Classification of Tumors of Testis

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ABSTRACT

In adult patients, testicular tumors consist predominantly of seminoma, embryonal carcinoma, teratoma, choriocarcinoma and mixtures of these. In infants and children, yolk sac tumor and teratoma are the usual tumors; in older age patients, it is predominantly spermatocytic seminoma and malignant lymphoma, although the others may occur as well. Leydig and Sertoli-granulosa cell tumors occur in all ages.

The introduction of tumor markers and the capability to demonstrate these in tissue are the most important recent developments. However, there is great need for correlation of histology with these markers and histological demonstration of them.

The incidence of testicular tumors is 2.1 to 2.2 per 100,000 per year. There has been doubling of incidence reported from 1958 to 1962. In the white male population 20 to 34 years of age, testicular tumors are the most common cause of death from neoplasia. They are extremely rare in blacks.

Testicular tumors may be classified clinically on the basis of history, physical, radiological and laboratory examinations or on pathology. Slight change in size and consistency of the testis, the earliest sign of testicular tumor, is rarely reported. Gradual or sudden enlargement and pain are the two most frequent symptoms.

Others consist of a nodule, hardness, heaviness and dragging sensation. In 10 to 20 percent of testicular tumors, the symptoms are acute and may lead to the erroneous diagnosis of epididymo-orchitis. Ten to 20 percent of testicular tumors come in with symptoms referable to metastasis. Indeed, Borski2 has reported that up to 35 percent of patients have evidence of metastasis at the time of the first examination.

Radiological examination is carried out solely to determine the existence and location of metastases. In addition to pyelography, chest x-rays, including tomography, lymphangiography, inferior venacavography, various scanning techniques and ultra sound and other techniques are being more frequently employed. These serve primarily to stage the tumor. Is it confined to the testis or has it already metastasized?

* The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.
TABLE I
WHO International Histological Classification of Testis Tumors

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<th>No.</th>
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<td>Sex cord/stromal tumors</td>
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<td>Tumors of collecting ducts, rete, epididymis, spermatic cord, capsule, supporting structures and appendices</td>
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<td>9.</td>
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There is great need for correlating the role of tumor markers, particularly Beta fraction of human chorionic gonadotropins and Alpha-fetoproteins, with histology and with histological demonstration of these markers in the tissue.

Two methods of clinical staging of tumor have been in use. The oldest is the one most commonly used in the United States:

Stage A. Tumor confined to the testis with no evidence of spread beyond the confines of the testis.

Stage B. Evidence of minimal retroperitoneal lymph node (fewer than six positive nodes) metastasis either by lymphangiography or dissection.

Stage B2. Evidence of involvement of more than six nodes.

Stage B3. Massive retroperitoneal involvement but with no evidence of spread above the diaphragm or to solid visceral organs.

Stage C. Metastatic tumor present above the diaphragm.

The UICC\(^6\) has proposed and the U.S. Joint Committee on Clinical Stage Classification has accepted TNM classification.\(^9\) The difference between the two classifications is that Stage A is subdivided in the T classification and the others are included in N and M categories. Briefly stated, these categories are as follows:

TX—the minimum requirements to assess fully the extent of primary tumor cannot be met. This includes those in which no orchiectomy has been carried out.

T0—No evidence of primary tumor.

T1—Tumor limited to the body of the testis.

T2—Tumor extending beyond tunica albuginea.

T3—Tumor involving the rete testis or epididymis.

T4—Tumor invading the spermatic cord and/or the scrotal wall (T4a—spermatic cord and T4b—scrotal wall).

For N and M and histopathological staging, the reader is referred to UICC-TNM Classification of Malignant Tumors.\(^6\)

From the pathological point of view, there have also been several classifications: Friedman and Moore,\(^5\) Dixon and Moore,\(^4\) Mostofi,\(^7\) Mostofi and Price,\(^8\) Collins and Pugh\(^3\) and most recently, the WHO classification.\(^9\) The classification being presented is the WHO classification which is most comparable to the Mostofi and Price classification. The broad categories of tumors of the testis and adnexae are listed in table I.

For the most part, testicular tumors are divisible into two main categories: those of germ cell origin and those of the specialized gonadal stromal cells. Germ cell tumors constitute about 94 percent of the neoplasms of the testis, tumors of specialized gonadal stroma (sex cord/stromal tumors), 4 to 6 percent.

Germ cell tumors are divided into those of one histological type (60 percent) and those of more than one histological type (table II).

Germ Cell Tumors

TUMORS OF ONE HISTOLOGICAL TYPE

Seminoma. In adult patients, this constitutes about 40 percent of testicular tumors. It usually occurs in patients in their 30's and 40’s. The size varies a good bit. The overlying tunica may be thickened. The cut surfaces are grayish white, lobulated, bulging and fairly well demarcated but are not encapsulated. Areas of hemorrhage and necrosis are usually confined to large tumors.
Microscopically, the tumor presents a fairly uniform appearance with cells supported by a delicate fibrovascular stroma. The cells are large, hexagonal or round, with clear or finely granular cytoplasm surrounded by a delicate cell membrane. The cytoplasm contains varying amounts of glycogen. The nucleus is usually large, centrally located, spherical, slightly elongated or irregular. It has a granular chromatin distribution, one to two nucleoli and a distinct nuclear membrane.

The cells occur in lobules, columns or cords, separated from each other by a delicate fibrous stroma which contains varying numbers of lymphocytes and amounts of granulomatous reaction. These are quite prominent in about 20 percent of cases. They are indicative of immunological reaction of the host to the tumor and have been associated with good prognosis. The overall five year mortality of seminoma is less than 6 percent and it has been demonstrated by us that tumors with variations in size, shape, and staining of cells, and especially with an average of three or more mitotic figures per high field (counting 10 high power fields), are indicative of poor prognosis. These have been designated as anaplastic seminoma. Occasionally, seminomas are entirely intratubular.

Six to 10 percent of seminomas show giant cells. Some of these are simply tumor giant cells. Others, as demonstrated by immunoperoxidase reactions, contain human chorionic gonadotropins and are therefore syncytiotrophoblasts. This finding explains the presence of this hormone in the serum of some patients. The presence of such cells sometimes leads to the erroneous diagnosis of choriocarcinoma but it is our belief that this diagnosis should be reserved for tumors that fulfill the requirement for such diagnosis. Seminomas usually metastasize as seminoma.

Spermatocytic seminoma. This type of tumor is usually found in older patients. Although spermatocytic seminoma is the most common testicular germ cell tumor of patients over the age of 65, the overall frequency of this tumor is about 4 percent. The tumors usually attain a large size. The cut surfaces are pinkish gray, soft and edematous and honeycombed with cysts containing pale yellow fluid.

Microscopically, three cell types must be recognized for this diagnosis. The predominant cell consists of intermediate sized cell with vesicular nuclei. The second cell is a large giant cell which may have a large bizarre nucleus or it may be multinucleated. Both of these cells, especially the intermediate cell, show the characteristic spireme or filamentous arrangement of chromatin. The third cell type is small and resembles lymphocytes or plasma cells, except that there is a good bit of cytoplasm. Mitoses are frequent.

Spermatocytic seminoma is differentiated from typical seminoma by the fact that para-aminosalicylic acid (PAS) is negative and there are cystic spaces. In addition, the stroma is loose, edematous and devoid of lymphocytes and granulomatous reaction. Only a rare metastasis has been reported.

Embryonal carcinoma. This type of tumor constitutes about 20 percent of testicular tumors. This group is seen mostly in the 20's age bracket, although it has been seen in older patients. The tumors are usually small. The cut surfaces have a variegated appearance with grayish white

| TABLE II |
| WHO International Classification of Germ Cell Tumors |

A. Tumors of one histological type
1. Seminoma
2. Spermatocytic seminoma
3. Embryonal carcinoma
4. Yolk sac tumor (embryonal carcinoma, infantile type; endodermal sinus tumor)
5. Polyembryoma
6. Choriocarcinoma
7. Teratomas
   a. Mature
   b. Immature
   c. With malignant transformation
B. Tumors of more than one histological type
1. Embryonal carcinoma and teratoma (teratocarcinoma)
2. Choriocarcinoma and any other types (specify type)
3. Other combinations (specify)
granular or smooth bulging tissue, show areas of necrosis and hemorrhage and have no evidence of encapsulation.

Microscopically, the tumor has been defined as composed of cells of primitive epithelial appearance, often with clear cytoplasm growing in a variety of patterns (acinar, papillary, tubular or solid). The cells are polyhedral but may vary from cuboidal to columnar. They have a small amount of homogeneously amphophilic or vacuolated cytoplasm surrounded by a large round or oval vesicular nucleus with irregular and coarse chromatin, varying amounts of nuclear vacuolization, irregular coarse chromatin distribution and one or two large nucleoli.

Solid embryonal carcinomas may be difficult to distinguish from seminoma except that embryonal carcinoma cells usually have less distinct cell borders and rare lymphoid or granulomatous stroma. More often the tumor cells form large or small acini, tubules or papillary structures. The stroma varies a great deal in that it may be loose and edematous, scanty or abundant, fibrous or hyalinized, or very cellular. A few syncytiotrophoblasts may be seen. Some embryonal carcinomas have been reported as demonstrating positive alpha-fetoproteins and chorionic gonadotropins.

Embryonal carcinomas usually metastasize as embryonal carcinoma but the metastasis may show teratomatous or choriocarcinomatous elements. There has been considerable improvement in survival of patients with embryonal carcinoma with the introduction of chemotherapy. This is the subject of a major national study at the present time.

Infantile embryonal carcinoma—yolk sac—endodermal sinus tumor. This is the most common testicular tumor in infants and children, constituting about 60 percent of germ cell tumors of this age group. It rarely occurs in pure form in adult patients but is more often seen in combination with an adult type of embryonal carcinoma or in tumors with both teratoma and embryonal carcinoma.

The tumor presents a homogenous, grayish white lobulated appearance with a resilient consistency and cystic areas exuding fatty and mucinous material. Histologically, it has a characteristic pattern of anastomosing glandular or tubular structures lined by low columnar, cuboidal or flattened epithelium. These may alternate with solid or papillary areas, of which the latter sometimes form characteristic Schiller Duval bodies. The cytoplasm varies a great deal from vacuolated to eosinophilic staining. It contains a considerable amount of lipid and glycogen. The nuclei may be round, oval, elongated or even spindle shaped. There are varying amounts of pinkish precipitate, some of which may give positive alpha-feto-protein reaction. All our yolk sac tumors give positive reactions.

These tumors have a fairly good prognosis, especially with chemotherapy. Metastases consist of the same histology as the primary tumors.

Polyembryoma. This tumor consists mainly of embryoid bodies and is extremely rare in pure form. Embryoid bodies consist of a disc, a cavity and a tubular form surrounded by loose mesenchyme in which syncytio-and cytoto phoblasts may be seen. The disc is comprised of single or multilayered undifferentiated large, epithelial-like cells, and the cavity, lined by flattened epithelial cells, simulate an amniotic cavity. Not all embryoid bodies show these features. Most often these structures are seen in tumors which are predominantly embryonal carcinoma and teratoma.

Choriocarcinoma. In its pure form, choriocarcinoma is extremely rare and is associated with gynecomastia and marked elevation of chorionic gonadotropins. In our experience, all patients with pure choriocarcinoma have presented with generalized metastasis and only careful examination has revealed a small primary testicular tumor. For diagnosis of pure choriocarcinoma, we have felt that the tumor should consist solely of two cell types,—syncytiotrophoblasts and cyto-
trophoblasts, with the former more or less forming the advancing edge or covering papillary projections. Chorionic gonadotropins are easily demonstrable in the syncytiotrophoblasts. Pure choriocarcinomas invariably metastasize as pure choriocarcinoma.

**Teratoma.** Teratoma is defined as a tumor composed of several types of tissue representing different germinal layers (endoderm, mesoderm and ectoderm). In infants, its incidence is about 40 percent, in adults about 7 percent.

Grossly, the tumor presents a variegated appearance with cysts containing mucoid or sebaceous material, solid areas, cartilage and bone. Microscopically, two major categories are recognized,—mature and immature teratoma. In the former, the tumor is composed of well differentiated tissue which may be arranged in an organoid pattern; in the latter, the differentiation is incomplete but the tissue is readily identifiable as embryonic tissue (cartilage, bone, and neuroectoderm).

A third and extremely rare category is the mature teratoma which shows definite malignant transformation, e.g., squamous carcinoma or mucinous adenocarcinoma and sarcoma. It should be emphasized that this category does not include tumors that can be identified as embryonal carcinoma, choriocarcinoma or seminoma.

Teratomas may metastasize as teratoma or embryonal carcinoma or admixture of the two but rarely as choriocarcinoma.

**Tumors of More Than One Histological Type**

In about 40 percent of testicular tumors more than one histological type may be present. The most frequent are embryonal carcinoma and teratoma. These constitute about 24 percent of testicular tumors. Grossly, they present solid and cystic areas and may attain a large size. Microscopically, both components, embryonal carcinoma and teratoma, are present in varying amounts. These tumors have been referred to as teratocarcinoma but we prefer to mention the components that are present. In addition, there may be embryoid bodies and scattered syncytiotrophoblasts. These tumors usually metastasize as embryonal carcinoma but may show both components and even choriocarcinoma in the metastasis.

Another combination that deserves special mention is the tumor that shows choriocarcinomatous foci in association with embryonal carcinoma, teratoma or seminoma. It has been customary to designate tumors by their most malignant component and, as such, many pathologists tend to designate such tumors as choriocarcinoma. The World Health Organization (WHO) classification lists the types that are present and reserves the term choriocarcinoma only for tumors that are pure choriocarcinoma.

Choriocarcinoma usually metastasizes through the blood stream. The others usually metastasize through lymphatics but may, on occasion, metastasize through the blood stream. Retroperitoneal lymph nodes are the primary sites of metastases. Inguinal lymph nodes are occasionally involved, especially if there has been surgical intervention in the scrotum. Other sites are mediastinal nodes, lungs, liver, kidneys, pleura, peritoneum, intestines and bones. The majority of metastases and fatalities occur in two years and almost all in five years.

**Other Germ Cell Tumors**

Deroids are rarely encountered in the testis while epidermal cysts, consisting of a cyst lined by keratinizing stratified squamous epithelium without skin appendages, are more frequent. Carcinoids may be primary or secondary, functional or non functional.

**Tumors of Specialized Gonadal Stroma Sex Cord/Stromal Tumors**

Clinically and pathologically, these tumors comprise a heterogeneous group, but they have two common features,—they are derived from the specialized
TABLE III
WHO International Classification of Sex Cord/Stromal Tumors

A. Well differentiated forms
1. Leydig cell tumor
2. Sertoli cell tumor
3. Granulosa cell tumor

B. Mixed forms (specify)

C. Incompletely differentiated forms

Stroma of the gonads and they are hormone producing cells of testis. The WHO classification (table III) recognizes the completely differentiated forms: Leydig cell, Sertoli cell, and granulosa cells, and the incompletely differentiated (tumors of gonadal stroma).

LEYDIG CELL TUMORS

These occur in all ages. In adult patients, about 40 percent show gynecomastia and other feminizing characteristics; in children, they invariably cause macrogenitosomia. If the lesion is not recognized and the child grows to adolescence, there may be premature closure of the epiphysis and development of strong muscular dwarfs.

Grossly, the tumors are yellowish brown, homogenous lobulated. The tumors recapitulate the normal evolution of Leydig cells. Most commonly, the cells are polygonal and have vacuolated or ground glass cytoplasm surrounding a round or oval vesicular nucleus. Many contain varying amounts of lipid material and lipofuchsin. Reinke’s crystals are seen in about 40 percent of the tumors. Binucleated cells are not uncommon. Other cells may be small or large with foamy cytoplasm or resemble fibroblast-like cells. The stroma is usually delicate and highly vascularized and has an endocrine type of distribution; however, it may be hyalinized and even calcified.

Two features of Leydig cell tumors merit consideration: (1) the distinction between hyperplasia and tumor and (2) the distinction between benign and malignant tumors.

The differentiation between hyperplasia and tumor may be difficult, especially in patients with adrenogenital syndrome. Leydig cell tumors, both in man and experimental animals, usually start as hyperplasia. In hyperplasia there are always entrapped seminiferous tubules surrounded by Leydig cells. In Leydig cell tumors, while this may be seen at the periphery, there is a distinct tumor without any seminiferous tubules in the main mass.

The distinction between benign and malignant Leydig cell tumor is more difficult. Variations in size, shape and staining qualities of cells and nuclei may lead to the erroneous diagnosis of malignancy while a tumor which consists of regular cells and is histologically benign may, in fact, behave in the same manner as a malignant one does. The presence of hemorrhage and necrosis, marked cellular anaplasia, vascular invasion and increased mitotic activity are the criteria found most useful by us. However, the presence of Leydig cells in the rete, epididymis and cord should not lead to the diagnosis of malignancy. The most reliable evidence of malignancy is metastasis, but this is of limited value as it is late in development.

SERTOLI, GRANULOSA, THECAL CELL TUMORS AND ADMIXTURES

These types are diagnosed usually by pathological examination. They occur at all ages but are more frequent in infants and children. In adult patients, about 40 percent show gynecomastia.

Grossly, the tumors are lobulated, homogeneously yellowish and bulging. Microscopically, the tumor shows the histology of one or more of these cell types. The cytoplasm is clear, vacuolated or amphophilic surrounding a round or oval vesicular nucleus with a single distinct nucleolus. Beginning as intratubular growths, the tumors break out to invade the stroma. Sertoli cell tumors tend to produce a basement membrane-like substance which may show calcification.

Mention may be made of the fact that as in Leydig cell tumors, the incidence
of metastasis is about 10 percent. The same criteria for malignancy apply here as in Leydig cell tumors but metastasis usually develops within one year.

Tumors and Tumor-like Lesions Containing Both Germ Cells and Stromal Elements

These may present themselves as two distinct tumors, e.g., seminoma and Leydig or Sertoli cell tumors, which is not unusual in the dog but rare in man, or as an admixture consisting of malignant germ cells and Sertoli-granulosa cells designated as gonadoblastoma by Scully. These tumors are usually in individuals with underlying gonadal disorder. Scully divided the patients into three categories: non-virilizing phenotypic female, virilizing phenotypic female and phenotypic male.

Grossly, the tumors range in size from barely detectable to huge tumors. The color and consistency range from gray to yellow or brown, and from soft fleshy to hard.

Histologically, the tumor consists of distinct aggregates of actively proliferating germ cells usually in intimate mixture with Sertoli or granulosa cells. A few Leydig cells may be present. It is the germ cell component that may metastasize.

OTHER TUMORS

The most important of these are lymphoma initially manifested as testicular tumor. These occur in all ages but are more frequent in older age patients. They are bilateral in about 20 percent of the patients. Grossly, they are grayish-white with areas of necrosis and hemorrhage. Histologically, there is intense infiltration of the interstitium.

The reader is also referred to WHO reference7 for other tumors and tumor-like lesions.

Summary

Testicular tumors consist predominantly of seminoma, embryonal carcinoma, teratoma, choriocarcinoma and mixtures of these in adult patients. In infants and children, yolk sac tumor and teratoma are the usual tumors. In older age patients it is predominantly spermatocytic seminoma and malignant lymphoma, although the others may occur as well. Leydig and Sertoli-granulosa cell tumors occur in all ages.

The introduction of tumor markers and the capability to demonstrate these in tissue are the most important recent developments. However, there is great need for correlation of histology with these markers and histological demonstration of them.

References