Further Observation on Serum Acid Phosphatase Activity in Carcinoma of the Prostate

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During the past three years serum acid and alkaline phosphatase determinations have been carried out by Barringer and Woodard (1), Gutman and Gutman and their co-workers (2-4, 10), Huggins (7-9), etc., as a means of facilitating early recognition of metastatic bone lesions from carcinoma of the prostate. In recent publications (5, 6) we have pointed out that, in our opinion, serum acid phosphatase values up to 4.0 King-Armstrong units per 100 cc. of blood serum should be considered normal. Values of from 4.0 to 6.0 units represent borderline figures which have no appreciable diagnostic importance provided no further increase of the phosphatase level takes place on subsequent determinations. A considerable elevation of the serum acid phosphatase is always indicative of metastatic bone involvement from carcinoma of the prostate, and repeated determinations in these cases have shown that there is a definite tendency of the serum acid phosphatase activity to increase as the disease progresses.

Recent reports by Huggins and his co-workers (7-9) indicate that bilateral orchidectomy may result in appreciable improvement in cases of prostatic cancer even if demonstrable metastases to the bones are present. This improvement coincides with gain in weight, increase in red blood count, regression in size and softening of the consistency of the prostate, and decrease of the serum acid phosphatase activity. Favorable results were also obtained by Huggins and his co-workers if the patients received stilbestrol medication.

It is obvious, therefore, that determinations of serum acid phosphatase activity are no longer of diagnostic value only. They are of value also as an objective indicator of the efficacy of castration or stilbestrol treatment of prostatic cancer, especially if metastatic bone involvement has occurred.

Up to the time of this writing, serum acid and alkaline phosphatase determinations have been carried out in 430 patients admitted to the New York State Institute for the Study of Malignant Diseases; 283 of these patients suffered from a variety of diseases other than prostatic cancer and in 147 patients carcinoma of the prostate was diagnosed.

The values for serum acid phosphatase activity in the group of 283 control cases were invariably below 6.0 King-Armstrong units. As a rule, determinations were carried out once but once.

On the other hand, serum acid and alkaline phosphatase determinations were made routinely every 3 months or oftener in all cases of carcinoma of the prostate. In 42 cases our observations are based on data collected for more than one year.

Of the 147 patients with carcinoma of the prostate, a positive biopsy was obtained in 105 instances. In the remaining 42 patients repeated attempts to obtain a satisfactory biopsy were unsuccessful in 21 instances and in 21 patients no biopsy was done for various reasons. In spite of that a diagnosis of carcinoma of the prostate was made from rectal and, frequently, cystoscopic examination. In all of these patients the prostate was definitely enlarged, indurated, and nodular, and infiltration into the pelvis with involvement of the seminal vesicles was present. Also partial encirclement of the rectum was felt in numerous patients of this group of 42.

No evidence of bone metastases was found in 100 of the 147 patients with carcinoma of the prostate. Seventy-seven had serum acid phosphatase levels below 4.0 King-Armstrong units once or on repeated determinations. In only 1 patient a serum acid phosphatase activity of more than 6.0 units was obtained (6.9 units). In the remaining 22 patients of this group serum acid phosphatase determinations yielded levels of from 4.0 to 6.0 units. In 8 of these 22, a tendency to gradual increase of the serum acid phosphatase activity was present, whereas in 14 instances a return to below 4.0 units was observed on subsequent determinations (see Table 1).

Table I: Serum Acid Phosphatase Determinations in 147 Patients with Carcinoma of the Prostate

<table>
<thead>
<tr>
<th>Units of serum acid phosphatase</th>
<th>Below 4.0</th>
<th>4.0 to 6.0</th>
<th>Tendency to increase</th>
<th>Retaining below 4.0</th>
<th>More than 6.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with no evidence of metastases</td>
<td>77</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Patients with bone metastases suspected clinically or roentgenologically</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Patients with bone metastases demonstrable in x-ray picture</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>33</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>81</td>
<td>10</td>
<td>14</td>
<td>42</td>
<td>147</td>
<td></td>
</tr>
</tbody>
</table>

*All phosphatase determinations were carried out by the King-Armstrong method.
Metastases were suspected from the clinical course in 8 patients, although metastatic bone lesions could not be demonstrated beyond doubt in this group. The suspicion of metastatic bone involvement was based on a rapid downhill course of the patients accompanied by increasing pain in the back and legs. Repeated blood chemistry determinations showed that none of these patients developed uremia. The serum acid phosphatase activity in these 8 subjects varied from 8.4 to 50.0 King-Armstrong units on last determination. Three of these 8 patients died 2 to 4 months after elevation of the serum acid phosphatase took place.

In this connection it is of interest that Simpson (11) was able to demonstrate, in a necropsy case of carcinoma of the prostate, extensive metastatic bone involvement microscopically, although metastatic bone changes could not be demonstrated roentgenologically. In our opinion it is probable that such microscopic bone involvement from prostatic cancer may occur more frequently than is indicated in the literature. Since determinations of serum acid phosphatase activity have been introduced as a routine procedure in cases of carcinoma of the prostate, metastases will be diagnosed on the living patient in numerous instances instead of at necropsy.

Definite metastases to the bones, demonstrable in the x-ray picture, were present in 39, or 26.5 per cent, of the 147 patients with prostatic cancer. As shown in Table I, 4 patients had serum acid phosphatase levels below 4.0 King-Armstrong units. Figures of from 4.0 to 6.0 units of serum acid phosphatase activity were determined in 2 others. The remaining 33 patients of this group had serum acid phosphatase values above 6.0 units. In 10 patients figures of more than 100 units were determined; the highest, obtained in 1 patient, amounting to 1,350 King-Armstrong units. Twenty-seven of these patients had demonstrable bone metastases and elevation of the serum acid phosphatase activity already present on admission. In the remaining 6, elevation of the serum acid phosphatase developed during the course of observation, and x-ray pictures, negative for metastatic lesions on admission, showed metastatic bone changes on subsequent examinations. In 3 of these 6 cases, elevation of the serum acid phosphatase activity preceded the roentgenological detection of bone metastases.

No relationship between the extent of metastatic involvement and the degree of serum acid phosphatase elevation could be established in our series of cases. In 4 patients, though almost the entire skeleton was involved by metastases, the serum acid phosphatase activity did not exceed 25 King-Armstrong units. On the other hand, metastatic lesions were confined to the pelvic girdle and the left femur in the patient who had a serum acid phosphatase level of 1,350 units.

If metastases to bones develop, with resulting elevation of the serum acid phosphatase, subsequent determinations show a definite tendency of the serum acid phosphatase activity to increase. This is either gradual or rapid, depending upon the activity of the metastatic lesion, until death occurs, provided no effective treatment is carried out. In 5 of the 33 patients with elevated serum acid phosphatase activity and demonstrable bone metastases we have had as yet no opportunity to repeat the determinations, either because the patients did not return or because they had been too recently admitted to our service. Follow-up determinations over a period of from 6 months to one year and 8 months in all of the remaining 28 cases yielded increasing values for serum acid phosphatase activity. The average serum acid phosphatase activity, which amounted to 36.4 King-Armstrong units on initial determination, yielded an average value of 120.7 units on last determination.

Although our patients with metastatic bone lesions causing elevation of the serum acid phosphatase activity number only 33, it is our impression that the degree of serum acid phosphatase elevation is a valuable help in prognosis. Of the 10 patients with serum acid phosphatase levels of more than 100 units, 2 were admitted only 2 and 4 weeks before the time of this writing. Of the remaining 8 patients, 5 died of the disease in an average time of 5.4 months. One case was lost trace of and only 2 patients, or 25 per cent, are alive. On the other hand, of 23 patients with serum acid phosphatase values ranging from 6.0 to 100 units, 12 died in an average time of 7.5 months and 11, or 47.8 per cent, are alive.

Our experiences with serum acid phosphatase determinations over a period of 2 years have confirmed our previous statements, which were that marked elevation of the serum acid phosphatase level is indicative of metastatic bone involvement from carcinoma of the prostate. Definitely elevated values for serum acid phosphatase were obtained in 33, or 84.7 per cent, of 39 patients with demonstrable metastatic bone changes. This ratio is analogous to the data presented by the Gutmans and their co-workers (4), who found increased serum acid phosphatase levels in 37, or 84.1 per cent, of 44 cases with metastatic bone lesions from prostatic cancer.

As has been stated in our previous publications (5, 6) we are of the opinion that figures for serum acid phosphatase activity up to 4.0 King-Armstrong units should be considered normal.

The interpretation of borderline figures between 4.0 and 6.0 King-Armstrong units is difficult in many instances. Of 22 patients without evidence of bone metastases, in whom such borderline values were obtained once or repeatedly, figures below 4.0 units were obtained on subsequent determinations in 14 cases. In
only 8 patients of this group was the level of from 4.0 to 6.0 units maintained, and it remains to be seen whether a further increase coinciding with roentgenological evidence of metastatic bone involvement will take place in these 8. The utmost conservatism should be used in the interpretation of these borderline figures, and final judgment withheld until follow-up determinations and the study of repeated x-ray pictures reveal whether the slight elevation was indicative of early metastatic bone involvement or of hemolysis or other extraneous factors.

It has been suggested by Huggins and his collaborators (9) that 10.0 King-Armstrong units should be regarded as the upper limit for serum acid phosphatase activity. However, our studies have convinced us that figures above 6.0 units represent an elevation of the serum acid phosphatase level which has diagnostic value. Serum acid phosphatase values ranging from 6.0 to 10.0 units were found once or repeatedly in 18 of our 147 cases with prostatic cancer. Only 1 patient with a serum acid phosphatase activity of 6.9 King-Armstrong units showed no evidence of bone metastases, and 4 patients, in whom metastases were suspected clinically or roentgenologically, showed a further increase of the serum acid phosphatase activity to values above 10.0 units. In the remaining 13 cases of this group evidence of metastatic bone involvement was demonstrable in the x-ray picture before the serum acid phosphatase activity exceeded 10.0 units on later determinations.

In concluding we wish to emphasize that the data presented are limited to figures obtained on patients prior to castration or stilbestrol medication. Studies in this field have been in progress on our service during the past 5 months, and the results will be reported as soon as sufficient time has elapsed to permit conclusions, based on a longer period of observation.

**SUMMARY**

Data of serum acid phosphatase determinations collected over a period of 2 years are presented. Two hundred and eighty-three of 437 patients in whom serum acid phosphatase determinations were carried out were control cases. In the remaining 147 patients carcinoma of the prostate was diagnosed.

Serum acid phosphatase levels up to 4.0 King-Armstrong units should be considered normal. Values of from 4.0 to 6.0 units represent borderline figures which are only diagnostic for metastatic bone lesions from carcinoma of the prostate if further elevation takes place. A considerable rise in the serum acid phosphatase activity is indicative of bone metastases from prostatic cancer. With one exception, such an elevation was not encountered in the group of controls or in patients not suspected of having bone metastases from carcinoma of the prostate.

Serum acid phosphatase determinations are a valuable diagnostic aid in the early recognition of bone metastases from prostatic cancer in new patients and in patients who are under constant observation.

If elevation of the serum acid phosphatase activity develops, there is a tendency to steady increase provided no effective treatment is initiated.

A relationship between the degree of serum acid phosphatase elevation and the extent of metastatic bone involvement could not be established in our series of cases.

Serum acid phosphatase levels of more than 100 King-Armstrong units have to be regarded as an unfavorable prognostic sign.

It is emphasized that the determination of serum acid phosphatase activity is also of value as an objective indicator of the effectiveness of castration or stilbestrol in the treatment of prostatic cancer, as suggested by Huggins and his co-workers (7-9). This is especially true for patients with metastatic bone lesions causing elevation of the serum acid phosphatase activity.

**REFERENCES**

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