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Evaluation of lymph node reactivity in differentiated thyroid carcinoma

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ABSTRACT

INTRODUCTION

Context: The development of metastases is the most notable characteristic of malignant neoplasias. The filter function of lymph nodes, which led to the idea of including lymphatic treatment in surgical management of metastases.

Objectives: To evaluate morphological alterations in neck nodes in the presence of differentiated thyroid carcinoma (DTC): hyperplasia, histiocytosis, desmoplasia, capsular rupture, necrosis and their relation to the biological behavior of these neoplasias.

Design: Retrospective study.

Setting: University referral unit.

Participants: 98 DTC patients, from 1977 to 1992, 18 cases were selected for histological analyses, of which 14 were female and 4 males, with an average age of 50.2 years. From these cases, 290 lymph nodes were analyzed (81 with metastasis), with an average of 16 lymph nodes/patient.

Main Measurements: Morphological evaluation of paraffin cuts stained by HE was done using an optical microscope, looking for presence of the abovementioned neoplasias and their UICC-TNM (1997) staging.

Results: Sinus histiocytosis was 2.4 times more frequent in the absence of lymph node metastasis (pNo). Disease recurrence occurred in 5 patients, all of whom were more than 40 years old ($p=0.24$) and 4 of whom had necrosis ($p=0.02$). Six patients with predominance of paracortical hyperplasia ($p=0.02$) did not show as much relapse into disease as those with less than 6 metastasis lymph nodes ($p=0.009$).

Conclusions: The presence of paracortical hyperplasia is associated with a better prognosis. The existence of necrosis or metastasis in more than 6 lymph nodes in patients over 40 years of age is related to higher risk of relapse of disease in DTC.

Key Words: Differentiated carcinoma. Thyroid. Lymph node. Reactivity

The development of metastases is the most notable characteristic of malignant neoplasias. The filter function of lymph nodes was suggested last century by Virchow, which led to the idea of including lymphatic treatment in surgical management of metastases. Although such local and regional disease control became a common objective in treatment of head and neck cancer, it was frequently seen to be inefficient and insufficient. From 1953 with the work of Black et al,¹ evidence emerged about the active role of lymph nodes in the fight against metastases. The subsequent characterization of lymphocyte subpopulations and their distribution within lymph nodes led to studies of lymphatic reactivity in cancer patients.^{2,6} The inconsistency of the results, together with the fact that the simple existence of a metastasis constituted the main aggravating factor in the diagnosis of epidermoid carcinoma, resulted in these findings not being applied clinically. In the light of evidence that lymph nodes do not function as effective mechanical barriers and their resection does not significantly improve the overall survival of these patients, the evaluation of their immunological function has gained new interest.

The contrasting behavior seen in differentiated

thyroid carcinoma (DTC) could contribute new ideas for the clarification of these questions, and the evaluation of lymph node reactivity is justified when the metastatic lymph nodes are not prognostic.

Table 1 - Histiocytosis and lymph node metastases

Metastases	Histiocytosis	
	Yes	No
Yes	19	62
No	121	88

Table 2 - Age, lymph nodes, necrosis and hyperplasia versus recurrence

Data		Recurrence		p-value
		Yes	No	
Age	< 40	0	5	0.24
	> 40	5	8	
Lymph nodes	< 6	0	9	0.009
	> 6	5	3	
Necrosis	Yes	4	2	0.02
	No	1	11	
Paracortical Hyperplasia		0	6	
Follicular Hyperplasia		5	2	0.02

Table 3 - Relationship between hyperplasia, histiocytosis and metastasis

		Paracortical	Other
		Hyperplasia	Hyperplasias
Metastasis	Yes	23	186
	No	02	79
Histiocytosis	Yes	19	69
	No	04	17

Table 4 - Relationship between capsule rupture, desmoplasia and necrosis

	Capsule Rupture	p-value
Desmoplasia (7 patients)	6	0.59
Necrosis (6 patients)	6	0.11
Both	4	0.14

METHODS

Via a retrospective study of 98 cases of DTC (modified or recurrent) submitted to cervical neck surgery at the Head and Neck Service of Heliópolis Hospital (Hosphel), São Paulo, Brazil, from 1977 to 1992, 18 cases were selected to evaluate the lymph node reactivity in the presence or absence of metastasis. There were 14 female and 4 male cases, with an age range from 10 to 75 years old (median of 51) and a follow-up time from 2 to 155 months (median of 57).

The histopathological evaluation of lymph node reactivity was done via morphological analysis under an optical microscope of laminae stained by hemotoxylin eosine, using the following criteria: hyperplasia (follicular, paracortical, mixed and sinus), histiocytosis, desmoplasia, capsule rupture, necrosis, calcification and internal metastasis extension (greater or less than 50% of the section surface).

The frequency of the different criteria was evaluated, considering the total number of lymph nodes and the presence of metastases. The classification of the patients followed the predominant reactivation and the simple presence of capsule rupture, necrosis, desmoplasia and calcification. The relationships between the different factors and with the recurrence were all analyzed.

Statistical Methods. The statistical analysis was done using Fisher's exact test with p values of < 5%, with the assistance of Graphpad Instat™ (1993 version) and EPI INFO (version 6.0).

RESULTS

After the examination of 290 lymph nodes, of which 81 had metastases, sinus histiocytosis was diagnosed in 140 lymph nodes (Table 1 and Fig. 1).

Disease recurrence correlated with age was observed in 5 cases with ages greater than 40 years, during a follow-up period of 15 to 45 months.

Comparing the average number of metastatic lymph nodes in the group that was free of disease with the number in the group with recurrence, we measured 4.4 and 8.4,

respectively. Six metastases was considered predictive of DTC recurrence. Necrosis occurred in 13 metastatic lymph nodes in six patients and this reaction was considered significant.

Table 2 shows the evaluation of hyperplasia, for which the paracortical and follicular areas were chosen for the study.

In lymph nodes with paracortical hyperplasia, the number of metastases and histiocytoses was not significant, with 23 lymph nodes being evaluated and metastases being absent in two of them. In other types of hyperplasia, the relationship was 186 evaluated and 79 with absence. For histiocytosis with paracortical hyperplasia, 19 lymph nodes were positive for metastases and 4 were negative, and with other forms of hyperplasia the relationship was 69 positive and 117 negative lymph nodes (Table 3).

Table 4 presents the relationship between capsule rupture, desmoplasia and necrosis was measured in 13 patients, with occurrence in 43 metastatic lymph nodes. There was more than one reaction in 10 cases.

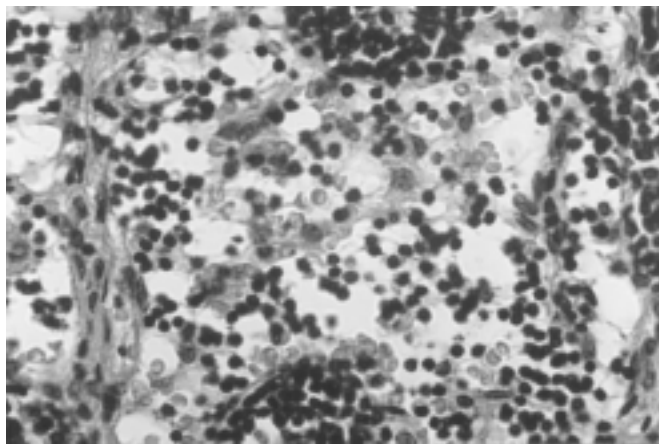


Fig. 1 - Sinus histiocytosis – Hematoxylin Eosine / 400x

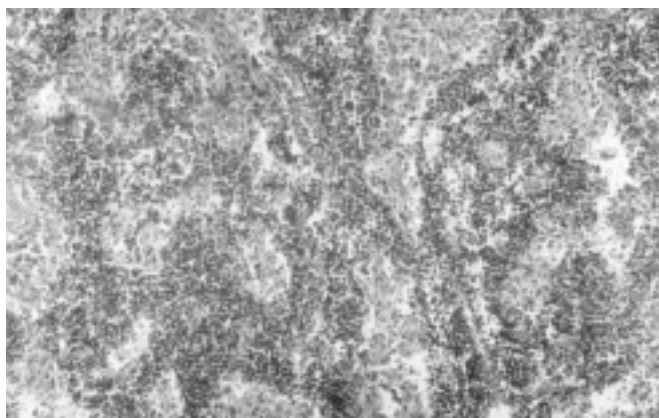


Fig. 2 - Follicular hyperplasia – Hematoxylin Eosine / 125x

DISCUSSION

The inverse relation between histiocytosis and metastasis occurs because of the need for lymph node structures to react against tumor cells. Berg² demonstrated that histiocytosis decreased as metastasis size increased, with predominance of this reactivity pattern in non-metastatic lymph nodes, which agrees with our experience (Table 1). Hoon et al⁷ showed that when a paracortical hyperplasia pattern is present, the incidence of metastasis and sinus histiocytosis is low, demonstrating that there is an effective lymphocyte immune reaction. This was present in our experience (Fig. 1).

The relationship between disease recurrence and age (Table 2) leads to the observation of worse prognosis in patients who are more than 40 years old, because of the incidence of distant metastasis producing regressive immune status.^{6,8} Regarding the number of metastatic lymph nodes (Table 2), the occurrence of more than 6 metastases increases disease recurrence in

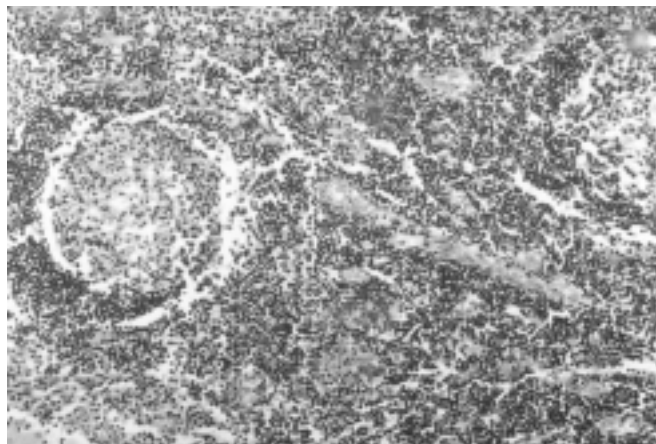


Fig. 3 - Paracortical hyperplasia – Hematoxylin Eosine / 250x

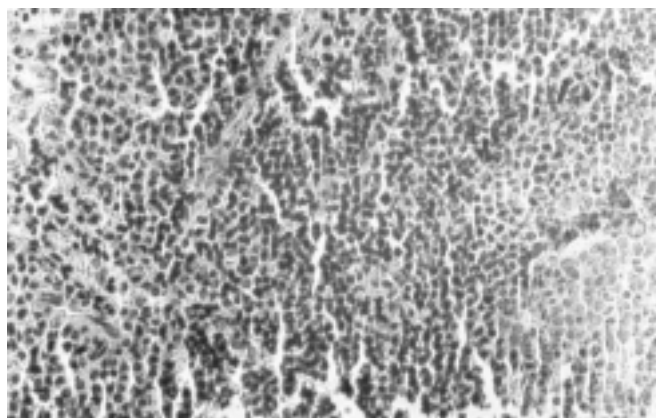


Fig. 4 - Sinus hyperplasia – Hematoxylin Eosine / 125x

patients who are more than 40 years old, as also reported by others.^{6,8-10}

The presence of necrosis (Table 2) possibly demonstrates a low immune reaction status in less differentiated neoplasias. At the same time, the simultaneous occurrence or non-occurrence of necrosis, desmoplasia and capsule rupture in the same patient (Table 4) may suggest a regional event,^{11,12} in spite of these factors not being prognostic. Furthermore, the inverse relationship between disease recurrence and paracortical hyperplasia, and the direct relationship to follicular hyperplasia demonstrate that the former is a protection reaction towards the proliferation of T cells and the latter is a proliferative pattern that indicates a worse prognosis¹³⁻¹⁵ (Table 3).

Finally, we conclude that this reactivity pattern in lymph nodes should be used routinely, in association with new histochemical reactions, so as to differentiate prognostic factors in the recurrence of DTC.

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RESUMO

Objetivos: Verificar as alterações morfológicas desencadeadas nos linfonodos cervicais na presença de carcinoma diferenciado da tireóide (CDT), estabelecendo a relação entre os achados: hiperplasia (folicular, paracortical, sinusal e mista), histiocitose, desmoplasia, ruptura capsular, necrose, calcificação e o comportamento biológico destas neoplasias. **Local:** Serviço de cirurgia de cabeça e pescoço do Hospital Heliópolis. **Método:** 18 pacientes com CDT foram submetidos a esvaziamento cervical (recorrente ou modificado) de 1977 à 1988. **Variáveis estudadas:** Foram analisados 290 linfonodos, sendo 81 metastáticos (24,4%) – média de 16 linfonodos por paciente. Foram analisados pela coloração HE e avaliados parâmetros como hiperplasia (folicular, paracortical, sinusal e mista), desmoplasia, histiocitose, ruptura capsular, necrose e calcificação) e estadiados pelo TNM do UICC de 1997. **Resultados:** a histiocitose sinusal foi 2,4 vezes mais frequente nos linfonodos sem metástases (pNo). A recidiva da doença ocorreu em 5 pacientes, todos com idade maior ou igual a 40 anos (p=0,24), dos quais 4 apresentavam necrose linfonodal (p=0,02). Os pacientes com hiperplasia paracortical não desenvolveram recidiva da doença (p=0,02), da mesma forma como aqueles com 6 linfonodos metastáticos (p=0,009). **Conclusões:** a presença de histiocitose tem relação inversa com a presença de metástase no linfonodo, e a hiperplasia paracortical associa-se a um melhor prognóstico. A existência de necrose ou metástase em 6 ou + linfonodos, em pacientes com idade acima de 40 anos, associa-se à recidiva da doença.