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ORIGINAL ARTICLE

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The desmoplastic limph node reaction as a prognostic factor of cancer of the tongue and floor of the mouth.

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To determine the prognostic significance of desmoplasia in metastatic lymph nodes of squamous cell carcinoma of the oral tongue and floor of mouth, 37 cases of this disease were studied. Desmoplasia was present in 59,4% of the cases and associated extracapsular spread in 40,5%. The association of desmoplasia with large lymph node involvement occurred in 59,4%. These relationships were statistically significant (p= 0,002 and 0,0069). The results obtained suggest that desmoplasia is a bad prognosis associated factor.

UNITERMS: Desmoplasia, Lymph node, Extracapsular spread

INTRODUCTION

The therapeutics of squamous cell carcinoma of the head and neck, particulary of the oral cavity cannot be reached without reference to the treatment approach to the cervical lymph nodes. The clinical and experimental evidence of immunoreactivity of the lymphoid tissue against neoplasia, has carried to a lot of efforts aiming the interpretation of the reactional changes looking for morphologic patterns of antineoplastic immunity10,11,25.

The study of cervical lymph nodes from a neck dissection would has the goal to assess for the prognosis through the analysis of these morphologic changes in the histologic structure of the node.

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Many attempts were tried with this direction, looking for correlate different types of lymph node reactions with the clinical course of the patients4,5,8,16,20. One of the most important and exhaustivelly studied factors is the extracapsular spread of the tumor17,18,19,22.

Among many types of reactional changes in the lymph nodes, we selected the desmoplastic reaction. It can be defined as one or more bands of connective tissue proliferation, with variable thickness, between the tumor and the lymphoid tissue. The aspect on light microscopy is like a pseudo capsule surrounding the tumor area. The presence of desmoplasia is dependent on the presence of neoplasia (fig. 1).

In a series of 37 patients with squamous cell carcinoma of the oral tongue and floor of mouth, this factor was studied about its presence and relation with other potentially prognostic factors.

The purposes of this study are:

1. Determine the presence and frequency of desmoplasia in metastatic lymph nodes in this series;
2. Identify the association of desmoplasia with other prognostic factors, and
3. Determine the prognostic significance of desmoplasia in metastatic lymph nodes.

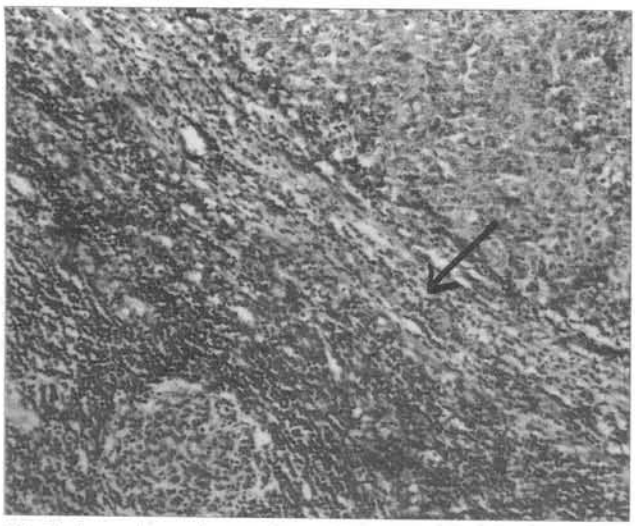

Fig.1: Lymph node section with an area of desmoplasia (arrow) between the tumor (arrow head) and lymphoid tissue.

LITERATURE REVIEW

Description and sistematization of neck dissection was first done by Crile (1906), that stated the concept of locoregional disease with lymphatic spread to the cervical lymph nodes. Crile considered lymph node as a barrier to tumor progression12. Gray14 studied the relation of the tumor with lymph vessels, and the "filter" function of lymph nodes. Several years later, Black et alli7 associated the presence of sinus histiocytosis in lymph nodes with better prognosis in breast cancer. Zeidmann27 and Engeset13 studied the barrier function of lymph nodes in rabbits and proved it experimentally.

Tsakraklides et alli25 described four patterns of morphologic changes in lymph nodes in response to breast cancer and associated better results with stimulated patterns (lymphocyte predominance and germinative center predominance) and worse results with unsimulated patterns (lymphocyte depletion and unstimulated node).

Noone et alli20 correlated better survival with the presence of lymphocyte predominance and germinative center predominance in lymph nodes of a series of patients with squamous cell carcinoma of oral cavity, pharynx and larynx.

Kalnins19, Pointon & Jelly22 and Johnson17,18 observed decreased survival in patients with lymph nodes showing extracapsular spread.

Schuller24 showed clinically and experimentally the presence of immunoreactivity in regional lymph nodes of patients with head and neck cancer.

Olsen21 listed the desmoplasia as a bad prognosis factor in metastatic lymph nodes of head and neck cancer.

MATERIAL AND METHODS

Thirty-seven patients with oral tongue and floor of mouth cancer were submitted to surgical procedure at the Head and Neck Service of Heliópolis Hospital between January 1978 and December 1987. These records were reviewed. All cases underwent ressection of the tumor en bloc with radical neck dissection, and had lymph node metastasis confirmed by histology. Thirty-five patients were male and 2 female (94,6% and 5,4%). The age ranged from 39 to 75 years with an average of 54 years. Twenty-six patients had the primary tumor in floor of mouth and 11 in the oral tongue. The T and N staging (clinical) is demonstrated in table 1.

Table 1

Preoperative staging of the cases

T \ N	0	1	2a	2b	2c	3
1	-	-	-	-	-	1
2	3	3	1	1	-	1
3	5	5	-	3	3	-
4	3	1	2	4	1	-

Date were collected by reviewing the records of the patients and personal contact, when it was possible. The age, sex, site and size of the tumor, clinical staging, treatment and follow-up were registered as well as the date of surgery, recurrence, last information and status of the patient.

Lesions were described with its size, site and macroscopic aspect and the lymph nodes with its chain location, size, number, mobility, surface and elasticity. All the cases underwent biopsy with topic anesthesia to confirm the diagnosis

Clinical staging was updated to the TNM classification - UICC/198715. All cases had its histologic slides reviewed to classificate according the type of lymph node reaction, presence of extracapsular spread and desmoplasia. to analyse the type of lymph node reaction, was used the classification proposed by Tsakraklides24 (fig. 2, 3, 4 and 5). Extracapsular spread is demonstrated in fig. 6.

Statistical analysis was done with the Fisher Exact Test23 and variables that were compared with the presence of desmoplasia were: age, sex, size and site of the tumor, histologic grade, pN staging, type of lymph node reaction and extracapsular spread.

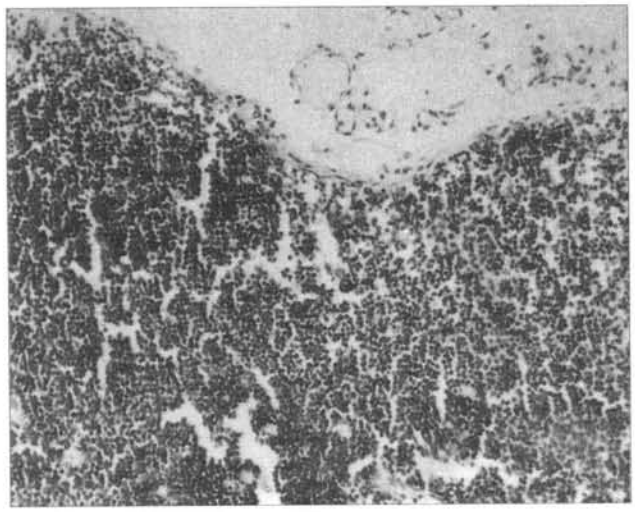

Fig.2: Lymph node section with lymphocyte predominance

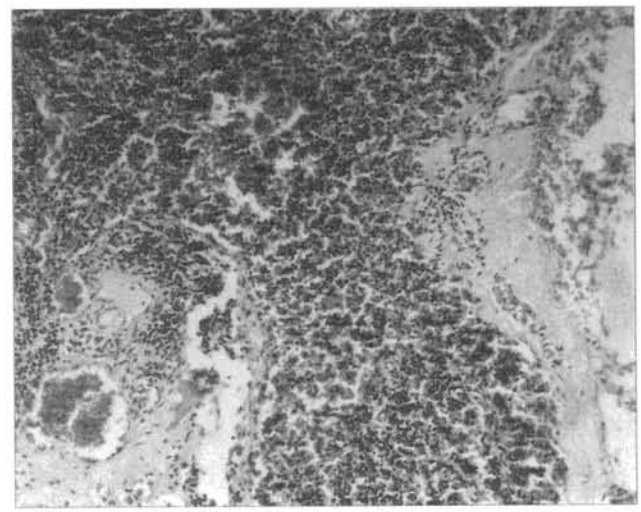

Fig.5: Section of an unstimulated lymph node

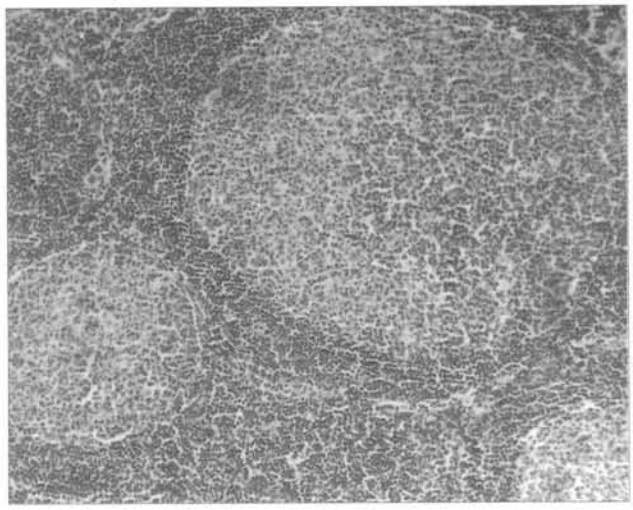

Fig.3: Lymph node section with germinative center predominance

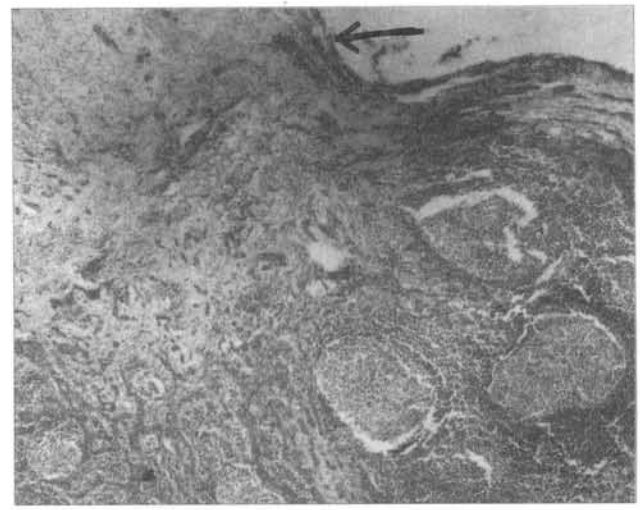

Fig.6: Lymph node with extracapsular spread of tumor

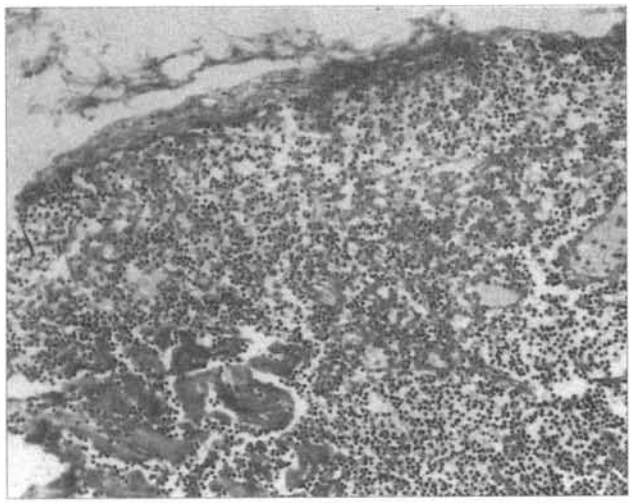

Fig.4: Lymph node section with lymphocite depletion

RESULTS

Table 2 shows the anatomo pathologic staging of the cases and can be noted, when comparing with table 1, there was underrated the N clinical status in twenty cases.

Histologic grade was classified as I in 4 cases (11%), II in 20 cases (54%) and III in 13 (35%). The type of lymph node reaction was divided in stimulated (47%) and unstimulated (53%).

Desmoplasia was encountered in 22 cases (59,4%) and extracapsular spread in 19 cases (51,3%); association of both in 15 cases (40,5%). Eleven cases (29,7%) did not show neither desmoplasia nor extracapsular spread; seven cases (19%) showed isolated desmoplasia and four (10,8%) isolated extracapsular spread.

Table 2

Postoperative staging of cases

N / T	0	1a	2a	2b	2c	3
1	-	-	-	1	-	-
2	-	3	1	4	-	1
3	-	1	1	10	4	-
4	-	1	1	4	5	-

Twenty-one (56,7%) of the 37 cases had its clinical course defined between one to 57 months. Eight cases (22%) had cervical recurrence; three (8,1%) had a new tumor; two dead by other causes and one case had pulmonary metastasis. About the remaining 16 cases, 8 (22%) had no evidence of disease and 8 were lost of follow-up, but in anyone there was evidence of recurrence in the last examination.

Among 8 cases with cervical recurrence, 7 had associated desmoplasia and extracapsular spread and one did not show any of these changes. Four cases showed isolated extracapsular spread; 3 of these cases had follow-up of 48, 88 and 151 months without evidence of disease and the last one had local recurrence in the 29th month. There was a loss of follow-up of 8 cases. Statistical analysis did not show significative difference between the groups with and without desmoplasia when this factor was compared with age (p=1,00), sex (p=0,99), size and site of the tumor (p=0,70 and 0,72), histologic grade (p=0,16) and type of lymph node reaction (p=0,18). There was statistical significance when desmoplasia was correlated with pathologic N status (p=0,0069) and presence of extracapsular spread (p=0,002).

DISCUSSION

The study of the lymph node metastasis in head and neck cancer was done initially to stablish its presence and mechanism of development12,16. The next step was the demonstration of the barrier function of lymph node against tumor3,13,27.

Analysis of morphologic changes of the lymph node and its relation with prognosis was done by Black et alli7,8,9. These authors correlated the presence of sinus histiocytosis with an increased suvival in breast cancer. Anastassiades & Price1 studied the sinus histiocytosis and proposed the hypothesis of an interation of host and tumor factors. The host factor would be reflected in lymph node changes.

Later, there were many experimental studies that showed the barrier function of lymph node and the effects of therepeutic methods (surgery and radiation therapy) on its function.

The description of patterns of morphologic changes in lymph node and its correlation with prognosis done by Tsakraklides et alli, was a frontier in the study of the immunologic activity of the lymphoid tissue, and many authors described these alterations as important in prognosis of different sites of tumors.

Extracapsular spread of cancer has been described as a bad prognosis associatec factor because it can indicate greater agressivity of the tumor and lower chances of local control of the disease (in the neck).

The interest in the study of desmoplasia as a bad prognosis associated factor, is in the fact that its histologic appearance opposes this concept. The immediate impression when it is observed at light microscopy, is of a barrier in the tumor-lymphoid tissue interface.

The main doubt to be discussed is if desmoplasia is a tumor or a host-induced reaction. It seems to be morphologically a host defense mechanism, but data of the literature that support our results, indicate a positive correlation between desmoplasia and bad prognosis. The real origin of desmoplasia cannot be defined with the results obtained and it is not a goal of this study.

It was not unexpected that the relations between age and sex have not had statistical significance because there was a few of cases in each situation, and the lack of dependence of the variables. The same can be concerned to the histological grade, size and site of the tumor.

Type of lymph node reaction did not have relation with desmoplasia too. The presence of desmoplasia is dependent of the tumor presence in the lymph node; patterns of lymph node reaction can be better diagnosed in nodes in wich structure did not had large destruction or replacement by tumor. It could explain the absence of relation between the variables.

More significant data encountered, were about the relation of desmoplasia with extracapsular spread and pN status (histological metastasis). Results show the larger the lymph node involvement, more frequent is desmoplasia. Tumor agressivity and the time of its permanence within the node could be important in desmoplasia development. The same reasoning can be applied to extracapsular spread.

All cases with cervical recurrence but one, had association of desmoplasia and extracapsular spread. One can ponderr over the main factor involved in these

recurrences was the extracapsular spread. However, the follow up of three cases with isolated extracapsular spread shows they did not have evidence of disease after 48, 88 and 151 months.

Finally, we observed that the results demonstrate an association between desmoplasia, extracapsular spread and extent of cervical disease, what suggests desmoplasia is a bad prognosis associated factor when present in metastatic lymph node of patients with squammous cell carcinoma of oral tongue and floor of mouth.

CONCLUSIONS

- In this series, desmoplasia was present (in lymph node) in 59,4% of the cases.

- There was association between desmoplasia and extracapsular spread in 40,5% and large lymph node involvement in 59,4%.

- Association of desmoplasia with these factors suggest that it is a bad prognosis associated factor.

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Resumo

Para determinar o significado do prognóstico da desmoplasia nos linfonodos metastáticos de carcinoma epidermóide da língua oral e do soalho da boca, 37 casos desta doença foram estudados. Desmoplasia estava presente em 59,4% dos casos e associada com rotura capsular em 40,5%. A associação de desmoplasia com envolvimento linfonodal extenso ocorreu em 59,4%. Estas relações foram estatisticamente significantes (p= 0,002 e 0,0069). Os resultados obtidos sugerem que a desmoplasia é um fator associado com mau prognóstico.