Rare disease

Haemolytic uraemic syndrome preceding acute lymphoblastic leukaemia

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Correspondence to Dr Christine Brittain, cbrittain@doctors.org.uk**Summary**

An 11-year-old girl presented with diarrhoea associated haemolytic uraemic syndrome (HUS) requiring haemodialysis. Four weeks following the resolution of her renal impairment, she was found to have cervical lymphadenopathy alongside deterioration in her renal function. While blood films during her acute illness were indicative of sepsis only, subsequent film revealed a diagnosis of acute lymphoblastic leukaemia (ALL). Thus, this report describes a rare case of diarrhoea associated HUS preceding the diagnosis of ALL, and may represent an unusual presentation of the malignancy.

BACKGROUND

Haemolytic uraemic syndrome (HUS) may be a rare presentation of acute lymphoblastic leukaemia (ALL), even when it is of the typical form which is rarely reported. In order to make the diagnosis, the clinician needs to be aware of this association, which we aim to highlight.

CASE PRESENTATION

An 11-year-old Caucasian girl presented acutely to accident and emergency with pallor, shaking and lethargy after a 4 day history of fever, vomiting and headache. She had non-bloody diarrhoea and had not passed urine for 6 h.

On examination, Glasgow coma scale was 14, she had cool peripheries with a capillary refill time of 2–3 s and pallor. Her ECG showed a broad complex tachycardia with a heart rate of 170 bpm and blood pressure (BP) of 90/60 mm Hg.

Emergency management was initiated after deterioration approaching asystolic arrest. Administration of epinephrine and atropine was followed by a short period of narrow complex tachycardia.

Venous blood gas showed a pH of 7.19 and potassium of 9.36 mmol/l. Treatment for acidosis and hyperkalaemia was initiated consisting of sodium bicarbonate, 10% calcium gluconate, actrapid with 10% dextrose and she was commenced on continuous salbutamol nebulisers, maintenance intravenous fluids (IVF) and calcium resonium. A second period of narrow complex tachycardia followed.

Subsequent investigations revealed acute renal failure with urea 36.4 mmol/l and creatinine 340 µmol/l. She was mildly anaemic and thrombocytopenic, with a normal white cell count. A blood film taken at this time was suggestive of septicaemia.

She was transferred to critical care with suspected HUS. Cardiac stabilisation treatment continued and she was commenced on ceftriaxone and acyclovir. Repeat bloods showed resolving hyperkalaemia (6.5 mmol/l) but worsening renal function and hypocalcaemia. Anaemia and thrombocytopenia worsened (haemoglobin 5.7 g/dl, platelets 31×10^9). A second blood film implied septicaemia

but was not typical of HUS. Stool sample did not detect *Escherichia coli* 0157.

Two units of blood were transfused during transfer to a specialist renal unit where she underwent 24 h of haemofiltration followed by 1 week of haemodialysis. Ultrasound scan showed evidence of an inflammatory nephritis. Ten days following discharge, bloods had all normalised.

At 4 weeks follow-up, examination revealed marked bilateral cervical lymphadenopathy and a 3–4 cm liver edge. Bloods indicated declining renal function, with slight anaemia and thrombocytopenia. She was started on augmentin for cervical lymphadenitis and was admitted to the ward where her BP was 122/90 mm Hg and urine contained trace blood with 2+ protein.

Further investigations yielded a raised lactate dehydrogenase of 1693 U/l with a reduced haptoglobin, C3 was within normal range and C4 was mildly low; antistreptolysin O titre was elevated at 400 IU/ml.

A blood film performed at this time was suggestive of malignancy with a normocytic anaemia, some anisopoikilocytosis, numerous nucleated red cells, mildly reduced platelets, lymphocytosis and many suspicious cells. These included probable lymphoblasts. Subsequent immunophenotyping indicated precursor T cell acute lymphoblastic leukaemia.

Imaging was performed to help assess the staging of the disease. Chest x-ray was normal with no evidence of a mediastinal mass and abdominal ultrasound showed an enlarged but texturally and structurally unremarkable liver, bilaterally enlarged kidneys consistent with infiltration and an enlarged spleen. Transfer to a renal unit was arranged due to increased risk of tumour lysis syndrome. She was commenced on IVF and rasburicase with good effect to renal function.

She subsequently underwent bone marrow aspiration (BMA) and trephine, Hickman line insertion, vas cath insertion and lumbar puncture (LP). During extubation, a respiratory arrest occurred, the cause of which was unknown. She was reintubated and transferred to paediatric intensive care unit where she required inotropic support and

haemofiltration, the latter due to rising blood potassium and phosphate levels.

Steroids were commenced as per UKALL 2003 regimen B. Vincristine and daunorubicin were delayed by 2 days awaiting improvement in her blood levels. She was extubated at that time and her inotropic support stopped, however haemofiltration continued a further day.

Her initial BMA was almost completely replaced by blasts but LP showed no central nervous system involvement. Her first intrathecal methotrexate was delayed until day 8. Following the commencement of treatment, her cervical lymphadenopathy was markedly reduced, and her day 8 BMA showed a good response with a reduction in blasts to 14%.

DISCUSSION

HUS is a condition characterised by acute renal failure, microangiopathic haemolytic anaemia and thrombocytopenia. It is classified into two types: the more common typical form is associated with a shiga-toxin-producing *E coli* 0157 diarrhoeal illness, where as the atypical form has a more heterogeneous aetiology.

Most cases report HUS following malignancy diagnosis. However, a literature search revealed five paediatric cases in which HUS precedes the diagnosis of ALL.^{1–5} The case presented here is a further example.

Within these six cases, the pattern and timing of presentation is highly variable. In just two of the cases, was a diarrhoeal prodrome described: Salcedo *et al* and this case. In the case by Sinha *et al* leukaemia was diagnosed simultaneously to the presentation of HUS, and in those reported by Martini *et al*, Hahn *et al* and Han *et al* the diagnoses occurred between 1 and 5 months.^{1–3 5}

Salcedo *et al* in 1986 reported the first case of a 4-year-old boy who presented with typical HUS, and was subsequently diagnosed with ALL 8 months later.⁴ Due to the long time elapse and the typical form of HUS, it has been suggested that the association could be coincidental. The case of typical HUS presented here, has a time elapse of just 7 weeks.

E.coli contains virulence factors that induce pro-inflammatory cytokines, interleukin (IL-) 8 and tumour necrosis factor α (TNF α).⁶ An association between elevated inflammatory markers and HUS is seen from raised levels of serum IL-6 in both typical and atypical forms of HUS, which normalises upon recovery.⁷ Urinary IL-6 and TNF α are also raised in HUS and reflect disease activity.⁷

Type one inflammatory cytokines have been linked to cause renal damage with several possible pathways implicated. Similar cytokines are released with malignancy and can result in vascular endothelial cell damage⁸ which may contribute to HUS pathogenesis when the two occur together.

Although associated with diarrhoea, our patients stool sample was *E.coli* 0157 negative. She did however have a raised antistreptolysin O titre. While group A β -haemolytic *Streptococcus* can cause HUS, our patient's negative blood culture and C3 within normal limits, make a streptococcal aetiology less likely.

In the atypical case reported by Hahn *et al*, negative BMA's were obtained prior to ALL diagnosis. They suggest

that this along with their patients' hepatosplenomegaly may be the result of a preleukaemic syndrome where BMA and blood films can be negative.² The recent case by Han *et al* reports a blood film being obtained during the acute HUS presentation where the patient had hepatomegaly, which showed no evidence of leukaemia.⁵ They then repeated a blood film 1 month later when the patient presented with hepatosplenomegaly and malaise, which showed abnormal cells confirmed by BMA to be lymphoblasts.⁵

While we did not obtain BMA until after ALL diagnosis, two negative peripheral blood films were obtained during the initial presentation of HUS. It was only when renal function continued to decline alongside the presence of lymphadenopathy and hepatomegaly that a third blood film was obtained showing blast cells.

We therefore report the sixth case of HUS preceding the diagnosis of ALL. This might suggest that HUS can be a presentation of occult ALL, even when HUS is associated with diarrhoea, a symptom also typical of infection-related HUS.

It is also notable that initial blood films were not indicative of malignancy despite onset of clinically and haemochemically diagnosable ALL within 7 weeks. Blood films should therefore be repeated at intervals in HUS, especially in the presence of features not usually seen in HUS such as hepatomegaly or lymphadenopathy.

Learning points

- ▶ HUS can occur due to an underlying malignancy such as ALL.
- ▶ If HUS is persistent or there are atypical features, then an underlying malignancy should be considered in the differential diagnosis.
- ▶ Initial blood films can be negative and so should be repeated when the clinical index of suspicion is high.

Competing interests None.

Patient consent Obtained.

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