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Urinary Hydroxyproline In Malignancies Involving Bone

by

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ABSTRACT The ratio of hydroxyproline to creatinine ("Spot" hypro test) in post-absorptive urine of patients with malignancies involving bone has been estimated. Of 33 cases with X-ray evidence of bone involvement, 27 (i.e. 81.8%) had an elevated ratio. In 6 cases with no X-ray evidence, 2 (i.e. 33%) had an elevated ratio. The sensitivity of this test in the diagnosis of bone malignancies has therefore been established as 82%. These results also indicate the prognostic value of this test in metastatic bone disease.

INTRODUCTION

The 'Spot' hydroxyproline test, viz. the ratio of post-absorptive urinary hydroxyproline to creatinine, has been found useful in the diagnosis and follow up of patients with metastatic bone disease from breast cancer and from a variety of other tumours (Kelleher and Smith, 1982). This project was undertaken to study the ratio in healthy subjects and in patients with malignant disease.

SUBJECTS, MATERIALS AND METHODS

The patients were drawn from those admitted to a unit in the Cancer Institute, Maharagama, over a 3-month period. Twenty-nine patients, of whom 14 were males, had definite X-ray evidence of metastatic bone disease. They provided 33 urine samples for analysis. Six female patients with no X-ray evidence of bone metastases were also investigated. Three patients were investigated more than once to assess the value of the test in monitoring progression of the disease. Urine was collected in the post-absorptive state after an overnight fast, and hydroxyproline estimated by the method of Bergman and Loxley (1970) and urinary creatinine by the alkaline picrate method (Varley, Gowenlock and Bell, 1980). Results were expressed as μmoles of hydroxyproline/mmole of creatinine.

The normal range for the hydroxyproline creatinine ratio was determined in a group of 30 healthy volunteers. Because financial constraints limited sample size, only females over 45 years were investigated, as hydroxyproline excretion has been shown by Hodgkinson and Thompson (1982) to increase in females after that age. Some males under 25 years were also analysed as this age group has a higher excretion (Hodgkinson and Thompson, 1982). However, no significant differences on account of age or sex were observed and the 'spot' hydroxyproline excretion (Mean ± 1 s. D.) in normals was 50.1 ± 26.2 μM/mM of creatinine. The upper limit of normal was therefore taken to be 102.5 μM/mM (i.e. mean + 2 s. D.).

RESULTS AND DISCUSSION

Table 1 presents the results of the 'Spot' hydroxyproline test in patients with X-ray evidence of metastatic bone disease, arising from a variety of primary tumours. Hydroxyproline excretion values were increased in 27 of the 33 cases, giving a test sensitivity of 81.8%. Kelleher and Smith (1982), in their review, report a test sensitivity of between 70 - 83%.

TABLE 1 The frequency of increased hydroxyproline/creatinine ratio (> 102.5 μM/mM creatinine, which is the Mean + 2 S.D. of healthy controls) in malignant disease with and without X-ray evidence of bone involvement, in male (M) and female (F) patients

	With X-ray evidence of bone metastases			Without X-ray evidence of bone metastases		
Diagnosis	No. of observations	M/F	Frequency of increased hydroxyproline excretion	No. of observations	M/F	Frequency of increased hydroxyproline excretion
Carcinoma of breast	6	0/6	5/6	3	0/3	1/3
Primary malignancies of bone	9	3/6	8/9	•	•	•
Carcinoma of thyroid	4	1/3	2/4	•	•	•
Multiple myeloma	4	3/1	3/4	•	•	•
Leukaemia	4	4/0	4/4	•	•	•
Other metastatic carcinomas	4	2/2	3/4	3	0/3	1/3
Carcinoma of bronchus	2	2/0	2/2	•	•	•
Total	33	15/18	27/33	6	0/6	2/6

The hydroxyproline excretion in patients with X-ray evidence of bone metastases was 357.6 ± 315.3 μM/mM creatinine, which is significantly higher ($p < 0.001$) than in the control population.

The results of the test on patients without X-ray evidence of bone metastases is also presented in Table 1. Of the 6 cases studied 2 had an elevated ratio. Such results may be taken as false positives or the X-ray pictures may be false negatives (Kelleher and Smith, 1982). It is hoped that a follow-up study of these patients will confirm the diagnosis either way.

Table 2 presents the results of the 'Spot' test in three patients observed more than once. In one case the decreasing ratio was compatible with tumour regression as judged by X-ray and clinical evidence; in the other two, an increased ratio was matched with tumour progression. The results are in agreement with previous reports (Kelleher and Smith, 1982) that this test is useful in monitoring progress of metastatic bone disease.

TABLE 2. Follow-up study of 3 patients with metastatic bone disease

Patient	Diagnosis	Date of investigation	Spot Hydroxyproline (μM/Mm Creatinine)	Progression of disease*
S.C.	Ewing's	14-09-84	371.7	Condition
S.C.	sarcoma	01-11-84	178.0	improved
S.C.		04-12-84	143.9	
S.K.	Acute leukaemia	12-09-84	517.7	Condition
S.K.	with bone metastases	01-11-84	934.3	deteriorated
E.	Carciuoma of breast	03-10-84	252.3	Condition
E	with bone metastases	01-11-84	410.5	deteriorated

* Progression of the disease assessed by X-ray and clinical evidence

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