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Pelvic Ependymoma With Clinical Response to GnRH Analog Therapy: A Case Report With an Overview of Primary Extraneural Ependymomas

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Summary

Extraneural ependymomas are rare tumors that occur in sacrococcygeal, pelvic and extra pelvic regions. While sacrococcygeal extraneural ependymomas are equally distributed among males and females, pelvic and extra pelvic ependymomas have been exclusively reported in women, mainly of child bearing age. We present a case of extraneural, pelvic ependymoma that showed clinical response to GnRH therapy with its immunohistochemical and electron microscopic analysis, and an overview of primary extraneural ependymomas based on a review of all such cases published in English literature.

Keywords

Ependymoma; Extraneural; Extraovarian; Pelvic; GnRH; Androgen receptor

Ependymomas are central nervous system (CNS) glial tumors arising from the ependymal lining of the ventricles and the central canal of the spinal cord. They are roughly equally distributed among males and females (1). Extraneural ependymomas are very rare and have been reported in the sacrococcygeal region, ovaries, broad ligaments, pelvic soft tissue, liver, lung, small intestine, mediastinum, and omentum (2–42).

Extraneural ependymomas show morphologic and immunohistologic features that are distinct from CNS ependymomas (2–4,36). Except for the ependymomas seen in the sacrococcygeal region which show uniform sexual distribution (37–42), extraneural ependymomas are exclusively reported among females, mainly of reproductive age group (2–35). We present a case of a 30-yr-old female with a large pelvic ependymoma who was treated with presurgical GnRH analog therapy and fertility-sparing surgical resection, and remains disease-free after over 30mo without post surgical treatment.

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We have summarized all published cases of extraneural, extrasacroccygeal ependymomas (Table 1) and we discuss the pathogenesis and clinical outcome of extraneural ependymoma.

CASE PRESENTATION AND CLINICAL COURSE

A 30-yr-old Korean female presented to our medical center seeking surgical treatment for a 1-yr history of pelvic pressure from a presumed “fibroid” that had grown despite self-administered herbal therapy. In 8 mo, the mass had grown from $18.2 \times 16.5 \times 11.9$ to $21 \times 19.7 \times 9.5$ cm by ultrasound measurement. Magnetic resonance imaging, ultrasound, and computed tomography scans showed equivocal attachments around the mass, but the mass was clearly away from the spinal column and did not infiltrate any structures (Fig. 1A). Her medical history included 1 abortion. She denied a family history of cancer and her menstrual history was unremarkable. Her body mass index was 20.6 cm/kg^2 . Her abdomen was soft, but distended to an equivalent gestational size of 20 wk. Her serum CA-125 level was 230 U/mL (reference range, 0–35 U/mL). lactate dehydrogenase and β -hCG levels were within normal ranges.

In preparation for surgery, she was given 2 injections of the GnRH analog leuprolide acetate (Lupron Depot, Lot 020312E, NDC# 0074-3641-03) over 4mo: 11.15 mg IM (covering 3 mo) and 3.75 mg IM (covering an additional 1 mo). With leuprolide therapy, her abdominal size decreased to an equivalent gestational size of 15 wk. During surgery, the mass was found to be broadly attached to the appendix, right pelvic side wall, cecum, and ascending colon. There appeared to be an inflammatory adhesion between the mass and the right fallopian tube. The uterus, bilateral ovaries, and left fallopian tube were grossly normal and free of masses. The mass was removed along with the appendix.

The patient had an uncomplicated postoperative course and did not receive further treatment. Four months postoperatively, the patient’s CA-125 level decreased to 11 U/mL. Six months postoperatively no masses were detected in magnetic resonance imaging scans of the head and pelvis, and the patient was asymptomatic. Thirty months postoperation, the patient is doing well.

PATHOLOGIC FINDINGS

The mass had a glistening yellow lobulated surface (Fig. 1B). It measured $20 \times 15 \times 9$ cm and weighed 1820 g. The cut surface was homogeneously yellow, soft, glistening, and lobulated, with multiple subcentimeter cystic spaces and punctate hemorrhages (Fig. 1C). Histologic examination revealed tumor cells arranged in multiple architectural patterns (pseudorosettes, trabecular, pseudopapillary, nested, cribriform, glandular, and cystic arrangements) separated by thick fibrous septae.

Three different morphologic cell types were observed in the tumor. The first type consisted of spindled cells with abundant fibrillary eosinophilic cytoplasm, forming a predominant background of pseudorosettes (Fig. 2A). The second type consisted of compact epithelioid cells arranged in tubules with lumens containing eosinophilic long cilia-like processes; these tubules rested in sharply retracted spaces and were scattered diffusely throughout (Fig. 2B). Unlike classic ependymal rosettes, these tubules had indistinct luminal borders, often were

composed of <5 cells in cross-section, and often formed fused, elongated, branching tubular structures on cut sections. The third cell type consisted of flattened cells which lined dilated gland-like regions scattered throughout (Fig. 2C). Rare foci of tumor necrosis and psammomatous stromal calcium deposits were scattered in the neoplasm. Mitotic figures were rare and tumor cell nuclei were of low-grade morphology.

Immunohistochemical studies highlighted the differences between the first (spindled cells) and second (compact tubules) neoplastic populations. The immunoprofile of the third neoplastic population (flattened cells lining dilated gland-like spaces) resembled the second, but also overlapped with the first. The spindled cells were positive for the glial markers glial fibrillary acidic protein (GFAP, Fig. 2D) and N-cadherin, whereas the ciliated tubules and flattened cells were negative. The tubules and flattened cells were strongly positive for cytokeratins (AE1/AE3, CK7, CAM 5.2, Fig. 2E) and E-cadherin, whereas the spindled cells were moderately positive. The luminal surfaces of the dilated gland-like spaces and the ciliated lumens of the tubules were positive for epithelial membrane antigen, whereas the spindled cells were negative. All 3 populations of neoplastic cells were strongly positive for vimentin and negative for CK20. Ki-67 mitotic index was 1%. Other negative immunostains included S100, CD99, WT-1, Calretinin, α -fetoprotein protein, actin, desmin, inhibin, synaptophysin, and smooth muscle actin. Given these morphologic and immunohistochemical characteristics, a diagnosis of a pelvic ependymoma with serosal adhesions was rendered.

The hormone receptor immunohistochemistry results were especially interesting—all 3 neoplastic cell populations had nuclear reactivity for estrogen, progesterone, and androgen hormone receptors (ER, PR, and AR, respectively). ER positivity was most diffuse and strong among the spindled cells, whereas PR positivity was most diffuse and strong among the tubules; AR reactivity was weak and patchy in all the 3 populations (Figs. 2F–H).

Ultrastructural study of the tumor showed the tubules had striking evidence of ependymal differentiation, including ciliated lumens corresponding to the epithelial membrane antigen immunopositive luminal surfaces, and intercellular desmosomal junctions (Fig. 3). Intermediate filaments were seen throughout the neoplastic cells; occasional glial-like filaments were seen but their identification was limited due to artifacts introduced by routine tissue processing.

DISCUSSION

Ependymomas are derived from the neuroectoderm and commonly arise in the ventricles and central canal of the spinal cord. They are primarily seen in children and young adults and are evenly distributed among males and females. Occasionally, CNS ependymomas can metastasize to extraneural sites (1). CNS ependymomas have distinct histology characterized by perivascular pseudorosettes, true ependymal rosettes, and fibrillary areas that stain intensely for GFAP and variably for cytokeratins (3,4,36).

In contrast, primary extraneural ependymomas are rare and have been described as having a wider range of microscopic architecture within the same tumor and displaying

immunostaining patterns distinct from CNS ependymomas (3). Extranural ependymoma histology includes perivascular pseudorosettes and occasionally true ependymal rosettes, along with mixtures of solid, macrocystic, microcystic, pseudopapillary, papillary, trabecular, and cribriform architectures (4). Although both CNS and extraneural ependymomas stain positive for GFAP, a significant number of extraneural ependymomas also stain positive for cytokeratins 34 β E12, CK18, CAM 5.2, and CK7. ER and PR are also strongly and diffusely positive in a majority of extraneural ependymomas, compared with CNS ependymomas that show weak and focal staining for these receptors in a minority of cases. CD99 and S100 are more commonly positive in CNS ependymomas than in their extraneural counterparts (3).

Depending on the primary site, extraneural ependymomas can be categorized as sacrococcygeal, pelvic, or extrapelvic. Sacrococcygeal ependymomas are the most common, with over 75 reported cases. They occur both in males and females and mostly arise in presacral soft tissue or in the subcutaneous tissue of the sacrococcygeal region. Morphologically, they resemble the myxopapillary-type CNS ependymomas (37–42). Immunohistochemically also they resemble CNS ependymomas more than other extraneural ependymomas do (3,40). Presacral ependymomas are frequently associated with destruction of sacral bone or dysfunction of sacral nerve. Up to 20% of sacrococcygeal ependymomas have been reported to develop distant metastasis that can occur 10 to 20 yr after the initial presentation. This is in contrast to CNS ependymomas which rarely metastasize outside of the cerebrospinal fluid pathway (41). The favored treatment of sacrococcygeal ependymomas is surgical removal of the tumor. Complete excision is important to minimize the risk of recurrence (42).

Extranural pelvic and extrapelvic ependymomas are rare, and are reported exclusively among females, mainly of child-bearing age. The most common site for pelvic ependymomas is the ovary where they may be seen either as pure ependymomas [19 reported cases (2–5,7–16)] or occasionally as a component of teratoma [2 reported cases (4,6)]. Because of variable morphologic patterns exhibited by extraneural ependymomas, ovarian ependymomas can often resemble various other primary ovarian tumors such as papillary serous tumors, granulosa cell tumor, adnexal Wolffian tumors, and even malignant peripheral neuroectodermal tumors. The diagnosis of ovarian ependymoma can be especially challenging when higher grade features are present, such as nuclear pleomorphism, high cellularity, high mitotic count, atypical mitoses, and geographic necrosis. Even in reports of extraneural ependymomas with such higher grade features, clinical course was mostly indolent, with reported follow-up times ranging from 1 to 9 yr (4,15,16,18–21). Morphologic characteristics of ependymoma such as fibrillary cytoplasmic processes and rosettes can be found in most ovarian ependymal tumors upon thorough sampling of tumor. Strong, diffuse staining with GFAP in a histologically low-grade tumor containing perivascular pseudorosettes helps differentiate ovarian ependymoma from other primary ovarian tumors. Papillary architecture and psammoma bodies can be seen in pelvic ependymal tumors and therefore cannot be taken as pathognomonic of Mullerian origin for an ovarian tumor (2–4).

Sites of origin for extraovarian pelvic extraneural ependymomas include the mesovarium [1 case (22)], broad ligament [4 cases (3,23–24)], uterosacral ligament [1 case (17)], and pelvic cavity soft tissue [4 cases (3,26,27)]. Extrapelvic extraneural ependymomas have been reported in liver [1 case (28)], lung [2 cases (3,29)], abdominal cavity [3 cases (21,30,31)], and mediastinum [9 cases (18–20,32–35)]. All of these ependymomas were also exclusively in females and showed variable morphologic patterns.

The histogenesis of extraneural ependymomas may be different based on their anatomic locations. Sacrococcygeal ependymomas are believed to arise from extradural filum terminale or from ependymal cell rests resulting from incomplete regression of the caudal cell mass (2,37–39). This belief is based on the fact that sacrococcygeal ependymomas are located in the vicinity of filum terminale and share the characteristic morphology of myxopapillary-type CNS ependymoma (3,37–40). Immunohistochemically also they resemble CNS ependymomas more than other extraneural ependymomas (3,40) and like CNS ependymomas, they are equally distributed among males and females (37–40).

Ovarian and other pelvic and extrapelvic ependymomas seem to occur exclusively in females, mainly of child-bearing age group. This suggests a different histogenetic origin for these tumors. Pure ovarian ependymomas have been regarded as monodermal teratomas and a germ cell origin for all ovarian ependymomas was speculated; however, recently Stolnicu et al. (4) showed that an ovarian ependymoma associated with a teratoma showed immunohistochemical characteristics similar to CNS ependymomas, whereas 2 pure ovarian ependymomas showed immunohistochemical features characteristic of extraneural ependymomas (i.e. positive for cytokeratins, ER, and PR), suggesting a different histogenesis for the 2 types of ovarian ependymomas—either a derivation from different precursors or differentiation along different pathways. Ectopic rests of ependymal tissue or neometaplasia of the peritoneum (capacity of the peritoneum to differentiate into a new tissue type) can be other possible explanations for the histogenesis of pure ovarian and other nonsacrococcygeal extraneural ependymomas; however, their exclusive occurrence in females of child-bearing age does not completely fit this hypothesis (2,17). Another hypothesis for the pathogenesis of extraneural ependymomas is that misdirected primordial germ cells (which have been seen in the mediastinum and sacrococcygeal regions) form ependymal tumors under the influence of female hormones (20). Supporting this hypothesis is the fact that ER and PR positivities have been reported in extraneural ependymomas (3,4,7,11,15,20,25–27,30–32) and that hormonal responsiveness of extraneural ependymomas has been reported in situations of postmenopausal hormone replacement therapy (HRT), pregnancy, and tamoxifen treatment. The patient who was given postmenopausal HRT had an ER-positive and PR-positive ovarian ependymoma and experienced a recurrence in 3 yr; however, was clinically stable for 2 yr after reexcision and cessation of HRT (11). Bilateral ER-positive and PR-negative ovarian ependymomas were discovered incidentally in a pregnant woman undergoing C-section (7). And in 1 case of omental ependymoma (ER and PR status unknown), the patient had residual disease after surgery and chemotherapy but was clinically stable on tamoxifen therapy (duration on tamoxifen unknown) (30).

Congenitally ectopic glial tissue or fetal neural tissue deposited from a previously aborted pregnancy have also been considered as possible origins for pelvic ependymomas (17).

Extraneural extrasacral ependymomas are indolent tumors that grow slowly and may recur (Table 1). Recurrences have been reported to occur from 6mo to up to 30 yr after the initial detection of an extraneural ependymoma (2–6,9,11,12,14,21,23,30). Rarely patients have been reported to have died of disease, after multiple recurrences (2,9) or delayed treatment of bulky disease (19). Often ovarian ependymoma patients present at FIGO Stage III, with dissemination of tumor nodules in the pelvic cavity (2,11–13,15).

Ours is the first report of a large pelvic ependymoma attached to the pelvic side wall and gastrointestinal organs (cecum, appendix, and ascending colon). The uterus, bilateral ovaries, and fallopian tubes were free of tumor. It resembles clinically and morphologically the 3 previously reported abdominal and pelvic cavity ependymomas with attachment to gastrointestinal organs (21,30,31), 2 of which were initially misdiagnosed as gastrointestinal autonomic nerve tumor based on focal positive staining for c-kit (21,30). Other diagnostic pitfalls in such cases of large, rapidly growing masses which may seem to be arising from the pelvic wall without any involvement of genital organs may include pelvic mesothelioma and sarcoma.

All cases of extraneural ependymoma in the literature have been treated by surgery with or without chemotherapy or radiation therapy. No case of extraneural ependymoma response to GnRH therapy has been reported. An example of CNS ependymoma responding to GnRH therapy was reported by Yoffe et al. (43) in 2005, in which an adolescent female with recurrent posterior fossa CNS ependymoma, intolerant of daily high-dose tamoxifen therapy due to the formation of large ovarian cysts, was switched to monthly 15 mg IM leuprolide acetate injections and remained cyst-free and ependymoma-free during 1 yr of follow-up.

Our case adds to the medical literature on the indolent course of extraneural ependymomas that are not part of an invasive or metastatic process. Our patient's response to presurgical GnRH agonist therapy as evidenced by shrinkage of the tumor size and her complete postsurgical cure without further medical therapy show that conservative, hormone-based therapies may be considered as a treatment option for patients with extraneural pelvic ependymoma, especially those patients who wish to preserve their fertility.

SUMMARY

In summary, extraneural ependymomas are indolent tumors that rarely cause death but may recur after many years, warranting long-term clinical follow-up. Anecdotally, surgery, chemotherapy, irradiation, and tamoxifen have been applied with mixed results. Extraneural ependymomas that are not in the sacral/presacral region are rare and have been reported most commonly in the ovaries, followed by mediastinum, paraovarian and pelvic soft tissue, abdominal/pelvic cavity, lung, and liver. All of these extraneural, nonsacroccygeal, ependymomas have been reported exclusively in females ranging from 13 to 76 yr in age with most patients being of child-bearing age. They show a variety of histomorphologic features, are GFAP-positive like CNS ependymomas, and unlike CNS ependymomas are

negative for CD99 and S100 and diffusely and strongly positive for ER, PR, and multiple epithelial markers. Our case study is the first to examine the presence of AR, which was weakly positive throughout the entire tumor. In the pelvis and ovaries, ependymomas may be confused with Mullerian origin malignant tumors, due to their variable morphology. Thorough sampling to look for pseudorosettes and ependymal rosettes, as well as immunostaining with GFAP, can be helpful in diagnosis.

The pathogenesis of extraneural ependymomas is unclear. “Neometaplasia” is a possible histogenetic pathway; however, their frequent occurrence in ovaries and posterior mediastinum, their exclusive presence in females of child-bearing age, and their strong and diffuse staining with ER and PR support the alternate possibility that the tumor may originate from misdirected primordial germ cells under the influence of female hormones.

There are no prior reports of GnRH therapy for extraneural ependymoma. We have described the first case of an extraovarian extraneural primary pelvic ependymoma that showed clinical response to GnRH therapy by shrinkage in tumor size and >30mo of disease-free survival after fertility-sparing surgical removal of the tumor. Our case suggests that GnRH analog therapy may be one of the treatment options for patients with extraneural pelvic ependymomas who desire fertility-sparing therapy.

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FIG. 1.

(A) Magnetic resonance imaging shows a large mass which has no connection to the spinal cord or sacral region. (B) The mass has a glistening yellow lobulated surface with focal nodular protrusions between tan fibrous bands, and a soft fleshy consistency. (C) The cut surface of the mass is homogeneously yellow, soft, glistening and lobulated, with multiple foci of punctate hemorrhages.

FIG. 2.

Microscopic sections. (A) Spindled cells with abundant fibrillary eosinophilic cytoplasm form a background of pseudorosettes in which compact epithelioid tubules rest in sharply retracted spaces (H&E, 10×). (B) The lumens of the tubules contain faint eosinophilic cilia-like processes (arrows) (H&E, 60×). EM confirmed these processes were cilia. (C) Flattened cells line dilated gland-like regions (H&E, 10×). (D–H) Immunohistochemical stains; see the “Pathologic findings” section of the main text. H&E indicates hematoxylin and eosin.

FIG. 3. Electron microscopy. (A) Ciliated lumens. (B) Intercellular desmosomal junctions. (C) Intermediate filaments.

TABLE 1

Summary of extraneural, nonsacrococcygeal ependymoma case reports

Organ, no. cases	Ages	Other organ involvement at presentation	Reported follow-up data	References
Ovary (21 cases)	16–76	FIGO Stages I–IV	<p><i>Recurrences and death:</i> 8 patients (ages 19–35; recurrences 0.5–30 yr later); of these, the patient with 0.5 yr to recurrence succumbed to disease burden (~9 yr later) and had been initially diagnosed with Stage I disease; 1 died of unknown cause (4 yr after diagnosis); 3 patients were alive with disease (initially diagnosed with Stage III disease); 2 patients were alive with unknown disease status (3 and 51 yr after diagnosis); outcome after recurrence was unknown for one patient.</p> <p><i>Alive, unknown disease status:</i> 2 patients [both age 25; 1 yr (Stage IV) and 5 yr (Stage I) later].</p> <p><i>Alive, no evidence of disease:</i> 8 patients (ages 23–68; 7mo to 5 yr later). 4 were Stage III, 3 were Stage II, 1 was Stage I.</p> <p><i>Died from unrelated cause:</i> 1 patient (age 35; Stage I, well without disease 14 yr later, and died of colorectal cancer 2 yr after that).</p> <p><i>No follow-up reported:</i> 2 patients</p>	(2–16,30)
Paraovarian (ligaments, mesovarium) (6 cases)	13–48	3 cases involved adjacent pelvic structures; of these, 1 patient also had omental involvement; another patient also had mesentery and retroperitoneum involvement	<p><i>Recurrences:</i> 1 patient (age 13; 11 yr later); patient was alive despite multiple recurrences, 50 yr after diagnosis.</p> <p><i>Alive, no evidence of disease:</i> 4 patients (ages 22–45; 6–18mo postsurgery follow-up)</p> <p><i>No follow-up reported:</i> 1 patient</p>	(3,17,22–24)
Mediastinum (9 cases)	20–71	2 cases involved adjacent lymph node(s); 1 case had vascular invasion; 1 case involved lung; 1 case involved parietal pleura	<p><i>Died from complications of resection:</i> 1 patient (incidentally found on chest x-ray at age 20; resected 26 yr later).</p> <p><i>Recurrences:</i> none reported.</p> <p><i>Alive, no evidence of disease:</i> 6 patients (ages 36–71; 1–9 yr postsurgery follow-up).</p> <p><i>No follow-up reported:</i> 2 patients</p>	(18–20,32–35)
Pelvis (4 cases)	25–32	2 cases involved abdominal structures	<p><i>Recurrences:</i> 1 patient (age 32).</p> <p><i>No follow-up reported:</i> 3 patients</p>	(3,26,27)
Abdomen (3 cases)	27–39	Infiltration of ileal wall, extension into liver, multiple omental masses	<p><i>Recurrences:</i> 2 patients (ages 27 and 39); outcomes unavailable.</p> <p><i>Alive, no evidence of disease:</i> 1 patient (age 37)</p>	(21,30,31)
Lung (2 cases)	48, 64	None	<p><i>Died from unrelated cause:</i> 1 patient (age 64; died of cerebral hemorrhage 6mo later).</p> <p><i>No follow-up reported:</i> 1 patient</p>	(3,29)
Liver (1 case)	41	Satellite nodules and diaphragm	No follow-up reported	(28)