REVIEW

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Primitive neuroectodermal tumors of the ovary: a multidecade review of the scientific literature

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Abstract

Primitive neuroectodermal tumor (PNET) is a general term used in scientific literature for a heterogeneous group of small round-cell malignant tumors primarily arising from neural crest cells. These are extremely aggressive neoplasms which usually occur within soft tissue or bone of young adults. Ovarian tumors composed of primitive neuroectodermal elements are extremely rare, with only few case reports in scientific literature. Due to being so exceedingly rare, PNETs are frequently misdiagnosed and there are no standard therapeutic guidelines. Young patients seem to have better prognoses and individualized strategy is recommended. Limited data suggests that various gene deletions as well as amplifications may be crucial factors for tumorigenesis and the aggressive behavior of PNET. In this paper, we performed a brief review of all cases of primary ovarian PNETs published in the scientific literature to date, in regard to their clinical, histopathological, and therapeutic aspects, with the aim to provide a more comprehensive understanding of this exceedingly rare pathology.

Keywords: primitive neuroectodermal tumor, Ewing tumor, gynecological neoplasm.

Introduction

Primitive neuroectodermal tumors (PNETs) are rare neoplasms of the Ewing family of tumors (EFTs). These entities have neuroectodermal origin and in exceptional cases may affect the gynecological tract [1]. To date, only a few cases have been reported in the scientific literature, affecting each of the following sites: vulva, vagina, uterine cervix, uterine body, ovaries, broad ligament, and rectovaginal septum [2]. Due to their exceptional appearance in the gynecological tract, their true incidence in the ovary is still unknown. PNETs affecting the ovaries are frequently due to the mass effect that they exert on the neighboring organs, and they often affect patients before the age of 40 years. From a histopathological (HP) point of view, PNETs are composed mainly of a relatively monomorphic proliferation of small blue cells, although cases with more primitive features may have a slightly eosinophilic or clear cytoplasm. The classical HP characteristic of PNET is the presence of rosettes, which can be either of Homer–Wright type, or Flexner–Wintersteiner type, the former being more commonly encountered [3]. Central-type PNETs (cPNETs) are malignant tumors composed of tissues closely resembling central nervous system (CNS) neoplasms, with variable degrees of differentiation. Peripheral-type PNETs (pPNETs) are characterized by the presence of *t*(11;22)(q24;12) translocation, which is responsible for the fusion between the Ewing sarcoma (*EWS*) and Friend leukemia integration-1 (*FLI-1*) genes. *EWS* gene can also suffer fusions with other genes, such as *ERG*, *E1AF* or *ETV1* [4]. However, these gene fusions are extremely rare encounters.

The occurrence of PNETs in the ovary is exceedingly rare, posing significant diagnostic and therapeutic challenges. Ovarian PNETs often mimic other more common ovarian malignancies, both clinically and histopathologically, leading to potential misdiagnoses and suboptimal treatments. This rarity not only hinders the establishment of standardized treatment protocols but also contributes to a limited understanding within the medical community [5].

Despite their significance, the literature on ovarian PNET remains fragmented, primarily limited to isolated case reports and small case series. This lack of comprehensive synthesis leads to gaps in knowledge, hindering the development of effective diagnostic and therapeutic strategies. Consequently, there is a pressing need for an exhaustive review of the existing literature to collate and analyze the available data on ovarian PNETs [5].

The objectives of this review are manifold. Primarily, it aims to consolidate the existing knowledge on ovarian PNETs, encompassing their clinical presentation, HP

characteristics, and treatment outcomes. By doing so, it seeks to provide a clearer understanding of this rare entity, which is pivotal for accurate diagnosis and effective treatment planning. Furthermore, this review aims to identify the challenges and limitations of current knowledge, thereby setting a direction for future research and clinical practice.

This review spans literature from the past several decades, including case reports, retrospective studies, and relevant clinical trials. It focuses on providing a comprehensive overview of ovarian PNETs, their clinical manifestations, diagnostic challenges, and therapeutic approaches. Additionally, it discusses the genetic and molecular aspects of these tumors, offering insights into their pathogenesis and potential targets for therapy.

The impact of this review is multifaceted. By providing a thorough synthesis of existing data, it aims to enhance the diagnostic accuracy and inform treatment strategies for ovarian PNETs. Moreover, it endeavors to stimulate further research in this domain, highlighting areas that require deeper investigation and understanding. Ultimately, this review aspires to contribute significantly to the body of knowledge on ovarian PNETs, aiding clinicians, pathologists, and researchers in better understanding and managing this rare but important entity.

Aim

This paper comprehensively reviewed the scientific literature spanning multiple decades on PNETs of the ovary. It delves into various dimensions of this rare pathology, encompassing its clinical, HP, and therapeutic aspects. The rarity of ovarian PNETs poses significant diagnostic and therapeutic challenges, which this paper seeks to address by synthesizing the scattered case reports and case series available in scientific literature.

Objectives

(*1*) To consolidate existing knowledge: this study aims to aggregate and analyze all reported cases of primary ovarian PNETs, a task complicated by the tumor's extreme rarity and the scattered nature of case reports.

(*2*) To enhance diagnostic accuracy: by collating and discussing the clinical and HP characteristics of ovarian PNETs, the paper seeks to aid in improving diagnostic precision, crucial for such a rare and often misdiagnosed tumor.

(*3*) To review therapeutic approaches: given the absence of standard treatment protocols for ovarian PNETs, this paper aims to review the therapeutic strategies employed in reported cases, thereby contributing to a more nuanced understanding of effective treatment methodologies.

(*4*) To identify genetic and molecular characteristics: the study endeavors to explore the genetic alterations and molecular features associated with ovarian PNETs, thereby contributing to the understanding of the tumor's pathogenesis and potential therapeutic targets.

(*5*) To provide a platform for future research: by presenting a thorough review of existing literature, this paper aims to lay the groundwork for future research in this domain, highlighting areas that require further exploration and investigation.

Materials and Methods

In order to perform a comprehensive literature review regarding PNETs of the ovary, a thorough search on *PubMed*®/*MEDLINE* and *Google Scholar* was conducted, using various combinations between the medical subject headings (MeSH) term "ovary" and "primitive neuroectodermal tumor", "PNET", "central-type PNET", "peripheral-type PNET". All case reports and case series published between 1984 and 2021 have been included in the research and their main characteristics have been summarized in Table 1. All studies have been analyzed and the following data have been retrieved: age, clinical aspects/symptoms, microscopic aspects, type of gene fusions and treatment. All the data has been analyzed through the Statistical Package for the Social Sciences (SPSS) software, in order to establish statistical correlation and incidences.

Data analysis

Forty-six cases of PNET have been reported in the scientific literature, to date. The average age at diagnosis was 28.5 years, with a median age of 24 years. Sixty-seven percent of all patients were aged between 15 and 40 years. The average largest dimension of the tumor was 13.2 cm, and the median size was 12 cm.

Regarding the symptoms that have led the patients to the doctor, 45.45% featured an abdominal mass, while 20.45% had abdominal pain. Only 4.5% discovered the tumor incidentally. Ascites was encountered in only 6.5% of cases, while 9% of patients presented with non-specific symptoms (virilism, constipation, loss of appetite, backache or vaginal bleeding). In 21.7% of cases, there were no clinical data described in the cited articles.

From a HP point of view, a neuroblastoma-type morphology was encountered in 11.36% of all cases, a medulloblastoma-like morphology in 15.91%, a medullo-epithelioma morphology in 8.7% of cases, an ependymoblastoma morphology in 6.5% of cases and an ependymoma morphology in 6.5% of cases. A pPNET was encountered in 13.9% of cases. Rare cases (10.9% of patients) had a mixed tumor, in which the PNET coexisted with either a germ cell tumor (*i.e.*, mature teratoma, immature teratoma), or with a sex cord stromal tumor (Sertoli–Leydig cell tumor), or with an adenocarcinoma. No HP date regarding the morphological subtype were available for 26.2% of cases.

Regarding the treatment, half (50%) of the patients underwent both surgery and adjuvant chemotherapy (CT) or radiation therapy (RT), while 19% of patients underwent solely surgical excision (salpingo-oophorectomy). A minority (4.5%) of cases chose to undergo strict cystectomy/surgical removal of the tumor, while the other 8.7% of cases underwent only CT, without any surgical intervention. No clinical data regarding the treatment weas available in 17.8% of cases.

The follow-up period varied between two months and 108 months, with an average of 19.42 months and a median of 12 months. 36.36% of all patients were still alive at the end of the follow up period, while 31.82% eventually died of disease. No clinical data regarding the clinical follow-up or the survival period was available in 31.82% of cases.

Among patients who died of disease, the mean survival period was of 11.1 months. Noteworthy is that 83.33% of all patients who underwent surgical excision were still alive at the end of the follow-up period, while from those who underwent both surgical excision and CT, only 52.94% were still alive at the end of the follow-up.

Table 1 – ***Comprehensive literature review of all cases of ovarian PNETs reported in the literature to date***

Author (year) [Ref.]	Age [years]	Clinical aspects	Size	Microscopic aspects	Type of gene fusion	Treatment	Survival
Burke & Beilby (1984) [6]	53	AM	15×12×10 cm	Neuroblastoma	NA	NA	NA
Kleinman *et al.* (1993) [7]	24	AM	17 cm	Medulloblastoma	NA	USO	NA
	20	AM, ascites	12 cm	Medulloepithelioma	NA	LSO, CT	DF >9 years
	32	NA	13.5 cm	Medulloepithelioma	NA	LSO, CT	DF >3 years
	16	AM, AP	4 cm	Neuroblastoma	NA	RSO, CT	DF >7 months
	13	AP	17 cm	Medulloepithelioma	NA	RSO	DOD after 20 months
	18	AM	20 cm	Ependymoblastoma	NA	RSO, RT	DOD after 3 months
	18	AM	19 cm	Neuroblastoma	NA	RSO, RT	DOD after 7 months
	18	AM, virilism	NA	Ependymoblastoma	NA	RSO, CT	DOD after 6 months
	26	NA	NA	Ependymoblastoma	NA	BSO, CT	One year alive with disease
	69	AM, ascites	11 cm	Medulloblastoma	NA	LSO, RT, CT	DOD after 6 months
	23	Ascites	NA	Medulloepithelioma	NA	TAH, BSO, RT, CT	DOD after 2 months
	16	NA	26	Neuroblastoma	NA	NA	NA
Kawauchi *et al.* (1998) [8]	29	NA	NA	Small round cell tumor (pPNET)	*EWS*/*FLI-1* fusion gene	NA	NA
Jung *et al.* (1999) [9]	17	NA	10 cm	Neuroblastoma	NA	NA	NA
Demirtas *et al.* (2004) [10]	25	AP, AD	8 cm	NA	NA	Surgical excision, CT	DF >3 years
Chow *et al.* (2004) [11]	13	Pelvic mass		pPNET	Multiple chromosomal aberrations	NA	NA
Fischer *et al.* (2006) [12]	78	AP, loss of appetite, weight loss	6.5×4.5 cm	PNET coexisting with endometrioid adenocarcinoma	NA	TAH, BSO, CT	DF >6 months
Anfinan *et al.* (2008) [13]	31	AM, AP	NA	NA	NA	TAH, BSO, CT	DOD after 15 months
Kuk *et al.* (2012) [14]	32	Incidental finding	8×5×1.5 cm	NA	NA	TAH, BSO, CT	DF >54 months
Lim *et al.* (2013) [15]	27	Incidental finding during pregnancy	NA	NA	NA	Ovarian cystectomy	DF >2 years
Huang *et al.* (2013) [16]	28	AP	12 cm	NA	*EWS*/*FLI-1* fusion gene	CT	DF >3 years
Ostwal *et al.* (2012) [17]	28	AM	10×9×4 cm	NA	*EWS*/*FLI-1* fusion gene	TAH, CT	Recurrence after 1.5 year; DOD soon after
Kim *et al.* (2004) [18]	18	AM	16×13.5 cm	NA	NA	TAH, CT, RT	DOD after 10 months
Chu *et al.* (2014) [19]	16	AM	16.5×9.2 cm	Medulloblastoma/ neuroblastoma	NA	CT	NA
Jaramillo-Huff *et al.* (2017) [20]	12	AP, AD	11.5×7.6×14.2 cm	PNET and mature teratoma	NA	Cystectomy	DF >12 months
Nili *et al.* (2018) [21]	23	AP	7×6 cm	Small round cell tumor	NA	TAH, BSO, CT	DF >15 months
	52	AP	10×7×6 cm	Small round cell tumor	NA	TAH, BSO, CT	NA
Ge *et al.* (2019) [22]	NA	NA	NA	NA	NA	NA	DOD in less than 33 months
Winkler *et al.* (2015) [23]	37	AP, constipation	10 cm	cPNET and immature teratoma	NA	SCHT, BSO, OMY, LND and incomplete reductive surgery; CT	NA
Chao *et al.* (2019) [24]	33	Backache and lower limbs pain	12×8.4 cm	NA	NA	CT, RT, palliative treatment	DOD after 2 years
	59	AM	16×13 cm	NA	NA	TAH, BSO, APPY, OMY; residual tumor of 1 cm	NA
	67	AD	NA	NA	NA	RSO, APPY, OMY, sigmoid colon resection; adjuvant therapy	DOD after 6 months

Author (year) [Ref.]	Age [years]	Clinical aspects	Size	Microscopic aspects	Type of gene fusion	Treatment	Survival
	14	AM, AD	30 cm	NA	NA	RSO, APPY, OMY, residual tumor of 1 cm; CT	DOD after 5 months
Chiang *et al.* (2017) [25]	39	Disseminated disease	NA	Medulloblastoma	NA	CT, S	DF
	12	AM	NA	Medulloblastoma	NA	S	NA
	15	Back pain	NA	Medulloblastoma	NA	S	DF >12 months
	24	AM	NA	Medulloblastoma	NA	S	NA
	36	AM	NA	Ependymoma	NA	S	DF >36 months
	14	AM, vaginal bleeding	NA	Ependymoma	NA	RT, S	DOD after 3 months
	28	NA	NA	Ependymoma	NA	S	NA
	NA	NA	NA	pPNET	NA	NA	NA
	NA	NA	NA	pPNET	NA	NA	DF >12 months
	16	Pelvic mass	NA	Glioblastoma	NA	S	DF >36 months
Matsuo *et al.* (2022) [26]	72	Pelvic mass	NA	cPNET, carcinosarcoma and mature teratoma	NA	LSO, APPY, OMY, CT	DF >12 months
McCluggage *et al.* (2022) [27]	20	NA	NA	Sertoli–Leydig cell tumor with embryonal rhabdomyosarcoma and cPNET areas	*DICER1* gene	CT	NA

AD: Abdominal distension; AM: Abdominal mass; AP: Abdominal pain; APPY: Appendectomy; BSO: Bilateral salpingo-oophorectomy; cPNET: Central-type primitive neuroectodermal tumor; CT: Chemotherapy; DF: Disease free; DOD: Died of disease; EWS: Ewing sarcoma; FLI-1: Friend leukemia integration-1; LND: Lymph node dissection; LSO: Left salpingo-oophorectomy; NA: Not available; OMY: Omentectomy; PNET: Primitive neuroectodermal tumor; pPNET: Peripheral-type primitive neuroectodermal tumor; RSO: Right salpingo-oophorectomy; RT: Radiation therapy; S: Surgery; SCHT: Supracervical hysterectomy; TAH: Total abdominal hysterectomy; USO: Unilateral salpingo-oophorectomy.

PNETs of the ovary can be divided into two types: cPNET and pPNET. The former variant resembles CNS tumors from HP point of view, while pPNET is a small round blue cell tumor, which frequently features EWS breakpoint region 1 (*EWSR1*) gene rearrangements. The pathogenesis of these tumors is still unclear, but most authors agree that most of the cPNETs feature a germ cell origin [2]. Multiple authors consider that cPNETs stem from a preexistent teratoma, which features central-type nervous tissue [28]. One of the first scientific articles that mentioned the connection between teratoma and PNET was published by Kleinman *et al.*, in 1993 [7]. They included these tumors in a category named primary neuroectodermal tumors of the ovary which could be further classified into differentiated, primitive and anaplastic. Based on their experience, only the primitive type featured a teratomatous component. The main differences between cPNET and pPNET have been outlined in Table 2.

Table 2 – ***Main differences between cPNET and pPNET***

	cPNET	pPNET
Definition	Malignant tumor composed of tissues closely resembling CNS neoplasms, with variable degrees of differentiation	Malignant small round blue cell tumor, some with *EWSR1* gene rearrangement
Incidence	cPNET > pPNET	
Mature cystic teratoma	Usually associated	No
GFAP	+	-
CD99	-	+
EWSR1 gene rearrangement	Absent	Usually present

CD99: Cluster of differentiation 99; CNS: Central nervous system; cPNET: Central-type primitive neuroectodermal tumor; EWSR1: Ewing sarcoma (EWS) breakpoint region 1; GFAP: Glial fibrillary acidic protein; pPNET: Peripheral-type primitive neuroectodermal tumor.

Clinical aspects

From an epidemiological point of view, PNETs are extremely rare tumors, but central type is more commonly encountered than peripheral type [28]. This aspect has been confirmed in our study, with 68% of all cases in which the HP features were mentioned, having had a central-type morphology. Although most authors claim that one can encounter these tumors in a wide range of age (between the second and the eight decade) [2], the average age in our study was 31.55 years, with most (79.41%) patients being situated in the 15–40 years interval.

Clinically, the scientific literature claims that more than half of the patients present to the hospital for a pelvic mass, information which was confirmed by our study, in which a mass was observed in 44.11% of all cases [28]. Other unusual symptoms described in the literature were local pain, hirsutism, loss of appetite and weight loss [7, 12].

Histopathological aspects

Grossly, the tumoral masses can be either solid, or if they associate a teratomatous component, they can be also present a cystic component. pPNETs can have a soft or fleshy consistency [28], while the cPNETs can have a tan-white or pink appearance [29]. Hemorrhage and necrosis can be also encountered [28]. Kleinman *et al.* reports different aspects within the different types of PNET (differentiated, primitive and anaplastic). According to their study, the tumors which were differentiated were smaller than the primitive ones, and had a smooth, intact surface, while the primitive ones had a nodular or bosselated surface. A cystic component was more commonly observed in the differentiated types, whilst the primitive ones featured small cysts upon sectioning [7]. The anaplastic cPNETs were reported to be large and feature a smooth, but bosselated surface [7]. The mean size reported in the literature is 14 cm, while in our study the average size was 11.38 cm [28].

From HP point of view, one can differentiate between cPNET and pPNET. The former are usually negative for cluster of differentiation (CD)99 and arise usually in teratomas that have nervous tissue within it [15, 30]. The cPNET has been more accurately described in scientific literature. One can separate cPNETs into differentiated, primitive, anaplastic and oligodendroglioma-like [7]. Some authors consider that cPNETs arise in association with other tumors, *e.g.*, teratoma, malignant mixed mesodermal tumor or endometrioid carcinoma, as a separate variant [31–34]. Kleinman *et al.* have described different morphological aspects of these tumors [7]. The differentiated type frequently takes on an ependymoma like-aspect [28], although astrocytoma, oligodendroglioma-like and neurocytoma-like aspects have also been described [32, 33]. These tumors usually feature cells organized in lobules and separated by delicate bands of paucicellular stroma. Perivascular pseudorosettes, formed by the cytoplasmic fibrillary processes of the cells can also be observed. Rare true rosettes have also been reported in most cases of differentiated type cPNET. Papillae or polypoid structures with edematous fibrovascular cores lined by a single layer of cells – cuboidal or flattened, have also been reported. Cysts of different sizes, with a peculiar sieve like aspect can be present in a minority of cases [7, 28]. The tumoral cells can be organized in tubules, ribbons or glanduliform structures. Mitoses are usually sparse, reaching up to three mitoses per 10 high-power fields (HPFs), although some authors report counts of more than 10 mitoses/HPF [7, 19]. Aside from the classical ependymoma morphology of the differentiated type, Kleinman *et al.* have also reported areas similar to a gemistocytic astrocytoma [7].

The primitive type of cPNET has a more immature aspect and is usually characterized by hypercellularity and can feature different morphological aspects, ranging from medulloepithelioma, neuroblastoma and medulloblastoma to ependymoblastoma [28]. The common feature was the presence of small blue hyperchromatic cells with little cytoplasm ranging from clear to eosinophilic, which are arranged in a lobular configuration [2]. The neoplastic cells were accompanied by fine fibrillar process and various amounts of necrosis [7]. Tumors with a medulloepithelioma-like morphology are characterized by the presence of neural tubules and differentiation towards neuronal, glial, and mesenchymal elements [28]. In the neuroblastoma type of cPNET, the presence of neuropil and Homer–Wright rosettes can be observed upon close examination, while in the ependymoblastoma type, ependymal structures with a primitive appearance can be observed [28]. Cases with a medulloblastoma-like morphology are characterized by nodules of tumoral cells which alternate with pale areas represented by neuropil. Desmoplasia can also be encountered [28]. These types of cPNET can be accompanied by a mature teratoma [29].

The anaplastic variant of cPNETs frequently have a glioblastoma-like morphology featuring characteristics of a high-grade glioma, like large areas of "pseudopalisading" necrosis, marked atypia and microvascular proliferations [28, 35, 36]. Oligodendroglioma-like aspects or myxo-papillary ependymoma appearances can also be featured in cPNETs [28].

pPNET is characterized by a diffuse pattern of growth and large cells that exhibit cytoplasmic processes that can be tapered, and which can feature cytoplasm lacking glycogen. Rosettes or pseudo-rosettes with a Homer–Wright or Flexner–Wintersteiner morphology can be observed, although the latter are rarely encountered [2]. Fibrosis and mitoses can be present in variable quantities, similar as the areas of necrosis [30]. These tumors need to be differentiated from neuroendocrine (NE) carcinomas of the ovary and also from small cell carcinoma of the ovary, hypercalcemic type [37, 38].

Immunohistochemical (IHC) analysis can help in differentiating the two types of PNETs, due to the marked membranous immunoreactivity of pPNET towards C99 (MIC2 protein). Nuclear immunoreactivity for FLI-1 and for NKX2.2 are also present in the pPNET [2, 30]. NE markers like CD56 and, less often, synaptophysin can also be expressed by these tumors, with the exception of chromogranin, which is usually negative in these tumors [2, 28]. pPNET can also express to a limited degree S100 protein, neuron-specific enolase (NSE), oligodendrocyte transcription factor-2 (Olig-2) and Leu-7 [2, 35]. In comparison, cPNET typically shows reactivity towards glial fibrillary acidic protein (GFAP), a feature not encountered in pPNET [28]. Pan-cytokeratin (CK) AE1/AE3 can be either negative or can show patchy immunoreactivity in a third of all cases [2, 11]. According to scientific literature, Ki67 index can have variable values, ranging between 3% [32] to 90% [15].

Genetic alterations

More than 80% of pPNET features a *t*(11;22)(q24;q12) translocation, representing the fusion between the *EWS* gene and *FLI-1* gene [2]. Several types of translocations have been described in the *EWS*/*FLI-1* gene fusion. Type 1 translocation, which has been reported to have a better prognosis, results from the fusion of EWS exon 7 to the exon 6 of *FLI-1*. Type 2 translocation is characterized by the fusion of *EWS* exon 7 to the exon 5 of the *FLI-1* gene [17, 39]. The presence of this fusion is essential for therapeutic purposes because studies have shown that *EWS*/*FLI-1* antagonists can show promising results in the *in vitro* treatment of EFTs [40, 41]. Reverse transcription–polymerase chain reaction (RT–PCR), karyotypic analysis or cytogenetics can help in identifying this translocation [30]. Fluorescence *in situ* hybridization (FISH) analysis can also reveal *EWSR1* rearrangements and can also detect a variant translocation – *t*(21;22)(q22.q12), which can be missed by RT–PCR testing [2, 17]. Chow *et al.* have reported a case of a pPNET in which multiple chromosomal aberrations, including losses of chromosomes in 1q, 1p, 6q, 6p, 4q, 7q, 13q, and 13q and chromosomal gains in Xq, 2p, 7p, 1q, 9q, 18q. Additionally, there were noted amplifications of the *N-MYC* and epidermal growth factor receptor (*EGFR*) genes and deletion of the retinoblastoma (*Rb*) gene [11]. Murdock *et al.* have also reported a partial deletion on chromosome 1p and two regions of deletions on 19q [35]. Chiang *et al.* noticed that cPNET usually lacks the classical *EWSR1* rearrangement [42]. Recently, McCluggage *et al.* have observed that a few gynecological tumors with neuroectodermal areas featured *DICER1* mutation. The presence of this mutation could have a prognostic impact, since these patients can benefit from a different type of CT regimen (Vincristine, Cyclophosphamide, Doxorubicin, Ifosfamide, and Etoposide) [27].

Differential diagnosis

Many neoplasms enter in the differential diagnosis, all of them being part of the "round small blue cell neoplasms". The main differential diagnosis is represented by ovarian small cell carcinoma – hypercalcemic type. These tumors also occur in young adults, and they usually arise in patients with paraneoplastic hypercalcemia. On HP examination, these tumors feature follicle-like structures, that can also have luminal eosinophilic secretions [30]. Occasionally, cytoplasmic hyaline globules can be noticed. These tumors are usually positive for epithelial membrane antigen (EMA), pan-CK AE1/AE3, CD10, calretinin, Wilms' tumor 1 (WT1), vimentin and chromogranin. However, they are negative for CD99 and S100, which can aid in the differential diagnosis process [43].

Ovarian small cell carcinoma of pulmonary type can also enter the differential diagnosis. These tumors have characteristics similar to small cell carcinomas encountered in the lung and can feature nuclear molding, large areas of necrosis and crush artifacts. However, the IHC tests show positivity for EMA and CKs, but no reactivity for CD99 [30, 44]. An immature teratoma with atypical neural tissue can be differentiated from PNETs by the lack of confluent growth of the neuroepithelium [45]. A cPNET with an ependymoma-like histology needs to be differentiated from a low-grade serous carcinoma, which can also show papillae lined by atypical cells. However, these epithelial neoplasms are paired-box 8 (PAX8) positive and CD99 negative [28].

Regarding the imaging aspects of ovarian PNET, there are no specific criteria typical for this diagnosis. However, some cases reported in scientific literature provide some insight regarding the possible imagistic findings. Nili *et al.* have observed upon magnetic resonance imaging examination that the tumor had a thick-walled cystic mass which featured rapid wall contrast enhancement, accompanied by diffuse serosal enhancement [21]. Huff *et al.* noticed on the computed tomography scan that the cystic tumor had a complex structure, with small areas of calcifications and adipose tissue [20]. The ultrasound examination of the same case was suggestive for the diagnosis of teratoma [20]. Although these features are not characteristic for ovarian PNET, they should be taken into consideration by the clinician, especially when facing ovarian tumors with unclear histogenesis and atypical clinical presentation.

Treatment

Due to the absolute scarcity of ovarian PNETs, there are no standard therapeutic guidelines. According to currently available literature data and based on tumor stage, most cases reported in the scientific literature were therapeutically managed by total hysterectomy with bilateral salpingo-oophorectomy and adjuvant CT or RT. Usually, ovarian PNETs respond very well to CT and RT, especially to multimodality therapy, which is the standard treatment for EWS [2, 23]. Ehrlich *et al.* have noticed an adverse outcome for PNETs arising in association with teratoma, although a CAV/IE (Cyclophosphamide, Doxorubicin, Vincristine/Ifosfamide and Etoposide) scheme of treatment can improve the prognosis in patients in which surgical treatment is not an option [44]. In comparison, our study showed a survival rate of 52.94% in patients who underwent both total hysterectomy and adjuvant CT/RT.

Fertility sparing treatment has been reported in several articles in the scientific literature. Demirtas *et al.* report the case of a 25-year-old patient who underwent left salpingo-oophorectomy (LSO), wedge resection of the right ovary, omentectomy (OMY) and complete para-aortic lymph node dissection (LND), followed by CT with Etoposide, Bleomycin and Cisplatin. Although the tumor has recurred and the patient followed another CT protocol with Vinblastine, Ifosfamide, Mesna and Cisplatin, she has successfully delivered a healthy baby, 16 months after the last therapy. The patient has been followed up for more than three years and has not developed any other recurrences [10]. Lim *et al.* report another particular case, in which the patient discovered the tumor during the beginning of the pregnancy. The patient underwent cystectomy, refused any other treatment during the pregnancy, and only after the delivery of the baby did, she accept the fertility sparing treatment (LSO, LND and OMY). She refused any adjuvant therapy, and she has had no relapses in the following 2.5 years [15]. Jaramillo-Huff *et al.* have also reported the case of a 12-year-old patient who underwent only ovarian cystectomy without any other further treatment, and who has been followed-up for more than one year [20]. A similar outcome has also been reported by Chu *et al.*, who reported on a 16-year-old patient that underwent LSO, LND and OMY followed by adjuvant CT and who has been followed-up for more than 13 months without any recurrences [19].

Conclusions

Ovarian PNETs are poorly understood tumors, with a variable morphology, dependent on the histological subtype (central or peripheral). cPNETs are characterized by a histology similar to that of the tumors of the CNS, which can be either differentiated (ependymoma-like), primitive (medulloblastoma or neuroblastoma-like) and anaplastic (glioblastoma-like). In comparison, pPNETs exhibit a non-specific small round blue cell tumor morphology, which needs to be differentiated from other tumors with similar morphology (ovarian small cell carcinoma of hypercalcemic type or of pulmonary type). However, since it is an under-recognized entity, their prognosis is still grim, an aspect amplified by the non-specific treatment options. One needs to be aware of this diagnosis when facing a tumor with a primitive HP aspect (small round blue cell tumor) arising in a teratoma, especially when rosettes are present. Additionally, in cases when the pathologist suspects an ovarian PNET based on tumor morphology and immunostaining for GFAP is negative, molecular testing for *EWSR1* rearrangements is recommended.

Conflict of interests

The authors declare that they have no conflict of interests.

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