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ORIGINAL ARTICLE

Primary peripheral neuroectodermal tumor (PNET) of the adrenal gland: a rare entity

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Summary

Purpose: *Ewing Sarcoma/Primitive Neuroectodermal Tumor (ES/PNET) is a malignant small round cell tumor belonging to the Ewing Sarcoma Family of Tumors. It occurs more commonly in children and young adults. Its localization in the adrenal gland is extremely rare.*
We reviewed 35 cases of ES/PNET of the adrenal gland reported in the literature and presented our case.

Methods: *Data were collected by searching for ES/PNET and adrenal gland key words on Google Scholar and PubMed in March 2018, including a case diagnosed in our department. We analyzed all reviewed cases for diagnosis, surgical and systemic therapy and outcome.*

Results: *To date 24 articles presenting cases of ES/PNET of the adrenal gland are reported in the literature. We included in our review 35 cases previously described and one new case. Histologically all cases consisted of sheets of small round cells. Immunohistochemistry was also performed in all cases. Most cases stained positive for CD99 and negative for lymphocytic markers. Markers of epithelial differentiation displayed variable results. In all cases tested, characteristic translocations were displayed supporting the diagnosis. All patients but four were treated surgically and the majority received adjuvant therapy. Only very few cases received neoadjuvant chemotherapy.*

Conclusions: *Primary ES/PNET of the adrenal gland is a rare tumor, showing specific morphological, immunohistochemical and cytogenetic characteristics. Treatment consists of surgery, chemotherapy and radiotherapy.*
Further investigations paired with long term follow-up are necessary to define prognosis for this rare entity.

Key words: *adrenal gland, CD99, Ewing sarcoma, primitive neuroectodermal tumor*

Introduction

ES/PNET are malignant neoplasms that derive from the neural crest [1,2] presenting in both skeletal and extraskeletal anatomic locations. They were first described in 1918 (PNET) by Stout in a 42 year-old male [3] and in 1921 (ES) in a 14 year-old boy [4]. They share characteristic histological, immunohistochemical and molecular features and thus are now considered part of ES/PNET Family of Tumors. This family includes ES of the bone, extraskeletal ES or peripheral PNET, PNET of the thoracopulmonary region (Askin tumor), as well as most recent histotypes with specific translocations (CIC-DUX4, BCOR-CCNB3) [5,6].

ES/PNET may occur at any age, but there is a predilection towards children and young adolescents. Its peak age is 15 years. In this age group it is the second most common bone malignancy after osteosarcoma. Its behavior is aggressive with 25%

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of cases having distant metastasis at presentation [5]. Extraskeletal ES/PNET affects more commonly the retroperitoneal, paravertebral soft tissues, head and neck region, abdomen and pelvis.

Anecdotal cases of different visceral locations of PNET have been reported in the kidney [7], urinary bladder [8], ureter [9], prostate [10], penis [11], seminal vesicle [12], testis [13], small bowel [14], rectum [15], liver [16], gall bladder [17], pancreas [18], maxillary sinus [19], trachea [20], lung [21], parotid gland [22], vulva [23], vagina [24], ovary [25], uterine cervix [26], uterus [28] and breast [29].

The adrenal gland is a rare primary location of extraskeletal ES/PNET. Since the first 3 cases of the adrenal gland ES/PNET were described by Marina et al. [30] in 1989, 32 additional cases have been reported [31-53]. The majority of articles about ES/PNET are case reports, sometimes associated with partial review. We have identified 35 cases described so far. This review discusses the clinical and pathological features of ES/PNET reported in the literature. We also add one more case of adrenal gland ES/PNET diagnosed and treated in our institution.

Table 1. Pathological features of Ewing Sarcoma/PNET of the adrenal gland

No.	*Author*	*Year*	*Gender*	*Age*	*Size (cm)*	*Laterality*	*CD99 staining*	*Cytogenetic profile*
1	Marina et al. [30]	1989	Female	17	NR	NR	NA	NA
2	Marina et al. [30]	1989	Male	7	NR	NR	NA	NA
3	Marina et al. [30]	1989	Male	4	NR	NR	NA	NA
4	Matsuoka et al. [31]	1999	Female	32	10	Left	Positive	NP
5	Pirani et al. [32]	2000	Male	57	15	Right	Positive	t(11;22)
6	Kato et al. [33]	2001	Male	11	13	Right	Positive	t(11;22)
7	Ahmed et al. [34]	2006	Female	28	10	Right	Positive	t(11;22)
8	Komatsu et al. [35]	2006	Female	53	3	Right	Positive	t(11;22)
9	Zhang et al. [36]	2010	Male	30	12	Right	Positive	NP
10	Zhang et al. [36]	2010	Female	21	10	Left	Positive	NP
11	Zhang et al. [36]	2010	Female	24	9	Left	Positive	NP
12	Zhang et al. [36]	2010	Male	22	17	Left	Positive	NP
13	Mohsin et al. [37]	2011	Female	20	NR	Right	NR	NP
14	Gonin et al. [38]	2011	Female	28	11	Right	Positive	t(11;22)
15	Stephenson et al. [39]	2011	Female	17	5	Right	Positive	FISH 22q12
16	Sasaki et al. [40]	2013	Female	17	15	Left	Positive	FISH 22q12
17	Abi-Raad et al. [41]	2013	Female	26	11.3	Left	Positive	FISH 22q12
18	Yamamoto et al. [42]	2013	Male	26	8	Right	Positive	*
19	Phukan et al. [43]	2013	Female	37	12	Left	Positive	NP
20	Dutta et al. [44]	2013	Female	40	15	Left	Positive	NP
21	Zahir et al. [45]	2013	Male	17	18.7	Right	Positive	FISH 22q12
22	Lim et al. [46]	2013	Male	20	11	Left	Positive	FISH 22q12
23	Blas et al. [47]	2013	Male	63	3.2	Left	Positive	FISH 22q12
24	Tsang et al. [48]	2014	Female	37	12	Left	Positive	FISH 22q12
25	Yoon et al. [49]	2014	Female	17	3.3	Left	Positive	FISH 22q12
26	Ait Batahar et al. [50]	2016	Female	16	15.9	Left	Positive	NR
27	Zhang et al. [51]	2016	Male	12	5.4	Right	Negative	NR
28	Zhang et al. [51]	2016	Male	27	6.4	Left	Positive	NR
29	Zhang et al. [51]	2016	Male	2	3.2	Left	Positive	NR
30	Zhang et al. [51]	2016	Male	48	7.7	Right	Positive	NR
31	Zhang et al. [51]	2016	Male	22	8.8	Left	Positive	NR
32	Zhang et al. [51]	2016	Female	56	11.6	Left	Positive	NR
33	Zhang et al. [51]	2016	Male	36	7.6	Left	Positive	NR
34	Pal et al. [52]	2016	Female	8	12.7	Right	Positive	NP
35	Eddaoualline et al. [53]	2018	Female	23	14	Left	Positive	FISH 22q12
36	Present case	2018	Female	30	24	Right	Positive	NP

NA: Not available, NP: Not performed, NR: not reported, * Not performed due to postmortem changes

Methods

Data were collected by searching the key words Ewing Sarcoma, PNET and adrenal gland in Google Scholar and PubMed in March 2018, including a case treated in our department. We included cases, whose diagnosis had been confirmed by immunohistochemical findings, electron microscopy and/or cytogenetic studies.

For each patient we collected demographic data, detailed histology report and cytogenetic results if realized. Also, staging, systemic treatment, radiotherapy, surgical treatment and clinical outcome were studied.

This study was a qualitative analysis for which no statistics was used. Survival analysis was not performed due to the small number of data available and the short follow-up period.

Results

Twenty-four articles from 1989 to 2018 were included in this review. The majority of the articles were single case reports while 2 of them were case series describing 4 and 7 cases respectively [36,51].

Table 2. Therapeutic approach features of Ewing Sarcoma/PNET of the adrenal gland

No.	*Author*	*Year*	*Surgical procedure*	*Adj/Neoadj Therapy*
1	Marina et al.30	1989	NR	C, A, P, VM, E + RT
2	Marina et al.30	1989	total resection	C, A, P, VM, DTIC, VCR + RT
3	Marina et al.30	1989	Adr + Neph	VAC, Dactin, P, VM + RT
4	Matsuoka et al. [31]	1999	Adr + Neph	Adj IE and cisplatin
5	Pirani et al. [32]	2000	Adr + Neph + IVCt	NM
6	Kato et al. [33]	2001	Adr	Neoadj VAC, Predn, Meth
7	Ahmed et al. [34]	2006	Adr	Adj Chemotherapy (5 drugs) x6
8	Komatsu et al. [35]	2006	Adr	NR
9	Zhang et al. [36]	2010	Adr	RT
10	Zhang et al. [36]	2010	FNB	Patient refused treatment
11	Zhang et al. [36]	2010	laparoscopic tylectomy	Chemotherapy for metastasis
12	Zhang et al. [36]	2010	Adr + Neph + Spl + IVCt	Chemotherapy for local recurrence
13	Mohsin et al. [37]	2011	Tru-cut biopsy	Neoadj VAC and Dactin
14	Gonin et al. [38]	2011	Adr + Lym	Adj Chemotherapy + RT
15	Stephenson et al. [39]	2011	Adr	VAC + RT
16	Sasaki et al. [40]	2013	Adr	Adj VA and Dactin/IE + RT
17	Abi-Raad et al. [41]	2013	Adr + Neph + Spl + IVCt	Adj VAC/IE x10 + RT
18	Yamamoto et al. [42]	2013	No	No therapy
19	Phukan et al. [43]	2013	Adr + Neph	NR
20	Dutta et al. [44]	2013	Adr + Neph + Resection of retroperitoneal tissue	Adj VAC/IE x6
21	Zahir et al. [45]	2013	No	VAC/IE
22	Lim et al. [46]	2013	Laparoscopic Adr	Adj VAC/IE
23	Blas et al. [47]	2013	Adr	Adj VAC/IE
24	Tsang et al. [48]	2014	Adr + Neph + partial diaphragm resection	Adj VAC/IE
25	Yoon et al. [49]	2014	Laparoscopic Adr	Adj VAC/IE x3 + RT
26	Ait Batahar et al. [50]	2016	CT guided biopsy	Chemotherapy
27	Zhang et al. [51]	2016	Adr	NR
28	Zhang et al. [51]	2016	Adr	NR
29	Zhang et al. [51]	2016	Adr	NR
30	Zhang et al. [51]	2016	Adr	NR
31	Zhang et al. [51]	2016	Adr	NR
32	Zhang et al. [51]	2016	Adr	NR
33	Zhang et al. [51]	2016	Adr	NR
34	Pal et al. [52]	2016	NCB + Adr	Neoadj VAC/IE x7
35	Eddaoualline et al. [53]	2018	Adr + Neph + Lym	Adj VAC/IE x12 + RT
36	Present case	2018	NCB + Adr	Neoadj VAC/IE

Adr: Adrenalectomy, Neph: Nephrectomy, Spl: Splenectomy, IVCt: Inferior Vena Cava thrombectomy, Lym: Lymphadenectomy NCB: Needle core biopsy, NR: not reported, Adj: Adjuvant, Neoadj:Neoadjuvant, VAC: Vincristine Adriamycin Cyclophosphamide, IE: Ifosphamide Etoposide, C:cyclophosphamide, A:adriamycin, P:platinum, VM: VM-26, VP: VP-16, Dactin: Dactinomycin, DTIC: deticene, VCR: vincristine, Pred: Prednisolone, Meth: Methotrexate RT: radiotherapy, AWD: Alive with disease, DOD: Died of disease, ANED: Alive with no evidence of disease, NCB: Needle core biopsy

Three articles were case series describing 26, 6 and 2 cases including 6 chest wall (Askin), 6 pelvic, 4 tumors involving extremities, 3 retroperitoneal, 1 presacral, 1 paraspinal 1 scapular, 1 extrapleural and 3 adrenal gland ES/PNET [30], 4 kidney, 1 prostate and 1 adrenal gland tumors [37] and 2 tumors located in the hard palate and adrenal gland [34].

A partial review of the literature was provided in several previous articles. Some case reports were not thoroughly analyzed, with essential data missing such as tumor size and type of adjuvant therapy. The series by Zhang et al. describes mainly imaging findings of adrenal PNETs [51] with details concerning therapy and disease outcome being absent.

We reported in Tables 1 and 2 the clinicopathological features and treatment modalities of the reported cases.

Patients' age ranged from 2 to 63 years (median age: 24 years). There was a slight female predominance (20 female and 16 male patients). Tumor size ranged from 3 to 24 cm in the most significant axis (median value: 15 cm). The right adrenal gland was involved in 14 and the left in 19 patients. The majority of patients had either stage III or stage IV disease at diagnosis, whereas almost half of stage IV cases were due to lymph node involvement.

Concerning initial symptoms, most patients presented with abdominal pain, abdominal distension, palpable tumor mass and non-specific symptoms such as anorexia, weight loss, fatigue and fever. Five patients, including our case, were asymptomatic [35,42,46,47]. In four cases the tumors were discovered incidentally by CT scan during evaluation for staging in a 53 year old patient with prostatic adenocarcinoma [47], on follow-up CT scan for Burkitt lymphoma [46] and on routine abdominal ultrasonography, performed for regular health screening in the case presented by Komatsu et al. as well as in our own. In the fifth case the tumor was an autopsy finding in a 26 year-old male that committed suicide [42].

On preoperative imaging studies adrenal gland ES/PNET usually presents as solitary, round to oval, large, well limited mass, with heterogeneous enhancement. It may have a capsule, hemorrhage, cystic degeneration and necrosis [51]. We can rarely observe calcifications. Out of 36 patients with adrenal gland ES/PNET only 1 presented with foci of calcification on CT [33]. Septation is not observed [51].

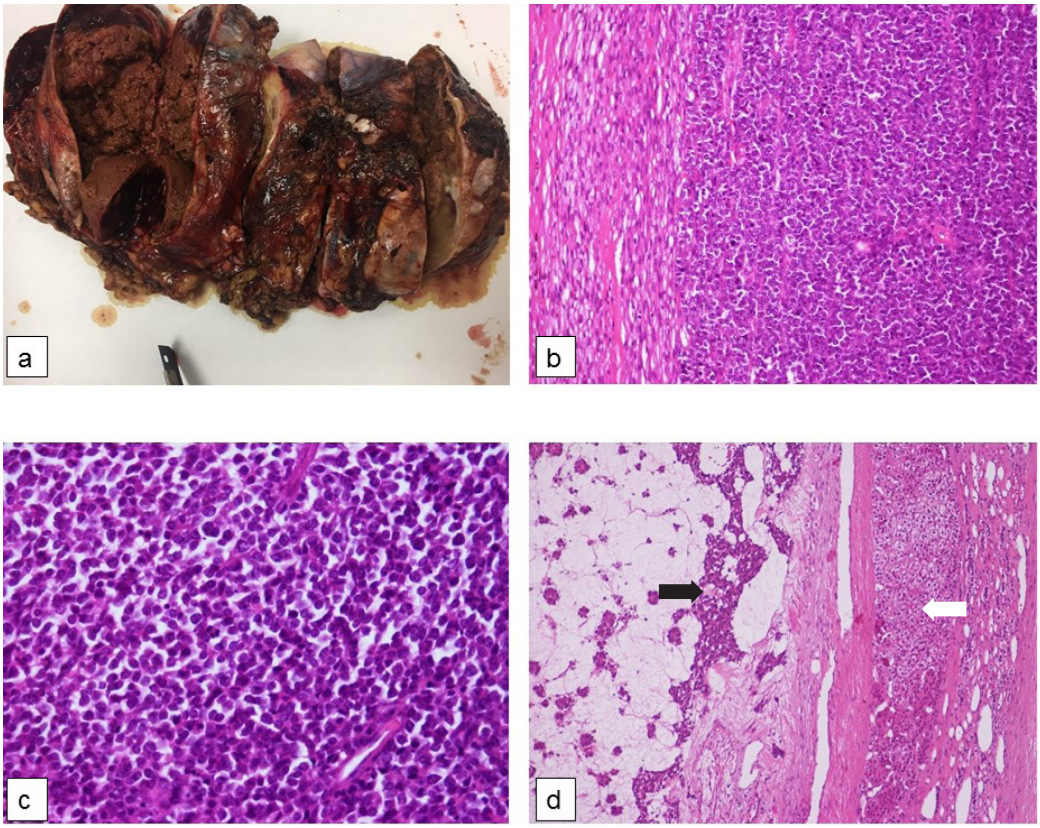

Figure 1. (a) Post-neoadjuvant surgical specimen of adrenal gland with marked hemorrhagic necrosis. On low power examination **(b)** ES/PNET appears as small blue round cell tumor composed of round or oval cells with scanty cytoplasm (HE x20). **(c)** On high power, mitotic figures are numerous (HE x40). **(d)** The present case showing remnant of tumor (black arrow) surrounded by adipose tissue and normal adrenal tissue (white arrow) to the right (HE x20).

In all cases, immunohistochemical and molecular findings supported the appropriate morphological diagnosis. Immunohistochemistry for MIC2 (CD99) was performed in all cases except from the first three which were diagnosed before the introduction of CD99 antibody [30], while Fli-1 was tested in 5 cases [43,48-50] including our own. CD99 whenever used was positive in all but one case [51] confirming its high sensitivity of 95% [54,55]. Fli-1 was positive in all tested cases. Vimentin displayed positive results with rare exceptions [35,36,51]. Markers of epithelial (AE1/AE3, EMA, CK8/18, and CK7), smooth muscle (Desmin) and neuroectodermal differentiation (NSE, Chromogranin A, Synaptophysin, CD56 and CD57) displayed variable results. Markers of lymphocytic (CD45, CD3, CD20, CD79a, CD30, CD5 and CD10) differentiation were uniformly negative. Melan-A displayed unexpected focal positivity and was weak in one case [44]. Molecular confirmation by RT-PCR or in situ hybridization was sought in several cases. Only three cases were not confirmed by either CD99 positivity or molecular studies [30]. Electron microscopy was used to confirm the diagnosis in a few older cases [30,34].

In only a few cases an initial biopsy was performed for diagnostic purpose followed by neoadjuvant therapy [36,37,50,52] and later by a more extensive surgical procedure [53]. That was also the case in our patient.

In the literature the majority of patients underwent open adrenalectomy. Besides, 7 cases underwent nephrectomy [30-32,43,44,48,53] plus resection of the diaphragm, IVC thrombus or retroperitoneal tissue when necessary. Another 2 cases underwent adrenalectomy plus nephrectomy, splenectomy and inferior vena cava (IVC) thrombus resection [36,42]. Lymphadenectomy was performed in a relatively small number of patients. It should be also noted that 3 cases underwent laparoscopic adrenalectomy [36,46,49].

The most common chemotherapy regimen used was vincristine, adriamycin and cyclophosphamide alternating with ifosfamide and etoposide (VAC/IE protocol) for both localized and metastatic disease. Some variations of the above regimen are also reported, including actinomycin D [37,40], methotrexate [33], platinum, teniposide and dacarbazine [30,31,53]. In only 5 patients chemotherapy was administered in the neoadjuvant setting,

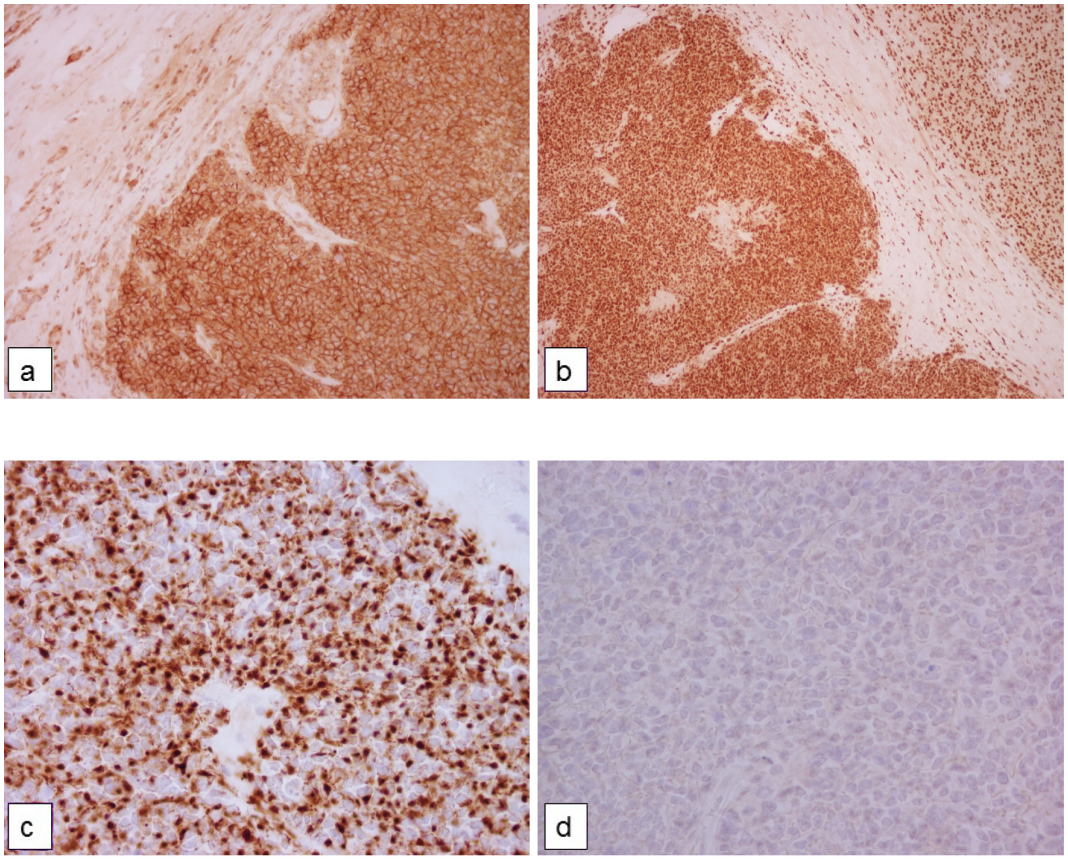

Figure 2. Tumor cells display almost always **(a)** positive membranous staining for CD99 (x20) and **(b)** usually positive nuclear staining for Fli-1(x20). **(c)** CK8/18 may sometimes show positive dot-like staining (x20), while **(d)** lymphocytic markers CD45 (x20) CD3, CD20 etc. are always negative.

versus 13 in the adjuvant and 5 in the metastatic setting.

In a rather limited number of patients radiotherapy (RT) was also given [30,36,38,39,41,49,53], mainly as adjuvant treatment. One patient received whole-abdomen RT [39] and another 3 in metastatic sites [30].

Follow-up time ranged from 1 to 36 months. Regarding outcome 9 patients succumbed to disease, 3 were alive with disease and 13 were alive with no evidence of disease. Data was missing in 9 cases, 1 patient was lost to follow up and in 1 case the tumor was discovered post-mortem. Survival seems to correlate with the clinical stage at presentation, notably the presence of metastatic disease.

Discussion

Diagnosis of adrenal PNET is not apparent, given the non-specific symptoms and imaging findings. However, imaging studies may be helpful for staging the patient and excluding metastasis from another ES/PNET primary [53].

Differential diagnosis of adrenal mass includes several benign and malignant tumors as well as metastatic neoplasms. In childhood the most common adrenocortical tumors are benign non-functional or functional adenomas. When functional they may be related to hormonal symptoms [56]. Adrenocortical carcinomas are equally rare and are often functional [56]. Tumors of the adrenal medulla are more common in children, may reach large dimensions and are also functional. Pheochromocytomas in particular can be easily differentiated from ES/PNETs morphologically.

In contrast, neuroblastomas are histologically similar to the ES/PNET family. They belong to a group of undifferentiated small round cell tumors, including also small cell carcinoma, alveolar rhabdomyosarcoma, retinoblastoma, hepatoblastoma, lymphoblastic lymphoma, nephroblastoma (Wilms' tumor), synovial sarcoma and desmoplastic small round cell tumor. Neuroblastoma is usually associated with high serum NSE and can be diagnosed through urinary VMA/HVA measurement. Immunohistochemical staining for CD99 is essential to support the diagnosis of ES/PNET, whereas neuroblastoma is negative. It should be noted that probably there are more cases of adrenal PNET than the ones reported, misdiagnosed as neuroblastomas, where CD99 IHC was not performed.

Despite the sensitivity of membranous CD99 positivity, it is not entirely specific, as other small round cell tumors may be rarely positive as well. For this reason, the diagnosis of adrenal PNET should be confirmed by cytogenetic or molecular studies. The most common mutation occurring in 80% to 90% of ES/PNET is the reciprocal translocation t(11;22)(q24;q12) of the EWSR1 gene on chromosome 22 with the FLI1 gene on chromosome 11 creating the EWS/Fli-1 fusion gene. Some other tumors namely desmoplastic small round cell tumors and myxoid liposarcoma may very rarely express EWSR1 translocation. The second most common translocation t(21;12)(22;12) occurs in about 10% of cases creates the EWS-ERG fusion. Few cases accounting for 1-5% may have one of several other possible translocations. It should be noted that a minority of ES/PNET accounting for less than 1% of cases has no EWS translocation [57].

Pathological diagnosis requires small round cell morphology, membranous immunohistochemical CD99 expression and one of the known genetic aberrations [49]. Our case showed marked hemorrhagic necrosis on gross examination (Figure 1). It displayed typical morphological, immunohistochemical and cytogenetic characteristics. The tumor consisted of sheets of small round/oval cells with scanty cytoplasm, numerous mitoses with occasional rosettes and pseudorosettes found. Immunohistochemical study was positive for CD99, Fli-1, Vimentin, CK8/18 (dot-like) and negative for AE1/AE3, S100, Chromogranin, Synaptophysin, CD57, CD45 (Figure 2) and Melan-A. Ki67 stained 80% of tumor nuclei. The presence of EWS-FLI1 translocation confirmed the diagnosis.

Extraskeletal ES/PNET is an aggressive neoplasm showing local invasion and tendency to metastasize to lymph nodes, lung, bone, abdominal organs, peritoneum, pleura and brain [58]. Patients with adrenal gland ES/PNET often present with distant metastases, local invasion of the neighboring organs or anatomical structures and less frequently with lymph node involvement. Probably due to lack of symptoms at the beginning, diagnosis is often made with a bulky disease. Local or distant recurrence has also been demonstrated in several cases, mainly when no neoadjuvant chemotherapy was used [31,34,36,40,51,53]. In most cases the diagnosis was only made postoperatively. However, it is well known that ES/PNET have a better outcome when surgical resection takes place after neoadjuvant chemotherapy. Besides, the follow-up time in most cases is limited. Thus, we cannot draw safe conclusions concerning the outcome of these neoplasms nor analyze the effect of different treatments or any other characteristic.

The presence of IVC thrombus is familiar in adrenal PNET, similarly to renal cell carcinoma, and in one case thrombus extended to the right atrium. It is unknown whether it is a biological predisposition or a matter of anatomical proximity.

Finally, it should be noted that one patient had a previous history of Burkitt lymphoma [46] and a second one had a concomitant stage I Gleason 7 prostate adenocarcinoma [47]. ES secondary to other malignancies has been reported in the literature, harboring the same translocations. They are described most commonly after hematologic malignancies [59].

Conclusions

ES/PNET of the adrenal gland is a sporadic and aggressive tumor with few cases reported in the literature. Clinical symptoms and imaging studies are not specific. Adrenal gland PNET diagnosis may be difficult due to lack of clinical suspicion and similar morphology with some other small round cell tumors. A combination of specific histological, immunohistochemical and cytogenetic findings are required. Current management should consist of neoadjuvant chemotherapy followed by surgical resection and adjuvant chemotherapy. Due to its rarity the therapeutic protocol is extrapolated from skeletal ES/PNET management. Its prognosis remains poor.

Further investigations paired with long-term follow-up are necessary to define optimal treatment and prognosis for this rare entity.

Conflict of interests

The authors declare no conflict of interests.

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