Different Patterns of Serum Chromogranin A in Patients With Prostate Cancer With and Without Undergoing Hormonal Therapy

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Elevated serum chromogranin A (CgA) levels have been detected in patients with prostate cancer who have developed resistance to hormonal therapy. We would like to re-examine these cases by using serial specimens to determine whether such elevated levels are also detectable in prostate cancer patients not undergoing hormonal therapy.

Serum CgA was measured in both random and serial specimens from prostate cancer patients with and without undergoing hormonal therapy. We found that serum CgA levels became elevated much earlier than did the levels of serum PSA in approximately one-third of prostate cancer patients devel-

oping resistance to hormonal therapy. On the other hand, serum CgA levels became elevated at later, more advanced stages of the disease in patients not undergoing hormonal therapy. Elevated serum CgA levels were usually detected in specimens containing highly elevated PSA. The early rise of serum CgA levels provides an early signal allowing a change of therapy to be made before the disease progresses to a fatal stage. Drugs targeting neuroendocrine cells should be considered for prostate cancer patients with elevated serum CgA levels. *J. Clin. Lab. Anal.* 13:308–311, 1999.

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INTRODUCTION

Chromogranin A is a marker for neuroendocrine cells and is also an indicator for neuroendocrine differentiation (ND) (1,2). In prostate cancer, detection of ND by the immunohistochemical technique was found to be associated with poor prognosis (3–5). ND is also considered to be a strong predictor of disease-specific survival (4). There has been controversy concerning whether or not ND is more important in androgen-independent and metastatic tumors than in hormone-sensitive and locally recurrent tumors (6). Using random specimens, elevated serum CgA levels were frequently detected in prostate cancer patients undergoing hormonal deprivation therapy while serum PSA levels remained normal. Consequently, serum CgA was regarded as superior to serum PSA as a marker for prostate cancer (5,7,8,9). It was also considered by Kadman et al. as a marker of hormonal resistance and neuroendocrine differentiation (5).

In this study we took advantage of the serial specimens collected from individual patients with prostate cancer from the Department of Urology, University of Utah Health Science Complex, and measured both serum PSA and CgA. We found that serum CgA rose early in patients developing resis-

tance to hormonal therapy. However, in prostate cancer patients not undergoing hormonal therapy, elevated serum CgA levels were usually detected at a more advanced stage of the disease.

MATERIALS AND METHODS

All serum specimens were obtained from patients visiting the clinics at the University Hospital, University of Utah Health Sciences Complex. Diagnoses were confirmed by clinical biopsies. Patients receiving hormonal treatment might have had an orchiectomy or were treated with the gonadotropin-releasing hormone agonist, even though Lupron was most frequently used. A few patients were receiving a combination of Lupron/Flutamide. All these treatments provided a growth advantage for neuroendocrine cells. All specimens have PSA determined by the Abbott kit, measured immediately after blood was drawn and then kept frozen at -70°C for a few months before the serum CgA level was determined.

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Serum CgA was assayed using an in-house serum CgA enzyme immunoassay kit on microplate based on the sandwich format (7).

RESULTS

Prostate Cancer Patients Developing Resistance to Hormonal Therapy

Shown in Figure 1 are the results of six patients with prostate cancer who developed resistance to hormonal therapy. Note the early rise of serum CgA levels (indicated by the arrow) in these patients in comparison to the level of serum PSA. The horizontal dotted lines indicate the upper normal cutoff for serum CgA, which is approximately 90 ng/mL (7). Early elevated serum CgA levels continued to increase in some patients though they may decline in some cases during the disease course. In most patients, the serum PSA level rose much later, anywhere from 3 months to over a year. Only patient 231 WCJ showed a concomitant decrease of serum CgA and PSA levels at a later stage. These results suggest that CgA and PSA are most likely derived from two different types of

cells proliferating at different rates. Apparently, the environment (deficient in androgen) promotes a proliferation of neuroendocrine cells in patients developing resistance to hormonal therapy. The response to the hormonal resistance of serum PSA, presumably derived from epithelial tumor cells, to the hormonal resistance appeared much later.

Prostate Cancer Patients Not Undergoing Hormonal Therapy

Earlier, we were not certain whether we could detect elevated serum CgA levels in prostate cancer patients who did not receive hormonal treatment. In these patients, none of the factors promoting the proliferation of neuroendocrine cells exists. However, we know that there are many ectopic tumor markers, such as the detection of elevated AFP levels in patients with metastatic colon tumors (10,11). Therefore, we made an effort to include specimens containing highly elevated serum PSA levels. As is well known, sera containing highly elevated PSA levels are most likely associated with metastasis. As shown in Figure 2 elevated serum CgA levels were detectable in random specimens containing highly elevated serum PSA levels.

Encouraged by these results we then looked into serial specimens from this group of prostate cancer patients who were not undergoing hormonal treatment. The results are shown in Figure 3. In contrast to prostate cancer patients developing resistance to hormonal therapy, we did not observe an early rise of serum CgA levels in comparison to serum PSA levels. In most cases, the rise and fall of serum CgA levels tends to parallel the change of PSA serum levels. Consequently, serum CgA levels rose when serum PSA levels started to increase. It appears from the results of random specimens (Fig. 2) and that of serial specimens (Fig. 3) that serum CgA levels were usually elevated at a more advanced stage of the cancer or associated with specimens containing highly elevated PSA levels.

Fig. 1. Monitoring serum CgA and PSA in individual prostate cancer patients developing resistance to hormonal therapy.

Fig. 2. Serum level of CgA in random specimens containing various serum concentrations of PSA.

Fig. 3. Monitoring serum CgA and PSA in individual prostate cancer patients not undergoing hormonal therapy.

DISCUSSION

Results of several investigations have indicated that serum CgA is a better marker for detecting resistance to hormonal therapy than is serum PSA (5,8,9). They discovered elevated serum CgA but not PSA in patients developing resistance when random specimens were tested. It was not yet possible to determine in those studies whether the lack of detection of elevated serum PSA levels was due to the rise of serum CgA levels first, unless specimens at later stages of the disease were selected for the study. Conceivably, if the measurements were made from specimens obtained at a relatively early stage, before serum PSA levels could increase, one might only detect an elevation of the serum CgA level. In our study the use of serial specimens allowed us to observe the elevation of serum CgA levels earlier than of PSA levels. The ramifications of this should be underscored: this early signal would enable therapy to be altered earlier than the monitoring of serum PSA had once allowed; that is, before it is too late. Drugs targeting neuroendocrine cells in addition to traditional epithelial tumor cells should improve the survival of

prostate cancer patients developing resistance to hormonal therapy.

Resistance to hormonal therapy could be developed by three different mechanisms: (1) a proliferation of androgen-independent neuroendocrine cells, as indicated in the elevation of serum CgA; (2) an increase in the expression of androgen receptor (12); and (3) an overexpression of bcl-2 oncoprotein (13). This explains why elevated serum CgA levels were only detected in about one-third of patients developing resistance.

There have been very few studies concerning serum CgA in prostate cancer patients not undergoing hormonal treatment. Hormonal treatment provides a growth advantage for neuroendocrine cells to proliferate since these cells do not express androgen receptors and consequently do not rely on androgen to grow. Such an environment does not exist for prostate cancer patients not receiving hormonal therapy. However it is not too surprising to find elevated serum CgA levels in these cancer patients since Aprikian et al. (14) were able to detect ND in 9 of 16 metastatic prostate tumors. Apparently ND occurred frequently at the malignant stage. At this advanced stage, epithelial tumor cells may or may not proliferate at the same time. Therefore, we may observe either the elevation of serum CgA levels alone or the concomitant rise of both serum PSA and serum CgA levels. The association of elevated serum CgA levels with specimens containing highly elevated serum PSA levels or with later, more advanced stages favors the view of an ectopic production of CgA.

As indicated by our results, it is important to monitor prostate cancer patients during treatment with both serum PSA and serum CgA. Monitoring serum PSA alone may not provide an adequate indication of the disease. Detection of elevated serum CgA levels indicates that the malignancy of the tumor may also be due to the proliferation of neuroendocrine cells which are more likely to be associated with poor prognosis and may require a different therapeutic design. In patients undergoing hormonal therapy, the early detection of resistance by the early rise of serum CgA levels allows an alteration of therapy to be made before it is too late (i.e., if only the serum PSA is monitored). For prostate cancer patients not undergoing hormonal therapy, the detection of elevated serum CgA will also suggest that drugs targeting neuroendocrine cells should be administered.

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