Durable disease control with apatinib, irinotecan and temozolomide in a case of metastatic primitive myxoid mesenchymal tumour of infancy

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Abstract

Primitive myxoid mesenchymal tumour of infancy (PMMTI) a rare and aggressive soft tissue tumour driven by alteration in the BCOR gene. Localised disease may be cured by surgical resection but metastatic disease often displays suboptimal chemotherapy response. Here we report the course of a patient with widely metastatic PMMTI, where durable disease control was achieved with the combination of apatinib, a VEGFR inhibitor, and chemotherapy with irinotecan/temozolomide.

Introduction

Primitive myxoid mesenchymal tumour of infancy (PMMTI) is an exceptionally rare myofibroblastic tumour that predominantly affects infants [1]. Previously classified as an undifferentiated sarcoma, the association with internal tandem duplication (ITD) in the*BCOR* gene has led to its recognition as part of a distinct nosological entity - "Sarcoma with *BCOR* Genetic Alterations" - in the 2020 WHO Classification of Soft Tissue tumours [11, 12, 16]. Owing to its rarity, diagnosis of PMMTI is challenging and the optimal strategy for management remains uncertain. Previous reports highlighted the relative chemoresistance of such an entity and described local recurrence as the main pattern of failure [2]. Herein, we report an exceptional case of PMMTI with metastasis where sustained remission was achieved with a combination of apatinib and chemotherapy.

Results

A term, female newborn with unremarkable antenatal course was noted to have a left dorsal foot swelling at birth. The lesion, which appeared to be solitary, had an irregular border and dilated veins were present on the overlying skin. Ultrasound and MRI showed a cystic mass encasing the metatarsal bones. After initial observation for the presumed lymphatic malformation, the lesion was biopsied and then debulked at three months of age. Pathology was interpreted as possible infantile fibrosarcoma, although *NTRK3* rearrangement was not demonstrated. The mass regrew rapidly leading to ulceration, and a left scapular mass became evident. PET-CT was performed and showed massive metastasis in the lungs, cervical and inguinal lymph nodes, right gluteus, left paraspinal region, and subcutaneous nodules suggestive of metastatic lesions.

Upon referral to our unit at 6-months of age, the pathology was reviewed. Histomorphologically, the cellular lesion was composed of sheets of spindle cells with slightly irregular nuclei, finely granular chromatin, occasional small nucleoli and small amount of clear or eosinophilic cytoplasm in a background capillary network. Mitosis was readily seen (up to 8 per 10 high power field). By immunohistochemistry (IHC), the tumour cells were positive for BCOR, SATB2, FL1, TLE1, BCL2, BCL6 and cyclinD1, while CD99 staining displayed a mainly cytoplasmic pattern. RNA-sequencing then confirmed the presence of *BCOR* -ITD. Overall, the integrated diagnosis was compatible with PMMTI.

Systemic therapy was started with palliative intent. We adopted a combination of apatinib, an oral multikinase inhibitor (15mg/kg/day), temozolomide (5mg/kg on Day 1, and 2.5mg/kg on Days 2-5) and irinotecan (1.75mg/kg daily on Days 1-5) (AIT regimen), repeated at 3 weekly-intervals. PET-CT after 4 cycles of AIT indicated progression of the primary lesion (measuring 6.6 x 4.5 x 6.5 cm) as well as numerous new metastases involving the cervical and inguinal lymph nodes, gluteal muscles, paraspinal region, and right hemithorax. A trial course of vincristine, doxorubicin and cyclophosphamide (VDC) was given, which unfortunately, was complicated by significant cytopenia and septic shock. Hence, VDC was withheld and AIT resumed.

Surprisingly, continuation of the AIT regimen led to clinical and radiographic regression of the primary and metastatic lesions. The lesion decreased in size and skin ulcerations resolved. Chemotherapy was gradually spaced out to 5-weekly intervals. PET-CT 16 months after the re-initiation of AIT (22 cycles given) indicated sustained partial response. The treatment regimen was largely tolerated other than reversible proteinuria and hypertension that necessitated transient interruption of apatinib between the 16^{th} and 18^{th} cycle. Subclinical adrenal insufficiency was also detected for which the patient was put on hydrocortisone. At 24 months of age, the patient enjoyed normal motor development and good quality of life.

Discussion

Since the first description of PMMTI in 2006, only 31 cases have been reported to date (Supplementary Table 1). Based on the published data, both sexes were equally affected and the mean age of onset was 6.6 months. Patients often presented with enlarging mass lesions involving the trunk which were sometimes painful. PMMTI was often locally aggressive even though metastasis has been infrequently reported.

Histologically, PMMTIs are typified by sheets of spindly cells in a delicate capillary network, overlaying a myxoid background. Based on the clinical and histologic overlap between PMMTIs and undifferentiated round cell sarcoma (URCS), Kao et al identified *BCOR*- ITD as a molecular driver that underlies most PMMTIs and half of URCSs [12]. A potential differential diagnosis that may be diagnosed in the same age group, infantile fibrosarcoma, will be deemed unlikely with the absence of *ETV6-NTRK3* fusion [16]. BCOR belongs to part of the non-canonical polycomb repressive complex 1.1. It is postulated that *BCOR* -ITD results in disruption of the complex leading to the depression of target promotors and consequent oncogenic effects [14]. *BCOR*- ITD is now established to characterise a range of histopathologic entities including also clear cell sarcoma of kidney, a subset of high-grade neuroepithelial tumours, and high grade endometrial stromal sarcoma [14, 19]. These highlight the importance of integrated histologic and molecular workup in the diagnosis of infantile soft-tissue tumours.

While the understanding of *BCOR* alteration as tumour driver might facilitate future identification of novel therapeutic vulnerability, the mainstay of PMMTI management remains surgical excision especially in the majority of patients where the disease is localised [2, 13]. There is also no effective therapeutic strategy agreed upon for patients with unresectable and/or metastatic disease. Memmot and colleagues recently reported a patient with infiltrative localised disease who progressed on neoadjuvant therapy with vincristine, actinomycin, and cyclophosphamide (VAC) but subsequently responded to ifosfamide and doxorubicin (ID), allowing a complete resection [13]. Based on the review of rare PMMTI cases who received systemic therapy with a report on outcome (n=7), anthracycline-containing regimen (ID or VDC) appeared to be active whereas VA/VAC did not demonstrate efficacy. Nonetheless, acute and chronic toxicities from such regimen in these very young patients are of concern as in our case where life-threatening sepsis developed. Combination of irinotecan and temozolomide is an established regimen for relapsed/refractory solid tumour

inclusive of sarcoma with good tolerability [3, 7, 18]. Apatinib, on the other hand, is an oral VEGFR-2 tyrosine kinase inhibitor that has gained orphan drug status from FDA on a number of adult-onset cancers including gastric and thyroid cancers. It has also shown to be of value in children with relapsed/refractory solid tumours [17], and a Phase II trial to evaluate the efficacy of AIT in relapsed/refractory neuroblastoma is ongoing (NCT05027386). The combinatory regimen may exert synergistic effect in soft-tissue sarcoma while limiting toxicities in infants which formed the basis of our decision to treat our patient with such an approach. The partial response and prolonged stabilisation of disease offers promising pilot data to support further evaluation of AIT in soft-tissue sarcomas where standard-of-care protocols are lacking.

In conclusion, we demonstrated, for the first-time, the clinical activity of AIT in a patient with progressive and metastatic PMMTI. The role of such a regimen in managing paediatric soft-tissue sarcomas warrants additional studies.

Declaration of interest

The authors report no conflict of interest.

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Appendix

Supplementary table 1. Literature of PMMI

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Legends

Figure 1. Clinical photo of the gross appearance of the tumour

Supplementary table 1. Literature on PMMTI.