Germinal Tumors of the Testes

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Testicular tumors are the most common solid cancers in patients 15 to 34 years old, accounting for 12 percent of all cancer deaths in this group. The overall incidence rate in the United States is 2.1 per 100,000 males. Unfortunately, evidence suggests that the mortality rate is increasing here and abroad. For unexplained reasons, testicular tumors are extremely rare in American Blacks as well as in Africa, Asia and New Zealand.

While the definitive etiology of testicular tumors is still unknown, several causal factors have been implicated including cryptorchidism, trauma, pre-existing endocrinopathy, atrophy and certain genetic factors. The incidence of testis tumors is high in patients with mal-descended or previously atrophic testes, but the exact rate has not been determined. Approximately one in 80 inguinal and one in 20 abdominal testes will become malignant. A number of factors may be responsible for the increased incidence of testicular tumors in the cryptorchid—gonadal dysgenesis, elevated temperature, interference with blood supply, endocrine disturbances, or perhaps the atrophy itself which is usually present.

It is difficult to attach a cause and effect relationship between tumor and trauma since the latter is virtually inevitable in a young person engaged in physical activities. Genetic factors have been suggested because of the relatively high incidence of testis tumors in twins, brothers and other members of the same family. There is also a slightly higher incidence of a second testis tumor developing in a patient with a tumor of the opposite gonad.

Staging and Classification

Several detailed, somewhat technical and cumbersome histopathological groupings and staging systems exist. Since adequate and accurate therapy is predicated on proper diagnosis, staging assumes great practical importance. Histopathologic classifications are obviously based on microscopic appearance. However, testicular cancers are often complex and may therefore differ in many respects from tumors of nongonadal origin.

A basic and commonly used classification in this country has been adapted from the one originally proposed by the Armed Forces Institute of Pathology: 1. Seminoma (typical, anaplastic, spermatocytic). 2. Embryonal carcinoma. 3. Teratoma (with malignant areas termed, teratocarcinoma). 4. Choriocarcinoma.

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A high percentage of testicular tumors are mixed and contain many of these elements.

A more practical, simplified classification combines embryonal carcinoma and teratocarcinoma since mode of spread and treatment are similar, making three histopathological groups:

1. Seminoma. (Fig. 1.)
2. Embryonal carcinoma and teratocarcinoma. Histologically "benign" or mature teratoma is included because metastases are known. (Figs. 2, 3.)
3. Pure choriocarcinoma, a rare entity. (Fig. 4.)
Tumors are staged (Fig. 5) as follows:

Stage A. Tumor limited to the testis.

Stage B. Metastasis to regional lymph nodes.

Stage C. Disseminated disease, commonly to the lung.

Since lymphangiography is not yet perfected (although our diagnostic acumen is improving), proof of Stage B disease should be documented by surgical exploration and pathologic examination.

Inguinal nodes are not considered part of "regional" disease and are usually
seen only with paratesticular or spermatogenic cord involvement—both of which may be caused by intrascrotal biopsy of the testis. Normally, testis tumors do not metastasize to the groin.

**Diagnosis**

**History**

A testis tumor commonly presents as a painless mass. Epididymitis, hydrocele, varicocele, spermatocoele and hematoma should be included in the differential diagnosis. Many testis tumors are mistakenly treated, for unnecessarily long periods of time, as inflammatory disease. Delay in diagnosis may be due to the patient's reluctance to be examined or his fear of serious disease. Often, however, it is the physician who delays. Very simply, there is a hesitancy to face the reality of a tumor.

The patient should be specifically questioned about gynecomastia or even nipple tenderness. Both may be seen not only with choriocarcinoma, but with other tumor types as well. A past history of hernia, cryptorchidism and atrophy should be sought. Abdominal or flank pain might well suggest extensive retroperitoneal nodal disease or hydronephrosis secondary to ureteral obstruction by the tumor. Many patients unfortunately have been operated on for an "abdominal mass" without prior palpation of the testes. A left neck mass is occasionally mentioned as an initial symptom of disease and supraclavicular lymph node metastasis should obviously be considered.

**Physical Examination**

The usual finding is a hard painless testicular mass not involving the scrotal wall or spermatogenic cord. Epididymitis may involve the vas deferens and spermatogenic cord (funiculitis), a phenomenon not associated with tumor. In patients with inflammation, the scrotal wall may be somewhat adherent to the mass and impossible to lift away or separate.

When a tumor is suspected, aspiration of fluid is contraindicated; testicular biopsy in situ is absolutely contraindicated. Violation of the testicular tunics may well change the course of disease, resulting in spermatogenic cord and inguinal lymph node involvement.

Hematoma is usually preceded by often insignificant trauma, which may have simply called attention to a pre-existing mass. The differential diagnosis of hematoma and tumor may indeed be difficult by physical examination alone. Hematoma, however, is rare; the most common misdiagnosis is epididymitis. Physical examination should also include very careful examination of the neck, breasts, abdomen and groin.

**Laboratory Studies**

Chest X-ray, intravenous pyelogram and urinary chorionic gonadotrophins are mandatory in any patient with a testicular tumor. In those receiving chemotherapy, complete blood and platelet counts, as well as renal function studies must also be frequently performed.

Remember that a routine chest X-ray may be normal while stereo studies and pulmonary tomograms reveal metastases. This is of practical importance if one contemplates changing or withdrawing chemotherapy on the assumption of a disease-free state. Chest X-rays should be obtained every three months for at least two or three years and then semiannually even when Stage A disease is documented.

It is very helpful to combine an intravenous pyelogram with a 24-hour lymphangiogram X-ray. Ureteral deviation is often noted at the site where lymph nodes are more obviously involved with characteristic tumor filling defect. Patients with massive retroperitoneal disease may have complete blockage of the lymphatics at that particular level. (Figs. 6, 7.) In those with large bulky retroperitoneal disease, lymphangiography may be complemented by venacavography.
While the decision to perform or omit radical node dissection should not be based solely on interpretation of the X-ray studies, they are a useful guide to the adequacy of chemotherapy, radiation therapy and lymphadenectomy.

Serum gonadotrophins have recently been found extremely valuable and indeed have even been positive when the urinary gonadotrophins are normal. Cochran and Walsh et al. noted that 25 percent of patients with testicular tumors had demonstrable levels of human chorionic gonadotrophin and that this test was a sensitive, specific indicator of tumor activity. Although serum alpha fetoproteins are not specific for testis tumor, they may be elevated. Definitive information on its usefulness is not yet available.

Treatment
Primary Tumor (Stage A)

The treatment of testicular cancer is often controversial, except for inguinal orchietomy with high ligation of the spermatic cord which is the treatment of choice for a primary tumor. Individual
The lymphangiogram shows filling defects in nodes adjacent to the right renal pelvis. Tumor-containing nodes were found and removed just below the right renal vein.

Ligation of the vas deferens and spermatic vessels facilitates total removal of intra-abdominal portions of the cord in the event of a subsequent lymph node dissection. In a patient with a primary tumor, cure is virtually assured (85 to 95 percent five-year survival) if the testis has not been previously biopsied or, of its own volition, invaded adjacent spermatic cord structures. Inguinal lymph node involvement is almost unheard of when the tumor is confined to the tunics. Further therapy should be based on a careful and accurate histopathologic examination of the primary tumor and not on a frozen section examination; therefore, a radical retroperitoneal lymph node dissection is not carried out at the time of radical orchiectomy for the primary tumor. It is also unnecessary to remove the scrotum unless the tumor has been previously biopsied in situ.

Regional Node Disease (Stage B)

The patterns and distribution of nodal metastases have been well documented since the turn of the century. This predictability of involvement as well as surgical accessibility account for the very acceptable cure rates (50-80 percent five-year survival) when tumor-containing nodes are found and removed surgi-
cally or, in the case of a seminoma, irradiated.\textsuperscript{11,12} Retroperitoneal lymph nodes are usually the first site of metastases for germinal adult testis tumors.\textsuperscript{13}

\textbf{Seminoma}

It is generally agreed that the treatment of choice for patients with seminoma is external radiation therapy with some type of supervoltage technique, usually cobalt which is the simplest and most readily available. There is no difference in results between patients treated by radiation therapy alone and those treated by orchietomy, radical retroperitoneal lymphadenectomy and postoperative irradiation of the lymphatic drainage areas.\textsuperscript{14} Some physicians favor radiation therapy to the mediastinum and left supra-area as well, but our policy has not been to irradiate these areas routinely. Determining the size of the portal is facilitated by lymphangiography and pyelography. Response to radiation therapy may be followed by subsequent X-ray studies.

Under certain circumstances lymph node dissection is recommended even in a patient with a pure seminoma. For instance, if a retroperitoneal mass has persisted following radiation therapy or if an elevated urinary gonadotrophin has not returned to normal after irradiation or chemotherapy, node dissection might well be considered. Nonseminomatous elements are occasionally found in the retroperitoneal nodes of a patient with a pure testicular seminoma. The cure rate for patients with seminoma is between 90 to 95 percent.\textsuperscript{15}

\textbf{Embryonal Carcinoma and Teratocarcinoma}

About 65 percent of testis tumors are nonseminomatous, usually of various combinations. Approximately 50 percent of patients will have metastatic disease in the retroperitoneal nodes. Since there is no accurate way of determining which patients will have nodal involvement, routine retroperitoneal lymph node dissection is performed on all patients with embryonal cell cancer or teratocarcinoma, regardless of whether X-ray studies show evidence of disseminated disease. To encompass all node bearing areas, the dissection is carried out from the renal pedicles bilaterally to the ipsilateral external iliacs, and must include the interaorto-caval, paracaval, precaval, pre-aortic and para-aortic, common and external iliac lymph nodes. The extent of node dissection, however, is uncertain and controversial. Morbidity is very small and we have had no deaths at our center following this procedure. A probable loss of seminal fluid on ejaculation (which has no effect on sexual potency) is a common complication and should be explained to the patient beforehand.

The question of whether or not to give prophylactic chemotherapy to patients with negative nodes has not been resolved. Certainly the cure rate is high without prophylactic chemotherapy and there is no absolute proof that it prevents metastases. In patients with positive nodes, however, many physicians administer prophylactic chemotherapy.

\textbf{Choriocarcinoma}

Patients with choriocarcinoma and negative chest X-rays (both routine, stereo and/or tomograms) as well as negative urinary gonadotrophins who have no evidence of disseminated disease should also undergo retroperitoneal lymphadenectomy. Unfortunately, a very high percentage of patients with choriocarcinoma have evidence of disseminated disease at the time of diagnosis. Fortunately, pure choriocarcinoma is extremely rare, accounting for only about one percent of all testis tumors.

In those patients who refuse radical lymph node dissection the retroperitoneal lymph nodes may be treated by external radiation therapy. The superiority of lymphadenectomy over radiation therapy in patients with embryonal carcinoma cannot be definitively proven al-
though it has been shown in those with teratocarcinoma. Various combinations of lymphadenectomy and irradiation have been successfully utilized.\textsuperscript{16}

Disseminated Disease (Stage C)

One of the most gratifying aspects in managing patients with disseminated testicular cancer is that the course of disease may be favorably influenced by chemotherapy.\textsuperscript{17} The administration of chemotherapy should be integrated with surgery and radiation therapy and must take into account the histogenesis and natural history of the tumors, as well as the biological variations and peculiarities of different histologic types.

Chemotherapy was first found potentially curative for testicular germinal tumors in the late 1950s.\textsuperscript{17} Complete and prolonged remissions in patients with metastatic seminoma treated with Sarcolysin were described by a group of Russian investigators.\textsuperscript{18} Subsequently other alkylating agents were discovered which produced significant regressions in 80\% of patients and complete disappearance of detectable tumor in about 40\%.

Embryonal carcinoma and choriocarcinoma of the testis have been effectively treated by intravenous Actinomycin D with or without added Leukeran and, occasionally, Methotrexate.\textsuperscript{17} In patients with gross metastatic embryonal carcinoma at the start of chemotherapy, about 50\% can be expected to show benefit for a few months; about 20\% will be rendered free of evidence of disease; and about 10\% will be free of evidence at two years.\textsuperscript{20} If full active treatment is continued for two years after disappearance of disease, very few patients will subsequently relapse. This treatment program causes prolonged control somewhat more frequently in choriocarcinomas than in teratocarcinomas. Mithramycin, a drug closely related to Actinomycin, is also active against embryonal carcinoma.\textsuperscript{21} The alkaloids of vinca rosea, Velban and Vin-

cristine, have some effect on testicular tumors, but have been primarily evaluated in combination with other agents.

The combination of Bleomycin and Velban has induced remissions in a high percentage of patients with testicular tumors.\textsuperscript{22} It is too early, however, to adequately determine the duration of remission. Recently, the combination of Bleomycin, Velban and Actinomycin has produced favorable responses in a significant number of patients, many of them prior treatment failures. Responsiveness has been particularly notable in the teratocarcinoma group.\textsuperscript{23} Cis-platinum used alone has produced many good remissions.\textsuperscript{24} However, as with Bleomycin alone, the responses are hard to maintain because of toxicity after cumulative doses.

All patients with metastatic testicular carcinoma should be treated with chemotherapy. The precise drug or drug combinations and the actual dosage should be recommended for the individual patient by a physician experienced in this area of therapy. The possibility of significant toxicity from all chemotherapeutic agents is great.

It is important to remember that significant palliation and prolongation of life can be achieved in these patients and that cure rates will probably increase significantly as present complete remission rates are translated, by time, into cures.\textsuperscript{6}

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The Increasing Social Role of Science

Today's public is more interested in solving social ills than in science and technology. At the same time, the increasing complexity and intrusiveness of science-based technology have increased the public's expectations of accountability and have sharpened its criticisms. Scientists now find it difficult to separate themselves from the institutional and political dimensions of their work. Those who sit on committees advocating curriculum reform have basically agreed on the desirability of broadening the curricula to produce scientists able and willing to work toward the goals of educating both themselves and the public about science and its role in society. --Dorothy Zinberg, 'A Strategy for Science Education in the 1970's.' Science 179:1187, 1974.