Primary neuroectodermal tumors of the ovary are rare monophasic teratomas composed exclusively or almost exclusively of neuroectodermal tissue. Approximately 60 neuroectodermal tumors of the ovary have been reported in the literature. These tumors were classified as ependymoma, astrocytoma, glioblastoma multiforme, ependymoblastoma or as primitive neuroepithelial tumors such as medulloblastoma, medulloepithelioma and neuroblastoma. Most tumors were diagnosed in the third and fourth decades of life, but occasionally they were first discovered in children, adolescents or older women. Microscopically, they are identical to equivalent neuroectodermal tumors of the central nervous system. The review of the literature shows that most patients with clinical stage I and II were treated surgically, whereas those with stage III or IV tumors received additional radiation or chemotherapy, or both. The clinical stage at the time of diagnosis is the most important prognostic parameter of these tumors.

**Key words:** Neuroectodermal, Ovarian tumors, Teratoma

**Introduction**

Benign teratomas account for over 90% of all ovarian germ cell tumors (Nogales et al., 2003). Also known as dermoid cysts, these teratomas are cystic and composed predominantly of skin and dermal appendages. Solid benign teratomas composed of numerous well differentiated somatic tissues are less common. The least common neoplasms in this histogenetical group are malignant germ cell tumors, such as embryonal carcinoma, yolk sac carcinoma, dysgerminoma and malignant mixed germ cell tumors corresponding to testicular seminoma or malignant nonseminomatous germ cell tumors.

Teratomas that contain immature neural tissues are called immature and are considered potentially malignant. Immature teratomas that contain large amounts of immature neural tissue and those that have ruptured or disseminated thorough the abdominal cavity are treated as malignant. Tumors composed exclusively of immature neuroectodermal tissue have been separated from other teratomas and are treated as a distinct group of neoplasms (Kleinmann et al., 1993). These monophasic teratomas, collectively called neuroectodermal tumors of the ovary, are quite rare; our review of the literature disclosed only 60 primary ovarian tumors of this type (Elesha, 1983; Reid et al., 1983; Auerbach et al., 1988; Bjersing et al., 1989; Carlsson et al., 1989; Carr et al., 1992; Guerrieri and Jarlsfelt, 1993; Kanbour-Shakir et al., 1993; Kleinmann et al., 1993; Yalcin et al., 1996; Hirahara et al., 1997; Lawlor et al., 1997; Okazaki, 1997; Kawachi et al., 1998; den Boon et al., 1999; Somjee et al., 1999; Yadav et al., 1999; Garcia-Barriola et al., 2000; Komuro et al., 2001; Mikami et al., 2001; Trabelsi et al., 2002; Skopelitou et al., 2002; Rangan et al., 2003; Chow et al., 2004; Demirtas et al., 2004; Takano et al., 2005; Erdogan et al., 2005; Fan et al., 2006).

Prompted by a recent diagnostic problem, posed by a primary ovarian ependymoma that has metastasized to the liver (Fan et al., 2006), we have reviewed the literature about primary ovarian neuroectodermal tumors. Here we will briefly review the pathology and clinical aspects of these unusual tumors, describe their unique features to indicate that they may be misdiagnosed by pathologists unaware of their existence.

**Histogenesis**

It has been generally accepted that teratomas of the ovary originate from parthenogenetically activated oocytes. Activated oocytes give rise to embryonic cells, which form early embryonic structures including the three germ layers: ectoderm, mesoderm and endoderm. In mature teratomas ectoderm differentiates, among others, into somatic tissues such as the epidermis and...
various cells of the central nervous system. The development of these tissues in benign teratomas occurs presumably the same way as in a developing embryo or fetus, and includes many intermediate stages of development. Thus, the central nervous system probably develops through several distinct stages, such as the formation of the neural plate and neural tube. In most teratomas, all neural tube cells differentiate into glial and neuronal cells, but in some immature teratomas the neural tubes may persist. The immature precursors of neural and glial cells in these neural tubes may proliferate and even implant on the peritoneum and thus behave as malignant cells.

In some germ cell tumors the cells forming the neural tube do not differentiate in the embryo. Instead, they may persist and continue forming neural tube like rosettes and medullary structures. These tumors will ultimately be composed of neural tube-like tissues and are then classified as medulloblastomas or medulloepitheliomas. If the immature neural cells continue developing along the neural cell lines and also acquire some malignant properties, the tumor composed of such cells will be a neuroblastoma. Monophasic teratomas composed of cells that have become malignant astrocytes will be classified as glioblastoma multiforme or astrocytoma, ependymoblastoma or ependymoma. Since all these monophasic teratomas stem from putative precursors in the embryonic neuroectoderm, all of them are collectively called neuroectodermal tumors of the ovary.

Classification

The neuroectodermal tumors of the ovary are microscopically identical to their neoplastic counterparts in the nervous system. For clinical-pathologic purposes they can be divided into three groups: (a) well differentiated, (b) anaplastic and (c) poorly differentiated (primitive) tumors (Kleinmann et al., 1993).

The group of well differentiated tumors comprises ependymomas and astrocytomas. Ependymomas are apparently more common than astrocytomas, and are the most common neuroectodermal tumors of the ovary (Elesha, 1983; Auerbach et al., 1988; Carlsson et al., 1989; Carr et al., 1992; Guerrieri et al., 1993; Kleinmann et al., 1993; Hirahara et al., 1997; Okazaki, 1997; Garcia-Barriola et al., 2000; Komuro et al., 2001; Mikami et al., 2001; Skopelitou et al., 2002; Erdogan et al., 2005; Takano et al., 2005; Fan et al., 2006).

Anaplastic neuroectodermal tumors are relatively rare. Most of these tumors were classified as glioblastoma multiforme (Bjersing et al., 1989; Kleinmann et al., 1993; Yadav et al., 1999; Trabelsi et al., 2002; den Boon et al., 1999).

Poorly differentiated (primitive) neuroectodermal tumors form a group that includes medulloblastoma, medulloepithelioma, neuroblastoma and ependymoblastoma (Reid et al., 1983; Kanbour-Shakir et al., 1993; Kleinmann et al., 1993; Yalcin et al., 1996; Lawlor et al., 1997; Kawauchi et al., 1998; Somjee et al., 1999; Rangan et al., 2003; Chow et al., 2004; Demirtas et al., 2004). Tumors composed of small cells that show only rudimentary signs of differentiation are called primitive neuroectodermal tumors.

Epidemiology

Most women diagnosed with neuroectodermal tumors of the ovary are in their third or fourth decade of life. Occasionally these tumors may be diagnosed in younger or older women and there are reports of neuroectodermal tumors in young children, adolescents, as well as older women (Carlsson et al., 1989; Guerrieri and Jarlsfelt, 1993; Kleinmann et al., 1993; Hirahara et al., 1997; Lawlor et al., 1997; Yadav et al., 1999; Chow et al., 2004; Erdogan et al., 2005). In the largest published series based on the material from the Massachusetts General Hospital, which also included the consultation materials of Drs. R.E. Scully and R.H. Young, the age range of the patients was 6 to 69 years (average 23 years) (Kleinmann et al., 1993). Anaplastic and primitive tumors tend to occur in younger patients than well differentiated tumors.

Clinical features

Most of the patients presented with symptoms of abdominal and pelvic pain accompanied by abdominal fullness or obvious swelling. Other presenting symptoms were weight loss and deepening of the voice with hirsutism (Kleinmann et al., 1993; Takano et al., 2005). There is also one report of a pregnant woman with bilateral ovarian ependymomas, which were diagnosed at the end of the pregnancy (Carr et al., 1992). This paper is the only record of a bilateral neuroectodermal ovarian tumor in the literature; all other reported tumors were unilateral.

Gross pathology

Most tumors are large and the average size of tumors is 10-14 cm (Kleinmann et al., 1993; Takano et al., 2005). Grossly, most neuroectodermal ovarian tumors are solid but may be partially cystic. Cysts are lined by gray-tan tissue and may contain papillary structures protruding into the lumen. The solid parts of the tumor are composed of grayish white soft tissue. Areas of necrosis or hemorrhage may be prominent, especially in large tumors. The external surface is mostly smooth and glistening. Tumors with external nodules and surface papillary components have also been reported (Kleinmann et al., 1993; Hirahara et al., 1997; Erdogan et al., 2005; Takano et al., 2005).

Histopathology

Morphologically, neuroectodermal tumors of the ovary are identical to their counterparts in the central nervous system. For clinical-pathologic purposes they can be divided into three groups: (a) well differentiated, (b) anaplastic and (c) poorly differentiated (primitive) tumors (Kleinmann et al., 1993).
nervous system. Tumor cells show either glial or neural differentiation, or correspond to developmentally unclassifiable nervous system precursors. Histologically, neuroectodermal tumors of the ovary are classified as ependymoma, astrocytoma, glioblastoma multiforme, medulloblastoma, medulloepithelioma, ependymoblastoma, neuroblastoma and primitive neuroectodermal tumor. Different variants have been described in some of these tumors, especially ependymoma, but given the small number of reported cases the classification that is used for their counterparts in the central nervous system is probably not applicable to neuroectodermal ovarian tumors.

All reported ependymomas, except one, occurred as pure tumors. That case was classified as ependymoma with an astrocytoma component (Kleinmann et al., 1993). Like their central nervous system equivalents, ovarian ependymomas can be further classified as cellular, papillary or myxopapillary, but the patterns of growth are often intermixed one with another (Fig. 1). Tumors are composed of small cells with hypochromatic, round-to-oval nuclei, and scanty cytoplasm. Nuclei show remarkable uniformity and mitotic figures are not numerous. Tumor cells are arranged in lobules separated by fibrovascular septa or form patternless sheets. Perivascular pseudorosettes formed by tumor cells radially surrounding blood vessels can be observed as well as ependymal rosettes composed of tumor cells surrounding a lumen. Psammoma bodies can be seen (Kleinmann et al., 1993; Erdogan et al., 2005; Takano et al., 2005). Some tumors are more cellular, contain more mitoses and show signs of nuclear anaplasia. Atypical mitotic figures in tumor cells are also reported (Erdogan et al., 2005; Takano et al., 2005). These tumors are appropriately classified as anaplastic ependymoma.

Astrocytomas are composed of cells resembling adult or fetal astrocytes. The tumors may also have the features of pilocytic or gemistocytic astrocytomas, and in some instances be admixed to typical ependymoma (Elesha, 1983; Kleinmann et al., 1993; Skopeliotou et al., 2002).

Fig. 1. Ependymoma. This cellular, grade II ependymoma is composed of cells forming nests, cords and indistinct canals. If a tumor of this type is found in an ovary the pathologist unaware of ovarian ependymomas might have problems with the diagnosis. However, as it was in the present case, other parts of the tumor contained papillae and cells arranged into perivascular pseudorosettes. The immunohistochemistry with the antibodies to GFAP was useful for formulating the final diagnosis.

(hematoxylin-eosin, x 400)
Glioblastomas are composed of neoplastic astrocytes arranged in sheets or lobules. They contain varying amounts of cytoplasm and may form eosinophilic fibrillary processes. The nuclei are round-to-oval, with some having irregular contours; nucleoli are occasionally prominent. Areas of necrosis are prominent, and sometimes surrounded by palisading tumor cells. Mitotic figures, as well as abnormal mitotic figures are prominent. Multinucleate giant cells are often present (Kleinmann et al., 1993).

Medulloepithelioma, medulloblastoma, ependymoblastoma, neuroblastoma and primitive neuroectodermal tumors are closely related tumors, which are all composed of primitive neuroblastic or primitive, developmentally uncommitted precursors, of neural and glial cells. Medulloblastomas have a most distinctive appearance and are characterized by papillary, tubular or trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube. Medulloepitheliomas are characterized by elongated glands and canals composed of cytologically malignant, mitotically active epithelium with numerous mitoses. Neuroblastomas are usually highly cellular tumors arranged in lobules with varying quantities of connective tissue. Other features of neuroblastomas are fibrillary neuropil, Homer Wright rosettes, palisading cells and scattered ganglion cells (Fig. 2). Ependymoblastomas are highly cellular tumors containing true rosettes and canals lined by multiple layers of markedly atypical, mitotically active cells (Burger et al., 2002). Primitive neuroectodermal tumors are highly cellular and composed of small cells with hyperchromatic, round to oval nuclei and scanty cytoplasm (Fig. 3). These cells are arranged into lobules separated by fibrovascular septa, but also may form patternless sheets. Varying amounts of finely fibrillar cell processes are present in the tumor. Areas of necrosis can be prominent (Kleinmann et al., 1993).

Ancillary studies

Immunohistochemistry

Ependymomas, astrocytomas and glioblastomas of the ovary react with antibodies to glial fibrillary acidic protein (GFAP). Ependymomas also show positivity for vimentin (Guerrieri et al., 1993; Erdogan et al., 2005; Takano et al., 2005). S-100 (Guerrieri et al., 1993;
Hirahara et al., 1997; Erdogan et al., 2005; Takano et al., 2005), epithelial membrane antigen (EMA) (Guerrieri et al., 1993; Hirahara et al., 1997; Erdogan et al., 2005; Takano et al., 2005), neuron-specific enolase (NSE) (Guerrieri et al., 1993; Hirahara et al., 1997; Erdogan et al., 2005; Takano et al., 2005), CEA (Erdogan et al., 2005) and cytokeratin (Guerrieri et al., 1993; Hirahara et al., 1997).

Primitive neuroectodermal tumors, medulloblastoma, and neuroblastoma show variable reactivity with antibodies to CD99, NSE and vimentin. Most cells are negative for, but scattered cells showing neural or glial differentiation will be positive for neurofilaments and synaptophysin, or GFAP and S-100. No cells react with antibodies for cytokeratin, desmin, chromogranin or inhibin (Nogales et al., 2003).

**Molecular markers**

Two papers reported chromosomal abnormalities in primitive neuroectodermal tumors of the ovary. In the first paper the authors reported the results of comparative genomic hybridization that revealed multiple chromosomal abnormalities including losses of chromosomes in 1p, 1q, 4q, 6p, 6q, 7q, 8q, 13q and 19q, as well as gains of chromosomes 1q, 2p, 7p, 9q, 18q and Xq. Loses of 13q14.1-q14.2, 1p31, and 4q34-q35 indicated that Rb gene, ARHI, and FAT were deleted. Gains of 2p24.1, 1q23 and 7p12.3-p12.1 demonstrated that N-myc oncogene, FASL GITL, and EGFR were amplified. RT-PCR analysis showed that N-myc and EGFR were overexpressed, while Rb and ARHI were underexpressed (Chow et al., 2004).

In the second paper, the authors reported a case of a primitive neuroectodermal tumor that possessed balanced chromosomal translocation t(11;22)(q24;q12), that is highly specific for tumors of the PNET/Ewing’s sarcoma family. EWS/FLI-1 chimeric mRNA that originated from the characteristic chromosomal translocation was detected by reverse transcription-polymerase chain reaction (Kawauchi et al., 1998).

**Differential diagnosis**

Ovarian ependymomas may contain large gland-like spaces, which superficially resemble neoplastic glands in endometrioid adenocarcinomas. Papillary ependymomas
may be confused with serous ovarian carcinomas. Both tumors may show complex papillary pattern of growth and contain calcifications or psammoma bodies. Sometimes, ependymal rosettes may resemble Call-Exner bodies of granulosa cell tumors, but in general the ependymal cells have long, fibrillary, cytoplasmic processes and lack the characteristic nuclear grooves of granulosa cells. Sertoli-Leydig cell tumors may be in the differential diagnosis of ependymomas when the ribbons of cells or tubules in an ependymoma mimic the sex cords or tubules of a typical or retiform variant of the Sertoli-Leydig cell tumor. Gland-like spaces lined by cells with fibrillary cytoplasmic processes, perivascular pseudorosettes and positivity for GFAP confirm the diagnosis of ovarian ependymoma (Kleinmann et al., 1993; Garcia-Barriola et al., 2000; Komuro et al., 2001).

Immature teratomas can closely resemble primitive and anaplastic neuroectodermal tumors because they can contain immature neuroectodermal cells. Immature teratomas show greater diversity of neuroepithelial differentiation as well as a more extensive and varied admixture of endodermal, mesodermal and other ectodermal tissues.

Various malignant "small blue-cell tumors" must also be distinguished from primitive neuroectodermal tumors and neuroblastosomas. This group of tumors includes small cell carcinomas (primary and metastatic), malignant lymphoma and leukemia, metastatic melanoma, metastatic round cell sarcomas, and the intra-abdominal desmoplastic small round cell tumor. Immunohistochemistry may be useful in such cases.

**Treatment and prognosis**

Most patients with clinical stage I and II of the disease operation as the only treatment, while most patients with clinical stages III and IV were treated with operation and subsequent radiation or chemotherapy, or combination of both. Clinical stage seems to be the most important prognostic parameter of survival and patients with clinical stages I and II, have less recurrences of tumor and overall longer survival. Therefore, if the tumor is limited to one ovary and the patient wants to preserve fertility, simple oophorectomy or conservative treatment with chemotherapy is probably sufficient treatment (Kleinmann et al., 1993; den Boon et al., 1999; Demitras et al., 2004). Ovarian ependymomas sometimes express estrogen and progestin receptors and this finding can suggest that hormonal responsiveness of this tumor can be used as a treatment modality (Auerbach et al., 1988; Carr et al., 1992). Mega-dose chemotherapy followed by peripheral progenitor cell rescue was reported in the literature as the treatment modality for metastatic primitive neuroectodermal ovarian tumor (Lawlor et al., 1997).

**References**


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Neuroectodermal ovarian tumors


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