Bilateral Testicular Cancer

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Testicular cancer is the most common cancer in men 15 to 35 years old.[1] The lifetime risk is 1 in 500.[2] Furthermore, the annual incidence of testicular cancer almost doubled between 1939 and 1970 from 2.0 to 3.7 per 100,000,[2] and the risk of bilateral testicular cancer is increasing as well.[3]

Because testicular cancer has become one of the most curable solid tumors[1] and its incidence is increasing, the primary care physician will be encountering patients with a history of testicular cancer more frequently. This report presents a patient with unilateral mixed nonseminoma who subsequently developed a seminoma in the contralateral testis 12 years later. Despite cure from the highly malignant embryonal component of the mixed nonseminoma, the patient was subjected to the further morbidity of a second cancer. This case emphasizes that to reduce further morbidity and mortality, proper management and an understanding of a patient's risk for contralateral testicular cancer are required by the primary care physician.

Case Report

A 44-year-old man came to our clinic for testosterone replacement 3 years after his second orchiectomy.

The patient's history of testicular cancer began at age 29 years, when he complained to his physician of a 2-month history of a nontender right testicular mass. The patient subsequently underwent right orchiectomy, and the mass was identified as a teratoma containing embryonal and seminoma components with vascular invasion. Clinical stage 1 disease was diagnosed and the patient underwent retroperitoneal lymphadenectomy. His lymph nodes were negative for tumor, but because of tumor vascular invasion, the patient received nearly 1 year of chemotherapy. Every 3 months for the next 3 years, the patient was seen for a physical examination, a chest roentgenography, and blood tests for beta human chorionic gonadotropin (beta-HCG) and alpha-fetoprotein, all of which were within normal limits. The patient subsequently fathered 2 more children.

Twelve years after the patient's testicular cancer was diagnosed, at the age of 41 years, he noticed a left testicular mass on routine self-examination despite previous normal physical examinations. The patient underwent a left orchiectomy and was found to have a pure seminoma. The beta-HCG and alpha-fetoprotein blood levels and findings on a computerized axial tomogram (CT) of the abdomen and pelvis and chest radiogram were normal. He received radiation therapy to the left pelvic and periaortic lymph nodes. At the present time follow-up examinations have shown no evidence of recurrence, and the patient, infertile but otherwise healthy, receives monthly intramuscular sustained-action testosterone injections.

Discussion

About 95 percent of testicular neoplasms are germ cell tumors. Germ cell tumors are divided into seminomas and nonseminomas because of differences in prognosis and responses to various treatment modalities, i.e., seminomas are radiosensitive and nonseminomas usually require therapeutic lymphadenectomy and chemotherapy.[2] Nonseminomas are further subdivided into embryonal cell carcinoma, teratoma, choriocarcinoma, and yolk sac tumor (endodermal sinus tumor). About 60 percent of germ cell tumors are a mixture of the above cell types and are classified as nonseminomas. Seminoma is the most common single histologic type in adults. Pure choriocarcinoma is very rare.

Germ cell tumors produce the tumor markers alpha-fetoprotein and beta-HCG. The presence of these markers in serum aid in the diagnosis of germ cell tumors, response to therapy, and the

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detection of recurrence. For patients with nonseminomas about 50 to 70 percent will have elevated alpha-fetoprotein levels, and 40 to 60 percent will have elevated beta-HCG. About 10 percent of seminomas will produce beta-HCG levels, but alpha-fetoprotein is uniformally absent. Patients who initially test negatively for tumor markers can become positive if they have tumor recurrence, progression with treatment, or a new primary tumor.

Germ cell tumors are highly malignant, metastasizing when the tumor is still small. Seminomas are the least malignant of germ cell tumors. About 50 to 70 percent of patients with nonseminomas have metastasis at the time of diagnosis compared with 20 to 30 percent of patients with seminomas. Germ cell tumors spread first through the lymphatic channels to the retroperitoneal lymph nodes (not inguinal), where they are disseminated, although hematogenous spread to the lungs and other viscera occurs early if choriocarcinoma or embryonal cell carcinoma is present. Vascular invasion at the site of the primary tumor portends early hematogenous metastatic spread. The clinician must be aware that the patient might initially complain of signs and symptoms produced by metastases (weight loss, back pain, supraclavicular node) or the effect of the tumor markers (gynecomastia) rather than discovery of the primary tumor (mass in the testis).

Patients with unilateral testicular cancer have up to a 5 percent chance of developing contralateral testicular cancer. Their relative risk for this disease is 23. The second tumor usually occurs within 20 years after the first tumor, with a median time of 4.2 years.[4] Because these contralateral tumors commonly occur when the patient is no longer being cared for by the oncologist or urologist, the primary care physician must know how to care for these patients and educate them about their risk of contralateral testicular cancer.

Contrary to some theories, most contralateral testicular cancers are believed to be a second primary, not metastatic, disease, because (1) there is little anatomic evidence of lymphatic connection between the testes; (2) cancer in the contralateral testicle occurs without evidence of other metastases; (3) tumors that are histologically different often occur, as in the case described; and (4) carcinoma in situ frequently occurs independently in the contralateral testis and is believed to be the universal precursor of germ cell testicular cancer.[5]

Bilateral inguinal hernias have been associated in some studies with an increased risk of testicular cancer.[6] Our patient had a history of bilateral inguinal hernias as a young adult. Ideally, clinicians would like to be able to predict who might develop contralateral cancer. Studies have shown that patients with a family history of testicular cancer, a personal history of cryptorchidism, infertility, or a testicular volume less than 12 mL have a higher risk of developing contralateral testicular cancer than do patients without these risk factors.[7-9] A more accurate method, however, of distinguishing patients at risk for contralateral testicular cancer is by testicular biopsy.

It is believed that carcinoma in situ (CIS) is the universal precursor of both seminomas and nonseminomas and can be accurately detected by random testicular biopsy.[10] As a result of their study of patients with unilateral testicular carcinoma, a group of Scandinavian researchers estimated that those with CIS of the contralateral testis have a 40 percent risk of developing invasive cancer in 3 years and a 50 percent risk in 5 years. In the same study, 473 patients without contralateral CIS did not develop invasive cancer during a 12- to 96-month follow-up period.[11]

Although detecting patients with CIS before invasive cancer develops has not proved to affect overall mortality,[11] it can reduce morbidity. If CIS is found in the contralateral testis, it can be treated effectively with radiation while preserving the Leydig cells and, hence, endogenous testosterone production, although the patient will be infertile.[12] Detecting and treating CIS, therefore, prevent the morbidity associated with taking lifelong exogenous testosterone, such as gynecomastia, water retention, and behavioral changes.[13] Fertility is usually not an issue, because most patients with contralateral CIS are infertile as a result of decreased spermatogenesis.[9] The patient in the case described here is interesting because he fathered 2 children between his first and second testicular cancers.

Physicians in Denmark, where the incidence of testicular cancer is one of the highest in the world and where many studies on testicular cancer have been done,[14] support the policy of performing a biopsy on all patients who have a history of unilateral testicular cancer. In the United States this

policy has not been accepted.[15] Some physicians choose to focus on only high-risk subgroups for biopsy, such as those who have a history of cryptorchidism, decreased testicular volume, or infertility.[16] Primary care physicians should therefore discuss with their patients who have unilateral testicular cancer the possibility of a testicular biopsy, because it might not have been offered or available at the time the patient was treated. Newer, less invasive methods for identifying CIS or at least reducing the size of the population that must undergo a biopsy are being studied. Two methods that hold promise are examination of the semen for CIS cells and the use of sonography.[10]

Another sign or symptom of CIS to look for during the history taking and physical examination, in addition to a history of infertility and decreased testicular volume, is a soft or tender testicle. Most patients with CIS, however, are asymptomatic, and the condition cannot be recognized on routine examination. Also, beta-HCG and alpha-fetoprotein blood levels are not elevated in men with only CIS present.[10]

Our case illustrates that the contralateral testicular tumor is histologically not necessarily the same as the patient's first tumor. In fact, seminoma is the most common type of contralateral tumor and, as one study recorded, comprises 69 percent of all contralateral tumors and 45 percent of contralateral tumors in patients with a nonseminomatous tumor initially.[17] Also, some studies have suggested that patients with unilateral seminoma are more likely to develop contralateral testicular cancer than patients with nonseminoma.[8,18] Nevertheless, as our case of mixed nonseminoma illustrates, patients with unilateral testicular cancer of other histological types are at risk for contralateral cancer as well.

Chemotherapy for unilateral testicular tumors is not curative of incipient CIS in the contralateral testicle.[19] If our patient had CIS as a precursor to the seminoma, as is presumed by present research, the course of chemotherapy he received for his first testicular tumor did not clear the contralateral testis of all malignant cells. Perhaps a blood-testis barrier, similar to the central nervous system barrier, gives tumors a sanctuary from chemotherapeutic drugs. CIS might also be inherently resistant to chemotherapy.[19] Only radiation therapy appears to cure CIS, as would orchiectomy.[15-20]

Although continuing care with the primary care physician is important to discuss risks and options, the primary care physician is unlikely to be the one to detect a contralateral tumor. The patient is usually the one who first notices any change. As a consequence, monthly self-examinations of the testicle are very important, and its importance must be emphasized to the patient by the physician.[17] As a matter of practice, primary care physicians need to provide their patients with education materials about testicular self-examinations and to review the technique with them.

Summary

Although the case we described is not common, the incidence of testicular cancer, as well as bilateral testicular cancer, is rising.[2,3] The primary care physician can help reduce morbidity in these patients by encouraging monthly self-examinations of the testicles and by paying attention to high-risk subgroups, such as those with a family history of testicular cancer, a personal history of cryptorchidism, infertility, or a contralateral testicular volume less than 12 mL.[7-9] The primary care physician should, in at least these cases, discuss the option of a testicular biopsy to rule out CIS in the contralateral testicle. Treatment and follow-up options can then be explored to reduce further sequelae from this disease.

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