Infantile Fibrosarcoma/Cellular Mesoblastic Nephroma-like Lesion – An Unusual Presentation in a 19-Year-Old Female

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Abstract

We report a case of a 19-year-old female patient with a cellular mesoblastic nephroma (CMN)/infantile fibrosarcoma (IFS)-like tumor, a low-grade malignant renal tumor that usually affects neonates and young infants. She presented with severe abdominal pain, anorexia, and weakness. Subsequent imaging revealed a large solid-cystic mass in her left kidney. The tumor showed different histological features, such as atypical cells in nests and lobules, cystic spaces, rhabdoid cells, and myxoid change. The initial diagnosis was an undifferentiated malignant round cell tumor, and she received adjuvant chemotherapy with the VAD protocol for Wilms tumor, but it was stopped due to poor tolerance. Immunohistochemistry was positive for vimentin, and SMA, and negative for other markers raising the possibility of CMN. The tumor tested negative for SS18, BCOR, NTRK1, EWS, NCOA2, and NUTM1 cytogenetic analysis. The patient developed local recurrence and distant metastasis within 9 months and died within 1 year. We also reviewed the literature on cases of CMN/IFS lacking the NTRK3-ETV6 fusion gene, which is present in about 70% of CMN cases. Unbiased sequencing revealed oncogenic rearrangements in MAPK-signaling genes, especially epidermal growth factor receptor (EGFR) and BRAF, in CMN and IFS cases without the fusion gene. EGFR internal tandem duplication was detected in all CMN tumors analyzed, making it a diagnostic marker and a potential therapeutic target. These findings increase our knowledge of this rare entity and offer insights into possible treatment options.

Keywords: Cellular mesoblastic nephroma, infantile fibrosarcoma, nephrectomy

Introduction

Congenital mesoblastic nephroma is the most common type of renal tumor in neonatal and early infancy, comprising 3%–10% of all childhood renal tumors.[1] Infantile fibrosarcoma (IFS) of the kidney, also known as cellular congenital mesoblastic nephroma, is a stromal tumor, most diagnosed in the first 3 months of life and is very rarely seen in adults. Adult fibrosarcoma differs from IFS in their clinical presentation because of the strong local aggressive nature and problematic appearance of metastasis in 50% of the cases, sometimes late.[2]

Case Report

A 19-year-old female patient presented with a month-long history of severe abdominal pain, anorexia, and weakness. On examination, a large tender lump was found in her epigastric, left hypochondriac, and iliac regions. Preoperative laboratory investigations were normal, except for anemia. A computed tomography scan revealed a large solid-cystic mass replacing most of her left renal parenchyma, indicating cystic renal cell carcinoma [Figure 1].

Fine-needle aspiration cytology and cell block were inconclusive. Urinary metanephrines were within the normal limits. The patient underwent R0 resection during surgery, and no complications occurred postoperatively. Intraoperatively, tumor was found to be a large vascular solid-cystic mass that had adhered to the descending mesocolon, duodenum, retroperitoneum, and left common iliac artery. Grossly, serial sections across the kidney showed an ill-defined large cystic lesion measuring 17 cm × 13 cm × 7 cm occupying both poles of the kidney, with a capsular breach and abutting the renal pelvis.

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Microscopically, the neoplasm showed varying histomorphology with atypical cells arranged in nests and lobules. The individual cells had moderate eosinophilic cytoplasm, ovoid-to-rounded vesicular nuclei with granular chromatin, and prominent nucleoli in a few. Mitotic activity was brisk (30–32/10 hpf). Large cystic spaces lined by flattened epithelial cells were seen. Foci showed rhabdoid cells with moderate-to-abundant eosinophilic cytoplasm and ovoid nuclei. Furthermore, areas with myxoid change and nests and islands of small round cells with scant cytoplasm and ovoid hyperchromatic nuclei were seen.

The patient underwent surgery and received an initial histomorphology diagnosis of an undifferentiated malignant round cell tumor. Then, the medical oncologist started adjuvant chemotherapy using the VAD protocol for Wilms tumor. However, the patient showed poor tolerance to the treatment, which caused its discontinuation.

Immunohistochemistry (IHC) analysis showed negative results for NSE (MO873), PANCK (AE1/AE3), DESMIN (D33), CD34 (QBEND-10), and WT1 (EP122). CD99 (EP8) was focal positive, VIMENTIN (V9) was positive, and SMA (1A4) showed patchy positivity [Figure 2]. In addition, the tumor tested negative for SS18, BCOR, NTRK1, EWS, NCOA2, and NUTM1 molecular testing. Based on the morphology and immunohistochemistry findings, the final diagnosis of a cellular mesoblastic nephroma (CMN)-like tumor is rendered. These tumors do not have an established significant role for chemotherapy. Unfortunately, the patient experienced local recurrence and distant metastasis within 9 months of surgery, with lung metastasis and pleural effusion. The disease was aggressive in this patient, and it being rare in adults, it was difficult to predict or comment on the prognosis. Sadly, the patient succumbed to the disease within 1 year of diagnosis.

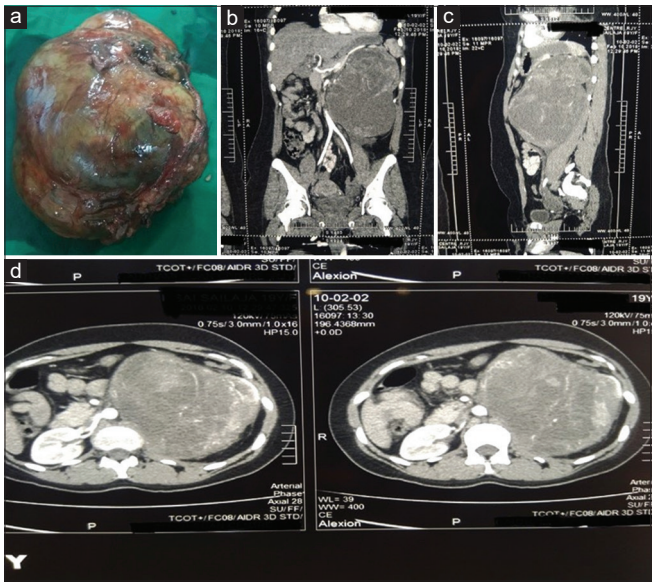

Figure 1: Gross and radiological findings. Grossly and radiological imaging shows solid-to-cystic mass occupying the left hypochondriac and the left lumbar regions. (a) Gross image of the left kidney; (b) Coronal section of the abdomen; (c) Sagittal section of the abdomen; (d) Axial section of the abdomen

Discussion

CMN and IFS are two entities that display similar histological and immunohistochemical characteristics and are typically observed in the pediatric population, specifically those under the age of 2 years.[3-5] However, we have come across an exceptional case of CMN/IFS-like tumor in a 19-year-old female. In this discussion, we will explore the distinctive features of this renal neoplasm, including its clinical presentation, histological examination, and immunohistochemical profile, which collectively led us to the diagnosis.

The differential diagnosis includes Wilms tumor, particularly posttherapy Wilms with stromal-type residual. The current case is unlikely to be Wilms tumor because the patient has not received any treatment and IHC for Wilms' tumor gene 1 (WT1) is negative. The presence of a monomorphic population of cells with no epithelial component and the negative IHC results for desmin indicate that tumor is not a mixed epithelial and stromal tumor. Clear-cell sarcoma of the kidney is also unlikely due to the monomorphic population of cells observed in the tumor, contrasting with the characteristic clear to eosinophilic cytoplasm and nests or cords with the obvious chicken-wire vascular pattern seen in clear-cell sarcoma.

Rhabdoid tumor is another unlikely diagnosis as it typically presents with large cells, eccentric nuclei, and prominent nucleoli, which differ from the monomorphic population of cells observed in this case. Metanephric stromal tumor can be ruled out based on the histological features of the tumor, as it typically presents uniform spindle cells arranged in a storiform or whorled pattern, in contrast to the monomorphic

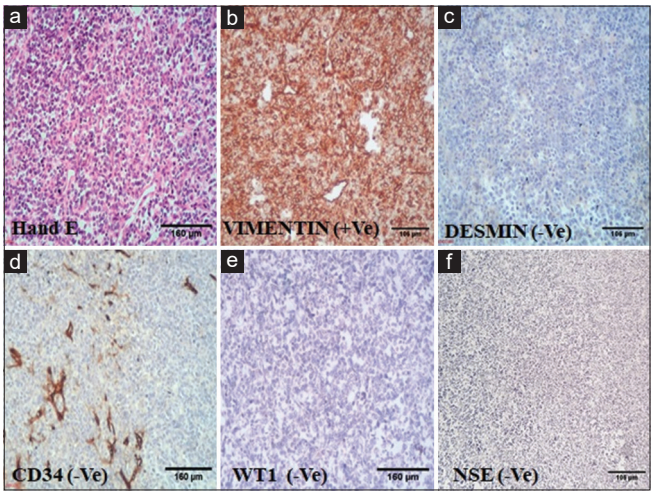

Figure 2: IHC studies to confirm infantile fibrosarcoma. (a) H and E image showing sheets of monomorphic cells with scant cytoplasm and vesicular nuclei; (b) IHC for vimentin is positive. (c-f) IHC for Desmin, CD34, WT1 and NSE is Negative. IHC: Immunohistochemistry. The images were captured at a 400X magnification

Table 1: Fusion partners in infantile fibrosarcoma/cellular mesoblastic nephroma of kidney: Insights from cases lacking the NTRK3-ETV6 fusion gene

Serial number	Age/sex	IHC	Fusion associated	Mets	Follow up	Remarks
1[6]	1/male	SMA[d], S100, ERG, CD31[f] and CD34, pan-TRK[n]	CLIP2-RET	LN/lung	ANED-8	Negative for ETV6 rearrangement
2[7]	1/female	NA	SPECC1L-RET	Lung/CNS	NA	
3[8]	18 months/ female	CD34, pan-TRK, SMA[n], S100[p]	BRAF P V600E	NO	AWD, 24 months	3 mitosis/hpf
4[9]	2/female	CD34, S100, SMA[n]. ALK[nd]	TPM3-ALK	Liver and lung	NED, 14 months	Size of tumor 9.3 cm, 4 mitosis/10 hpf, <10% necrosis
5[9]	10/female	CD34, S100, SMA[p]. ALK[p]	CLIP1-ALK	NO	NED, 13 months	Size of tumor 14 cm, 4 mitosis/10 hpf, <5% necrosis

[d]Diffuse positive, [f]Focal positive, [n]Negative, [p]Patchy positive, [nd]Not done, [P]Positive. ANED: Alive without evidence of disease, NO: Not present, AWD: Alive with disease, NED: No evidence of disease, LN: Lymph node, NA: Not applicable, IHC: Immunohistochemistry, SMA: Smooth muscle actin, ALK: Anaplastic lymphoma kinase, ERG: Erythroblast transformation-specific [ETS]-related gene

cells observed here. IHC for CD34, which is typically positive in metanephric stromal tumor, was also negative.

We think that this case is CMN or IFS based on the clinical presentation, histological examination, and IHC profile. This is a rare finding in a 19-year-old patient. We send the case out for molecular testing to look for NTRK fusion genes and other genetic abnormalities that are common in CMN/IFS. The results are negative for all the tests we do, i.e., SS18, BCOR, EWS, NCOA2, and NUTM1. More recent publications have identified additional genetic abnormalities in CMN/IFS-like tumor [Table 1].

We present five cases of IFS-like tumors involving the kidney from published literature baring other fusions other than classic NTRK fusion, which is seen in most of the cases. The clinical, pathological, and molecular features of these cases are summarized in Table 1. These cases have CLIP2-RET, SPECC1 L-RET, TPM3-ALK, CLIP1-ALK, and BRAF p.V600E mutation detected.[6-9] The clinical behavior of these tumors varied from indolent to aggressive, with some cases showing metastasis to lymph nodes, lungs, liver, or central nervous system. Unbiased sequencing of CMN/IFS cases lacking the NTRK3-ETV6 fusion gene uncovered significant oncogenic rearrangements in MAPK signaling genes, namely epidermal growth factor receptor (EGFR) and BRAF. Specifically, EGFR internal tandem duplication was detected in all analyzed CMN tumors, thus establishing it as a valuable diagnostic marker and a promising target for therapeutic interventions.[10]

These reviews illustrate the importance of further molecular testing for CMN/IFS neoplasm even in the absence of NTRK-associated fusion, as it can help to establish the more appropriate diagnosis, exclude other entities, and identify potential therapeutic targets. Unfortunately, we were unable to perform further testing on our case due to the lack of tissue availability. We hope this information will help pathologists and clinicians consider further molecular testing to identify specific fusion associated to pursue further testing as they may have potential targetable treatments.

Acknowledgment

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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