EDITORIAL

It is my great pleasure to present the new issue of RAD, the first issue which is, in accordance with the new publishing policy of the journal, published entirely in English. It is also my great pleasure to confirm that we have kept most of our promises given when we formed the new Editorial Board and in the last year's issue (RAD, 30:7, 2006). So, we are being published in English, have become regular, are indexed in Biomedicina Croatica, are available on-line (http://hrcak.srce.hr), and will soon be available in other databases as well (like EBSCO Publishing's databases).

This issue of RAD, as we have already announced, introduces papers from the Fourth Scientific Meeting on Brain Disorders: "Scientific Basis of Diagnosis and Treatment of Vertigo" that was held on March 16th 2006 in Zagreb, preceded by the invited review for which we thank our scientists working in the USA. We primarily thank Prof. Ivan Damjanov, MD, PhD, a corresponding member of the Croatian Academy of Sciences and Arts, a worldwide known pathologist, as well as a well known patriot.

For the symposium papers we thank our guest editor Prof. Vida Demarin, MD, PhD, an associate member of the Department of Medical Sciences and a member of the RAD Editorial Board, for her great effort.

For the next issue of our journal we announce papers from the symposium "55 YEARS FROM ORGANIZING BEGINNING OF ALLERGOLOGY IN CROATIA: FUTURE WE BUILT ON THE PAST" which will be held in October 2007.

On behalf of the Editorial Board I guarantee that we will continue in our effort to introduce RAD to the most significant international databases, a process in which we expect a continued support of the members of the Department of Medical Sciences, as well as the entire biomedicine community.

Marko Pećina

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Review
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OVARIAN NEUROECTODERMAL TUMORS

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Summary

In this paper we have reviewed the publications dealing with primary neuroectodermal tumors of the ovary.These rare monophasic teratomas are composed exclusively or almost exclusively of neuroectodemal tissue and are thus an important paradigm of a type of malignancy that develops from ovarian germ cells. Approximately 60 neuroectodermal tumors of the ovary have been reported in the literature. Histologically, the tumors were classified as gliomas, such as ependymoma, ependymoblastoma, astrocytoma, glioblastoma multiforme, or as primitive neuroepithelial tumors such as medulloblastoma, medulloepithelioma, and neuroblastoma. Microscopically, they are identical to equivalent neuroectodermal tumors of the central nervous system. Most tumors were diagnosed in the third and fourth decades of life. Neuroectodermal tumors are rarely diagnosed in other age groups, although there are published reports of such tumors in children, adolescents or older women. The review of the litarature 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.Patients whose tumors were recognized early in the course of the neoplastic disease and treated appropriately had a good prognosis, but those with tumors in advanced stages advanced tumors had poor prognosis.

Key words: Ovary; Neuroectodermal tumor; Germ cell tumor

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INTRODUCTION

Teratomas of the ovary belong to the germ cell tumor and are thought to originate from activated germ cells, which have become activated in a process equivalent to parthenogenetic activation of germ cells in some animal species[1]. Benign teratomas account for over 90% of all ovarian germ cell tumors [2]. 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 corresoponding 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 through 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 [3]. These monophasic teratomas, collectively called neuroectodermal tumors of the ovary, are quite rare; our review of the literature disclosed approximately 60 primary ovarian tumors of this type [3-39] .

During the last ten years we have encountered two neuroectodermal ovarian tumors: aprimitive neuroectodermal tumor in a 25 year-old woman and an ependymoma of the ovary in a 50 year old woman. We became interested in this form of tumors and thus decided to review the publications dealing with this problem.In this paper we have tabulated the published cases of ovarian neuroectodermal tumor and have reviewed the relevant data from the literature that are useful for the diagnosis of these tumors.

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 embyonic 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 the same way as they differentiate in the embyo. 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 aor 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 ependymomoma. 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 [2].

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 [3-9].

Anaplastic neuroectodermal tumor are relatively rare .Most of these tumors were classified as glioblastoma multiforme [18,19].

Poorly differented (primitive) neuroectodermal form a group that includes medulloblastoma, medulloepithelioma, neuroblastoma and ependymoblastoma[3]. Tumors composed of small cells that show only rudimentary signs of differentiation are called primitive neuroectodermal tumors.

REVIEW OF PUBLISHED CASES

Our review of the literture on PubMed revealed that thereare approximately 60 published ovarian neuroectodermal tumor.These cases have been tabulated to present all the relevant data and are presented in three tables: Table 1 dealing with well differentiated neuroectodermal tumors, Table 2 dealing with poorly differentiated (primitive

neuroectodermal tumors, and Table 3 dealing with anaplastic neuroectodermal tumors..

Table 1 - Well differentiated neuroectodermal ovarian tumors reported in the literature

Cases of well differentiated neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Therapy	Reccurence +/–	Outcome (y)	Diagnosis	Source,y
25	IA	OP	–	NED (5)	EPEND	Kleinmann et al.,1993
16	IA	OP	–	NA	EPEND	Kleinmann et al.,1993
49	IA	OP	–	NED (4)	EPEND+ASTRO	Kleinmann et al.,1993
36	IIA	OP	–	NED (3)	EPEND	Kleinmann et al.,1993
35	III	OP+CHEM	+	AWD (5)	EPEND	Kleinmann et al.,1993
30	III	OP+CHEM+RAD	+	DOD (5)	EPEND	Kleinmann et al.,1993
39	III	OP+CHEM	+	AWD (5)	EPEND	Auerbach et al., 1988
16	I	OP	+	NED (51)	EPEND	Carlsson et al. 1989
25	IV	OP+CHEM+RAD	–	NED (1)	EPEND	Carr et al., 1992
68	IA	OP	–	NED (1)	EPEND	Guerrieri et al., 1993
19	I	OP	+	DOD (9)	EPEND	Hirahara et al., 1997
41	IIIA	OP+CHEM	–	NED (4)	EPEND	Okazaki, 1997
30	III	OP+CHEM	–	NED (2)	EPEND	Garcia-Barriola et al.,2000
26	III	COP+CHEM+RAD	+	AWD (8)	EPEND	Mikami et al., 2001
23	IIIC	OP+CHEM	–	NED (1)	EPEND	Takano et al., 2005
76	IIB	OP	–	NA	EPEND	Erdogan et al., 2005
NA	NA	NA	NA	NA	EPEND	Fan et al., 2006
NA	NA	NA	NA	NA	ASTRO	Elesha SO, 1983
22	NA	OP	–	NED (8mo)	ASTRO	Skopelitou et al., 2002
NA	NA	NA	NA	NA	ASTRO	Berger et al., 1969

OP – operation, CHEM – chemotherapy, RAD – radiation, NED – no evidence of disease, NA – not available, AWD – alive with disease, DOD – died of disease, EPEND – ependymoma, ASTRO – astrocytoma

EPIDEMIOLOGY

Most women diagnosed with neuroectodermal tumor 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 [2, 4, 6, 7, 12, 18, 21, 24]. In the largest published series based on the material from the Massacchussetts 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) [3]. Anaplastic and primitive tumors tend to occur in younger patients than well differentiated tumors.

Table 2 – Primitive neuroectodermal ovarian tumors reported in the literature

Cases of primitive neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Therapy	Reccurence +/-	Outcome (y)	Diagnosis	Source,y
24	IA	OP	NA	NA	MEDBL	Kleinmann et al.,1993
20	IA	OP+CHEM	–	NED (9)	MEDEP	Kleinmann et al.,1993
32	I A	OP+CHEM	–	NED (3)	MEDEP	Kleinmann et al.,1993
16	IC	OP+CHEM	–	NED (7mo)	NEUBL	Kleinmann et al.,1993
13	III	OP	+	DOD (20mo)	MEDEP	Kleinmann et al.,1993
18	III	OP+RAD	+	DOD (3mo)	EPENBL	Kleinmann et al.,1993
18	III	OP+RAD	+	DOD (7mo)	NEUBL	Kleinmann et al., 1993
18	III	OP+CHEM	+	DOD (6mo)	EPENBL	Kleinmann et al., 1993
26	III	OP+CHEM	+	AWD (1)	EPENBL	Kleinmann et al., 1993
69	III	OP+CHEM+RAD	+	DOD (6mo)	MEDBL	Kleinmann et al., 1993
23	III	OP+CHEM+RAD	+	DOD (2mo)	MEDEP	Kleinmann et al., 1993
16	NA	NA	NA	NA	NEUBL	Kleinmann et al., 1993
NA	NA	NA	NA	NA	PNET	Boor et al., 1975
22	NA	OP	+	NED (4)	NEUBL	Block et al., 1984
NA	NA	NA	NA	NA	NEUBL	Reid et al., 1983
NA	NA	NA	NA	NA	PNET	Shuangshoti et al., 1987
NA	NA	NA	NA	NA	NEUBL	Theppisai et al., 1977
25	IC	OP+CHEM	+	NED (4)	PNET	Demitras et al., 2003
NA	NA	NA	NA	NA	PNET	Rangan et al., 2003
13	NA	OP+CHEM+RAD	+	DOD (17mo)	PNET	Chow et al., 2004
15	NA	CHEM+OP	+	DOD	NEUBL	Somjee et al., 1999
29	NA	OP+CHEM	+	DOD (11mo)	PNET	Kawauchi et al., 1998
13	NA	OP+CHEM	–	NED (18mo)	PNET	Lawlor et al., 1997
35	NA	OP+CHEM	–	NED (3.5)	PNET	Kanbour-Shakir et al., 1993
78	NA	OP+CHEM	–	NED (6mo)	PNET	Fischer et al., 2006
NA	NA	CHEM	+	DOD (13mo)	PNET	Ateser et al., 2007

MEDBL – medulloblastoma, MEDEP – medulloepithelioma, NEUBL – neuroblastoma, EPENBL – ependymoblastoma, PNET – primitive neuroectodermal tumor

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 [2, 11]. There is also one report of a pregnant woman with bilateral ovarian ependymomas, which were diagnosed at the end of the pregnancy [5]. This paper is the only record of a bilateral neuroectodermal ovarian tumor in the literature; all other reported tumors were unilateral.

Table 3 - Anaplastic neuroectodermal ovarian tumors reported in the literature

Cases of anaplastic neuroectodermal ovarian tumors reported in the literature						
Case reports (age, y)	FIGO Stage	Reccurence Therapy	+/–	Outcome (y)	Diagnosis	Source,y
6	IA	OP	+	DOD (2)	GBM	Kleinmann et al.,1993
17	IA	OP	-	NED (4)	GBM	Kleinmann et al.,1993
15	IA	OP	-	NED (3)	GBM	Kleinmann et al.,1993
16	IIA	OP	+	DOD (5)	GBM	Kleinmann et al.,1993
15	IIA	OP	+	AWD (1)	GBM	Kleinmann et al.,1993
22	IIB	OP	NA	NA	GBM	Kleinmann et al.,1993
22	III	OP+CHEM+RAD	+	DOD (4mo)	GBM	Kleinmann et al., 1993
41	NA	OP	-	NED (3.5)	GBM	den Boon et al., 1999
34	NA	OP	-	NED (3)	GBM	Bjersing et al., 1989
16	NA	OP+CHEM	-	AWD	GBM	Yadav et al., 1999
NA	NA	CHEM	+	DOD	GBM	Nishida et al., 1984

GBM – glioblastoma

GROSS PATHOLOGY

Most tumors are large and the average size of tumors is 10-14 cm [3,13]. 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 [3,13,14].

HISTOPATHOLOGY

Morphologically, neuroectodermal tumors of the ovary are identical to their counterparts in the central 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 occured as pure tumors. That case was classified as ependymoma with an astrocytoma component [3]. 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.. Tumors are composed of small cells with hypechromatic, 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 [13,14]. Some tumors are more cellular, contain more mitoses and show signs of nuclear anaplasia. Atypical mitotic figures in tumor cells are also reported [13,14]. 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 [3,15-16]. 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 [3].

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 higly 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. Ependymoblastomas are highly cellular tumors containing true rossettes and canals lined by multiple layers of markedly atypical, mitotically active cells [28]. Primitive neuroectodermal tumors are highly cellular and composed of small cells with hyperchromatic, round to oval nuclei and scanty cytoplasm

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 [3].

ANCILLARY STUDIES

Immunohistochemistry

Ependymomas, astrocytomas and glioblastomas of the ovary react with antibodies to glial fibrillary acidic protein (GFAP). Ependymomas also show positivity for for vimentin [6,11,12], S-100 [6,7,11,12], epithelial membrane antigen (EMA) [6,7,11,12], neuron-specific enolase (NSE) [6,7,11], estrogen and progesterone receptors [3,5,11] , CEA [12] and cytokeratin [6,7].

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 [2, 22].

Molecular markers

Two papers report chromosomal abnormalities in primitive neuroectodermal tumors of the ovary. In the first paper the authors report 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, 1 p31, 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 [21].

In the second paper, the authors report a case of a primitive neuroectodermal tumor that possesed 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 [24].

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 [3,11,30].

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 distinghished from primitive neuroecotdermal tumors and neuroblastomas. 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 received 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 reccurences 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 [3,17,20]. 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[4,6]. Mega-dose chemotherapy followed by peripheral progenitor cell rescue was reported in the literature as the treatment modality for metastatic primitive neuroectodermal ovarian tumor [25].

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Sažetak

Ovarijalni neuroektodermalni tumori

U ovom smo radu pregledali objavljenu literaturu o primarnim neuroektodermalnim tumorima jajnika. Ovi rijetki monofazični teratomi, sastavljeni isključivo ili gotovo isključivo od neuroektodermalnog tkiva, predstavljaju važnu paradigmu tumora koji se razvijaju iz zametnih stanica jajnika. Do sada je u literaturi opisano oko 60 slučajeva neuroektodermalnih tumora jajnika. Većinom se dijagnosticiraju u žena u trećem i četvrtom desetljeću života, a rijetko se pojavljuju u djece, adolecenata i starijih žena. Ovi se tumori dijele na gliome, kao što su ependimom, ependimoblastom, astrocitom, glioblastom, te na primitivne neuroepitelne tumore, kao što su meduloblastom, meduloepiteliom i neuroblastom. Histološka slika ovih tumora identična je tumorima koji se pojavljuju u središnjem živčanom sustavu. Većina bolesnica s niskim kliničkim stadijem bolesti (I i II) liječena je kirurški, dok su bolesnice s višim kliničkim stadijem (III i IV) dodatno liječene zračenjem, kemoterapijom, ili s oba modaliteta. Klinički stadij bolesti pri dijagnozi najznačajniji je prognostički pokazatelj kod ovih tumora. Bolesnice kod kojih je tumor dijagnosticiran i odstranjen u ranom kliničkom stadiju imaju dobru prognozu, dok je prognoza u uznapredovalim stadijima bolesti loša.

Ključne riječi: jajnik, neuroektodermalni tumori