Dramatic bone remodeling following larotrectinib administration for bone metastasis in a patient with TRK fusion congenital mesoblastic nephroma

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Abstract
Mesoblastic nephroma is the most frequent renal tumor in newborns and young infants, and the cellular type is characterized by an ETV6–NTRK fusion, which constitutively activates the tropomyosin-related kinase (TRK) signaling pathway. Larotrectinib is a highly selective TRK inhibitor with activity in adult and pediatric patients who have TRK fusions. We present a rare case of a patient with mesoblastic nephroma metastatic to bone who had a dramatic response to larotrectinib.

KEYWORDS
bone metastasis, ETV6–NTRK, larotrectinib, mesoblastic nephroma, TRK inhibitor

1 | INTRODUCTION

First described in 1967, congenital mesoblastic nephroma (CMN), is a renal tumor distinct from Wilms tumor. Histologically, CMN has been divided into three subtypes, "classical," "cellular," and "mixed." Cellular CMN is characterized by high cellularity, numerous mitoses, and cellular pleomorphism. Early work reported phenotypic changes in cellular CMN similar to infantile fibrosarcoma, including trisomy 11 and the ETV6–NTRK3 fusion. Knezevich et al. discovered that patients with cellular CMN are highly likely to harbor NTRK fusions (eight of nine samples), whereas none of the patients with classical CMN had this rearrangement (zero of four samples). These data were independently corroborated by Rubin et al.

Patients with cellular CMN usually have a good prognosis following nephrectomy, with event-free and overall survival greater than 94%. However, there are rare case reports of patients with local failure and/or metastatic disease. Patients diagnosed with metastatic disease are usually treated with vincristine/actinomycin-D or doxorubicin/vincristine/cyclophosphamide.

Larotrectinib is a highly potent and selective, orally administered tropomyosin-related kinase (TRK) inhibitor. Larotrectinib has recently been shown to have broad, rapid, and durable clinical activity in adults and pediatrics. A recommended phase 2 dose of 100 mg/m2 (maximum dose of 100 mg) BID has been established for pediatric patients. Here, we report on a patient with metastatic CMN enrolled on the phase 2 portion of the globally enrolling phase 1/2 pediatric trial (NCT02637687).

1.1 | Case presentation

The patient is a 23-month-old male who was initially diagnosed with a Stage II cellular CMN of the right kidney. The tumor was identified prenatally and the right kidney was surgically removed at the sixth day of life. The tumor was found to have an NTRK3 fusion by
fluorescence in situ hybridization (FISH) for the ETV6 partner gene and the patient was monitored for recurrence at regular interval. At 12 months of age, the patient developed a lesion on the distal tibia measuring $5.2 \times 2.9 \times 2.4$ cm (Fig. 1A) with significant cortical destruction (Figs. 1B and 1C) and an associated soft-tissue component that measured 1.43 cm (Fig. 1A). The lesion was biopsied and results were consistent with recurrent mesoblastic nephroma; genomic analysis using whole exome sequencing and transcriptome sequencing (RNA-Seq) of the lesion revealed an $ETV6–NTRK3$ fusion. The patient was enrolled on the larotrectinib pediatric study (NCT02637687) and to date has received eight cycles of therapy without any grade 2 or greater toxicities. At initial presentation, the patient had a cast that was replaced with a boot after three cycles, and after eight cycles the patient has a full range of motion in the lower extremity without the braces, and the most recent evaluation showed complete disappearance of the soft-tissue component (Fig. 2A) and near-complete reconstitution of the cortex of the distal right tibial metastatic focus (Figs. 2B and 2C). There was development of calcified matrix in the bone marrow possibly due to healing or in response to larotrectinib (Fig. 2B).

2 | DISCUSSION

CMN is a rare tumor that typically affects neonates and young infants and accounts for 5% of all pediatric renal tumors. The treatment of choice is surgical resection after which event-free survival and overall survival rates are in excess of 90%. There are three histologic subtypes of CMN: classic, mixed, and cellular variants. The cellular variant has similarities with congenital infantile fibrosarcoma and both are characterized by a t (12;15) (p13;q25) translocation resulting in a fusion of $ETV6$ and $NTRK3$. However, variant TRK fusions have been identified and reported. This has important implications for testing strategies in these tumors, as negative result for $ETV6–NTRK3$ fusion does not rule out other TRK fusions. The use of either $NTRK3$ FISH or next-generation sequencing will expand the number of cases in which an oncogenic fusion is identified and facilitate optimal diagnosis and treatment for patients. In a report of the International Society of Pediatric Oncology/Gesellschaft fur Padiatrische Onkologie und Hamatologie, 58% of cases with cellular variant CMN had the $ETV6–NTRK3$ fusion, and none were detected in classical type.

Recurrences are rare and have been described in approximately 4% of the cases. Relapses more commonly occur locally, but distant metastasis in the lung and liver have been reported; bone metastases are extremely rare and account for 5.5% of reported cases with metastasis. Subsets of patients who are at high-risk for recurrence include those who are older than 3 months of age at diagnosis, those with a cellular type that contains an NTRK gene-fusion, and those with an incomplete surgical resection of the mass. Gooskens et al. estimated that recurrence with cellular CMN was as high as 10% with a mortality of 57% in the cohort reviewed.
The case report here is unique because of the metastatic disease pattern, with bone involvement and the clinical challenge of locally controlling the disease. The lesion incorporated over half the length and the entire width of the tibia, but appeared to have spared the physis and epiphysis without joint collapse. Surgical options included local intrasional curettage and bone graft, wide local resection, and reconstruction or below knee amputation. In an effort to avoid these potentially morbid procedures, we elected observation and immobilization with a long leg, bent knee cast to prevent weight bearing.

Assessing the response of bone metastases to therapy is usually difficult, with a slow and subtle healing process. Sclerosis of lytic lesions usually begins to appear 3–6 months after the start of effective therapy and can take more than 1 year to mature. In this case the dramatic response observed to larotrectinib, a highly selected TRK inhibitor, promoted significant robust bone healing and obviated the need for surgical resection or amputation. This compound has proven active in adults and children with an overall response rate of 75%. The median time to response was reported to be 1.8 months (range, 0.9–6.4). Side effects of the drug have been minimal, with largely grade 1–2 toxicities. In our case, the first evaluation performed 8 weeks after starting treatment showed a partial response (30% decrease in size of soft-tissue component). Currently the patient is in complete response, with complete resolution of the soft-tissue tumor, 8 months after starting therapy.

Our patient did not experience any grade 2–4 toxicities. Administration of this agent as the first line of therapy in the presence of a recurrence following surgery is an attractive option in patients with NTRK fusion cancers since this can lead to the avoidance of chemotherapy and the associated complications resulting from central line placement, mucositis, and neutropenia. In addition, the dramatic bone healing with restoration of skeletal integrity has allowed us to circumvent the need for an aggressive and potentially morbid surgical procedure in this patient.

In summary, larotrectinib was a highly effective agent in a patient with cellular mesoblastic nephroma metastatic to bone and led to resolution of the soft-tissue component and reconstitution of cortical bone thereby decreasing the need for radical surgical procedures.

**CONFLICT OF INTEREST**

MR is a consultant for Loxo Oncology and holds a patent 62/318,041 issued to Loxo Oncology. MCC is an employee of Loxo Oncology and owns stock in Loxo Oncology and Bayer AG, and holds a patent 62/318,041 issued to Loxo Oncology.

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