Case Report: iMDT Corner

Poor outcome in congenital mesoblastic nephroma with *TPM3::NTRK1* fusion: a case report from multi-disciplinary treatment to molecular tumor board

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Background: Congenital mesoblastic nephroma (CMN) is a rare renal tumor with good prognosis in children; however, cellular CMN is a special subtype with poor prognosis. The *ETV6* fusion gene has been found in some cellular CMNs, whereas CMNs with *TPM3::NTRK1* fusion gene have not been reported. This study aims to share the progression and treatment of a case of CMNs with *TPM3::NTRK1* fusion gene, in order to provide experience for the diagnosis and treatment of such specific diseases.

Case Description: We report a case of CMN with *TPM3::NTRK1* fusion gene and a 3-year course of disease that originated during the fetal period. The child experienced rapid tumor progression 22 months after birth, followed by tumor recurrence 3 months after complete resection of CMN. Although traditional chemotherapy could not prevent the tumor progression. The tropomyosin receptor kinase (TRK) inhibitor larotrectinib resulted in significant inhibitory effects on metastatic lesions in the lungs, liver, and peritoneum. However, the patient ultimately died as the tumor became resistant to larotrectinib.

Conclusions: CMN, is a rare pediatric renal tumor that warrant prompt surgical management. A watchful waiting approach may allow for aggressive growth of metastatic disease, as seen in this case of cellular CMN with *TPM3::NTRK1* fusion gene, TRK inhibitors can play significant roles in the treatment of CMN with *TPM3::NTRK1* fusion gene, but we still need to pay attention to the phenomenon of drug resistance to larotrectinib caused by site mutations of TRKA.

Keywords: Congenital mesoblastic nephroma (CMN); *TPM3::NTRK1*; larotrectinib; molecular tumor board (MTB); case report

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Introduction

Congenital mesoblastic nephroma (CMN) is a rare low-grade malignant kidney tumor in infants younger than 3 months, accounting for up to 87% of all renal tumors in the first 2 months of life (1-3). About 90% of children with CMN present with an abdominal mass and hematuria by their first birthday (4,5). The 5-year survival rate can reach over 90% for children with CMN who undergo complete surgical resection, making it the most ideal treatment for CMN (4-6).

However, there are still many factors affecting the prognosis of CMN, such as pathological type, fusion gene, and age (7). The pathological types of CMN can be divided into classic, cellular, and mixed types. Cellular CMN and infantile fibrosarcoma (IFS) share similar histopathological features and chromosomal aberration [t(12; 15) (p13; q25)] resulting in *ETV6::NTRK3* fusion gene (8-12). Currently, *ETV6::NTRK3* and trisomy 11 are the most common genetic abnormalities in CMN (4,10,13); other rare genetic abnormalities include *EML4::NTRK3* (14), *EML4::ALK* (15), *EGFR::KDD* (16,17) and *BRAF* internal duplication (18).

The *ETV6::NTRK3* translocation has been reported in extremity-based IFS (19,20), pediatric gastric mesenchymal sarcoma (21), papillary thyroid cancer (22), and pleomorphic xanthoastrocytoma (23), but it hasn't been described in CMN. The CMN with *TPM3*::*NTRK1* fusion gene reported in this study was initially observed, but it rapidly progressed following complete resection at 2+ years of age. A temporary response was achieved with treatment with the *NTRK* inhibitor, larotrectinib. This case is instructive that CMN should be treated promptly with surgery when feasible and target therapies may be helpful in the case of relapsed/refractory/progressive disease. We present this case in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-126/rc).

Highlight box

Key findings

- We report a case of congenital mesoblastic nephroma (CMN) with *TPM3::NTRK1* fusion gene with a poor outcome.

What is known and what is new?

- CMN is a rare low-grade malignant kidney tumor and the overall survival rate can reach over 90% with complete surgical resection.
- The patient with CMN with *TPM3::NTRK1* fusion gene reported in this study underwent a delayed surgery, and he had rapid recurrence with metastatic disease.

What is the implication, and what should change now?

- Patients with CMN should undergo prompt surgical resection given the potential for rapid growth and metastatic spread with delayed treatment. In the event of unresectable disease, targeted agents such as larotrectinib should be considered for patient such as this one with a *TPM3::NTRK1* fusion.

Case presentation

A boy with CMN was seen at Children's Hospital of Nanjing Medical University. Prenatal ultrasonography at 37 weeks of gestation revealed that the child had a right renal mass. Ultrasonography revealed a mass measuring approximately 2.6 cm × 1.8 cm after birth. At that time, we communicated with the parents and informed them that there were two treatment options: surgical resection or close follow-up. We explained in detail the pros and cons of both options to the parents, who preferred close follow-up, with an ultrasonography reexamination scheduled every 3–6 months until the child reaches 22 months of age, and the size of tumor was stable for several months prior to that based on regular ultrasonography. When the child was 28 months old, he was admitted to the hospital due to recurrent fevers and rapid enlargement of the renal mass. Abdominal computed tomography (CT) suggested that the volume of the right kidney had increased, and a low-density shadow could be seen in the superior portion of the right kidney, with a size of approximately 5.3 cm × 6.4 cm × 5.5 cm. Mild enhancement and multiple vascular shadows inside the tumor could be seen in the arterial phase (*Figure 1*). No enlarged lymph nodes were detected in the retroperitoneal space. No metastatic lesions were found in the cerebrum, lungs, spine, liver, gallbladder, pancreas, spleen, kidney, or bone marrow according to CT, magnetic resonance imaging (MRI), B-ultrasound, and bone marrow examination. There were no significant abnormalities in the serum levels of carbohydrate antigen 19-9 (CA19-9), neuron-specific enolase (NSE), alpha fetoprotein (AFP), and carcinoembryonic antigen (CEA). We organized multi-disciplinary treatment (MDT) after a thorough examination and ultimately concluded that the tumor could be completely removed after the evaluation by the Department of Urology, Hematology, and Radiology. We believe that based on the rate of tumor's progression, there is a higher likelihood of malignancy. Therefore, the tumor could be a Wilms' tumor, neuroblastoma, or renal sarcoma. Given the age of onset, any of these three types

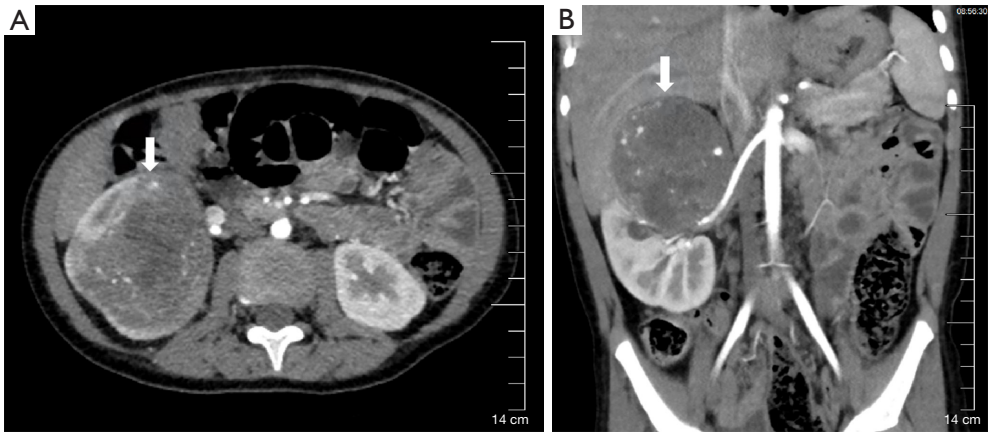

Figure 1 CT scan of the child confirmed a tumor of the left kidney. (A) Axial arterial phase contrast-enhanced CT image of the abdomen showed a large mass in the right kidney (down arrow). (B) Coronal reconstructed image showed a mildly enhanced mass in the superior of the right kidney (down arrow). CT, computed tomography.

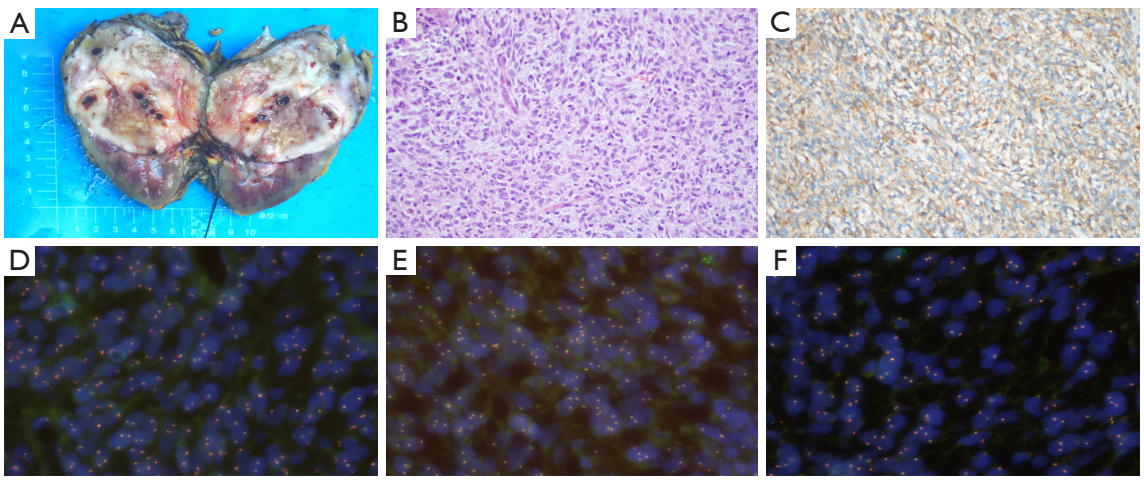

Figure 2 Pathological and molecular characteristics of this tumor. (A) The vertical section of this tumor showed an invasion of the right renal pelvis. (B) Hematoxylin-eosin staining (×200) showed diffused proliferative round tumor cells and bundled spindle tumor cells in the field of vision. (C) Pan-TRK staining (×200) showed a strong cytoplasmatic positivity of immunohistochemical marker pan-TRK among tumor cells. (D-F) Break-apart FISH analysis (×1,000) for *NTRK1* (D), *NTRK2* (E), and *NTRK3* (F) rearrangements confirmed *NTRK1* rearrangement (red probe for 3' and green probe 5'): The proportion of cell with the abnormal signal of 2F1R (2 fusion 1 red) reached to 47% for *NTRK1* and the proportion of cell with 2F (2 fusion) signal reached to 99% for *NTRK2* and for *NTRK3*. TRK, tropomyosin receptor kinase; FISH, fluorescence in-situ hybridization.

of tumors could occur. Based on the CT results, the tumor is most likely originating from the kidney, thus indicating a higher likelihood of Wilms' tumor or renal sarcoma. However, the possibility of neuroblastoma originating from the adrenal gland on one side invading the kidney cannot be ruled out. The phenomenon of neuroblastoma compressing one kidney is more common, while the rapid and extensive invasion of renal tissue in a short time is uncommon. The right kidney was subsequently resected and a retroperitoneal lymph node dissection was performed. The pathological results indicated that the tumor capsule was intact and the tumor had invaded the renal pelvis (*Figure 2A*). No tumor cells were detected in the cutting edge and lymph nodes that were adjacent to the right renal hilum,

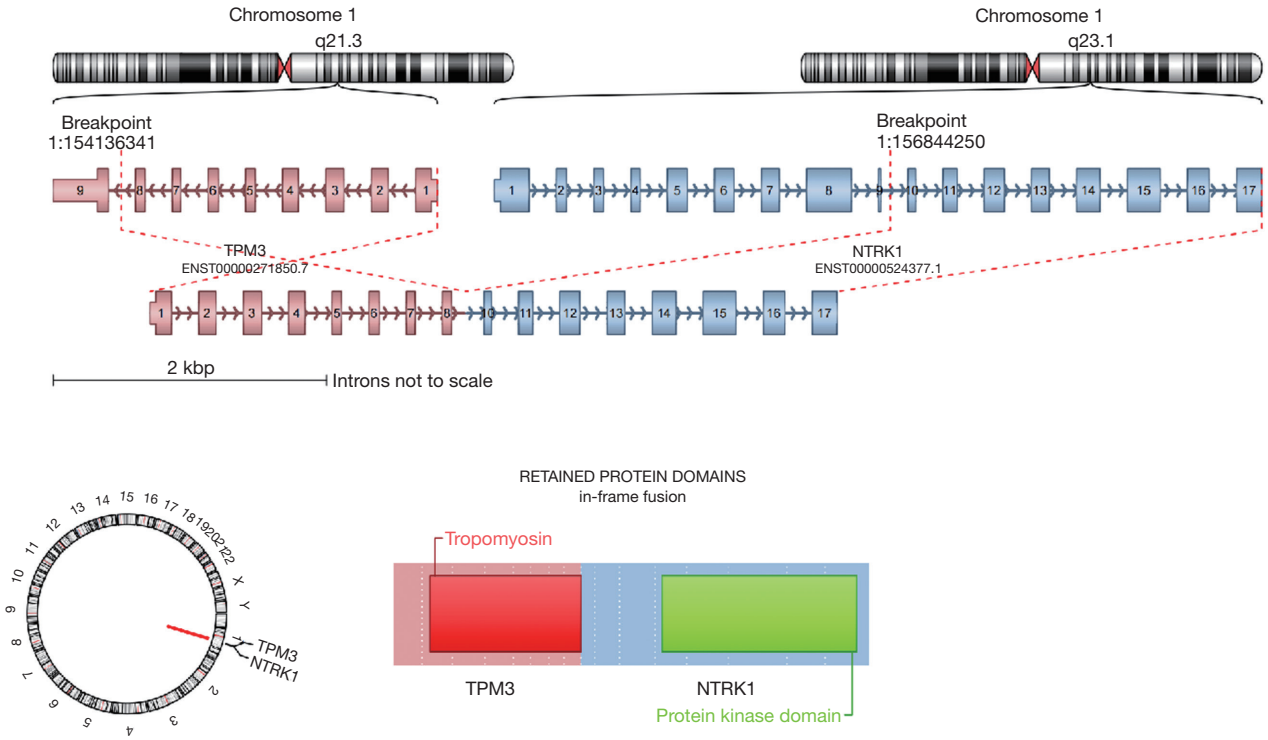

Figure 3 Sequencing results of *TPM3-NTRK1* fusion gene. Sequencing analysis of *TPM3-NTRK1* fusion gene illustrated that the fusion occurred between exon 1–8 of *TPM3* (chromosome 1) and exon 10–17 of *NTRK1* (chromosome 1).

inferior vena cava, and abdominal aorta. Hematoxylin-eosin staining showed diffused proliferative round tumor cells and bundled spindle tumor cells in the field of view (*Figure 2B*). Immunohistochemistry showed pan-NTRK (+++) (*Figure 2C*), pan-cytokeratin (pan-CK) (–), TLE1 (–), SATB2 (–), BCOR (–), WT-1 (–), CK (–), epithelial membrane antigen (EMA) (–), vimentin (partial+), desmin (–), CD99 (+), SMARCB1 (+), CyclinD1 (–), NSE (–), leukocyte common antigen (LCA) (scattered+), and Ki67 (30%+). These morphological features were consistent with the diagnosis of cellular CMN. Molecular analysis was performed and was negative for rearrangements of *ETV6*, *NTRK2*, and *NTRK3*, but positive for rearrangement of *NTRK1* (*Figure 2D-2F*). To identify the fusion partners of *NTRK1* and other potential abnormal genes, a screen was performed evaluating 231 genes, 120 fusion products, 17 amplifications, and 24 variant genes on Illumina HiSeqX PE 150 bp platform (Illumina, San Diego, CA, USA). The results revealed a *TPM3::NTRK1* fusion gene (*Figure 3*). According to the pathological and molecular characteristics, an MDT including the Departments of Hematology, Oncology, Pathology, Urology and Radiology was organized, and a watchful waiting surveillance plan was adopted based on the good prognosis and complete resection of the tumor.

No metastases were found 2 months after surgery, but a right retroperitoneal mass and liver (*Figure 4A,4B*) and lung metastases were detected 3 months after surgery. Considering that there was no uniform chemotherapy protocol for CMN, the patient was treated with vincristine, epirubicin, cyclophosphamide, and dactinomycin after discussion. The metastases in the retroperitoneum, liver, and lungs continued to grow despite treatment, and there was a decrease in muscle strength in both lower limbs due to the thoracic vertebral metastasis after two courses of chemotherapy (*Figure 4C*). We organized a molecular tumor board (MTB) including the Departments of Pathology, Hemato-oncology, Urology, and Radiology, and selected the drug larotrectinib targeting tropomyosin receptor kinase (TRK) because of the rapid progression. Following initiation of treatment with larotrectinib, it was found that the lesions in the right retroperitoneum, liver (*Figure 4D*), and lungs (*Figure 5A-5D*) were significantly reduced, and the intraspinal mass in T5–T7 did not further enlarge during 4 months of larotrectinib

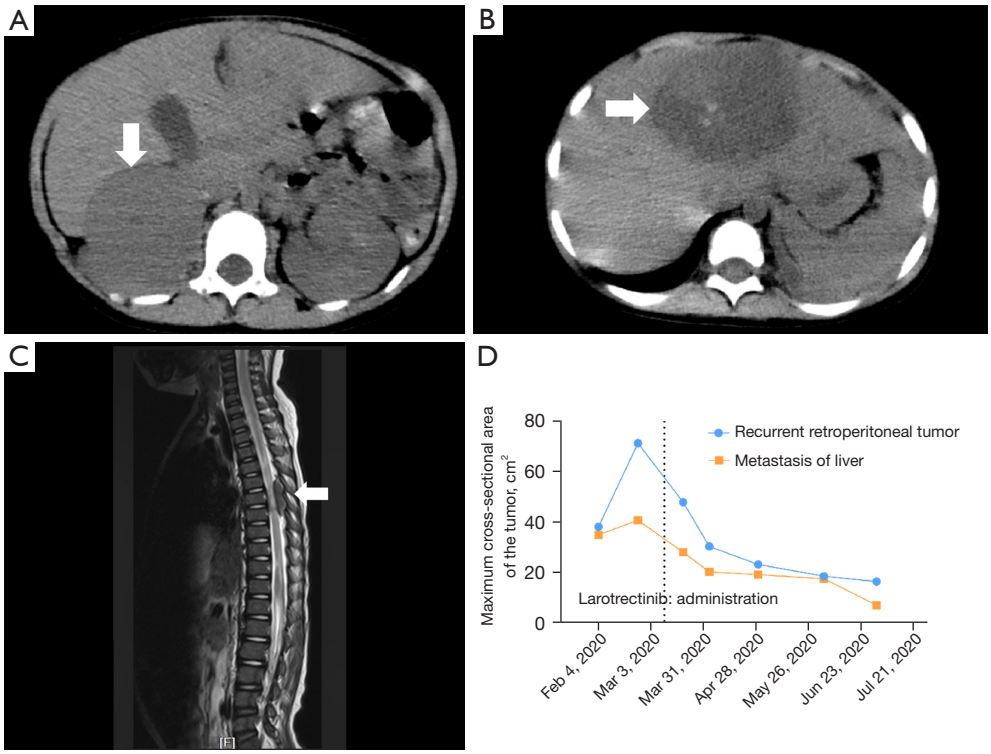

Figure 4 Tumor recurrence and efficacy of larotrectinib. (A) CT scan showed CMN recurrence in the right retroperitoneum 3 months after surgery (down arrow). (B) CT scan showed liver metastasis 3 months after surgery (right arrow). (C) MRI indicated epidural lesion of T5–T7 after two courses of chemotherapy (left arrow), and CMN metastasis was considered. (D) Changes in the size of right retroperitoneal and liver lesions from the time of recurrence to 4 months after larotrectinib administration. CT, computed tomography; CMN, congenital mesoblastic nephroma; MRI, magnetic resonance imaging.

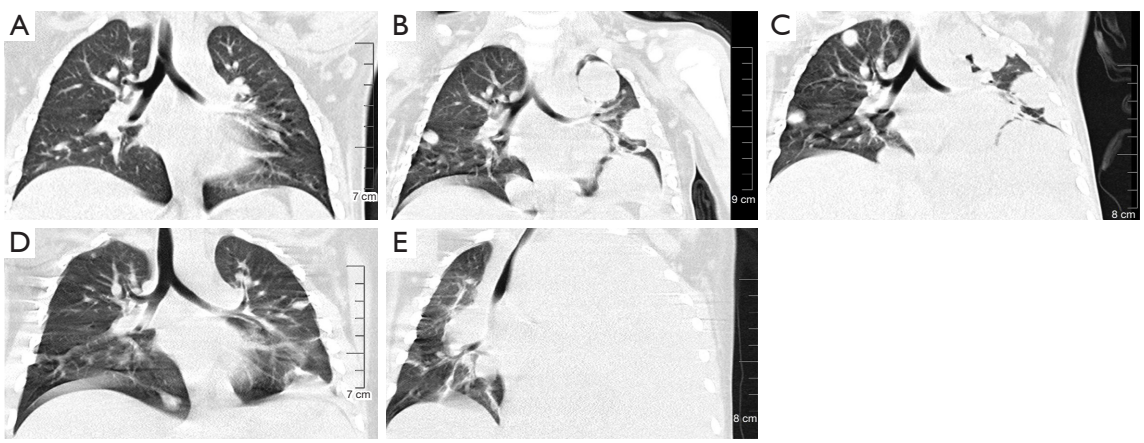

Figure 5 Changes in pulmonary metastatic lesions during the course of the disease. (A) We did not detect any lung metastasis before surgery. (B) Multiple lung metastases were observed 3 months after surgery. (C) The pulmonary metastatic lesions were still progressing after two courses of chemotherapy. (D) We found a significant reduction in the number and size of lung metastases after 3 months of using larotrectinib alone. (E) The pulmonary metastases progressed again rapidly after 5 months of larotrectinib administration.

administration. The child eventually developed fever, diarrhea, skin ulcers, and oxygen hyposaturation rapidly, and CT chest showed significant progression of pulmonary metastases 5 months after larotrectinib administration (*Figure 5E*). The patient was transitioned to received palliative treatment and died 2 months later.

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Children's Hospital of Nanjing Medical University (ethical approval No. 202306001-1) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

International multidisciplinary team (iMDT) discussion

Currently, for patients with a confirmed diagnosis of CMN, early surgery can achieve desirable treatment outcomes. Numerous clinical studies have proven this conclusion (1-6), which is also the advantage of early surgery. However, for patients with an unclear diagnosis, the decision to proceed with surgical treatment still needs to be approached cautiously. Some benign tumors can stabilize long-term, and there is even a possibility of spontaneous regression in some cases of neuroblastoma. For these newborns, aggressive surgical treatment could lead to significant trauma. The strong willingness of the parents to follow-up observation, and the results of 1–2 rechecks of ultrasounds showing no significant increase in the tumor, have increased the parents' confidence in conservative treatment for the child. These are the main reasons why we did not perform early surgery. An initial watchful waiting approach was adopted in this case, and the patient rapidly progressed after 2+ years of observation. This experience suggests that even if a tumor behaves in an indolent manner initially, it is prudent to proactively perform surgery on any patient with a high suspicion of CMN. Previous literature has shown that cellular CMNs are more malignant and more likely to achieve distant metastasis than classical and mixed CMNs (8). While CMN is typically considered a low-grade malignant tumor (24), its properties may change over time and prompt surgical management is indicated.

We report a rare cellular CMN with *TPM3::NTRK1* fusion gene for the first time through this study. The immunohistochemical results of pan-TRK (+++) indicated that there might be rearrangement of *NTRK*, which has been shown to be the most common fusion gene in cellular CMN (3,4,8-10,13,16). The fluorescence in-situ hybridization (FISH) results showed that there was no rearrangement of *NTRK3* and *ETV6*, but sequencing revealed a rearrangement of *NTRK1* in this case. *NTRK1* rearrangement has not been reported in cellular CMN in the literature, indicating that this might be a newly discovered molecular subtype of CMN with *NTRK1* rearrangement. The *TPM3::NTRK1* fusion gene has been frequently reported in adult cancers (25-30), where it is associated with a poor prognosis (30). Our literature review located few reports of pediatric tumors with *TPM3::NTRK1* fusion gene and no reports on CMNs with *TPM3::NTRK1* fusion gene (21-23). Previous studies have found that cellular CMN and IFS are similar histologically, and they are both commonly associated with the *ETV6::NTRK3* translocation (8,17). Some scholars even believe that cellular CMN is a special type of IFS developing in the kidneys (8). Interestingly, there have been reports of IFS with the *TPM3::NTRK1* fusion gene (19,20) identified in our patient.

The lesions in the lungs, liver, and posterior peritoneum were significantly reduced through the treatment of larotrectinib. The tumor progressed again 5 months later and the child was admitted to the palliative care unit with parental consent. Previous studies have shown that the rapid progression of solid tumors with *NTRK* fusion gene after treatment with type I TRK inhibitors is due to the mutant sites in F589L, G595R, G667C, G667S, and A608D of TRKA kinase (31-33), and we consider that the progression of this CMN 5 months after treatment with larotrectinib may be related to this mechanism. However, we were unable to verify this hypothesis through genetic testing due to the lack of consent from the child's guardian. With the development of the second-generation type I TRK inhibitor, especially the application of LOXO-195 and TPX-0005 in clinical trials (34-37), we hope to greatly reduce the drug resistance caused by site mutations of TRKA kinase.

Discussion among physicians from Children's Hospital of Nanjing Medical University

Department of Urology

Malignant tumors originating from the kidneys in children include Wilms' tumor, CMN, cystic nephroma, and renal rhabdomyosarcoma. Based on the patient's clinical presentation, we first considered the possibility of CMN. Following the patient's admission, further examinations

revealed that the tumor was localized to one side of the kidney, with extensive infiltration into the renal parenchyma, but no distant metastasis. Therefore, the chosen surgical approach was nephrectomy of the affected kidney along with lymph node biopsy. The tumor was completely resected during surgery, and postoperative pathology indicated that the tumor had not breached the capsule and there was no tumor cell infiltration in the lymph nodes, demonstrating the successful achievement of complete tumor resection. However, the child experienced a local recurrence at the primary site after 3 months postoperatively, with multiple liver and lung metastases. Despite chemotherapy, rapid disease progression occurred. This outcome suggests a high degree of malignancy and rapid progression of the tumor, as well as insensitivity to chemotherapy agents, which contradicts our traditional understanding of CMN.

Department of Radiology

After the child was admitted to the hospital, a contrast-enhanced CT scan revealed a relatively large solid mass in the upper pole of the right kidney, measuring approximately 77 mm × 62 mm × 75 mm, which had increased in size compared to previous examinations. The CT value of the mass was approximately 20–40 Hounsfield unit (HU), and it contained multiple small linear low-density shadows with clear borders. The enhancement of the mass was uneven, and there were multiple tortuous small vascular shadows inside, with the solid portion of the mass having a CT value of approximately 40–100 HU. No obvious enlarged lymph nodes were observed, but there was slight displacement of the inferior vena cava due to compression. The preliminary diagnosis is a possible Wilms' tumor or a CMN. A subsequent CT scan, when the child had a recurrence, showed a soft tissue density mass in the right retroperitoneum, measuring approximately 6.9 cm × 7.7 cm, with uneven enhancement after contrast. There was also a round mixed low-density shadow of unclear border in the left lobe of the liver, measuring approximately 7.3 mm × 5.8 mm, with uneven enhancement at the edge after contrast, as well as multiple nodules in both lungs. The MRI results showed an extradural mass at the T5–T7 thoracic vertebrae, indicating possible tumor metastasis.

Department of Pathology

The pathology results of the patient show that the tumor invaded the renal pelvis, but did not penetrate the renal capsule, and no metastasis was found in the ureter or surrounding tissues. HE staining showed diffuse proliferation of round tumor cells and spindle-shaped tumor cells arranged in bundles in the tumor. The diagnosis is considered to be CMN. The tumor is positive for *TPM3::NTRK1* fusion gene, with strong positive NTRK immunostaining and negative CyclinD1, further supporting the diagnosis of CMN. This tumor is rare, with an extremely low incidence, and it has been reported that most cases are low-grade malignant, but there are also a few malignant cases. After undergoing chemotherapy, the tumor rapidly progressed. Considering the fusion gene status, targeted TRK therapy may be considered for treatment.

Department of Hematology and Oncology

The child has a long medical history, with a renal mass detected at 37 weeks of gestation. After birth, regular follow-ups showed no change in the size of the tumor. In October 2019, there was a rapid increase in the size of the mass. Following a multidisciplinary assessment, the child underwent a right nephrectomy and lymph node biopsy. Post-surgery pathology indicated no tumor metastasis and suggested a diagnosis of CMN with a positive *TPM3::NTRK1* fusion gene. Three months after surgery, there was a recurrence of the tumor. CMN is a rare, mostly low-grade malignant tumor with no established chemotherapy regimens. In most cases, treatment recommendations rely on the experience of other research centers. After internal discussions, the child received vincristine, epirubicin, cyclophosphamide, and dactinomycin chemotherapy, which showed limited effectiveness. Considering the rapid progression of the tumor and the positive *TPM3::NTRK1* fusion gene, it was decided to initiate treatment with TRK targeted therapy based on the advice of the pathology department.

Several questions arise concerning the diagnosis and treatment of this patient

Question 1. Some scholars have proposed that cellular CMN is a special type of IFS. The current evidence supporting this viewpoint is that both types of tumors show an abundance of spindle-shaped cells in their pathological results, and they have similar fusion gene types. Personally, I believe that these pieces of evidence are not sufficient. Therefore, I am curious to know if there is any other evidence currently available to support this viewpoint

Expert opinion 1: Dr. David Van Mater

IFS and cellular CMN both have a "sarcoma-like" histology.

Both lesions are generally curable with complete resection and commonly share NTRK translocations. However, it remains unknown if IFS and cellular CMN represent the same neoplasm arising in a different site or if they simply share some features but remain biologically distinct.

Expert opinion 2: Dr. Laura S. Hiemcke-Jiwa

The arguments that support a close relationship between IFS and CMN are: (I) similar clinical characteristics (both infants); (II) similar morphology, including composite IFS cases mimicking classic/mixed CMN; (III) similar molecular alterations including *ETV6::NTRK3* and EGFR kinase domain duplications (KDDs); (IV) similar RNA expression profile (see https://doi.org/10.1016/j.anndiagpath.2021.151885).

Question 2. CMN has long been considered a tumor with a good prognosis, but in this study, this particular case had a poor prognosis. Currently, there is no consensus on the treatment approach for CMN with a poor prognosis among different medical institutions. The chemotherapy regimen we adopted in this study was also based on previous literature reports. Therefore, the question arises as to whether there is a standardized and effective treatment approach for CMN

Expert opinion 1: Dr. David Van Mater

While there is no standard chemotherapy regimen, I think there is consensus that surgery should be utilized upfront. Larotrectinib is Food and Drug Administration-approved for the treatment of any tumor with a *NTRK* fusion. It is a very rational approach (especially in light of the similarities to IFS).

Question 3. Larotrectinib is an effective targeted drug for tumors with NTRK fusion genes. However, resistance to larotrectinib is also a challenge faced by clinicians. With the use of second-generation TRK inhibitors such as LOXO-195, this problem can be resolved. Therefore, in order to prevent pediatric patients with tumors from facing a situation where they have no effective treatment options due to resistance to second-generation TRK inhibitors, it is worth exploring whether a treatment regimen combining larotrectinib with other targeted drugs is feasible in preclinical research on CMN

Expert opinion 1: Dr. David Van Mater

There may be some merit to this idea of combining larotrectinib with other agents, but I think it is beyond the scope of this paper. I think it would be more interesting to prove that this patient developed a mutation in *NTRK1* rendering it resistant to larotrectinib, but that was not feasible as you noted.

Conclusions

With the development of second-generation sequencing and microarray technique, increasing attention has been paid to the personalized treatment of tumor based on molecular typing. As a special type of MDT, MTB addresses the problems of tumor diagnosis and treatment at the molecular level, and it has played an important role in the precision diagnosis and treatment of various tumors in recent years (38,39). Gooskens *et al.* found that the histological subtype was the most important factor affecting the prognosis of CMN, and cellular CMN had the worst prognosis among all CMN subtypes (40). CMN has multiple types of genetic abnormalities, with *NTRK* rearrangement being the most common type of genetic abnormality. Therefore, personalized treatment based on these abnormal molecular phenotypes will bring new treatments to recurrent and refractory CMN. Our literature review revealed one case of larotrectinib being used in the treatment of CMN with *ETV6::NTRK3* fusion gene, and the patient had a good response (41). Albert *et al.* also asserted that CMN with *NTRK* rearrangement is a suitable target for TRK inhibitors (42). The case in this study was a rare cellular CMN with *TPM3::NTRK1* fusion gene, metastatic spread, and poor response to traditional chemotherapy. Molecular-targeted therapy based on MTB induced a partial response and delayed progression, though it ultimately did not impact survival. This result demonstrates that personalized therapy based on MTB is feasible and effective in the diagnosis and treatment of CMN.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-126/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Children's Hospital of Nanjing Medical University (ethical approval No. 202306001-1) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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