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Serum Levels of CYFRA 21-1 in Nasopharyngeal Carcinoma and its Possible Role in Monitoring of Therapy

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CYFRA 21-1 is a fragment of cytokeratin expressed by simple epithelia and their malignant counter-parts. Serum CYFRA 21-1 levels were studied in 240 new cases of nasopharyngeal carcinoma and 19 patients who developed distant metastases. A reference range of <2 U/ml for our local Chinese population was established in 55 sex- and age-matched healthy volunteers. The nasopharyngeal carcinoma patients had significantly higher marker levels than the healthy controls and the mean level increased with advancing stage. However, the low percentage of elevation in early stages means that the marker is not useful for screening. The overall percentage (52.5) of elevation in 240 newly diagnosed squamous cell carcinoma of the nasopharynx is comparable to that of squamous cell carcinoma of the lungs, suggesting that the expression of CYFRA 21-1 is related to the cell type rather than the tissue type of the carcinoma. 46 (95.8%) of 48 patients with metastatic nasopharyngeal carcinoma showed an elevated value of CYFRA 21-1. This extremely high percentage implies that it is very unlikely for a patient with a normal value to have distant metastasis. This may permit major economies in radiological screening for distant metastasis. Preliminary results from serial measurement of the marker indicated its potential for monitoring response to treatment and for early detection of distant metastasis. Copyright © 1996 Elsevier Science Ltd

Key words: CYFRA 21-1, nasopharyngeal carcinoma

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INTRODUCTION

CYFRA 21-1 is a fragment of cytokeratin 19, an acidic subunit of cytokeratin intermediate filament expressed by simple epithelia and their malignant counter-parts [1]. Immunoradiometric assay of CYFRA 21-1 using monoclonal antibodies KS 19-1 and BM 19-21 of mouse origin provides an indirect measurement of cytokeratin 19. This new assay has been widely evaluated [2–4] and found to be a sensitive (52–63%) and specific (91%) tumour marker for squamous cell carcinoma (SCC) of the lung and is superior to carcinoembryonic antigen, tissue polypeptide antigen and squamous cell carcinoma antigen. The level of CYFRA 21-1 was found to correlate with tumour size and UICC staging [2, 3]. It was also found to be useful for monitoring patients with SCC of the lung during and following chemotherapy.

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Nasopharyngeal carcinoma (NPC) is one of the most common cancers in South East Asia [5]. The majority of the tumours are undifferentiated or poorly differentiated squamous cell carcinomas [6].

The serum expression of CYFRA 21-1 in NPC was investigated in the present study to assess its diagnostic and prognostic value for this type of tumour.

PATIENTS AND METHODS

240 consecutive patients with untreated NPC who presented between 1992 and 1993 were entered into the study. Serum samples were collected at the time of histological diagnosis and the sera were stored at −80°C before assay. Sera from 19 NPC patients with distant metastases being detected during follow-up over the same period of time and 55 sex- and age-matched healthy volunteers were also included. Serial serum samples from 12 patients being followed up at intervals from 1 to 6 months were available for preliminary testing of the value of the marker for monitoring the response to therapy. CYFRA 21-1 levels were measured

by the Centocor CYFRA 21-1 solid-phase immunoradiometric assay kits (Centocor, Diagnostic Division, Pennsylvania, U.S.A.).

Grouped TNM staging of Ho's classification, [7] employed for staging, is summarised below:-

I. Tumour confined to the nasopharyngeal mucosa.

II. Tumour extending to nasal fossa, oropharynx, or adjacent muscles of nerves below the base of skull (T2) and/or N1 involvement.

III. Tumour extending beyond T2 limits of bone involvement (T3) and/or N2 involvement.

IV. N3 involvement irrespective of the primary tumour.

V. Haematogenous metastasis and/or involvement of skin or lymph node(s) below the clavicles (M).

Statistical analysis was by Student's *t*-test.

RESULTS

A very narrow range of 0.3–0.7 U/ml was obtained based on mean ± 2 S.D. of the serum CYFRA 21-1 levels of the healthy controls. However, since all healthy subjects had values below 2.0 U/ml, this value was arbitrarily taken as the upper limit of the reference range.

The characteristics of the 240 patients with histologically proven NPC, the mean and range of CYFRA 21-1 for these patients in different stages and that of the healthy control group are shown in Table 1. The NPC metastatic group included distant metastases to lung, bone and liver. There is a general increase of mean CYFRA 21-1 levels from the healthy controls towards higher stages of NPC. The differences between each of these groups are statistically highly significant ($P < 0.005$) except that between NPC of stages III and IV ($P = 0.95$).

In view of the similarity between stages III and IV, these stages were combined to form the 'advanced NPC' group while stages I and II were combined to form the 'early NPC' group as illustrated in Table 1. Inter-group comparison showed that the difference in mean serum CYFRA 21-1 between the healthy controls, the 'early NPC', the 'advanced NPC' and NPC metastatic group are all statistically highly significant ($P < 0.005$).

The distribution of CYFRA 21-1 levels are shown in Fig. 1. 126 (52.5%) of the 240 newly diagnosed NPC patients have elevated levels of CYFRA 21-1.

The percentages of NPC patients with raised values increased from stage I to metastatic NPC as: 6.3, 15.5, 40.0, 54.2, 95.8. All except 2 patients with distant metastases showed elevated CYFRA 21-1 levels. One of these two exceptions had lung metastasis and the other had bony metastasis.

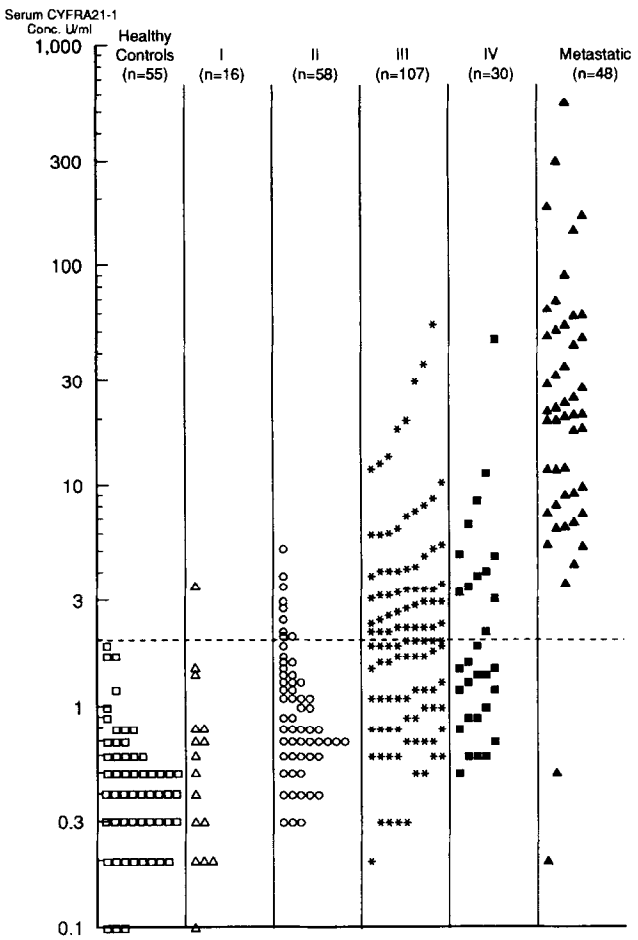

Fig. 1. Serum CYFRA 21-1 levels in healthy controls and nasopharyngeal carcinomas in relation to staging.

The changes in level of 7 patients who did not develop distant metastasis after treatment (at follow-up of 8.5 to 31.0 months, median 14.0 months from the time of diagnosis) are shown in Fig. 2. Patients with an elevated pre-treatment level fell to the normal range post-treatment while

Table 1. *Serum CYFRA* 21-1 *levels in healthy controls and NPC patients*

Population	Number	Mean age	Sex ratio M:F	CYFRA 21-1 concentration mean ± S.D. (U/ml)	CYFRA 21-1 range (U/ml)
Healthy controls	55	45.7	3.7:1	0.5 ± 0.1	0.1–1.9
NPC stage I	16	45.1	3.0:1	0.8 ± 0.2	0.1–3.5
NPC stage II	58	44.0	1.6:1	1.2 ± 0.1	0.3–5.2
NPC stage III	107	49.5	3.7:1	4.1 ± 0.7	0.2–54.6
NPC stage IV	30	42.7	5.0:1	4.1 ± 1.5	0.5–46.8
NPC metastatic*	48	48.6	5.0:1	50.6 ± 13.4	0.2–555.0
'Early NPC' (stages I & II combined)	74			1.1 ± 0.1	0.1–5.2
'Advanced NPC' (stages III & IV combined)	137			4.1 ± 0.6	0.2–46.8

*Comprised of 29 patients with distant metastatic disease at presentation (NPC stage V) and 19 patients who developed distant metastases after treatment.

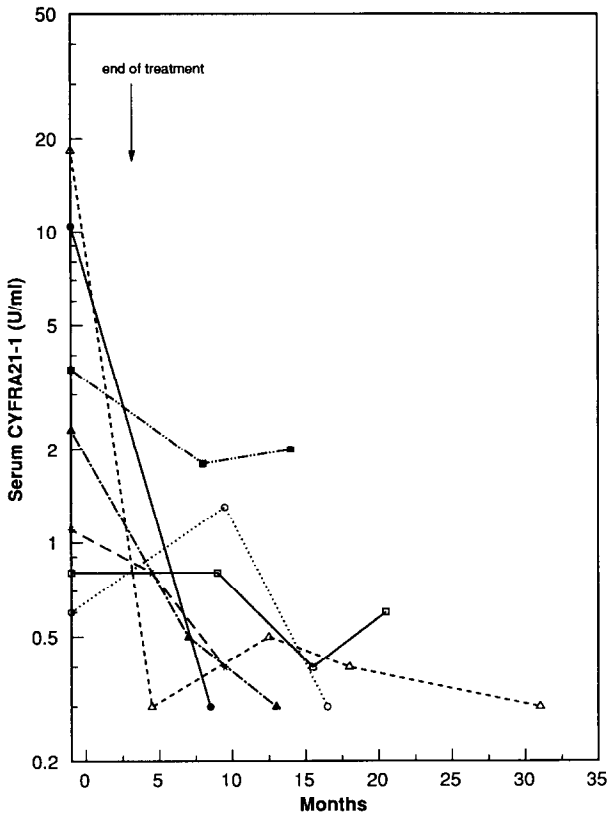

Fig. 2. Changes of serum CYFRA 21-1 levels in NPC patients who did not develop distant metastasis after treatment.

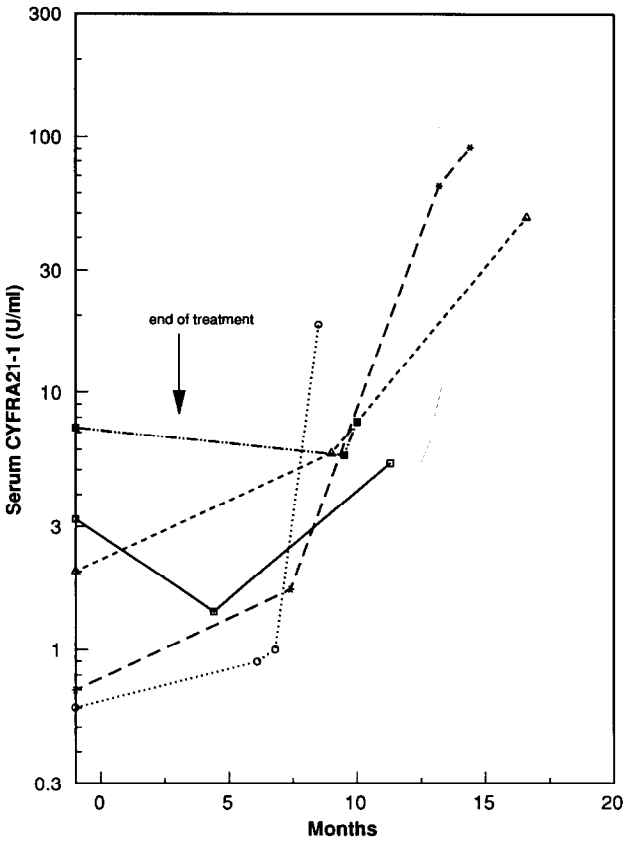

Fig. 3. Changes of serum CYFRA 21-1 levels in NPC patients who developed distant metastases after treatment.

those with a normal level before treatment remained so during follow-up.

The concentration–time curve of 5 patients who developed distant metastases of lung, bone or liver are illustrated in Fig. 3 with the clinical detection of the metastases as the end-point. Consistent rising trends in CYFRA 21-1 levels were observed in these patients.

DISCUSSION

The cut-off value of <2.0 U/ml established in the normal Chinese population is lower than the commonly used <3.3 U/ml [3, 4]. Although there is a significant difference between the mean levels of the healthy controls and NPC patients of different stages, CYFRA 21-1 is of little diagnostic value because of the very low percentage of the 'early NPC' cases who have raised levels. The overall percentage (52.5) of newly diagnosed NPC patients with elevated CYFRA 21-1 level is very close to the 52–63% found in SCC of the lung [2–4]. This suggests that the expression of serum CYFRA 21-1 is related to the cell type of the carcinoma rather than the tissue type.

The increase in mean serum CYFRA 21-1 level with advancing stage indicates some correlation between the marker level and tumour burden. Similar stage-dependence has been observed in SCC of the lung [2–4]. The lack of significant difference between stage III and IV disease might reflect equivalent tumour load beween some patients in these two different clinical stages. This is the likely explanation as there are two factors, the size of the primary tumour (T stage) and the site of the lymph nodes (N stage), both contributing towards the overall staging in Ho's classification [7].

The extremely high percentage (95.8) of NPC patients with distant metastases showing raised levels of CYFRA 21-1 suggests that the marker might be a useful aid in the management of NPC patients. As a routine, patients are currently subjected to radiological screening for possible lung, liver or bone metastases before radiotherapy, which is the mainstay of treatment. This is because radical radiotherapy with a curative intent is for patients without distant metastasis, while treatment for patients with disseminated diseases is only for palliation. However, with the marked increase in patient load in recent years, ultra-sound scans of the liver and radionuclide scans of bone cannot always be facilitated before treatment is initiated. As our results have suggested that distant metastasis in patients with a normal value of CYFRA 21-1 is very unlikely, radiological screening is less urgent for these patients and resources could be focussed on those with elevated CYFRA 21-1 levels. This is considered reasonable as only 4% (2 out of 48 patients) of distant metastases would be missed.

Although serum antibody (IgA) titre against viral capid antigen (VCA) associated with the Epstein–Barr virus (EBV) is still the most valuable marker to aid the diagnosis of NPC [8], it is not useful for monitoring the response to treatments [9]. A multicentre study has suggested increases

in anti-VCA, anti-EA (early antigen) IgG and IgA after remission are highly suggestive of systemic relapse [9]. Interleukin-2 receptors are the other marker that has been proved to be useful for monitoring response of NPC to treatment and for detection of distant metastasis in a retrospective series [10].

The preliminary result from the 12 patients with serial values of CYFRA 21-1 is very encouraging. This marker has a high potential for monitoring the response of NPC patients towards the treatment and for early detection of distant metastasis. This potential needs to be fully explored in a longitudinal study.

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