Familial Cryptorchidism and Testicular Tumors in Non-Twin Brothers*

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ABSTRACT

This paper reports simultaneous occurrence of cryptorchidism and testicular tumor in three brothers within a single family. Two of the brothers had seminoma and the third brother had embryonal carcinoma. Tumor markers such as alpha fetoprotein, assay for β subunit of human chorionic gonadotrophic hormone, and carcinoembryonic antigen were all negative. The simultaneous occurrence of familial cryptorchidism and testicular tumor has not been reported, although familial occurrence of both entities has been described separately. Because of the known risk of testicular malignancy in cryptorchidism, aggressive screening and examination are recommended in the form of either serial palpation or serial testicular biopsies. Hormonal replacement with testosterone cypionate is recommended for pubertal patients undergoing bilateral orchiectomy as a result of tumor removal. The overall prognosis of patients with cryptorchidism and abdominal testicular tumor seems to be good provided an early diagnosis is made.

Case Reports

Case 1

P.C., a 13-year-old Mexican-American male, was diagnosed to have bilateral cryptorchidism on a routine clinic visit. A right inguinal hernia repair was performed at age four; however, there was no documentation of testes noted at that time. Prior to the current admission, a trial of chorionic gonadotrophic hormone injections, 1000 units three times a week, was given for two weeks with no testicular descent. Plasma testosterone was 5200 pg per ml (normal value range is 1000 to 3000 pg per ml).

He was then admitted for exploratory laparotomy and bilateral inguinal exploration. Physical examina-
tion revealed normal penis, presence of some pubic and axillary hair (Tanner Stage III), no palpable testes in the scrotum and inguinal canal, and a right inguinal hernia scar. Laboratory investigations demonstrated a serum alpha fetoprotein (AFP) level of less than 25 ng per ml (normal less than 25 ng per ml), carci noembryonic antigen (CEA) of 0.4 ng per ml (normal 0 to 2.5 ng per ml) and human chorionic gonadotrophin (HCG) β subunit radioimmunoassay was 0.0 mIU per ml (normal up to 6 mIU per ml). Results of routine hematologic, blood chemistries, chest x-ray, bone survey, and liver scan were all within normal limits. Exploratory laparotomy revealed intraperitoneal testes of normal size and appearance. Bilateral testicular and lymph node biopsies were performed and the patient underwent bilateral orchiectomy. Microscopic examination of the left testis revealed pure seminoma (figure 1). A single lymph node in the mesentery of the left testis showed metastatic seminoma with granulomatous reaction. The right testis and the right-sided lymph nodes showed no evidence of neoplasm.

No enlarged lymph nodes were felt in the retroperitoneum. An intravenous pyelogram (IVP) was done post operatively and was normal. He had an uneventful postoperative course and was treated with 3000 rads to the periaortic and pelvic nodes and 2000 rads to the chest. He has been in complete remission for the past two years and continues to receive monthly testosterone cypionate.* Subsequent tests for metastases, including determinations of AFP and CEA levels, immunoassay for HCG chest x-ray and abdominal ultra sound, have all been negative.

Case 2

A.C., 14-year-old brother of P.C., was also found to have bilateral cryptorchidism on a routine examination. Pertinent physical findings showed a well developed male (Tanner IV), with no scrotal testes. Alpha fetoprotein levels were less than 1.0 ng per ml (normal less than 2.5 ng per ml). Carci noembryonic antigen levels initially were 3.2 ng per ml (grey zone 2.6 to 5.0 ng per ml). Repeat levels obtained a month later were 0.8 ng per ml (normal 0 to 2.5 ng per ml) and have since continued to be in normal range. Human chorionic gonadotrophin β subunit radioimmunoassay was less than 3 mIU per ml (normal up to 6 mIU per ml). Chest x-ray, liver and spleen scan, and intravenous pyelogram were all interpreted as within normal limits. On exploratory laparotomy, he was found to have bilateral intra-abdominal testes with multiple nodules on the surface of both testes. Biopsy revealed seminoma in the right and left intra-abdominal testes. Lymph node biopsies revealed no metastatic disease. Patient had an unremarkable postoperative course. A computerized tomography (CT) scan done post operatively revealed two enlarged periaortic nodes which were felt to represent metastatic disease. Patient received radiation therapy, 3000 rads to the abdomen and 2000 rads to the mediastinum. He has been in complete remission for the past two years and is receiving monthly testosterone cypionate.* Follow-up evaluation for metastases has been normal.

Case 3

Information received from the physician in Texas caring for J.C., the 25-year-old brother of A.C. and P.C., indicated that he also had bilateral cryptorchidism. On exploratory laparotomy at age 23, he was found to have bilateral intra-abdominal testes with a large embryonal carcinoma with rupture and hemorrhage involving the right testis. He is currently receiving chemotherapy.

Case 4

Information received from the physician caring for J.C., the 21-year-old brother of the previous patients indicated that he had a diffuse intra-abdominal mass and bilateral cryptorchidism. Biopsy of an enlarged supraclavicular node revealed seminoma. Laboratory investigations demonstrated an AFP level of less than 0.1 IU per ml (normal less than 10 IU per ml), CEA was 1.9 ng per ml (normal 0 to 2.5 ng per ml), and HCG β subunit radioimmunoassay was 39.0 mIU per ml (normal up to 6 mIU per ml). The patient is currently receiving chemotherapy.

* Depo-Testosterone®, The Upjohn Company, Kalamazoo, MI 49001.
Discussion

The familial occurrence of testicular tumor has been reported but is rare. In a recent review, seven examples of monozygotic twins in whom testicular tumors developed at similar ages were reported. Both seminomatous and non-seminomatous germ cell tumors occurred and, with the exception of one pair, the histologic type was similar. Seventeen non-twin brothers have also been described in the literature in whom no correlation of the histologic type of tumor was noted (table I). The age of detection of the tumor ranged from 18 to 53 years. Lynch and associates described four cases of testicular neoplasm in an inbred Dutch kindred family containing more than 2000 members. In contrast to our patients, the simultaneous occurrence of cryptorchidism and testicular tumor was not described in any of the other cases.

Despite a paucity of published reports, familial occurrence of cryptorchidism in siblings is known to occur. In a recent study of the genetics of undescended testes, the occurrence of cryptorchidism was confirmed in 1.5 to 4 percent of the fathers and in 6.2 percent of the brothers of 452 index cases less than one year of age with isolated undescended testes. Bilateral undescended testes were associated with a higher recurrence risk for siblings. Also, concordant undescended testes were found more frequently among monozygotic than dizygotic twins. The pattern of inheritance of cryptorchidism is still not clear at this time but may be of multifactorial etiology. Of interest is the fact that none of the cases with familial cryptorchidism was reported to have simultaneous presence of testicular tumors.

There is a recognized association between cryptorchid testes and subsequent development of testicular neoplasia. In bilateral cryptorchidism, bilateral tumors occur simultaneously or sequentially in 25 percent of cases; if one testis becomes malignant there is a 30 percent chance of the other testis becoming malignant. Most of the tumors associated with cryptorchid testes develop at or after puberty. An altered environment, gonadal dysgenesis or atrophy, and hormonal imbalance have been implicated as possible oncogenic factors. Orchiopexy neither decreases nor prevents the tumorigenic potential of the cryptorchid testes. Owing to this risk of malignancy, lifelong follow-up is being urged for patients with cryptorchidism and testicular palpation as a self-screening method for cancer detection is being promoted. One method of follow-up advocated for previously cryptorchid males is testicular biopsy to de-

**TABLE I**

Testicular Tumors in Non-Twin Brothers

<table>
<thead>
<tr>
<th>Type of Tumors (Age at Onset)</th>
<th>Type of Tumors (Age at Onset)</th>
<th>Reference</th>
</tr>
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<tr>
<td>? (18)</td>
<td>Lt. Seminoma (34)</td>
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</tr>
<tr>
<td>Seminoma (32)</td>
<td>Teratoma (53)</td>
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</tr>
<tr>
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<td>Teratoma (31)</td>
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<td>Teratoma (32)</td>
<td>Seminoma (31)</td>
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<tr>
<td>Chorio-carcinoma (36)</td>
<td>Embryonal carcinoma (44)</td>
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<td>Seminoma (27)</td>
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</tr>
<tr>
<td>Seminoma (45)</td>
<td>3rd Brother embryonal</td>
<td>31</td>
</tr>
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<td>Seminoma (25)</td>
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</tr>
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<td>Embryonal carcinoma (37)</td>
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</tr>
<tr>
<td>Malignant</td>
<td>3rd Brother terato-carcinoma (32)</td>
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<tr>
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<td>Seminoma (32)</td>
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<td>Seminoma (14)</td>
<td>Present cases</td>
</tr>
<tr>
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<td>Embryonal carcinoma (2)</td>
<td>Present cases</td>
</tr>
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</table>
tect the intratubular germ cell neoplasia. Evidence for this recommendation is based on the fact that 8 percent of 50 men previously treated for maldescended testes had an intratubular neoplasia (carcinoma-in-situ) pattern.

As in patients with hypogonadism and functional prepubertal castrate syndrome, supplementation with testosterone should be instituted in pubertal patients following bilateral orchiectomy. Testosterone cypionate intramuscular, 200 mg every two to three weeks, is preferred over the 17 α-alkylating agents such as methyl testosterone. The latter carries the risk of hepatic dysfunction and hepatocellular carcinoma. Administration of testosterone cypionate has not been reported to potentiate development of tumor nor was a recurrence of seminoma seen in our two patients over a three year period.

Although one might expect tumors in undescended testes to be more frequently associated with metastases before detection, it is of interest that the overall five-year-survival of patients with tumors related to cryptorchidism, corrected and uncorrected, (61 percent versus 63 percent) is comparable to that of patients with tumors in normally descended testes. Depending on the histologic type and stage of the tumor, adjuvant therapy with lymph node dissection, radiotherapy, and/or chemotherapy may be instituted. Both the cases (1 and 2) under our care had seminoma Stage II which responded to radiation therapy alone.

The cases reported here thus serve to emphasize the following: (1) both cryptorchidism and testicular tumors may be familial; (2) cryptorchid testes carry a significant risk of malignancy; (3) supplementation with testosterone cypionate seemed not to carry risk of tumor potentiation in pubertal males castrated as a result of removal of seminoma; and (4) abdominal seminomas are amenable to treatment with radiation therapy alone when diagnosed early.

Summary

The findings of familial cryptorchidism and testicular tumors in three non-twin brothers within a single family strongly suggests that all male members of such families be carefully screened for both cryptorchidism and associated testicular tumor. Because of the known risk of testicular malignancy in cryptorchidism, aggressive screening and examination is recommended. This screening may be in the form of (serial) frequent palpation or serial testicular biopsies. Cryptorchidism is also associated with a high incidence (57 to 93 percent) of inguinal hernias. As with our first case, a significant number of cryptorchid patients will have had previous herniorrhapies. Thus, in patients with inguinal hernia, every attempt should be made to palpate the testes. Hormonal replacement with testosterone was not associated with tumor recurrence in our patients. Since the overall prognosis of patients with abdominal testicular tumor diagnosed at an early stage seems to be good, screening of cryptorchid males for testicular tumors is indicated.

Acknowledgments

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References

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