

## Serum leucine aminopeptidase in head and neck cancer

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### Abstract

Serum leucine aminopeptidase (LAP) activity was assayed in patients with head and neck cancer. The levels were found to be significantly higher than the controls. However, the rise in serum LAP was nearly the same in all the patients studied, irrespective of the character or histopathology of the lesion but varied with respect to the site involved, i.e. from about 40 per cent in cancer of the hypopharynx to more than 100 per cent in cancer of the nasopharynx. Serum LAP activity was found to increase with the extent of the lymph node spread. After treatment the levels were found to be reduced.

**Key words:** Leucine aminopeptidase; Neoplasm staging; Neoplasm metastasis; Lymph nodes; Head and neck neoplasms

### Introduction

Leucine aminopeptidase (LAP; L-Leucyl-peptide hydrolase; EC 3.4.1.1.) is a proteolytic cellular derived enzyme. It is secreted by the mucosa of small intestine and is active in the terminal phases of protein digestion (Smith and Hill, 1960). Although the enzyme is widely distributed in various tissues in the body the duodenum, liver and kidney show its highest activity. Some studies have suggested that LAP is elevated in the sera of patients with hepatitis, acute pancreatitis, hepatobiliary diseases, carcinoma of the pancreas, medullary carcinoma of the breast, chronic leukaemias and in lymphomas of various histological types (Pineda *et al.*, 1960; Nagaoka and Yamashita, 1983; Gupta *et al.*, 1989). It has been shown to be a useful marker for the malignancy of monocyte-macrophage cell lines with a specificity for the histiocytic series (Aziz *et al.*, 1988). There are however, no reports of it in patients with head and neck cancer except in two cases of carcinoma of the tongue and floor of the mouth with metastases

to cervical lymph nodes where the levels have been reported to be high (Phillips and Manildi, 1970). We have therefore assayed serum LAP activity in patients with head and neck cancer. The effect of radiotherapy on serum LAP levels has also been studied in these patients.

### Material and methods

Serum LAP levels were estimated in a group of 50 patients (40 males and 10 females) with head and neck cancers and the results have been compared with a group of 25 healthy controls (12 males and 13 females). The diagnosis of the disease was confirmed by histopathology. Out of the 50 patients studied, 15 had carcinoma of the oropharynx, 13 of the larynx, 12 of the hypopharynx, six of the oesophagus, three of the nasopharynx and one of the nose.

The character of the lesion was determined and 30 patients had proliferative and 20 ulcerative types of growth. Histopathology showed that 46 patients had squamous cell carcinoma, three undifferentiated carcinoma and one adenocystic carcinoma. The TNM stage of

TABLE I  
SERUM LAP ACTIVITY IN RELATION TO THE SITE IN HEAD AND NECK  
CANCER

| Group       | No. of subjects | Serum LAP (G-R units/0.02 ml)  |         |
|-------------|-----------------|--------------------------------|---------|
|             |                 | Mean $\pm$ SEM                 | Range   |
| Controls    | 25              | 113.8 $\pm$ 4.67               | 81–151  |
| Patients    |                 |                                |         |
| Oropharynx  | 15              | 189.4 $\pm$ 20.70 <sup>a</sup> | 108–383 |
| Larynx      | 13              | 184.4 $\pm$ 14.50 <sup>a</sup> | 119–275 |
| Hypopharynx | 12              | 158.0 $\pm$ 11.28 <sup>a</sup> | 97–205  |
| Oesophagus  | 6               | 165.0 $\pm$ 12.34 <sup>a</sup> | 119–216 |
| Nasopharynx | 3               | 234.0 $\pm$ 20.78 <sup>a</sup> | 194–265 |
| Nose        | 1               | 157.0                          | –       |

<sup>a</sup> Difference statistically significant when compared with controls ( $p < 0.05$ ).

TABLE II  
SERUM LAP ACTIVITY IN RELATION TO THE EXTENT OF REGIONAL  
METASTASIS (LYMPH NODE) IN HEAD AND NECK CANCER

| Group          | No. of subjects | Serum LAP (G-R units/0.02 ml)  |         |
|----------------|-----------------|--------------------------------|---------|
|                |                 | Mean $\pm$ SEM                 | Range   |
| Controls       | 25              | 113.8 $\pm$ 4.67               | 81–151  |
| Patients       |                 |                                |         |
| N <sub>0</sub> | 18              | 166.2 $\pm$ 10.68 <sup>a</sup> | 97–265  |
| N <sub>1</sub> | 16              | 181.9 $\pm$ 19.10 <sup>a</sup> | 108–383 |
| N <sub>2</sub> | 6               | 186.3 $\pm$ 24.98 <sup>a</sup> | 108–254 |
| N <sub>3</sub> | 10              | 196.0 $\pm$ 14.07 <sup>a</sup> | 140–286 |

<sup>a</sup> =  $p < 0.05$  versus controls.

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TABLE III  
EFFECT OF TREATMENT ON SERUM LAP ACTIVITY IN HEAD AND NECK CANCER

| Group                       | No. of subjects | Serum Lap (G-R units/0.02 ml) |        |
|-----------------------------|-----------------|-------------------------------|--------|
|                             |                 | Mean ± SEM                    | Range  |
| Controls                    | 25              | 113.8 ± 4.67                  | 81-151 |
| Patients                    |                 |                               |        |
| Pre-treatment               | 45              | 183.1 ± 8.93 <sup>a</sup>     | 97-383 |
| Post treatment              |                 |                               |        |
| Radiotherapy                | 33              | 143.5 ± 7.42 <sup>a,b</sup>   | 81-238 |
| Radiotherapy + chemotherapy | 7               | 140.4 ± 23.26                 | 43-238 |
| Radiotherapy + surgery      | 5               | 101.5 ± 13.84 <sup>b</sup>    | 70-140 |
| Total                       | 45              | 138.4 ± 6.83 <sup>a,b</sup>   | 43-238 |

a =  $p < 0.05$  versus controls; b =  $p < 0.05$  versus pre-treatment.

cancer was determined in one patient as stage I, in 16 as stage II, 30 as stage III and in three as stage IV. The extent of lymph node metastasis was also determined and it was found that 18 patients did not show involvement of the lymph nodes (N<sub>0</sub>), 16 showed the presence of unilateral mobile lymph nodes (N<sub>1</sub>), six had contralateral or bilateral mobile lymph nodes (N<sub>2</sub>) while 10 had bilateral fixed lymph nodes (N<sub>3</sub>). None of the patients studied were suffering from hepatobiliary, pancreatic or gastrointestinal tract diseases. These were ruled out by clinical findings and relevant biochemical and other investigations.

The effect of radiotherapy treatment was studied in only 45 patients, since five patients did not complete the treatment. In addition a course of chemotherapy (Cisplatin) was given to seven patients and surgery was performed in five patients.

Serum levels were estimated by separating the serum

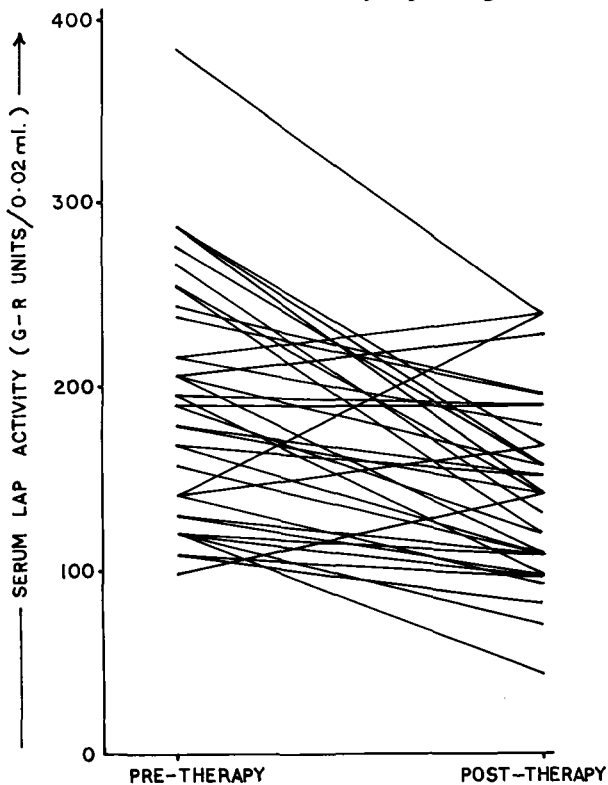


FIG. I EFFECT OF RADIOTHERAPY ON SERUM LAP ACTIVITY IN HEAD AND NECK CANCER .

FIG. 1

Effect of radiotherapy on serum LAP activity in head and neck cancers.

from 3 ml of venous blood. LAP activity was estimated according to Martinek *et al.*, (1964). Results were statistically analysed by the Student's *t*-test. The unpaired *t*-test was used when the results of all the cancer group versus the control group comparisons in Tables I and II were made. The paired *t*-test was used when the pre- versus the post-treatment results of Table III were calculated.

**Results**

Mean LAP activity in patients with head and neck cancer was found to be 179.7 ± 8.22 G-R units/0.02 ml serum. The value was significantly higher when compared to the mean value for the control group (113.8 ± 4.67 G-R units/0.02 ml serum;  $p < 0.001$ ). For the two different types of lesion, the rise in LAP was nearly the same in the two groups. Although Histopathology showed that 92 per cent of the patients were of the squamous cell type carcinoma, the rise in LAP was approximately the same in all the patients studied except for one case of adenocystic cancer. The determination of the TNM stage of cancer showed that 92 per cent of the cases were stage II and III and the rise in serum LAP was nearly the same in these patients. For the different sites of cancer the mean rise in serum LAP varied, i.e. from nearly 40 per cent in patients with carcinoma of the hypopharynx to 106 per cent in patients with carcinoma of the nasopharynx (Table I). The rise in serum LAP in the presence of lymph node metastasis was directly proportional to the extent of the regional lymph node spread (Table II).

In 89 per cent of the patients, serum LAP activity was reduced after completion of radiotherapy treatment while in others it increased (Figure 1). The mean post-radiotherapy value was significantly lower than the pre-radiotherapy value, but higher when compared to the control group. The pre-radiotherapy value returned to normal in only five patients: surgery was performed on these patients in addition to radiotherapy treatment (Table III).

**Discussion**

Our data show a nearly 50 per cent increase in mean serum LAP concentration in about 70 per cent of the patients studied. The average rise in serum LAP was similar in all the patients studied, irrespective of the character, TNM stage or histopathology of the lesion but increased with respect to the site or the extent of lymph node metastasis. Others have reported a rise in serum LAP in hepatoma and in patients with a variety of primary tumours including cancer of the pancreas, breast, gastro-

intestinal tract and lungs with hepatic metastasis (Pruzanski and Fischl, 1964; Mehrotra *et al.*, 1984). The proportional increase in serum LAP observed, in the present study, with the advanced stage of lymph node metastasis (the highest levels being observed when the patient has cancer of the nasopharynx) suggest that LAP activity may be related to the involvement of lymphoid tissue. Nagaoka and Yamashita (1983) reported a rise in serum LAP in relation to the presence of lymph nodes in experimental animals.

Following radiotherapy, a decrease in serum LAP was observed. The decrease in serum LAP, however, was more when the tumour was excised prior to radiotherapy. The decrease in serum LAP, following radiotherapy in patients with localized malignant disease, or following surgery in cases of cancer of the pancreas, with liver metastasis, has been reported by others (Pruzanski and Fischl, 1964; Phillips and Manildi, 1970). Pre- and post-radiotherapy estimations of serum LAP may aid in the diagnosis and prognosis of squamous cell carcinomas of the head and neck.

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