BMJ Case Reports

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Journal:	*BMJ Case Reports*
Manuscript ID	bcr-2020-234810.R1
Manuscript Type:	Case report
Date Submitted by the Author:	13-May-2020
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Keywords:	Acute renal failure < Renal medicine, Chronic renal failure < Renal medicine, Renal intervention, Oncology, Paediatric oncology < Oncology

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TITLE OF CASE

Bilateral primary renal diffuse large B-cell lymphoma: a rare presentation of paediatric renal disease mimicking juvenile nephronophthisis

SUMMARY

A 12 year old boy presented with a prolonged history of headache, fatigue, and hypertension. Initial investigations were consistent with presumed non-oliguric end stage renal disease, leading to a provisional diagnosis of juvenile nephronophthisis. Subsequent imaging demonstrated bilaterally enlarged kidneys without cystic change. Mutation analysis was negative for nephronophthisis, causing diagnostic uncertainty which prompted renal biopsy. Histology revealed a primary renal diffuse large B-cell lymphoma (PRL) which was highly responsive to chemotherapy including the anti-CD20 monoclonal agent, rituximab. Renal function improved during lymphoma treatment, with residual chronic kidney disease stage 3a once chemotherapy was completed. Atypical diagnostic features should always prompt re-evaluation of a patient. In this case, the delayed malignancy diagnosis did not have an adverse effect on patient survival or morbidity. The outcome for PRL has improved markedly following the introduction of rituximab.

BACKGROUND

Juvenile nephronopthisis is an uncommon but important cause of end stage renal disease (ESRD) in the paediatric population. Classically, children present in early adolescence with the biochemical features of ESRD – elevated urea, creatinine, elevated parathormone, anaemia of chronic disease, but often with a normal blood pressure and bland urine (no haematuria or cellular elements with minimal proteinuria). The commonest mutation, NPHP1, accounts for approximately 85% of cases. Histological confirmation by renal biopsy is not required in the presence of classic symptoms and confirmatory genetic testing. We describe an adolescent male with a ‘classic’ clinical presentation, in whom subsequent identification of atypical features prompted biopsy which revealed an extremely rare malignancy. This facilitated prompt treatment and resulted in an improvement in renal function with complete remission of malignancy.

CASE PRESENTATION

A 12-year-old boy was referred by his primary care physician with a 6-8 week history of progressive malaise, daily generalised headache associated with wakening from sleep, persistent nausea with vomiting, and a reduced appetite. He had polydipsia and polyuria including nocturia and nocturnal drinking, and also reported a two year history of poor weight gain. A casual blood pressure on admission was 169/111 mmHg (>99th centile for age, gender and height). There was no other past medical history. Both parents and an older sister had a background of significant anxiety and/or depression, partly related to an eviction and temporary homelessness several

years previously. There was no family history of renal disease or other physical illness.

Examination showed a pale, slim and sallow boy with height 0.4th centile and weight 2nd centile. No previous growth measurements were available. Repeat blood pressure readings stabilised to 130-140/90-100mmHg (>99th centile for age, gender and height). Abdominal palpation suggested enlarged ballotable kidneys without other organomegaly. There was no evidence of peripheral oedema or ascites. Fundoscopy was normal.

INVESTIGATIONS *If relevant*

Initial investigations revealed marked renal dysfunction with a normocytic anaemia, normal platelets and a preserved white cell count: creatinine 647μmol/l (7.31mg/dL), urea 39.2mmol/l (109.8mg/dL), potassium 6.0mmol/L, parathormone 25.2pmol/L (252pg/ml), haemoglobin 8.1g/dL, platelets 210x10^9/L, white cell count 7.6 x10^9/L. Lactate dehydrogenase was mildly elevated at 285 U/L and urate was normal at 371 umol/L (6.3mg/dL). Urinalysis demonstrated no haematuria with only 1+ proteinuria. A formal urine protein:creatinine ratio was 49mg/mmol (434mg/g).

Immunology investigations were all negative (table 1). Epstein Barr virus PCR and Immunoglobulin G to EBV antigens were negative, confirming no current or prior exposure.

Investigation	Result
Anti-Nuclear Antibody (ANA)	Negative
Antineutrophil Cytoplasmic Antibodies (ANCA)	Negative
DNA antibodies	0.9 IU/ml - Normal
Anti-glomerular basement membrane antibodies (GBM)	<0.8 Units - Normal
C3	108 mg/dL (80 - 170)
C4	35 mg/dL (14 - 44)

Table 1: Immunology investigations

Abdominal ultrasound demonstrated bilaterally enlarged kidneys, 12.6cm right, 11.9cm left (both >99th centile) with loss of corticomedullary differentiation, patchy increased parenchymal echogenicity and mild left sided hydronephrosis (Figure 1). There were no cystic or focal changes and no lymphadenopathy.

Magnetic resonance angiography was undertaken as part of a pre-transplant assessment. This confirmed abnormal enlarged kidneys and found bilateral hydronephrosis (Figure 2).

Given the absence of cystic change classically seen in advanced nephronophthisis, the history and imaging was re-visited. The presentation with hypertension was also somewhat atypical though blood pressure responded well to amlodipine, and psychological assessment confirmed an element of anxiety. Headaches remained an issue despite excellent blood pressure control, suggesting they were not solely a

symptomatic manifestation of hypertension. In an effort to avoid renal biopsy associated with a greater rate of complications, genetic analyses were expedited for abnormalities in the NPHP1 gene. Though NPHP1 mutations are only responsible for 85% of cases, it was agreed that genetic confirmation would be sufficient to avoid a biopsy given evidence to suggest ESRD at presentation. Analysis was available one month later, with no evident mutation in NPHP1. Limitations and risks of renal biopsy were discussed with the family, including insufficient tissue, reduced likelihood of diagnostic tissue and increased risk of complications notably haemorrhage in biopsy from a kidney with advanced disease. A percutaneous needle biopsy was performed without incident. Histological examination unexpectedly revealed diffuse infiltration of undifferentiated highly abnormal cells with minimal cytoplasm and large, variably shaped nuclei consistent with either a high-grade lymphoma or sarcoma. Further cell typing confirmed the tumour expressed the B cell markers CD20, CD79a and bcl6. Myc protein was expressed in less than 5% of the cells. Ki67 was 100% positive indicating a high proliferation rate. Tdt, CD10, bcl2, CD3, cyclin D1, MUM1, ALK1 and CD5 were negative; in-situ hybridisation for EBV was negative. The immunophenotype was consistent with a high grade non-Hodgkins B-cell lymphoma. A bone marrow biopsy, lumbar puncture and whole-body MRI displayed no evidence of extra-renal disease supporting a diagnosis of bilateral primary renal lymphoma (PRL).

DIFFERENTIAL DIAGNOSIS

This case at initial presentation (prior to imaging) was very classical for juvenile nephronophthisis. Nephronophthisis is the commonest monogenic cause of end stage renal disease in children and adolescents. An autosomal recessive ciliopathy, it is characterised by a tubulo-interstitial nephropathy in isolation or as part of a ciliopathy syndrome with extra-renal manifestations in around 20% of cases (eg Senior-Loken, Joubert). [1] Large scale deletions in the NPHP1 gene account for around 85% of cases with isolated renal disease in the commonest subtype, juvenile nephronophthisis (NPHP type 1). [2]

In juvenile nephronophthisis, end stage renal disease (ESRD) develops at a median age of 13 years, though symptoms of polyuria and polydipsia can begin insidiously as early as 6 years of age and will predate declining glomerular filtration rate (GFR), anaemia and growth restriction. Hypertension is uncommon even in advanced disease due to a urinary concentrating defect. [3] Ultrasound usually demonstrates normal or small-sized kidneys with increased echogenicity and loss of corticomedullary differentiation. Cysts are often absent on initial scans though develop as the disease progresses. Hydronephrosis is not a characteristic feature. [4]

The presence of bilateral nephromegaly, stage 2 hypertension (systolic and/or diastolic BP ≥ 95th centile) mild-moderate hydronephrosis, and negative genetic analyses all combined to cause pause. Other important causes of bilateral nephromegaly were all considered and discounted. Autosomal dominant polycystic kidney disease (ADPKD) can rarely present in early adolescence with progressive renal failure, enlarged kidneys, hypertension and a urinary concentrating defect. Advanced cystic changes are established before any significant decline in GFR, and a positive family history supports the diagnosis. Haematuria (sometimes secondary

to cystic haemorrhage) and proteinuria are typical in advanced disease. [5] The absence of cystic change on ultrasound made a different cystic renal disease highly unlikely.

Tuberous sclerosis complex (TSC) may present with enlarged kidneys, renal impairment and hypertension in association with extensive bilateral angiomyolipomas. The risk of renal cell carcinoma and oncocytoma is also increased and can present bilaterally. Cystic changes are present in 50% and rarely can reflect a contiguous gene syndrome involving genes associated with ADPKD. ESRD is uncommon in early adolescence. [6] Other syndromic features are often present, particularly neuro-cutaneous stigmata. The imaging was not consistent with the typical appearance of angiomyolipomata, nor were there any other associated features.

Wilms tumour is the commonest paediatric renal malignancy affecting around 1 in 10,000 children. It is associated with renal enlargement and the presence of embryonal precursor lesions termed nephrogenic rests, with bilateral disease in 5-8%. [7]ESRD is uncommon with the exception of patients with WAGR syndrome, associated genito-urinary abnormalities, or where significant surgical removal of renal tissue has been necessary. [8]

Nephromegaly may also occur in children with overgrowth syndromes such as Beckwith-Wiedemann (BWS) and Simpson-Golabi-Behmel syndrome (SGB), and is particularly common in Perlman syndrome[9]. A genetic aetiology underlies many of these conditions, usually affecting the cell cycle directly or related modifying factors, and there is often an increased risk of associated malignancy.

Further causes of bilateral nephromegaly in association with ESRD include secondary renal infiltration by a haematolymphoid malignancy or deposition disorders such as sarcoidosis and amyloidosis. The two year history of poor weight gain, and notably reduced height was felt initially to make a diagnosis of malignancy highly unlikely, but would be consistent with the development of progressive renal dysfunction.

The confirmed diagnosis of primary renal lymphoma was surprising given the above, but had characteristic histological findings in the absence of evidence of extra-renal disease.

TREATMENT

In view of the significant lymphoma burden, tumor lysis syndrome was felt to represent a very real risk, particularly in the context of severe renal dysfunction. Prophylactic continuous veno-venous haemofiltration (CVVH) was commenced shortly before the administration of the first dose of corticosteroids, and continued for 48 hours with no significant elevation in potassium, phosphate, or urate. Imaging immediately following this already demonstrated a significant reduction in renal size bilaterally to 10.4cm on the right, 10.2cm on the left (95th centile), and CVVH was discontinued. Chemotherapy was then intensified consisting of a 21 day cycle combining cyclophosphamide, doxorubicin and vincristine with prednisolone and the anti-CD20 monoclonal antibody Rituximab (R- CHOP), for a total of six cycles.

Intrathecal chemotherapy consisting of cytarabine and hydrocortisone or cytarabine and methotrexate was administered with cycle 2, 4 and 6. Intravenous methotrexate was not given due the creatinine clearance of <30ml/min. Nutritional support was needed via a naso-gastric tube, with supplemental feeds suitable for patients with marked renal dysfunction. At no point during the subsequent chemotherapy was any additional renal support required.

OUTCOME AND FOLLOW-UP

His initial chemotherapy cycle was complicated with episodes of febrile neutropenia, severe mucositis and neutropenic sepsis secondary to a suspected *Pneumocystis jirovecii* pneumonia. He developed an acute kidney injury most likely due to a combination of nephrotoxic antibiotics and challenging fluid management during this period. He had a prolonged in-patient stay with an episode of confirmed fungal sepsis, and a temporary loss of vision lasting <72 hours, which remains unexplained. Follow up imaging demonstrated a good chemotherapy response with ongoing reduction in kidney size, improved corticomedullary differentiation and reduced echogenicity. The hydronephrosis resolved, suggesting that tumour infiltration may have impacted on upper tract drainage, with no recurrence of hydronephrosis on all subsequent imaging. This all coincided with improving renal function. Six months following the initiation of chemotherapy with completion of the final cycle, ultrasound demonstrated small kidneys, 5.7cm right (<0.4th centile), 8.1cm left (0.4th centile) with cortical scarring on the right and two identifiable masses suspected to be renal pseudotumours. Functional imaging confirmed much poorer overall right sided function (16% right, 84% left). Further imaging demonstrated an increased size of the ‘pseudotumours’, so a right open wedge renal biopsy was undertaken to guarantee obtaining diagnostic tissue. This showed typical ‘end-stage’ features including sclerosed renal parenchyma. There was no evidence of B-cell lymphoma recurrence. Renal function is stable nine months after completion of chemotherapy with a serum creatinine of 100-120μmol/L (1.13 - 1.36 mg/dL), estimated glomerular filtration rate of 55ml/min/1,73m^2. He remains in remission requiring no medications, though supplemental feeding via gastrostomy to support weight gain is ongoing, as is psychological support.

DISCUSSION

This is an unusual case of primary renal lymphoma presenting in a child with hypertension and headaches. His symptoms were initially attributed to significant renal dysfunction presumed to reflect end stage renal disease given evidence of anaemia, hyperparathyroidism and growth retardation. The presence of features inconsistent with juvenile nephronophthisis (enlarged kidneys, hypertension), prompted further investigation which revealed the diagnosis. One additional hypothesis is that the presence of residual small kidneys following treatment could have reflected an underlying structural renal disease/dysplasia which was at increased risk for malignant change.

Primary renal lymphoma (PRL) is defined as non-Hodgkin’s lymphoma originating directly from within renal tissue without systemic involvement. It is a rare presentation, accounting for <1% of all extranodal lymphoma. [10] Several proposed

diagnostic criteria exist though there is broad consensus on three key features: 1. Presence of histologically confirmed lymphomatous renal infiltration 2. Renal enlargement without obstructive features 3. Absence of extra-renal lymphoma at presentation (See Table 2) [11,12]

Malbrain Criteria [12]	**Stallone Criteria** [11]
1. Histological confirmation	1.Lymphomatous renal inflammation
1. Enlarged kidney without obstruction	2. Enlarged kidneys without obstruction
2. No nodal or extranodal lymphoma	3.No extra renal lymphoma at diagnosis
3. Renal disease unattributable to other causes	
4. Improvement in renal function after treatment	

Table 2: Proposed diagnostic criteria for Primary Renal Lymphoma

Whether PRL is a true disease entity has been questioned due to the widely held view that renal parenchyma lacks lymphatic tissue. [13] Subsequent case series support the view that PRL exists as opposed to reflecting secondary infiltration from an occult primary. [11,14] Proposed explanatory mechanisms include locally invasive lymphoma originating in the renal capsule rich in lymphatics, or the malignant transformation of lymphoid tissue arising within the renal parenchyma as a consequence of chronic inflammation. [15,16] More recently, using RNA sequencing of single cells Stewart et al have demonstrated that lymphatic cells are identifiable within the fetal kidney from the first trimester. [17]

Presentation is usually unilateral, with bilateral disease usually reported at 10-20% [11] (though a recent population based analysis reported bilateral disease in only 2.7% of 559 cases with a median age of 72 at presentation) [18]. The commonest presenting symptoms include flank pain and an abdominal mass alongside classical “B” symptoms of fevers, fatigue, weight loss and night sweats. [14,16,19] Abnormal urinalysis is rare and hypertension is variable. [16,19] Renal impairment as a consequence of tumour infiltration commonly accompanies bilateral disease though has been reported in unilateral presentations. [20] The commonest histological subtype matches the diffuse large B-cell variant in our case [13] though ultrasound more typically shows hypo /anechoic changes. [20,21]

Survival data suggests two disease epochs. A 2016 review of all available reported cases of PRL from 1989 calculated a mean survival time of 21 months for bilateral PRL and 68 months for unilateral PRL. [22] Prior to the introduction of rituximab, PRL conferred a very poor prognosis. Recent reports indicate that PRL is often highly sensitive to anti-CD20 therapy, with not a single death reported since rituximab became commercially available. [23–25]

At the time of writing there are 34 cases which are identifiable as or reported as PRL in children in the literature (see Table 3). Applying the less stringent Stallone criteria, [11] 10 cases where extra renal disease was identified at presentation can be excluded, leaving 24 cases with a median age of 6 at presentation. Of these, 16 cases (67%) were B-Cell in origin (including 5 cases of Burkitt’s lymphoma), 6 (25%) were T-Cell in origin, with 2 (8%) cases reporting indeterminate histology. In contrast to reported literature involving adult populations, 20 cases (83%) had bilateral disease at presentation. 11 cases (46%) had acute renal impairment at presentation,

all of which had bilateral disease. 11 patients (46%) were in remission at the time of publication, 8 (33%) had died, 1 case (4%) was lost to follow up and the remaining 4 cases (17%) did not report outcomes.

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Included

N	Age	Yr	Sex	Side	Histology	Symptoms	HTN	ARF	Extra-renal Disease	Anaemia	Urinalysis	Therapy	Outcome	Ref
1	12	1974	M	R	B-cell (Burkitt's)	Fever, Anorexia	?	N	N	?	?	Vincristine, Cyclophosphomide, Cytosine Arabosidase,, Prednisolone	Remission	[26]
2	14	1983	M	B	Unknown	Vomiting, flank pain, polyuria, polydipsia	N	Y	N	N	1+ protein	Radiotherapy	Not reported	[27]
3	3	1986	F	B	T-Cell	Adbo mass	Y	Y	N	N	?	Chemotherapy NOS, Radiotherapy	Remission	[28]
4	4	1989	M	B	T-Cell	?	?	?	N	?	?	Chemotherapy NOS	Remission	[29]
5	10	1991	M	B	T-Cell	Abdo mass	Y	Y	N	N	?	Chemotherapy NOS	Remission	[30]
6	2	1993	F	B	B-Cell	Vomiting, Abdo distention	N	N	N	Y	?	None	Died	[31]
7	5	1994	F	B	B-Cell	Fever, weight loss, night sweats	?	N	N	Y	?	m-BACOD	Died	[32]
8	4	1994	M	B	B-Cell	Fever, nausea, vomiting	?	N	N	N	?	LSA2-L2	Died	[33]
9	6	1995	M	L	B-Cell	Painless haematuria	?	N	N	?	?	NHL-902	Remission	[34]
10	3	1996	M	B	B-Cell	Fever, vomiting, anorexia	?	Y	N	N	Negative	POG Protocol 9317	Remission	[35]
11	11	1997	F	B	B-Cell	Anorexia, vomiting, fatigue, weight loss	Y	Y	N	Y	2+ protein	NHL-B 93	Died	[36]
12	15	1997	F	B	B-Cell	Abdominal mass	?	N	N	Y	?	Chemotherapy NOS	Died	[37]
13	12	2004	M	B	B-Cell (Burkitt's)	?	?	?	N	?	?	?	Not reported	[38]
14	2	2006	M	B	T-Cell	Abdo distention	?	Y	N	Y	?	cyclophosphamide, Vincristine, Prednisolone, L-asparaginase	Lost to follow up	[39]
15	5	2007	F	B	T -Cell	Nil	Y	N	N	N	Trace protein	CCG1961	Died	[40]
16	12	2010	F	B	B-Cell (Burkitt's)	?	?	Y	N	Y	Negative	LNH B0	Not reported	[41]
17	12	2010	M	R	B-Cell	Abdominal mass	?	N	N	?	?	Berlin-Frankfurt-Munster 90 protocol	Remission	[42]
18	2	2010	F	B	T-Cell	Fever, abdo distention	?	Y	N	Y	1+ Blood 2+Protein	Vincristine, Prednisolone, Daunomycin, L-Asparaginase, Methotrexate, 6-Mercaptopurine	Remission	[43]
19	7	2011	F	B	Unknown	Fever, joint pain, abdo distention	?	N	N	Y	Negative	CHOP	Not reported	[44]
20	4	2015	M	B	B-Cell	Abdo distention,	N	Y	N	N	1+ Protein	FAB-LMB 96	Remission	[45]

					(Burkitt's)	fever								
21	8	2015	?	B	B-Cell	Fever, joint pain	?	N	N	Y	Trace protein	R-CHOP	Remission	[46]
22	10	2017	M	L	B-Cell	Abdominal mass	?	N	N	N	?	Nephrectomy, NHL-BFM 95	Died	[47]
23	4	2018	M	B	B-Cell	Fatigue	N	Y	N	Y	Negative	R-CHOP	Remission	[48]
24	4	2018	M	B	B-Cell (Burkitt's)	?	?	Y	N	?	?	None	Died	[49]
Excluded														
N	**Age**	**Yr**	**Sex**	**Side**	**Histology**	**Symptoms**	**HTN**	**ARF**	**Extra-renal Disease**	**Anaemia**	**Urinalysis**	**Therapy**	**Outcome**	**Ref**
25	4	2012	F	B	B-Cell	Abdo distention, headache	N	N	CNS	?	?	NHL-BFM 95	Died	[50]
26	14	2002	M	B	B-Cell	Flank pain, headache	Y	Y	Bone	N	2+ protein	CCG-5942	Remission	[51]
27	3	2008	M	B	B-Cell	Abdo distention, pain, fever	Y	N	Orbit	Y	?	BFM-90	Died	[52]
28	6	1997	F	B	T-Cell	Abdo pain, fever	N	Y	Lung, choroid plexus	Y	?	None	Died	[53]
29	4	1997	M	R	T-Cell	Abdo distention, vomiting	?	N	Local lymph nodes	?	?	CHOP	Remission	[54]
30	6	1973	M	B	?	Anorexia	Y	Y	Tonsils	Y	Negative	Vinc, Dactin, Radiotherapy	Not reported	[55]
31	6	1994	M	B	T-Cell	Anorexia, weight loss, fatigue, abdo pain	?	Y	Bone Marrow	N	?	ALL protocol	Remission	[56]
32	12	2013	F	R	B-Cell	Gross Haematuria	?	N	Thyroid	N	Negative	Nephrectomy, Chemotherapy NOS	Remission	[57]
33	4	2000	M	B	B-Cell (Burkitt's)	Abdo distention, fever	N	Y	CNS	Y	1+ Protein	None	Not reported	[58]
34	4	1995	M	R	B-Cell	Calf pain, shoulder pain	?	?	Bone	N	?	Nephrectomy	Not reported	[59]

Table 1: Primary Renal Lymphoma: Paediatric Cases

LEARNING POINTS/TAKE HOME MESSAGES

- This is a case in which inconsistent features of an initially classic presentation of a rare condition prompted further investigation to elicit the diagnosis.
- Careful clinical evaluation is essential in patients presenting with presumed “ESRD”. Patients should be thoroughly investigated for potentially reversible causes. The presence of nephromegaly requires extensive assessment, which may include a renal biopsy where the underlying diagnosis is unclear.
- Juvenile nephronophthisis typically presents in end stage renal disease in early adolescence with normal blood pressure and normal to small sized kidneys
- Primary renal diffuse large B-cell lymphoma is an extremely rare paediatric presentation but reminds that clinical presentation with a treatable malignancy may also be highly variable. Bilateral nephromegaly should always prompt consideration of malignancy.

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FIGURE/VIDEO CAPTIONS

Figure 1.1: Renal Ultrasound – Right Kidney

Figure 1.2: Renal Ultrasound – Left Kidney

Figure 2: Magnetic Resonance Angiogram

PATIENT'S PERSPECTIVE

Everything that has happened to me came as a shock to me, my family and friends. It all started with a sickness bug that got worse every day and I got sent home from school. My dad took me to the doctors who tested my blood pressure which was very high and recommended I go to hospital. My mum took me to the hospital where I had some blood tests done. This got me worried but then I met a doctor who was very nice and funny which calmed me down. He then told me the results of the blood tests and they weren't good. He told me I had kidney disease. As soon as he told I broke down in tears.

It took a few weeks of tests and scans before the cause of the kidney failure was discovered and that reason was cancer. This devastated my whole family but thanks to the doctors we were convinced I could beat cancer and return to full health. It took a long and painful 6 months but I beat cancer. When we found out it was gone it was the happiest day of my life. I am now a year in remission and my kidney function has returned to a working function. I will probably still need a transplant in the future but my dad put himself through painful weight loss surgery to allow him to give me one and I can't thank him enough for that. It has been a long journey with a way to go but I would like to tell anyone going through life-threatening illness to never give up and stay positive. I hope you get doctors as good as mine who refused to give up on me and worked very hard to return me to health, especially my main consultants, but special thanks also go to the nurses of the kidney and cancer wards who looked after me daily and always managed to cheer me up when I was down and to my family who were with me every day. I thank you all.

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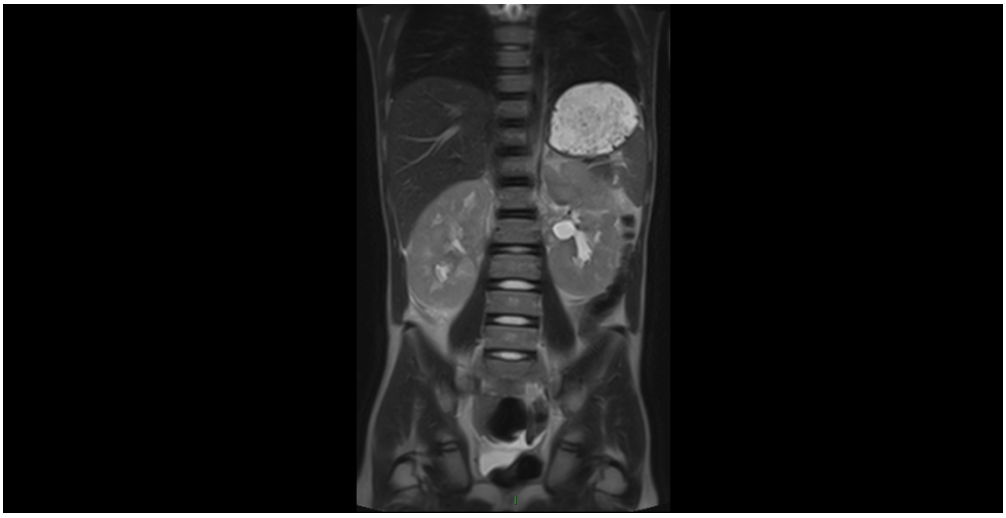

Figure 2: Magnetic Resonance Angiogram

417x212mm (310 x 310 DPI)

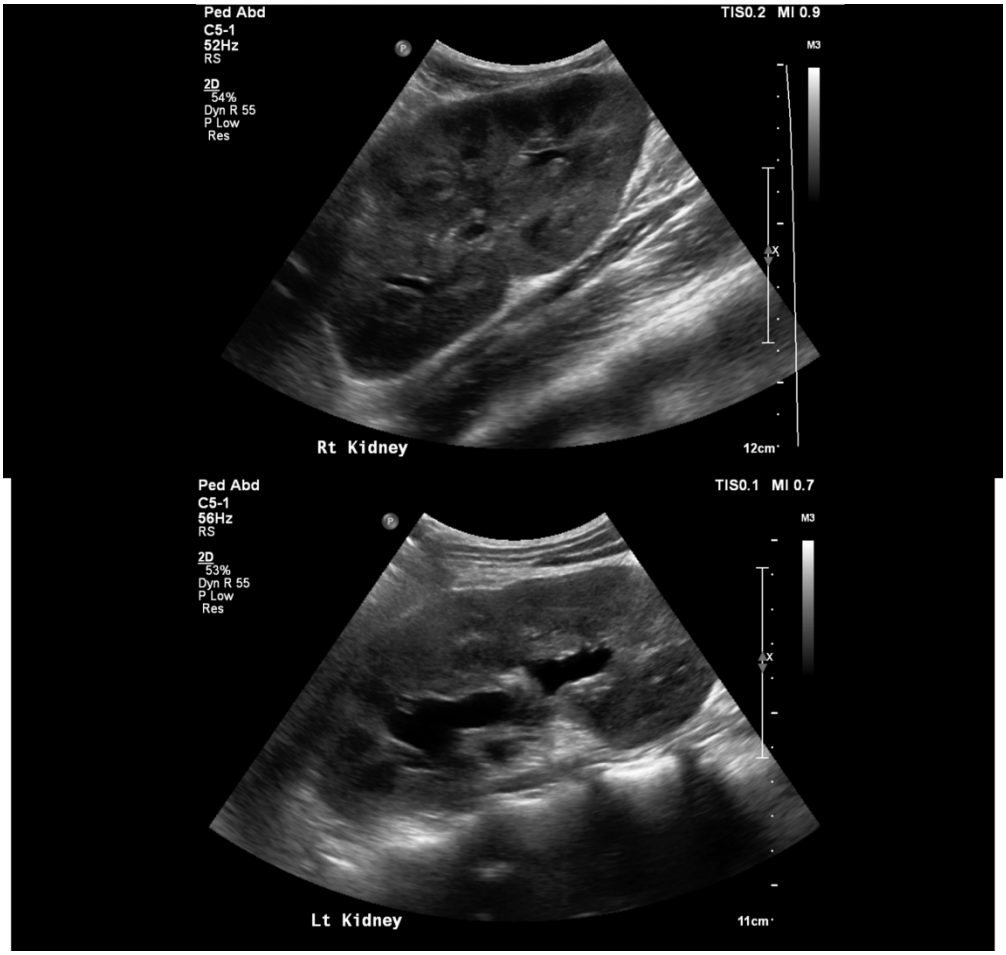

Figure 1.1: Renal Ultrasound - Right Kidney
Figure 1.2: Renal Ultrasound - Left Kidney

1876x1776mm (72 x 72 DPI)