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Non-Hodgkin Lymphomas of the Thyroid

A Clinico-Pathological Review of 29 Cases Applying the Lukes-Collins Classification and an Immunoperoxidase Method

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Summary. Twenty-nine cases of non-Hodgkin lymphomas presenting in the thyroid were classified according to Rappaport and Lukes and Collins. In the Rappaport classification there were 19 histiocytic, three mixed, five nodular PDL and two undifferentiated lymphomas. According to Lukes and Collins, 21 cases were follicular center cell lymphomas, eight were immunoblastic sarcomas. Cases classified as histiocytic according to Rappaport fell into the immunoblastic sarcoma and large cleaved or non-cleaved follicular center cell lymphoma groups. Immunoperoxidase studies confirmed the B cell nature of some of these cases.

Survival was dependent on clinical stage, but this appeared to reflect the predominant cell type. Thus, follicular center cell lymphomas of the large non-cleaved type presented predominantly in stage I, while immunoblastic sarcoma was mostly stage IV and tumors of the small cleaved follicular center cell (FCC) type had excellent survival despite a usual presentation in stage IV. It is concluded that probably only lymphomas of the large non-cleaved FCC type and immunoblastic sarcoma (IBS) occur as true primary thyroid tumors, while small cleaved FCC lymphomas most likely represent systemic disease when first presenting in the gland. The median survival for large non-cleaved lymphomas in stages I and II was 31.5 months compared to 5.5 months for stage IV IBS. Although strongly suggestive these correlations were not statistically significant.

An association with severe chronic lymphocytic thyroiditis was observed in 22 cases, including all cases of immunoblastic sarcoma as well as nine of ten large non-cleaved follicular center cell tumors.

The prognostic significance of the Lukes-Collins classification is discussed in relation to these examples of thyroid lymphoma.

Key words: Non-Hodgkin lymphomas – Thyroid neoplasms – Lukes-Collins classification – Immunoperoxidase

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Introduction

The existence of lymphomas of the thyroid has long been a matter of debate. However, that they occur rarely is now generally accepted (Hedinger, 1969; Neracher and Hedinger, 1975; Selzer et al., 1977; Leontsakis et al., 1976), and lymphomas are included in both current classifications of thyroid neoplasms (Meissner and Warren, 1969; Hedinger and Sobin, 1974).

Despite their rarity, lymphomas of the thyroid are of considerable practical and theoretical interest. In practice, the histologic diagnosis of malignant lymphoma of the thyroid can be extremely difficult and raises the question, whether one is faced with a true primary tumor or with a local presentation of an otherwise disseminated process. In addition, the differential diagnosis from carcinoma may be difficult, and there are still other problems in the distinction of lymphoma from the various expressions of chronic lymphocytic thyroiditis which often coexists with lymphoma.

Recent advances in basic immunology have profoundly altered our understanding of the morphology and function of lymphocytes and their tumors and have resulted in a number of new classifications of lymphoid neoplasms (Lennert, 1975; Lukes and Collins, 1974, 1975, Table 2). The morphological phases of transformation of the small B lymphocyte to the transformed lymphocyte in reactive follicles have been described (Kojima et al., 1973; Lennert, 1973; Lukes and Collins, 1973), and the neoplastic counterparts of this process have been termed follicular center cell lymphomas (Lukes and Collins, 1973). Also, the large 'primitive' cell previously considered to be a reticulum cell or a histiocytic derivative has been identified with some confidence as an expression of the transformed lymphocyte. Finally, at least two functionally different subtypes, T and B cells, are distinguishable by immunological techniques. A corresponding functional division appears to be present among the lymphomas (Lukes et al., 1978a, b). Subsequently it has been shown that, with very few exceptions, tumors previously called reticulum cell sarcoma or malignant lymphoma histiocytic are tumors of transformed lymphocytes, either corresponding to the large cell in the follicular center cell phase, or to the fully transformed immunoblast (Lukes and Collins, 1977; Lukes et al., 1978a, b).

These observations are of particular interest with regard to thyroid lymphomas, most of which in the past have been classified as lymphomas of histiocytic type, or as reticulosarcomas (reticulum cell sarcomas) (Burke et al., 1977). The designation histiocytic lymphoma conceals five separate types of lymphoma recognisable by the Lukes-Collins classification (1975). These types are large cleaved and large non-cleaved follicular center cell lymphomas, and immunoblastic sarcomas of T and B cell types, as well as a "true" histiocytic type (Lukes and Collins, 1974, 1975; Lukes et al., 1978a, b) and they appear to have biological and clinical significance. The present study was therefore undertaken to examine thyroid lymphomas, most of which were formerly classified as malignant lymphoma histiocytic, for their distribution among the Lukes-Collins types.

In addition, the general association between lymphoma and autoimmune disease is well recognized. For example, there is a high incidence of lymphoma

in Sjögren's syndrome (Talal and Bunim, 1964; Anderson and Talal, 1972; Zulman et al., 1978) and our preliminary report of 33 patients with immunoblastic sarcoma gives a history of various associated immunologic disorders (Lichtenstein et al., 1979). A number of reports of thyroid lymphomas have discussed possible relationship with preceding Hashimoto's thyroiditis (Lindsay and Dailey, 1955; Kenyon and Ackerman, 1955; Cureton et al., 1957; Crile, 1963; Cox, 1964; Woolner et al., 1966; Burke et al., 1977). On this basis case histories were obtained on our patients in order to search for evidence of a possible predisposing role of the abnormal immune state of chronic thyroiditis in relation to the development of the different forms of lymphoma identifiable by the Lukes-Collins classification.

Materials and Methods

Cases for this study were drawn from the files of the Los Angeles County/University of Southern California Medical Center, from the participating hospitals in the Southern California Lymphoma Group, from the California Tumor Tissue Registry, and from the consultative service of one of the authors (RJL). Twenty-three cases coded as lymphosarcoma, reticulosarcoma, plasmacytoma of the thyroid, or cross-filed as lymphoma-undifferentiated carcinoma, were drawn from the California Tumor Tissue Registry files. A further 12 cases were obtained from the other sources listed, making 35 in all. On review, six cases were rejected. In five of these, the quality of the sections precluded a definitive diagnosis of malignant lymphoma and blocks were not available for additional sections. In the remaining case the diagnosis was revised to undifferentiated carcinoma.

Of the 29 remaining cases, 25 represented surgical material and four autopsy material. All had been diagnosed clinically as neck masses in the thyroid region, or as thyroid tumors. In all 29 cases a histologic diagnosis of a lymphoma involving the thyroid had previously been issued by one of us (RJL), or was subsequently agreed by two of us (RM/RJL) on review. Three cases were retained in the study despite the fact that available sections showed no residual thyroid tissue, even though the surgical report clearly gave the thyroid gland as the site of origin. H & E stained sections were examined in all cases. In addition, periodic acid Schiff and methyl green-pyronin stains were performed in those cases in which blocks were available. Immunologic surface marker studies were performed on one case as described elsewhere (Lukes et al., 1978a).

The patients were not systematically evaluated either clinically or by laboratory techniques since the case material was collected from numerous hospitals over a lengthy time period through a morphologic consultation service.

Immunoperoxidase Method

Serial 4 μ sections were made from representative blocks of 24 cases and were analyzed for the presence of cytoplasmic immunoglobulin components (light chains) with a panel of specific antisera, using an immunoperoxidase technique.

The PAP (peroxidase-anti-peroxidase) immunoperoxidase procedure was selected for this study by virtue of its sensitivity and relative freedom from nonspecific background. The method has been described in detail elsewhere (Taylor, 1978a), and the mode of application in this study is summarized in Table 1.

The dilutions of antisera, shown in Table 1, were determined following separate checkerboard titration studies of different dilutions of each of the primary antisera, to achieve optimal contrast between specific staining and nonspecific background reactions. Negative controls, omitting each of the stages of the PAP procedure in turn (Table 1), or substituting rabbit antiserum of irrelevant specificity (e.g. anti-human serum albumin and anti-lysozyme) for the specific primary rabbit anti-immunoglobulin serum, were performed. Positive controls included sections from paraffin blocks of cases of myeloma and B cell lymphoma of predetermined light and heavy chain type. All

Table 1. The peroxidase-anti-peroxidase (PAP) immune complex method

1. Paraffin sections-xylol-alcohol
2. Block endogenous peroxidase with methanol containing 0.3% hydrogen peroxide, 30 min
3. Normal swine serum 1/20, 10 min[a]
4. Rabbit antiserum to human immunoglobulin components,[b] 30 min
5. Swine anti-rabbit immunoglobulin 1/20, 30 min
6. PAP 1/100, 30 min
7. Diaminobenzidine reaction, counterstain with hematoxylin, dehydrate, and mount in permount

The reactions are carried out in tris buffer (pH 7.6), with washes after stages 3, 4, 5 and 6 in tris saline (a solution of tris buffer 1/10 in normal saline)

[a] Normal swine serum is employed, prior to the addition of specific antisera, to reduce the effects of nonspecific tissue binding of immunoglobulin

[b] Dilutions determined according to checkerboard titrations:anti-κ, anti-λ-1/1000; anti-γ, anti-α-1/400; anti-μ-1/200; anti-lysozyme (muramidase)-1/400; anti-albumin-1/500

Table 2. The Lukes-Collins classification

B cell
- Small lymphocyte (CLL)
- Plasmacytoid lymphocyte
- Follicular center cell (FCC)[a]
  - small cleaved
  - large cleaved
  - small non-cleaved
  - large non-cleaved
- Immunoblastic sarcoma (IBS)
- Hairy cell leukemia

T cell
- Small lymphocyte
- Convoluted lymphocyte
- Sézary-Mycosis fungoides
- (Cerebriform lymphocyte)
- Immunoblastic sarcoma (IBS)

U cell

Histiocytic

[a] Follicular, follicular and diffuse, diffuse; with or without sclerosis

antisera and the PAP reagent were obtained from Dakopatts, Mercia Diagnostics, Sandown Road, Watford, Herts, England. Specificity of primary antisera was checked by orthodox immunodiffusion against myeloma monoclonal proteins.

Morphology

Histologically the tumors were classified according to Rappaport (1966) and according to Lukes and Collins (1974; Lukes et al., 1978a, b) (Table 2).

Clinical information was obtained by questionaires mailed to the pathologists contributing the cases.

The probability of survival in relation to clinical stage, cell type and cell type combined with stage was computed. Significance was tested by Wilcoxon test.

Table 3. Thyroid lymphomas: age distribution

Age (years)	No. of cases	%
30–39	3	10.3
40–49	2	6.9
50–59	5	17.3
60–69	11	37.9
70–79	6	20.7
80–89	2	6.9
Total	29	100.0

Table 4. Thyroid lymphomas: presenting clinical symptoms

Symptom	No. of patients	%
Rapid thyroid enlargement	13	44.9
Neck mass	9	31.2
Gradual swelling of neck	6	20.6
Preexisting thyroid enlargement	7	24.1
Dysphagia	4	13.8
Dyspnea	3	10.3
Hoarseness	3	10.3
Hypothyroidism	3	10.3

Results

Clinical Findings

Age and Sex Distribution. Our 29 cases included 24 females and five males. The median age was 64 years with a range from 34 to 82 years. The age distribution (Table 3) showed a clear peak in the seventh decade.

Presenting Signs. Details on clinical presentation were available on 28 of the patients. Table 4 lists the foremost complaints in order of frequency. The presenting feature was a rapidly enlarging thyroid in 13 cases, a neck mass in nine cases and a gradual swelling of the neck in six cases. A preexisting chronic enlargement of the thyroid was present in eight cases. Hoarseness, dyspnea and dysphagia were observed in three and four cases respectively, and were associated with widespread local tumor infiltration. A previous history of hyperthyroidism was found in three patients.

The tumor was located in the right lobe of the thyroid in eight cases and on the left side in ten. Involvement was bilateral in five cases and in the isthmus in one. Location was not stated in five cases. In all but one case, preoperative diagnosis was of a presumptive thyroid carcinoma. In one case, a nodular goiter in connection with hypothyroidism led to thyroidectomy.

Table 5. Results of limited staging (21 patients)[a]

Cell type	Stage I	Stage II	Stage III	Stage IV
Small cleaved		1		2
Large cleaved	1			
Small non-cleaved				2
Large non-cleaved	5[b]	1[b]		1
IBS	1	2		5
Total	7	4	–	10

[a] 16 patients were clinically staged though not all extensively; 5 patients were stage IV due to widespread local invasive growth according to surgical reports

[b] An additional four cases had a likely stage I/II presentation

Laboratory Findings

Information about thyroid function was sparse. Besides three cases with hypothyroidism, there was one case with questionable hyperthyroidism. There were no clinical abnormalities of thyroid function reported in the remaining 25 patients, but there had not been a systematic work-up in most patients. In two patients with hypothyroidism a prior diagnosis of Hashimoto's disease had been established by biopsy five years previously. Testing for thyroid antibodies was performed in six cases. In one the result was positive for microsomal antibodies, but negative for anti-thyroglobulin. In a second antibody levels were reported to be "questionably positive." A serum electrophoresis or immunoelectrophoresis was performed in six patients and was normal.

Results of preoperative thyroid scans were available for eight patients. Five had a solitary "cold nodule," while three showed multiple cold nodules with "spotty" uptake in both lobes. Histologically, three of these cases were associated with a small cell lymphoma, and five with a lymphoma of a large cell type.

Therapy was variable and it was not possible to show any relationship of survival to therapy. Most frequently, therapy consisted of thyroidectomy only. In a minority of cases, surgery was followed by radiation or chemotherapy. In a few cases with widespread local infiltration, radiation therapy was employed alone.

Staging

Clinical staging procedures were performed in 16 patients drawn from more recent years, but detailed information as to the applied staging techniques was not always available.

On five cases from the California Tumor Tissue Registry, the stage could be derived from clinical and surgical information. Thus Table 5 summarizes the presentation of 21 patients. Seven patients presented in stage I, four in stage II, and 10 in stage IV, which was mostly due to widespread local invasion of soft tissue.

Table 6. Thyroid lymphomas: distribution of cases classified according to Rappaport

Type	No. of cases	%
PDL, nodular	5	17
Mixed,[a] nodular	3	10
Histiocytic,[b]	19	66
nodular	2	
diffuse	17	
Undifferentiated	2	7
Total	29	100

[a] One case contained various areas with different appearances, some showing a mixed pattern, some a histiocytic pattern

[b] One case with clearly plasmacytoid features would probably have been classified as plamacytoma

Table 7. Thyroid lymphomas: distribution of cases classified according to Lukes and Collins

Type	No. of cases	%
Small cleaved	5	17
follicular	2	
follicular/diffuse	3	
Large cleaved	2	7
follicular/diffuse	2	
Small non-cleaved (transformed)	2	7
diffuse	2	
Large non-cleaved (transformed)	12	41
follicular/diffuse	4	
diffuse	8	
IBS[a]	8	28
Total	29	100

[a] IBS is always diffuse.

Breakdown of stage at presentation according to cell type shows that six of seven large non-cleaved FCC tumors presented in stage I and II and only one in stage IV. Of eight IBS only three were localized and five were in stage IV. Stage IV presentation was also present in both cases of the small non-cleaved FCC type. Also, two of three small cleaved FCC tumors presented in stage IV on the basis of demonstrable bone marrow involvement.

Table 8. Cytologic types of lymphomas in thyroid according to the Lukes-Collins classification (adapted from Lukes et al., 1978b)

Cytology	Clinical
FCC-small cleaved	
Wide range of cell sizes, but small cells predominate. Nuclei have basophilic compact chromatin and many show deep cleavage planes. Nucleoli are inconspicuous and cytoplasm is indistinct. Transformed lymphocytes present in small numbers (10%–20%). 75% are follicular, remainder diffuse.	Asymptomatic presentation typical. Low turnover rate cell. Marrow involved at presentation in >70%. Paradox of widespread distribution but prolonged median survival. Occasionally leukemic, resembling CLL, but "cleaved" nuclear morphology.
FCC-large cleaved	
Nuclei larger than nuclei of reactive histiocytes. Prominent nuclear irregularity. Mitoses variable-related to number of *non-cleaved* cells. Cytoplasm moderate and pyroninophilic. Frequent association with intercellular material and sclerosis. Small cleaved and non-cleaved cells generally present in small numbers.	Commonly present in mesentery, retroperitoneum, or inguinal area. *Also often extranodal.*
FCC-small non-cleaved	
Cells resemble small transformed lymphocytes. Nuclei round but variable in size (by definition do not exceed size of histiocyte nucleus). Nuclear chromatin finely dispersed. 1–3 small nucleoli. Moderate amount of pyroninophilic cytoplasm with cohesive cell borders. "Starry sky" reactive histiocytes common. When nuclei uniform in size and configuration and nucleoli small, fulfill criteria for Burkitt lymphoma. When more nuclear variation and prominent nucleoli, Burkitt-like or non-Burkitt lymphoma (seen in US). Minimal follicular pattern in ~10%. Generally diffuse, obliterating lymph node architecture.	Abdominal presentation chracteristic in US cases, often children, may become manifest as lymphoma-leukemia (then equals B subtype of ALL). Rapidly growing tumor, but Burkitt type may respond dramatically to low doses of cytoxan.
FCC-large non-cleaved	
Similar to small non-cleaved, but cells and nuclei larger. More cytoplasm but lightly stained. Nuclei round or oval, but irregular forms often present. Nucleoli prominent-frequently two at the nuclear membrane on short axis of an oval nucleus; characteristic feature. Mitoses numerous. Individual cell necrosis and necrotic zones common. A minor proportion of accompanying small and large cleaved cells or lymphomatous follicles indicates FCC nature. Follicular in ~10% of cases.	Aggressive neoplasm with high turnover rate. Rapid dissemination.

IBS-B cell	
Cells resemble large non-cleaved FCC, but more deeply staining amphophilic and pyroninophilic cytoplasm. *Often plasmacytoid features.* Cleaved cells and follicular pattern not present. Presents as relatively monomorphous collections of large abnormal immunoblasts. Differentiated from T-IBS by plasmacytoid features. Nucleoli often central and prominent, nucleus appears vesicular owing to margination of chromatin with resultant thick nuclear membrane.	Abnormal immune states (immunosuppression, α-chain disease, SLE, Hashimoto thyroiditis, drug hypersensitivity). IBL frequently precedes development of lymphoma. Rapidly progressing neoplasm.
IBS-T cell	
In sections transformed lymphocytes have pale, water-clear cytoplasm with well defined interlocking plasma membranes giving a cohesive appearance. Nucleus round or oval with fine, evenly distributed chromatin and one or more small but distinct nucleoli. Reactive histiocytes may be present in large numbers.	Entity may be distinguished morphologically and immunologically from B-IBS. No prior abnormal immune disorders found as yet. Clinically appears less aggressive than B cell type.

Histopathology

According to the Rappaport classification histiocytic lymphoma accounted for two thirds (19 of 29) of cases (Table 6). All poorly differentiated lymphocytic and mixed cases were nodular, as were two of the 19 histiocytic cases.

The case distribution according to the Lukes-Collins classification is shown in Table 7, and Table 8 gives a definition of the observed cell types. Follicular center cell lymphomas accounted for 21 cases or 72%, while immunoblastic sarcoma occurred with a frequency of 28%. Functionally at least 83% were of B cell type. The 21 FCC lymphomas are B cell neoplasms by definition. Of the eight cases of IBS seven were classified as B cell type on morphologic basis even though only three were positive for cytoplasmic Ig. One case was regarded as T cell type morphologically.

Lymphomas of the *small cleaved FCC* type with a follicular pattern accounted for five cases. The diagnosis of this type of lymphoma in the absence of coexisting Hashimoto's disease was quite straight forward. The lymphoid follicles were predominantly composed of cleaved FCC, as opposed to reactive follicles which show a wide range of small cleaved FCC and transformed cells, plus tingible body macrophages. Cleaved nucleated cells were also found in the inter-follicular tissue. In two cases an associated chronic lymphocytic thyroiditis was also present, and the diagnosis was more difficult.

Lymphomas of *large cleaved FCC* type occurred in two cases. Both were follicular and diffuse and one had evidence of sclerosis in the tumorous areas, without associated thyroiditis. Chronic lymphocytic thyroiditis was noted in the other case, which was difficult to classify and had a very short survival

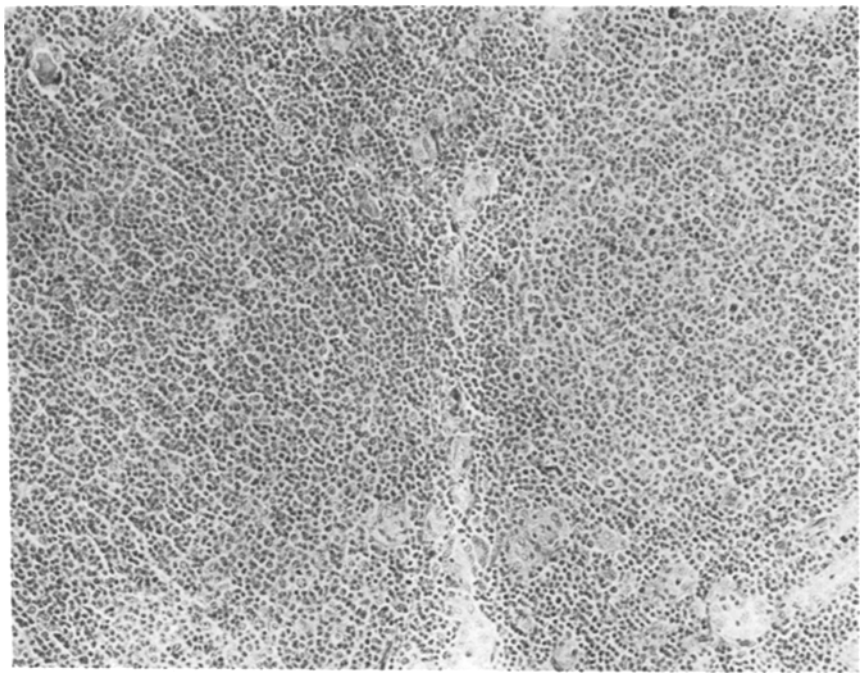

Fig. 1. Follicular area of a small cleaved FCC tumor (H&E 46×)

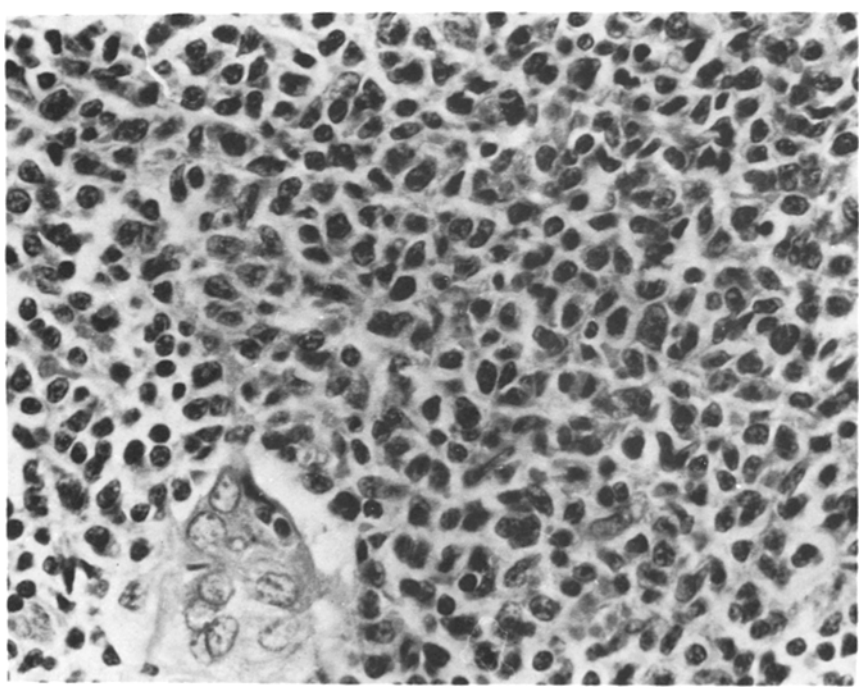

Fig. 2. Small cleaved FCC lymphoma with abundance of irregularly shaped lymphocytes with dense chromatin, nuclear clefts and scant or absent cytoplasm (H&E 740×)

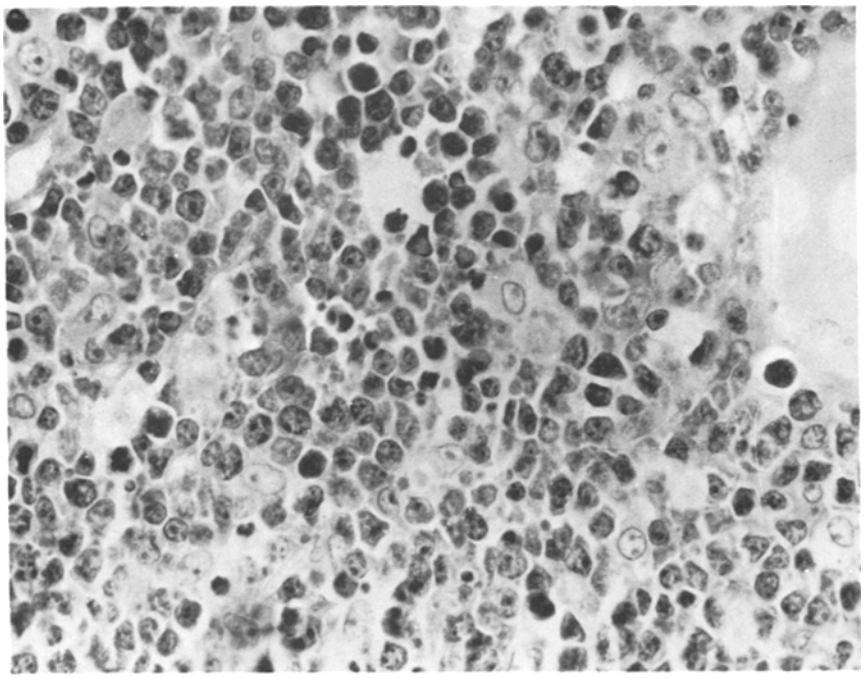

Fig. 3. Small non-cleaved FCC lymphoma (so-called non-Burkitt type) with predominance of round transformed lymphocytes, the nuclei of which are smaller than the nuclei of the phagocytes. Note many pyknotic cells and mitoses (H&E 740 ×)

indicating that a proportion of transformed cells may have been present in parts of the tumor not sampled.

Tumors of *small non-cleaved or transformed FCC* type (Burkitt-like) occurred in two patients. In both cases the pattern was diffuse. In one only a small biopsy was available and showed definite sclerosis, probably due to a chronic thyroiditis which had been histologically proven five years previously. This patient presented with gastric involvement with cytologic features typical of this type shortly after the diagnosis of lymphoma was established in the thyroid, a behavior typical of this tumor (Wright, 1978).

Lymphomas of the *large non-cleaved or transformed FCC* type occurred in 12 cases and *immunoblastic sarcomas (IBS)* in eight. Together they accounted for 69% of this series and also formed the bulk of the histiocytic lymphoma group according to the Rappaport classification. Large non-cleaved FCC tumors, four of which had a partially follicular pattern, and B-IBS were distinguished by the criteria outlined in Table 8. Problems of fixation in several cases which had been stored for more than 15 years and which had been processed at various institutions sometimes made this distinction difficult by distortion of cytologic details.

Large polyploid cells, resembling Reed-Sternberg cell variants were present in four cases of IBS.

Fig. 4. Diffuse infiltration of thyroid by a large non-cleaved FCC tumor. Note residual inflammatory infiltrate in the lower right hand corner (H&E 46×)

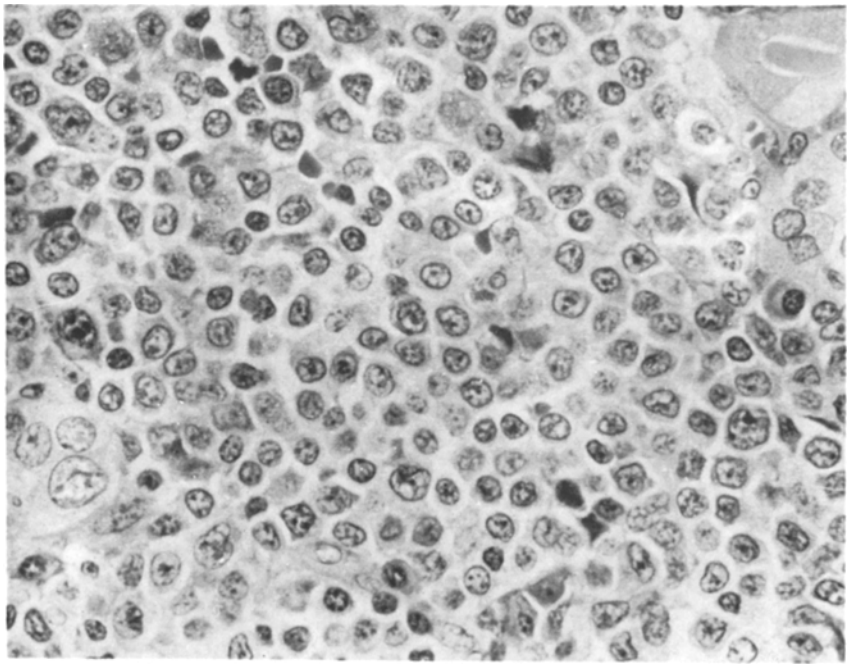

Fig. 5. Cytology of large non-cleaved FCC tumor. Note the vesicular nuclei with one or two medium sized nucleoli sometimes appositioned at the nuclear membrane. Cytoplasm is clearly visible. Note also differences in nuclear appearance of the thyroid epithelial cells (H&E 740×)

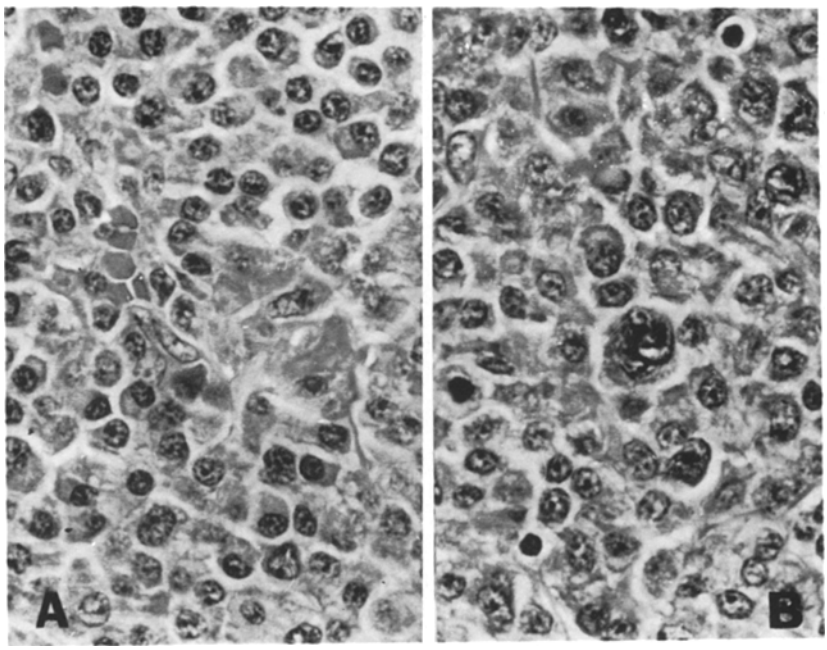

Fig. 6. Immunoblastic sarcoma of B cell type with plasmacytoid features of the tumor cells (**A**) and more pleomorphic areas (**B**) (H & E 740×)

The affected thyroid tissue usually showed complete destruction of epithelial structures in the large cell lymphoma group. Sometimes residual single epithelial cells were found. The PAS stain was helpful in distinguishing these cells from reactive histiocytes and to detect residual small foci with thyroid colloid (strong PAS positivity) in cases where no residual unaffected gland tissue was visible.

Evidence of local invasive growth was present in 11 cases, all of which were of IBS or large non-cleaved FCC type. Involvement of regional lymph nodes was found in 13 cases, namely four small cleaved FCC, one small non-cleaved FCC and three large non-cleaved FCC tumors and 5 IBS.

Chronic lymphocytic thyroiditis of Hashimoto's type was diagnosed if the non-tumerous thyroid showed the following features: a lymphocytic infiltrate, focal or diffuse, with an admixture of plasma cells, formation of reactive follicles and eosinophilic changes of epithelial cells (Meissner, 1978). Small focal lymphoid infiltrates, probably representing nonspecific thyroiditis, which are frequently encountered in a tumorous or goiterous thyroid, were not considered sufficient histological proof of potentially autoimmune thyroiditis for the purpose of this study. Involvement with thyroiditis was classified semiquantitatively as focal or diffuse (if the foci were large and coalescent) and graded as one + to three +.

Nine of our 29 patients lacked sufficient thyroid uninvolved by tumor for evaluation, but in two a histologic diagnosis of Hashimoto's disease had been established on earlier biopsies. The results from these 22 patients are summarized

Table 9. Thyroid lymphoma: histologic association with chronic lymphocytic thyroiditis of Hashimoto type (22 cases)

Cell type	No. of cases	No, of cases with histologic thyroiditis
Small cleaved	4	2
Large cleaved	2	1
Small non-cleaved	1	1
Large non-cleaved[a]	10	9
IBS	5	5
Total	22	18

[a] One case also showed a small papillary carcinoma.

in Table 9. Eighteen (82%) had definite evidence for chronic thyroiditis, the association being highest among IBS (100%) and large non-cleaved FCC tumors (90%).

The most frequent finding was that of a diffuse (13) infiltrate of massive 3+ type (11). Fibrosis, destruction and scarring of the glandular tissue were present in 11 cases and correlated with the degree of lymphoid infiltration in their expression. Epithelial changes ranged from focal to extensive Hurthle cell transformation. Oxyphilic epithelial change was not observed in cases free of thyroiditis, either in tumor or in the transition zone between tumor and uninvolved thyroid. This tends to confirm Lindsay and Dailey's (1955) assumption that the epithelial changes are not caused by the tumor alone.

Immunoperoxidase

Sections from 24 cases were examined by this method (Table 10). In five no specific staining for immunoglobulin was detectable. Morphologic plasma cells were present in these cases and showed no detectable staining. The tissue in all five cases had been stored for 17 years or more, and details of original fixation and processing were unknown.

Immunoglobulin containing plasma cells were demonstrable at or around the tumor margins in the remaining 19 cases, serving as an intrinsic positive control. In seven of these, tumor cells lying adjacent to positive staining plasma cells showed no evidence of staining for immunoglobulin. In 12 cases tumor cells contained immunoglobulin components. In four the pattern of staining was clearly monoclonal (exclusively κ or λ) and in three probably so. In one case a polytypic ("polyclonal") pattern was observed in cells that were considered to be part of the neoplastic population. In four cases the staining was so slight as to preclude an assessment of clonality. Plasma cells showed a polyclonal pattern of staining in all cases, and were so numerous in some that an assessment of the clonality of the tumor cell population was difficult. In 22 cases tumor cells showed no specific staining with anti-lysozyme sera, but in two there was weak staining of tumor cells with anti-lysozyme; one of

Table 10. Thyroid lymphoma: pattern of immunoperoxidase staining of Ig (24 cases)

Pattern of Ig staining	No. of cases	Lymphoma type	
Tumor cells *Ig negative*	12		
– reactive plasma cells also negative	(5)	– Small cleaved FCC	(1)
		– Large non-cleaved FCC	(3)
		– IBS	(1)
– reactive plasma cells definitely positive	(7)	– Small cleaved FCC	(1)
		– Large cleaved FCC	(1)
		– Large non-cleaved FCC	(3)
		– IBS	(2)
Tumor cells *Ig positive*	12		
– monoclonal and possibly monoclonal	(7)	– Large cleaved FCC	(1)
		– Small non-cleaved FCC	(1)
		– Large non-cleaved FCC	(2)
		– IBS	(3)
– polyclonal	(1)	– Small non-cleaved FCC	(1)
– weak or equivocal staining	(4)	– Large non-cleaved FCC	(3)
		– IBS	(1)

these also contained immunoglobulin. These findings established a definite B cell nature of at least seven cases.

Survival

The survival of 28 patients was known. Two were excluded for the further calculations because the follow-up period was less than one year.

Figure 7 shows the probability of overall survival in the 26 patients. The median survival was 21 months. Five patients survived for five years or more and the probability of five year survival was 40%. In all, 15 patients died, 12 due to their disease, three of unrelated causes. Of those who died of disease, ten did so within 24 months, the others at 51 and 61 months. Figure 8 analyzes the probability of survival by clinical stage in 18 patients with confirmed clinical staging. Stage I and II cases were predominantly of the large non-cleaved group, while the stage IV contained principally IBS and two small non-cleaved cases. Stage I and II patients had a median survival of 28 months, those in stage IV of seven months. The difference in medians was significant at a confidence level of $p=0.01$.

Figure 9 shows the survival according to cell types. Again there is a striking difference in the median survival between large non-cleaved FCC tumors and IBS, 31.5 months for the large non-cleaved versus eight months for the IBS, although this difference was not statistically significant due to the small number of cases.

In Fig. 10 the survival is analyzed by a combination of cell type and limited clinical stage on 14 cases of large non-cleaved FCC and IBS. Again, median survival for the large non-cleaved tumors in stage I and II was 31.5 months

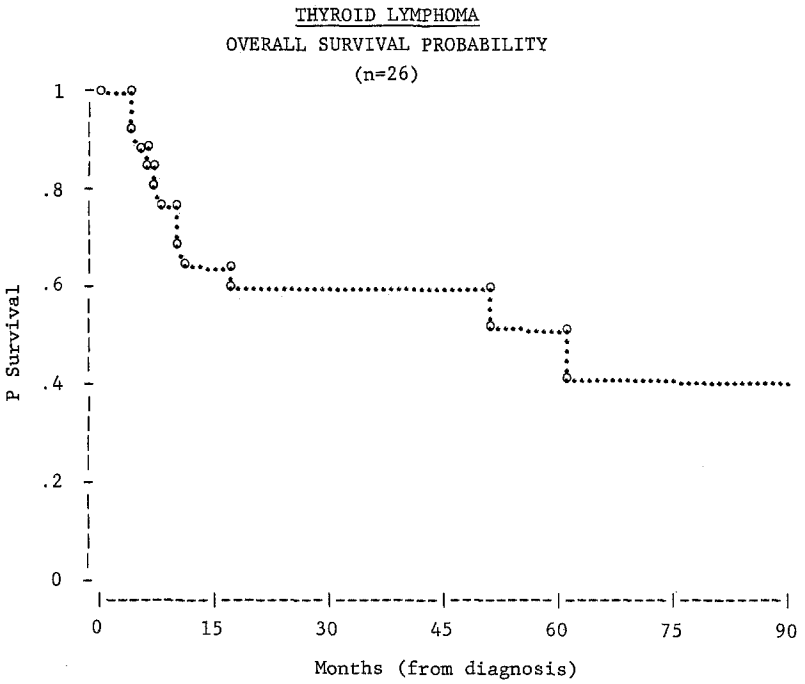

Fig. 7. Overall survival probability of 26 cases of thyroid lymphoma. Probability of five year survival 40%

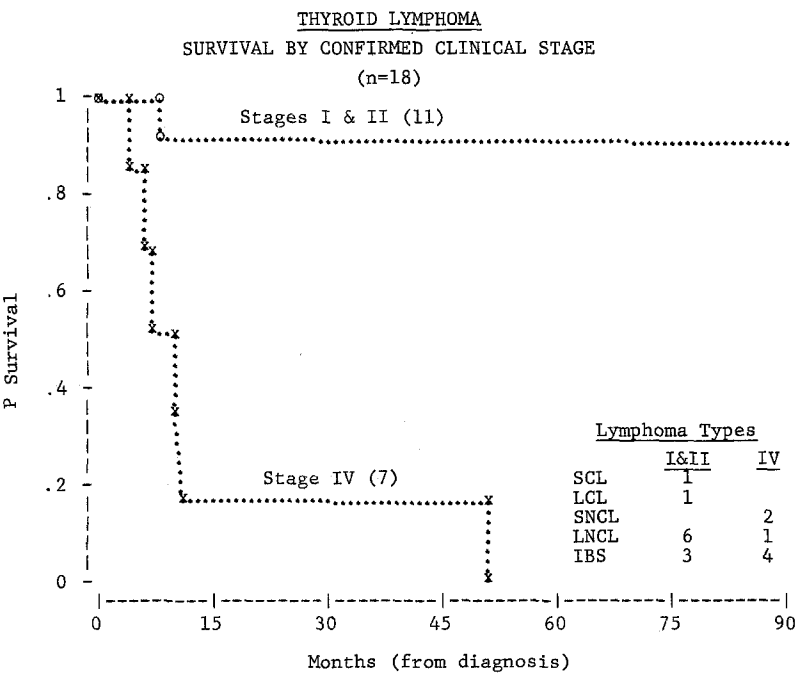

Fig. 8. Survival by clinical stage. Difference in survival between stage I/II and stage IV disease is statistically significant ($p=0.01$)

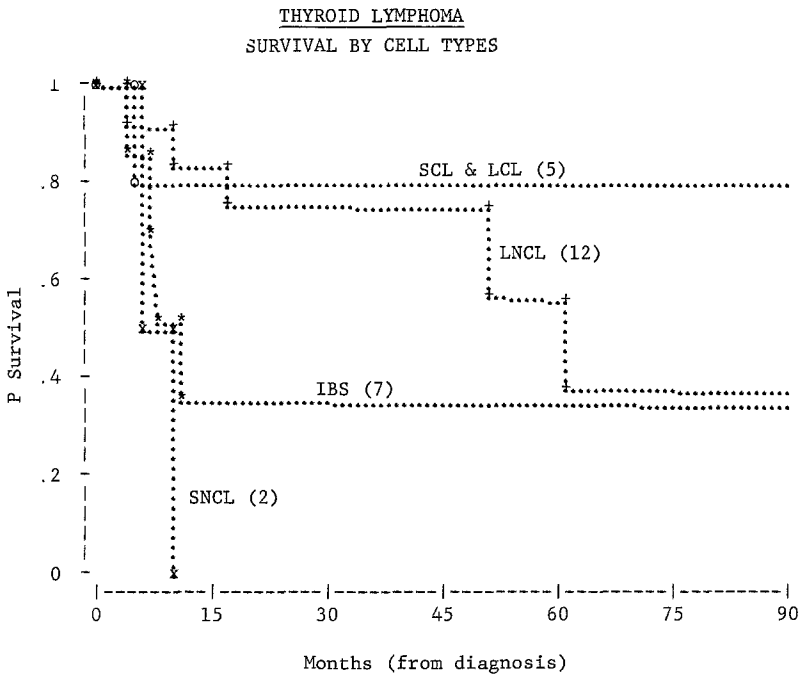

Fig. 9. Survival of thyroid lymphoma by cell type (SCL = small cleaved; LC = large cleaved; S/LNCL = small/large non-cleaved FCC lymphoma; IBS = immunoblastic sarcoma)

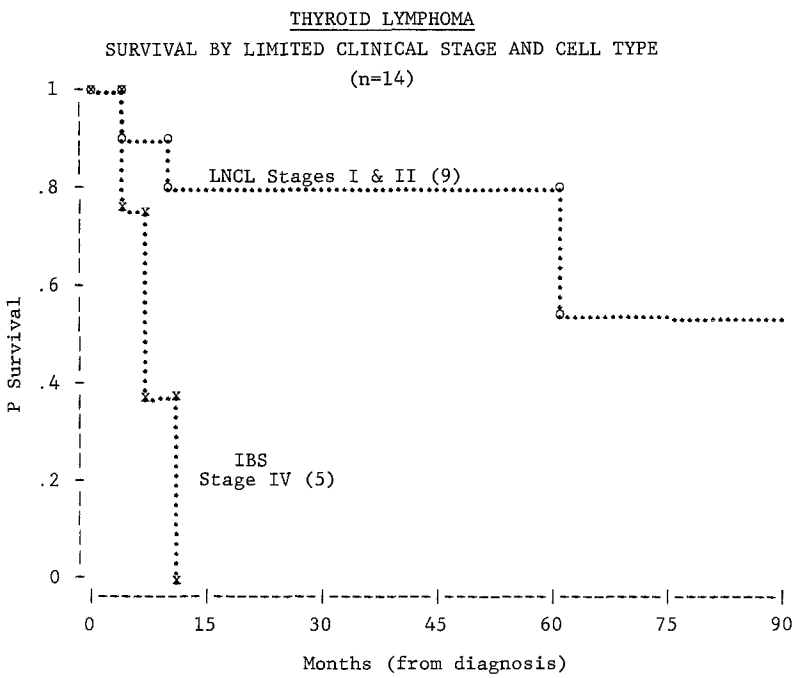

Fig. 10. Survival by cell type and limited clinical stage showing close similarity to survival curve by stage alone and indicating a possible relation between cell type and clinical stage

versus 5.5 months for IBS stage IV. This difference was not statistically significant ($p=0.058$) because the number of cases in each group is small. Comparison of Fig. 8, 9 and 10 strongly suggests, however, that survival my mainly be dependent on the prevalent cell type, since the survival for stage alone is very similar to the survival according to cell type as well as according to cell type and stage. We cannot prove this hypothesis, however, because of the limited number of cases and the short follow-up period. The Chi-square test on stage versus cell type showed no significant correlation ($p=0.12$). Age, local invasion and local node involvement had no detectable relationship to survival.

Discussion

The findings in this study indicate that malignant lymphomas do in fact occur in the thyroid, and that those which are primary in the gland arise preferentially in the abnormal immune state of chronic lymphocytic thyroiditis of Hashimoto type. Recognition and clinically meaningful classification of thyroid lymphoma can be achieved by a functional immunologic approach. Distinction of primary and secondary tumors can also be achieved to some degree because certain cell types seem primarily to involve the gland as part of an otherwise generalized disease, while others are usually restricted to the organ. Functionally, lymphomas of the thyroid are almost exclusively of B cell type.

We found histologic evidence for chronic thyroiditis of Hashimoto type in 18 of 22 cases or 82% of all cell types and in 90%–100% in cases of large non-cleaved FCC tumors and IBS. The biologic significance of this marked association between lymphoma and chronic thyroiditis was confirmed by examination of the thyroids from 100 consecutive autopsies from the files of the LAC-USC Medical Center. Only one case of chronic thyroiditis, and four cases with focal lymphoid infiltrates were identified.

This association parallels the observation of lymphomas in other autoimmune disease, notably Sjögren's syndrome (Talal and Bunim, 1964; Anderson and Talal, 1972; Zulmann et al., 1978). Lymphomas have also been observed in a wide variety of congenital and acquired immunologic disorders e.g. therapeutic immunosuppression, SLE, glutensensitive enteropathy, Waldenström's disease, immunoblastic lymphadenopathy and CLL (Lukes et al., 1978 b). Many patients with IBS have clinical signs of preexisting immunologic disorders (Lichtenstein et al., 1979). It has been proposed that these lymphomas which are tumors of transformed lymphocytes possibly develop through a "switch-on" of the lymphocyte transformation sequence in an altered immune state (Lukes and Collins, 1974). Immunohistological studies have shown that IBS arising in these circumstances is often of B cell type (Taylor, 1976, 1978b; Zulmann et al., 1978). The findings in this study now provide evidence for the B cell nature of the majority of lymphomas arising in chronic thyroiditis.

It is postulated that these lymphomas represent the emergence of a malignant clone following a phase of prolonged antigenic stimulation of an immune system that develops progressive abnormalities or is abnormal ab initio. The predominance of B cell lymphomas in patients with chronic lymphocytic thyroiditis

suggests a defect in the control of the B cell system, either an intrinsic failure of the B cells to respond to control signals or an abnormality of the T cell helper/suppressor cell system that normally modulates the B cell response. Therefore, it may be assumed that FCC lymphomas associated with chronic lymphocytic thyroiditis (13 of 17 cases) could arise from prolonged follicular hyperplasia and IBS from a loss of control over the post-follicular immunoblast-plasma cell step of lymphocyte transformation in chronic immunologic reaction. The potential origin of FCC lymphomas from abnormal follicles is also supported by the observation of a seeming morphologic transition from abnormal reactive follicles to unequivocal tumor in some cases with severe thyroiditis, a finding also reported by Burke et al. (1977). Possibly both autoimmunity and the associated lymphoma could stem from the same underlying immunodeficiency (Vianna, 1978). This postulate ist consistent with growing evidence for a key role of genetics in the susceptibility for disease, as expressed by reported associations between certain HLA types and "autoimmune" diseases. Thus, Terasaki (1978) recently found an increase of HLA-type AW 30 in patients with Hashimoto's disease, while Grave's disease was associated with an increased frequency of B8. Similarly, Brewerton and Albert (1977) reported an association of Sjögren's syndrome with HLA B8-DW3. However, the rarity of lymphoma in Hashimoto's disease (Crile, 1978) suggests that other factors are also involved.

This study is the first to compare the use of the Rappaport classification (Rappaport, 1966) and the Lukes-Collins classification on a series of thyroid lymphomas, two other studies already having applied the similar Kiel classification (Schwarze and Papadimitriou, 1977; Heimann et al., 1978).

Recognition of the cytologic types of Lukes and Collins (1974; Lukes et al., 1978b) and appropriate classification of the tumors was feasible in this series. One of the main features of the Lukes-Collins classification is its attempt to relate the lymphomas to the basic immunologic process and to classify the tumors according to their functional origin (Lukes et al., 1978a, b; Lukes and Parker, 1978). The traditional Rappaport classification does not relate to the underlying process. It has furthermore been shown that the cytologic types of Rappaport are highly heterogeneous, particularly the histiocytic one (Lukes and Collins, 1974; Lukes, 1978; Strauchen et al., 1978; Li and Harrison, 1978). Using the Rappaport classification, 19 cases, or 66% of the series, fell into the histiocytic group, which is in general agreement with most previous studies that have reported a clear predomiance of this type, or reticulosarcoma in the older nomenclature (Crile, 1963; Rayfield et al., 1971; Shimkin et al., 1969; Woolner et al., 1966; Burke and Butler, 1977; Abel and Finnerty, 1969; Ayala et al., 1968; Bisbee and Thoeny, 1975; Shin, 1976; and Schwarze and Papadimitriou, 1977). A direct comparison can, however, only be made with the study of Burke and Butler (1977) for that is the only one in which the histologic classification was carried out strictly according to the Rappaport system.

The 19 cases in the histiocytic group in this report could be divided into 10 large transformed FCC, one large cleaved FCC, and eight IBS. The B lymphocytic nature of these tumors was demonstrated by the findings in seven of them of a monoclonal cytoplasmic Ig pattern by the immunoperoxidase method. In another four cases staining was of weak or equivocal nature, and in a

further eight cases tumor cells only or tumor cells and reactive plasma cells did not stain immunologically due to effects of poor fixation, processing and prolonged storing.

IBS of B cell type is distinguished from the lymphomas of the large non-cleaved (transformed) FCC type by predominance of a larger cell with coarsely clumped chromatin in a vesicular nucleus, and a larger amount of deeply staining, often amphophilic cytoplasm. The tumor cells in a typical case exhibited a variable degree of plasmacytoid features associated with marked pyroninophilia. In one case there was a range of cells from slightly abnormal plasma cells to fully transformed and sometimes pleomorphic immunoblasts, which accounts for the original diagnosis of plasmacytoma in this case. Judged by the illustrations, both cases of More et al. (1972) would be classified as IBS in the Lukes-Collins scheme. In the four cases of plasma cell neoplasm of the thyroid reported by Shimaoka et al. (1978), three were associated with generalized disease and serum paraproteinemia. Histologically they exhibited nearly mature plasma cells infiltrating the thyroid and all had plasmacytosis of the bone marrow. The other case presented histologic features and a clinical course which would be in keeping with immunoblastic sarcoma. It thus becomes obvious that IBS of B cells has a broad range of morphologic expressions reaching from tumors dominated by large transformed cells or immunoblasts to tumors composed of cells with primarily plasmacytoid differentiation.

It is essential to recognize these tumors as a group of post follicular lymphocyte neoplasms conceptually (Lukes et al., 1974, 1978b), and to differentiate them from "well differentiated" plasmacytoma and multiple myeloma which, though they share a common origin from cells of the B cell series, are different diseases clinically.

Burke and Butler (1977) acknowledged that their "histiocytic" cases exhibited features of immunoblastic sarcoma and constituted tumors of transformed lymphocytes rather than histiocytes. Our present study confirms these suspicions and substantiates the cytologic heterogeneity of "histiocytic" lymphoma.

In contrast to Burke and Butler (1977) who found only one lymphoma of small lymphocytes (nodular poorly differentiated lymphocytic type of Rappaport) in an otherwise homogeneous group of histiocytic tumors, nine cases or 30% of our series fell into the non-histiocytic types. Five cases were of the small cleaved FCC type with a follicular pattern (nodular PDL), two of the large cleaved FCC type (mixed or histiocytic) and two of the small non-cleaved (undifferentiated) type. They were of the so-called non-Burkitt type according to the WHO criteria (Berard et al., 1969) and were also found in the thyroid by Rayfield et al. (1971). One of the cases had simultaneous gastric involvement, rendering the decision as to the primary site impossible. Involvement of abdominal viscera as well as endocrine organs is a common feature in this lymphoma (Wright, 1978).

In three cases of FCC lymphoma, two of small cleaved and one of a partially follicular large non-cleaved cell type, separation of reactive and neoplastic components was difficult. This was particularly so in the large non-cleaved case in which many follicle centers (including those in a neck node) consisted predomi-

nantly of cleaved cells of various sizes, but lacked the transformed cell component seen in typical reactive follicles. In this case coexisting diffuse areas of the tumor served to establish the diagnosis.

In the small cleaved FCC tumors the loss of the lymphocytic mantle of the follicles and the finding of the abnormal cleaved cells in the interfollicular area pointed to a diagnosis of lymphoma. In the case of a large non-cleaved FCC lymphoma a severe thyroiditis of predominantly diffuse type was also present and separation of tumor and inflammatory elements was again difficult. The finding of cohesive areas of monomorphous and cytologically malignant cells permitted a diagnosis. This last criterion is of general importance in the separation of benign and malignant lymphatic proliferations, and was strictly observed in these cases, as suggested by Burke and Butler (1977). Other features aiding in the differential diagnosis between thyroiditis and lymphoma were the observation of the mixture of cell types comprising the inflammatory infiltrate, and the finding of capsular and soft tissue invasion, and local lymph node involvement in lymphomas (Burke and Butler, 1977).

Lymphomas of the thyroid are almost exclusively of the B cell type because they either belong to the FCC tumors and may be follicular or follicular and diffuse or they can be shown to contain cytoplasmic Ig in the case of the diffuse IBS. Actually, of our 21 cases of FCC lymphomas 11 were follicular or follicular and diffuse. By use of the immunoperoxidase method we could demonstrate positive Ig in 12 cases, monoclonal marking for light chains occurring in seven cases of diffuse tumors, namely four large non-cleaved FCC tumors and three IBS. That all FCC lymphomas are of B cell origin has been shown repeatedly by functional studies (Lukes et al., 1978a, b; Lennert, 1975; Green et al., 1975; Leech et al., 1975). We thus have evidence for the B cell nature of at least 24 of our 29 cases. One IBS was felt to be of T cell type morphologically. A case of a T cell lymphoma in the thyroid was recently reported by Dunbar et al. (1977). The description of the morphology does not allow a classification, but the published EM picture of a rosette-forming cell does not represent a fully transformed lymphocyte or immunoblast. Thus T cell lymphomas may occur in the thyroid, albeit rarely; however, the majority appear to be of B cell type.

The differential diagnosis between lymphoma and anaplastic carcinoma of the small cell type according to the WHO classification (Hedinger and Sobin, 1974) was not specifically examined in this study, since we did not study all small cell tumors of the thyroid, but only definite lymphomas. The diagnosis of carcinoma rests upon the demonstration of epithelial structures, which may be found only after extensive search of many blocks and slides (Neracher and Hedinger, 1975; Meissner and Warren, 1969). Similarly, the diagnosis of lymphoma should be made by attention to the positive identifying features described earlier. It must be stressed though, that to achieve a high standard of morphologic diagnosis, cytologic detail must be ecxellent and adequate fixation and thin sections are absolute prerequisites (Lukes et al., 1978a, b; Lukes, 1978; Maurer and Lukes, 1979). In questionable cases electronmicroscopy may be helpful in detecting either epithelial or lymphoid cellular differentiation (Came-

ron et al., 1975; Egloff, 1977), or the application of immunoperoxidase might detect cytoplasmic Ig in some larger cells which always are part of small cell lymphomas.

In four of our IBS cases polyploid cells, which sometimes closely resembled Reed-Sternberg cells, were found. In none of these cases was a diagnosis of Hodgkin's disease tenable, since the general features of the process did not relate to any of the histologic types of this disease and since Reed-Sternberg cells may be observed in association with any type of immunoblastic reaction, as for instance infectious mononucleosis (Tindle et al., 1972). Similar appearing cells do occur in both types of large cell lymphomas (FCC and IBS). In view of the postulate that Reed-Sternberg cells may be a product of abnormal lymphocyte transformation (Anagnostou, 1977; Taylor, 1978b; Lukes and Parker, 1978) this is perhaps not surprising. Hodgkin's disease has been reported in the thyroid (Abel and Finnerty, 1969; Gibson et al., 1968; Schwarze and Papadimitriou, 1977), but was not observed in several large series of thyroid neoplasms (Neracher and Hedinger, 1975; Selzer et al., 1977; Hedinger, 1969; Woolner et al., 1966), and its occurrence as a true primary in the thyroid seems questionable (Schwarze and Papadimitriou, 1977).

The clinical usefulness of the application of the Lukes-Collins classification to thyroid lymphoma is suggested by the survival data and by the observation, that the predominant cell type seems to distinguish between true primary lymphomas of the thyroid and lymphomas presenting in the thyroid in an otherwise disseminated disease.

In our series the overall chance of five year survival was 40%, the median survival 21 months. Separately examining survival in relation to stage, cell type, and stage combined with cell type, it became apparent that the survival patterns for stage and cell types were very similar, which could indicate that stage and survival could be directly related to cell type; due to the small case groups we were not able to demonstrate this relationship statistically. Nevertheless, our data suggest that tumors of the large non-cleaved FCC type have a tendency to be restricted to the thyroid, while the IBS tend to be more aggressive and locally infiltrative. Two cases with Stage I and II IBS on the other hand, show that this disease is potentially curable by resection. One of these patients died 11 months after surgery due to a myocardial infarction, and the other is currently free of disease at 24 months.

Both cases of the small non-cleaved FCC tumor (non-Burkitt type) had the typical short survival and presented in stage IV. The tumors of the small cleaved FCC type on the other hand demonstrated the paradox between presentation in stage IV due to bone marrow involvement paired with a long survival. None of our patients in this group died, the longest survival being 131 months.

True primary lymphomas of the thyroid seemed to be restricted to the large non-cleaved FCC type and IBS, because they presented mainly in stage I involving the gland only or were characterised by local invasive growth in higher stages. Lymphomas of the small cleaved FCC type predominantly had a stage IV due to bone marrow involvement when clinically presenting in the thyroid, a behaviour identical to that in nodal presentation. Lymphomas

of this type can therefore hardly be regarded as a primary when presenting in the thyroid and more likely represent systemic disease ab initio. This may also be true for the small non-cleaved FCC type.

Thus it becomes of great clinical importance to determine the exact cell type according to Lukes and Collins, since it seems to have an important prognostic meaning and may considerably influence further workup and treatment of the patient.

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References

Abel, W.G., Finnerty, J.: Primary Hodgkin's disease of thyroid. N.Y. State J. Med. **69**, 314–315 (1969)

Anagnostou, D., Parker, J.W., Taylor, C.R., Tindle, B.H., Lukes, R.J.: Lacunar cells of nodular sclerosing Hodgkin's disease. Cancer **39**, 1032–1043 (1977)

Anderson, L.G., Talal, N.: The spectrum of benign to malignant lymphoproliferation in Sjogren's syndrome. Clin. Exp. Immunol. **10**, 199–221 (1972)

Ayala, A., Sloane, J., Wolha, R.J. Jr.: Coexistent lymphoma, adenocarcinoma and struma lymphomatosa. J.A.M.A. **204**, 829–831 (1968)

Berard, C.W., O'Conor, G.T., Thomas, L.B., Torloni, H.: Histopathological definition of Burkitt's tumor. Bull. W.H.O. **40**, 601–607 (1969)

Bisbee, A.C., Thoeny, R.H.: Malignant lymphoma of the thyroid following irradiation. Cancer **35**, 1296–1298 (1975)

Brewerton, D.A., Albert, E.: Rheumatology. In: HLA and disease, Dausset, J., Svejgaard, A. (eds.), pp. 94–107. Copenhagen/Munksgaard/Baltimore: Williams & Wilkins Co. 1977

Brown, J., Solomon, D.H., Beall, G.N., Terasaki, P.I., Chopra, I.J., van Herle, A.J., Wu, S.Y.: Autoimmune thyroid diseases – Graves' and Hashimoto's. Ann. Intern. Med. **88**, 379–391 (1978)

Burke, J.S., Butler, J.J., Fuller, L.M.: Malignant lymphomas of the thyroid: A clinical pathologic study of 35 patients including ultrastructural observations. Cancer **39**, 1587–1602 (1977)

Cameron, R.G., Seemayer, T.A., Wang, N.S., Ahmed, M.N., Tabah, E.J.: Small cell malignant tumors of the thyroid. A light and electron microscopic study. Hum. Pathol. **6**, 731–740 (1975)

Cox, M.T.: Malignant lymphoma of the thyroid. J. Clin. Pathol. **17**, 591–601 (1964)

Crile, G. Jr.: Lymphosarcoma and reticulum cell sarcoma of the thyroid. Surg. Gynecol. Obstet. **116**, 449–450 (1963)

Crile, G. Jr.: Struma lymphomatosa and carcinoma of the thyroid. Surg. Gynecol. Obstet. **147**, 350–352 (1978)

Cureton, R.J.R., Harland, D.H.C., Hosford, J., Pike, C.: Reticulosarcoma in Hashimoto's disease. Br. J. Surg. **44**, 561–566 (1957)

Dunbar, J.A., Lyall, M.H., MacGillivray, J.B., Potts, R.C.: T-cell lymphoma of the thyroid. Br. Med. J. **2**, 679 (1977)

Egloff, B.: Nicht-epitheliale Tumoren des Schilddrüse. Verh. Dtsch. Ges. Pathol. **61**, 298–224 (1977)

Gibson, J.M., Prinn, M.G.: Hodgkin's disease involving the thyroid gland. Br. J. Surg. **55**, 236–238 (1968)

Green, I., Jaffe, E., Shevach, E.M., Edelson, R.L., Frank, M.M., Berard, C.W.: Determination of the origin of malignant reticular cells by the use of surface membrane markers. In: The reticuloendothelial system. International Academy of Pathology Monograph, Rebuck, J.B., Berard, C.W., Abell, M.R. (eds.), No. 16, pp. 282–300. Baltimore: The Williams and Wilkins Co. 1975

Hedinger, C.E.: Sarcomas of the thyroid gland. In: Thyroid cancer. UICC Monograph Series, Hedinger, C.E. (ed.), No. 12, pp. 47–52. New York/Berlin: Springer 1969

Hedinger, Chr., Sobin, L.: Histological typing to thyroid tumors. International histological classification of tumors No. 11. Geneva: World Health Organization 1974

Heimann, R., Vannineuse, A., de Sloover, C., Dor, P.: Malignant lymphomas and undifferentiated small cell carcinoma of the thyroid: a clinicopathological review in the light of the Kiel classification for malignant lymphomas. Histopathology **2**, 201–313 (1978)

Kenyon, R., Ackerman, L.V.: Malignant lymphoma of the thyroid apparently arising in struma lymphomatosa. Cancer **8**, 964–969 (1955)

Kojima, M., Imai, Y., Mori, N.: A concept of follicular lymphoma. A proposal for the existence of a neoplasm originating from the germinal center. In: Malignant Diseases of the Hematopoietic System. GANN Monograph on Cancer Research No. 15. Akazaki, K., Rappaport, H., Berard, C.W., Bennett, J.M., Ishikawa, E. (eds.), pp. 195–207. Tokyo: University of Tokyo Press 1973

Leech, J., Glick, A., Horn, R., Collins, R.: Immunologic histochemical and ultrastructural studies of malignant lymphomas presumed to be of follicular center cell origin. J. Natl. Cancer Inst. **54**, 11–21 (1975)

Lennert, K.: Follicular lymphoma. A tumor of the germinal centers. In: Malignant diseases of the hematopoietic system. GANN Monograph on cancer research No. 15. Akazaki, K., Rappaport, H., Berard, C.W., Bennett, J.M., Ishikawa, E. (eds.), pp. 217–231. Tokyo: University of Tokyo Press 1973

Lennert, K., Stein, H., Kaiserling, E.: Cytological and functional criteria for the classification of malignant lymphomata. Br. J. Cancer Suppl. **2**, 29 (1975)

Lennert, K.: Maligne Lymphome. Handbuch der speziellen pathologischen Anatomie und Histologie. Band I/3B. O. Lubarsch, F. Henke, R. Roessle, E. Uehlinger (eds.). New York/Berlin/Heidelberg: Springer 1978

Leontsakis, B., Georgiadis, N.: Malignant tumors of the thyroid. Int. Surg. **61**, 455–459 (1976)

Li, C.Y., Harrison, E.G. Jr.: Histochemical and immunohistochemical study of diffuse large-cell lymphomas. Am. J. Clin. Pathol. **70**, 721–732 (1978)

Lichtenstein, A., Levine, A.M., Lukes, R.J., Taylor, C.R., Cramer, A.D., Lincoln, T.L., Feinstein, D.I.: Immunoblastic sarcoma: a clinical description. Cancer **43**, 343–352 (1979)

Lindsay, S., Dailey, M.E.: Malignant lymphoma of the thyroid gland and its relation to Hashimoto disease: A clinical and pathologic study of eight patients. J. Clin. Endocrinol. **15**, 1332–1353 (1955)

Lukes, R.J., Collins, R.D.: New observations on follicular lymphoma. In: Malignant diseases of the hematopoietic system. GANN monograph on cancer research No. 15. Akazaki, K., Rappaport, H., Berard, C.W., Bennett, J.M., Ishikawa, E. (eds.), pp. 298–215. Tokyo: University of Tokyo Press 1973

Lukes, R.J., Collins, R.D.: Immunologic characterization of human malignant lymphomas. Cancer **34**, 1488–1503 (1974)

Lukes, R.J., Collins, R.D.: New approaches to the classification of the lymphomata. Br. J. Cancer **31**, Suppl. 2, 1–28 (1975)

Lukes, R.J., Collins, R.D.: The Lukes-Collins classification and its significance. Cancer Treatment Rep. **61**, 1–9 (1977)

Lukes, R.J., Taylor, C.R., Parker, J.W., Lincoln, T.L., Pattengale, P.K., Tindle, B.H.: A morphologic and immunologic surface marker study of 299 cases of non-Hodkgin's lymphomas and related leukemias. Am. J. Pathol. **90**, 461–486 (1978a)

Lukes, R.J., Parker, J.W., Taylor, C.R., Tindle, B.H., Cramer, A.D., Lincoln, T.L.: Immunologic approach to non-Hodgkin's lymphoma and related leukemias. An analysis of the results of multiparameter studies of 425 cases. Semin. Hematol. **15**, 322–351 (1978b)

Lukes, R.J., Parker, J.W.: The pathology of lymphoreticular neoplasms. In: Immunopathology of the Lymphomas. Twomey, J.J., Good, R.A. (edsl), pp. 239–279. New York: Plenum Press 1978c

Lukes, R.J.: Functional classification of malignant lymphoma of Lukes and Collins. Recent Results Canc. Res. **64**, 19–30 (1978d)

Maurer, R., Lukes, R.J.: Eine neue funktionelle Interpretation maligner Lymphome. Die Lukes-Collins Klassification und ihre Grundlagen. Schweiz. med. Wschr. **109**, 76–86 (1979)

Meissner, W.A., Warren, J.: Tumors of the thyroid gland. Atlas of tumor pathology, 2nd series, Fasc. 4, pp. 121–123. Washington: Armed Forces Institute of Pathology, 1969

Meissner, W.A.: Pathology. In: The thyroid: A fundamental and clinical text, Werner, S.C., Ingbar, S.H. (eds.), 4th ed., p. 450. Hagerstown, Maryland: Harper & Row 1978
Neracher, H., Hedinger, C.: Klassifizierung der Schilddrüsenmalignome nach der Nomenklatur der WHO 1974. Schweiz. med. Wschr. **105**, 1000–1036 (1975)
Rappaport, H.: Tumors of the hematopoietic system. In: Atlas of tumor pathology, Section 3, Fasc. 8. Washington: Armed Forces Institute of Pathology 1966
Rayfield, E.J., Nishiyama, R.H., Sisson, J.C.: Small cell tumors of the thyroid. A clinicopathologic study. Cancer **28**, 1023–1030 (1971)
Schwarze, E.W., Papadimitriou, C.: Maligne Lymphome der Schilddrüse. Verh. Dtsch. Ges. Pathol. **61**, 328–335 (1977)
Selzer, G., Kahn, L.B., Albertyn, L.: Primary malignant tumors of the thyroid gland: A clinicopathologic study of 254 cases. Cancer **40**, 1501–1510 (1977)
Shimaoka, K., Gailani, S., Tsukada, Y., Barcos, M.: Plasma cell neoplasms involving the thyroid. Cancer **41**, 1140–1146 (1978)
Shimkin, P.M., Sagerman, R.H.: Lymphoma of the thyroid gland. Radiology **92**, 312–316 (1969)
Shin, K.H., Lott, J.S., Corbett, W.E., Garrett, P.G.: Malignant lymphoma of the thyroid gland. Can. J. Surg. **19**, 442–446 (1976)
Strauchen, J.A., Young, R.C., DeVita, V.T. Jr., Anderson, T., Fantone, J.C., Berard, C.W.: Clinical relevance of the histopathological subclassification of diffuse "histiocytic" lymphoma. N. Engl. J. Med. **299**, 1382–1387 (1978)
Talal, N., Bunim, J.J.: The development of malignant lymphoma in the course of Sjogren's syndrome. Am. J. Med. **36**, 529–540 (1964)
Taylor, C.R.: An immunohistological study of follicular lymphoma, reticulum cell sarcoma and Hodgkin's disease. Eur. J. Cancer **12**, 61–75 (1976)
Taylor, C.R.: Immunoperoxidase techniques: theoretical and practical aspects. Arch. Pathol. Lab. Med. **102**, 113–121 (1978a)
Taylor, C.R.: Upon the nature of Hodgkin's disease and the Reed-Sternberg cell. Recent Results Canc. Res. **64**, 214–231 (1978b)
Tindle, B.H., Parker, J.W., Lukes, R.J.: "Reed-Sternberg" cells in infectious mononucleosis? Am. J. Clin. Pathol. **58**, 607–617 (1972)
Vianna, N.J.: Epidemiology of lymphoreticular malignancies in man. In: Immunopathology of the lymphomas, Twomey, J.J., Good, R.A. (eds.), p. 181. New York: Plenum Press 1978
Volpé, R.: Lymphocytic (Hashimoto's) thyroiditis. In: The thyroid: A fundamental and clinical text, Werner, S.C., Ingbar, S.H. (eds.), 4th ed., pp. 996–1008. Hagerstown, Maryland: Harper & Row 1978
Welch, J.W., Chesky, V.E., Hellwig, C.A.: Malignant lymphoma of the thyroid. Surg. Gynecol. Obstet. **106**, 70–76 (1958)
Woolner, L.B., McConahey, W.M., Beahrs, O.H., Black, B.M.: Primary malignant lymphoma of the thyroid. Am. J. Surg. **111**, 502–523 (1966)
Wright, D.H.: Burkitt's lymphoma and infectious mononucleosis. In: Immunopathology of the lymphomas, Twomey, J.J., Good, R.A. (eds.), p. 391. New York: Plenum Press 1978
Zulman, J., Jaffe, R., Talal, N.: Evidence that the malignant lymphoma of Sjögren's syndrome is a monoclonal B-cell neoplasm. N. Engl. J. Med. **299**, 1215–1220 (1978)

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