Virchows Arch [Pathol Anat] (1984) 404:117–126

Virchows Archiv A

Undifferentiated thyroid tumors of diffuse small cell type

Histological and immunohistochemical evidence for their lymphomatous nature

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Summary. A histological review of 72 undifferentiated thyroid tumors was performed in order to discover small cell anaplastic carcinomas and Non-Hodgkin lymphomas. Cases suspected to be lymphoma were examined for the presence of Ig and keratin and lectins with a PAP-procedure.

Among the 72 cases, 68 (94,5%) were anaplastic carcinomas of various types. Four cases (5,5%) were diffuse small cell tumors, which had previously been regarded as anaplastic carcinomas. All four could be identified as Non-Hodgkin lymphomas by histology, immunohistochemistry, repeat biopsy or autopsy.

The findings suggest that the majority of small cell anaplastic thyroid tumors are lymphomas and that true anaplastic small cell carcinoma of the thyroid must be extremely rare. Its diagnosis requires electronmicroscopy and/or immunohistochemistry to demonstrate the epithelial nature of tumor cells.

Key words: Thyroid neoplasms – Undifferentiated carcinomas – Lymphomas

Currently two histological classifications of thyroid neoplasms are in worldwide use (Hedinger and Sobin 1974; Meissner and Warren 1969). Both recognize an undifferentiated carcinoma of so-called small cell type. According to Meissner and Warren (1969), compact and diffuse subtypes are recognized.

Whether these neoplasms are carcinomas or malignant Non-Hodgkin lymphomas has been a matter of debate for quite some while (Williams 1981). As late as 1969, Meissner and Warren (1969) wrote that many tumors reported as Non-Hodgkin lymphomas of the thyroid might have been classified as small cell anaplastic carcinoma if enough blocks or slides had been

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examined. The existence of a small cell anaplastic carcinoma – though rare – was confirmed in a large series of cases of thyroid neoplasms by Neracher and Hedinger (1975).

Nevertheless, primary Non-Hodgkin lymphomas of the thyroid gland have become an accepted entity, more clearly defined clinically and morphologically by several reports over the last few years (Burke et al. 1977; Chak et al. 1981; Compagno and Oertel 1980; Heimann et al. 1978; Maurer et al. 1979; Schwarze and Papadimitriou 1980). Also, the evidence for the lymphomatous nature of small cell anaplastic tumors of the thyroid has been growing (Cameron et al. 1975; Macaulay et al. 1978; Rayfield et al. 1971).

Against this background the present review of anaplastic thyroid tumors was undertaken. Its aim was to see whether cases previously reported as small cell anaplastic carcinoma were truly carcinomas or could be identified as malignant lymphomas by morphology and/or immunohistochemistry. The results show that 4 so-called small cell anaplastic carcinomas were indeed Non-Hodgkin lymphomas.

Material and methods

The cases for this study were part of a series of 327 primary malignant neoplasms of the thyroid seen at the Institute of Pathology of the University of Zurich during the years 1962–1973 which had previously been reported (Neracher and Hedinger 1975). The 78 cases originally classified as anaplastic carcinoma were selected for review. The slides and blocks of 5 cases were lost; one case was excluded on review because it was felt to represent neither carcinoma nor lymphoma of the thyroid. Thus 72 cases were left for re-examination. Of all cases HE stained paraffin sections were available and in a majority PAS-, Romanowsky-, van Gieson and Silver-stains could be reviewed or were prepared in addition.

All slides were reviewed independently by two examiners without knowledge of the diagnosis previously established by one of the authors (CH), with the aim of identifying

a) cases fulfilling the criteria of a pure undifferentiated carcinoma of diffuse small cell type according to Meissner and Warren (1969) or Hedinger and Sobin (1974).

b) Cases representing malignant Non-Hodgkin lymphomas.

From the paraffin blocks of the 4 cases suspected of being lymphoma new slides were prepared and stained with HE and methyl green-pyronin. An immunoperoxidase procedure described elsewhere (Knecht et al. 1981) was performed to detect cytoplasmic-Ig and keratin.

The reactions for lectins (Ulex europaeus lectin I, Peanut lectin, Helix pomatia agglutinin, Soybean agglutinin) were kindly carried out by Dr. Peter Möller, Institute of Pathology, University of Heidelberg, Germany, according to a method described elsewhere (Schwechheimer et al. 1984).

Follow-up information on these cases was obtained from the patient files. In two cases additional biopsies or autopsy materials were available for review.

Results

The results are summarized in Tables 1 and 2. Of 72 undifferentiated thyroid neoplasias 68 were classified as carcinomas of various type and 4 were identified as Non-Hodgkin lymphomas on the basis of the biopsy alone.

On breaking of the code, it was found that the 4 lymphoma cases were those previously diagnosed as small cell carcinomas.

The 68 carcinomas were usually easily identified and classified on the basis of a few slides. In no instance was there a change of the previous

Table 1. Histologic classification of 72 undifferentiated neoplasms of the thyroid

Undifferentiated (anaplastic) carcinoma		68/ 94.5%
– predom. spindle cell type	28/ 41.2%	
– predom. giant cell type	19/ 27.9%	
– partly follicular	14/ 20.6%	
– partly papillary	3/ 4.4%	
– with squamous metaplasia	4/ 5.9%	
	68/100%	
Malignant Non-Hodgkin's-lymphomas		4/ 5.5%
		72/100%

diagnosis. The majority contained several morphologic elements – like spindle or giant cells, follicular or papillary remnants – rendering recognition of the epithelial nature easy. We subclassified them according to the presence of these elements.

Thus 28 cases or 41.2% had a predominance of spindle cells. Giant cells were the foremost element in 19 cases (27.9%). A quarter contained elements of a better differentiated carcinoma of follicular or papillary type, suggesting that anaplastic carcinoma may derive from these neoplasms by dedifferentiation. 14 cases (20.6%) had a partly follicular architecture, 3 (4.4%) were papillary in some areas. Squamous metaplasia was observed in 4 cases.

The pertinent findings of the 4 cases with a Non-Hodgkin lymphoma are summarized in Table 2.

Morphologically all four tumors were lymphomas of diffuse large cell "histocytic" type according to Rappaport. In the Lukes-Collins classification two tumors were regarded as immunoblastic sarcomas (Figs. 1 and 2) of B-cell type and two as large non-cleaved FCC lymphomas (Figs. 3 and 4). Recognition of these neoplasms as lymphomas was achieved by observation of the typical cytological features of lymphomas of transformed lymphocytes as has been described for lymphomas in general (Lennert 1978; Maurer et al. 1982) and for thyroid lymphomas in particular (Maurer et al. 1979). These cytological features clearly separate the lymphomas from any of the recognized types of thyroid carcinoma.

Histologically all four lymphoma cases showed a complete destruction of the underlying thyroid tissue, at least in central parts of the lesion. At the margin of the tumor, a transitional zone could be seen, where the typical monotonous lymphomatous infiltrate intermingled with the thyroid tissue, the latter gradually vanishing in the tumor (Fig. 5). In this zone, remaining solitary thyroid follicles were frequently seen, sometimes invaded by and filled with lymphoma cells (Fig. 5). It is important to recognize these follicles as remnants of thyroid tissue and not to confound them with follicular parts of the tumor which would erroneously lead to a diagnosis of carcino-

Table 2. Synopsis of 4 cases of thyroid lymphoma primarily diagnosed as anaplastic carcinoma of small cell type

Case age + sex	Therapy surgery	RTX	Follow-up	Revised histology	Immuno-peroxydase
1 71 years male	left hemithyroidectomy	+	Died after 6 months. Autopsy: Tumorinfiltration of trachea and oesophagus, lungs and kidney	M.L. diffuse, "histiocytic" Large non-cleaved FCC, diffuse	−Ig: + (K, poss. monoclonal) −Keratin: − −Lectins: −
2 59 years male	left total, right subtotal thyroidectomy, left radical neck dissection	6000 R on both supraclavicular regions and mediastinum + 2000 R on left neck	7 mth postop. obstructive jaundice. Laparotomy: retroperitoneal tumor with invasion of pancreas, enlarged mesenteric lymph nodes. Dx: malignant lymphoma. Death 18 days postop. No autopsy	M.L. diffuse, "histiocytic" Immunoblastic sarcoma, B-cell type	−Ig: − −Keratin: − −Lectins: −
3 61 years female	total thyroidectomy	6000 R on involved area	Alive, NED after 11 years	M.L. diffuse, "histiocytic" Large non-cleaved FCC, minimally follicular	−Ig: + (K, monoclonal) −Keratin: − −Lectins: −
4 53 years female	total thyroidectomy	6000 R on involved area	Alive, NED after 9 years	M.L. diffuse "histiocytic" Immunoblastic sarcoma, B-cell type	−Ig: − −Keratin: − −Lectins: −

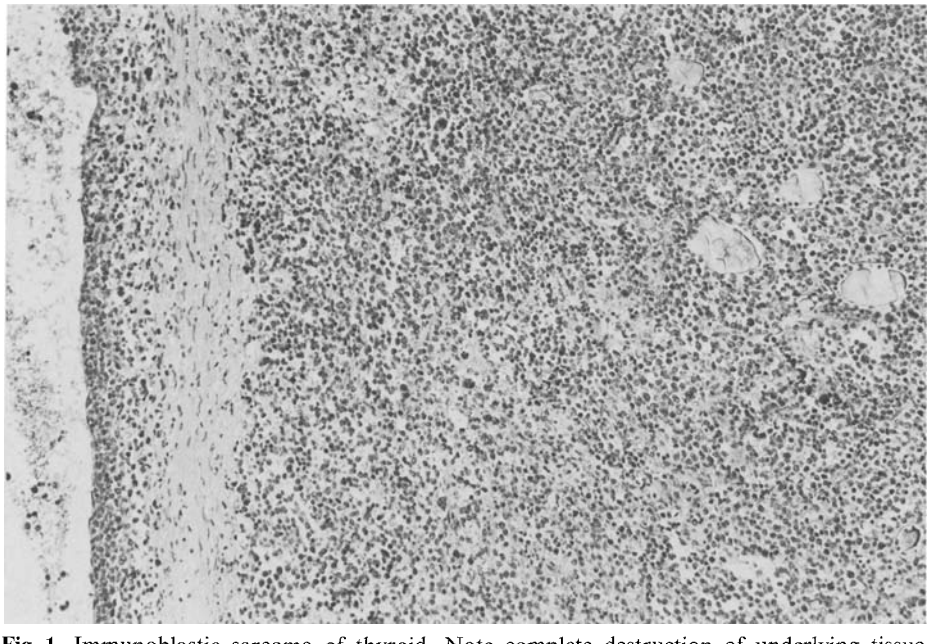

Fig. 1. Immunoblastic sarcoma of thyroid. Note complete destruction of underlying tissue with only few residual thyroid follicles (*right half of picture*) and invasion of a large artery with subintimal accumulation of tumor (HE, × 100)

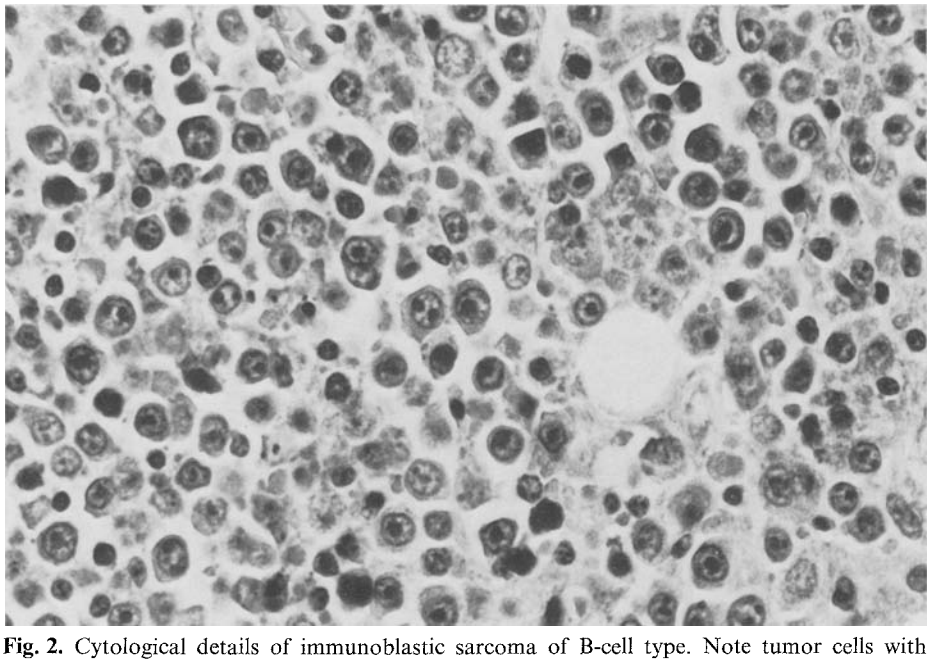

Fig. 2. Cytological details of immunoblastic sarcoma of B-cell type. Note tumor cells with large nuclei with prominent nucleoli and with abundant basophilic cytoplasm (HE, × 500)

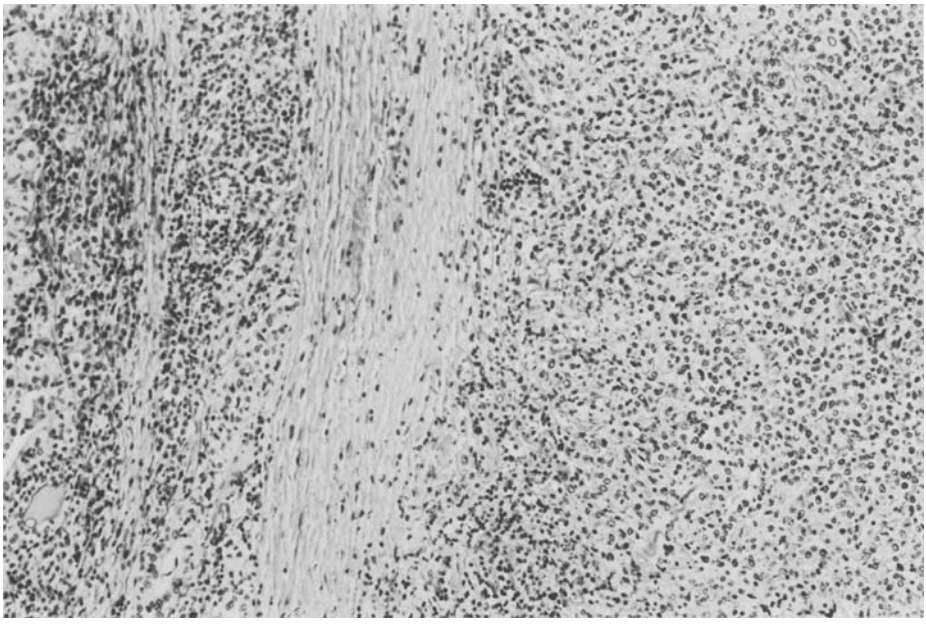

Fig. 3. Large-non cleaved FCC lymphoma of thyroid, completely destroying thyroid tissue within an encapsulated nodule and infiltrating adjacent thyroid tissue (*right half of picture*) (Giemsa, ×100)

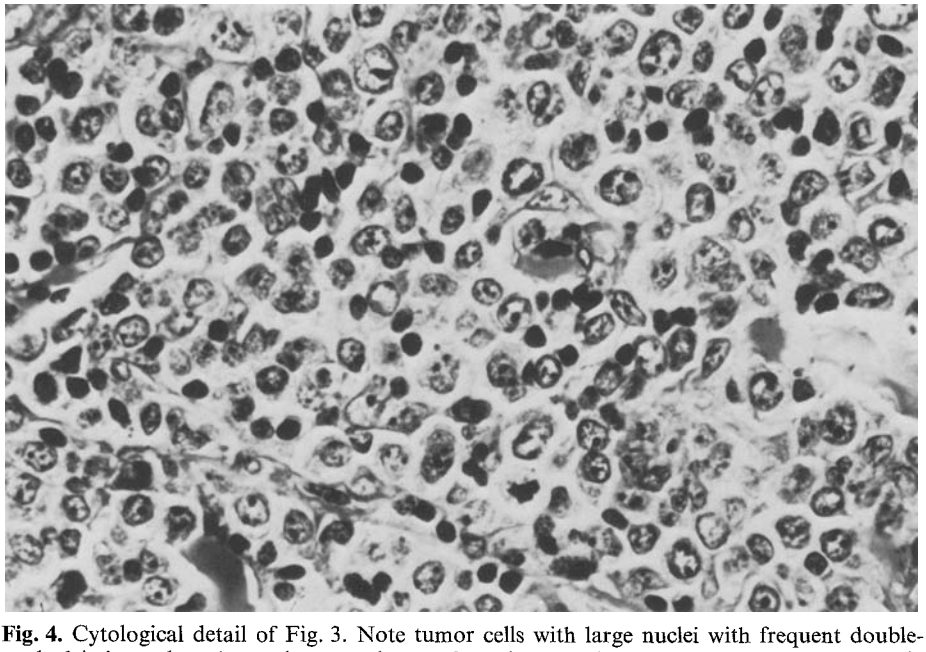

Fig. 4. Cytological detail of Fig. 3. Note tumor cells with large nuclei with frequent double-nucleolei situated at the nuclear membrane. Cytoplasm is clearly visible but not particularly basophilic. (Giemsa, × 500)

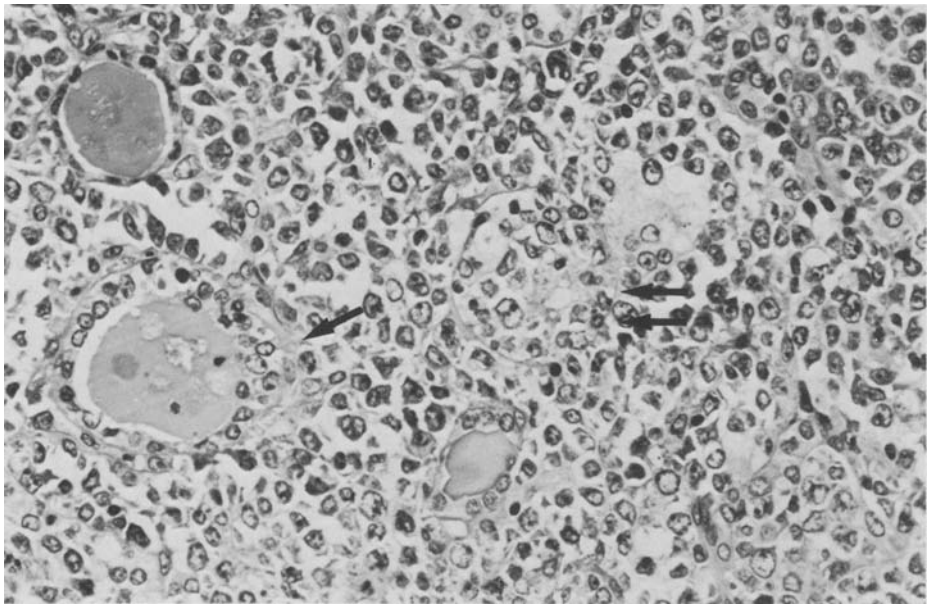

Fig. 5. Thyroid lymphoma with residual thyroid follicles. One follicle (*double arrows*) is filled with tumor cells contained by residual basal lamina of follicle. Another follicle (*single arrow*) is being invaded by lymphoma cells. Note also cytologic difference between lymphoma cells and follicular epithelial cells (HE, × 320)

ma. This distinction is also achieved by recognizing the clearly different cytology of follicular epithelial cells compared with the lymphoma cells (Fig. 5). The follicular epithelial cells exhibit no frank cytological signs of malignancy. Admittedly, the nuclei of follicular epithelial cells undergoing regression within the lymphoma may look small and condensed, thus having a lymphocyte-like appearance. Since these cells lack pleomorphism and mitotic activity, the change can be recognized as reactive rather than neoplastic. Lymphoma cells also invade vessel walls without completely destroying them, coming to lie under the intima (Fig. 1). Immunohistochemistry resulted in a definitely monoclonal staining pattern for kappa light chain in one case (case 3). In a second case there was a strong reaction with an anti-kappa-antibody and the staining pattern was indicative of monoclonality (case 1) but not unequivocally so.

The reactions for keratin and all four lectins were negative in all cases, supporting the non-epithelial and probably lymphomatous nature of the proliferated cells.

Follow-up information indicates that two patients (no 3 and 4, Table 2) were alive with no evidence of disease, 9 and 11 years after the diagnosis. Both had thyreoidectomy and radiotherapy. The other two patients died 6 and 7 months after diagnosis due to widespread diffuse "histiocytic" lymphoma.

Discussion

The distinction between undifferentiated small cell carcinoma and primary malignant lymphoma of the thyroid is an intriguing problem for the pathologist. Yet, this distinction is of utmost clinical importance in view of the very different therapeutic and prognostic implications of both these diagnoses. While Meissner and Phillips (1962) stated that small cell anaplastic carcinomas of diffuse type were much more frequent in surgical material than malignant lymphomas, the findings of our study indicate that the majority of undifferentiated small cell neoplasms of the thyroid gland represent Non-Hodgkin lymphomas and that true undifferentiated carcinomas of diffuse small cell type are very rare.

The diagnosis of anaplastic carcinoma of small cell type requires positive identification of the epithelial nature of the tumor cells (Maurer et al. 1979; Williams 1981), which must be achieved by electronmicroscopy and/or immunohistochemistry, because the published criteria for the recognition of small cell carcinoma on histological sections (Meissner and Phillips 1962; Meissner and Warren 1969) are unreliable.

However, lymphomas can be recognized in conventional histological sections with a high degree of confidence, provided that the pathologist is aware of this possibility, is familiar with the variable forms of expression of lymphoid cells and has excellent histological sections at his disposal. The distinction between small cell carcinoma and malignant lymphoma thus depends on both architectural and cytological features (Williams 1981).

We agree with Meissner and Phillips (1962) and Meissner and Warren (1969) that the microscopic diagnosis of small cell carcinoma rests upon the finding of differentiated epithelial structures as we found them in about 25% of our cases. The crucial point though, is to find truly *neoplastic epithelial* structures. The misreading of residual thyroid follicles with regressive epithelial changes as neoplastic, or the interpretation of rounded tumor cell masses within follicles with preserved reticulin framework (Fig. 5) as epithelial (Williams 1981), are the most important reasons for erroneous diagnosis of anaplastic carcinoma in our opinion. It is interesting to note, that the classical descriptions of the cytology of diffuse small cell anaplastic carcinoma (Meissner and Phillips 1962; Meissner and Warren 1969) stress the resemblance of tumor cells to plasma cells – and yet the diagnosis is based on a few follicles found after examination of many sections. One would assume that these represent thyroid follicles, as they are found near the margin of the tumor. It is important to recognize the regressive nature of these changes in the follicular epithelia. The lack of cellular pleomorphism and mitoses as well as the rarity of these structures are evidence against their neoplastic nature (Fig. 5). The diagnosis of small cell anaplastic carcinoma must therefore be corroborated by electronmicroscopic or immunohistochemical demonstration of the epithelial nature of the tumor cells, notably through finding of hemidesmosomes and basement membrane material (Aldinger et al. 1978; Cameron et al. 1975; Egloff 1977; Saito and Sharma 1975; Williams 1981) or the presence of antigens associated with epithelial structures like keratin.

Our results are in agreement with those of several recent reports. Thus, Rayfield et al. (1971) examined 67 cases of anaplastic thyroid tumor and could easily separate 53 spindle and giant cell tumors, the remainder being small cell lesions. Among them, no carcinoma was identified. All cases could be classified as Non-Hodgkin lymphomas on morphological grounds alone. Cameron et al. (1975), using electronmicroscopy, identified as lymphoma two of three small cell neoplasms of uncertain type on light microscopy. The third case was identified as a carcinoma by demonstration of hemidesmosomal cell connections and basement membrane material.

Positive confirmation of the B-lymphocytic origin of small cell thyroid neoplasms was reported by Macaulay et al. (1978) in 5 of 6 cases.

In view of this evidence it is safe to assume that the overwhelming majority of small cell thyroid neoplasms reported as carcinomas are indeed lymphomas. Given the observations of Cameron et al. (1975), Saito and Sharma (1975) and Egloff (1977), one cannot deny the existence of an undifferentiated carcinoma of diffuse small cell type, although we saw none in the present series.

For *practical purposes* we suggest therefore, that in a case of small cell anaplastic thyroid neoplasm the pathologist should attempt to substantiate a diagnosis of malignant lymphoma first. In our experience this is possible on morphology alone in the majority of cases, a minority may need immunohistochemical studies for confirmation of the lymphocytic origin. It is important to have fresh frozen tissue set aside for eventual examination with monoclonal antibodies which have enlarged the spectrum of possibilities to differentiate between lymphoma and carcinoma.

These stringent criteria for diagnosis of small cell anaplastic carcinoma of the thyroid must be adhered to because of the profound therapeutic and prognostic implications. Even though most lymphomas of the thyroid are of the aggressive diffuse large cell type (Burke et al. 1977; Heimann et al. 1978; Maurer et al. 1979; Schwarze and Papadimitriou 1980) they may be curable with modern multi-agent chemotherapy programs even beyond stage I. Anaplastic carcinoma, however, still has a dire prognosis and attempts at cure involve extensive surgery prior to local irradiation.

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Accepted June 1, 1984