CASE REPORT

Wilms tumor with Mulibrey Nanism: A case report and review of literature

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Abstract

Background: Mulibrey-Nanism (Muscle-liver-brain-eye Nanism = dwarfism; MUL) is a rare genetic syndrome. The underlying TRIM37 mutation predisposes these children to develop tumors frequently. In the largest published series of MUL, 8% patients were reported to develop Wilms tumor (WT). The published literature lacks data regarding the best treatment protocol and outcome of this cohort of children with WT and MUL. We report here a 2-year-old boy with WT and MUL and present a review of literature on WT in MUL.

Case: Our patient had associated cardiac problems of atrial septal defect, atrial flutter and an episode of sudden cardiac arrest. We managed him successfully with chemotherapy, surgery and multi-speciality care. He is alive and in remission at follow-up of 6 months.

Conclusion: A total of 14 cases (including present case) of WT have been reported in MUL and treatment details were available for six cases. They were managed primarily with surgery, chemotherapy with/without radiotherapy, and all achieved remission. The outcome data is available only for two cases, one has been followed up till 15 years post treatment for WT and other is our patient.

KEYWORDS
atrial flutter, atrial septal defect, Mulibrey Nanism, Wilms tumor

INTRODUCTION

Mulibrey-Nanism (MUL) (Muscle-liver-brain-eye Nanism = dwarfism), is an autosomal recessive disorder caused by mutations in the TRIM37 gene.1 TRIM37 is a 130 kDa protein located in the peroxisomes and expressed in several tissues of the body.2 It is implicated in various biological processes, such as post-translational modifications, signal transduction, DNA repair, immunological signaling, autophagy and oncogenesis.3 The most frequently encountered “Fin-major mutation” c.493-2A>G has been reported in Finnish patients probably due to a founder effect.3 Non-Finnish MUL patients have been reported with other mutations.4 The syndrome is characterized by growth failure of perinatal onset, dysmorphic facies, muscular dystonia, venous
congestion secondary to constrictive pericarditis and yellowish dots in fundi. They have an increased tendency to develop cystic and benign adenomatous lesions in various parts of the body, cutaneous nevi flammi, gonadal dysfunction especially in females, type II diabetes mellitus, fibrous dysplasia and malignancy, mainly Wilms tumor (WT). There are very few reports of WT in MUL and the published literature lacks data regarding the best treatment protocol and outcome of this cohort. Here we report a child of WT with MUL and provide a review of literature.

2 | METHOD

We reviewed medical records of our case of a child with MUL and WT and looked at treatment details, complications and outcome. We performed a review of the literature for the similar cases. MED-LINE/ PubMed/Google/Google Scholar/EMBASE/Cochrane were searched from inception to March 2021, and the following terms were used for data searching: “Mulibrey Nanism” OR “TRIM37” AND “Wilms tumor”. Full-text manuscripts or abstracts, published in English language peer-reviewed journal were included. Articles published in languages other than English for which formal translation was not available were excluded. Free full-text articles available at https://pubmed.ncbi.nlm.nih and selected full-text articles indexed in Web of science or Scopus are downloaded using the EBSCO discovery services.

3 | RESULTS

A 2-year-old boy presented with incidentally detected mass in left side of his abdomen. Computerized tomography (CT) scan of abdomen showed a heterogeneously enhancing, solid cystic lesion measuring 59 × 56 × 82 mm in the upper pole of the left kidney. Liver was also enlarged with hypodense lesions in segments IVb/V and VI. CT chest showed no evidence of metastasis. Renal and liver biopsies were done at another center. Review of renal biopsy confirmed the diagnosis of WT. Liver biopsy showed no tumor. He was born of non-consanguineous parents with birth weight of 2800 g (between 2 and 0, Z score as per WHO growth chart) and length of 56 cm (between –2 and 0, Z score as per WHO growth chart). On examination, child had a triangular face, low nasal bridge, high broad forehead, low set ears, a high-pitched voice, distended abdomen, left sided balloonable renal mass and hepatomegaly. Neurological examination revealed mild hypotonia and normal mental functions. His present height was 87 cm (15th–50th centile as per WHO growth chart) and weight was 10 kg (third centile as per WHO growth chart). Echocardiography showed moderate size secundum atrial septal defect (ASD) with bidirectional shunt predominantly left to right and restrictive filling of right ventricle as evidenced by tissue doppler imaging. Final diagnosis was considered WT stage 4 due to multiple nodules seen in liver. He was started on neo-adjuvant chemotherapy as per SIOP2001 protocol.

He received five doses of weekly injection vincristine and one dose of injection actinomycin-D. Doxorubicin was not given in view right ventricular dysfunction and was replaced with cyclophosphamide. After week 5 of chemotherapy child was admitted with febrile neutropenia and started on intravenous antibiotics. On the second day of this admission he complained of restlessness, vomiting and hypotension, closely followed by generalized tonic-clonic seizures and went into sudden cardiac arrest. Child was revived after cardiopulmonary resuscitation. As he was still in coma and had jerky respiration so was intubated and ventilated. His condition improved over next 48 h and he was extubated. Electroencephalogram was normal. Magnetic resonance imaging of brain was normal except for presence of a choroid plexus/xanthogranulomatous cyst in left lateral ventricle and a shallow and J shaped Sella turcica. He developed hoarseness of voice which was possibly due to vincristine and intubation. Subsequently, he developed an episode of paroxysmal tachycardia with heart rate >220/min, diagnosed as atrial flutter (AF) on electrocardiogram. It was aborted with injection amiodarone. Gradually his voice returned and he could swallow food. In view of cough, he was tested for SARS-COV-2 by PCR and it was detected to be positive. He was shifted to COVID-19 care ward where he had a second episode of atrial flutter and required to be shifted to intensive care unit again. He was managed successfully for AF and his cardiac rhythm reverted to normal. Once he was negative for COVID-19 he was discharged.

In view of child not tolerating chemotherapy well, having abnormal facies, cardiac anomaly, hepatomegaly and abnormal findings in MRI brain; it was suspected that child has some underlying syndrome. So, a karyotyping with standard 400–450 G banding technique was performed and it was reported as normal. Mitomycin C sensitivity testing was done on 72 h PHA stimulated unsynchronized cultures to rule of Fanconi Anemia and was reported as normal. Finally a clinical exome sequencing using selective capture and sequencing of the protein coding regions of the genome genes was performed. The library was sequenced to mean >80–100× coverage on Illumina sequencing platform. The sequences obtained was aligned to human reference genome (GRCh38.p13) using Sentieon aligner and analyzed using Sentieon for removing duplicates, recalibration and re-alignment of indels.7 Sentieon haplotype caller was used to identify variants which are relevant to the clinical indication. Gene annotation of the variants was performed using VEP program against the Ensembl release 99 human gene model.7 In addition to SNVs and small indels, copy number variants (CNVs) were detected from targeted sequence data using the Exome Depth (v1.1.10) method.10 Clinically relevant mutations were annotated using published variants in literature and a set of databases—ClinVar, OMIM (updated on February 20, 2020), GWAS, HGMD (v2019.4) and SwissVar.11–14 Common variants were filtered based on allele frequency in 1000 Genome Phase 3, gnomAD (v2.1), EVS, dbSNP (v151), 1000 Japanese Genome and our internal Indian population database. Non-synonymous variants effect was calculated using multiple algorithms such as PolyPhen-2, SIFT, MutationTaster2 and LRT. Only non-synonymous and splice site variants found in the clinical exome panel consisting of 6670 genes were used for clinical interpretation. Sequencing was reported to
show the presence of heterozygous nonsense variation in exon 15 of the TRIM37 gene variant c.1336C>T (chr17: g. 59049372 G>A; Depth: 130×) resulting in a stop codon and premature truncation of the protein at codon 446 (p. Arg446Ter). This mutation was reported as a pathogenic variant for Mulibrey-Nanism. Another heterozygous missense variation in exon 2 of the TRIM37 gene variant c.80T>A (chr17: g.59104336A>T; Depth: 94×) that results in the amino acid substitution of Glutamine for Leucine at codon 27 (p. Leu27Gln; ENST00000262294.12) was detected but was analyzed to be of unknown significance.

The genomic DNA samples of the parents were analyzed for the reported variants in TRIM37 gene using PCR followed by DNA sequencing. Mother was negative for both c.80T>A and c.1336C>T mutations and father was heterozygous for c.80T>A and negative c.1336C>T. Although the c.80T>A has been reported to be of unknown significance, parental testing has proven that it is inherited from father and the other known mutation is de novo. The child satisfied the clinical criteria for diagnosis of MUL due to presence three major criteria (small for gestational age at birth, J-shaped Sella turcica on MRI, typical facies) and two minor criteria (high pitched voice and hepatomegaly). Along with heterozygous pathogenic mutation, the second heterozygous novel mutation could possibly be considered deleterious causing MUL in him.

Positron emission tomography-CT done after completion of 5-weeks of chemotherapy showed reduction in size of renal tumor with multiple non-FDG avid liver lesions. CT chest was suggestive of
minimal cardiomegaly with basal areas of parietal pericardium showing
evidence of early calcification. He underwent nephrectomy and histo-
pathology was suggestive of favorable histology WT (blastic 40%,
epithelial 30% and stromal 30%). Review of tissue block of liver
lesions was not suggestive of WT metastasis and a possibility of
benign hamartomas was kept. Post operatively tumor was classified as
stage-I. Figure 1 illustrates his treatment course. He was given further
four weekly doses of vincristine at 50% dose in view of previous toxic-
ity and a single dose of actinomycin-D. At present, he is well 6-months
after finishing his planned chemotherapy. He underwent fundus exa-
nination which was within normal limits. His endocrinology work-up
showed presence of hypothyroidism which was treated with thyroxine.
The patient is currently on oral antiarrhythmic (Metoprolol and
Amiodarone) and has not experienced further episodes of atrial flutter.

| MULIBREY NANISM |
|------------------|
| OR               |
| MUL              |
| 1970-2020        |
| Total Manuscripts|= 78 |
| Published in English|= 72 |

**FIGURE 2** Algorithm for review of literature

**4 | REVIEW OF LITERATURE**

On review of literature, we found a total of 14 cases including
one case of ours.6,15-19 The algorithm used for review of litera-
ture is shown in Figure 2. Table 1 show details of all the cases.
The mean age of the subjects was 19 months (Male: Female ratio
1:1). Other than our case, histopathology detail was available for
only one other case which was cystic partially differentiated
nephroblastoma. Staging details were available for three patients.
Two were classified as stage 1 and one as stage IV and managed
accordingly. Largest series of eight patients of Wilms tumor has
been reported from Finland in a cohort of 101 cases of MUL but
it lacked details of treatment and outcome.19 The treatment
details were available for six cases. They were managed mainly
with surgery, chemotherapy with/without radiotherapy, and all
are in remission. The longest survivor was 15 years at the time of
reporting.

MUL is associated with an increased frequency of benign and
malignant tumors and also shows disturbed control of organ develop-
ment. Karlberg et al. noted a total of 210 tumorous lesions in 66/89
Finnish patients (74%). The benign tumors included cysts, vascular
abnormalities (peliosis), adrenal adenoma, parathyroid adenoma, thy-
roid goiter, pancreatic cystadenoma, renal angiomyolipoma, ovarian
fibro thecoma and phaeochromocytoma. Thirteen of the 89 patients
(15%) had a malignant tumor, such as WT, renal papillary carcinoma,
thyroid papillary and medullar carcinoma, ovarian and endometrial car-
cinoma, acute lymphoblastic leukemia, Langerhans cell histiocytosis
and carcinoid tumor.20

WT can be the first presentation, with MUL being diagnosed sev-
eral years later as seen in three cases found in this review of literature.
Children with WT should be assessed for possible syndromic associa-
tion and be managed accordingly.

Two out of 14 patients initially treated for WT, required
pericardiectomy several years later. Our case also has early
signs of pericardial thickening and may later require cardiac
intervention. Although cardiac affliction is known, arrhythmia
as a predominant symptom seen in our patient has not been
described previously. Other features seen in patients associ-
ated with MUL and WTs included bone dysplasia, constrictive
pericarditis requiring pericardiectomy, and massive ascites
requiring repeated abdominocentesis.

**5 | DISCUSSION**

Our patient presented with WT. In view of child not tolerating chemo-
therapy well, having abnormal facies, cardiac anomaly, hepatomegaly
and abnormal findings in MRI brain; it was suspected that child has
some underlying syndrome thus genetic testing was performed. Our
patient showed three major signs (small for gestational age lacking
catchup growth, craniofacial features, shallow and J-shaped Sella tur-
cica) and two minor signs (peculiar high-pitched voice and hepatomeg-
aly) as described by Karlberg et al., depicted in Table 2.21 Finland
### TABLE 1  Cases of Wilms tumor and Mulibrey Nanism syndrome

| Sr. No. | Publication       | No. of cases | Age (months) | Sex | Histopathology of WT | Stage | Treatment                                                                 | Chronology of diagnosis of MUL and WT: Synchronous/MUL before WT/WT before MUL | Other features                                                                 | Disease status |
|---------|-------------------|--------------|--------------|-----|-----------------------|-------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------|
| 1       | Simila et al.⁶    | 1            | 24           | F   | NA                    | NA    | Chemotherapy (Actinomycin-D, VCR) + surgery + RT                          | Synchronous                                                                  | Nil                                                         | Remission      |
| 2       | Seemanova et al.¹⁵| 1            | 18           | M   | NA                    | NA    | Chemotherapy + surgery                                                   | WT before MUL                                                                | Bone dysplasia/Constrictive pericarditis/Inguinal Hernia/ Hypotonia/ Ventriculomegaly | Remission      |
| 3       | Hämäläinen et al.¹⁶| 1            | 18           | F   | NA                    | IV    | 27 Weeks chemotherapy (Actinomycin-D, VCR and Doxorubicin) + surgery @ 6 weeks + RT (10 gray) | Synchronous                                                                  | Bone Dysplasia                                            | Remission      |
| 4       | Husova et al.¹⁷   | 1            | 18           | M   | NA                    | NA    | Chemotherapy + surgery                                                   | WT before MUL                                                                | Constrictive pericarditis, ascites                        | Remission      |
| 5       | Seppo Taskinen et al.¹⁸| 1         | 7            | F   | Cystic partially differentiated nephroblastoma | I     | Chemotherapy (Actinomycin-D, VCR) + Surgery                              | WT before MUL                                                                | Simple renal cyst in contralateral kidney                  | Remission      |
| 6       | Sivunen et al.¹⁹  | 8            | 30 (mean)    | NA  | NA                    | NA    | NA                                                                        | MUL before WT                                                                 | NA                                                         | NA             |
| 7       | Present Study     | 1            | 24           | M   | Triphasic nephroblastoma favorable histology | I     | Pre surgery—VCR, Actinomycin-D and cyclophosphamide (5 weeks) Post-surgery—VCR and Actinomycin-D (5 weeks) | Synchronous                                                                  | ASD, Benign nodules in liver and Simple renal cyst in contralateral kidney | Remission      |

Abbreviations: ASD, atrial septal defect; F, female; M, male; MUL, Mulibrey Nanism; NA, information not available; RT, radiotherapy; VCR, vincristine; WT, Wilms tumor.
account for the maximum number of MUL cases. MUL can resemble closely to 3M syndrome.

MUL is associated with an increased frequency of benign and malignant tumors and also shows disturbed control of organ development. The association of TRIM37 mutations with increased risk of cancer indicates a pro-survival process in TRIM37-deficient tumor cells. Wang et al. reported interaction of lysosomal protein mTOR with TRIM37, leading to transcriptional activation of genes involved in lysosome biogenesis and macroautophagy/autophagy. Autophagy could be a way for the cell to survive the loss of TRIM37.

The missense variation in exon 2 of the TRIM37 gene variant c.1336C>T is a reported pathogenic variant and is probably de novo acquired in our patient.

The coexisting liver lesion which was initially considered as hepatic metastasis and was later diagnosed as benign liver hamartomas, emphasizes the need to look out for associated benign tumors. These patients are highly prone to tumorigenesis and careful diagnosis can help in assigning the correct stage and formulating relevant treatment protocol.

Heart is the most frequently affected organ in MUL with constrictive pericarditis, myocardial hypertrophy and variable myocardial fibrosis constituting the main components of Mulibrey heart disease. Mariata et al. reported 49 adults with MUL heart disease, noted these patients to be highly susceptible to develop congestive cardiac failure and need for pericardiectomy in one third of the patients. ASD similar to our case have been reported in MUL. Our patient had two episodes of AF and an episode of sudden cardiac arrest which has not been reported previously in children with MUL. Structural heart defect, particularly ASD especially ostium primum is known to be associated with arrhythmias, with increasing frequency with age. Cases of resistant to treat arrhythmia have been managed successfully with ASD closure in adults, but reports in children are limited. Our patient responded to anti-arrhythmic drugs. The temporal proximity of AF and COVID-19 infection might raise questions if the AF was due to COVID-19. However, the first episode of atrial flutter happened about 1 week before the patient was tested positive for COVID-19 as depicted in Figure 1. Atrial flutter is not a known side-effect of the chemotherapy that the patient had received. Most likely underlying cardiac defect contributed to the episodes of atrial flutter.

WT although rare in children with MUL, is treatable. Our case highlights the need to watch out for cardiac arrhythmia in these patients. Although a lot could not be gathered from review of literature regarding treatment protocol, but it appears that these children tolerate standard treatment protocol well and can achieve remission.

**CONFLICT OF INTEREST**

All authors have nothing to disclose.

**AUTHOR CONTRIBUTIONS**

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, K.U., D.T., M.S.S., A.Y., K.B., J.S., N.R., S.P.Y.; Methodology, K.U., D.T., D.G., M.S.S., A.Y., R.K., V.R., K.B., S.N., J.S., N.R., S.P.Y.; Investigation, K.U., D.T., M.S.S., R.K., V.R., M.S.D., K.B., S.N., J.S., N.R., S.P.Y.; Formal Analysis, K.U., M.S.S., A.Y., R.K., V.R., K.B., S.N., J.S., N.R., S.P.Y.; Resources, K.U., D.T., D.G., M.S.S., A.Y., V.R., M.S.D., S.N., J.S., N.R., S.P.Y.; Writing—Original Draft, K.U., D.G., J.S., N.R., S.P.Y.; Writing—Review & Editing, D.T., M.S.S., R.K., K.B., N.R., S.P.Y.; Visualization, K.U., D.T., M.S.S., A.Y., R.K., V.R., M.S.D., K.B., S.N., J.S., N.R., S.P.Y.; Supervision, R.K., V.R., K.B., N.R., S.P.Y.; Funding Acquisition, D.T., A.Y., R.K., K.B., S.N., J.S., N.R., S.P.Y.; Data Curation, K.U., D.T., D.G., M.S.S., A.Y., R.K., V.R., M.S.D., K.B., S.N., J.S., N.R., S.P.Y.; Project Administration, K.U., D.T., K.B., N.R., S.P.Y.; Software,

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**TABLE 2** Diagnostic criteria for Mulibrey Nanism and the diagnostic findings in our patient

| Signs | Our patient |
|-------|-------------|
| **Major signs** | |
| Growth Failure (A or B or C) | |
| (A) Small for Gestation Age (SGA) lacking catch up growth | ✓ |
| (B) Height in Children 2.5 below population mean for age | |
| (C) Height in adult 3.0 SD below population mean | |
| Characteristic Radiological Findings (A or B) | |
| (A) Slender long bones with thick cortex and narrow medullary channel | |
| (B) J-shaped Sella turcica | ✓ |
| Characteristics craniofacial features | ✓ |
| Scaphocephaly, triangular face, high and broad forehead, low nasal bridge and telecanthus | ✓ |
| Characteristic ocular findings | ✓ |
| Yellowish dots in Retinal mid peripheral region | |
| Mulibrey Nanism in Sibling | |
| **Minor signs** | |
| Peculiar High pitched Voice | ✓ |
| Hepatomegaly | ✓ |
| Cutaneous Naevi Flammei | |
| Fibrous Dysplasia of Long Bone | |

Note: For the diagnosis, three major signs and one minor sign or two major signs with three minor signs are required.
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ETHICAL STATEMENT
Institutional approval N/A. Informed consent of parent obtained.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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