Immunohistochemical Demonstration of Human Chorionic Gonadotropin in Tumors of the Urinary Bladder

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ABSTRACT

All transitional cell carcinomas of the bladder diagnosed in male patients within a five year period were studied for human chorionic gonadotropin (hCG) production. Biotin-avidin immunoperoxidase analysis for hCG was performed on all paraffin blocks containing carcinoma-in-situ, grade I, grade II, and grade III transitional cell carcinoma. Of a total of 29 patients, one case of carcinoma-in-situ (1/5), and five cases of grade III transitional cell carcinoma (5/15) were found to have hCG-positive tumor cells. The findings indicate that transitional cell carcinoma should be added to the list of malignant tumors capable of producing hCG.

Introduction

Primary carcinomas of the urinary bladder that produce human chorionic gonadotropin (hCG) have been occasionally reported.1,3,4,5,7,8 Recently, two hCG-producing carcinomas of the bladder were found almost simultaneously at the University of Connecticut Health Center. Both cases were initially diagnosed as invasive grade III/III transitional cell carcinomas prior to the clinical appearance of gynecomastia. Subsequent measurements of serum hCG revealed markedly elevated levels in both. This study was undertaken to address the question of hCG production by transitional cell carcinomas. To eliminate the possibility of metastatic gestational choriocarcinoma, the study was limited to male patients.

Materials and Methods

All transitional cell carcinomas accessioned over a five year period at the University of Connecticut Health Center and the Veterans Administration Hospital, Newington, Connecticut were studied. The study was limited to male patients. The time period extended from January 1, 1979 to December 31, 1983. The surgical specimens were fixed in 10 percent neutral-buffered formalin and processed in the usual fashion for paraffin embedding. Biotin-avidin immunoperoxidase analysis for human chorionic gonadotropin was performed on all par-
affin blocks containing carcinoma. Paraffin sections were cut, deparaffinized, and rehydrated in graded alcohols to water. The sections were treated with one percent \( \text{H}_2\text{O}_2 \) for 20 minutes and washed with phosphate-buffered saline (PBS). The tissue sections were pre-incubated with normal goat serum for 20 minutes and then incubated overnight with rabbit anti-human chorionic gonadotropin.* After washing with PBS, the sections were incubated with biotinylated goat anti-rabbit IgG for one hour. After washing with PBS, the sections were incubated with avidin:biotinylated horseradish peroxidase complex for one hour. The sections were washed with PBS and the color reaction product developed with diaminobenzidine. The sections were counterstained with hematoxylin, dehydrated in graded alcohols to xylene and coverslipped.

Results

There were 29 male patients with carcinoma of the bladder. In these patients, 37 lesions were examined (table I). Four patients had lesions of two different grades at different sites within the bladder. An additional four patients had lesions of two different grades on repeated biopsies of the same site. Six patients with hCG-positive tumor cells were found. None of these patients had a testicular neoplasm.

Five carcinoma-in-situ lesions were examined. One positive case was found. In this case (Patient #1) hCG-positive cells were present, but rare and scant in number. Two years later, the patient had a cystectomy for invasive carcinoma, grade III. Immunoperoxidase studies of this tumor revealed no hCG-positive cells. The patient died two years later.

Ten grade I transitional cell carcinomas and seven grade II carcinomas were all negative for hCG activity.

Fifteen grade III transitional cell carcinomas were studied, and five positive cases were found.

Patient #2 was a 34 year old male who presented with an invasive, highly anaplastic carcinoma involving the bladder and the prostatic urethra. By immunoperoxidase, the tumor cells were negative for prostatic-specific acid phosphatase and prostatic-specific antigen. Gynecomastia developed shortly after presentation, and serum hCG levels were markedly elevated. Immunoperoxidase revealed numerous hCG-positive tumor cells (figure 1). In some areas up to 30 positive cells per high power field were noted. The patient developed widespread metastases, had a rapidly deteriorating course, and died.

Patient #3 was a 58 year old male with invasive grade III transitional cell carcinoma. A radical cystectomy was performed and multiple carcinoma-in-situ lesions involving the non-papillary portions of the bladder and both ureters were present. The patient developed lung metastases and died approximately a year after diagnosis. Gynecomastia was clinically evident in this patient, and serum hCG levels were elevated. Immunoperoxidase stain revealed many hCG-positive tumor cells. On the average, there were approximately two to three positive cells per high power field.

* Ortho Diagnostic Systems, Inc, Raritan, NJ.

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Number Examed</th>
<th>Number Positive for hCG</th>
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<tbody>
<tr>
<td>Carcinoma-in-situ</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Transitional cell carcinoma, Grade I/III</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Transitional cell carcinoma, Grade II/III</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Transitional cell carcinoma, Grade III/III</td>
<td>15</td>
<td>5</td>
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Patient #4 was a 79 year old male. The biopsy from this patient showed a papillary transitional cell carcinoma. Most areas appeared non-invasive and grade II. However, foci of superficially invasive grade III carcinoma were also present. In figure 2, which is from this patient, are shown several hCG-positive tumor cells in an otherwise typical grade II lesion. Overall, hCG-positive tumor cells were rare and scant in number. Twenty months after the diagnosis, the patient was well with no evidence of recurrence.

Patient #5 was a 58 year old male with invasive grade III, stage C, transitional cell carcinoma. A radical cystectomy was performed and multiple carcinoma-in-situ lesions involving the non-papillary portions of the bladder were noted. Immunoperoxidase stain for hCG revealed rare, widely scattered hCG-positive tumor cells. The patient was alive and well with no recurrence three years after cystectomy.

Patient #6 was a 78 year old male with invasive grade III transitional cell carcinoma. Pelvic node dissection revealed metastatic carcinoma and a cystectomy was not performed. Immunoperoxidase revealed rare, isolated hCG-positive cells. The patient was lost to follow-up.

Discussion

This study indicates that human chorionic gonadotropin is not uncommon in transitional cell carcinomas of the bladder. Interestingly, hCG-positive cells occurred in tumors that were cytologically severely abnormal, i.e., carcinoma-
in-situ and grade III/III carcinomas. Grade I and grade II carcinomas with mild to moderate nuclear abnormalities were negative.

It is conceivable that the high grade bladder carcinomas represented extragonadal choriocarcinomas of germ cell origin rather than transitional cell carcinomas. Indeed, in four of the six cases, many of the hCG-positive cells resembled multinucleated syncytial trophoblastic cells. However, the authors are more inclined to believe that these were cases of transitional cell carcinoma associated with cells that were functionally and morphologically similar to syncytiotrophoblasts.

The findings in four of the six cases support this view. Patient #1 had a morphologically classical transitional cell carcinoma-in-situ. Patients #3 and #5 showed multiple concomitant transitional cell carcinoma-in-situ lesions in the urothelium away from the main tumor mass. Patient #4 had a characteristic papillary transitional cell carcinoma with a few hCG-positive syncytial cells in areas of otherwise typical papillary grade II lesions.

The interpretation that so-called choriocarcinomas of the bladder may actually represent altered transitional cell carcinomas has been expressed in several previous case reports. The present study indicating the presence of hCG-producing cells in a series of typical transitional cell tumors provides strong evidence for this view. The finding of hCG-positive cells primarily in high grade lesions suggests that this change is associated with increasing anaplasia. The previous case reports of hCG-producing bladder tumors have similarly all been invasive, high grade, and anaplastic.

It is of interest that the one case of carcinoma-in-situ associated with hCG activity subsequently developed a grade III invasive lesion.

Thus, it appears that the presence of hCG-positive cells in bladder tumors is not an indication of choriocarcinoma but rather a reflection of altered cell differentiation in a transitional cell carcinoma. This observation indicates that transitional cell carcinoma of the bladder should be added to the growing list of malignant tumors that are capable of hCG production.

References