UCL
CENTRE FOR NEPHROLOGY
ROYAL FREE

TMA cases

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Conflict of interest statement

Honoraria and consulting: Alexion, Otsuka

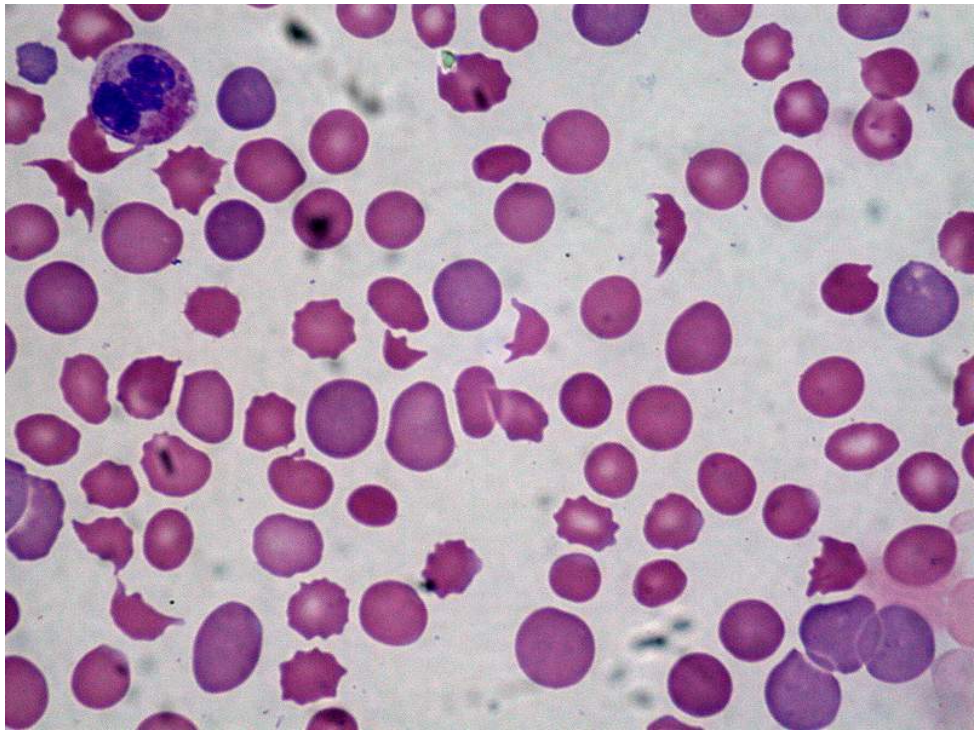
Case A – presentation and history

- 28 year old Bulgarian woman, previously well
- Presented to local hospital at 3 am one Friday with abdominal pain, headache and vomiting for ~2 days
- Painless, patchy rash over the last 2 weeks associated with symptoms of a viral infection
- No diarrhoea
- No medications
- One daughter aged 6 (healthy)
- No significant family history

Examination

- Pale, tachycardic (HR 104 bpm), BP 140/90
- Apyrexial, respiratory rate 24/min, Sats 99% on air
- Very sparse and patchy purpuric rash on legs
- Euvolaemic
- Cardiovascular, respiratory, abdominal and neurological examination otherwise normal
- Urinalysis showed ++ haematuria
- Not pregnant

Labs



- Hb 8.3 g/dL
- Plt 65 x10^9/L
- LDH 1051 IU/L
  - Haptoglobin <0.2 g/L
- Blood film: microangiopathic haemolytic anaemia
- Creat 709 µmol/l
- LFTs, Ca^{2+}/PO_4^-, CK normal, CRP 29
- WBC/Coagulation normal, DAT -ve
- CXR, USS renal tract normal

Transferred to renal unit within 12h of presentation

Diagnosis

- aHUS

Patient: Treatment

- Treatment with daily plasma exchange started 12 hours after presentation (before autoimmune serology back)
  - 60 ml/kg (1.5x plasma volume) FFP (Octaplas)
  - Continued for 10 days (2 days after remission achieved)
    - Platelet count >150x10^9, haemoglobin > 9 g/dL, falling LDH
- 9x haemodialysis sessions also needed
- Recovered renal function (creatinine ~200 uml/l)

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- Relapse (MAHA and AKI) 13 days after stopping PEx
- Daily PEx restarted, then weaned to weekly

Genetic test result (available 8 weeks later)

- Sequencing of genes for complement regulators revealed heterozygous stop codon (c.942G>A, p.Trp314X) in SCR 6 of CFH

- Mutant CFH unable to localise to host cells as lacks all C-terminal domains
- Proves the diagnosis is aHUS

Ongoing treatment

- Remained dependent on weekly PEx
  - 18 months later: Hypertensive on 4 agents, creatinine stable at 180 µmol/l
- Funding approved for eculizumab
- Loaded and changed to fortnightly eculizumab
- Creatinine now 150
- 2 antihypertensive agents
- Persistently low C3 (most recent 47 mg/dL)

Discussion points

- How long should eculizumab continue?
- Role for liver transplantation?

Patient B

- 22 year old Polish man (UK resident)
- Presents to local A&E with abdominal pain, vomiting and dark stools for 3 days
  - Sent home
- Re-presented to A&E at a renal centre, now with epigastric pain and yellow eyes
  - Triaged to minors

CLINICAL NOTES

ENP-ID | LOCUM PRINT NAME | OTHER

SHO ANAH — Limited English

22 ♂ Abd pain & vomiting.

PMH
nil

HPC

- Since sunday evening vomiting +++
  - not able to tolerate solids
  - tolerating some fluids
  - Initially very dark & almost black, now more yellow
  - *Blood.
  - vomiting every hour or so — today vomiting has improved ~ 7 episodes.

DIH
NKDA.
nil

SAH
- stopped smoking 1 year ago ~ 15/day
- Alcohol 6 unit/week
- no drugs

Last night started sharp epigastric pain
- Better after food
? Persistant.
no aggravating/alleviating factors.

SFH
nil

- no urinary symptoms.
- Urine has been very dark.
- has had 6 episodes of loose stool since sunday which has been dark
- *chest pain *SOB *pyrexia *rigors.

O/E

Temp 36° RR ~ 99 BP 159/82 Sats 98% on RA.
GCS 15 Yellow sclera bilaterally no hepatic flap

S1+S2+0 sclear

*Ankle oedema

- soft
- mild epigastric tenderness
- ↑ deep palpation
- *Guarding
- *Rebound
- ↓ sounds

PR
- *Masses.
- *Blood
- *Melena.
- Soft non tender prostate
- Rusty coloured stool on glove.

Urine dip
very dark brown in colour.

Glc Trace
Ke Trace.
Bld 3+
Pro 3+
Nit -ve.
Leuk -ve.

DRUGS PRESCRIBED

TIME	DRUG	DOSE	ROUTE	DR'S SIG.	GIVEN BY (SIGN)	TIME GIVEN
	Paracetamol	1g	PO			
2045	Paracetamol	1g	IV		DSC	2110

FLUID ADMINISTRATION

FLUID TYPE	VOLUME	ADDITIVES	RATE	DR'S SIG.	COMMENCED BY (SIGN)	BATCH No.	START	FINISHED
Saline	1L		24				1755	

DATE	(Each entry must be signed)
	ABG on arr
	pH = 7.47. Glc = 6.9 Na = 129.1 pCO_2 = 4.89 Lact = 1.54. K = 5.13 pO_2 = 12.51 HCO_3 = 26.1 BE = 2.6
	Plan **Imp ?Hepatitis.** Analgesia. IV fluid Bloods CXR Medical/hepatology review & admission. SHO ANNAL

DATE	(Each entry must be signed)

ABG on arr

pH = 7.47 · Glc = 6.9 · Na = 129.1
pCO_2 = 4.89 · Lact = 1.54 · K = 5.13
pO_2 = 12.51
HCO_3 = 26.1
BE = 2.6

Plan — Imp ?Hepatitis.

Analgesia
IV fluid
Bloods
CXR
Medical/hepatology review & admission.

SHO ANNL

19:00

~~Hb = 11.8~~
~~WBC = 11.66~~
Hb = 12.2 · ~~[illegible]~~ · Na = 133
WBC = 12.19 · PT = 11.7 · K = 5.13 from ABG
pH = 13 · INR = 1.1 · Urea = 52.4
APTT = 27.9 · Creat = 1008
CRP = 28

Bilirubin = 69
ALT = 37 ·
AST Haemolysed
Alk ph = 64
Alb = 43

CXR :- NAD

A+ transferred to Regus

Blood tests

- HB 12.2, WCC 12.19, Plt 13
- Na 132, K 6.2, $HCO3^-$ 26, Urea 54.7, Creat 1056
- Clotting normal, CRP 28, D-dimer 2693, Fibr 2.7
- Bili 63, LDH 7230, other LFTs normal

Additional blood tests

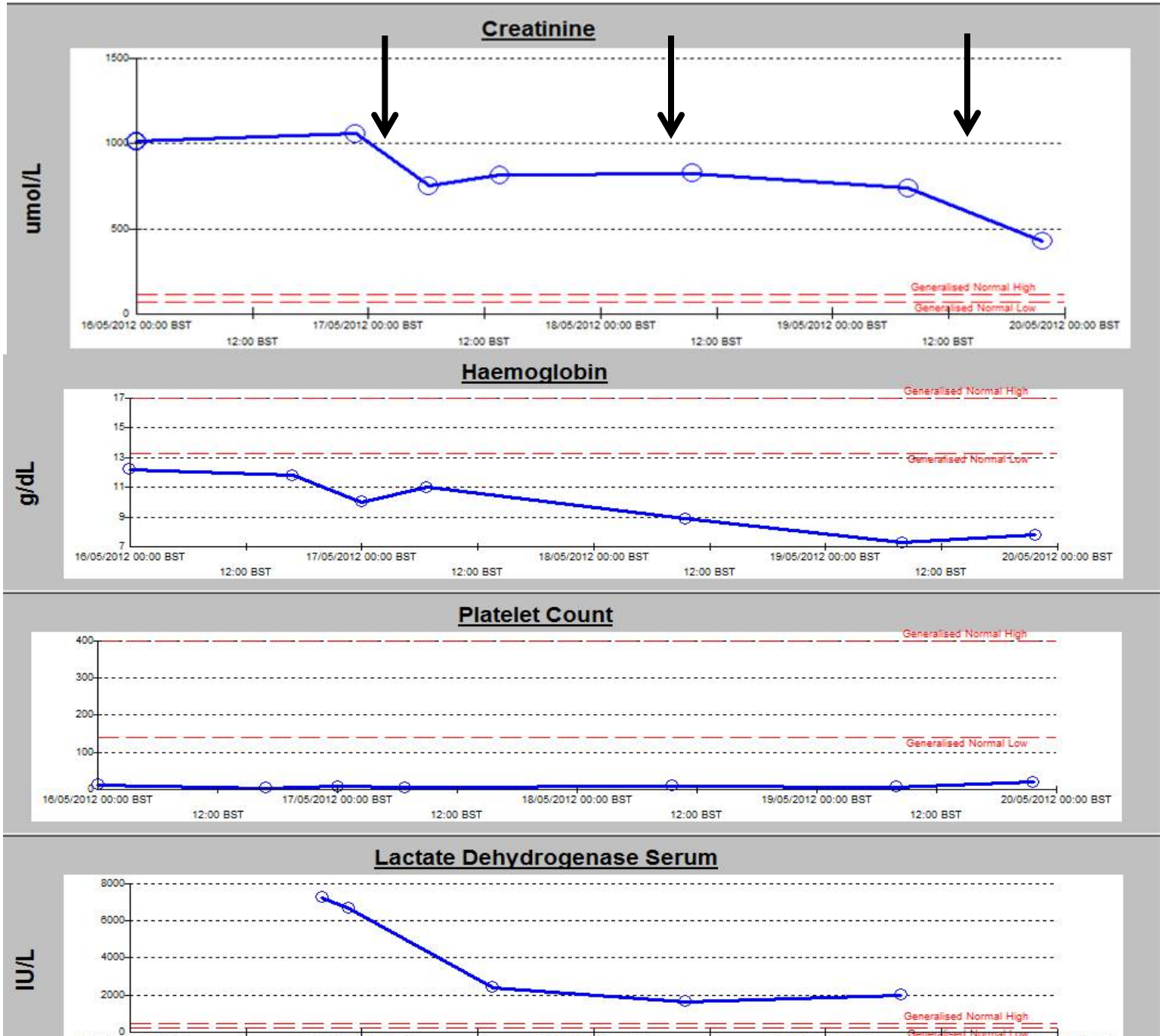
- LDH 7230, MAHA on blood film
  - 15-20 fragments per HPF
- ADAMTS13 35%
- Troponin 1.56 (NR <0.03)
- C3 105 (NR 70-165); C4 22 (NR 16-54)
- Viral and autoimmune serology negative
- ASOT and E. coli O157 serology negative

Diagnosis?
Treatment?

Treatment commenced

- Femoral line inserted and HD and PEx started within 6h of presentation
- Access clotted
- Re-wired
- PEx and HD restarted but poor flows
- New line inserted…

24h 48h 72h


Creatinine
umol/L
1500
1000
500
0
Generalised Normal High
Generalised Normal Low
16/05/2012 00:00 BST
12:00 BST
17/05/2012 00:00 BST
18/05/2012 00:00 BST
19/05/2012 00:00 BST
20/05/2012 00:00 BST
Haemoglobin
g/dL
17
15
13
11
9
7
Platelet Count
400
300
200
100
0
Lactate Dehydrogenase Serum
IU/L
8000
6000
4000
2000

Outcome

- PEA arrest on PEx day 3
- Thrombolysed, extended CPR attempted
- Patient died
- Post mortem showed extensive patchy microthrombotic lesions of myocardium

Discussion points

- TMA can be fatal
- Delivery of extracorporeal therapies not always possible
- Would prompt administration of Eculizumab have affected the outcome?

Patient C

- 35 year old Greek Cypriot woman
- No PMH
- Presented to local hospital with 1 months' history of vomiting, SOB and reduced urine output
- No diarrhoea, fever
- BP 170/115
- Urinalysis: protein +++, blood ++, not pregnant

Patient C - labs

- Creatinine 781 umol/l, bicarb 17, K 5.2
- Hb 8.6 g/dL (MCV 89)
- Normal clotting, haptoglobin <0.2
- Platelets 86 $x10^9$/L
- LDH 2309 IU/L, bilirubin 32, other LFTs normal
- CRP 34, Corr Ca 1.86, PO4 1.7, urate 0.54,
- Occasional fragments (5/100) on blood film

Patient C – further tests

- ADAMTS13 level >40% normal
- Autoimmune/infection/endocrine screens negative
  - ANA, ANCA, GBM, ACL, stool culture
- Complement C3 59 mg/dL (70-165)
- Complement C4 18 mg/dL (16-54)
- USS showed smaller right kidney
  - 27% function on MAG3
- BP control required 3x antihypertensives and UF

Diagnosis?

Who would do a kidney biopsy?

Patient C: Kidney biopsy report

- Severe shrinkage of capillary loops and tuft congestion
- Interlobular arteries show loose concentric intimal thickening with virtual occlusion (IgM positive)
- Arterioles have patchy hyalinosis
- Index of chronic damage 18%

- Diagnosis?

Patient C - treatment

- Plasma exchange x9 sessions then stopped
  - Haematological indices normalised
- Recovered some renal function after 11 months of haemodialysis
- Restarted HD a further 1 year later

Patient C – genetic tests (months later)

- CFH, CFB, CFI, C3, CFHR5 genes all normal by sequencing and copy number analysis
- Diagnosis?

Patient C – further treatment

- Live related kidney transplant performed
- Good graft function
- Diagnosis?

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- Graft lost to recurrent renal TMA after 14 months (despite PEx)

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- Diagnosis?

Patient C – most recent progress

- Funding agreed for eculizumab when transplanted
- Retrospective transplant waiting list weighting agreed by NHSBT
- Cadaveric transplant performed 4 months later
  - 57 yo DBD
  - Eculizumab started immediately pre-op (once XM –ve)
- Creat now 94 umol/L
- No plans to withdraw eculizumab

Discussion points

- What is diagnosis?
- Who would have performed LRTx?

Patient D

- 30-year-old UK woman of Ghanaian and Grenadan ancestry
- Hypertensive during only pregnancy (7 years ago)
- Presented with abdominal pain and vomiting
- No family history of kidney disease or hypertension
- No diarrhoea, rash or pyrexia
- BP 186/133 at presentation
- Heavy proteinuria and microscopic haematuria

Patient D - labs

- Creat 1153 µmol/l, K 3.2
- Hb 75 g/L
- Plt 65 x10^9/L, haptoglobins <0.2, normal clotting
- LDH 3705 IU/L
- Blood film: microangiopathic haemolytic anaemia
- LFTs, Ca^{2+}/PO_4^-, CK normal, CRP 12
- WBC normal, coagulation normal, DAT -ve
- CXR, USS renal tract normal

Patient D – further investigations

- ADAMTS13 level 82% normal
- Autoimmune and endocrine screens negative
- Complement C3 66 mg/dL (70-165)
- Complement C4 6 mg/dL (16-54)

Diagnosis?

Who would biopsy?

Patient D: Kidney biopsy report

- Shrunken ischaemic glomeruli with tuft contraction
- Capillary wall thickening and wrinkling
- Arteries show mural thickening and early onion skinning
- Index of chronic damage 30% (patchy)

- Diagnosis?

Patient D - treatment

- Plasma exchange x4
- Needed dialysis
- Required 4 antihypertensives to control bp
- Resolution of MAHA but remained dialysis dependent (on peritoneal dialysis)

Patient D – further treatment

- Eculizumab started
- Came off all but one antihypertensive over ~3 months
- Genetic tests all -ve
- Then came off dialysis
  - Creat ~300 umol/l

Discussion points

- What is the diagnosis?
- Did she benefit from eculizumab?
- Does she still need eculizumab?