European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

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Katherine Crombie &
Bernadette Brennan

Challenges in Managing Renal Ewings Sarcoma in a Patient with Severe Pre-Existing Renal Impairment.

Moderation: Malgorzata Krawczyk

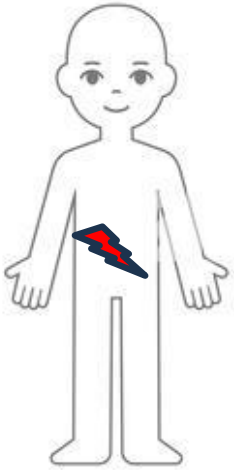
Funded by the European Union's EU4Health Programme

COI declaration

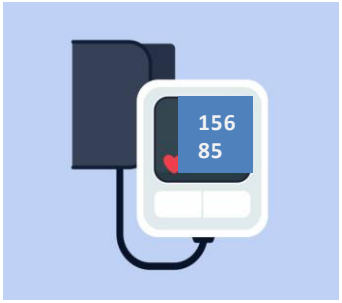
- Katherine Crombie: Nothing to Declare
- Bernadette Brennan: Nothing to Declare

Initial Presenting Case

- 9 Year Old



Abdominal Pain



Severe Hypertension

Significant renal impairment

Initial Investigations: Bloods

- Urea: 9.7mmol/L
- Creatinine: 124umol/L
- Na: 138mmol/L
- K: 4.0mmol/L
- EGFR: <10 ml/min/1.73m2

- Adj Calcium: 2.41mmol/L
- Phosphate: 1.29mmol/L

- CRP: 53mg/L
- LDH: 261 IU/L

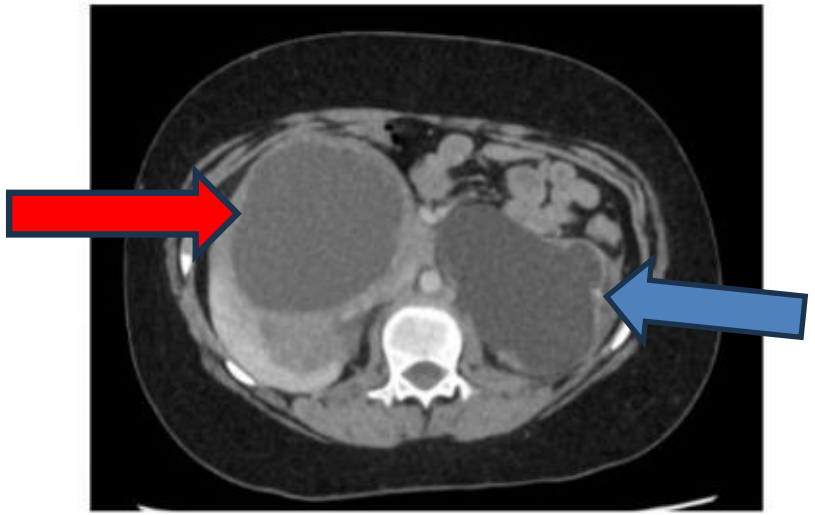
Hb: 99g/L
WCC: 12.9x10^9/L
Neut: 7.4 x10^9/L
Plts: 374 x10^9/L

Initial Investigation: Imaging

- Ultrasound and CT Scan:

Large right sided renal mass

with left sided hydronephrosis.



WORKING DIAGNOSIS

RIGHT RENAL WILMS TUMOUR WITH LEFT SIDED PUJ OBSTRUCTION

Further investigation

MRI

Complex, solid/cystic mass in the right kidney upper pole measuring 11 x 12 x 8.3 cm.

Intermediate to low T2, intermediate T1 signal, solid, diffusion restricting tissue posteriorly.

Anteriorly more cystic with proteinaceous contents to cystic parts of mass.

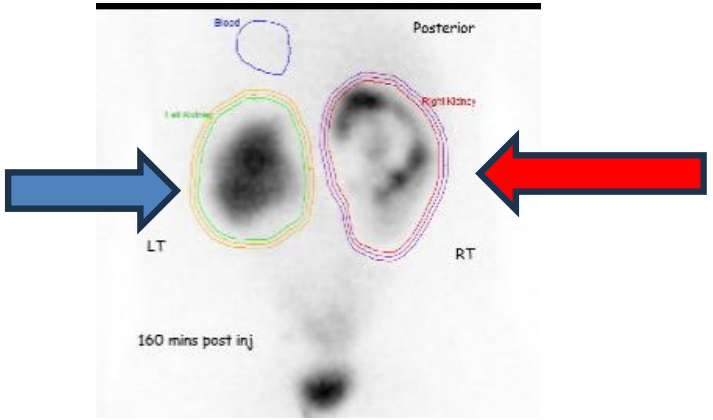
Along margins of the cystic component there is irregular, nodular diffusion restricting solid tissue

NM Renogram

Normal drainage right kidney

Poor function left kidney

Left PelviUriteric Junction Obstruction



What does this mean

- Two renal pathologies in the same patient:

1. A pre-existing PUJ obstruction in the left kidney. Previously undiagnosed.

AND

2. A new tumour of the previously normally functioning right kidney causing mass effect.

Acute Kidney Injury.

Question 1

Would you do a biopsy on this patient?

Yes

No

1. Biopsy in renal tumours

Approximately 85% of all renal tumours in children are Wilms Tumours.

Core Biopsy rarely changes management in children aged 6/12-7yrs with typical clinical and imaging presentation.

TABLE 1 Summary of recommended indications for diagnostic core needle biopsy of renal neoplasms in children, adolescents and young adults without features of genetic predisposition, under SIOP-RTSG protocols

	Features typical of WT (i.e. *not* requiring biopsy) *all* criteria required	Biopsy *not* recommended if *any* of these criteria met	Biopsy recommended if *any* of these criteria met	Indication to be discussed in tumour board meetings if *any* of these criteria met
Clinical criteria	Age ≥6 months but <7 years, No infectious syndrome	Age <3 months (upfront surgery indicated)	Age ≥10 years, Age between 7 and 10 years, Tumour volume[a] <200 ml	Age ≥3 months but <6 months, Infectious syndrome, Urinary tract infection
Radiological criteria	Obvious renal origin, Unilateral tumour with volume over 80 ml, Solid or mixed (solid and cystic) without calcification, Metastases absent or limited to lungs and age >2 years	Totally cystic tumour (primary surgery, if indicated), Bilateral kidney tumours in children ≥6 months but <7 years and/or typical nephroblastomatosis at imaging (presumptive chemotherapy)	Uncertain renal origin, Atypical metastases: bones (any age), central nervous system (any age), pulmonary (<2 years)	Intratumour calcifications, Tumour volume under 80 ml, Large necrotic adenopathy, Bilateral kidney tumours and ≥7 years
Biochemical criteria	Normal urinary catecholamines, Normal serum calcium, LDH less than 4× upper limit of normal		Elevated urinary catecholamines, Hypercalcaemia *and* age <4 years	LDH over 4× upper limit of normal

Further Investigation

BIOPSY

FLI1: Positive Nuclear Staining

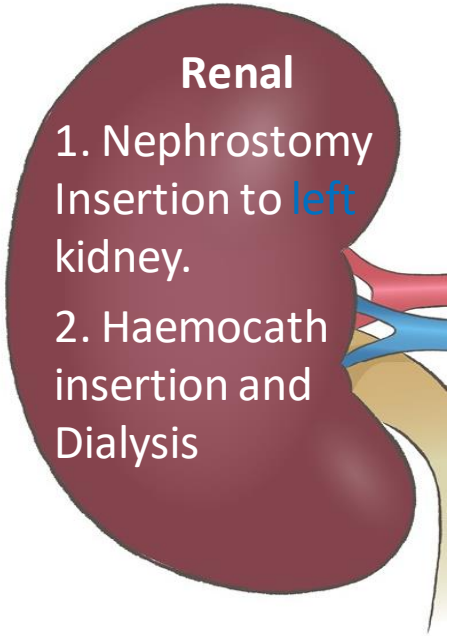
Molecular analysis: rearrangement of EWSR1 gene

Diagnosis:

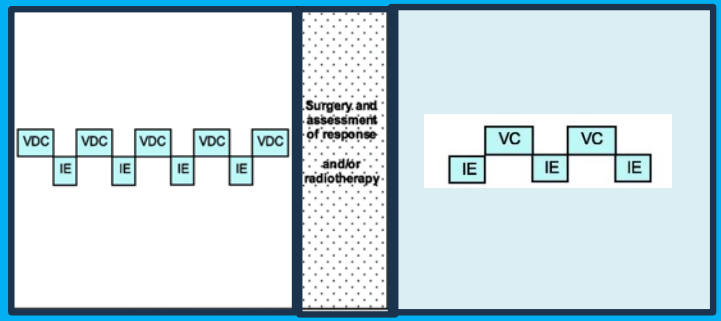
EWSR1:FLI1 Fusion Positive Renal Ewings Sarcoma

MDT Discussion: Management

1. Management of Tumour
2. Aim to preserve kidney function if possible



Oncological: EuroEwing 2012 Protocol:



Question 2

- Which of these treatments need to be adjusted in view of this patient‘s renal function (EGFR <10)?

Vincristine
Doxorubicin
Cyclophosphamide
Ifosfamide

Etoposide
Hydration
Doxarazoxane
Piperacillin/Tazobactam
Vancomycin

MDT Discussion: Management

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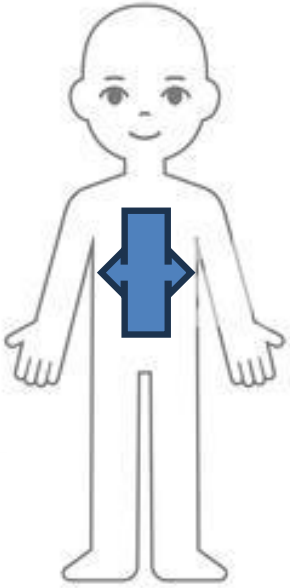
Chemotherapy

Chemotherapy Doses

Hydration

Timing



Dialysis

Diet, Nutrition and Fluids

Frequency

Timing

Drug	Dialysed	Dose	Administration	Fluids
Vincristine	Unlikely	Normal	IV Bolus	No adjustment
Doxorubicin	Not Dialysed	Normal	Diluted Infusion	May need adjustment
Cyclophosphamide	Dialysed	50-100% of normal if EGFR<10	Min 12 hrs prior to dialysis	Mesna may be unnecessary if aneuric or on dialysis, hydration normally given
Doxarazoxane	Probably Dialysed	50% of normal dose if EGFR<40		
Ifosfamide	Dialysed	60% of normal dose if EGFR<15	Min 12hrs prior to dialysis	Mesna may be unnecessary if aneuric or on dialysis, hydration normally given. Given for 5 days with fluids so will need adjustment
Etoposide	Not Dialysed	50% of normal dose if EGFR<15	Infusion	Given for 5 days with fluids so may need adjustment

Supportive Care

Infection

- Adjustment of IV Antibiotic doses for renal function
- Additional Antibiotic Cover if elevated CRP: IV Vancomycin split between Haemocath Lumens
- Management of Fever Whilst on Haemodialysis
- Treatment of Sepsis:
  - IV meropenem AND Vancomycin
  - Fluid Bolus: 0.9% sodium chloride NOT plasmalyte due to the potassium content

Transfusion of Blood Products

- To co-incide with dialysis sessions unless clinically urgent

Communication

- Between Teams
- Other clinical teams (A&E)
- The patient and their family

Question 3

- What are your next steps now he has completed his initial chemotherapy?

- Nephron sparing surgery + radiotherapy
- Nephron sparing surgery only
- Total resection + radiotherapy
- Total Resection only

MDT Discussion

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SURGERY

Nephron Sparing surgery vs Total Resection

RADIOTHERAPY

- Is there a role for radiotherapy in this patient?
- Timing of Radiotherapy
- Implications on longer term management

Management Plan

- Not for pre-operative radiotherapy as did not meet EuroEwing 2012 Pre-Operative Radiotherapy Indications:

Expected Marginal Resection OR Radiotherapy is anticipated to be required for another indiation and judged to be a technical advantage by the MDT

- Would likely need post-operative radiotherapy
- For Total Nephrectomy

Total Nephrectomy

- Difficult resection – tumour adherence to many surrounding structures
- Clear Margins

Tumour Sample

MACROSCOPIC:

- Weight 398g
- Measures 15.5cm superior to inferior, 11cm medial to lateral, 5cm anterior to posterior.
- The specimen appears intact without any areas of rupture.
- The cut surface shows a well encapsulated, completely necrotic tumour predominantly in the middle and medial portion measuring 8 x 5 x 4.5cm.
- The tumour capsule appears to be calcified adjacent to the renal sinus and extends into the adjacent kidney. The rest of the kidney appears unremarkable.

MICROSCOPIC

- Tumour is completely necrotic with no viable tumour (100%) limited to kidney.
- IVC Node, Renal Artery Node and Aorta Node – no evidence of tumour

Question 4

- Would you still give radiotherapy to this patient?

Yes

No

Radiotherapy in Renal Ewings Sarcoma

- Renal Ewings Sarcoma is rare.
- There are a number of published case reports and case series that highlight the significant risk of metastasis and poor overall outcome in these patients[1].
- Due to the small number of cases there is no consensus on the use of radiotherapy to the nephrectomy bed post surgery[2].

EuroEwing 2012 Radiotherapy Guidelines

- **Postoperative radiotherapy :**

Considered for all patients except:

A) Those who have negative resection margins of at least 1mm; and a good histological response (>90% necrosis) to pre-operative chemotherapy; and with removal of all tissues originally involved by the prechemotherapy tumour volume

B) The anticipated adverse side effects of radiotherapy outweigh the additional benefit for local control (anticipated to be an improvement of approximately 10%) for an individual patient.

MDT Discussion: Radiotherapy

- Although clear margins and almost complete necrosis.

- Decision made for patient to have post-operative radiotherapy due to nature of difficult resection and adherence of tumour to surrounding structures.

- Given Photon beam radiotherapy (45 Gy in 25 fractions)

Follow up and Future Management

- Remains under regular surveillance imaging
- Patient is now dialysis dependent
- Will not be eligible for a renal transplant until 5 years after completion of treatment

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DISCUSSION

Funded by the European Union's Health Programme

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

Take home messages

- Cases such as this are challenging both in the management of the current problem, but also when considering the risk of relapse vs long term morbidity from treatment alongside pre-existing conditions.

- MDT collaboration, discussion and clear documentation is essential in successful management of complex cases such as this.

- Consider use of biopsy in cases where there is diagnostic uncertainty.

References

1. Bradford, Kathryn MD[*]; Nobori, Alexander MD[†]; Johnson, Brittany MD[‡]; Allen-Rhoades, Wendy MD[§]; Naik-Mathuria, Bindi MD, MPH[‡]; Panosyan, Eduard H. MD[‖]; Gotesman, Moran MD[‖]; Lasky, Joseph MD[‖,¶]; Cheng, Jerry MD[#]; Ikeda, Alan MD[¶]; Goldstein, Jeffrey MD[†]; Singh, Arun MD[**]; Federman, Noah MD[*]. Primary Renal Ewing Sarcoma in Children and Young Adults. Journal of Pediatric Hematology/Oncology 42(8):p 474-481, November 2020. | DOI: 10.1097/MPH.0000000000001804
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3. Jackson TJ, Brisse HJ, Pritchard-Jones K, et al. How we approach paediatric renal tumour core needle biopsy in the setting of preoperative chemotherapy: A Review from the SIOP Renal Tumour Study Group. Pediatr Blood Cancer. 2022;69:e29702. https://doi.org/10.1002/pbc.29702.
4. CCLG Clinical Management Guidelines: Renal Tumours, January 2020