

FINE-NEEDLE ASPIRATION BIOPSY (FNAB) DIAGNOSIS OF GERM CELL TUMORS: HISTOLOGIC AND CYTOLOGIC CORRELATIONS

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Fine-needle aspiration biopsy is a rapid and relatively inexpensive technique which has been used extensively in the diagnosis of a large variety of neoplastic and non-neoplastic lesions in many organs. The simplicity of the technique and its relatively minor trauma to the patient, along with the rapid response rate, are some of the important advantages of this technique compared to surgical biopsies.¹

Germ cell tumors represent a group of neoplasms, presumably derived from the germ cell, which usually occur in the ovary and testis, but also in several extragonadal locations, such as the retroperitoneum, mediastinum, pineal gland, sacrococcygeal area, and head and neck region.²⁻⁵ Histologic classification of these tumors is somewhat controversial, but the World Health Organization classification is now used in most countries (Tables 1 and 2). This classification recognizes several subtypes of germ cell tumors which may occur in pure form, or as mixed germ cell tumors containing elements of two or more subtypes.

Several studies have demonstrated the usefulness of FNAB in the diagnosis of germ cell tumors.⁶⁻¹⁴ Distinction of germ cell tumors from other types of neoplastic and non-neoplastic lesions, as well as distinction between the various subtypes of germ cell tumor, may have important therapeutic implications and may thus be crucial to planning proper management of the patient. When the germ cell tumors occur in the gonad, fine-needle aspiration is infrequently performed, since resection is usually indicated regardless of the underlying pathology. However, FNAB may play an extremely useful role when germ cell tumors occur in extragonadal locations or when diagnosis of a metastatic lesion is required for planning further management of the patient. Occasionally, however, a mass in the gonad may not require resection. For example, in the case of malignant lymphoma, the patient may

be treated by chemotherapy without surgical excision. In such cases, fine-needle aspiration biopsy may be used to diagnose this tumor and rule out other lesions, including germ cell tumors.

In this review, we briefly outline the histologic and corresponding cytologic features which may be useful in diagnosing and subtyping the germ cell tumors. We hope this will help those interested in the FNAB diagnosis of germ cell tumors.

Seminoma/Dysgerminoma

Seminoma and dysgerminoma are identical neoplasms occurring in the testis and ovary, respectively.²⁻⁵ The histologic appearance of seminoma/dysgerminoma is quite characteristic. The tumor cells are medium-sized and polyhedral, with round vesicular nuclei that have reticular chromatin and prominent nucleoli. The cytoplasm may vary from clear to granular. The tumor cells are arranged in cords or irregular nests separated by fibrous septa. Variable numbers of lymphoplasmacytic cells or epithelioid and giant cells, occasionally forming granulomas, may also be seen (Figure 1). Scattered syncytiotrophoblastic giant cells may be seen in some cases.

Cytologically, seminoma/dysgerminoma have a characteristic pattern consisting of cellular smears in which large numbers of tumor cells are present singly or in variably sized, loose clusters (Figure 2).⁶⁻²⁰ The cytoplasm is usually slightly granular and eosinophilic to light blue, but may also contain large "punched-out" vacuoles due to the presence of large aggregates of glycogen (Figure 3). Periodic acid-Schiff (PAS) staining of smears may be used to confirm the presence of large amounts of intracytoplasmic glycogen (Figure 4). Some of the cells have abundant glycogen, resulting in completely clear cytoplasm. The background of the smears usually contains lymphocytes, plasma cells and, occasionally, epithelioid cells with giant cells, sometimes with granuloma formation (Figure 2). In some cases, the inflammatory component may overshadow the tumor cells. Another important

diagnostic feature in smears from seminoma/dysgerminoma is the presence of a tigroid pattern, which is usually due to fragmentation of the cytoplasm of the tumor

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cells. Such a pattern is usually more pronounced in tumors which are rich in glycogen, such as seminoma/dysgerminoma, Ewing sarcoma and rhabdomyosarcoma. Occasionally, the background in seminoma/dysgerminoma may contain lymphoglandular bodies.¹⁶

Spermatocytic Seminoma

Spermatocytic seminoma only occurs in the testes and should be clearly separated from the classic seminoma.²⁻⁴ Histologically, three cell populations based on size are seen, i.e., small, intermediate and large cells, including giant cells. The cells are arranged in sheets with scattered microcysts. Fibrous septa and lymphoplasmacytic infiltrate, which are frequent in classic seminoma, are absent. Although the nuclei vary in size, they exhibit a uniformly round configuration. Some of the nuclei have a filamentous chromatin pattern resembling spermatocytes. Spermatocytic seminoma always occurs in pure form and has not been observed as one of the elements in mixed germ cell tumors. However, these neoplasms may develop a sarcomatous component in rare instances.

Fine-needle aspiration biopsy diagnosis of spermatocytic seminoma has been described in only one previously reported case.²² The smears from this tumor showed scanty cellular yield consisting of a small cellular group with some cohesiveness. These groups were composed of mononucleated or binucleated cells with gross chromatin clumping and uniform central nuclei. These cells correspond to the intermediate and large cells. In addition to these cells, small isolated and dispersed cells with finely distributed chromatin and small amounts of eosinophilic cytoplasm may also be seen. These cells correspond to the small cells seen in histologic sections. Compared to classic seminoma, the smears from spermatocytic seminoma show a clean background without any inflammation or necrosis. Tigroid pattern is also absent. Furthermore, the tumor cells in spermatocytic seminoma lack glycogen vacuoles within the cytoplasm. Mitoses are frequent in all cell types.

Embryonal Carcinoma

Embryonal carcinoma is uncommon in a pure form, but is frequently seen as one of the components in mixed germ cell tumors.²⁻⁵ Histologic appearance is characterized by a varied mixture of glands, tubules, micro-acini and papillary structures, as well as a solid sheet-like growth pattern (Figure 5). Usually there is extensive necrosis and hemorrhage. The tumor cells are moderate-sized with ill-defined cell borders, prominent nucleoli, coarse chromatin

TABLE 1. WHO classification of germ cell tumors of the ovary.

Dysgerminoma Variant	With syncytiotrophoblast cells
Yolk sac tumor (endodermal sinus tumor) Variants	Polyvesicular vitelline tumor; hepatoid; glandular

Embryonal carcinoma	
Polyembryoma	
Choriocarcinoma	
Teratomas	
Immature	
Mature	Solid; cystic (dermoid cyst); with secondary tumor formation
Monodermal	
Struma ovarii	
Variant	With thyroid tumor (specify type)
Carcinoid	
Strumal carcinoid	
Mucinous carcinoid	
Neuroectodermal tumors	
Sebaceous tumors	
Others	
Mixed germ cell tumors	

and distinct nuclear membranes. Moderate pleomorphism is usually present. There may be giant tumor cells, some of which may represent syncytiotrophoblasts.

The FNAB smears from embryonal carcinoma are usually cellular and are arranged in sheets and clusters which may show a solid, papillary or glandular pattern.⁶⁻¹⁴ The tumor cells have ill-defined cell borders, high nuclear cytoplasm ratio and light basophilic granular cytoplasm (Figure 6). The nuclei are irregular with coarse chromatin and usually contain multiple nucleoli. Some of the clusters may contain delicate branching capillaries. The background in embryonal carcinoma is usually necrotic with scattered inflammatory cells. Mucoid material as well as tigroid pattern in the background are not seen. The tumor cells in embryonal carcinoma also seem to lack the large "punched-out" cytoplasmic glycogen vacuoles, although a small amount of glycogen may be present.

Yolk Sac Tumor

Yolk sac tumor has extremely varied morphology, characterized by a multitude of histologic patterns.²⁻⁵ These include endodermal sinus, reticular, papillary, solid, glandular-alveolar, myxomatous, sarcomatoid, macrocystic, polyvesicular vitelline, hepatoid and parietal patterns. In a given tumor, any combination of these patterns may be seen, although one usually predominates. In addition, linear or globular deposits of eosinophilic basement membrane-like material may be seen in the intercellular spaces (Figure 7). These features may be

TABLE 2. WHO classification of germ cell tumors of the testis.

Seminoma	Spermatocytic seminoma
Embryonal carcinoma	Polyembryoma
Embryonal carcinoma and teratoma (teratocarcinoma)	

Teratoma	Mature; immature; with malignant transformation
Choriocarcinoma	
Yolk sac tumor	

TABLE 3. Immunocytochemical staining of germ cell tumors.

Antigen	PLAP	AFP	HCG	CK	Leu MI	Ki-I (CD-30)	LCA
Seminoma/dysgerminoma	+++	-	±*	±	-	-	-
Yolk sac tumor	++	+++	-	++	-	-	-
Embryonal carcinoma	-	±	±*	+	++	+++	-
Choriocarcinoma	-	-	+++	++	-	-	-
Teratoma	-	±**	-	++	-	-	-
Spermatocytic seminoma	-	-	-	-	-	-	-
Malignant lymphoma	-	-	-	-	-	± [†]	+++
Adenocarcinoma	-	-	-	+++	++	-	-

*Syncytiotrophoblastic cells; **intestinal component; [†]large-cell anaplastic lymphoma; PLAP=placental alkaline phosphatase; AFP=alpha-fetoprotein; HCG=human chorionic gonadotropin; CK=cytokeratin; LCA=leukocyte common antigen.

helpful in establishing the diagnosis in suspected yolk sac tumors. In many of the cases, some of the tumor cells may contain eosinophilic hyaline inclusions within the cytoplasm (Figure 8).

Fine-needle aspiration biopsy findings in yolk sac tumors have been described in several studies.^{2-5,22-27} The aspiration smears are moderately cellular, and contain tightly arranged clusters of epithelial cells with relatively abundant cytoplasm. These cells may be arranged as solid sheets, papillary or glandular structures, or as small globular structures (tumor balls) (Figure 9). No studies have been performed to correlate the various histologic patterns of yolk sac tumors with corresponding appearances in the aspiration smears. Generally, two types of cells may be encountered in yolk sac tumors.^{24,27} One cell (type A) has relatively well-defined borders and somewhat granular cytoplasm. Nuclei are round to slightly irregular and usually have well-developed nucleoli. In addition, many of these cells contain large "punched-out" clear vacuoles within the cytoplasm, corresponding to the deposits of intracytoplasmic glycogen (Figure 9). These vacuoles are essentially similar to glycogen vacuoles seen in seminoma/dysgerminoma. The second cell (type B) usually forms syncytial clusters with indistinct cell borders. The cytoplasm is full of numerous vacuoles in all parts of the cytoplasm (hypervacuolated cells) (Figure 10). The nature of these vacuoles is not known, but they are not related to

glycogen. The relative numbers of type A and type B cells vary considerably from case to case. Generally, reticular and myxomatous patterns contain large numbers of hypervacuolated cells, while papillary, endodermal sinus and solid patterns are usually dominated by type A cells. Further studies to correlate the various histologic and cytologic patterns are clearly needed. An important diagnostic feature in the FNAB smears from yolk sac tumors is the presence of eosinophilic inclusions within the cytoplasm (Figure 11). Globular or linear deposits of eosinophilic intercellular material may also be present in some cases, corresponding to the basement membrane-like material encountered in a histologic section (Figures 7 and 12).

The background in aspiration smears from yolk sac tumors is usually mucoid (Figure 9). In addition, a few inflammatory cells, especially macrophages, may be present. A tigroid pattern is usually not seen, although in one case the author has seen a focal tigroid pattern surrounding clusters of type A cell.

Choriocarcinoma

Most of the choriocarcinomas are of gestational origin. Nongestational choriocarcinomas are of germ cell origin and are usually seen as part of a mixed germ cell tumor. Pure choriocarcinoma is extremely rare in both gonadal and extragonadal locations.²⁻⁵ The histologic appearance of both types of choriocarcinoma is identical and is characterized by proliferation of malignant trophoblastic epithelium, consisting of two distinct cell populations, namely cytotrophoblasts and syncytiotrophoblasts (Figure 13). In many of the cases, large sheets and trabeculae of cytotrophoblasts are capped by a population of syncytiotrophoblastic cells. In other cases, there may be random intermixing of the two types of cells. When the syncytiotrophoblastic cells are absent or their number is relatively small, distinction from embryonal carcinoma may be difficult. Extensive hemorrhage and necrosis are frequently encountered.

FNAB diagnosis of choriocarcinoma is based on the recognition of the two cell populations which characterize this tumor, i.e., cytotrophoblasts and syncytiotrophoblasts.^{2-5,28} Cytotrophoblasts are intermediate-sized cells which usually occur in sheets and clusters of variable sizes and shapes. The nuclei are usually round, with coarse chromatin and well-developed single nucleoli. The cytoplasm may vary from clear to slightly basophilic, with a few small round vacuoles, but usually no glycogen

FIGURE 1. Photomicrograph of a dysgerminoma (hematoxylin and eosin stain, 150x).



FIGURE 3. Higher magnification photomicrograph showing loosely arranged cells in an aspiration smear from seminoma. Many of the tumor cells contain large glycogen vacuoles (Diff-Quik stain, 300x).



FIGURE 5. Photomicrograph featuring embryonal carcinoma (hematoxylin and eosin stain, 200x).

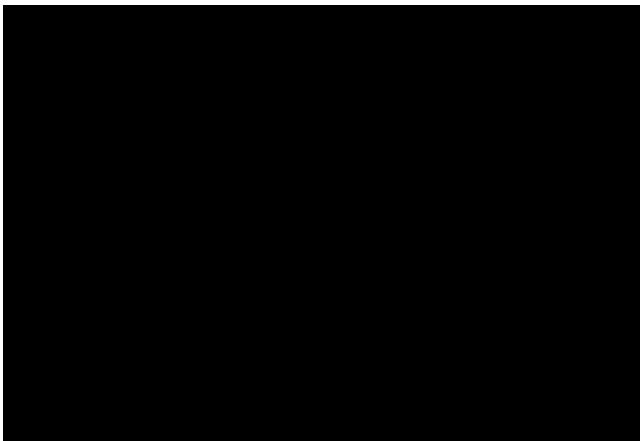


FIGURE 2. Aspiration smear from a dysgerminoma, showing large numbers of lymphocytes and tigroid background. The tumor cells are large with uniform round nuclei (Diff-Quik stain, 150x).



FIGURE 4. Aspiration smear from seminoma, showing abundant PAS-positive material (glycogen) within the cytoplasm (PAS stain, 300x).

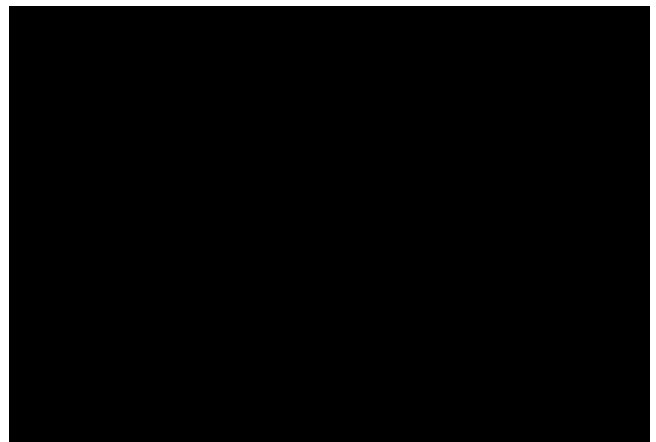


FIGURE 6. A large cluster of tumor cells from embryonal carcinoma, featuring high nuclear-cytoplasmic ratio, irregular nuclei and multiple small nucleoli (Diff-Quik stain, 250x).



FIGURE 7. Photomicrograph of a yolk sac tumor in which small deposits of eosinophilic basement membrane-like material are also noted (hematoxylin and eosin stain, 150x).

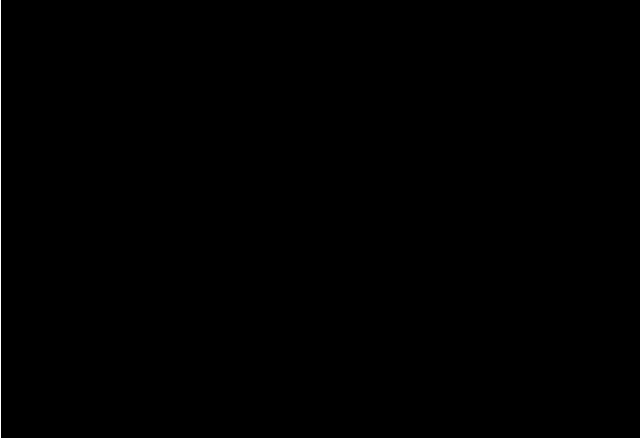


FIGURE 9. Clusters of type A cells in a smear from endodermal sinus tumor in which some of the cells have large glycogen vacuoles (Diff-Quik stain, 250x).

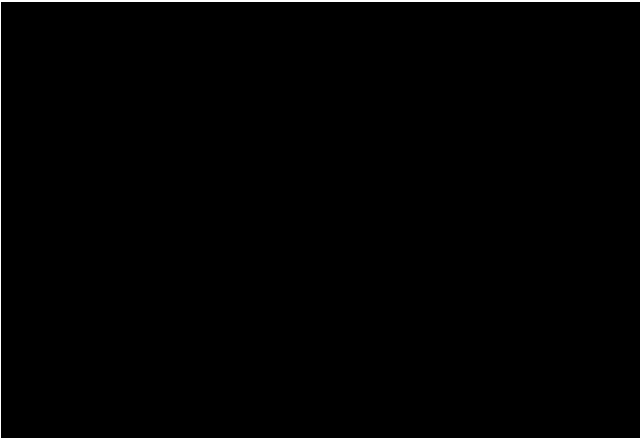


FIGURE 11. A cluster of cells from a yolk sac tumor, featuring an intracytoplasmic inclusion (Diff-Quik stain, 200x).

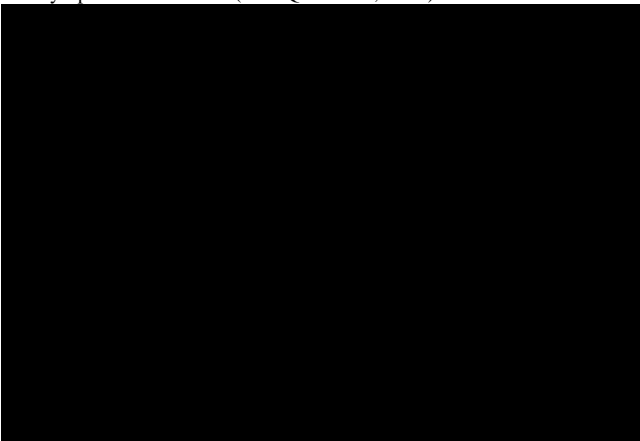


FIGURE 8. Photomicrograph showing a yolk sac carcinoma, in which some of the cells contain eosinophilic inclusion bodies within the cytoplasm (hematoxylin and eosin stain, 150x).



FIGURE 10. Another cluster of cells from a yolk sac tumor, consisting of hypervacuolated cells (Diff-Quik stain, 250x).

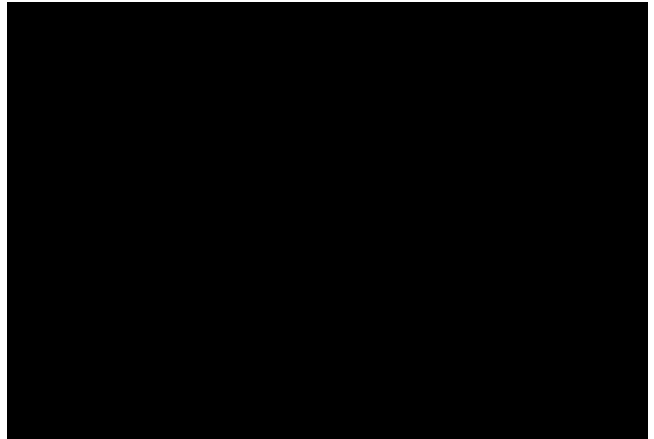


FIGURE 12. Aspiration smear from a yolk sac tumor featuring several tight clusters of tumor cells with a mucoid background and intercellular eosinophilic basement membrane-like material (Diff-Quik stain, 150x).

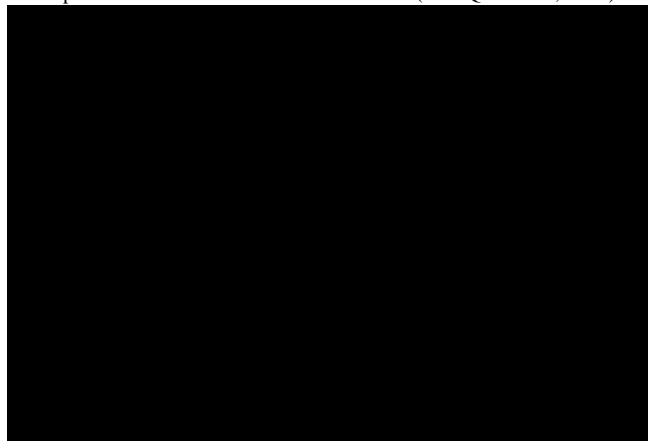


FIGURE 13. Histologic appearance of a choriocarcinoma, characterized by cytotrophoblasts and syncytiotrophoblasts (hematoxylin and eosin stain, 250x).



FIGURE 14. Aspiration smear from choriocarcinoma, featuring clusters of syncytiotrophoblasts and occasional cytotrophoblasts (Diff-Quik stain, 200x).



FIGURE 15. Photomicrograph showing an area in a mature teratoma, in which keratinized squamous epithelium and a mucin-filled cystic space lined by columnar cells is noted (hematoxylin and eosin stain, 150x).



FIGURE 16. Immature teratoma with predominant neuroectodermal tissue (hematoxylin and eosin stain, 150x).

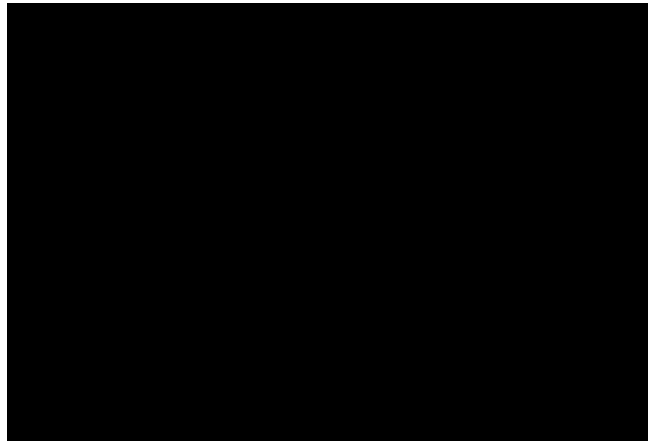


FIGURE 17. Aspiration smear from a mature teratoma, featuring ciliated columnar cells with squamous cells in a mucoid background (Diff-Quik stain, 150x).

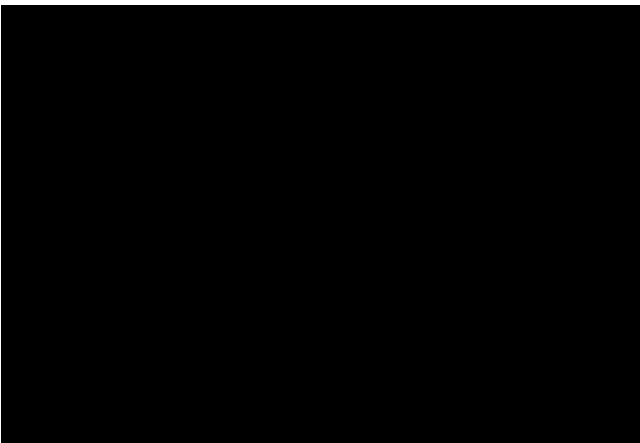


FIGURE 18. Aspiration smear from an immature teratoma with predominant neuroectodermal elements consisting of undifferentiated round cells with large numbers of intertwining cytoplasmic processes and rosette formation (Diff-Quik stain, 150x).

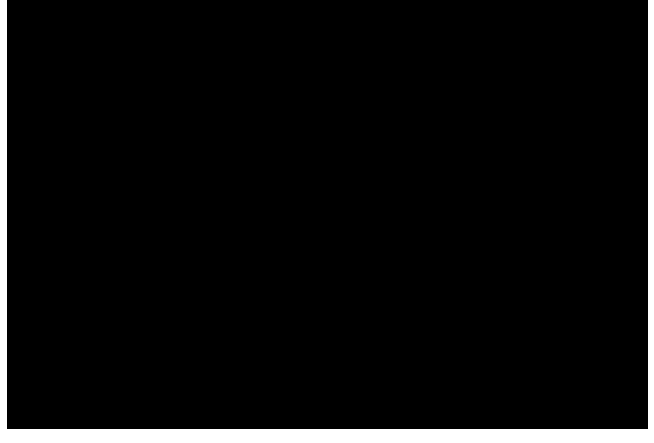


FIGURE 19. Mixed germ cell tumor consisting of embryonal carcinoma and seminoma (hematoxylin and eosin, 100x).

vacuoles. Syncytiotrophoblasts are large cells with multiple, pleomorphic, dense nuclei and abundant cytoplasm. Variable numbers of small round uniform cytoplasmic vacuoles may be present, although large glycogen vacuoles are not seen. Syncytiotrophoblasts may be present at the periphery of cytotrophoblastic clusters or may be randomly intermixed with these cells (Figure 14). In most cases, choriocarcinoma has an extensively necrotic and hemorrhagic background. Therefore, the number of diagnostic and viable cells in the smear may be small. Smears in which only cytotrophoblasts are present may be difficult to diagnose with certainty, since distinction from embryonal carcinoma may be problematic.

Teratoma

Teratoma is a germ cell tumor containing elements derived from three germinal layers, namely ectoderm, mesoderm and endoderm.²⁻⁵ The histologic appearance of teratomas may differ significantly, depending upon the types of tissue present and their degree of maturity. Most commonly represented tissues include skin and appendages, gastrointestinal and respiratory epithelium with muscular walls, squamous islands, transitional epithelium, neuroglia and retinal pigmented tissue, among others (Figure 15). Mature teratomatous elements resemble the normal adult tissues, while the immature components mimic embryonal or fetal tissues. In many tumors, primitive neuroectodermal elements may predominate. These include sheets of immature epithelium, neuroepithelial tubules and rosettes, neuroblastic elements, immature glial and primitive retina with melanin pigmentation (Figure 16).

Fine-needle aspiration biopsy findings in cases of teratoma are quite variable, depending upon the various

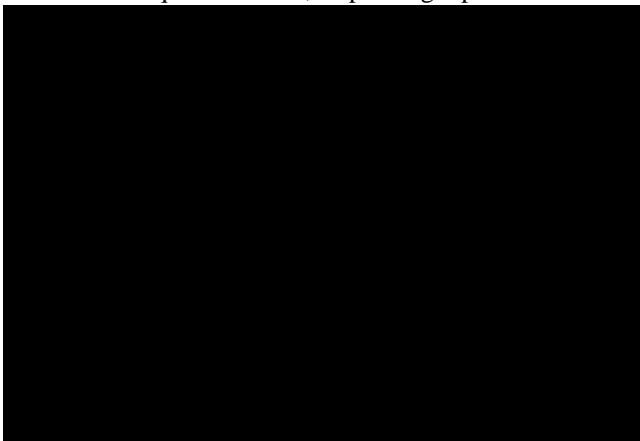


FIGURE 20. A smear from a mixed germ cell tumor containing seminoma cells (left) and clusters of embryonal carcinoma cells (right). Several inflammatory cells are present in the background (Diff-Quik stain, 100x).

types of tissues present and degree of their maturity.^{2-5,29}

Since most of the mature teratomas have elements of skin and adnexa, as well as intestinal and respiratory epithelium, the presence of keratinized squamous cells mixed with ciliated and goblet cells may be seen in the aspiration smears (Figures 15 and 17). The background is frequently mucoid. In immature teratoma, large numbers of blastemal cells representing a variety of fetal and embryonal tissues may be seen. Primitive neuroectodermal elements may present as large numbers of loosely arranged, small undifferentiated cells with large numbers of delicate intertwining cytoplasmic processes with attempted rosette formation (Figure 18).

Mixed Germ Cell Tumors

Mixed germ cell tumors are more frequent in the testes than ovaries and may also be encountered in extragonadal locations.²⁻⁵ The usual combinations include teratoma with embryonal carcinoma or seminoma with yolk sac carcinoma, although any conceivable combinations of various elements may be seen.¹⁹ In most cases, it is not difficult to recognize the various components, although in some cases, extensive necrosis and hemorrhage in areas of choriocarcinoma and embryonal carcinoma may hinder precise diagnoses. Furthermore, a thorough sampling of a germ cell tumor may be necessary for identification of relatively minor components.

Fine-needle aspiration of most germ cell tumors may be made, provided this possibility is kept in mind at the time of the biopsy and a thorough sampling of the various parts of the tumor is performed. In cases where one component is dominant and the others are relatively minor, FNAB may miss these components. Generally, diagnosis is based on recognition of two or more elements of germ cell tumors (Figure 20).

Rare Subtypes

FNAB diagnosis of some of the rare germ cell tumors, such as monodermal teratomas and polyembryomas, have not yet been described. It is expected that as the experience with FNAB diagnosis of germ cell tumors expands, these tumors will also be diagnosed successfully.

Immunocytochemistry

Immunocytochemistry may be extremely helpful in confirming the FNAB diagnosis of germ cell tumors. These studies may be performed on the aspiration smears and cytospin preparations as cell blocks obtained from the aspirated material. A number of antibodies may be used for differentiating germ cell tumors from other non-germ cell tumors, such as malignant lymphoma and adenocarcinoma, and making precise distinction among the various subtypes of germ cell tumors.^{13,16} These antibodies include leucocyte

common antigen (LCA), cytokeratin (CK), placental alkaline phosphatase (PLAP), alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), Leu MI and Ki-I (CD-30). The various patterns of staining in the different subtypes⁵ of germ cell tumors are given in Table 3. These staining patterns should be interpreted with caution, since some overlap exists between the subtypes of germ cell tumors regarding expression of various markers. Distinction of germ cell tumors from malignant lymphoma may be helped by LCA, since malignant lymphomas are usually positive, while germ cell tumors stain negatively. Distinction of embryonal carcinoma from adenocarcinoma may be difficult, since the immunohistochemical staining pattern is similar. Positive reaction for PLAP and Ki-I antigen, however, may serve to distinguish the two tumors.

In summary, there is a close correlation between the histologic and cytologic appearances of germ cell tumors. The diagnosis may be helped by immunohistochemical studies performed on the aspirated material. Extensive necrosis and hemorrhage in some cases may hamper diagnosis. Many published studies on FNAB diagnosis of germ cell tumors have demonstrated the effectiveness of this technique as a rapid and reliable procedure for the diagnosis of germ cell tumors.

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