Pergamon

Oral Oncol, Eur J Cancer, Vol. 32B, No. 4, pp. 242–245, 1996

Printed in Great Britain
0964-1955/96 $15.00 + 0.00

0964-1955(95)00084-4

Strong Association Between Hyperferritinaemia and Metastatic Disease in Nasopharyngeal Carcinoma

S. Ho, S.F. Leung, W.T. Leung, S.Y. Tsao,* W.H. Kwan, P. Choi and P.J. Johnson

Department of Clinical Oncology at the Sir Y.K. Pao Cancer Centre, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong

We have investigated the role of serum ferritin, in relation to disease stages, in patients with nasopharyngeal carcinoma. Patients with localised disease (Ho's stage I–IV) had levels which were not significantly different from age, sex matched normal subjects and there was no relationship between mean serum ferritin levels and stage. However, in patients with metastatic disease levels were grossly elevated with mean levels increased more than 6-fold compared to normal subjects and patients with localised disease. Furthermore, among the small group of patients with localised disease but hyperferritinaemia, the subsequent development of metastatic disease within 1 year was significantly much higher (32.4%) than in those with levels falling within the reference range (10.3%). Hyperferritinaemia is strongly associated with, and may predict, metastatic disease in patients with nasopharyngeal carcinoma. Copyright © 1996 Elsevier Science Ltd

Keywords: nasopharyngeal carcinoma, hyperferritinaemia, metastatic

Oral Oncol, Eur J Cancer, Vol. 32B, No. 4, pp. 242–245, 1996.

INTRODUCTION

Elevated serum ferritin levels have been found in states of iron overload [1, 2] and in many malignant diseases such as leukemia, breast cancer, Hodgkin's disease and hepatocellular carcinoma [3]. Serum ferritin has been suggested to be a valuable tumour marker for squamous cell carcinoma of the head and neck [4].

Nasopharyngeal carcinoma (NPC) is the predominant head and neck cancer found in South East Asia [5]. Serum antibody (IgA) titre against viral capsid antigen (VCA) associated with Epstein Barr Virus (EBV) is the major serology test adopted to aid the diagnosis of NPC [6]. However, there are about 20% of histopathologically proven cases showing a negative IgA VCA titre. Thus, there is a need for a marker which is either more sensitive than, or complementary to, the IgA VCA titre. A prognostic marker better than IgA VCA is also required for monitoring the responses to treatment and for early detection of residual, recurrent or metastatic diseases [7–10].

In this study, the serum ferritin levels of the normal Chinese population were investigated with the intention of establishing a reference level, and the significance of hyperferritinaemia in relation to disease stage of NPC was evaluated.

Correspondence to P.J. Johnson.
*Present address: Gleneagles Hospital Ltd, 6A Napier Road, Singapore 1025.
Received 20 Oct. 1995; accepted 14 Nov. 1995.

MATERIALS AND METHODS

Serum samples from 184 volunteers with no apparent illness, 279 untreated patients with histologically proven NPC of stage I–IV (Ho's stage classification) [5], and a group of 63 patients with proven metastatic NPC (stage V, Ho's stage classification) were collected for determination of serum ferritin levels. In 21 of the latter group, metastases were presented at the initial diagnosis, while in the other 42 cases metastases were detected during follow-up. The metastases were documented by various radiological modalities such as chest X-ray, computed tomography, ultrasound scan, radioisotope bone scan together with biopsy proof when deemed necessary.

The clinical status of the patients of stage I–IV was reviewed at 1 year from diagnosis to document the number of patients developing haematogenous metastases within 1 year. Sera were collected over a period of 3 years (1985–1987) and stored at −70°C before assay. Serum ferritin levels were measured using the Hybritech TANDEM-R FER immunoradiometric assay kits.

Student's *t*-test and chi-square test were employed in statistical analysis.

RESULTS

The 184 healthy controls were divided into three groups according to sex and age: group (i) males, group (ii) females aged <50; and group (iii) females aged ≥ 50. The range and mean value of serum ferritin levels of the three groups of

Table 1. Serum ferritin levels in healthy controls and NPC patients

	n	Mean age	M:F	Serum ferritin levels (ng/ml) Mean ± 2 S.D.	Range
Healthy controls					
Males	94	44.6	—	267 ± 268	28–569
Females (age < 50)	61	37.7	—	88 ± 176	10–458
Females (age ⩾ 50)	29	59.4	—	205 ± 276	16–485
NPC patients					
Stage I	36	45.6	2.3:1	307 ± 590	13–1371
Stage II	67	44.8	2.1:1	256 ± 408	10–998
Stage III	115	45.9	2.8:1	293 ± 424	10–1269
Stage IV	61	46.9	4.6:1	316 ± 408	17–1067
Metastatic	63	47.8	5.3:1	1920 ± 5566	103–14490

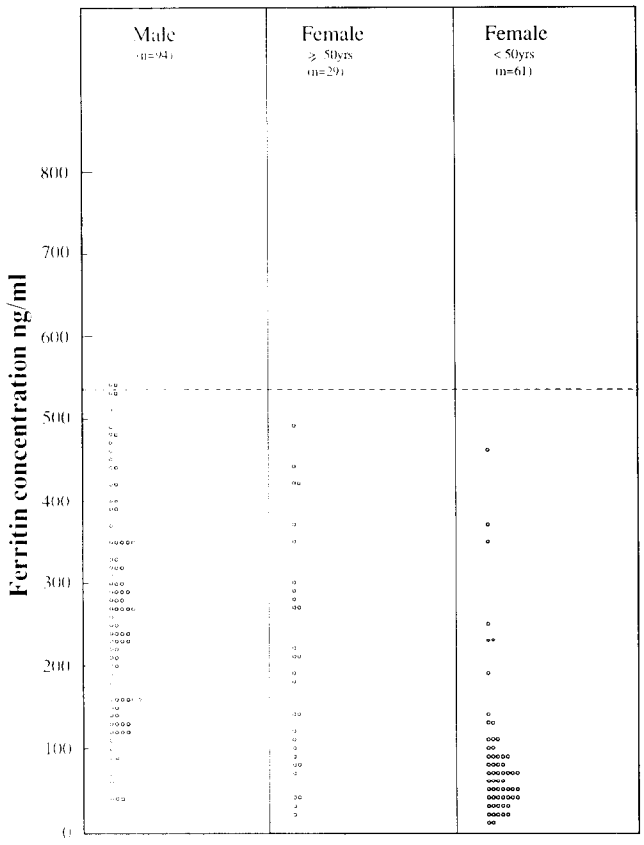

Fig. 1. Serum ferritin levels in healthy controls.

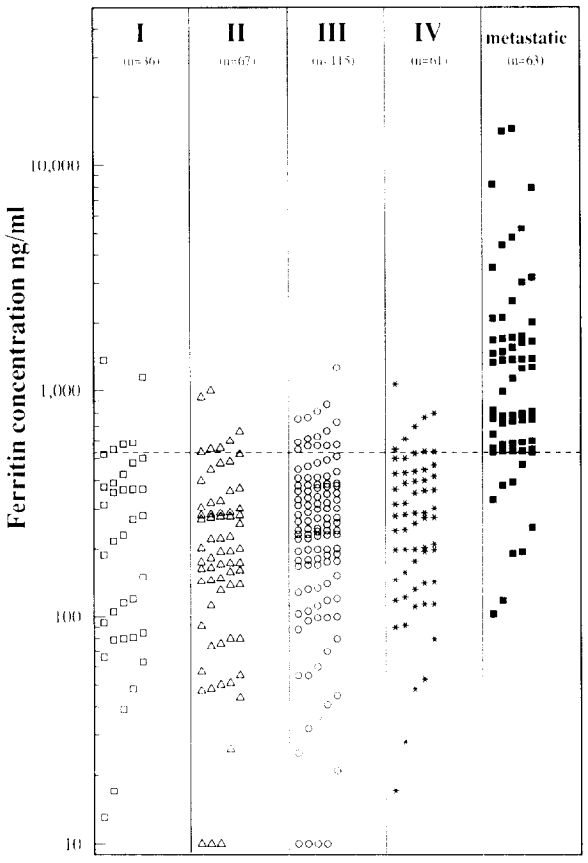

Fig. 2. Serum ferritin levels in NPC.

healthy controls and the NPC patients are shown in Table 1. The distribution of ferritin concentrations is illustrated in Figs 1 and 2.

Among the healthy controls, females with age <50 have significantly lower mean serum ferritin levels compared to the males and older females (⩾50) ($P<0.001$). The mean serum ferritin levels of older females (⩾50) is also significantly lower than that of males ($P<0.05$). Only 3 (1.6%) of the whole group of healthy controls had serum ferritin ⩾535 ng/ml (mean + 2 S.D. for males) which was chosen as the cut-off value in analysing the data of the NPC patients.

There was no significant difference in the mean serum levels of male healthy controls and NPC patients for each of stages I–IV. The percentages of patients with elevated values from stages I to IV were 13.9, 10.4, 1.0 and 14.8, respectively. Thus there is no increasing trend with advancing stage. A total of 37 patients (13.3%) with stage I–IV disease had serum ferritin concentrations lying on or above the upper limit of the reference range. All these patients had undergone routine radiological screening including chest X-ray, computed tomography, ultrasound scan and radioisotope bone scan for distant metastases and were found to have no evidence of haematogenous spread of disease at the time of diagnosis.

However, the mean serum ferritin level of the metastatic group was grossly elevated in comparison to the other four different stages of NPC with a mean value of 1920 ng/ml

Table 2. Serum ferritin levels in patients with haematogenous metastatic NPC

Site of metastasis	*n*	Serum ferritin level (ng/ml) Mean ± S.D.	Range
1. Lung	9	600 ± 750	103–1395
2. Bone	20	1668 ± 3796	191–8205
3. Liver	19	3069 ± 8790	248–14 490
4. Bone marrow	1	1260	1260
5. Skin	1	1133	1133
6. Infraclavicular fossa	1	502	502
7. Multiple (more than one)	12	1747 ± 2522	382–4800

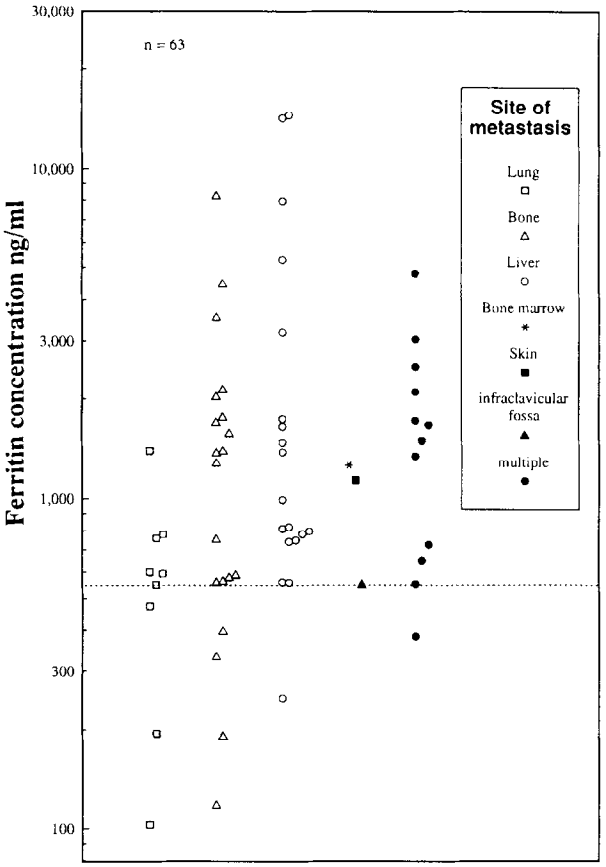

Fig. 3. Serum ferritin levels in metastatic NPC.

($P<0.001$). 54 (85.7%) of the 63 metastatic NPC patients showed elevated values of serum ferritin. This group of 63 patients was further stratified according to the site of metastasis as shown in Table 2. The distribution of ferritin concentration according to sites of metastasis is illustrated in Fig. 3. Table 2 shows an increase in mean serum ferritin level from lung metastases to bone metastases and is highest with liver metastases. However, the differences are not statistically significant ($P>0.10$).

On reviewing the clinical status of each patient in stage I–IV at 1 year from diagnosis, 12 (32.4%) of the 37 patients with elevated pretreatment serum ferritin levels had presented with haematogenous metastases. On the other hand, only 25 (10.3%) of the 242 patients with normal pretreatment serum ferritin levels had developed metastastic diseases ($P<0.005$). The number and percentage of patients that developed distant metastases for the four different stages are shown in Table 3. No patient in stage I developed distant metastasis within the first year. The percentage is higher in patients with elevated serum ferritin levels for all other stages.

Table 3. Number and percentage of patients who developed haematogenous metastases within 1 year from diagnosis

Stage	Ferritin level ⩾535 ng/ml	Ferritin level <535 ng/ml
I	0/6 (0%)	0/30 (0%)
II	1/7 (14.3%)	5/60 (8.3%)
III	4/15 (26.7%)	9/100 (9.0%)
IV	7/9 (77.8%)	11/52 (21.2%)
Total	12/37 (32.4%)	25/242 (10.3%)

DISCUSSION

Ferritin is the major soluble iron storage protein from which iron may be mobilised for the synthesis of haemoglobin, myoglobin and other iron containing proteins [1]. It is present in most tissues of the body but its highest concentration is found in cytoplasm of the reticuloendothelial cells, liver cells, spleen cells and developing red cell precursors in bone marrow. Serum ferritin levels are low but they reflect the amount of iron storage of the body.

It had been reported that, as in our series, in healthy adults, the mean serum ferritin levels are higher in males than in females [1, 4, 11]. A lower mean serum ferritin concentration was found in females compared to males and young women (age <50 years) have a particularly low mean level. The occurrence of a lower mean serum ferritin concentration in younger patients agrees with the observation of Maxim and Veltri [4].

Elevated serum ferritin concentrations have been observed in a large variety of malignant diseases such as malignant lymphoma, carcinomas of the breast and liver [3]. Serum ferritin has been suggested to be a useful marker of several malignant diseases including Hodgkin's disease [12], hepatocellular carcinomas [13], breast cancer [11], testicular germ cell tumours [14] and head and neck cancers [4]. However, the study on squamous cell carcinomas of the head and neck had included only one case of NPC.

Serum ferritin level has no diagnostic value for NPC stage I–IV as the mean value for each of these stages is not significantly different from that of healthy males. The mean concentration of healthy males was chosen for comparision because NPC has a higher incidence in males (Table 1). This observation is different from that of Maxim and Veltri [4]. They found significantly higher ferritin levels in head and neck cancer patients (including one case of NPC) than in healthy controls.

No correlation exists between the mean serum ferritin levels and staging of NPC as far as the disease remained localised (stage I–IV). This is again different from the findings of Maxim and Veltri [4] who observed significantly higher ferritin levels in advanced (stages III and IV) head and neck cancers than those with stage I and II diseases.

Increasing ferritin level with advancing stage of disease has

also been reported for Hodgkin's disease [12]. The stage independence of mean serum ferritin level for NPC is in line with the results with testicular germ cell tumours [14] and breast cancer [15]. The serum ferritin level showed no value in staging after orchiectomy in germ cell tumours and no statistically significant difference was found between breast cancer patients with different disease staging.

Serum ferritin levels showed a wide variation in both the healthy controls and NPC patients with stage I–IV disease. This was more prevalent in metastatic NPC with a wide range of 103–14 490 ng/ml. The levels are much higher than in the healthy controls and patients with stage I–IV NPC. The high percentage of metastatic cases showing elevated levels of serum ferritin suggested that it might serve as a good indicator of metastases in NPC. Jacobs *et al.* [12] also reported high ferritin levels in Hodgkin's disease with systemic symptoms.

There seemed to be a general increase (although statistically not significant) in ferritin level when the site of metastasis changed from lung to bone and bone marrow, and then to liver. The higher serum concentration of ferritin associated with liver and bone could result from a disorder of iron metabolism of liver cells and developing red cell precursors in bone marrow which are known to contain a higher concentration of ferritin than lung cells [2].

The risk of developing distant metastases within 1 year seemed to be much higher in patients with elevated serum ferritin levels. The reported distant metastatic rate is 20–35% at 5 years [16] but early metastases up to 32.4% had already been detected within 1 year in our group of patients with hyperferritinaemia. This might reflect the presence of microscopic haematogenous metastases of size below the detection limit of available radiological modalities at diagnosis but manifested within 1 year as they continued to grow. In any event the group of patients with elevated ferritin level must be placed under very close observation for early detection of distant metastasis, particularly in patients with stage III or IV disease.

NPC seemed to behave differently from other types of head and neck cancers [4] in the expression of serum ferritin. The level of serum ferritin is not changed by localised disease irrespective of its staging (I–IV) suggesting that iron metabolism is not disturbed by the malignancy when it remains confined to the head and neck region. Disorder of iron metabolism is associated with haematogenous metastasis of the disease to other organs.

The value of serum ferritin level for early detection of haematogenous metastasis in NPC needs to be clarified by serial determination of the marker level in serum samples of patients attending follow-up post-treatment, with the clinical detection of distant metastasis as the end-point.

CONCLUSION

Serum ferritin levels are not elevated in stage I–IV NPC patients with the disease confined to the head and neck region, and there is no correlation with staging. Thus, it is not a useful marker for diagnosis of localised NPC. However, there is a strong association between elevated serum ferritin levels and distant metastases and, therefore, serum ferritin might serve as a good indicator of haematogenous spread of the disease. The value of serum ferritin level in early detection of distant metastasis has to be investigated by a prospective study on patients being followed-up after treatment.

1. Jacobs A, Miller F, Worwood M. Ferritin in serum, clinical and biochemical implication. *N Engl J Med* 1975, **292**, 951–956.
2. Worwood M. Ferritin in human tissues and serum. *Clin Haematol* 1982, **11**, 275–307.
3. Jacobs A. Serum ferritin and malignant tumours. *Med Oncol Tumour Pharmacother* 1984, **1**, 149–156.
4. Maxim PE, Veltri RW. Serum ferritin as a marker in patients with squamous cell carcinoma of the head and neck. *Cancer* 1986, **57**, 305–311.
5. Ho JHC. An epidemiologic and clinical study of nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1978, **4**, 183–198.
6. Henle G, Henle W. Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carinoma. *Int J Cancer* 1976, **17**, 1–7.
7. Henle W, Ho JHC, Henle G, Chan JCW, Kwan HC. Nasopharyngeal carcinoma: significance of changes of Epstein–Barr virus-related antibody patterns following therapy. *Int J Cancer* 1977, **20**, 663–672.
8. Lymn TC, Hsu MM, Hsieh T, Tu SM. Prognosis of nasopharyngeal carcinoma by Epstein–Barr virus antibody titre. *Arch Otolaryngol* 1977, **103**, 128–132.
9. De-Vathaire F, Sancho-Garnier H, De-The H, *et al.* Prognostic value of EBV markers in the clinical management of nasopharyngeal carcinoma (NPC): a multicentre follow-up study. *Int J Cancer* 1988, **42**, 176–181.
10. Lynn TC, Tu SM, Kawamura A, Jr. Long-term follow-up of IgG and IgA antibodies against viral capsid antigens of Epstein–Barr virus in nasopharyngeal carcinoma. *J Laryngol Otol* 1985, **99**, 567–572.
11. Marcus DM, Zinberg N. Measurement of serum ferritin by radioimmunoassay: results in normal individuals and patients with breast cancer. *J Natl Cancer Inst* 1975, **55**, 791–795.
12. Jacobs A, Slater A, Whittaker JA, Canelloo G, Wiernik PH. Serum ferritin concentration in untreated Hodgkin's disease. *Br J Cancer* 1976, **34**, 162–166.
13. Melia WM, Bullock S, Johnson PJ, Williams R. Serum ferritin in hepatocellular carcinoma: a comparison with alpha-fetoprotein. *Cancer* 1983, **51**, 2112–2115.
14. Szymendera JJ, Kozlowicz-Gudzinska I, Madej G, Sikorowa L, Kaminska JA, Kowalska M. Clinical usefulness of serum ferritin measurements in patients with testicular germ cell tumours. *Oncology* 1985, **42**, 253–258.
15. Pattanapanyasat K, Hoy TG, Jacobs A, Courtney S, Webster DJT. Ferritin-bearing T-lymphocytes and serum ferritin in patients with breast cancer. *Br J Cancer* 1988, **57**, 193–197.
16. Altun M, Fandi A, Dupuis O, Cvitkovic E, Krajina Z, Eschwege F. Undifferentiated nasopharyngeal cancer (UCNT): current diagnostic and therapeutic aspects. *Int J Radiat Oncol Biol Phys* 1995, **32**, 859–877.

Acknowledgements—The authors would like to thank Miss Rebecca Yau and Mr M.K. Man for their assistance in preparing this manuscript.