AMBIGUOUS GENITALIA!!! WHAT IS IT??

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- 20/12/2011- FT child- born by vaccum assisted delivery
- BW- 2.16 kg
- Newborn period treated for- RDS, hypocalcemia & hyperbilirubinemia.
- Had ambiguous genitalia with deformed penis, abnormal urinary orifices & empty scrotum

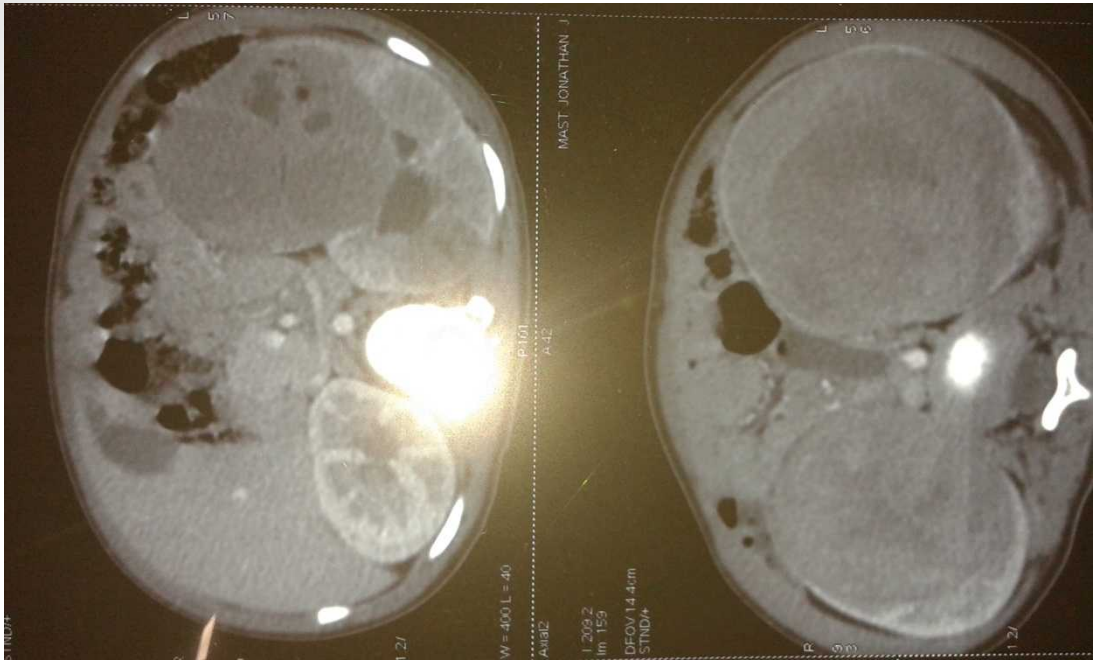
- Karyotyping done - 46 XY - normal
- ECHO - Normal
- USG- showed both renal sizes are towards upper limit of normal range. Both kidneys 5.2 cm. mild increase in echogenicity of both renal parenchymal echogenicity. No pelviectasia

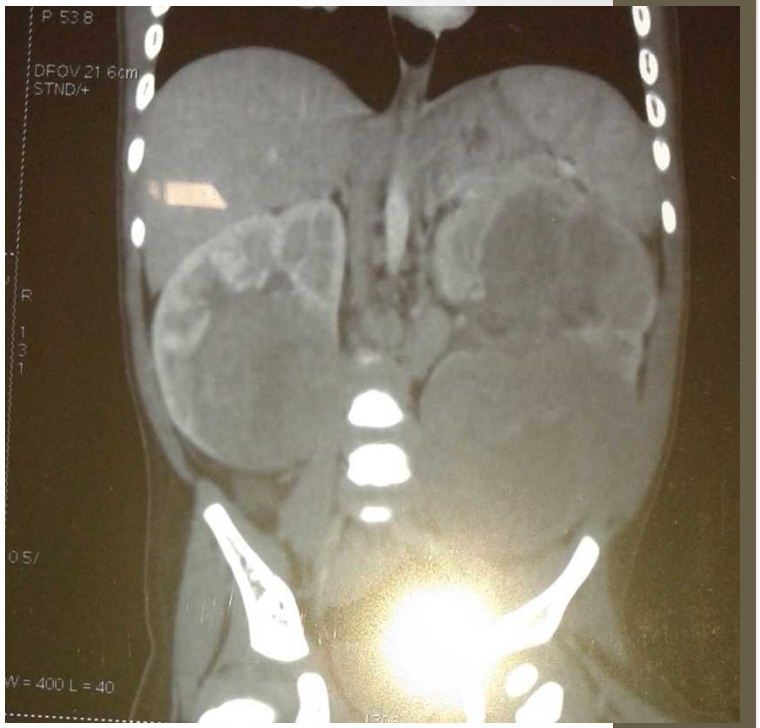
- Discharged well
- Found to have aniridia at 3 months of life
- At 10 months underwent cystoscopy & diagnostic laparoscopy on view of ambiguous genitalia & deformed penis.

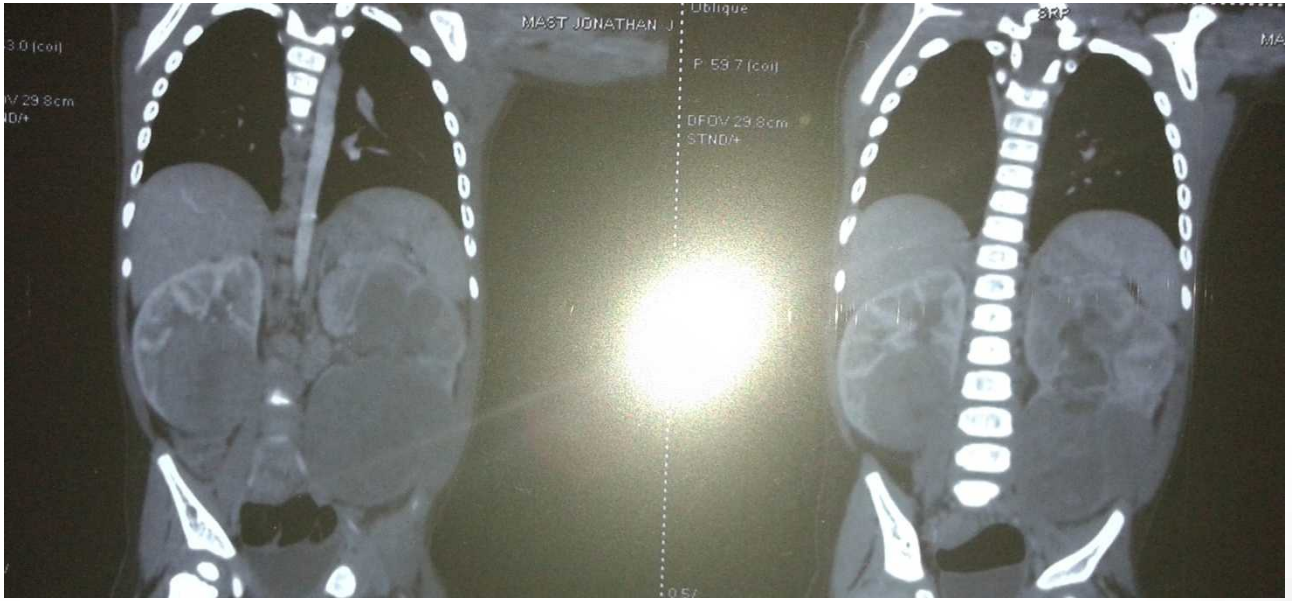
CYSTOSCOPY & LAPROSCOPY

- It revealed anterior & posterior urethra normal with dilated opening of prostatic utricle, bladder & ureteric orifice normal.
- B/L intra-abdominal testis
- Rt- seen as 2mm proximal to internal ring
- Lt- hypoplastic just inside internal ring

- At 1&½ year of life- flank mass was found
- CT- showed B/L nephromegaly with well defined heterogeneously enhancing mass lesion in both kidneys. No renal vein or IVC extension.
- Mild perirenal & pararenal stranding with multiple retroperitoneal lymph nodes.
- Normal excretion of right kidney & left kidney delayed excretion


MAST JONATHAN J
W = 400 L = 40
DFOV 14.4cm
STND/+


P 53.8
DFOV 21.6cm
STND/+
W = 400 L = 40


MAST JONATHAN J
Oblique
P 59.7 [coil]
DFOV 29.8cm
STND/+

- Pre-op chemotherapy planned started
  - week I vincristine & dactinomycin
  - week II vincristine

- Surgery

Surgery done on 3/10/13

- Left nephroureterectomy with nodal mass resection & right lower pole biopsy
- Right kidney with tumour involving mid-lower pole of 6x5 cm identified capsule opened.
- Tumour bulk excised seeing that normal lower pole parenchymal calyces & ureter.
- Capsule closed & b/l intra-abdominal testis identified

HISTOPATHO

- Left nephrectomy- features consistent with nephroblastoma (wilm's tumour) with triphasic morphology with heterogeneous element.
- Tumor does not infiltrate renal capsule.
- Lymph node shows involvement by tumour only Left side.
- Right kidney- showing features consistent with nephroblastoma

- Radiotherapy 24/10/13 to 5/11/13 testis
- Post-op chemotherapy continued. Total 24 cycles were given.
- Poorly defined echogenic focus seen in lower pole probably residual/ resolving mass- 19/2/2014
- Last chemo finished on 19/4/2014

Genetic Analysis

- Loss of paternal alleles in the region spanning Chr11: 30,632,101 - 41,827,770.
- Biallelic presence of paternal and maternal alleles at Chr11: 17,445,018 - 28,606,232 and Chr11:44,102,486 - 44,678,690
- Heterozygous deletion of short arm of chromosome 11- “11p”

- Repeat CT scan Normal- no residual tumor.
- Further following-up- renal functions WNL
- Planned-orchidopexy.

DISCUSSION

- WAGR syndrome is characterized by Wilms tumor, aniridia, genitourinary anomaly, and mental retardation.

- The constellation of WAGR syndrome occurs in association with an interstitial deletion on chromosome 11 (del(11p13)) (prevalence is about 0.4% of children with Wilms tumors).

- The incidence of bilateral Wilms tumor in children with WAGR syndrome is about 15%.

- Germ line mutations were identified at chromosome 11p13 in children with WAGR syndrome.
- Deletions involved a set of contiguous genes that included *WT1* and the *PAX6* gene.
- Inactivating mutations or deletions in the *PAX6* gene lead to aniridia,
- Deletion of *WT1* confers the increased risk of Wilms tumor

- Some of the sporadic cases of aniridia are caused by large chromosomal deletions that also include *WT1* results in a 67-fold increased relative risk of developing Wilms tumor.

- The incidence of Wilms tumor in children with sporadic aniridia is estimated to be about 5%

- Patients with sporadic aniridia and a normal *WT1* gene, however, are not at increased risk of developing Wilms tumor

- Children with familial aniridia, generally occurring for many generations, and without renal abnormalities, have a normal *WT1*gene and are not at an increased risk of Wilms tumor

Aniridia	With systemic defects	With ocular defects
Alone	WAGR	Ectopia lentis (50%)
		Spontaneous lens dislocation
		Arcus juvenilis
		Keratoconus
		Cataract (50-85%)
		Glaucoma (30-50%)
		Nystagmus
		Optic nerve hypoplasia (75%)
		albinism

- Children with WAGR syndrome or other germline *WT1* mutations are at increased risk of developing hypertension, nephropathy, and renal failure and are monitored throughout their lives

- Features associated with germline *WT1* mutations that increase the risk of developing renal failure include the following:
  - Stromal predominant histology.
  - Bilateral disease.
  - Intralobar nephrogenic rests.
  - Wilms tumor diagnosed before age 2 years.

Bilateral Wilms Tumor

- 5% to 10%- bilateral or multicentric tumors.
- Prevalence higher in individuals with genetic predisposition syndromes than those without predisposition syndromes.
- Only 16% of persons with bilateral Wilms tumor have a *WT1* germline mutation, and only 3% of persons with bilateral Wilms tumors have affected family members.
- Bilateral Wilms tumor with *WT1* mutations are associated with early presentation in pediatric patients (age 10 months vs. age 39 months for those without a mutation) and a high frequency of *WT1* nonsense mutations in exon 8.
- The presence of bilateral or multifocal disease implies that a patient has a genetic predisposition for Wilms tumor

- The COG: The NWTS Group established standard treatment for Wilms tumor in North America, consisting of initial nephrectomy followed by chemotherapy and, in some patients, radiation therapy.

- Société Internationale d'Oncologie Pédiatrique (SIOP): The SIOP is a European consortium, and their trials provide preoperative chemotherapy before definitive resection for patients with renal tumors

Screening Children Predisposed To Wilms Tumor

- Beckwith-Wiedemann syndrome or other overgrowth syndromes,
- WAGR syndrome
- Denys-Drash syndrome
- sporadic aniridia
- isolated hemihypertrophy

- Ultrasound every 3 months at least until they reach age 8 years
- Newborns with sporadic aniridia- look for WT1 & PAX6

Genetic counseling

- One major abnormality such as:
  - Beckwith-Wiedemann symptoms (macroglossia, neonatal or postnatal macrosomia, abdominal wall defects, or visceromegaly); or
- One condition such as:
  - Hemihypertrophy.
  - Overgrowth syndrome or mental retardation.
  - Aniridia.
  - Diffuse mesangial sclerosis.
- Two or more minor malformations such as:
  - Inguinal or umbilical hernia.
  - Hypospadias.
  - Renal abnormalities.
  - Ectopic testis.

- After genetic counseling takes place, a search for *WT1* mutations should be considered for patients who have the following:
  - Bilateral Wilms tumor.
  - Familial Wilms tumor.
  - Wilms tumor and age younger than 6 months.
  - Genitourinary abnormality.
  - Mental retardation association.

Follow-up

Children treated for Wilms tumor are at increased risk of developing the following:

- Second malignant neoplasms.
- Congestive heart failure (influenced by dose of doxorubicin received, radiation to the heart, and female gender).
- Complications of pregnancy.
- Cumulative incidence of end-stage renal disease due to chronic renal failure at 20 years from diagnosis of Wilms tumor is low at 3.1% for patients with bilateral Wilms tumor and less than 1% for those with unilateral Wilms tumor

PROBLEMS FACED

- WERE WE JUSTIFIED IN GIVING CHEMOTHERAPY FOR WILMS WITHOUT A PATHOLOGICAL DIAGNOSIS?
- ARE WE JUSTIFIED IN RADIATING WITH INTRA-ABDOMINAL TESTIS?