

A Retroperitoneal/omental tumor with characteristics of Ewing's sarcoma/peripheral primitive neuroectodermal tumor (EWS/pPNET) and desmoplastic small round cell tumor (DSRCT) with unique pathologic and immunohistochemical features, presented as a renal tumor

O Tulunay, Y Beduk, A Yalcinkaya, R Karaboga

Citation

O Tulunay, Y Beduk, A Yalcinkaya, R Karaboga. *A Retroperitoneal/omental tumor with characteristics of Ewing's sarcoma/peripheral primitive neuroectodermal tumor (EWS/pPNET) and desmoplastic small round cell tumor (DSRCT) with unique pathologic and immunohistochemical features, presented as a renal tumor.* The Internet Journal of Pathology. 2008 Volume 8 Number 2.

Abstract

We present a unique case of retroperitoneal/omental tumor with characteristics of Ewing's sarcoma/peripheral primitive neuroectodermal tumor (EWS/pPNET) and desmoplastic small round cell tumor (DSRCT) in a young adult. This highly aggressive neoplasm must be distinguished from other primitive tumors that require different therapy. The tumor presented as a large mass originating from the right kidney, an evolving as a perirenal mass invading the kidney. Multiple recurrences within the following four post-operative years demonstrated a tumor with a unique location and the coexpression of FLI-1 and WT1. Immunohistochemistry of the tumor shows the known immunophenotypic overlap between EWS/pPNET and DSRCT. The capacity of simultaneous multidirectional phenotypical expression of the tumor may serve a support to the concept that EWS/pPNET and DSRCT form single group tumors. The patient died of disease four years post-operatively. The accurate distinction between these entities has clear prognostic and therapeutic implications.

INTRODUCTION

Ewing's sarcoma/peripheral primitive neuroectodermal tumor constitutes a group of malignant small round cell tumors (SRCTs) of presumed neuroectodermal origin that occur most commonly in bone and soft tissues of children and young adults^[1]. Accurate diagnosis of SRCTs is hindered by their significant morphologic and genetic overlap and complicated by their rarity. EWS/PNET is characterized by a balanced chromosomal translocation which generates a fusion transcript of the EWS gene and the Friend leukemia virus integration 1 (FLI-1). Cases of primary EWS/pPNET of the kidney^[2], retroperitoneum^[3], and omentum^[4] have been sporadically reported in the literature. To our knowledge, the present case is the second case to be reported of EWS/pPNET observed in retroperitoneum/omentum as a multilocular cyst with intracystic hemorrhage and necrosis. The tumor was unique with its location, and the coexpression of FLI-1 and Wilms tumor-associated (WT1) tumor suppressor gene, which are

diagnostic of EWS/pPNET^[5] and DSRCT^[6], respectively.

CASE REPORT

A 28 years-old man presented with a recent vague right lumbar pain had a right nephrectomy in a community hospital of a small city with a final diagnosis of high grade, sarcomatoid renal cell carcinoma, with disseminated perirenal infiltration. Two years later, he was referred to admit to the urology department for further evaluation. The laboratory studies was within normal limits. MRI and CT scan demonstrated multiple mass located on the left lower quadrant of the abdomen; one was on the anterolateral aspect of the descending colon extending into the inferior aspect of the liver; the second mass was located retroceally and anterior to the right iliac muscle, lateral to the the right psoas muscle, and the third one was anterior to iliac artery bifurcation, and next to the right psoas muscle. They showed internal cystic degenerations, were lobulated, necrotic and highly hemorrhagic. Excision of the tumor was followed by four cycles of polychemotherapy (gemcitabine and

cisplatin) which was switched to phosphamide and doxorubicine following a follow-up CT scan. Six months later CT scan was demonstrated disease progression. Abdominal ultrasonography (USG) and the CT scan was demonstrated a huge cystic mass with lobulated contours, measuring 24 cm in cranio-caudal dimension. There was a large, hemorrhagic and cystic tumor inferior to the liver, involving omental tissue and the right psoas muscle. Six months later he was readmitted and the omental mass was excised, a left double-j catheter was inserted. Three months later, subhepatic and mesenteric masses disappeared but the right pelvic hipodense residual lesion expanded. The double-j catheter was removed and two cycles of chemotherapy (vincristine, endoxan) was administered. Four months later he was readmitted, and referred to the radiation oncology for radiotherapy. Abdominal USG and CT scan was revealed some benefit of the former lesions, but also showed new lesions with cystic appearance. Five months later abdominal CT scan demonstrated a huge, cystic mass with lobulated contour, occupying almost the whole abdomen, with a right sided dominance. The tumor was found to be filling the whole right upper abdomen, right pelvis and left mesenteric tissue. The right psoas muscle and anterior abdominal wall were infiltrated by the tumor. He developed acute trombosis of the right superficial and deep femoral, popliteal and crural veins, as well as intestinal obstruction. He was cachectic. No operation was planned, and put on coumadine treatment, and one month later a segment of left colon disclosed tumoral involvement of serosal aspect was resected for ileus, and he was died of disease within three months (disease specific death within four years and three months).

GROSS FEATURES

The first operation recorded in the pathology report were demonstrated a tumor, 9.7x5 cm, attached to the right kidney measuring 11.5x6x5 cm. Renal parenchymal tissue adjacent to the fragmented and highly necrotic tumor had been destructed by the tumor and was quite haemorrhagic. Two hematoxylin and eosin (HE) stained tumor slides provided were demonstrated the same histology of the recurrent tumors. All recurrent tumors were multilobated, soft and friable. Grayish-yellow and gray-tan tumor tissues were in continuity with omental adipous tissues. The first recurrent tumor was consisted of twenty one pieces of tissues, the largest 13x9x3.5 cm. Multiple gray-white soft nodules within adipous tissue and large hemorrhagic and cystic spaces with dark red-brown bloody substance were evident.

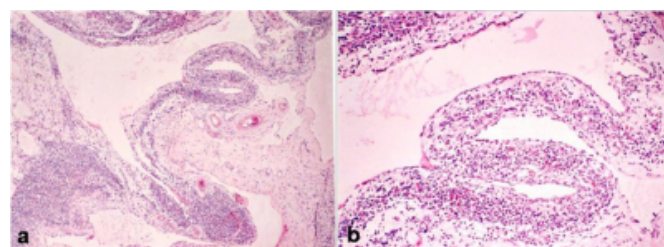
Seven specimens, the largest 7x6x4 cm, were excised from the left psoas and inferior vena cava regions one year later. The largest mass, 20x8x4 cm, was from right operated kidney zone. Three tissues, the largest 5x4x3 cm, were from the right psoas and inferior vena cava regions. The specimen excised six months later was tissues of various sizes, the largest 15x8x4 cm. Four omental tissues from right lower pelvis, the largest 27x18x8 cm, were found multifocally occupied by tumor growth. The specimen, 19x19x11 cm, excised six months later was consisted of an left colon segment with omentum, and lymph nodes with no metastases. Colon specimen was demonstrated focal transmural necrosis and reactive inflammatory cell infiltration, predominating polymorphonuclear leucocytes and an tumor mass attached to submucosa.

HISTOPATHOLOGIC FEATURES

The nephrectomy specimen was disclosed a tumor leaning on the right kidney. All specimens were demonstrated a tumor with unique microscopic features. Large nodular cystic recurrent tumors were tightly adhered to the peritoneum, and also invaded the serosal surface of a colon segment. No metastasis was detected in organs or in the lymph nodes. The tumor was consisted of solid and cystic areas with considerable hemorrhage and necrosis. Microscopically, the wall of the cystic tumor consisted of various sized islands of small round cells (Fig. 1).

Figure 1

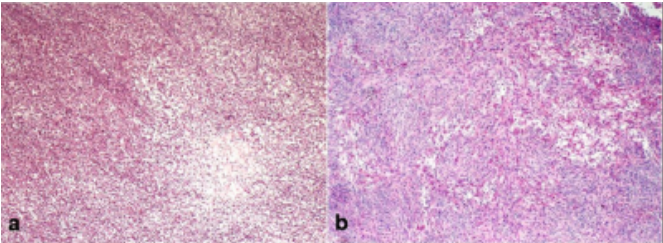
Figure 1: The wall of the cystic structures adhered to the peritoneum consists of various sized nodular tumor tissue of small round cells (a. HE, '10, '25).



The solid sheets of tumor cells were arranged as irregular masses divided into lobules by hemorrhage and necrosis (Fig.2).

Figure 2

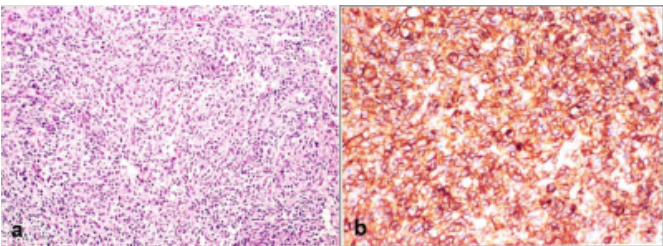
Figure 2: The tumor characterized by solid sheets of cells with monotonous appearance and degenerated hypocellular areas (a. HE, ×50). More condensed areas of the tumor consist of necrotic and hemorrhagic background with many round eosinophilic globules (b. HE, ×50).



Individual cell outlines were distinct and cells were small, uniform, round, and exhibited hyperchromatic nuclei with frequent indentations and small nucleoli and numerous typical and atypical mitotic figures (Fig. 3). The cells were demonstrated scant round cytoplasm and also displayed spindled areas.

Figure 4

Table 1: Details and results of the antibody panel



There was a well-developed vascular network becoming clearly apparent in areas where the cells undergo degeneration and necrosis which was striking feature of the tumor. Such areas were characterized by the association of the degenerated cells with distinct vascular structures having thickened, fibrosed walls and dilated lumina, the so-called “filigree pattern”. Necrosis was common and dominated in some microscopic fields. Rosette formations or ribbon-like cell arrangements were not apparent. Recurrent tumors were demonstrated “storiform-like” pattern consisting of plump spindle cells arranged in short fascicles around slit-like vessels and contained areas showing more cellular pleomorphism with few multinuclear tumor giant cells, and groups of histiocyte-like cells, all of which were reminiscent of malignant fibrous histiocytoma (Fig. 4). The tumor cells contained cytoplasmic glycogen, none to moderate, as demonstrated by Periodic acid-Schiff (PAS) stain with diastase control. Weigert’s reticulin stain was demonstrated

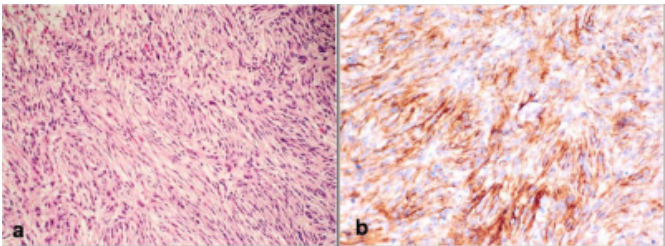
reticulin fibers outlining tumor lobules, with rare fibers between the tumor cells.

IMMUNOHISTOCHEMICAL (IHC) FEATURES

IHC analysis performed on paraffin-embedded tissue sections using the streptavidin-peroxidase procedure (Table 1).

Figure 5

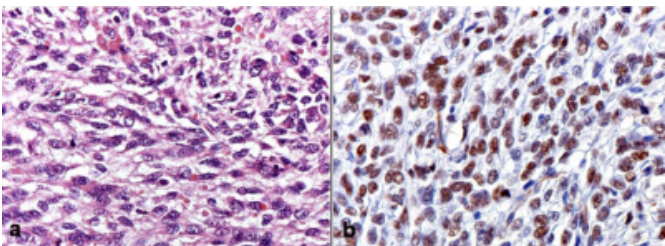
Figure 4: The third recurrent tumor demonstrating short fascicles of histiocyte-like spindled cells with storiform pattern (a. HE, ×50) shows diffuse and intense membranous MIC-2 (CD99) positivity (b. Peroxidase, ×50).



Immunohistochemistry was revealed diffuse and intense membranous positivity of tumor cells for MIC-2 (CD99) (Fig. 4, 5). Nuclear staining for FLI-1, and WT-1 was moderate to intense (Fig. 5, 6).

Figure 6

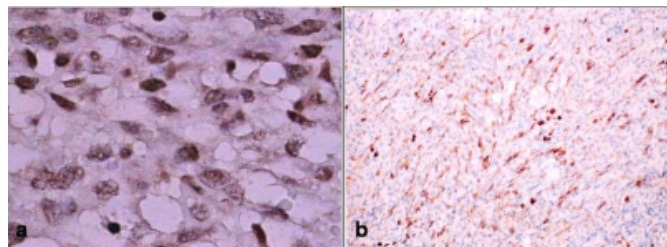
Figure 5: Tumor cells with round to oval hyperchromatic nuclei with frequent indentations and small nucleoli (a. HE, ×100) displays diffuse and intense nuclear WT-1 positivity (b. Peroxidase, ×100).



The tumor cells were diffusely and moderately immunoreactive for VIM, A1AT, S-100, focally and weakly positive for neurone specific enolase (NSE). Focal strong CD117 (c-kit) positivity, in scattered spindle cells strong neurofilament (NF) staining were observed (Fig. 6).

Figure 7

Figure 6: Diffuse and intense nuclear ALK-1 (a. Peroxidase, '250), and focal intense cytoplasmic NF [removed]b. Peroxidase, '50) of the tumor cells.



{image:7}

The tumor was negative for pan-cyokeratin (panCK) (AE1/AE3), epithelial membrane antigen (EMA), desmin, smooth-muscle actin (SMA), alpha fetoprotein (AFP), CD68, glial fibrillary acidic protein (GFAP), synaptophysin, CD57 (Leu7), calretinin, mesothelin, HMB45, factor VIIIIR, CD31, and CD34. The final diagnosis of the tumor, made after through pathological and immunohistochemical investigation was EWS/pPNET and DSRCT of retroperitoneum/omentum demonstrating FLI-1 and WT1 expression arising as a multilocular cyst with intracystic hemorrhage.

DISCUSSION

EWS, pPNET and DSRCT are tumors belong to SRCTs which are a spectrum of clinical and pathologic features, and some are histogenetically related. To distinguish between EWS/pPNET and other SRCTs is sometimes difficult by conventional morphologic methods, especially if the tumor arises in an unusual region. The typical PNET may resemble a primitive fibrosarcoma, malignant schwannoma, or malignant fibrous histiocytoma. It is apparent that virtually all SRCTs show immunoreactivity for the MIC2 gene product[7], thus, this marker was used as part of a panel immunostains, given the lack of complete specificity was diffusely and intensely positive.

Ordenez[8] has shown that, all 37 but two DSRCTs have been originated within the abdominal and/or pelvic peritoneum, and 8 tumors have also involved the retroperitoneum as was observed in the present tumor. The tumor was identified as a tumor with features of ESW/pPNET and DSRCT with multilocular cystic and hemorrhagic appearance, arising in the retroperitoneum/omentum similar to the case has been

reported by Tanida et al[4]. Although the characteristic histology of DSRCT; a nesting pattern of cellular growth within dense desmoplastic stroma was missing in the tumor, WT1, suggested as a useful marker to separate DSRCT from EWS/PNETs[6], was positive along with FLI-1. Nakatsuka et al[[[9]]] have shown that, cases of EWS/PNET have been positive for polyclonal and monoclonal antibodies against WT-1. This observation supports the study in which hybrid features of these tumors has been shown[10]. In this study an hypothesis have had formulated that EWS/pPNET and DSRCT form a single group tumors in which polyphenotypism, neural differentiation, and desmoplasia are epiphenomena governed by local microenvironment, or by the involvement of variable gene products (FLI-1 versus WT-1) as transcriptional activators.

Mimicry of a fibrohistiocytic tumor in recurrent tumors was not supported by their immunophenotype. Although the tumor was not expressed CK, EMA and desmin, their expressions may be seen in EWS/pPNET[6]. It has been stated that, keratin along with EMA, and desmin coexpression would allow a diagnosis of DSRCT. Although desmin has value to differentiate DSRCT, in two PNETs that had rosettes and neural features desmin has been described[11], and the presence of the fusion of the EWS to the WT1 is considered a feature unique to DSRCT[6]. Diffuse nuclear WT1 expression observed in the present tumor represents the accumulation of the hybrid gene protein and supports the known immunophenotypic overlap between EWS/pPNET and DSRCT[10], and also demonstrates the necessity of further studies for its credence.

Expression of WT1 has been reported in several neoplasms, including mesothelioma[12] which was in the differential of the present tumor. The tumor cells were absolutely nonreactive for mesothelial markers; calretinin and mesothelin. In the present tumor neural and neuroendocrine markers, including GFAP, CD57, and synaptophysin were negative. S100 and NSE expressions were diffuse and focal, respectively. Moderate cytoplasmic NF positivity observed in spindled cells was also focal. c-kit expression observed focally in the present tumor has either been detected in EWS/PNET[13], or in DSRCT[14]. The markers used to differentiate angiolipoma; HMB45, Factor VIIIIR, CD31, and CD34 were negative as was for AFP.

Despite all therapeutic modalities, the outcome is dismal in EWS/PNET and DSRCT since they are highly aggressive

neoplasms. Outcome of our patient does not seem influenced by combined chemotherapy, and poor response to chemotherapy may underlay the failure of an improved survival. More aggressive surgical treatment may have been indicated to improve survival at the time of the first laparotomy which was crippled by a mispresentation of the tumor as a renal tumor. Obedience to follow-up programmes are also essential to restore the outcome of which was defective in our setting.

Here, we describe a rare case of an intra-abdominal SRCT in a young man exhibited the light microscopic appearance of a EWS/pPNET with FLI-1 and WT1 expression; the markers which are suggested having a definitive role in the differential diagnosis of EWS/PNET, and DSRCT, respectively^[569]. This brings forward a tumor with hybrid characteristics of EWS/PNET, and DSRCT, as strengthen before, may belong to the same family of tumors exhibiting a similar clinical behavior. Additional clinical studies are needed, before the latter statement becomes valid.

References

1. Toskos M. Peripheral primitive neuroectodermal tumors. diagnosis, classification and prognosis. *Perspect Pediatr Pathol* 1992;16:27-98.
2. Quezado M, Benjamin DR, Tsokos M. EWS/FLI-1 fusion transcripts in three peripheral primitive neuroectodermal tumors of the kidney. *Hum Pathol* 1997;28:767-71.
3. Angervall L, Enzinger FM. Extraskelatal neoplasm resembling Ewing's sarcoma. *Cancer* 1975;36:240-51.
4. Tanida S, Tanioka F, Inukai M, Yoshioka N, Saida Y, Imai K, Nakamura T, Kitamura H, Sugimura H. Ewing's sarcoma/peripheral primitive neuroectodermal tumor (pPNET) arising in the omentum as a multilocular cyst with intracystic hemorrhage. *J Gastroenterol* 2000;35:933-40.
5. Folpe AL, Hill CE, Parham DM, O'Shea PA, Weiss SW. Immunohistochemical detection of FLI-1 protein expression. A study of 132 round cell tumors with emphasis on CD99-positive mimics of Ewing's sarcoma/primitive neuroectodermal tumor. *Am. J. Surg. Pathol.* 2000;24:1657-62.
6. Chang F. Desmoplastic small round cell tumors: cytologic, histologic, and immunohistochemical features. *Arch Pathol Lab Med* 2006;130:728-32.
7. Weidner N, Tjoe J. Immunohistochemical profile of monoclonal antibody O13: antibody that recognizes glycoprotein p30/32MIC2 and is useful in diagnosing Ewing's sarcoma and peripheral neuroepithelioma. *Am J Surg Pathol* 1994;18:486-94.
8. Ordonez NG. Desmoplastic small round cell tumor. I: A histologic study of 39 cases with emphasis on unusual histological patterns. *Am J Surg Pathol* 1998;22:1303-13.
9. Nakatsuka S, Oji Y, Horiuchi T, Kanda T, Kitagawa M, Takeuchi T, Kawano K, Kuwae Y, Yamauchi A, Okumura M, Kitamura Y, Oka Y, Kawase I, Sugiyama H, Aozasa K. Immunohistochemical detection of WT1 protein in a variety of cancer cells. *Mod pathol* 2006;19:804-14.
10. Katz RL, Quezado M, Senderowicz AM, Villalba L, Laskin WB, Tsokos M. An intra-abdominal small round cell neoplasm with features of primitive neuroectodermal and desmoplastic round cell tumor and a EWS/FLI-1 fusion transcription. *Hum Pathol* 1997;28:502-9.
11. Parham DM, Dias P, Kelly DR. Desmin positivity in primitive neuroectodermal tumors of childhood. *Am J Surg Pathol* 1992;16:483-92.
12. Amin KM, Litzky LA, Smythe WR, Mooney AM, Morris JM, Mews DJY, Pass HI, Kari Csaba, Rodeck U, Rauscher III FJ, Kaiser LR, Albelda SM. Wilms' tumor 1 susceptibility (WT1) gene products are selectively expressed in malignant mesothelioma. *Am J Pathol* 1995;146:344-56.
13. Ahmed A, Gilbert-Barnes E, Lacson A. Expression of c-kit in Ewing family of tumors: a comparison of different immunohistochemical protocols. *Pediatr Dev Pathol.* 2004;7:342-7.
14. Zhang PJ, Goldblum JR, Pawel BR, Fisher C, Pasha TL, Barr FG. Immunophenotype of desmoplastic small round cell tumors as detected in cases with EWS-WT1 gene fusion product. *Mod pathol* 2003;16:229-35.

Author Information

Ozden Tulunay, M.D.

Professor of Pathology, Department of Pathology, School of Medicine, Ankara University

Yasar Beduk, M.D.

Professor of Urology, Department of Urology, School of Medicine, Ankara University

Aysegul Yalcinkaya, M.D.

Resident of Pathology, Department of Pathology, School of Medicine, Ankara University

Resul Karaboga, M.D.

Resident in Urology, Department of Urology, School of Medicine, Ankara University