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Small non-Cleaved Follicular Center Cell Lymphoma: Clinicopathologic Comparison of Burkitt and non-Burkitt Variants in Finnish Material*

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Abstract—*A retrospective clinical and histopathological analysis was made of patients with small non-cleaved-type malignant lymphoma according to the classification of Lukes-Collins. Nineteen cases were classified as the Burkitt type and 41 cases as the non-Burkitt type. The non-Burkitt type was more variable cytologically. A bimodal age distribution was seen in both subgroups. One half in both subtypes had an advanced disease (stage III-IV). Lymphadenopathy was slightly more common in the non-Burkitt type. No patient with non-Burkitt's lymphoma had mediastinal involvement* ($P < 0.01$). *Liver and spleen were not involved by the tumor of the Burkitt type* ($P < 0.005$). *Gastrointestinal involvement was seen in both types without differences. No statistical differences between the overall survivals of these subtypes were observed.*

INTRODUCTION

THE SMALL non-cleaved (SNC)-type of malignant non-Hodgkin's lymphoma (NHL) is a high-grade malignancy of proposed B-cell derivation [1, 2] which is classified pathologically within the undifferentiated category of Rappaport [3]. Two variants, Burkitt type and non-Burkitt type, are included in this neoplastic disease [2]. Since the initial description of the disease, occurring typically in the jaws and abdominal viscera of African children, many reports have also been published of non-African cases of Burkitt's type [4-6]. Attempts have also been made to establish clinicopathologic differences of these two subcategories (Burkitt vs non-Burkitt) [7-9]. For this aim our experiences with 60 SNC lymphoma cases are summarized.

MATERIALS AND METHODS

The study population consisted of 60 patients with histologically confirmed SNC follicular center cell (FCC)-type NHL diagnosed according to the criteria of Lukes and Collins [2]. The patients were included in our material of 301 patients with NHL described earlier in detail [10-12]. These patients were seen between the years 1957 and 1978 in Tampere University Central Hospital district, an area with about 410,000 inhabitants in Southwestern Finland.

The histological material was collected mainly from the files of the Department of Pathology of Tampere University Central Hospital and also from the local laboratory of the Cancer Foundation of Pirkanmaa. The pretreatment surgical biopsies were formalin fixed and paraffin embedded. Specimens were cut to 5 μm thick sections and stained by the following methods: hematoxylin-eosin, Giemsa, Herovici, hematoxylin-PAS with and without diastase, Gomori and methyl green-pyronin.

Methods for pretreatment clinical staging underwent considerable evolution during the period concerned. The more vigorous methods were used in the early 1970s, coincident with the introduction of combination chemotherapy and high-energy radiotherapy. More details of staging methods and therapy used are given previously [11, 12]. However, the clinical stage at the time of

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diagnosis was recorded according to the principles of the Ann Arbor staging classification [13].

The survival times were calculated from the date of diagnosis of malignant lymphoma. The follow-up was until death or ranged from 29 to 212 months for those patients who were alive at the end of the follow-up. The relative survival curves were calculated using the method of Hakulinen [14] applying the normal mortality tables from Finland [15]. A log-rank test was employed for the evaluation of differences between survival curves [16, 17].

RESULTS

Histopathology

The morphological criteria of SNC FCC lymphoma were fulfilled by 60 (20%) cases out of 301 patients of our original study material. Nineteen (6%) cases were subclassified as the Burkitt type and 41 (14%) were classified as the non-Burkitt type.

Typical histological features of both variants of SNC FCC are presented in Figs 1 and 2. The Burkitt type was characterized by middle-sized uniform lymphoid cells with rounded or ovoid nuclei smaller than those of normal histiocytes. There was a high nuclear to cytoplasmic ratio. Several small inconspicuous nucleoli and small amounts of pyroninophilic cytoplasm were seen. The 'starry sky' pattern due to the presence of reactive histiocytes was often prominent. The non-Burkitt cells were of the same but of a more variable size and shape with more nuclear irregularity. The nucleoli were more prominent than those in the cells of the Burkitt type. Often such large nucleoli were centrally located in the nuclei. The starry sky pattern was more inconspicuous. A high mitotic ratio was seen in both types.

Partial involvement of tissue by tumor were seen in two cases of the non-Burkitt type. The main part of both types (83% of non-Burkitt and 82% of Burkitt cases) had a diffuse growth pattern. One case of the non-Burkitt type had a primarily follicular growth pattern. Moreover, various degrees of follicularity were seen without differences between both subtypes. No residual morphologic characteristics of any other lymphoma types were seen in any of the cases.

Age and sex

A bimodal age distribution with peak incidences under 10 yr and between the sixth and eighth decades were seen in both subgroups (Fig. 3). As an entire group, patients with non-Burkitt type were older than those with Burkitt type, the median ages for both sexes being over 60 yr. Females with non-Burkitt type were not observed in the age groups under 50 yr. Male patients in both groups were evenly distributed over the decades. Six (32%) of the patients with Burkitt type and four (10%) with non-Burkitt type were under the age of fifteen.

Staging

One-half in both subgroups had advanced disease (stage III or IV) at the time of diagnosis (Table 1). Of the Burkitt patients 3/19 (16%) were known to have B symptoms as well as 12/41 (29%) of non-Burkitt cases. No differences in clinical staging were seen in patients with Burkitt type under and over 30 yr of age.

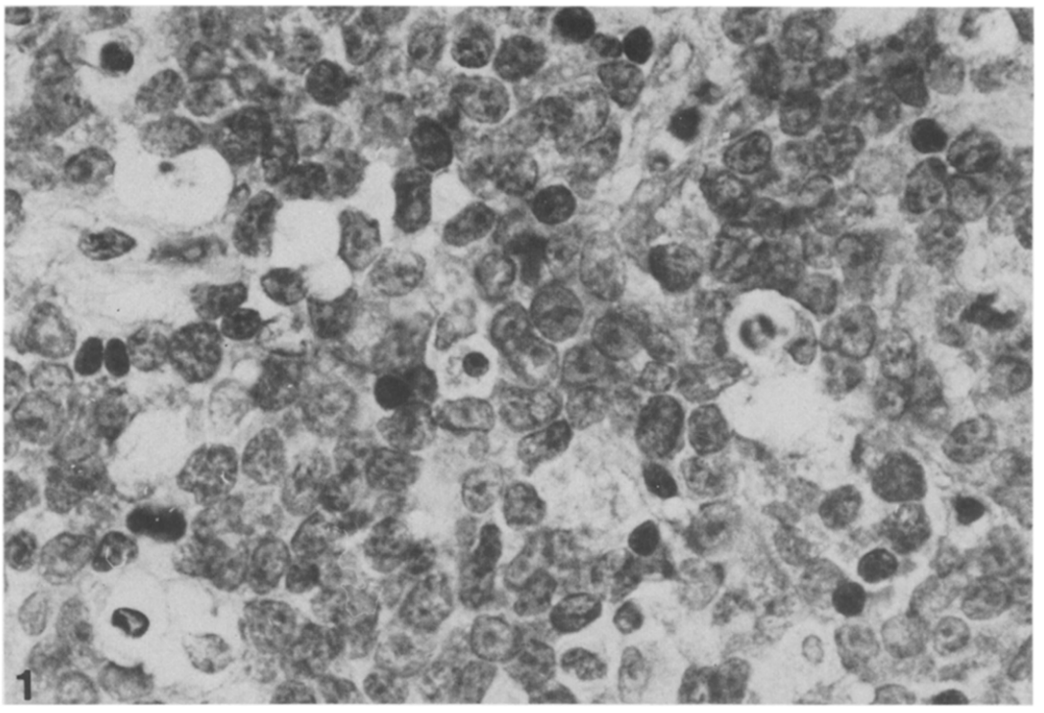
Sites of origin

The sites involved by the tumor at the time of diagnosis are presented in Table 2. Lymphadenopathy was slightly more common in the non-Burkitt group ($P < 0.1$). No patients in the non-Burkitt group had mediastinal involvement compared with 4/19 (21%) in the Burkitt group ($P < 0.01$). Liver and spleen were not involved by the Burkitt-type tumor ($P < 0.005$). At the time of diagnosis the involvement of bone marrow was seen in 6/19 (32%) of Burkitt cases compared to 8/41 (20%) of the non-Burkitt patients. The difference was not significant. The leukemic phase of lymphoma was seen in three cases of Burkitt and five of non-Burkitt types. Later three additional Burkitt cases became leukemic.

The most frequent sites of gastrointestinal involvement included the stomach and small bowel in both groups. No differences were seen between the two variants. Later six additional Burkitt and three non-Burkitt patients revealed symptoms and signs related to a visceral abdominal disease. Nine patients with non-Burkitt-type NHL got pleural or pulmonry involvement (only one with Burkitt type). Central nervous system manifestation was seen later in four Burkitt cases and two non-Burkitt cases. Primary central nervous system manifestation was not seen at the time of tumor diagnosis. Facial bone involvement was not present in any of the

Table 1. Distribution of clinical stages by histologic type and sex

	Stage			
	I	II	III	IV
Burkitt type				
Males	3	3	1	4
Females	2	2	1	3
non-Burkitt type				
Males	4	7	4	10
Females	5	4	4	3



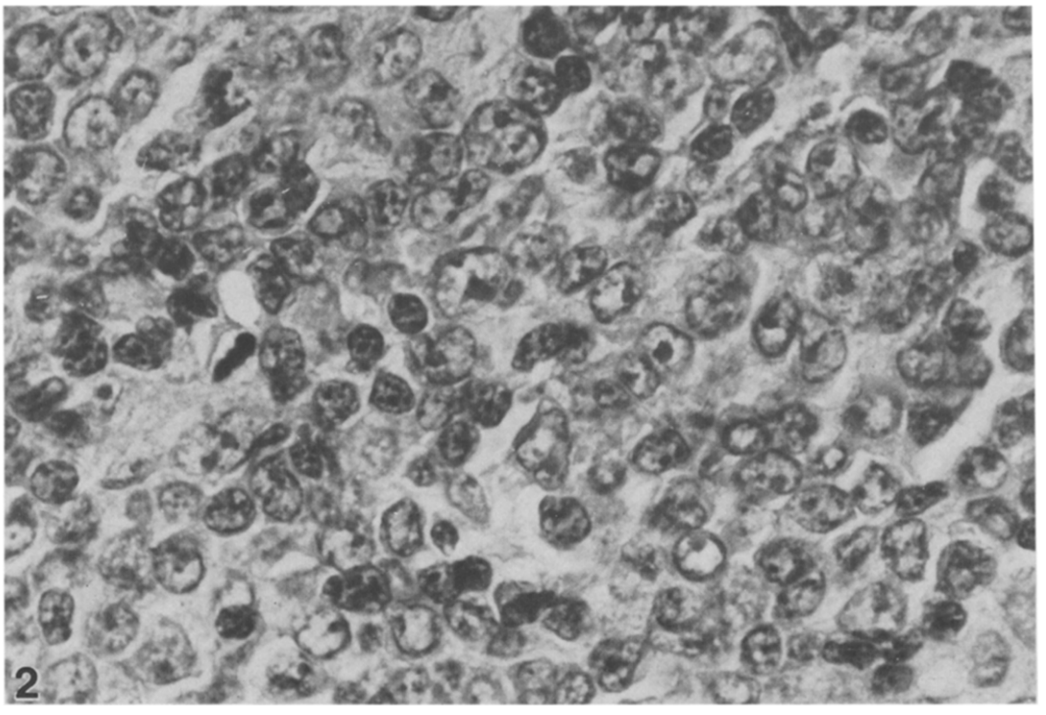


Fig. 1. *Small non-cleaved FCC lymphoma, Burkitt type* (*HE*, ×330).
Fig. 2. *Small non-cleaved FCC lymphoma, non-Burkitt type* (*HE*, ×330).

Table 2. Sites involved by tumor at diagnosis

	Burkitt type	non-Burkitt type
Lymph nodes		
Cervical	7	20
Axillary	3	16
Inguinal	5	14
Para-aortic/iliac	1	13
Mediastinum	4	-
Bone marrow	6	8
Peripheral blood	3	5
Gastrointestinal tract	2*	5‡
Waldeyer's ring	3	7
Soft tissue sites	4†	4§
Liver	-	6
Spleen	-	8

*Small bowel 2.
†Breast, nose, skin, lower extremity.
‡Stomach 2, small bowel, oesophagus, colon.
§Orbita, skin, thyroid gland, upper extremity.

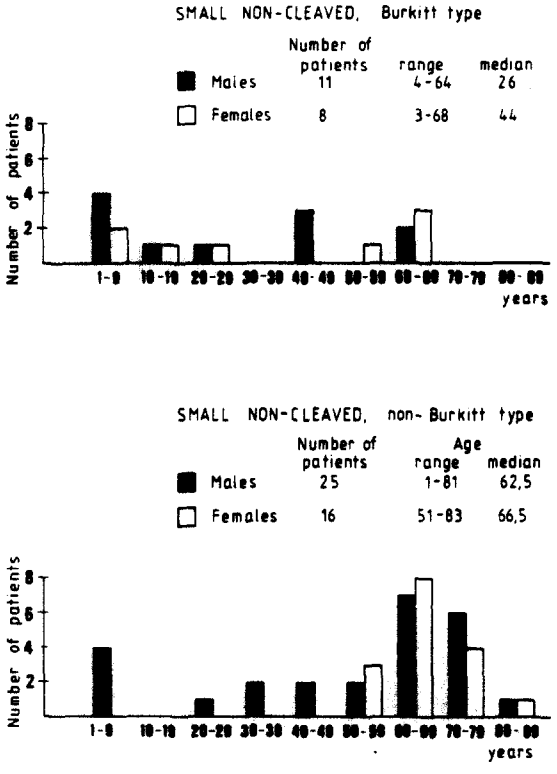


Fig. 3. Age distribution by histologic type.

cases. None of the female patients had proved ovarian involvement at the time of diagnosis.

Survival

Relative survival curves [14] for both Burkitt and non-Burkitt patients are shown in Fig. 4. No statistical differences between the overall survivals of these subtypes were seen. Median survivals were short: 9.2 months for Burkitt type and 14.8 months for non-Burkitt type. After 3 yr no mortality was seen in the Burkitt group. However, only three patients were alive for analysis after that time. They consisted of one

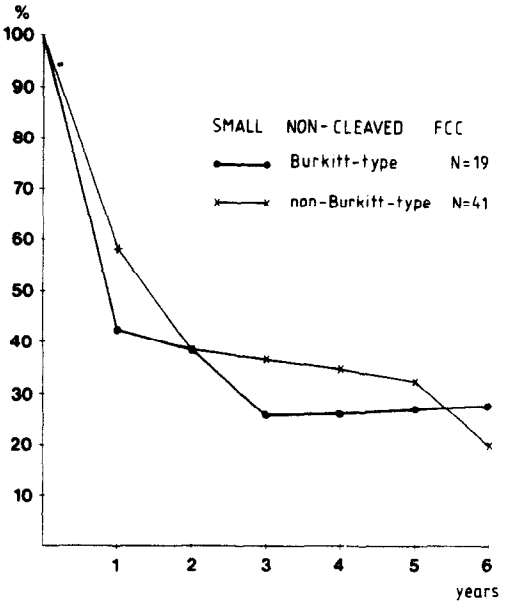


Fig. 4. Relative survival curves.

male and two female patients. In the non-Burkitt group there were three female and two male patients who remained alive more than 5 yr. In both subgroups there was one boy under 10 yr of age, and all the other long-term survivors were of a median age of 60 (range 32-69) yr. All of these patients who remained alive after 5 yr were assigned as in either stage I (five) or II (three) at the time of diagnosis.

DISCUSSION

Sixty (19.9%) patients were diagnosed as SNC FCC-type NHL in our original material of 301 cases with NHL [10]. Nineteen cases fitted in the category of the Burkitt type and the remaining 41 were of the non-Burkitt type. The SNC FCC type represented about two-thirds of all childhood non-Hodgkin's lymphomas. The incidence of SNC type is higher than in other series reported in the literature. In the material of Lukes *et al.* the proportion of SNC FCC lymphomas was 7.7% [18]. Of 473 cases of NHL seen at the National Cancer Institute, 66 (14%) were classified as undifferentiated lymphomas (39 cases were of the Burkitt type and 27 of the non-Burkitt type) [7]. Reported frequencies of this histologic type of non-Hodgkin's lymphoma vary considerably, and it is often difficult to compare them because of different classification criteria used and also because of the composition of the patient population.

The morphologic criteria of the Burkitt type of SNC FCC in the classification of Lukes and Collins used in this study are close to WHO's histopathologic definition of Burkitt's tumor [19]. The histopathologic separation from the non-Burkitt type can be made as indicated earlier

by others [8]. Both subtypes are proliferations of intermediate-sized lymphoid cells with a high nuclear to cytoplasmic ratio. The Burkitt type has the characteristic monomorphic cytologic picture. The non-Burkitt type is more variable cytologically and has more cleaved follicular center cells as previously described [20]. Often a pronounced 'starry sky' pattern is associated with the Burkitt type but it is not a discriminating feature. There is some morphologic overlapping between the two subtypes but the reproducibility of the SNC group as a whole is rather good [21]. The follicular growth pattern features found in this study are similar to those reported earlier [9, 22], supporting the B-cell and FCC origin of this type of NHL. However, this is a disputed subject [23]. Our patients had only the primary diagnostic biopsies. Thus no evidence of reported histologic progression or conversion was seen [24].

A memorandum of World Health Organization has summarized the important clinical and pathological features of Burkitt's tumor [19]. The disease is usually multifocal and predominantly extranodal, with involvement of one or more of the following sites: abdominal and/or pelvic viscera, retroperitoneal soft tissues, facial bones and/or long bones, thyroid gland, salivary glands and central nervous system. Clinically, previous reports have also noted the predominantly extranodal and abdominal presentation of non-Burkitt and especially Burkitt types of malignant lymphoma. A predominance of nodal sites of presentation have been reported for non-Burkitt cases and also partly for Burkitt cases in non-endemic areas [4–9]. In the present study prominent primary nodal involvement in both types was observed. Extranodal and abdominal presentation was less frequent at the time of diagnosis but became more prominent during the evolution of the disease. Also, the noted mediastinal involvement of the Burkitt type is seldom seen. High incidence of mediastinal tumor mass is typically seen in the lymphoblastic lymphoma. The morphologic criteria for the Burkitt type of lymphoma are well defined [19] and it can be distinguished from the immature appearing lymphoid cells of the convoluted and non-convoluted groups of lymphoblastic lymphoma since lymphoma cells of Burkitt type have coarser nuclear chromatin, more prominent nucleoli and better defined and more basophilic cytoplasm [25]. The noted anatomic presentation of liver and spleen for the non-Burkitt type is exceptional and difficult to explain, but has been described also earlier [26]. Bimodal age distribution in both types as reported also in earlier studies [7, 9] was found. Females with the non-Burkitt type and under 51 yr of age were lacking in our material but this observation is possibly accidental due to the small number of patients.

The small non-cleaved-type NHL belongs to the group of high-grade lymphomas with an aggressive clinical course [27]. No published reports have indicated significant differences in overall survival between the two subtypes of this category [7, 9]. They are rapidly fatal diseases with short median survivals. In our study patients with the Burkitt type seem to be cured after 3 yr, but the small number of cases precludes any definite conclusion. In some earlier studies there was also found a trend of the same type [4, 5, 7] for the possibility of cure.

The results of the present study are not against the clinico-pathologic validity of the classification of Lukes and Collins. There are a few discriminating subtyping features for SNC FCC malignant lymphoma. However, the clinical picture can obviously be more heterogeneous than earlier described but no significant differences between the courses of both subtypes were observed in this study or previously. Our data suggest that the incidence of the small non-cleaved FCC malignant lymphoma may be higher than is supposed in earlier studies. Due to the retrospective nature of this study the patients were not examined for Epstein-Barr antigen nor cytogenetically to make the diagnosis of the Burkitt-type lymphoma more specific.

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