CASE 5

Short case number: 3.14.5
Category: Renal and Urinary Systems
Discipline: Medicine_nephrology
Setting: Urban: Emergency department
Topic: Haematuria [SDL]

Case

69 year old Douglas Spencer presents very concerned, he has just passed urine and noticed a large amount of blood. He informs you that he has been well recently; on further history he mentions that he has had a dull ache in the right loin area, but it has not been very severe and that his urine has been a bit darker than normal.

Questions

1. What are the key features of history and examination that need to be determined in patients presenting with haematuria?
2. Summarise the possible diagnoses that could be responsible for Douglas' presentation.
3. Outline the assessment of patients who present with macroscopic or microscopic haematuria?
4. In a table summarise the features of renal adenocarcinoma and transitional cell carcinoma of the bladder under the following headings; clinical features, predisposing factors, investigation, management and prognosis.
5. Outline the following features of Adult polycystic kidney disease under the following headings; genetics, clinical features, investigations & screening and management.
6. Briefly summarise possible renal involvement and/ or complications in the following clinical conditions malignant diseases, systemic vasculitis and systemic lupus erythematosus

Suggested reading:

- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014. Chapter 17.

ANSWERS

1. What are the key features of history and examination that need to be determined in patients presenting with haematuria?

History - have there been previous episodes of discoloured urine or obvious blood? Was the haematuria painless, if painful the site and radiation of the pain? Have there been any associated symptoms to suggest a urinary tract infection (dysuria, frequency, fever etc) or prostatitis? Is there a past or family history of renal disease (± deafness – Alport's disease) or renal calculi? Is there a past history of hypertension and has a renal cause been excluded e.g. polycystic kidney disease? Is the haematuria following a period of excessive exercise? Has there been recent trauma to the kidney, bladder or urethral region? Are there systemic symptoms - weight loss, night sweats; recurrent respiratory infections (IgA nephropathy) etc? Is there a history of a bleeding diathesis ? Need to obtain a medication history e.g. previous ingestion of analgesics; anticoagulants etc? Has there been exposure in the past to industrial chemicals e.g. hydrocarbons, petroleum-based, permanent hair dyes? Previous history of or exposure to tuberculosis? History of overseas travel?

Examination - general appearance – presence of pallor, uraemia, bruising, purpura, petechiae, etc
- temp., pulse, blood pressure,urinalysis (look for presence of blood, WBC/nitrites, protein, bilirubin (dark urine – dipstick negative for haemoglobin)

INTERPRETATION OF DIPSTICK-POSITIVE HAEMATURIA		
Dipstick test positive	Urine microscopy	Suggested cause
Haematuria	White blood cells	Infection
	Abnormal epithelial cells	Tumour
	Red cell casts }	
	Dysmorphic erythrocytes } (phase contrast microscopy }	Glomerular bleeding*
Haemoglobinuria	No red cells	Intravascular haemolysis
Myoglobinuria	No red cells	Rhabdomyolysis
*Glomerular bleeding implies that the GBM is fractured. It can occur physiologically following very strenous exercise but usually indicates intrinsic renal disease and is an important feature of the nephritic syndrome.		

Examine for - palpable kidney - unilateral - renal cell carcinoma, solitary kidney, hydronephrosis
- bilateral – adult polycystic disease, hydronephrosis, bilateral renal cell carcinoma, diabetic nephropathy
- renal tenderness - calculi, infarction, infection, haemorrhage into cyst
- prostatic enlargement, nodules, tenderness
- urethral mass, tenderness
- site of bleeding at external genitalia (need to exclude menstrual bleeding)

2. Summarise the possible diagnoses that could be responsible for Douglas' presentation.

(Macroscopic haematuria has a positive predictive value of 83% for bladder cancer and 22% for all urothelial tumours , rising to 41% in patients over the age of 40. Severe infections or renal infarction can also cause macroscopic haematuria, usually accompanied by pain. Recurrent episodes of painless, gross haematuria in association with respiratory infections are characteristic of IgA nephropathy).
Differential diagnoses for Douglas - (on the basis of being otherwise well, Macroscopic haematuria and dull ache in right loin region) – right renal tumour (adenocarcinoma, transitional cell carcinoma of right renal pelvis, squamous carcinoma [following chronic inflammation or irritation due to a calculus],lymphoma), right obstructive uropathy with right hydronephrosis, staghorn (struvite) calculus, glomerulonephritis, adult polycystic disease, renal infarction.

3. Outline the assessment of patients who present with macroscopic or microscopic haematuria?

Appropriate history and examination,including urinalysis, as outlined in Part 1 (making sure to exclude menstrual bleeding where appropriate).
Once the presence of haematuria is established further assessment is required with renal imaging to exclude an anatomical bleeding lesion: renal ultrasound, CT KUB, (IVU – intravenous urogram to image the collecting system if high risk of lesion in ureters, e.g. industrial exposure to chemicals, or if persistent unexplained macroscopic haematuria)
If anatomical lesion present —> refer to a urologist for full assessment and management (CT KUB may indicate evidence of associated condition e.g. metastases, lymphadenopathy, hepatic cysts etc.)
If anatomical lesion absent —> look for features of significant renal disease e.g. proteinuria, hypertension, abnormal renal function, family

history of renal disease, history suggestive of a systemic disorder.

if YES —> Consider renal biopsy

if NO —> Observation (urine test,BP, creatinine every 6 – 24 months. Re-refer if anything changes)

4. In a table summarise the features of renal adenocarcinoma and transitional cell carcinoma of the bladder under the following headings; clinical features, predisposing factors, investigation, management and prognosis.

Disease	Renal adenocarcinoma	Transitional cell carcinoma of the bladder
linical eatures	~60% have haematuria 40% loin pain, 25% with a mass. Systemic effects* - fever, raised ESR, disorders of coagulation, polycythaemia, abnormalities of plasma proteins and liver function tests. Pyrexia of unknown origin, Neuropathy (rarely)	> 80% have haematuria (usually macroscopic and painless). Tumour in distal ureter or at ureteric orifice may cause obstructive symptoms
redisposing actors	tobacco (most prominent risk factor), obesity(esp. women), hypertension, unopposed oestrogens, exposure to asbestos, petroleum products & heavy metals, chronic renal failure, tuberous sclerosis	chemical carcinogens excreted in the urine e.g. naphthylamnes,benzidine in the chemical and dye industries
vestigation	ultrasound initially (solid tumour vs cyst, CT of abdomen and chest for staging	investigations of haematuria, cystoscopy, IVU (intravenous urogram) retrograde ureteropyelogram if suspicious defect in ureter or renal pelvis
lanagement	radical nephrectomy + perirenal fascial envelope and ipsilateral para-aortic lymph nodes, immunotherapy with interferon and interleukin-2 (resistant to radiotherapy/chemotherapy) [consider nephrectomy even if metastases present]	transurethral resection of the tumours; intravesical chemotherapy (epirubicin, mitomycin C, BCG) for multiple low-grade tumours, diathermy for recurrences during 'check' cystoscopies ? radical cystectomy with urinary diversion to ileal conduit or continent cathetisable bowel pouch for invasive bladder tumours
rognosis	5 year survival rate – 75% if confined to kidney, 5% if distant metastases	5 year survival rate – 50 – 60% with superficial tumours , 20-30% with deep muscle invasion. Overall 33% survive for 5 years
Systemic effects may be due to tumour secretion of products such as renin, erythropoietin, PTH-related peptide and gonadotrophins. The effects disappear when the		

umour is removed but may reappear when metastases develop, and so can be used as markers of tumour activity

5. Outline the following features of Adult polycystic kidney disease under the following headings; genetics, clinical features, investigations & screening and management.

Genetics

Autosomal dominant polycystic disease (ADPKD) is seen predominantly in adults. (autosomal recessive polycystic disease is mainly in infants and children) ADPKD occurs in 1:400 – 1:1000 individuals worldwide and accounts for ~4% of ESRD in the United States. Over 90% of cases are inherited as an autosomal dominant trait, with the remainder likely representing spontaneous mutations. Mutations in the *PKD-1* gene on chromosome 16 (ADPKD-1) account for 85% of cases, whereas mutations in the *PKD-2* gene on chromosome 4 (ADPKD-2) represent the remainder. ESRD occurs in ~50% of patients with the former mutation with mean age of onset of 52 years but in a minority with *PKD-2* with a mean age of 69 years. Other genes are responsible rarely.

Clinical features

Affected individuals are usually asymptomatic until later life. After the age of 20 there is often insidious onset of hypertension. One or both kidneys may be palpable and the surface may be nodular. There is then a gradual reduction in renal function. Common clinical features comprise

- vague discomfort in loin or abdomen due to increasing mass of renal tissue.
- acute loin pain or renal colic due to haemorrhage into a cyst
- hypertension
- haematuria (with little or no proteinuria)
- urinary tract infection
- renal failure

About 30% of patients have hepatic cysts but disturbance of liver function is rare. Sometimes (almost always in women) this causes massive and symptomatic hepatomegaly, usually concurrent with renal enlargement, but occasionally with only minor renal involvement.
Berry aneurysms of cerebral vessels are an associated feature (largely restricted to certain families), and about 10% of patients have a subarachnoid haemorrhage. Mitral and aortic regurgitation are frequent but rarely severe. Colonic diverticulae and abdominal wall hernias may occur.ADPKD is not a pre-malignant condition.

Investigations and screening.

The diagnosis is usually based on family history, clinical findings and ultrasound which demonstrates cysts in ~95% of affected patients over the age of 20 (but may not detect small developing cysts in younger patients). It is important to identify multiple cysts, not just two or three. It is sometimes possible to make a specific genetic diagnosis but the genes involved are particularly difficult because of their size, the existence of a

closely related *PKD-1* pseudogene, and the wide variety of mutations which affect different families. Screening for intracranial aneurysms is not generally indicated. The risk-benefit ratio of intervention in asymptomatic aneurysms in this disease is not known.

Management.

Nothing has yet been found to alter the rate of progression of renal failure in ADPKD. Good control of blood pressure is important because cardiovascular morbidity and mortality are so common in renal disease, but there is no evidence that control of moderate hypertension retards the development of renal failure in this condition. Patients with ADPKD are usually good candidates for dialysis and transplantation. Sometimes kidneys are so large that one or both have to be removed to make space for a renal transplant.

6. **Briefly summarise possible renal involvement and/ or complications in the following clinical conditions malignant diseases, systemic vasculitis and systemic lupus erythematosus**

ENAL EFFECTS OF MALIGNANCIES
irect involvement Kidney: hypernephroma (primary adenocarcinoma), lymphoma Urinary tract e.g. urothelial tumours, cervical carcinoma
mmune reaction Glomerulonephritis: especially membranous nephropathy Systemic vasculitis (rarely): usually ANCA-negative.
Metabolic consequences Hypercalcaemia (lung, breast, renal, ovarian, colonic and thyroid carcinoma, lymphoma, multiple myeloma) Uric acid crystal formation in tubules: usually in tumour lysis syndromes.
emote effects of tumour products Light chains in myeloma (paraprotein deposition), amyloidosis (renal involvement more common in acquired systemic amyloidosis than hereditary systemic) Antibodies in cryoglobulinaemia

Multiple myeloma can exert its effects on the kidneys through :- paraprotein deposition, hypercalcaemia, infection, NSAIDs, amyloid, dehydration.
Prostatic cancer can result in an obstructive uropathy through ureteric involvement.

SYSTEMIC VASCULITIS

Medium to large-vessel vasculitis (e.g. classical polyarteritis nodosa – rare, all age groups can be affected, male to female ratio 2:1, hepatitis B as risk factor) only causes renal disease when arterial involvement leads to hypertension or

renal infarction. In contrast, small-vessel vasculitis commonly affects the kidneys with rapid and profound impairment of glomerular function by causing a focal inflammatory glomerulonephritis usually with focal necrosis and often with crescentic changes. It can either present as a systemic illness with acute phase response, weight loss and arthralgia and in some patients pulmonary haemorrhage which can be life-threatening or a kidney-limited disorder with rapidly deteriorating renal function and crescentic nephritis.
Causes of small-vessel vasculitis:-

- Microscopic polyangiitis } usually associated with antineutrophil
- Wegener's granulomatosis } cytoplasmic antibodies (ANCA) these are (associated with ENT, lung) non-specific, therefore biopsy may be required
- Henoch- Schönlein purpura - associated with IgA nephropathy (ANCA usually absent) - rash on the buttocks
- Churg- Strauss syndrome
- Mixed essential cryoglobulinaemia

Treatment of the primary types of small-vessel vasculitis with cyclophosphamide and corticosteroids is life-saving. Death from extrarenal manifestations of the disease is prevented and renal function can be salvaged in acute disease, even if the glomerulonephritis is so severe as to cause oliguria. In these circumstances, plasma exchange offers additional benefit.

SYSTEMIC LUPUS ERYTHEMATOSUS

Subclinical renal involvement, with low-grade haematuria and proteinuria but minimally impaired or normal renal function is common. This is usually due to glomerular disease although serologically and sometimes clinically overlapping syndromes (e.g. MCTD, Sjögren's) may cause interstitial nephritis. SLE can produce almost any histological pattern of glomerular disease and an accordingly wide range of clinical features, ranging from rapidly progressive glomerulonephritis to nephrotic syndrome. In severely affected patients the most common histological pattern is an inflammatory, diffusively proliferative glomerulonephritis with distinct features to suggest lupus. In controlled trials, the risk of ESRF in this type of disease is significantly reduced by cyclophosphamide treatment, often given as regular IV pulses.

Many patients go into relative remission from SLE once ESRF (an immuno-suppressed state) has developed. Patients with ESRF caused by SLE are usually good candidates for dialysis and transplantation. Although it may recur in renal allografts, the immunosuppression required to prevent allograft rejection usually controls SLE too.