Plasma growth hormone and digital clubbing in carcinoma of the bronchus

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Abstract

Growth hormone is a secretory product of some primary bronchial neoplasms and has been associated with the development of hypertrophic pulmonary osteoarthropathy and acromegaly in occasional patients with such tumours; it has not, however, generally been considered important in the pathogenesis of digital clubbing. Plasma levels of growth hormone at the time of diagnostic bronchoscopy were measured in 60 patients with histologically proved bronchial carcinoma, divided according to whether clubbing was present (n = 21) or absent (n = 39), and in 13 control subjects undergoing the same procedure but with no neoplasm. The median plasma level of growth hormone (and interquartile range) was 0.74 (0.5-1.0) mU/l in five control subjects with no pulmonary disease, 0.83 (0.4-1.3) mU/l in eight subjects with non-neoplastic pulmonary disease, 1.1 (0.6-3.3) mU/l in patients with carcinoma but without clubbing, and 3.1 (0.8-9.0) mU/l in 21 patients with carcinoma and clubbing. The highest growth hormone level was seen in a patient with a small cell carcinoma and pronounced clubbing; levels had fallen to normal by the time chemotherapy was completed and clubbing completely resolved. Thus growth hormone or a similar substance might have a role in the pathogenesis of clubbing in patients with bronchial neoplasms.

Clubbing of the fingers and toes depends on expansion of the soft tissues around the terminal phalanges due to vasodilatation, and an increase in vascular connective tissue.¹ It is related to hypertrophic osteoarthropathy, a less common condition characterised by soft tissue swelling around joints, usually the wrists and ankles, with periosteal formation of new bone.^{2,3} The two conditions have many causes in common, though clubbing occurs frequently without hypertrophic osteoarthropathy and the latter may occur without clubbing, though this is very unusual. Some believe clubbing to be merely the earliest and most obvious feature of hypertrophic osteoarthropathy.^{4,5} Whatever the relation between them, both changes are associated with bronchial carcinoma.

Despite its prevalence, the pathogenesis of clubbing remains obscure. The similarities between clubbing, osteoarthropathy, and

acromegaly have stimulated several studies that have sought a role for growth hormone or a related substance in the pathogenesis of these changes in bronchial carcinoma.⁶⁻⁸ Although there is some evidence for such a mechanism in some cases of acromegaly associated with bronchial neoplasia,^{6,7} and to a lesser extent in hypertrophic osteoarthropathy,⁸ there is little information to link growth hormone to clubbing. As part of a larger study of the endocrinological changes associated with bronchial carcinoma, we have reassessed the possible association of this hormone with clubbing in patients with a bronchial neoplasm.

Methods

We studied a consecutive series of patients referred for diagnostic bronchoscopy, many of whom were suspected of having bronchial carcinoma. Informed written consent was obtained in all cases, and all were approached and examined in exactly the same way irrespective of the suspected diagnosis. A history and clinical examination were obtained in the 24 hours before bronchoscopy. Clubbing was assessed independently by one of us (MAG) and by a physician caring for the patient, and was considered present only when all of these four criteria were satisfied¹ for at least five fingers:

- 1 loss of the hyponychial angle on the dorsum of the finger when viewed laterally;
- 2 alteration in texture of the soft tissues with increased fluctuation and mobility of the nail;
- 3 increase in volume of the distal segment;
- 4 increased curvature of the nail in one or both planes.

Of the series of 80 patients, 67 had primary bronchial carcinoma and the remainder had either no abnormality or a non-neoplastic condition. Of those with bronchial carcinoma, 21 were considered to have definite clubbing and 39 to have no sign of it. In seven the findings were equivocal and their data were excluded from the analysis.

Venous blood was drawn before 1100 h prior to bronchoscopy after an overnight fast and before administration of any sedative drug. Patients were supine for 15 minutes before venesection but had been awake for at least one hour. Blood was collected in previously cooled heparinised plastic tubes and centrifuged within one hour for 15 minutes at 1700 rev/min and 4°C. Plasma was pipetted off and frozen at -20°C until the assay.

Growth hormone was measured in

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duplicate by a double antibody radio-immunoassay, sera and reagents being supplied by the Scottish Antibody Service and used according to their protocol. With this assay normal adult levels after an overnight fast are under 2 mU/l. Control samples were obtained from the regional endocrine unit at the Liverpool Royal Children's Hospital. During the period when the assays were performed there was a negative bias of 3% by comparison with the mean of the National External Quality Assessment Scheme. The coefficients of variation were 9.2% for the lower pool (mean 0.8 mU/l), 7.3% for the medium pool (mean 7 mU/l), and 12.4% for the high pool (mean 33.0 mU/l).

Sections of the tissue biopsy specimens obtained at bronchoscopy were stained with haematoxylin and eosin and immunolabelled for human growth hormone by the peroxidase-antiperoxidase method,⁹ a primary polyclonal antiserum raised in rabbit being used (Dako). Tumours were typed morphologically according to the World Health Organisation classification.¹⁰

The extent of disease was documented from clinical examination and further investigations as appropriate. All patients underwent routine radiography of the chest and haematological and biochemical screening before bronchoscopy. After histological confirmation of a diagnosis of bronchial carcinoma, many were assessed by radioisotope or ultrasound scanning of the liver, skeletal radiography, or radioisotope scanning and, occasionally, radioisotope scanning of the brain.

For statistical analysis we used the SPSSX statistical package. As the data were non-normally distributed, differences between groups were assessed by Kruskal-Wallis analysis of variance. Results are presented as medians with interquartile ranges.

Table 1 Plasma concentrations of growth hormone in subjects with and without bronchial carcinoma according to the presence or absence of clubbing (median values with interquartile ranges)

	Plasma growth hormone (mU/l)
CONTROL SUBJECTS	
No pulmonary disease (n = 5)	0.74 (0.5-1.0)
Non-neoplastic pulmonary disease (n = 8)	0.83 (0.4-1.3)
BRONCHIAL CARCINOMA GROUP	
No clubbing (n = 39)	1.10 (0.6-3.3)
Clubbing (n = 21)	3.10 (0.8-9.0)

Table 2 Plasma concentrations of growth hormone in subjects with bronchial carcinoma with and without clubbing according to histological type (median values with interquartile ranges)

	Plasma growth hormone (mU/l)		
	All	No clubbing	Clubbing
Squamous cell carcinoma (n = 25)	2.3 (0.6-2.7)	1.4 (0.5-1.6)	4.8 (0.7-8.9)
Adenocarcinoma (n = 12)	1.9 (0.5-3.5)	1.6 (0.5-3.2)	2.5 (1.1-3.5)
Small cell carcinoma (n = 17)	5.4 (0.8-8.4)	3.9 (0.8-7.3)	7.5 (0.6-10.6)
Non-small cell carcinoma (n = 6)	4.6 (0.5-10.0)	1.4 (0.3-3.4)	7.8 (0.8-13.7)

Results

The mean and interquartile range of plasma growth hormone levels for control subjects and patients with bronchial carcinoma are shown in table 1. The eight subjects with non-neoplastic pulmonary disease had chronic bronchitis (4), pneumonia (3), and pulmonary fibrosis (1). Growth hormone plasma levels are shown according to histological tumour type in table 2 and in the figure.

There were significant differences in plasma growth hormone levels between control subjects and the two groups of patients with carcinoma ($p = 0.003$) that were unrelated to tumour type ($p = 0.21$). Of the 10 subjects with the highest growth hormone levels, seven had clubbing and six had a small cell carcinoma. There was no correlation between plasma growth hormone levels and metastatic disease ($p = 0.29$). Immunochemical examination failed to show immunoreactive growth hormone in the biopsy tissue of any patient.

The highest level of growth hormone (24.0 mU/l) was found in a 63 year old woman with a small cell carcinoma and no evidence of metastasis. She had pronounced clubbing of all fingers and toes at the time of diagnosis. Her plasma growth hormone had fallen to 9.0 mU/l after three cycles of chemotherapy and to 2.0 mU/l after the full course of six cycles. Repeat bronchoscopy at this time, seven months after diagnosis, showed no evidence of residual disease and her clubbing had completely resolved. She remains well with no recurrence of carcinoma or clubbing 18 months after diagnosis.

Discussion

This paper describes an association between plasma growth hormone concentrations and clubbing in patients with bronchial carcinoma. Raised levels of growth hormone and a paradoxical rise in its concentration after administration of glucose have been reported in patients with bronchial tumours,¹¹⁻¹³ but the cause of these phenomena has remained obscure.

Stress is unlikely to be responsible. Great care was taken in this study to ensure that all patients were approached and examined in exactly the same way and values in control subjects were within the normal range and showed little scatter (table 1 and figure). Nor can the results be explained by the presence of metastatic disease as no significant correlation was found. Andrews showed that plasma growth hormone concentrations in patients with primary and metastatic carcinoma were significantly higher when deposits were present in the liver than when they were absent or in other organs and were independent of the site of the primary tumour.¹³ We do not believe that dissemination to the liver can explain the raised levels in our patients. Although not all were specifically investigated for liver metastases, ultrasound and radioisotope scanning of the liver were performed in two patients with high growth hormone concentrations and clubbing and no metastases were found. There is no

Scattergram showing plasma concentrations of growth hormone (HGH) in control subjects and in patients with bronchial carcinoma divided according to the presence or absence of digital clubbing. ● Squamous carcinoma; ○ adenocarcinoma; △ small cell carcinoma; ▲ non-small cell carcinoma; ★ no neoplasm.

particular reason why hepatic deposits should increase plasma growth hormone. Although 95% of the breakdown of growth hormone occurs in the liver, no reduction in its metabolism has been found in cirrhosis, where the high concentrations that are sometimes found are considered to be due to increased production.¹⁴ Plasma concentrations of growth hormone are generally considered to be linearly related to its secretion and not to reflect alterations in its breakdown or clearance.¹⁵

Nor do we believe that general debility or weight loss associated with malignancy explains the increased growth hormone in our patients. Plasma concentrations were measured at initial diagnosis and shortly after presentation, when the disease was generally not advanced, as the infrequency of clinically apparent metastatic disease showed. There was no difference in duration of disease between the groups and weight loss was a feature at presentation in only four of the patients with carcinoma, two with clubbing and two without, each of whom had lost about 10% of their premonitory body weight.

The association between increased plasma growth hormone and clubbing in this study, though significant, is not clearcut; there is considerable overlap between groups and the numbers in each group were small. Previous studies have suggested several agents as a possible cause of clubbing.^{5,16} A role for a growth hormone like substance has often been

implied⁴ but it might be one of several factors and may act synergistically with other factors.

If growth hormone is being secreted in excess in some patients with bronchial carcinoma, there are three likely sources. It has been found in bronchial tumours^{17,18} and as a product of bronchial carcinoma cell lines in culture.¹⁹ We did not find growth hormone in the biopsy tissue from our patients, but the samples were small and may be unrepresentative. Alternative sources include the surrounding lung²⁰ and possibly the pituitary after its stimulation by growth hormone releasing hormone like substances from the tumour or surrounding lung.^{21,22} Further studies are needed to clarify the relation between bronchial carcinoma, growth hormone, and clubbing.

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