classification of non-Hodgkin's malignant lymphomas. Lancet 11:405–408

Grundmann E (1975) The pros and cons of cancer registration. Recent Results Cancer Res 50:1–5

Grundmann E (1978) Ziele des Registers für Onkologische Nachsorge der GBK in Münster. GBK Mitteilungsdienst 6/24:2–3

Grundmann E (1979) X. Internationales Symposium der GBK zum Thema Tumorzentren. GBK Mitteilungsdienst 7/27:6–9

Kayser K, Burkhardt H-U, Jacob W (1978) The regional registry of gastrointestinal cancer North Baden (2.2 million inhabitants). Virchows Arch [Pathol Anat] 380: 155–162

Lennert K (1969) Die derzeitige Häufigkeit der einzelnen Lymphknotenerkrankungen in Schleswig-Holstein. Dtsch Med Wochenschr 94:2194–2202

Lennert K (1976) Klassifikation und Morphologie der Non-Hodgkin-Lymphome. Blut 18:145–166

Lennert K (1978) Malignant Lymphomas. Hdb d spez path Anat u Histol, I Band, 3 Teil, Bandteil B. Springer, Berlin Heidelberg New York, p 399

Lennert K, Mohri N (1974) Histologische Klassifizierung und Vorkommen des M Hodgkin. Internist (Berlin) 15:57–65

Lennert K, Mohri N, Stein H, Kaiserling E (1975) The histopathology of malignant lymphoma. Brit J Haematol 31, Suppl: 193–203

Lukes RJ, Butler JJ (1966) The pathology and nomenclature of Hodgkin's disease. Cancer Res 26, 1063–1081

Lukes RJ, Collins RD (1974) Immunologic characterizations of human malignant lymphomas. Cancer 34:1488–1503

Rappaport H (1966) Tumors of the hematopoietic system, In: Atlas of tumor pathology. Washington DC, AFIP

Remagen W (1979) The role of a cancer registry in the diagnostics of bone tumors. Pathol Res Pract 164:121–125

Roulet F (1930) Das primäre Retothelsarkom der Lymphknoten. Virch Arch 277:15–47

Rüdiger K-D, Wöckel W, Schreiber D (1979) Gedanken zu den Aufgaben und zur Arbeitsweise eines Referenzzentrums "Maligne Lymphome". Zentralbl Allg Pathol 123:448–451

Stalsberg H (1973) Lymphoreticular tumors in Norway and in the European countries. J Natl Cancer Inst 50:1685–1702

Tokunaga M, Sato E, Tanaka S, Sakai N (1978) Malignant lymphoma occurring in Kagoshima prefecture, Japan: pathological and descriptive epidemiological survey based on 849 biopsy materials. Gan 69:673–678

Tulinius H (1977) Zur Epidemiologie der Nicht-Hodgkin-Lymphome. Strahlentherapie 153:209–217

Virchow R (1863) Die krankhaften Geschwülste. A. Hirschwald, Berlin

Accepted June 3, 1980