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Case study

NF2 and *ATRX* gene copy number losses on a case of ovarian ependymoma ☆

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Summary Ovarian ependymomas are rare glial neoplasms that typically occur in women on their third to fourth decades of life. They are histologically similar to ependymomas of the central nervous system but may have a broader immunophenotype. We describe a 27-year-old woman who presented to the emergency department with a 3-week history of cough and shortness of breath. Further workup disclosed a left pelvic mass and extensive intra-abdominal metastases. Pathology revealed sheets of monomorphic cells within a fibrillary stroma, papillary projections, true ependymal rosettes, and pseudorosettes consistent with an ependymoma of ovarian origin. Next-generation sequencing showed *ATRX* and *NF2* copy number losses. Fluorescence in situ hybridization for *EWSR1* demonstrated monosomy of 22q in greater than 90% of cells. These molecular alterations have not been previously reported in ovarian or extra–central nervous system ependymomas.

1. Introduction

Ependymomas are rare, glial neoplasms derived from ependymal cells that are largely limited in distribution to the central nervous system (CNS). Infrequently, primary ependymomas are identified outside the CNS. It has long been postulated that these tumors may arise from ependymal rests deposited outside the nervous system during embryogenesis, or may represent a type of monodermal teratoma if arising from the ovary [1]. Case reports of ependymomas originating in the sacrococcygeal region, omentum, lung, mediastinum, and female reproductive tract support a widespread potential distribution [2]. Ependymomas of the ovary tend to occur in women in their third to fourth decades and typically share histologic and immunohistochemical features with CNS ependymomas, including true ependymal rosettes, perivascular pseudorosettes, papillary structures, and immunoreactivity for glial fibrillary acidic protein (GFAP) and synaptophysin. However, extra-CNS ependymomas tend to exhibit multiple histologic patterns within the same tumor and display immunoreactivity for keratin, and estrogen and progesterone receptors [3]. Because of their extreme rarity,

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certain features of these neoplasms, including their clinical behavior, molecular profile, and optimal therapy are incompletely characterized. Herein we present a case of primary ependymoma of the ovary and discuss pertinent clinical findings, histopathologic features, and molecular alterations that were identified in this tumor.

2. Case presentation

A 27-year-old woman presented to the emergency department complaining of a cough and shortness of breath for 3-weeks. A computed tomographic scan of the chest and abdomen revealed a large left pleural effusion with atelectasis, pericardiac lymphadenopathy, a left pelvic mass likely arising from the ovary, and multiple peritoneal metastases. Serum CA-125 level was elevated (155 ng/mL). A subsequent core needle biopsy showed a neoplasm with immunohistochemical positivity for CAM5.2, EMA, AE1/AE3, CD56, S100, WT1, synaptophysin, and chromogranin consistent with neural or neuroendocrine differentiation. The patient underwent hysterectomy and bilateral salpingo-oophorectomy that included peritoneal sampling and omentectomy. Complete surgical cytoreduction of the tumor was not possible because of the extent of tumor burden at that time. The tumor seemed to replace the left ovary and involve serosal surfaces of the vermiform appendix, uterus, fallopian tubes, spleen, and descending colon. After surgery, the patient received 4 cycles of chemotherapy consisting of paclitaxel, ifosfamide, and cisplatin in preparation for a subsequent debulking procedure followed by additional adjuvant chemotherapy. Three months later, a second surgical exploration revealed tumor involvement of the gallbladder serosa, diaphragm, right retroperitoneum, peritoneal cavity, 15 costophrenic angle lymph nodes, and a right internal mammary lymph node, which were resected. Fifteen months after diagnosis and treatment, the patient is stable without evidence of residual disease and taking 25 mg daily of exemestane.

3. Pathologic findings

On macroscopic examination, the left ovary was completely replaced by a 5.0 × 4.0 × 3.0-cm mass with a soft, yellow, focally hemorrhagic cut surface. Microscopically, the tumor demonstrated a wide range of morphologic patterns including areas that were solid, papillary, micropapillary, macrocystic, microcystic, and nested (Fig. 1A-E). Perivascular pseudorosettes and true rosettes were readily seen (Fig. 1F). Columnar cells with cilia mimicking ependymal linings were a prominent histologic feature (Fig. 2A). Focal areas demonstrated dystrophic calcifications, hemorrhage, hyalinized fibrovascular cores, and stromal sclerosis (Fig. 2B). The nuclei were monotonous with a salt and pepper appearance and inconspicuous nucleoli. Nuclear anaplasia was absent. Cytoplasmic clearing and vacuolization with signet ring forms were also seen (Fig. 2C). Periodic acid–Schiff stain with diastase confirmed the presence of glycogen in these areas. Mitotic activity ranged from 0 to 1 mitoses per 50 high-power fields. There was no residual ovarian parenchyma, and the presence of tumor types, such as teratoma, was not observed. Lymphovascular invasion and

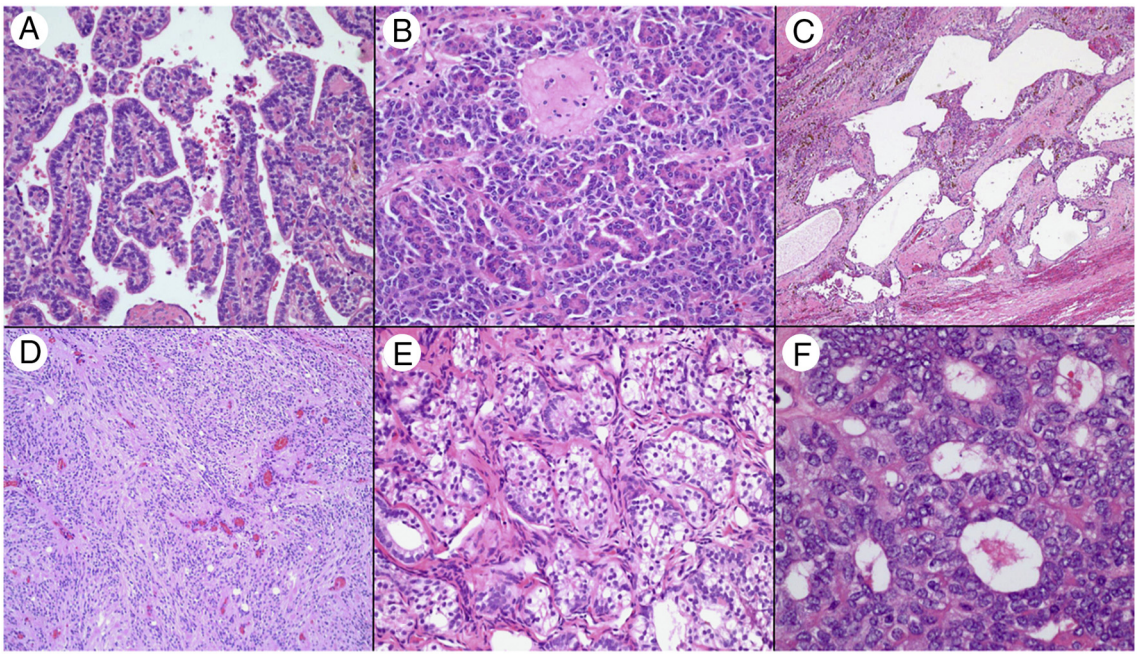

Fig. 1 Histologic findings. A, Papillary projections (H&E, original magnification ×100). B, Hyalinized fibrovascular core with adjacent micropapillary pattern (H&E, ×100). C, Macrocystic pattern (H&E, ×40). D, Sheets of monomorphic cells with fibrillary stroma and perivascular pseudorosettes (H&E, ×40). E, Nests of cells with cytoplasmic clearing (H&E, ×100). F, True ependymal rosettes (H&E, ×400). H&E, hematoxylin and eosin.

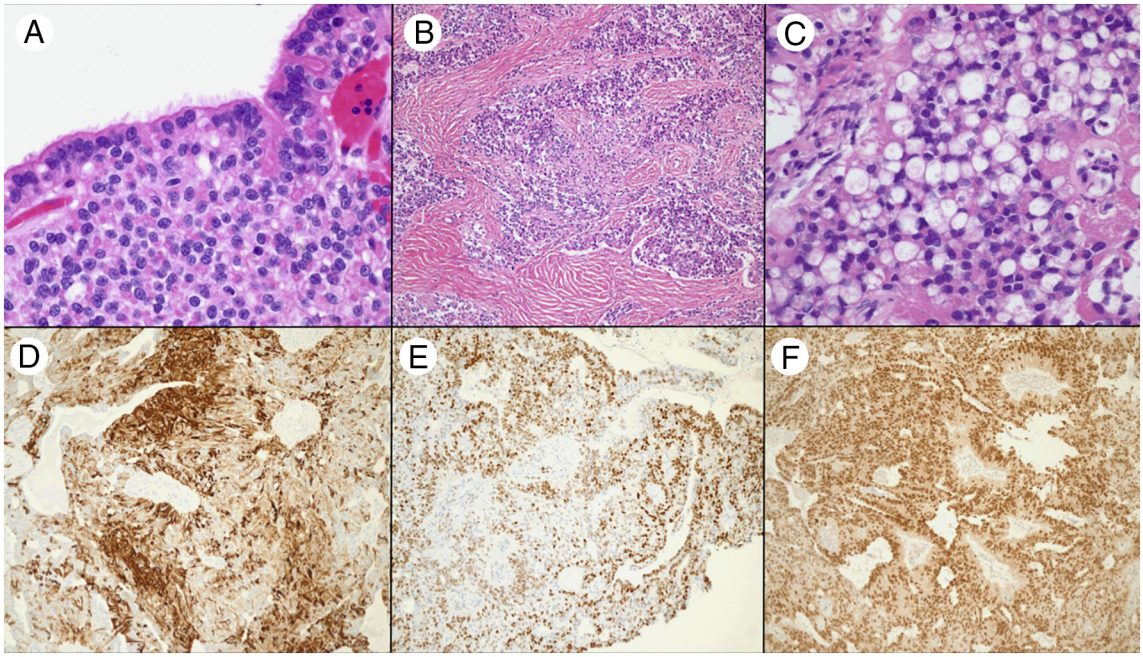

Fig. 2 A, Columnar to cuboidal cells with cilia mimicking ependymal linings (H&E, ×400). B, Stromal sclerosis (H&E, ×40). C, Cytoplasmic vacuolization with signet ring forms (H&E, ×400). D, GFAP (×100). E, ER (×100). F, PAX-8 (×100).

infrequent microscopic foci of necrosis were also identified. The tumor cells were immunoreactive for GFAP, ER, PR, CD99, vimentin, calretinin, CD56, S100, AE1/AE3, and PAX-8, whereas they were negative for SOX-10, CK7, CK20, SALL4, Ber-EP4, MOC-31, inhibin, TTF-1, CD10, HMB45, and LCA. EMA and CAM5.2 were expressed in rare lesional cells, whereas synaptophysin and chromogranin showed weak, dot-like expression. GFAP, ER, and PAX-8 are shown in Fig. 2D-F. Ki-67 was positive in approximately 1% of cells. A final diagnosis of ovarian ependymoma with metastases was rendered. Tumor grade was compatible with grade II of the World Health Organization (WHO) system.

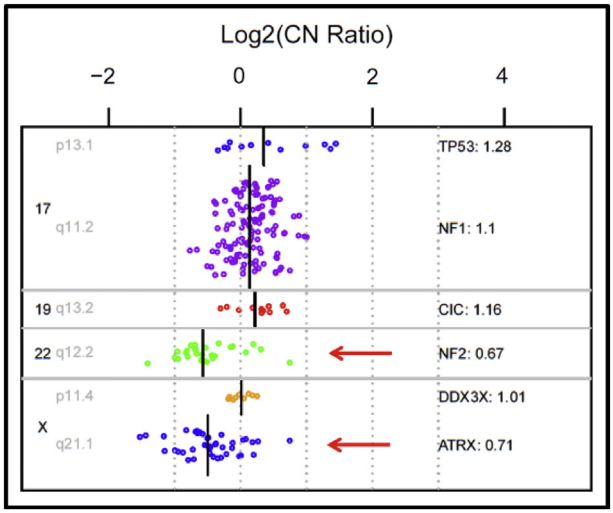

Fig. 3 Copy number analysis showing copy number loss of the *NF2* and *ATRX* loci.

Tumor resected in the second surgical procedure was morphologically similar except for an increase in cells with cytoplasmic clearing. No necrosis was seen.

3.1. Next-generation sequencing findings

Tumor nucleic acid was extracted from formalin-fixed, paraffin-embedded sections, and massive parallel sequencing was performed on the ThermoFisher Scientific Ion Proton platform (Waltham, MA). A targeted, laboratory-developed panel (GlioSeq, Molecular and Genomic Pathology Laboratory; Pittsburgh, PA), which evaluates mutations, copy number alterations, and gene fusions commonly identified in glial

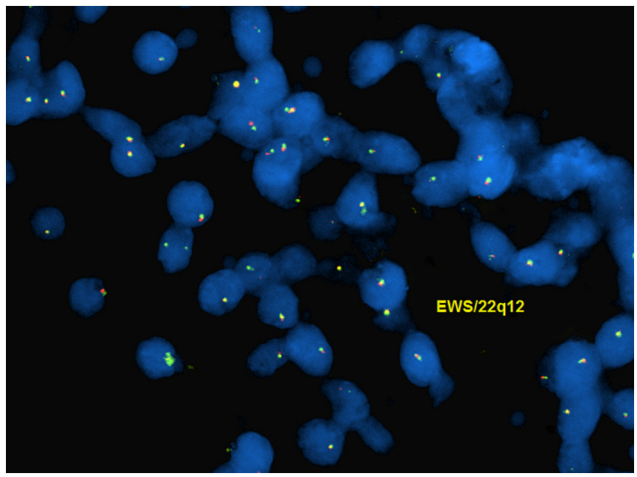

Fig. 4 *EWSR1* FISH break-apart probe showing monosomy of 22q12 gene region. FISH, fluorescence in situ hybridization.

Table Summary of reported cases of ovarian ependymomas

Author/year	Age (y)	Sites of involvement throughout entire follow-up history	Size of ovarian mass (cm)	Histology	Positive immunohistochemistry	Diagnosis	Follow-up
Kleinman et al 1984 [7]	25	Left ovary	1	Solid, cystic, papillary	GFAP	Ependymoma, ungraded	ANED at 5 y
	25	Right ovary (primary), left ovary, uterine serosa, lateral pelvic wall, cul-de-sac, omentum, diaphragm, retrosternal nodule	8	Solid, papillary	GFAP	Ependymoma, ungraded	REC at 2 y Dead, cause unknown
	35	Left ovary, peritoneum, omentum, serosa of the left fallopian tube and uterus	10	Solid, cystic, papillary	GFAP	Ependymoma, ungraded	ANED at 7 mo
Dekmezian et al 1986 [8]	38	Left ovary, omentum, serosa of the uterus	9.5	Papillary with psammoma bodies	GFAP	Ependymoma, ungraded	ANED at 17 mo
Auerbach et al 1988 [9]	38	Left ovary, vaginal apex, omentum, diaphragm, liver serosa	10	Glandular, myxoid, papillary with psammoma bodies	GFAP, keratin	Ependymoma, ungraded	REC at 5 y ANED at 5 y
Carlsson et al 1989 [10]	46	Right ovary, liver, spleen, peritoneum, abdominal wall sigmoid colon	10	Solid, papillary	GFAP, S100 (focal)	Ependymoma, ungraded	REC at 16 y ANED at 21 y
Carr et al 1992 [11]	25	Bilateral ovaries, peritoneum, liver, diaphragm	Right 14 Left 16	Solid with occasional papillae	GFAP, PR	Ependymoma, WHO II	ANED at 1 y
Kleinman et al 1993 [12]	25	Left ovary	NA	Classic, papillary in 5/6 cases, psammoma bodies in 2/6 cases, cystic spaces in 5/6 cases	GFAP in 4/6 cases	Ependymoma, ungraded	ANED at 5 y
	16	Left ovary	16			Ependymoma, ungraded	NA
	49	Left ovary	10.5			Ependymoma and astrocytoma, ungraded	ANED at 4 y
	36	Right ovary, colon	16			Ependymoma, ungraded	ANED at 3 y
	35	Left ovary	10			Ependymoma, ungraded	AWD at 5 y
	30	Right ovary, uterus, urinary bladder, pelvic wall, cul-de-sac, omentum, diaphragm	8			Ependymoma, ungraded	DOD at 5 y
Guerrieri and Jarlsfelt 1993 [13]	68	Left ovary	18	Solid, papillary and microcystic	GFAP, vimentin, NSE, S-100, EMA, cytokeratin	Ependymoma, WHO II	ANED at 1 y
Hirahara et al 1997 [14]	19	Right ovary	NA	Solid, papillary	GFAP, LMWCK, S-100, EMA, NSE	Ependymoma, WHO II	DOD after 9 y
Garcia-Barriola et al 2000 [15]	30	Bilateral ovaries, peritoneum, uterus	Left 20	Solid, papillary	GFAP	Ependymoma, WHO II	REC shortly after surgery ANED at 4 y

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Table (*continued*)

Author/year	Age (y)	Sites of involvement throughout entire follow-up history	Size of ovarian mass (cm)	Histology	Positive immunohistochemistry	Diagnosis	Follow-up
Komuro et al 2001 [16]	26	Ovary, peritoneum, omentum	NA	NA	GFAP	Ependymoma, WHO II	REC at 6 y ANED after 8 y
Erdoğan et al 2005 [17]	76	Left ovary, colonic mesentery	14	Solid	GFAP, S-100, vimentin, CEA, EMA	Anaplastic ependymoma, WHO III	NA
Takano et al 2005 [18]	23	Left ovary, pelvic cavity, subphrenic area, omentum, and mesentery	NA	Solid, papillary, focal chondroid, microcystic, trabecular	GFAP, ER, PR, vimentin, S-100, EMA, NSE	Anaplastic ependymoma, WHO III	ANED at 16 mo
Fan et al 2006 [19]	62	Ovary, liver	NA	NA	NA	Ependymoma, WHO II	REC at 2 y
Idowu et al 2008 [3]	36	Left ovary, left fallopian tube, omentum, uterine serosa, sigmoid colon, pelvic cavity, mesentery	NA	Solid, papillary, microcystic	GFAP, ER, CK18	Ependymoma, WHO II	REC at 5 y
Stolnicu et al 2011 [20]	22	Right ovary, pelvic cavity	14	Microcystic, macrocystic, solid, papillary with psammoma bodies	GFAP, ER, PR, EMA, NSE, CAM5.2, CK7, CK18, CK34βE12, S100, vimentin	Anaplastic ependymoma, WHO III	REC at 1 y AWD at 2.5 y
	32	Left ovary, peritoneum, omentum	15	Macrocystic, microcystic, solid, papillary.	GFAP, ER, PR, CD99, EMA, NSE, CAM5.2, CK7, CK18, CK34βE12, S100, vimentin	Anaplastic ependymoma, WHO III	REC at 8 mo ANED at 3 y FU
	35	Left ovary	4	Myxopapillary, trabecular, microcystic	GFAP, CK18, NSE, S100, vimentin	Myxopapillary ependymoma, WHO I	DNED, dead by colon cancer at 14 y
Schuldt et al 2014 [21]	61	Right ovary, peritoneum, endometrial cavity	NA	Solid, pseudoglandular, clear cells	GFAP, ER, PR, EMA, CK8, CK7, CK18, CK34βE12, S100, vimentin	Anaplastic ependymoma, WHO III	NA
Hino et al 2016 [22]	21	Left ovary, liver, diaphragm, colon	16	NA	GFAP, ER, PR, CAM5.2, EMA	Ependymoma, WHO II	REC shortly after surgery ANED at 2 y
Liang et al 2016 [5]	35	Right ovary, peritoneum	NA	Classic, papillary, clear cells	NA	Ependymoma, WHO II	NA
	50	Right ovary, peritoneum and omentum	13	Classic, papillary and clear cells	GFAP, ER, PR	Ependymoma, WHO II	AWD at 59 mo

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Table (*continued*)

Author/year	Age (y)	Sites of involvement throughout entire follow-up history	Size of ovarian mass (cm)	Histology	Positive immunohistochemistry	Diagnosis	Follow-up
	36	Ovary, broad ligament, peritoneum and omentum	7	Classic, papillary, clear cell	GFAP, focal EMA (perinuclear dot-like), keratin cocktail	Anaplastic ependymoma, WHO III	AWD at 9 mo
	29	Ovary, peritoneum	18	Classic, papillary, clear cells	GFAP, ER, PR, EMA (perinuclear dot-like), focal CD99, S100	Anaplastic ependymoma, WHO III	AWD at 4.5 mo
Gorski et al 2017 [6]	29	Bilateral ovaries, peritoneum, omentum	Right 14 Left 8	Solid, papillary with psammoma bodies	GFAP, ER, PR, EMA (dot-like), progesterone, S100 (focal), WT-1 (focal), P53 (rare), PAX-8 (patchy)	Anaplastic ependymoma, WHO III	AWD at 22 mo
Yust Katz et al 2018 [2]	37	Ovary, peritoneum, uterus	NA	NA	NA	Anaplastic ependymoma, WHO II	AWD at 3 y

Abbreviations: AWD, alive with disease; ANED, alive with no evidence of disease; DNED, dead with no evidence of disease; NA, not available; REC, recurrence.

tumors and other CNS neoplasms, was used [4]. The tumor was negative for tested gene mutations and fusions, but showed evidence of copy number losses of the *NF2* (22q12.2) and *ATRX* (Xq21.1) loci (Fig. 3).

3.2. Fluorescence in situ hybridization findings

EWSR1 Dual-Color Break-apart Probe (Abbott Molecular, Des Plaines, IL) was used to determine translocation or loss of region 22q12.2. Sixty (90.9%) of 66 cells displayed monosomy. No translocation was present (Fig. 4).

4. Discussion

Ovarian ependymomas are very uncommon with 32 reported cases (Table) [2,3,5-22]. Some reviewers have used the WHO grading system for CNS ependymomas to grade extra-CNS ependymomas. This system designates tumors as grade I, II, or III depending on tumor subtype, mitoses, and other histologic features. Of the 32 reported cases, 10 were classified as WHO grade II, 9 as WHO grade III (anaplastic), 1 as WHO grade I (myxopapillary ependymoma), and 12 were not graded. Our case showed a wide range of histomorphologies with low Ki-67 (1%) and focal microscopic necrosis, compatible with a grade II neoplasm. A recently conducted multi-institutional study observed that histologic grade of CNS ependymomas does not strongly correlate with clinical outcomes and suggested that other factors such as tumor location, clinical management, and molecular characteristics play an important role [23]. Consequently, risk may be more accurately stratified based on tumor location, resectability, and molecular findings [24]. It is unclear if this is also true for extra-CNS ependymomas, for which resectability and treatment protocols may have more weight in predicting patient outcomes.

Metastasis of ovarian ependymomas is not uncommon. Most cases have documented spread throughout the abdominal cavity with involvement of the pelvic cavity, peritoneum, omentum, mesentery, broad ligament, diaphragm, liver, colon, spleen, uterus, vaginal apex, cul-de-sac, retrosternal, subphrenic, or pararectal regions. Ten patients showed recurrence, and 2 died of disease. Some of the reported cases lacked adequate follow-up, making it difficult to accurately assess recurrence and mortality rates. However, in cases where adequate follow-up was available, the presence of metastases did not strongly correlate with shortened overall survival.

By comparing 10 CNS ependymomas and 5 extra-axial tumors, Idowu et al [3] observed that extra-CNS ependymomas consistently exhibited multiple histologic patterns, whereas CNS cases displayed little to no histologic variability. In addition, extra-CNS tumors were more likely to be immunoreactive for 34βE12, CK18, CAM5.2, CK7, ER, and PR. Both groups diffusely stained with GFAP. The authors proposed that these differences may be related to the disparate

environments of the CNS versus other locations [3]. From a diagnostic standpoint, extra-CNS ependymomas may be difficult to differentiate from epithelial tumors and neuroendocrine tumors of the ovary. A common diagnostic pitfall is the presence of papillary structures with ciliated columnar cells and psammoma bodies mimicking serous carcinoma. The clue to the diagnosis is the identification of perivascular and true ependymal rosettes accompanied by diffuse and strong GFAP positivity in a tumor lacking overt atypia. Of note, serous carcinoma can have focal, weak staining for GFAP [3]. Neuroendocrine tumors could also pose difficulty because of their monomophic nested morphology, pseudoacinar patterns, and expression of keratin, synaptophysin, chromogranin, and CD56, also seen in ependymomas. However, strong GFAP positivity would be unlikely. Other ovarian glial and neuroectodermal tumors can express GFAP; in those cases, sampling is important to identify classic features of these neoplasms, for example, palisading necrosis, vascular proliferation, and pleomorphism in glioblastoma. Overreliance on immunostains, especially PAX-8, may lead to misinterpretation, as positivity for this marker has been observed in a previously reported ovarian ependymoma and our case [8]. The rate of PAX-8 expression in CNS and extra-CNS ependymomas has not been explored to this date.

Molecular analysis of ependymomas has largely focused on primary CNS tumors, which are divided into 3 broad groups by location: the spine, posterior fossa, and supratentorium; these categories are each further divided into subgroups based on molecular abnormalities [9]. In this classification scheme, *NF2* gene alterations such as *NF2* gene mutations with concomitant loss of 22q are found predominantly in adults with spinal ependymomas. Loss of 22q can also be seen to a lesser extent in the intracranial subgroups [25]. Analysis of a large group of ependymal tumors also showed that *NF2* mutations occur exclusively in grade II (or higher) intramedullary spinal tumors [25,26].

The molecular findings in this case are worthy of further discussion. Via a combination of fluorescence in situ hybridization and next-generation sequencing techniques, we were able to demonstrate *EWSR1* monosomy and copy number losses in *NF2* and *ATRX*. Both *EWSR1* and *NF2* are located within the cytogenetic band of 22q12.2, which supports 22q loss in this neoplasm. Notably, *NF2* mutations and/or chromosome 22q loss are also commonly seen in intramedullary spinal ependymomas, raising the possibility that spinal and extra-CNS ependymomas may share some molecular characteristics. Copy number alterations in *ATRX* (Xp21.1), a gene involved in chromatin remodeling and transcription regulation, have not been described in ependymal tumors, but *ATRX* mutation or loss is frequently seen in IDH-mutant astrocytic tumors as well as a subset of pediatric glioblastomas [4,27]. Hence, loss of *ATRX* copy number is unusual in this setting and its significance in this case is still uncertain.

Molecular profiling of extra-CNS ependymomas is scarce in the literature. Two recent studies did not find any genomic alterations in 3 ovarian ependymomas tested with a next-generation sequencing panel of 50 genes [5,6]. Of note, these panels did not test for *NF2* or *ATRX* alterations. Therefore, ours would be the first case to report genetic alterations in an ovarian ependymoma. Further study is required to determine if extra-CNS ependymomas recapitulate molecular subgroups identified in their CNS counterparts.

5. Conclusion

Ovarian ependymomas are extremely rare neoplasms with relatively favorable clinical outcomes, even in the presence of widespread metastases. Accurate diagnosis should rely on the recognition of classic morphologic features and appropriate use of immunostains. Further research is needed to define the particular molecular alterations associated with these neoplasms and to determine whether these findings have prognostic or theranostic significance.

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