

Ferritin, finger clubbing, and lung disease

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ABSTRACT The serum ferritin concentration has been determined by an immunoradiometric assay in 90 subjects with a variety of pulmonary diseases. No association between ferritin concentrations and finger clubbing has been found in any of the diseases studied. Ferritin levels were significantly raised in the subjects with bronchial carcinoma, but were not useful in monitoring recurrence of the tumour. Pulmonary artery and pulmonary vein ferritin concentrations were similar to systemic venous concentrations. It is therefore unlikely that the tumour releases ferritin into the pulmonary circulation. Ferritin levels were raised in patients with acute pneumonias but did not correlate with the total white cell count or erythrocyte sedimentation rate. Serum ferritin concentrations were also increased in a variety of chronic lung diseases but were normal in subjects with asbestosis.

Finger clubbing is a common and well-recognised physical sign but its pathogenesis is obscure. Histological examination of clubbed fingers has revealed an increase in vascular connective tissue.¹ Blood flow to clubbed fingers is increased² and most of the blood probably passes through arteriovenous anastomoses.³

The frequent association of clubbing with right to left shunts has led to the hypothesis that a circulating factor normally removed by the lungs acts on the finger tips to increase their blood flow. The chemical nature of the circulating vasodilator has never been demonstrated. Hall⁴ pointed out that ferritin, which is normally inactivated in the lungs, inhibits the vasoconstrictor effect of catecholamines. Ferritin was originally called vaso-depressor material (VDM) because of this action.⁵ It also has an antidiuretic effect.⁶ Hall⁴ and Hall and Laidlaw⁷ showed that reduced ferritin was present in mixed venous blood but only in arterial blood if clubbing was present. The increased blood flow to clubbed fingers was abolished by rutin, a specific ferritin antagonist. They postulated that reduced ferritin caused vasodilatation in the finger tips and, consequently, finger clubbing.

This theory could not be confirmed until recently because the original bioassay of ferritin was insensitive. Recently a radioimmunoassay⁸ has been developed, and this has been used in this study in an attempt to correlate the presence of clubbing with

the serum ferritin concentration. The concentration of ferritin in a variety of lung conditions has also been examined and its usefulness as a tumour marker in bronchial carcinoma⁹ has been assessed.

Methods

The details of the 90 subjects studied are shown in table 1. Those with bronchial carcinoma were subdivided histologically into epidermoid, small cell, and adenocarcinoma subgroups and also according to the presence or absence of extrapulmonary metastases. The diagnosis of asbestosis had been made in each case by the pneumoconiosis medical panel from five to 11 years previously and the progression of the disease over this period was assessed radiologically. The chronic lung disease group comprised eight patients with untreated pulmonary tuberculosis (four with clubbing), six with cryptogenic fibrosing alveolitis (four with clubbing), nine with

Table 1 Details of subjects

Group	Number	Age (mean \pm SD)	Sex		Clubbing	
			M	F	Present	Absent
All	90	60.3 \pm 11.8	68	22	41	49
Bronchial carcinoma	24	64.3 \pm 9.1	15	9	12	12
Asbestosis	28	62.9 \pm 7.8	28	0	14	14
Chronic lung disease	26	56.2 \pm 12.8	16	10	13	13
Hereditary clubbing	2	54.5 \pm 0.5	2	0	2	0
Acute pneumonia	10	56.1 \pm 19.6	7	3	0	10

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bronchiectasis (four with clubbing), and three with a lung abscess (one with clubbing). Two subjects with hereditary clubbing and 10 with acute bacterial or mycoplasma pneumonia were also studied. The presence or absence of finger clubbing was assessed independently by two physicians and only subjects in whom agreement was reached were included in the study.

Serum ferritin concentrations were determined by an immunoradiometric assay⁸ with antibodies to human spleen ferritin, and human spleen ferritin as standard. In patients with bronchial carcinoma, ferritin concentrations were also determined with a radioimmunoassay for acidic (HeLa cell) ferritin.¹⁰ The distribution of ferritin concentrations in healthy adults is skewed, but the level is less than 300 ng/ml in 95% of normal subjects. Ferritin levels were measured in each patient at presentation. Repeat estimations were made in five subjects from one week to 14 months after resection of a bronchial carcinoma. In three patients with bronchial carcinoma ferritin estimations on pulmonary artery and pulmonary venous blood draining the tumour were made at thoracotomy. The normal and malignant lung tissue was also analysed for the basic (spleen type) and acidic (HeLa cell type) ferritin in two of these subjects.

A full blood count was carried out in all the patients, erythrocyte sedimentation rate (ESR) (Westergen method) in 72, and aspartate transaminase, alanine transaminase, and alkaline phosphatase in all except the asbestosis patients. None of the patients had the haematological features of iron deficiency and none had raised liver enzymes.

The significance of the ferritin concentrations was assessed by the two-tailed Kolmogorov-Smirnov test. Their relationship to the white blood count (WBC) and ESR was tested by using the Spearman rank correlation coefficients.

Results

RELATIONSHIP TO FINGER CLUBBING

The observed ferritin concentrations were not related to the presence of finger clubbing in the whole group of patients (excluding those with acute pneumonia) or in those with bronchial carcinoma or chronic lung disease analysed separately. No relationship to finger clubbing emerged when the carcinoma group was subdivided histologically or according to the presence of metastases. Ferritin and finger clubbing were not related in the asbestosis group as a whole or in those with progressive or static disease analysed separately. The single patient with hypertrophic osteoarthropathy caused by a bronchial carcinoma had a ferritin level of 518 ng/ml. One patient, with a

lung abscess, was tested before and after finger clubbing appeared but her ferritin concentrations were normal (140 and 227 ng/ml) on both occasions. The ferritin concentration was 679 ng/ml in a patient with tuberculosis when his clubbing was mild and 894 ng/ml when it had progressed significantly. The ferritin concentration was normal in both patients with hereditary clubbing.

BRONCHIAL CARCINOMA

The serum ferritin concentrations were significantly higher in the bronchial carcinoma group than in normal subjects¹¹ ($p < 0.002$). There was no significant difference between the histological subgroups but those with metastases had a higher ferritin concentration than those without ($p < 0.05$). In view of the high levels seen in these patients, serial measurements were made in five patients after resection of the primary tumour to see if changes in the concentration indicated recurrence of disease (figure). No trend was apparent.

To test whether the high ferritin concentrations were caused by ferritin released by the primary tumour, the systemic venous concentrations were compared with those in the pulmonary artery and vein in three patients (table 2). The pulmonary vein values were not significantly different from the pulmonary artery values. HeLa cell type ferritin was not detected in blood from the pulmonary artery, pulmonary vein, or systemic blood in these subjects (table 2).

ASBESTOSIS

The ferritin concentrations in the subjects with asbestosis were similar to those in the normal population.¹¹ There was no association with progression of the asbestosis.

CHRONIC LUNG DISEASE

The ferritin concentration was significantly higher ($p < 0.05$) in patients in this group than in normal people.¹¹ There was no significant difference between the aetiological subgroups.

ACUTE PNEUMONIA

The ferritin concentration was significantly increased ($p < 0.0001$) during acute pneumonia relative to the normal population.¹¹ It was not correlated with the total white blood cell count or ESR.

Discussion

The possibility that ferritin is the vasodilator responsible for finger clubbing was raised by the findings of Hall⁴ and Hall and Laidlaw.⁷ More recently the presence of clubbing in thalassaemia has been

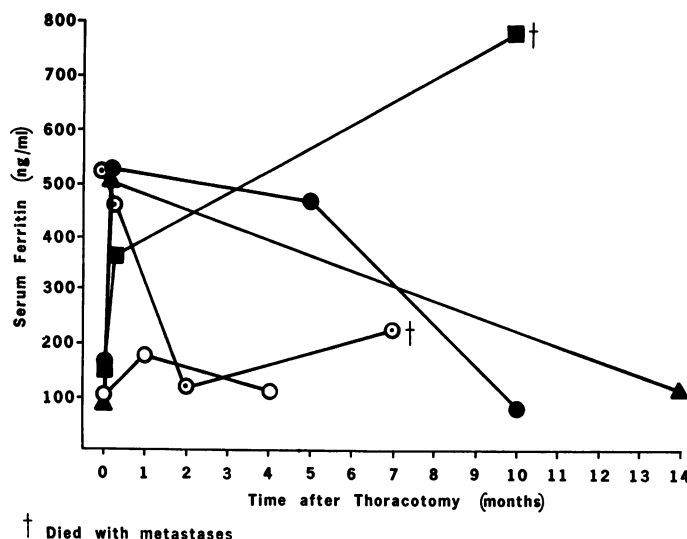


Figure Serial ferritin estimations in five subjects before and after resection of bronchial carcinoma.

Table 2 Serum ferritin measurements during thoracotomy

Patients	Spleen type ferritin concentration ng/ml (HeLa type ferritin concentration ng/ml)		
	Pulmonary artery	Pulmonary vein	Systemic vein
1	92 (< 2)	118 (< 2)	108 (< 2)
2	551 (< 2)	490 (< 2)	518 (< 2)
3	84 (< 2)	82 (< 2)	93 (< 2)

correlated with the severity of iron overloading.¹² Ferritin is an iron-storage protein and, although it was not measured, its serum concentration would almost certainly be raised in these patients. In addition, koilonychia, which in some respects is the opposite of clubbing, is a feature of severe iron deficiency.

Extrapulmonary conditions that affect serum ferritin concentration were excluded in this study by the history, examination, full blood count, and measurement of hepatic enzymes. Iron deficiency decreases ferritin levels¹³ and iron overload,^{13 14} and liver disease¹⁴ are known to increase them. None of these subjects appeared to be iron deficient or overloaded and none had elevated liver enzymes.

The ferritin concentrations in the 41 subjects with finger clubbing were not significantly different from the 39 subjects (excluding those with acute pneumonia) without clubbing. There was no relationship to clubbing when the bronchial carcinoma, asbestosis, or chronic lung disease groups were analysed

separately. The ferritin level was not related to clubbing in any of the histological subgroups of the bronchial carcinoma or in either those with or without metastases. Both patients with hereditary clubbing had normal ferritin levels.

The ferritin concentration is therefore not related to the presence or absence of finger clubbing. Nevertheless, it is possible that high levels in the early stages of clubbing could be a necessary factor in its development and that once clubbing is established the ferritin level is immaterial. One patient with a lung abscess, however, was studied before and after clubbing appeared but her ferritin levels were normal on both occasions. One other subject with tuberculosis was studied when his clubbing was progressing and later when it was fully developed. His ferritin levels were similar on the two occasions. Thus ferritin does not appear to play any role in the early stages of clubbing and a search for other vasoactive agents is needed.

Biochemical markers of tumour mass have proved useful in many types of neoplasm although not for bronchial carcinoma. Ferritin has been suggested as a tumour index substance. It has been detected in breast carcinoma tissue¹⁵ and its serum level correlates with recurrence of the tumour after initial surgery.^{16 17} Alpha-two H globulin is almost identical to ferritin^{18 19} and has also been used as a tumour index substance.²⁰ Aungst, using a bioassay, detected ferritin in seven out of nine subjects with bronchial carcinoma and two subsequent studies have demonstrated it in 61% and 72% of such patients.²¹⁻²³ Ferritin has been found in extracts of bronchial carcinoma, but not in normal lung.²³

In the present study, the ferritin concentration was significantly raised in the subjects with bronchial carcinoma, but was not related to the histological type. The ferritin concentration in venous, pulmonary arterial, and pulmonary venous blood measured during resection of the tumour were all similar suggesting that it was not being liberated into the pulmonary circulation in clinically significant amounts by the tumour. The high serum ferritin values seen in bronchial carcinoma may be caused by the "reticulo-endothelial block" to iron uptake seen in other tumours,¹⁹ and which results in increased iron stores.

Samples of bronchial carcinoma removed from two patients showed increased quantities of acidic (HeLa cell type) ferritin compared to normal lung tissue but even so the predominant ferritin was still the more basic type found in liver and spleen. The acidic ferritin content, expressed as a percentage of the total ferritin, was 0.89 for normal lung and 4.6 and 7.1 for the tumours. Although increased levels of acidic ferritin were detected in the tissues there was no corresponding increase of acidic ferritin in the serum of these two patients. No acidic ferritin was detectable in samples from the pulmonary artery and vein or in systemic venous blood of 80% of the patients with carcinoma of the lung who were tested. The highest level in the remaining 20% was only 3 ng/ml so it is unlikely that this acidic ferritin is being released from the carcinoma into the circulation in quantities which could be clinically significant.

The usefulness of spleen type ferritin as a predictor of relapse in bronchial carcinoma after attempted curative resection of the primary tumour was observed in five patients. The high values seen one week after operation were probably the result of the trauma of the operation. The subsequent values did not correlate well with the clinical course of the disease. Nevertheless, among the whole group of bronchial carcinoma subjects those with metastases did have a significantly higher ($p < 0.05$) ferritin concentration than those without. This has been previously noted²³ but, in the individual subject, serial estimation of ferritin concentrations do not appear to be useful in monitoring progress. Further studies with larger numbers of subjects are required.

The influence of acute lung disease on ferritin concentration was studied. The ferritin concentration was significantly higher than normal ($p < 0.0001$). Ferritin is known to be an "acute phase protein" and its level is raised in inflammatory conditions.²⁴ In this study the ferritin level was not related to the total white cell count (WBC) or the ESR, which were used as indices of the severity of the inflammation. In addition, the ferritin values were not related to the WBC in the patients with bronchial carcinoma,

asbestosis, or chronic lung diseases or to the ESR except in the asbestosis group. From these results the high ferritin levels seen during acute pneumonias may be caused by metabolic changes in the lung rather than by the systemic inflammatory reaction. The explanation of the finding of raised ferritin concentrations in the chronic lung disease group but of normal values in the asbestosis group is obscure.

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