Renal Inflammatory Myofibroblastic Tumor in an Infant: Case Report with Review of Literature

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Abstract

Inflammatory myofibroblastic tumor (IMT) is an intermediate-grade neoplasm of myofibroblastic lineage occurring due to a cytogenetic clonal abnormality of chromosome 2p23. Pediatric renal IMTs are rare and infant renal IMTs are almost anecdotal. We herein report a 1-year-old female child who presented with a firm mass in the right lumbar region. Biopsy, and later, surgical resection revealed a tumor composed of spindle cells with intermixed plasma cells. On immunohistochemistry (IHC), the lesional cells were positive for smooth muscle actin and anaplastic lymphoma kinase (ALK). A diagnosis of IMT was made based on morphology and IHC. Diagnosis of renal IMTs become challenging especially in a tiny biopsy wherein clear cell sarcoma of kidney, Wilms tumor with predominant mesenchymal component, congenital mesoblastic nephroma, and metanephric stromal tumor are the differential diagnoses in this age group. Renal IMTs generally have better prognosis as compared to extrarenal IMTs. Approximately, 50 to 60% of these tumors harbor *ALK* gene rearrangement as demonstrated by positivity for *ALK* IHC. *ALK* inhibitors like crizotinib or ceritinib can be given for advanced metastatic tumors.

Keywords
- inflammatory myofibroblastic tumor
- kidney
- ALK inhibitors

Introduction

Inflammatory myofibroblastic tumor (IMT) is a rarely metastasizing intermediate-grade neoplasm of myofibroblastic origin.[1] It occurs in people of all age groups; however, children and young adults are more commonly affected.[1] The most common site of occurrence is the lung; however, it is also known to occur in the bladder, spleen, breast, pancreas, liver, colon, spermatic cord, prostate, peripheral nerves, orbit, and kidneys.[2–4] Of the limited cases (less than 50) of renal IMT published in literature, only 8 cases are in the pediatric age group including one in an infant.[4,5] In the kidney, due to nonspecific clinical and radiological features, it is difficult to distinguish a renal IMT from the more common Wilms tumor (WT) until tissue diagnosis by biopsy or surgery. Herein, we present a case of infant renal IMT in a 1-year-old female child who presented with a right-sided suprarenal mass.

Case Report

A 1-year-old female child, developmentally normal with no significant family history of malignancy, was brought to the hospital with complaints of fever and right-sided abdominal

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lump of 1.5 months' duration. This was associated with constipation, vomiting, decreased appetite, and weight loss (around 3 kg loss during this period). There was no history of hematuria. Apart from a 6×6 cm firm mass palpable in the right lumbar region, physical examination was unremarkable. Computed tomography (CT) scan report revealed a large, relatively well-defined heterogeneous mass lesion with minimal calcification in the right suprarenal region. F18-fluorodeoxyglucose positron emission tomography/CT (F18-FDG PET/CT) revealed a $7.1 \times 6.7 \times 7.9$ cm FDG avid large well-defined heterogeneously enhancing soft tissue mass with central necrosis and few specs of calcification in the right suprarenal region with maximum standardized uptake value of 11.63. The scan also revealed metabolically active aortocaval lymph nodes (1.1×0.8 cm) suspicious for metastasis. Laboratory data at presentation showed: total leucocyte count 5,330/mm^3, hemoglobin 6.3 g/dL, platelet count 3.95 lakh/mm^3, international normalized ratio 1.21, prothrombin time 14.00 second, increased spot urine vanillylmandelic acid (VMA) 80 mg/g creatinine (normal range: 4.9–16.9 mg/g creatinine), serum urea 54.4 mg/dL (normal 12.84–42.8 mg/dL), serum creatinine 0.46 mg/dL (normal 0.1–0.4 mg/dL), and serum uric acid 7.49 mg/dL (normal 2.6–6 mg/dL). Though imaging revealed a large suprarenal mass displacing the kidney, the relative isoattenuation was atypical, and hence, a biopsy was planned. On morphological examination, the tumor was found to be composed of spindle cells with intermixed plasma cells. Mitotic activity and necrosis were not seen. On immunohistochemistry (IHC), the lesional cells were positive for smooth muscle actin (SMA), negative for S-100 protein, desmin, synaptophysin, and chromogranin. IHC for anaplastic lymphoma kinase (ALK) (ALK1 clone) showed weak positivity. There was no evidence of a neuroblastic tumor. A diagnosis of IMT was made based on morphology and IHC. Since the mass was surgically resectable, child was taken up for the same. The mass was found to be renal in origin on laparotomy, and hence, a right-sided nephrectomy with lymph node sampling and diaphragmatic rent repair was performed.

Macroscopically, a $10 \times 9 \times 6.8$ cm circumscribed solid gray-white tumor was identified in the upper pole of the right kidney (►**Fig. 1A**). The tumor did not involve the renal sinus and pelvicalyceal system. Microscopically, the tumor consisted of proliferation of banal looking myofibroblasts without any cytological atypia and with conspicuous presence of intratumoral lymphocytes, plasma cells, and histiocytes (►**Fig. 1B**). Necrosis was not seen. On IHC, the lesional cells showed positivity for SMA (►**Fig. 1C**), along with diffuse and strong positivity for ALK antibody (Ventana D5F3 clone) (►**Fig. 1D**).

Unfortunately, the child developed abdominal distension from postoperative day 2 with features of intestinal obstruction. Reexploration revealed diaphragmatic hernia through the rent with ileal obstruction which was repaired. Meanwhile, the child developed nonoliguric renal failure with *Escherichia coli* sepsis and shock and succumbed to infection on postoperative day 8.

Discussion

IMT was first described by Brunn in the lung in 1937.[6] They called it plasma cell granuloma due to the presence of

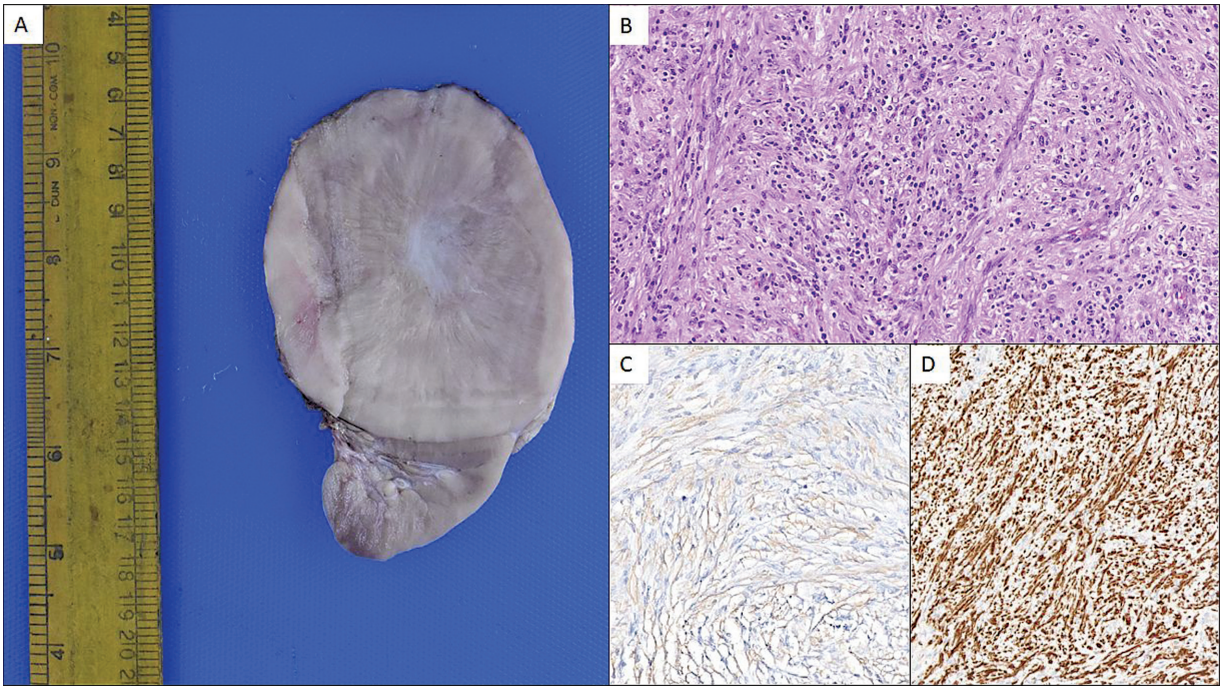

Fig. 1 Inflammatory myofibroblastic tumor. (**A**) Gross photograph of right nephrectomy specimen, showing circumscribed solid gray-white tumor in the upper pole of the right kidney. (**B**) Bland spindle cells with lymphocytes and plasma cells. Hematoxylin and eosin, ×200. (**C**) Immunopositivity for smooth muscle actin (SMA) in tumor cells. Diaminobenzidine ×200. (**D**) Diffuse and strong immunopositivity for ALK1 amplification (Ventana D5F3 antibody) in tumor cells. Diaminobenzidine ×200.

predominant lymphocytes and plasma cells with mature germinal center.[6] Later in the year 1954, Umiker and Iverson coined the term "inflammatory pseudotumor" due to the presence of chronic inflammatory infiltrates.[7] Initially, it was believed that IMT represented a reactive inflammatory process; however, later it was established that IMT occurs due to a cytogenetic clonal abnormality of 2p23.[1] This clonal cytogenetic aberration includes 3′ kinase region of anaplastic lymphoma tyrosine kinase (*ALK*) gene rearrangement with various partner genes, like *TPM3, TPM4, CLTC, CARS, ATIC, SEC31L1, PPFIBP1, DCTN1, EML4, PRKAR1A, LMNA, TFG, FN1, HNRNPA1*, and others.[1] The rearrangement with *ALK* is seen in approximately 50% of cases.

In addition, *ROS1* and *NTRK3* gene rearrangements are seen in 5 to 10% of IMTs.[1]

Microscopically, IMT shows spindle-shaped cells with intermixed lymphoplasmacytic infiltrates without cytological atypia and necrosis. In addition, the lesional cells of IMT are immunopositive for SMA and focally positive for epithelial membrane antigen, while negative for CD34, S-100 protein, and pancytokeratin. This immunoprofile reflects the myofibroblastic differentiation in the spindle cells of IMT. Immunopositivity for *ALK* is noted in 50 to 60% cases of IMT with a relatively higher percentage in the younger age group correlating well with the underlying *ALK* gene rearrangement.[1] *ALK* IHC displays distinct staining patterns based on the underlying fusion partner of the *ALK* gene. *RANBP2-ALK* is associated with nuclear membranous pattern, *RRBP1-ALK* with perinuclear accentuated cytoplasmic pattern, and *CLTC-ALK* with a granular cytoplasmic pattern.[1,] Both ALK1 and D5F3 clones recognize the C-terminal of *ALK* tyrosine kinase; however, D5F3 clone is superior to ALK1 clone in detecting *ALK* protein expression in terms of intensity and extent of staining in IMTs.[8,9] The D5F3-based immunoassay includes tyramide-induced amplification step which increases the signal differences between specific and background staining thus eliminating equivocal staining and background nonspecific staining.[10] This was exemplified in our case which showed weak staining by the conventional *ALK1* clone as against the D5F3 clone wherein the staining was strong and diffuse granular. The *ALK* gene rearrangement can also be detected by fluorescence in situ hybridization (FISH) test. However, researchers studying nonsmall cell lung carcinoma found ALK IHC to be a good predictor of targeted therapy response when compared to FISH test.[11]

The suprarenal mass in our patient in the infantile age group was clinically thought to be a neuroblastoma. Raised levels of spot urinary VMA also contributed to this clinical impression. A false positive VMA can be caused by dietary intake of caffeic acid and its derivatives; drug interactions like acetaminophen, caffeine, nicotine, tricyclic antidepressant, phenoxybenzamine, and stressful conditions like hypertension, emotional stress, and renal dysfunction.[12] This reiterates the need for preparation prior to sampling urine for VMA. Although diagnosis of a neuroblastic tumor was categorically excluded, interpretation of biopsy findings was challenging due to the rarity of occurrence of IMT in this age group and consideration of several other tumor entities. Histologic differential diagnoses of renal IMT in infants essentially include clear cell sarcoma of kidney (CCSK), WT with predominant mesenchymal component, congenital mesoblastic nephroma (CMN), and metanephric stromal tumor (MST). With the exception of CMN (both conventional as well as cellular variants) and MST, other tumors are malignant with aggressive behavior requiring multimodal therapy comprising of chemotherapy, surgery, and radiotherapy. Thus, the importance of accurate diagnosis of IMT on a small biopsy sample has a significant impact on management of the patient. Microscopically, fine arborizing vessels with variable amounts of spindle cell stroma is the hallmark of CCSK. The tumor cells of CCSK are diffusely positive for BCOR, and are negative for SMA, ALK1, and CD34. In a limited biopsy material, it may be difficult to differentiate mesenchymal predominant WT from IMT. Absence of plasma cells with WT1 positivity would point toward WT. CMN shows bland spindle cells arranged in an interlacing fascicular pattern embedded in a collagenized stroma. The tumor cells of CMN show positivity for cyclin D1, SMA, and pan-TRK and are immunonegative for ALK. MST can be differentiated from IMT by the presence of spindle cells with alternating cellularity, perivascular cuffing, and angiodysplasia. The spindle cells of MST show characteristic immunopositivity for CD34.[13,14]

On the other hand, the differential diagnoses of IMT vary considerably in adult patients.

Xanthogranulomatous pyelonephritis, sarcomatoid renal cell carcinoma, malignant fibrous histiocytoma, and sarcomatoid variant of urothelial carcinoma are included in the differential diagnoses. Xanthogranulomatous pyelonephritis shows presence of foamy histiocytes with interspersed plasma cells. Sarcomatoid carcinomas will show marked atypia histologically. On IHC, sarcomatoid renal cell carcinoma shows positivity for PAX8; sarcomatoid urothelial carcinomas will be positive for GATA 3.[4]

The 8 cases of pediatric IMT published in literature ranged from 9 months to 14 years, with only one patient being in the infantile age group.[2,4,15–20] All patients in this series underwent local excision or nephrectomy without any chemotherapy or radiotherapy. None of them showed any recurrence or metastases. The clinical details, macroscopic, and microscopic findings of all reviewed cases are enlisted in ►**Table 1**.[2,4,15–20]

The unexpected clinical outcome in our patient is due to Gram-negative sepsis and subsequent organ dysfunction. Otherwise, nephrectomy is the gold standard approach for treating renal IMTs.[21,22] The Children's Oncology Group has advocated a potential role of crizotinib in unresectable solid *ALK* positive IMT in the pediatric age group.[23] However, possibly due to the presence of various partners of *ALK* gene, this tumor does not show a uniform response to crizotinib therapy and may benefit by increasing the dose of the drug.[23] The Children's Oncology Group also noted a discordance between metabolic response by FDG PET/CT and anatomical response after *ALK* targeted therapy due to the varying underlying biology and *ALK* gene partners.[23] Renal IMT has a favorable outcome, when compared to extrarenal IMT, which are relatively more frequent and associated with

Table 1 Literature review of the clinical and histopathology findings of the pediatric renal IMT

Sr. No.	Author, year	Age (y/mo), gender	Laterality	Presenting symptoms	Gross size (in cm)	Smooth muscle actin (SMA)	Epithelial membrane antigen (EMA)	Desmin	ALK 1 IHC	Treatment	Follow-up (mo)	Recurrences
1	Itoh et al, 1982[15]	12 y, Male	Right	Painless hematuria	10 × 08 × 05	Not done	Not done	Not done	Not done	Local excision	Not available	Not available
2	Vujanić et al, 1992[16]	8 y, male	Right	Hematuria	7.5 × 05 × 2.5	Not done	Not done	Not done	Not done	Right nephrectomy	36	No
3	Tarhan et al, 2004[17]	10 y, female	Right	Intermittent fever, headache	03 × 03 × 2.5	Positive	Negative	Negative	Not done	Right nephrectomy	18	No
4	Boo et al, 2006[18]	9 y, female	Left	Intermittent abdominal pain	12 × 6.5 × 5.5	Positive	Negative	Not done	Not done	Left nephrectomy	06	No
5	Ho et al, 2005[19]	3 y, female	Left	Intermittent fever and left upper quadrant abdominal pain	08 × 06 × 04	Positive	Not done	Not done	Positive	Left nephrectomy	09	No
6	Czerwinski and Dave, 2012[20]	14 y, female	Left	Recurrent urinary tract infection (with spina bifida associated neurogenic bladder)	5.7 × 5.1 × 4.1	Positive	Not done	Not done	Not done	Left nephrectomy	12	No
7	Dogan et al, 2015[2]	3 y, male	Right	Right flank pain and recurrent fever	06 × 5.5 × 5.5	Positive	Not done	Positive	Positive	Right nephrectomy	06	No
8	Tareen et al, 2022[4]	9 mo, female	Right	Gross hematuria	05 × 4.7 × 4.5	Negative	Negative	Negative	Negative	Right nephrectomy	02	No
9	Present case, 2022	1 y, female	Right	Fever and right-sided abdominal pain	10 × 09 × 6.8	Positive	Not done	Negative	Positive	Right nephrectomy	Death	–

Abbreviations: ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; IMT, inflammatory myofibroblastic tumor.

local recurrence and metastasis.[20,21] In future, studies may be directed toward the role of various ALK fusion partners in assessing response to crizotinib therapy. The ALK inhibitor ceritinib shows near complete response in pediatric IMTs.[24] Ceritinib is also more economical than crizotinib and is suitable for low and middle-income countries.[24] Other options available for unresectable IMT include steroids, anti-inflammatory drugs, and radiation therapy.[25]

Conclusion

We herein report an exceedingly rare occurrence of renal IMT in an infant with an emphasis on diagnostic difficulty, especially in a biopsy sample. We discussed differential diagnoses which underline the significance of accurate diagnosis of IMT. Most tumors occurring in the kidney in the infantile age group are malignant except CMN and the patients require multimodal treatment. There is a potential role of ALK inhibitors in treatment of IMTs in advanced, metastatic settings.

Patient Consent

The authors certify that they have obtained all appropriate patient consent.

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None.

Conflict of Interest

None declared.

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