Michael Mahany. *Black Bear at Wibel Mining Camp.* Photograph. Anchorage, Alaska.

The pathology and current concepts of classification of testicular germ cell tumors are reviewed.

Pathology of Germ Cell Tumors of the Testis

Isabell A. Sesterhenn, MD, and Charles J. Davis, Jr, MD

Background: *An increasing incidence of testis tumors has been noted over the second half of the 20th century. Congenital malformation of the male genitalia, prenatal risk factors, nonspecific and specific exposures in adulthood, and male infertility have all been associated with the etiology of germ cell tumors.*

Methods: *The histologic classification, pathology, and current concepts of testicular germ cell tumors are reviewed.*

Results: *Germ cell tumors occur at all ages. The tumors are identified as pure form (those of one histologic type) and mixed form (more than one histologic type). Over half of germ cell tumors consist of more than one cell type, requiring appropriate sampling for the correct diagnosis and correlation with the serum tumor markers. Burned-out germ cell tumors may occur in patients with metastatic disease with no gross evidence of a testicular tumor.*

Conclusions: *Appropriate management of testis tumors relies on accurate pathology and classification of these tumors.*

Introduction

The majority of testis tumors originate from the germ cell, which is the principal cell type of the testis. An increasing incidence of testis tumors, particularly in men of European origin, has been noted over the second half of the 20th century.[1] Germ cell tumors occur at all ages. Congenital malformation of the male genitalia, prenatal risk factors, nonspecific and specific exposures in adulthood, and male infertility have all been associated with the etiology of germ cell tumors. Over half of germ cell tumors consist of more than one cell type, requiring appropriate sampling for the correct diagnosis and correlation with the serum tumor markers (human chorionic gonadotropin [hCG] and α-fetoprotein [AFP]). The most recent WHO histologic classification of testis tumors[2] is similar to the 1998 classification,[3] differing most significantly with respect to the classification of teratomas and polyembryomas (Table 1). Since mature and immature teratomas have the same genetic changes and biologic potential specific for the prepubertal and postpubertal patient, teratomas are no longer subclassified as mature and immature. Polyembryoma was

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Abbreviations used in this paper: hCG = human chorionic gonadotropin, AFP = α-fetoprotein, hPL = human placental lactogen, H&E = hematoxylin-eosin.

Table 1. — Histologic Classification of Testis Tumors

Germ Cell Tumors
Intratubular germ cell neoplasia, unclassified
Other types
Tumors of One Histologic Type (Pure Forms)
Seminoma
Seminoma with syncytiotrophoblastic cells
Spermatocytic seminoma
Embryonal carcinoma
Yolk sac tumor
Trophoblastic tumors
Choriocarcinoma
Trophoblastic neoplasms other than choriocarcinoma
Monophasic choriocarcinoma
Placental site trophoblastic tumor
Teratoma
Dermoid cyst
Monodermal teratoma
Teratoma with somatic type malignancies
Tumors of More Than One Histologic Type (Mixed Forms)
Mixed embryonal carcinoma and teratoma
Mixed teratoma and seminoma
Choriocarcinoma and teratoma/embryonal carcinoma
Others

once classified with tumors of one histologic type; however, in recognition of the different cell types present in polyembryoma, it is now classified with tumors of more than one histologic type. The tumors are staged according to the TNM classification (Table 2).[4,5]

Precursor Lesions

Several terms are used to refer to intratubular malignant germ cells, including intratubular germ cell neoplasia-unclassified, carcinoma in situ, and intratubular preinvasive tumor. In the postpubertal patient, they are seen in approximately 82% of testes harboring a germ cell tumor.[6] However, they are rarely present in prepubertal children.[7-12] In testicular biopsies for infertility, intratubular malignant germ cells are seen in 0.3% to 1.8% of cases.[13]

There are no specific macroscopic features for these lesions. Histologically, the malignant germ cells are large with abundant pale, glycogen-rich cytoplasm. The irregularly outlined nuclei are enlarged, with one or two prominent nucleoli (Fig 1). They are located at the periphery of the seminiferous tubules between residual Sertoli cells. They often have a segmental distribution, and they can extend into the rete. At the site of invasion into the adjacent stroma, they often elicit a lymphocytic response. By immunohistology, placental alkaline phosphatase (PLAP) can be identified in up to 99% of cases with membranous and/or cytoplasmic reaction (Fig 2).[6,13-15] CD117a (c-*kit*)[16,17] shows a membranous reaction. They are strongly positive for OCT3/4 (POU5F1), a marker of pluripotent stem cells.[18] Intratubular malignant germ cells appear to have a similar appearance in all germ cell tumor types with PLAP and CD117a, but other antibodies such as 43-9F[19,20] and TRA 1-60[21,22] indicate different immunophenotypes adjacent to different germ cell tumor types. Generally, the malignant germ cells are similar to the associated germ cell tumor type with respect to their DNA ploidy.[23-25] They do not show an increased number of isochromosome 12p [i(12p)] until they become invasive.[26-28]

Tumors of One Histologic Type

Seminoma

Seminomas comprise 35% to 70% of germ cell tumors, depending on the patient population (Table 3). The tumor is most commonly seen in patients between 30 and 50 years of age, and the testis is usually enlarged. The cut surface of seminomas is usually grayish-white, bulging, and glistening (Fig 3). Histologically, the tumor cells are large with abundant pale or amphophilic cytoplasm, depending on the glycogen content. The nuclei have a coarse chromatin distribution with prominent nucleoli. These cells occur in sheets, lobules, or columns. The supporting stroma shows varying amounts of lymphocytic infiltrate or granulomatous reaction (Figs 4–6). Both are prominent in approximately 20% of cases. This reaction apparently represents a host response. Immunohistochemically, the tumor cells react with antibodies to PLAP and CD117a (Table 4).[6,29,30] OCT4, a marker of pluripotent cells, is demonstrable in the nucleus of seminoma cells.[18,31] Other markers include VASA[32] and CD143.[33] The cytokeratins are occasionally positive.[34]

Variants of Seminoma

A number of seminomas show increased mitotic activity, averaging 3 mitoses per high-power fields throughout the tumor (Fig 7). In addition, these seminomas often show more cellular atypia and pleomorphism. These tumors may express CD30, which has been interpreted by some as evidence of early differentiation toward embryonal carcinoma. This type of seminoma usually presents at a higher stage.[35,36] Others have questioned the significance of these findings in seminoma. When examined by immunohistochemistry, approximately 25% of seminomas contain syncytiotrophoblastic giant cells compared with 7% when examined only by hematoxylin-eosin (H&E) staining.[37] These are usually multinucleated cells with vacuolated cytoplasm, or they are flattened cells that are associated with vascular spaces (Fig 8). They react positive for hCG and other placental glycoproteins such as human placental lactogen (hPL) and pregnancy-specific β1-glycoprotein.[37,38] This type of tumor is often associated with elevated serum levels of hCG.

Spermatocytic Seminoma

This germ cell tumor accounts for approximately 1.2% to 4.5% of germ cell tumors.[39,40] Spermatocytic seminoma is

usually seen in men over 40 years of age. Approximately 5% of patients have bilateral disease.[39] Spermatocytic seminoma develops only in the testis, unlike other germ cell tumor types that also involve the ovary, retroperitoneum, mediastinum, and other sites. Grossly, the tumors are usually large. The cut surface is yellowish, soft, and mucoid, with cystic or spongy areas (Fig 9). Microscopically, the tumor consists of three cell types: large mononucleated or multinucleated cells with abundant cytoplasm, intermediate cells, and small cells with hyperchromatic nuclei (Fig 10). The nuclei of the large and intermediate cells have a characteristic filamentous chromatin distribution. Mitoses occur frequently. Using cytophotometry, large cells have DNA values up to 4*2*C, whereas small cells are diploid or near diploid and medium cells have an intermediate value. The edematous stroma is generally devoid of a lymphocytic infiltrate. Lakes of pink proteinaceous material can be seen.

The adjacent seminiferous tubules often show intratubular spermatocytic seminoma (Fig 11). The typical intratubular germ cell neoplasia unclassified is not present. About 20% of spermatocytic seminomas contain PLAP in isolated or small clusters of cells.[39] CD117a (c-***kit***) can also be demonstrated (I.A.S., unpublished data, 2004). AFP and hCG are not demonstrable. Most spermatocytic seminomas react diffusely with antibodies to VASA.[32] NY-ESO-1 has been demonstrated in spermatocytic seminoma but not in other germ cell tumor types.[41] Cytokeratins are usually seen in a dot-like pattern. Spermatocytic seminoma has a good

Table 2. — TNM Classification of Tumors of the Testis

T – Primary Tumor

Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumor is classified after radical orchiectomy; see pT. In other circumstances, TX is used if no radical orchiectomy has been performed

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass morethan 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s) or lung
M1b	Other sites

pTNM Pathological Classification

pT – Primary Tumor

pTX	Primary tumor cannot be assessed (see T–Primary Tumor, above)
pT0	No evidence of primary tumor (eg, histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion

pN – Regional Lymph Nodes

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

pTNM Pathological Classification *(continued)*

S – Serum Tumor Markers

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N* *and* hCG (mIU/mL) <5,000 *and* AFP (ng/mL) <1,000
S2	LDH 1.5–10 × N* *or* hCG (mIU/mL) 5,000–50,000 *or* AFP (ng/mL) 1,000–10,000
S3	LDH >10 × N* *or* hCG (mIU/mL) >50,000 *or* AFP (ng/mL) >10,000

*N = upper limit of normal for the LDH assay.

Stage Grouping

Stage 0:	pTis	N0	M0	S0, SX
Stage I:	pT1–4	N0	M0	SX
Stage IA:	pT1	N0	M0	S0
Stage IB:	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS:	Any pT/TX	N0	M0	S1–3
Stage II:	Any pT/TX	N1–3	M0	SX
Stage IIA:	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB:	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC:	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III:	Any pT/TX	Any N	M1, M1a	SX
Stage IIIA:	Any pT/TX	Any N	M1, M1a	S0
	Any pT/TX	Any N	M1, M1a	S1
Stage IIIB:	Any pT/TX	N1–3	M0	S2
	Any pT/TX	Any N	M1, M1a	S2
Stage IIIC:	Any pT/TX	N1–3	M0	S3
	Any pT/TX	Any N	M1, M1a	S3
	Any pT/TX	Any N	M1b	Any S

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prognosis. Only one fully documented case of a metastasizing spermatocytic seminoma has been reported.[42]

Variants of Spermatocytic Seminoma

Spermatocytic seminoma is occasionally associated with a sarcoma. Macroscopically, these tumors are large with a variegated appearance. Generally, the sarcoma is undifferentiated, but in some cases it may be differentiated, eg, rhabdomyosarcoma or chondrosarcoma.[39,43-46] The recognizable foci of spermatocytic seminoma often show marked nuclear pleomorphism (Fig 12). The sarcoma metastasizes extensively.

Embryonal Carcinoma

In pure form, this tumor comprises 3% to 4% of germ cell tumors. However, it is present in approximately 40% of tumors of more than one histologic type. It is seen most often in men between 20 and 40 years of age and less often in adolescents (15 to 20 years of age). It has not been described in the prepubertal testes. In pure form, it is not associated with elevated serum levels of AFP. Grossly, the tumors are usually small and located close to the rete. The cut surface is grayish-white with foci of hemorrhage and necrosis. They are not encapsulated (Fig 13). Microscopically, the cells are large and embryonic in appearance and have pale, amphophilic or eosinophilic cytoplasm. The cell borders are ill-defined, and there is frequent nuclear overlap. The nuclei are vesicular, with a see-through appearance. Nucleoli are prominent and mitoses are common. The growth patterns include papillary, acinar, tubular, and solid forms (Figs 14–15). The stroma is variable and may consist of loose, immature cells. In the solid pattern, degenerating cells may mimic syncytiotrophoblastic cells (Fig 15). These findings are contrary to those in seminoma, which consists of large cells with well-defined cell borders (Fig 16). Vascular and lymphatic invasion (Fig 17) and infiltration of paratesticular tissue and the epididymis are common. The adjacent seminiferous tubules may show intratubular embryonal carci-

Table 3. — Frequency of Various Histologic Types of Germ Cell Tumors in Adults

Germ Cell Tumor	Adults (%)	Infants/Children (%)
Pure seminoma	26.9	2.5
Seminoma + SCT	8.1	
Spermatocytic seminoma	2.4	
ECA	3.1	
YST	2.4	58–82
Teratoma	2.7	14–38
Choriocarcinoma	0.1	
Intratubular malignant germ cells	0.6	
ECA + YST + teratoma + SCT	14.3	
ECA + YST + teratoma + seminoma + SCT	7.4	
ECA + YST + teratoma	4.7	
YST + teratoma	2.5	0.85
ECA + teratoma + teratocarcinoma	1.4	
Teratoma + seminoma		0.45
Other combinations	24.0	

ECA = embryonal carcinoma
YST = yolk sac tumor
SCT = syncytiotrophoblasts

Adapted from Mostofi FK, Sesterhenn IA, Davis CJ Jr. Immunopathology of germ cell tumors of the testis. *Semin Diagn Pathol.* 1987;4:320-341. Copyright 1987, with permission from Elsevier.

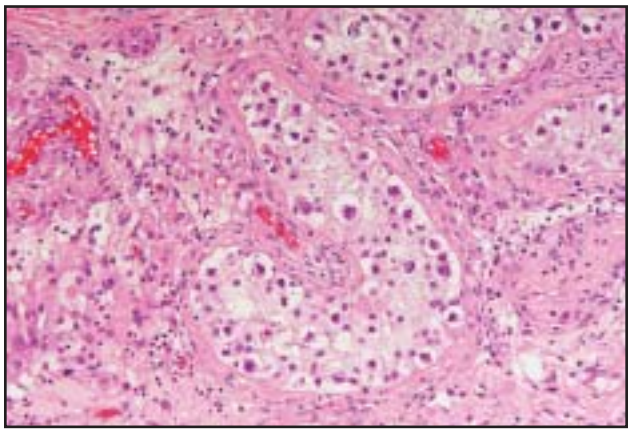

Fig 1. — Intratubular malignant germ cells (H&E, original magnification × 160).

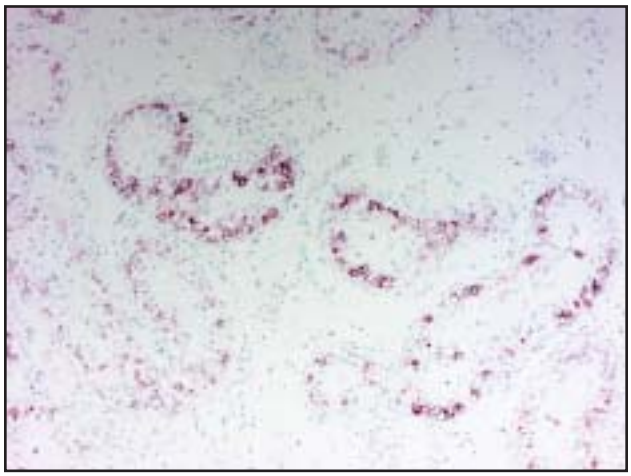

Fig 2. — Intratubular malignant germ cells with membranous and cytoplasmic staining (anti-PLAP, original magnification × 80).

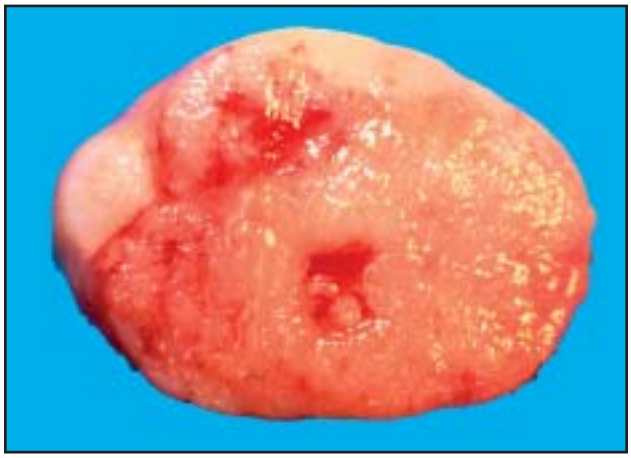

Fig 3. — Seminoma with homogeneous pale cut surface.

noma with extensive degenerative change and calcification (Fig 18). AFP is seen in approximately 13% of cases in isolated or small clusters of cells that appear to be insufficient in number to cause a measurable elevation of serum AFP,[47,48] and hPL can also be found.[37,48] OCT4 has been demonstrated in most embryonal carcinomas consistent with its pluripotentiality.[18,31] The presence of CD30 is common[49] and cytokeratins are often demonstrable, but vimentin and epithelial membrane antigen (EMA) are not. Syncytiotrophoblastic cells producing hCG can be found scattered throughout the tumor. These cells may also be positive for pregnancy-specific β1-glycoprotein.[37] Patients with pure embryonal carcinoma or embryonal carcinoma exceeding 40% in a mixed germ cell tumor with vascular and/or lymphatic invasion often present in advanced stage.[50-52]

Yolk Sac Tumor

Yolk sac tumor is the most common germ cell tumor in infants and children, accounting for approximately 65% of germ cells tumors.[53] It is seen in about 2.4% of adult patients, but in tumors of more than one histologic type, it is seen in 42% of cases. On gross examination, the tumor is soft, homogenous, grayish-yellow, and not encapsulated. Microscopically, the yolk sac tumor has at least 10 different patterns, which may explain the difficulties recognizing yolk sac tumor elements in the mixed germ cell tumor. The common pattern is the reticular or microcystic pattern (Fig 19). The cells are small, ranging from cuboidal to flattened endothelial in appearance. The nuclei are of variable sizes. Mitoses are frequent, and hyaline globules are common. The solid pattern consists of cells that are smaller than seminoma cells (Fig 20). They form sheets or nodular aggregates with occasional cystic structures. If these cells are eosinophilic and resemble hepatocytes, they are of the hepatoid pattern, which is invariably positive for AFP. A glandular-alveolar pattern is not uncommon. The presence of immature glands resembling teratoma but without other teratomatous components is interpreted as the enteric pattern. The endodermal sinus pattern is characterized by papillary structures with a central fibrovascular core covered by a layer of cuboidal tumor cells. These structures are known as Schiller-Duval bodies[54] (Fig 21). The polyvesicular vitelline pattern consists of cysts of varying sizes separated by edematous, cellular, or fibrous stroma. In

Table 4. — Immunohistochemistry of Germ Cell Tumors

Germ Cell Tumors	Antibodies
Intratubular malignant germ cell (intratubular germ cell neoplasia, unclassified)	PLAP, CD117a, OCT4, 43-9F, TRA1-60
Seminoma	PLAP, CD117a, OCT4, VASA, cytokeratins
Spermatocytic seminoma	VASA, NY-ESO-1, cytokeratins (PLAP,* CD117a*)
Embryonal carcinoma	AFP,* OCT4, CD30, cytokeratins, PLAP, hPL
Yolk sac tumor	AFP, PLAP, cytokeratins, AAT, albumin, ferritin
Trophoblastic tumors	hCG, hPL, SP1, PLAP, Mel-CAM, HLA-G, cytokeratins
Teratoma	AFP,** PLAP, and markers specific for the different tissue types

* rare cells
** intestinal-like glands and hepatoid cells

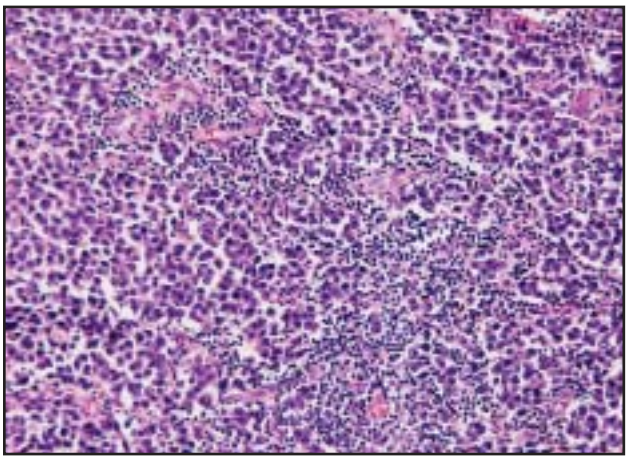

Fig 4. — Seminoma (H&E, original magnification × 80).

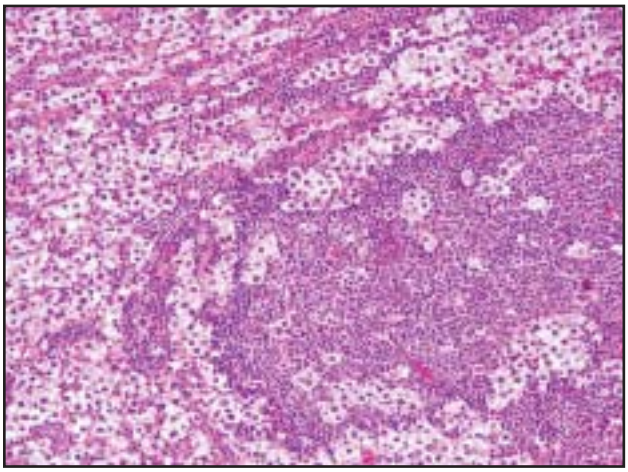

Fig 5. — Seminoma with marked lymphocytic infiltrate (H&E, original magnification × 80).

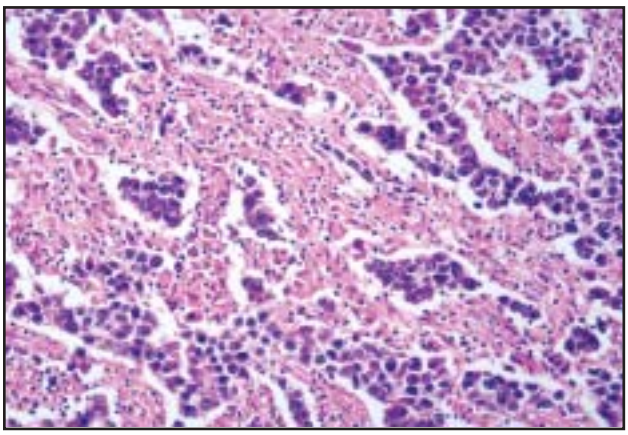

Fig 6. — Seminoma with granulomatous stroma (H&E, original magnification × 100).

the myxomatous pattern, the myxoid stroma predominates, with scarce epithelial elements. Immunohistochemically, AFP is focally demonstrable in approximately 92% of yolk sac tumors (Fig 22). The tumor is also positive for low-molecular-weight cytokeratin. Alpha-1 antitrypsin, albumen, ferritin, and others can be also identified.[47] The prognosis is similar in both children and adults.

Trophoblastic Tumors

These are the rarest (>1%) of germ cell tumors. Patients often present with disseminated disease. In addition to choriocarcinoma, the monophasic choriocarcinoma and placental site trophoblastic tumors are recognized. Microscopically, the tumors are small and hemorrhagic, resembling an infarct. Peripherally, a small rim of grayish-white tissue may be seen. Histologically, the tumor consists of syncytiotrophoblastic, cytotrophoblastic, and intermediate trophoblastic cells. The syncytiotrophoblastic cells often cover nodules of cytotrophoblastic cells, forming the advancing edge (Fig 23). Hemorrhage is extensive. The syncytiotrophoblastic cells are large, with eosinophilic cytoplasm. The cytoplasm may be vacuolated, sometimes containing erythrocytes or pale-staining eosinophilic material. They are often multinucleated but may be mononuclear. The nuclei are large and hyperchromatic. The cytotrophoblastic cells have pale-staining cytoplasm and distinct cell borders. The nuclei have 1 or 2 nucleoli. The intermediate trophoblastic cells are mononuclear cells with abundant pink cytoplasm. The syncytiotrophoblastic cells are usually positive for hCG and may have other placental glycoprotein such as human placental glycogen and pregnancy-specific β1-glycoprotein. The intermediate trophoblastic cells are positive for hPL and hCG and may contain Mel-CAM and HLA-G.[55] PLAP and cytokeratins may be seen in all of the cells. Monophasic choriocarcinomas consisting only of cytotrophoblastic cells or intermediate trophoblasts have been reported (Fig 24).[56] A cystic trophoblastic tumor variant has been described following chemotherapy and occasionally in primary tumors.[57]

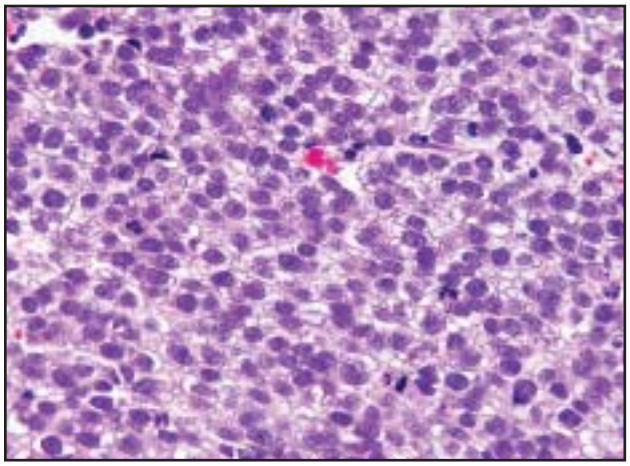

Fig 7. — Seminoma with high mitotic index; note 3 mitotic figures (H&E, original magnification × 320).

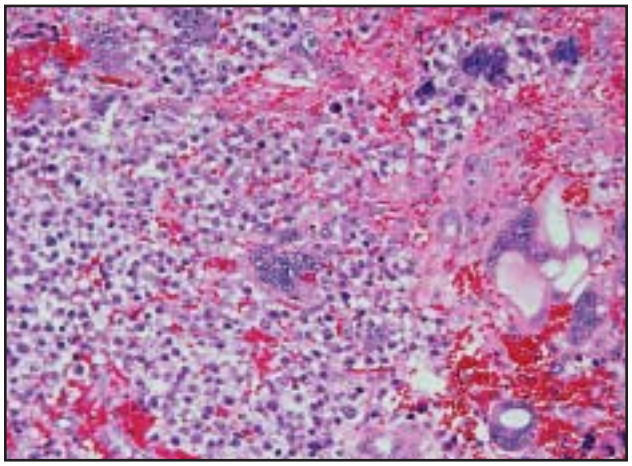

Fig 8. — Seminoma with syncytiotrophoblastic cells (H&E, original magnification × 160).

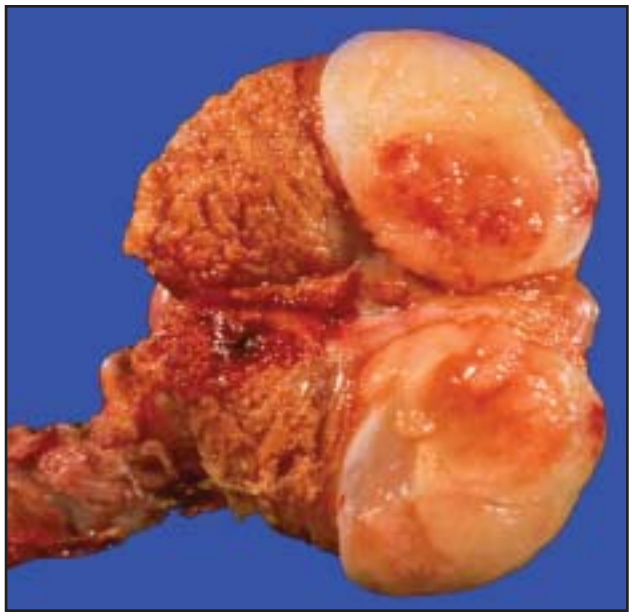

Fig 9. — Spermatocytic seminoma; note cystic and mucoid area.

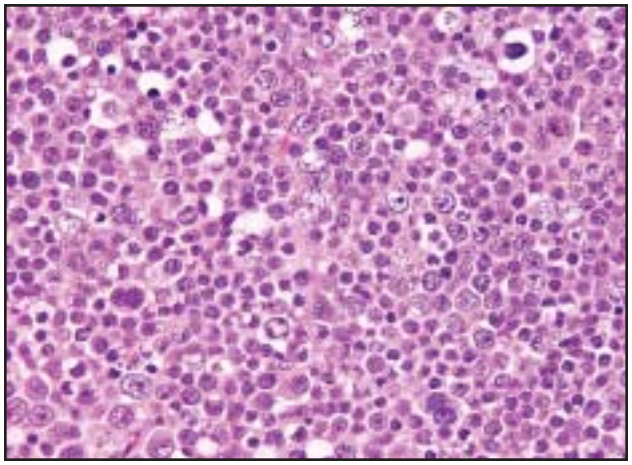

Fig 10. — Spermatocytic seminoma; note three different cell types (H&E, original magnification × 320).

Teratoma

In infants and prepubertal children, teratomas constitute about 35% of germ cell tumors. They are diploid, lack chromosomal imbalances, do not show i(12p), and are benign.[58-60] Since genetically mature and immature teratomas in prepubertal children are identical and their clinical course is the same, separation into mature and immature teratoma is not required. In adults, they are found in 2.7% to 7% in pure form[37,61] but in 47% to 50% of mixed germ cell tumors.[37,62,63] In postpubertal patients, teratomas are hypotriploid and show chromosomal imbalances, including a gain of i(12p).[64,65] They are potentially

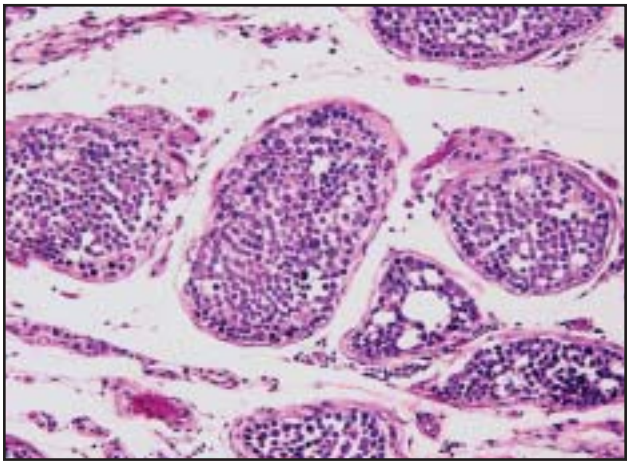

Fig 11. — Intratubular spermatocytic seminoma with 3 different cell types (H&E, original magnification × 160).

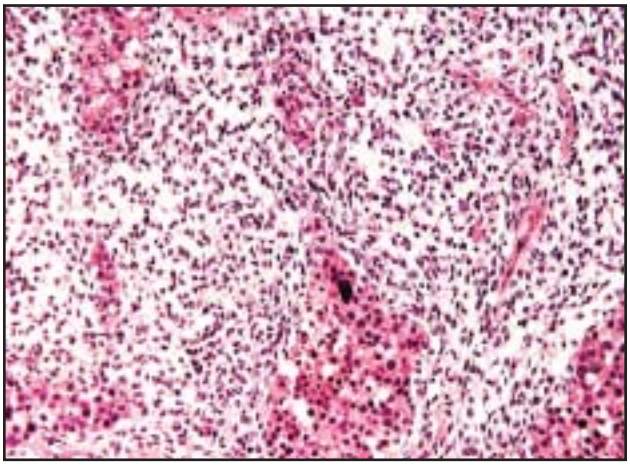

Fig 12. — Spermatocytic seminoma with sarcoma (H&E, original magnification × 160).

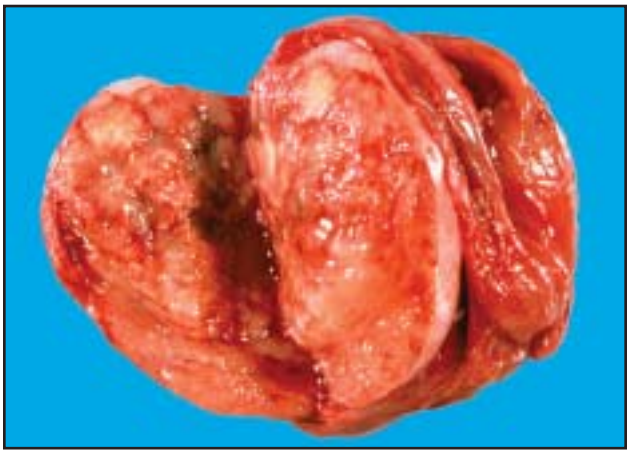

Fig 13. — Embryonal carcinoma, nodular tumor with focal hemorrhage and necrosis.

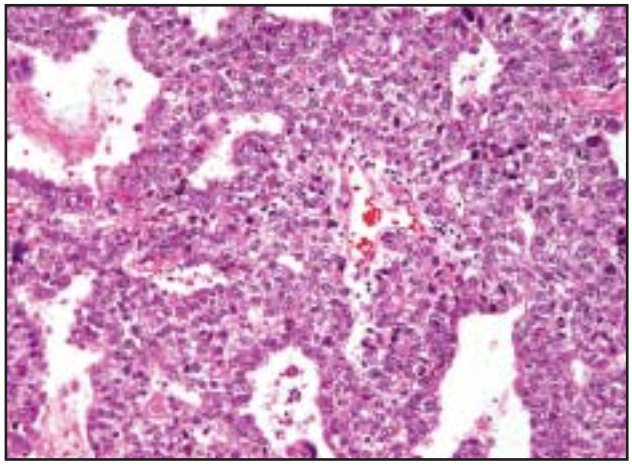

Fig 14. — Embryonal carcinoma with tubular pattern (H&E, original magnification × 160).

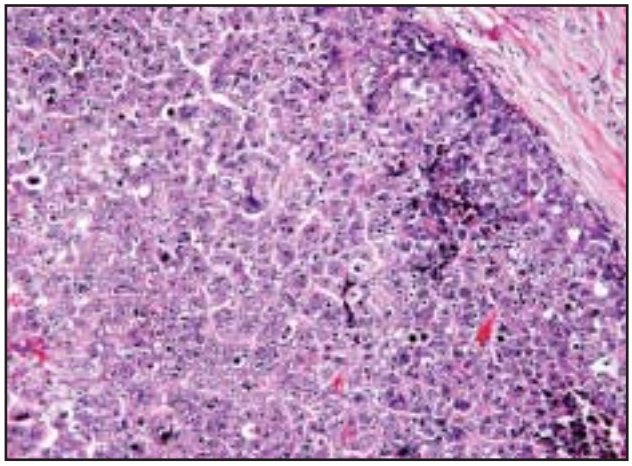

Fig 15. — Embryonal carcinoma solid pattern (H&E, original magnification × 160).

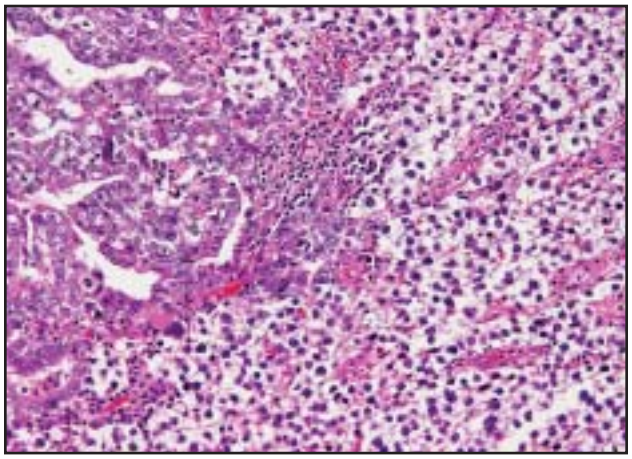

Fig 16. — Embryonal carcinoma (left) and seminoma (right) (H&E, original magnification × 160).

malignant since metastases can develop in up to 29% of cases. Therefore, as in the pediatric group, a distinction between mature and immature teratomas is unnecessary. However, the dermoid cyst and epidermal cyst are benign. Macroscopically, the tumors are well demarcated and show cystic areas that may contain mucoid or gelatinous material. The solid areas may consist of cartilage or bone.

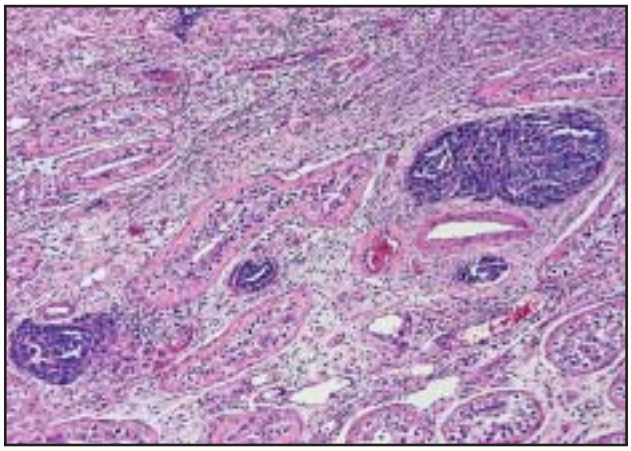

Fig 17. — Lymphovascular invasion by embryonal carcinoma (H&E, original magnification × 80).

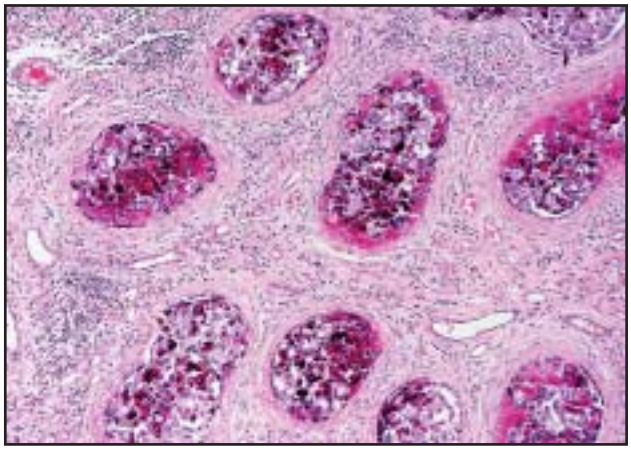

Fig 18. — Intratubular embryonal carcinoma with necrosis and calcification (H&E, original magnification × 80).

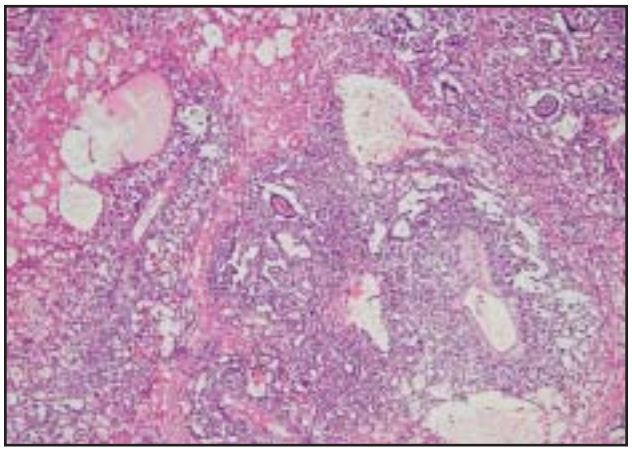

Fig 19. — Yolk sac tumor with reticular papillary growth pattern (H&E, original magnification × 36).

Histologically, these tumors are complex, representing the three germ cell layers: endoderm, ectoderm, and mesoderm. The tissues may be mature (Fig 25) or immature (Fig 26) in appearance. Enteric or salivary glands, respiratory epithelium, smooth and skeletal muscle, fat, cartilage, bone, glial, or neuroectodermal tissues are often haphazardly distributed. However, in infants and children, these tissue types often assume an organoid arrangement. Intratesticular and extratesticular lympho/vascular inva-

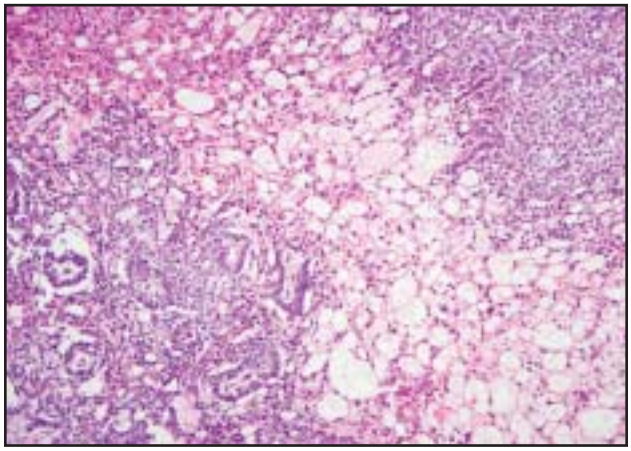

Fig 20. — Yolk sac tumor with solid reticular and papillary areas (H&E, original magnification × 80).

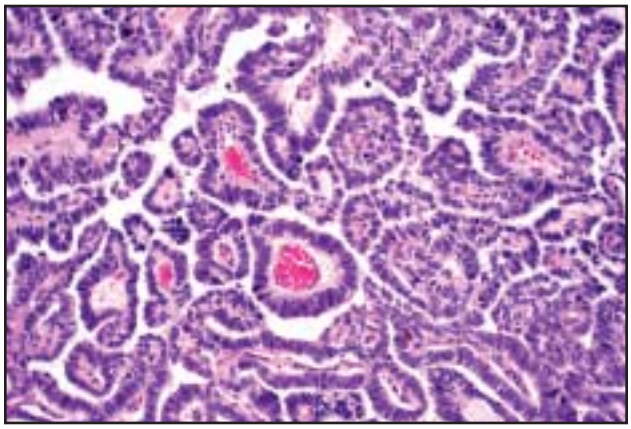

Fig 21. — Yolk sac tumor with Schiller-Duval bodies (H&E, original magnification × 100).

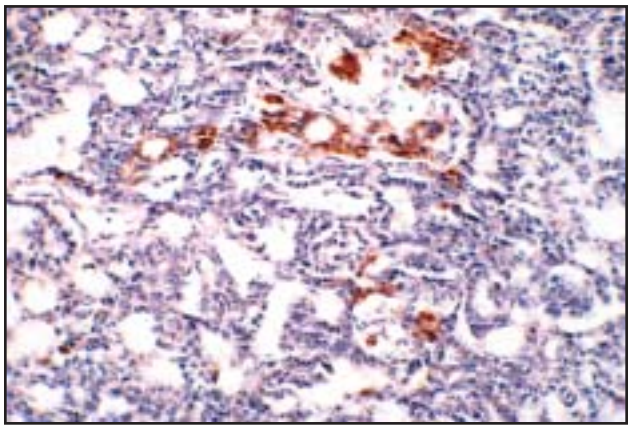

Fig 22. — Yolk sac tumor (anti-AFP, original magnification × 100).

sion may be seen (Fig 27), which in at least some cases explains the presence of metastases irrespective of the benign-appearing teratoma. The dermoid cyst (Fig 28) consists of a predominant cyst lined by keratinizing squamous epithelium with skin appendages. The cyst may contain a nubbin with glial tissue, bone, teeth, or other cell types. The typical intratubular malignant germ cells are not present. This tumor is benign and is rare in the testis compared with the ovary.[44,66]

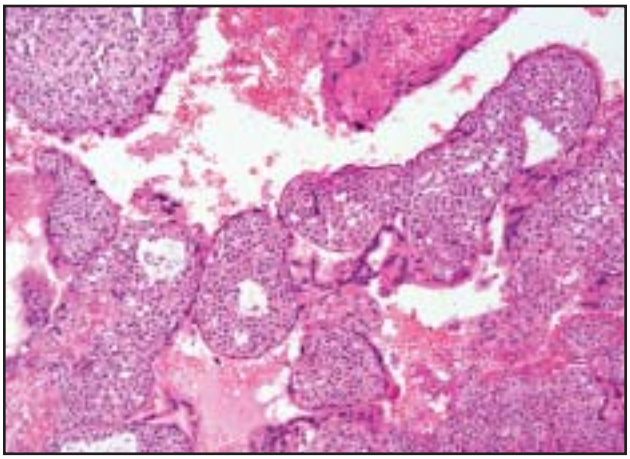

Fig 23. — Choriocarcinoma (H&E, original magnification × 80).

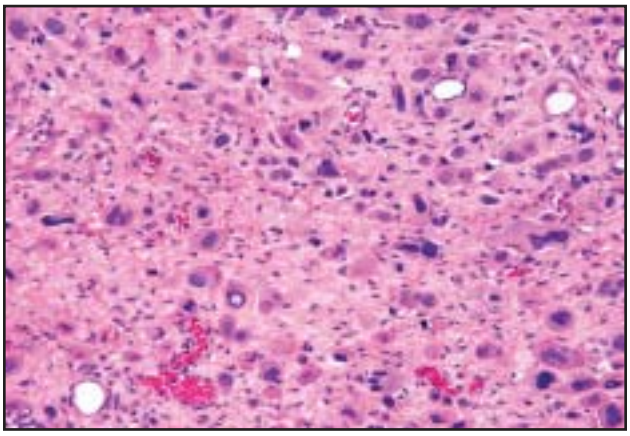

Fig 24. — Placental site trophoblastic tumor (H&E, original magnification × 160).

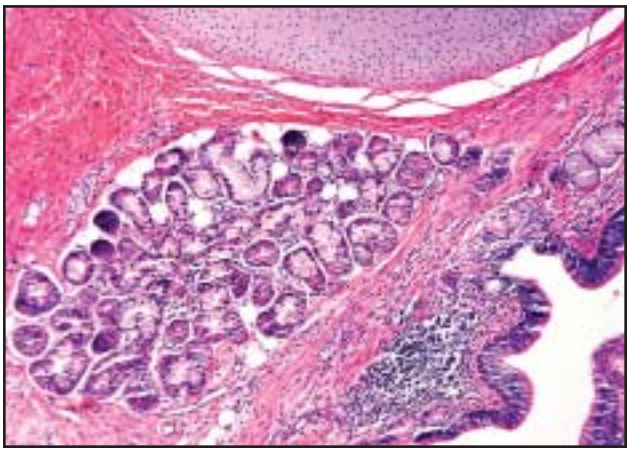

Fig 25. — Mature teratoma (H&E, original magnification × 80).

Variants of Teratoma

Monodermal teratomas are rare. They consist of a single cell type (eg, cartilaginous tissue only[67] or peripheral neuroectodermal tumor[68-71]). The nature of the epidermal cyst, lined by keratinizing epithelium only, is uncertain. Some consider it a tumor-like lesion, while others favor the interpretation of a monodermal teratoma (Fig 29A–B). The latter view is supported by the presence of intratubular malignant cells in rare examples of epidermal cyst. These are benign.

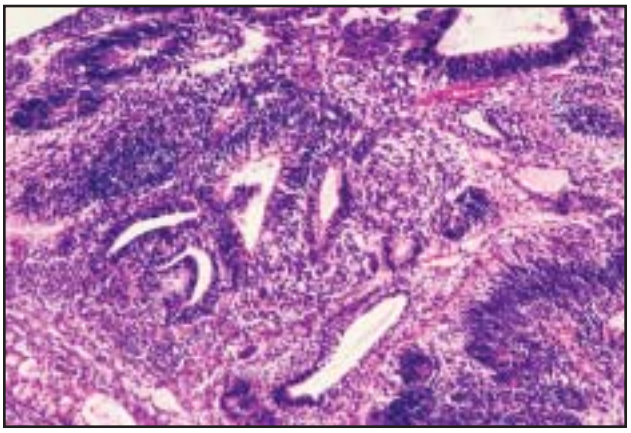

Fig 26. — Immature teratoma (H&E, original magnification × 80).

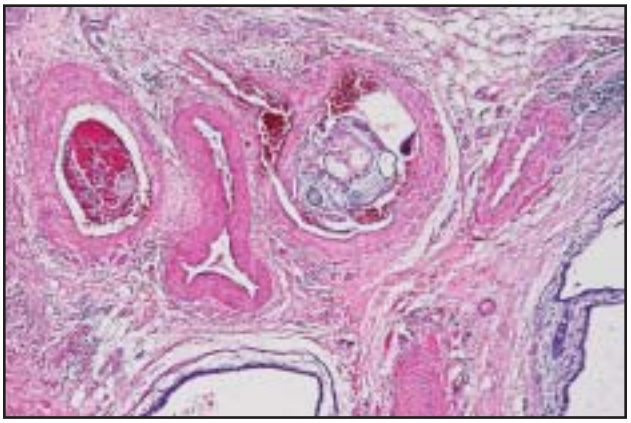

Fig 27. — Vascular invasion by teratoma and paratesticular tissue (H&E, original magnification × 32).

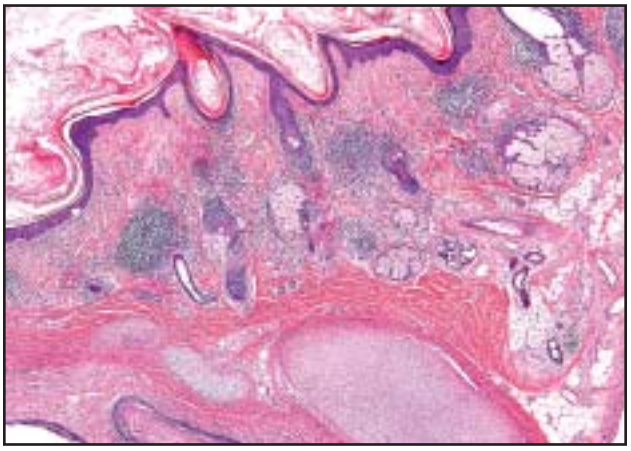

Fig 28. — Dermoid cyst (H&E, original magnification × 32).

Teratomas with somatic-type malignancies have malignant areas indistinguishable from those arising in other organ sites, such as rhabdomyosarcoma, adenocarcinoma (Fig 30), and nephroblastoma (Fig 31). The presence of these tumor types in the primary tumor should be included in the diagnosis since they may be the only component in metastasis, thus raising the possibility of a second primary tumor.[72,73] In metastases, such elements are associated with a poor prognosis.

Tumors of More Than One Histologic Type

More than half of the germ cell tumors are a mixture of two or more of the basic germ cell tumor types, with the exception of spermatocytic seminoma. The mixed types that contain seminoma occur at a later age than those without a seminomatous component. Serum elevations of hCG indicate the presence of syncytiotrophoblastic cells either singly or as part of choriocarcinoma. Elevated serum levels of AFP are usually seen in tumors containing yolk sac elements. Teratomatous glands may also cause a serum elevation of AFP. Macroscopically, these tumors have a variegated appearance, with cystic and solid areas with or without hemorrhage or necrosis (Fig 32). Histologically, 59% of mixed germ cell tumors contain seminoma, 41% contain yolk sac tumor, and 47% contain embryonal carcinoma and teratoma. Syncytiotrophoblastic cells are present in 42%. The most common mixed germ cell tumor is the combination of teratoma, embryonal carcinoma, yolk sac tumor, and syncytiotrophoblastic cells with or without seminoma (Figs 33–35).[37,52,74] Polyembryoma consists of a mixture of yolk sac tumor and embryonal carcinoma forming embryoid bodies (Fig 36). They are associated with syncytiotrophoblastic cells, and a teratoma is also usually present.

The pathology report should list all of the histologic types to enable correlation with serum tumor markers. Furthermore, the percentage of each cell type should be estimated, particularly of embryonal carcinoma.[51,52]

Burned-Out Germ Cell Tumor

In a number of patients with metastatic disease and no gross evidence of a testicular tumor, the only evidence of a primary tumor in that location is a homogeneous scar with remote hemorrhage.[44] This is commonly seen in choriocarcinomas[75,76] or in association with teratoma. This scar can have hematoxylin-staining bodies that contain calcium and DNA,[77] and it is commonly associated with intratubular malignant germ cells (Fig 37).

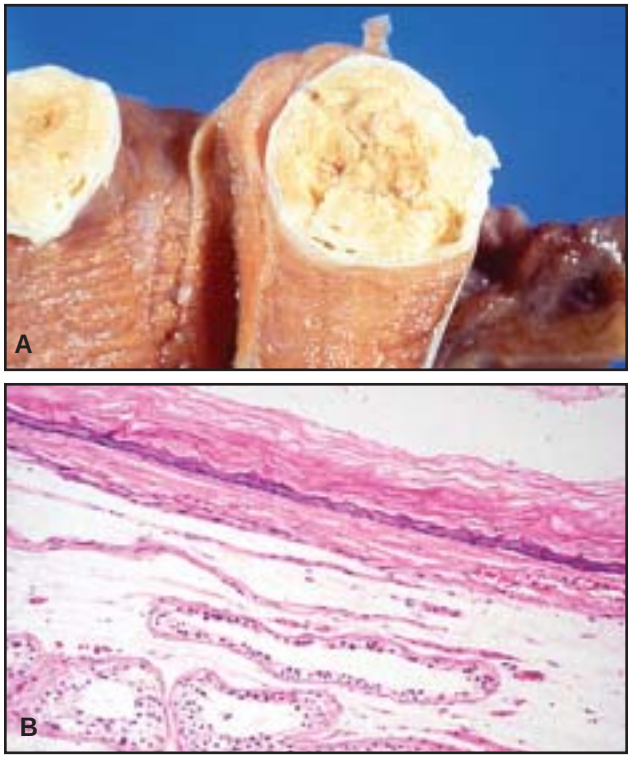

Fig 29A–B. — (A) Epidermoid cyst, note keratin lamellae with onion appearance. (B) Epidermoid cyst consisting of keratinizing squamous epithelium (H&E, original magnification × 80).

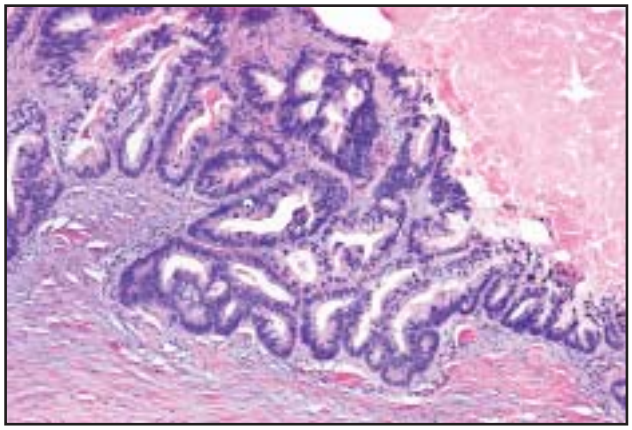

Fig 30. — Teratoma with somatic-type malignancy: adenocarcinoma (H&E, original magnification × 100).

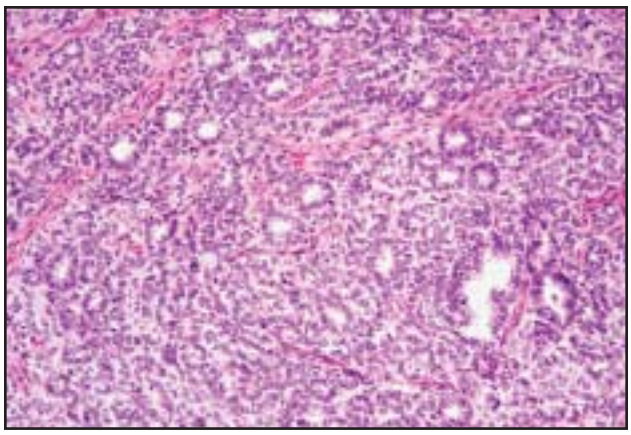

Fig 31. — Teratoma with somatic-type malignancy: nephroblastoma (H&E, original magnification × 80).

Tumor Spread, Metastases, and Treatment Effects

With the exception of spermatocytic seminoma, germ cell tumor types usually develop retroperitoneal lymph node metastases. Tumors from the right testis spread to the interaortocaval, precaval, and paraaortic region with crossover to the left-sided lymph nodes. The left testis drains into the paraaortic and preaortic regions. Interaortocaval lymph node involvement is present in higher-stage disease.[78] From there, the tumors usually grow along the thoracic duct into the left supraclavicular lymph node and the subclavian vein and then show disseminated spread. Choriocarcinomas have a tendency to metastasize via the blood stream into the lung and brain. The metastases usually reflect the histology of the primary tumor. However,

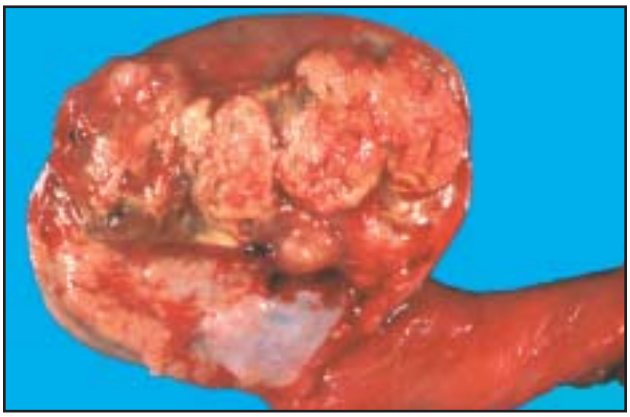

Fig 32. — Mixed germ cell tumor. Note nodular cut surface with variegated appearance (cartilage, hemorrhage, and necrosis).

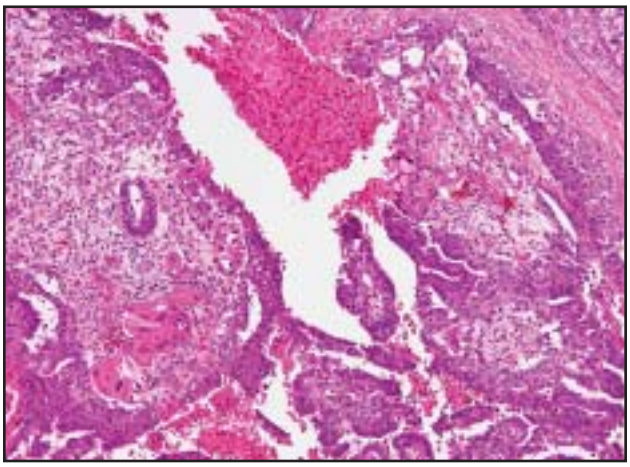

Fig 33. — Germ cell tumor consisting of teratoma, embryonal carcinoma yolk sac tumor and syncytiotrophoblasts (H&E, original magnification × 80).

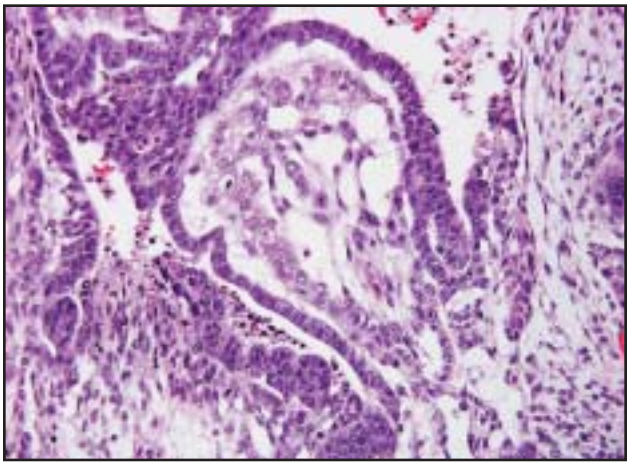

Fig 34. — Embryonal carcinoma and yolk sac tumor (H&E, original magnification × 80).

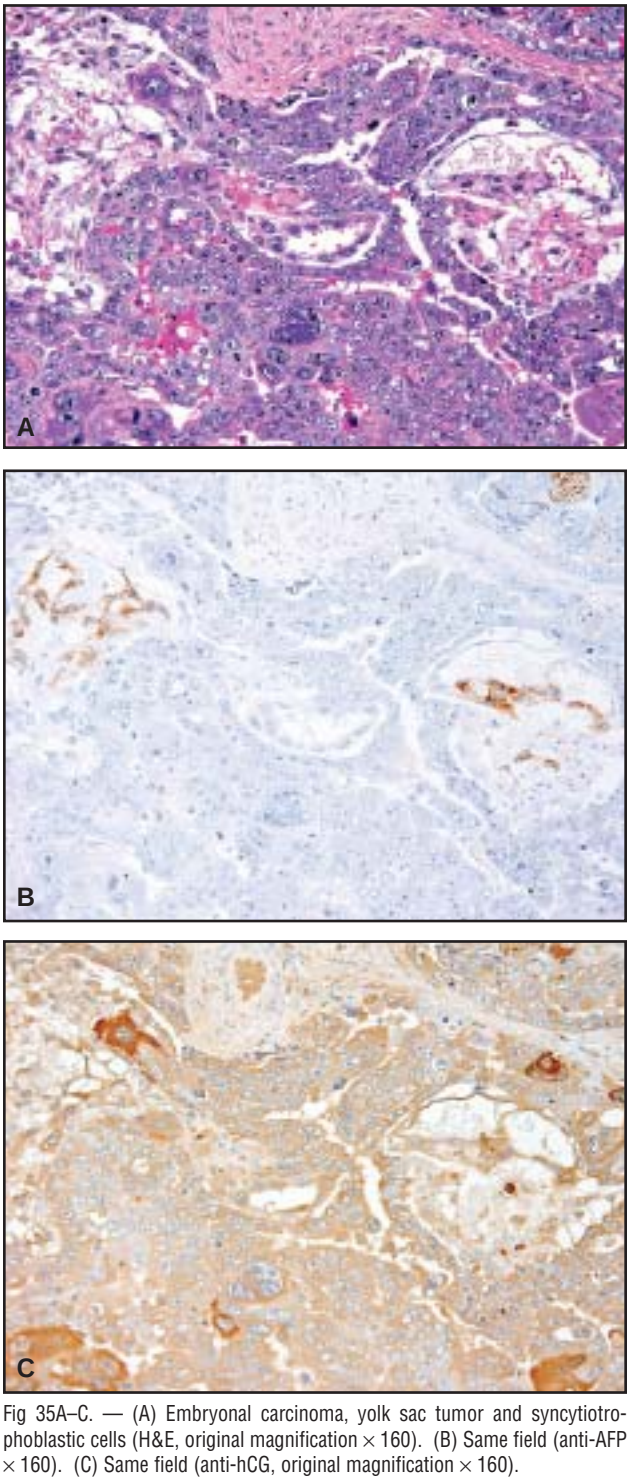

Fig 35A–C. — (A) Embryonal carcinoma, yolk sac tumor and syncytiotrophoblastic cells (H&E, original magnification × 160). (B) Same field (anti-AFP × 160). (C) Same field (anti-hCG, original magnification × 160).

different histologic cell types are found more often in metastases than are present in the primary tumors. This may be due to maturation of the primary germ cell type into another cell type, or it may be due to metastases from the intratubular germ cell neoplasia unclassified type that may mature at different sites to a specific germ cell tumor type. The most important predictors of metastases are the presence of vascular/lymphatic invasion in the primary tumor and the presence of embryonal carcinoma comprising over 40% of the primary tumor.[51,52,79-82] Chemotherapy or irradiation may result in necrosis with ghosts of tumor cells. These may be better seen in periodic acid-Schiff-stained sections. Fibrosis consists predominantly of collagen with or without calcifications and/or foreign body giant cells. Residual tumor contains teratoma in up to 40% of cases and in approximately 10% of somatic type malignancies, eg, rhabdomyosarcoma or adenocarcinoma. In rare cases, AFP may not be demonstrable in metastatic viable yolk sac tumor even though the primary tumor is positive for AFP.[83] Long-term follow-up is necessary since delayed metastases up to 32 years following treatment have been reported.[84,85]

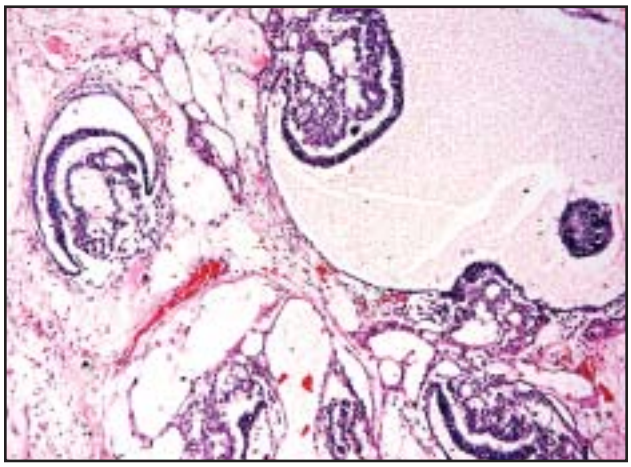

Fig 36. — Polyembryoma (H&E, original magnification × 80).

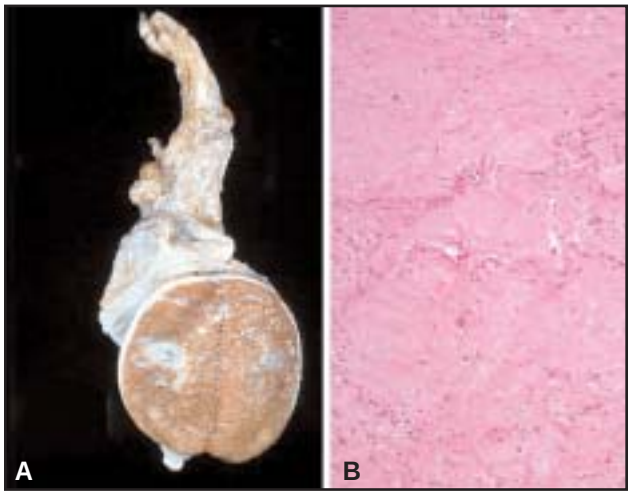

Fig 37. — (A) shows the cut surface of testis with scar; (B) shows the homogenous acellular scar (H&E × 160).

Appropriate management of testis tumors relies on accurate pathology and classification of these tumors.

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