CLINICOPATHOLOGICAL CONFERENCE

Lactic acidosis and abnormal liver function in advanced HIV disease

M Shahmanesh, J Cartledge, R Miller

A 48 year old man receiving HAART presented with late stage HIV disease, non-specific symptoms, a normal sized liver, ascites, and lactic acidosis. Following a failed liver biopsy worsening acidosis developed, requiring ICU support. Progressive liver failure occurred. Endoscopy showed oesophageal varices and a transjugular liver biopsy showed non-cirrhotic cholestasis; findings that were ascribed to HAART.

Sex Transm Infect 2002;78:139–142

central and peripheral nervous systems examination was normal. The patient was fully orientated and had normal mentation.

What would be your differential diagnosis at this stage? Are there any unusual features of the case?

DISCUSSANT

(Dr R Miller)

This white male with advanced HIV disease, taking HAART, presents with non-specific generalised symptoms and ascites. The differential diagnosis is wide (table 1). Tuberculosis is high on the differential diagnosis. Although in the absence of fever this would be an unusual presentation. The viral hepatitis: reactivation of hepatitis B or new infection with hepatitis A or C. The short history and the absence of stigmata of chronic liver disease make this less likely. In the absence of a relevant travel history, disseminated infections such as leishmaniasis and histoplasmosis are unlikely. Secondly, neoplasia, particularly non-Hodgkin's lymphoma involving the liver, or primary effusion lymphoma. Gastrointestinal malignancies such as carcinoma of the pancreas or liver could present in this manner. In the context of advanced HIV infection, lymphoma would be higher in the differential diagnosis than other malignancies. Thirdly, the presentation may be drug induced. Nucleoside reverse transcriptase inhibitor (NRTI) antiretroviral drugs have been associated with syndromes of hepatic steatosis with lactic acidosis^{1,2} and with fulminant liver failure.³ The presence of ascites in this patient would be very atypical of

CASE PRESENTATION

(Dr M Shamanesh)

A 48 year old white homosexual man was admitted to hospital in early March 2001. He reported a 4 month history of increasing fatigue, nausea, anorexia, diarrhoea, and feeling "bloated," associated with weight loss of 8 kg. He did not complain of fever or night sweats. The patient's symptoms had persisted despite empirical treatment of his diarrhoea with tinidazole and subsequently metronidazole instigated by his primary care physician. Microscopy and culture of blood and stool were persistently negative throughout the pre-admission period, as were "hot" stools for ova and parasites and prolonged cultures for mycobacteria.

He was first found to be HIV-1 antibody positive in 1997 during an admission with *Pneumocystis carinii* pneumonia. The CD4+ T lymphocyte count at that time was 20 cells $\times 10^6/l$. He was immune to hepatitis B. In April 1997 he was started on highly active antiretroviral therapy (HAART) with zidovudine, didanosine, and indinavir. One year later he developed renal stones and, consequently, indinavir was changed to nevirapine. He remained on co-trimoxazole as secondary prophylaxis of *P. carinii* pneumonia. Whereas the HIV viral load became undetectable shortly after commencing HAART, the CD4+ T lymphocyte count had risen to only 120 cells $\times 10^6/l$ by the time of the admission in March 2001. Liver function tests performed 8 months before admission were normal.

The patient was a teacher; he had no significant travel history, was a non-smoker, and drank alcohol only occasionally. Systematic inquiry was non-contributory. Examination on admission showed the patient was afebrile, had no lymphadenopathy, and normal skin. He was not jaundiced and there were no stigmata of chronic liver disease. His pulse was 100 and regular and blood pressure = 140/100. Auscultation of the heart and examination of the chest was normal. SpO_2 (on air) was 99%. Examination of the abdomen revealed a distended abdomen with shifting dullness; the liver and spleen were not enlarged. The

See end of article for authors' affiliations

Correspondence to: Dr R F Miller, Department of Sexually Transmitted Diseases, Windymer Institute of Medical Sciences, Royal Free and University College Medical School, University College London and Mortimer Market Centre, Camden and Islington Community Health Services NHS Trust, London WC1E 6AU, UK rmiller@gum.ucl.ac.uk

Accepted for publication 24 January 2002

Table 1 Differential diagnosis of patient's presentation with non-specific symptoms and ascites

Infections	<ul style="list-style-type: none"> • Tuberculosis • Viral hepatitis A, B, C • Leishmaniasis • Histoplasmosis
Neoplasia	<ul style="list-style-type: none"> • Non-Hodgkin's lymphoma of liver • Primary effusion lymphoma • Carcinoma of the pancreas • Carcinoma of the stomach
Drug induced	<ul style="list-style-type: none"> • Nucleoside reverse transcriptase inhibitors
Others	<ul style="list-style-type: none"> • Budd-Chiari syndrome • Cardiovascular causes—for example, right heart failure or constrictive pericarditis • Nephrotic syndrome

Key points

- Lactic acidosis in a patient with advanced HIV has a wide differential diagnosis
- Liver biopsy in HIV infected patients may carry an increased morbidity compared to the general population
- Non-cirrhotic portal hypertension may develop rapidly following hepatitis in HIV infected patients

NRTI associated hepatic toxicity. Other causes that should be considered include Budd-Chiari syndrome, cardiovascular causes, including right heart failure or constrictive pericarditis and the nephrotic syndrome. Although diagnoses, including Wilson's disease or chronic active hepatitis are possible, presentation with one of these conditions would be unusual in the absence of stigmata of chronic liver disease.

CASE PRESENTATION

(Dr Shahmanesh)

On admission, investigations showed haemoglobin = 11.9 g/dl, MCV = 114 fl; serum B12 and red cell folate were normal. The white cell count = $3.2 \times 10^9/l$ and platelets = $178 \times 10^9/l$. Urea and electrolytes were normal, except for a raised creatinine of 173 $\mu\text{mol/l}$ (normal range = 70–150 $\mu\text{mol/l}$). Liver function tests were abnormal with ALT = 116 IU/l (NR = 7–63 IU/l), ALP = 324 IU/l (NR = 45–122 IU/l), and γGT = 583 IU/l (NR = 11–50 IU/l); the serum albumin was normal. A resting, uncuffed serum lactate = 4.75 mmol/l (NR = 0.6–2.4 mmol/l). Arterial blood gases, taken while breathing room air, showed a compensated metabolic acidosis: pH = 7.47 (normal 7.36–7.44) standard base excess = –4.6 mmol/l, HCO_3^- = 18 mmol/l, PaO_2 = 13.4 kPa, and Paco_2 = 3.4 kPa.

Urine analysis showed a heavy growth of *Escherichia coli* sensitive to ciprofloxacin. Blood cultures were negative; stool cultures were negative for bacterial pathogens including *Clostridium difficile*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, and *E. coli*. "Hot" stools for ova, cysts, and parasites revealed no *Giardia*, *Cryptosporidium*, or *Microsporidium*. Three early morning urine samples for mycobacterial culture were negative, as was prolonged culture of blood for mycobacteria. Serum cryptococcal latex agglutination test was negative. An ascitic tap revealed a transudate (protein = 9 g/l), six white cells, predominately lymphocytes; staining and culture showed no organisms and cytology was negative. Hepatitis B serology showed anti-HB core positivity; HBs Ag was negative and anti-HBs Ag was positive. Hepatitis C antibody was negative as was hepatitis C RNA. Measurement of the tumour marker Ca 125 showed a level of 208 kU/l (NR = 0–35 kU/l); the α fetoprotein was normal. An autoantibody and metabolic screen was negative. Serum immunoglobulins were normal, apart from a raised IgA = 5.6 g/l (NR = 0.9–4.5 g/l). A 24 hour urinary protein estimation was normal.

A chest radiograph was normal. An abdominal ultrasound scan revealed massive ascites with a normal sized liver, with no evidence of cirrhosis, a normal sized spleen, no intra-abdominal lymphadenopathy, and normal flow through the hepatic and portal veins. A computed tomograph (CT) scan of the abdomen confirmed these findings. A CT scan of the chest revealed an hiatus hernia but was otherwise normal. An echocardiogram showed no pericardial effusion and normal ventricular function. How would you interpret these findings?

DISCUSSANT

(Dr Miller)

The imaging confirms the clinical diagnosis of ascites. The abnormal liver function tests suggest hepatitis rather than cholestasis. In keeping with the absence of signs of chronic liver disease, admission bloods suggest no failure of liver synthetic

function. Several elements of the differential diagnosis are excluded at this stage; the viral, metabolic, and autoimmune hepatitis, Budd-Chiari syndrome, cardiovascular, and renal causes. There are no positive findings to support a diagnosis of lymphoma or tuberculosis. However, the absence of intra-abdominal lymphadenopathy, analysis of ascites showing a transudate, and the absence of acid fast bacilli or abnormal lymphocytes does not preclude a diagnosis of lymphoma, tuberculosis, or other rarer fungal infections, such as histoplasmosis, and so they remain part of the differential diagnosis.

This patient has a raised resting venous lactate. It is always important to identify whether this is simple hyperlactataemia or the elevated lactate is associated with an underlying metabolic acidosis (as in this case) and so represents a lactic acidosis.^{2,4} In a metabolic acidosis, both the pH and the standard bicarbonate are low.

The lactate measured in a resting uncuffed venous blood sample is a reflection of the balance that is maintained between the rate of lactate production by metabolically active tissues, which in turn depends on intracellular oxygen levels and mitochondrial biochemical function, and the rate of clearance of lactate by the liver and kidney. Each day, up to 70% of the total lactate production (approximately 1.2 mmol/24 h/70 kg body weight) is taken up by the liver. In normal circumstances, the concentration of lactate in blood is maintained within a tightly controlled physiological range. In conditions that result in excess production of lactate, hepatic and renal clearance of lactate is increased and skeletal muscle, which normally produces lactate, may utilise it metabolically. This explains how the huge sudden elevations of lactate that occur during physical exercise are rapidly restored to normal.

Causes of increased lactate production may be divided into two categories: type A which includes causes due to poor tissue perfusion with or without hypoxia, including haemorrhagic shock, myocardial infarction with left ventricular failure, and septic shock; and type B which includes causes in which there are no signs of tissue hypoxia or underperfusion, including drugs such as biguanides (for example, metformin), severe liver disease, malignancy such as leukaemia or lymphoma, and mitochondrial disorders, both inherited and secondary to drugs such as NRTI.⁵

In this case there is no clinical evidence of tissue hypoperfusion, therefore it seems more likely that type B lactic acidosis has developed. Although reduced lactate clearance by the liver may be a factor, this is unlikely in the absence of abnormal liver synthetic function. This leaves drugs and malignancy as possible explanations of the presentation. Antiretroviral therapy, in particular NRTI, has been associated with development of lactic acidosis together with acute hepatic steatosis.^{1,2,5} Again, I am concerned that ascites is not typical of NRTI induced hepatic toxicity. The syndrome of acute steatosis/lactic acidosis has a high mortality, even when NRTI are discontinued and full intensive care unit (ICU) support is given. It is a relatively uncommon problem, occurring in ≤ 1.5 cases treated with NRTI per 1000 person years.¹

CASE PRESENTATION

(Dr Shahmanesh)

The patient continued on HAART and co-trimoxazole. He remained afebrile but continued to lose weight. He was given diuretics and subject to fluid restriction as treatment of ascites, paracentesis was performed and 11 litres of ascites was removed with simultaneous intravenous 20% albumin replacement. Two weeks after admission a percutaneous liver biopsy was performed. Six hours after the liver biopsy the patient became pyrexial. Over the following 8 hours he became increasingly unwell with tachycardia, raised blood pressure, and anxiety. On examination he was agitated with signs of intravascular fluid depletion, he was peripherally shut down and hyperventilating (respiratory rate > 40/min). Arterial blood gases showed a

Table 2 Possible explanations for the patient's acute deterioration

Differential diagnosis	Pro	Con
Related to liver biopsy: (a) Bleed into capsule or abdomen	<ul style="list-style-type: none"> Temporal relation with biopsy Speed of deterioration Marked intravascular volume depletion 	<ul style="list-style-type: none"> No abdominal pain No change in abdominal girth No drop in haemoglobin
(b) Sepsis	<ul style="list-style-type: none"> Temporal relation Fever preceding deterioration Hypovolaemia and acidosis 	<ul style="list-style-type: none"> Lack of positive cultures
Intercurrent problems: Nosocomial infection	<ul style="list-style-type: none"> Temporal association with biopsy 	
HAART associated Mitochondrial toxicity	<ul style="list-style-type: none"> Patient immunosuppressed Previous exposure to HAART 	<ul style="list-style-type: none"> No steatosis on liver ultrasound

severe metabolic acidosis: pH = 6.93, standard base excess = -29 mmol/l, bicarbonate = 1.5 mmol/l, and lactate = 23 mmol/l. The urinary pH = 5.0 (normal = 4.5–8.0), blood urea = 14 mmol/l, creatinine = 188 µmol/l, and ALT was mildly raised at 54 IU/l, but other liver function tests were normal. Haemoglobin = 11.6 g/l, WCC = 15×10^9 /l with a neutrophil predominance. A clotting screen and platelet count were normal. Could you summarise the clinical situation?

DISCUSSION

(Dr Miller)

Clinically, there are few specific clinical signs of acute metabolic acidosis. However, hyperventilation (Kussmaul's acidotic respiration) is strongly suggestive and should alert the physician to the diagnosis. The signs and symptoms of chronic metabolic acidosis are more non-specific and commonly include fatigue and anorexia.

In this case there was a progressive deterioration shortly after a percutaneous liver biopsy. The severe hyperventilation and anxiety on the background of a compensated metabolic acidosis are suggestive of worsening acidosis and this was confirmed by the results of the arterial blood gases analysis. The urine pH suggests that the renal tubules are still able to excrete excess acid; however, intravascular volume depletion and prerenal failure may have compromised the ability of the kidneys to excrete acid. The biochemical liver function tests do not suggest a marked deterioration of liver function being the cause of the patient's general deterioration.

In this situation, a concern is the effect of acidosis with the resultant shift of potassium out of cells, on cardiac function, the potential for circulatory collapse, and the danger of prolonged intravascular volume depletion on renal perfusion. There are several possibilities when considering an explanation for the acute deterioration. These are given in table 2.

CASE PRESENTATION

(Dr Shahmanesh)

All medication including HAART was stopped. The patient was transferred to ICU where he was given crystalloid fluid replacement and haemofiltration was started. The cause of the patient's deterioration was investigated with a "septic screen" which included multiple blood, urine and stool cultures and an ascitic tap. An ultrasound scan of the abdomen showed no subcapsular haematoma or intra-abdominal bleed. Chest radiography and an electrocardiogram were normal. The patient was treated presumptively for a septic precipitant of the deterioration with intravenous teicoplanin and ceftazidime. Subsequently, the acidosis was controlled by haemofiltration. However a coagulopathy developed. The platelet count

dropped to 55×10^9 /l, the APTT increased to 131, the INR = 1.92, and the fibrinogen fell to 0.82 g/l.

Two days after admission to ICU the patient had haematemesis consisting of 1 litre of altered blood, requiring support with blood and fresh frozen plasma. At this stage it was reported that the histology from the liver biopsy was a section of normal colonic mucosa. There was no liver tissue in the biopsy specimen.

Five days after admission to ICU the patient developed hiccups and became increasingly drowsy (Glasgow coma scale = 11). The blood ammonia level was 179 µmol/l (NR <40 µmol/l) and the bilirubin had risen to 42 µmol/l.

Was it appropriate to treat presumptively for a septic cause of deterioration in this patient? What are the possible reasons for the patient's reduced level of consciousness?

DISCUSSION

(Dr Miller)

In the pre-HAART era it was shown that the morbidity, and mortality especially from haemorrhage, of liver biopsies in HIV infected individuals, was higher than in the general population.⁶ These data have not been re-evaluated in the era of HAART. In this case, the finding that the attempted liver biopsy had inadvertently perforated bowel increased the possibility of sepsis. Use of co-trimoxazole, even at doses used for prophylaxis, may inhibit bacterial growth in culture. Given these difficulties in diagnosing sepsis and in the absence of any other obvious precipitating factor for the deterioration, it would be reasonable to presumptively treat for sepsis.

The most likely cause for the patient's reduced level of consciousness, in view of the raised ammonia and increasingly abnormal synthetic liver function, would be hepatic encephalopathy following an upper gastrointestinal bleed. However, in view of profound immunosuppression, various infectious causes including bacterial and viral meningitis should be considered as well as generalised sepsis. Another possibility might be reduced metabolism by the liver of drugs used for sedation of the patient while on ICU; in this case, however, no sedative drugs had been administered.

CASE PRESENTATION

(Dr Shahmanesh)

Investigations included a cranial CT which was normal and a CT of the abdomen that showed ascites. The diagnosis was felt to be hepatic encephalopathy. The hepatic encephalopathy was managed conservatively. Three weeks after admission to ICU, he had a further haematemesis on the background of worsening coagulopathy, rising conjugated bilirubin, low fibrinogen, and normal haptoglobin and LDH levels.

What are the possible reasons for the haematemesis?

DISCUSSION

(Dr Miller)

The coagulopathy, which is probably a combination of failure to produce clotting factors and disseminated intravascular coagulation, leaves the patient vulnerable to gastrointestinal bleeds. Possible causes include oesophagitis, gastritis, an acute gastric erosion, an acute stress ulcer, a duodenal ulcer or oesophageal varices, although this latter possibility would be unexpected on the background of an acute hepatic deterioration, without prior chronic liver disease.

CASE PRESENTATION

(Dr Shahmanesh)

Endoscopy revealed oesophagitis and grade II varices that were treated with banding. Cranial magnetic resonance imaging (MRI) was normal. Biochemical tests of renal and liver function, in particular synthetic function, continued to deteriorate. Urea = 18 mmol/l, creatinine = 200 µmol/l, bilirubin = 131 µmol/l, ALT = 62 IU/l, ALP = 342 IU/l, and albumin = 19 g/l.

Three weeks after his admission to ICU he was transferred to the renal unit. A ^{99m}Tc MAG-3 (benzoylmercaptoacetyl-triglyceride) isotope renogram demonstrated acute tubular necrosis. At this time the CD4+ T lymphocyte count had dropped to 60 cells × 10⁶/l.

Five days later he became breathless with a productive cough. He developed type II respiratory failure; P_{O₂} = 7.25 kPa and p_{CO₂} = 13.25 kPa (breathing air). The serum bilirubin continued to rise. A chest radiograph was abnormal, showing bilateral diffuse infiltrates. Why do you think the patient deteriorated?

DISCUSSION

(Dr Miller)

The acute deterioration suggests either a hospital acquired pneumonia or an aspiration pneumonia, secondary to the patient's depressed cerebral function. However, in view of the patient's profound immunosuppression, opportunistic infections, in particular fungal infections, would have to be part of the differential diagnosis.

CASE PRESENTATION

(Dr Shahmanesh)

The patient was transferred back to ICU and mechanical ventilation was commenced in order to maintain oxygenation. A serum cryptococcal antigen and blood cultures were negative. A bronchoscopy with bronchoalveolar lavage was negative for *Pneumocystis carinii*, fungi, and acid fast bacilli. Over the next 2 days there was further deterioration in biochemical tests of liver function, the bilirubin rose to 487 µmol/l and, despite nutritional support, the serum albumin dropped to 18 g/l. The hepatic transaminases and alkaline phosphatase remained unchanged. An abdominal ultrasound scan showed an irregular liver capsule suggestive of cirrhosis, and a large spleen. A transjugular liver biopsy was performed. The biopsy showed marked cholestasis with foci of hepatocyte rosette formation. No significant inflammation was seen and histochemical stains for α₁-antitrypsin globules, fungi, and mycobacteria were negative. The patient continued to deteriorate and died of liver failure. What is your assessment of the situation so far?

DISCUSSION

(Dr Miller)

The patient has rapidly deteriorating synthetic liver function without hepatitis or significant cholestasis. The oesophageal varices and splenomegaly suggest portal hypertension. It seems that the patient has progressed rapidly from hepatitis to portal hypertension and decompensated liver disease. Liver function tests had been normal only 8 months before admission.

Clearly sepsis secondary to the failed percutaneous liver biopsy may have contributed to the deterioration which was then exacerbated by further sepsis and gastrointestinal bleeds.

The underlying aetiology remains obscure, viral hepatitis (A, B, and C) metabolic and autoimmune causes have been excluded. There remains the possibility that this could be drug induced, possibly by NRTI.

If this was NRTI induced, then the liver biopsy would show microvesicular and macrovesicular steatosis, possibly with mild portal inflammation.^{2,7} In this patient these features were not present. Although unusual, this presentation with very rapid progression from hepatitis to development of non-cirrhotic portal hypertension and liver failure has recently been described.⁸

COMMENT

(Dr J Cartledge)

There are several key points that emerge from caring for this patient. Firstly, that lactic acidosis in a patient with advanced HIV disease should not automatically be ascribed to NRTI-antiretroviral drugs, as there is a wide differential diagnosis to consider. In this patient, on presentation, there was a mild hyperlactataemia associated with NRTI drugs and, subsequently, a marked lactic acidosis developed caused by sepsis following a failed liver biopsy.

Secondly, percutaneous liver biopsy in an HIV infected patient may carry an increased morbidity compared to biopsy in the general population. Within our own unit, percutaneous liver biopsy, if performed, is now conducted under ultrasound guidance in all cases. Finally, in the context of HIV infection, it is always important to be aware of "new" presentations or alterations to the natural history of disease processes, as is illustrated here by the rapid development of non-cirrhotic portal hypertension following a hepatic episode.

ACKNOWLEDGEMENTS

We thank Dr R Jalan, consultant hepatologist, for help with care of the case and Dr M Novelli for histopathological expertise.

Source of funding: Nil.

Conflict of interest: Nil.

CONTRIBUTORS

MS abstracted the patient's clinical records, prepared the case for presentation, and with RM wrote the first draft of the manuscript; JC was the consultant in charge of the case and contributed to writing the drafts of the manuscript; RM wrote the final version of the manuscript.

Authors' affiliations

M Shahmanesh, J Cartledge, Department of Genito-Urinary Medicine, Mortimer Market Centre, Camden and Islington Community Health Services NHS Trust, London WC1E 6AU, UK
R Miller, Department of Sexually Transmitted Diseases, Windeyer Institute of Medical Sciences, Royal Free and University College Medical School, University College London and Mortimer Market Centre, Camden and Islington Community Health Services NHS Trust, London WC1E 6AU, UK

REFERENCES

- 1 **Fortgang IS**, Beditsos PC, Chaisson RE, *et al.* Hepatomegaly and steatosis in HIV-infected patients receiving nucleoside analog antiretroviral therapy. *Am J Gastroenterol* 1995;**90**:1433–6.
- 2 **Pau D**, Watson C, Peters B, *et al.* Hyperlactataemia and hepatic steatosis: mitochondrial toxicity of nucleoside reverse transcriptase inhibitors. *Sex Transm Inf* 2001;**77**:381–4.
- 3 **Lai KK**, Gang DL, Zawacki JK, *et al.* Fulminant hepatic failure associated with 2',3'-dideoxyinosine (ddI). *Ann Intern Med* 1991;**115**:283–4.
- 4 **John M**, Moore CB, James IR, *et al.* Chronic hyperlactataemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001;**15**:717–23.
- 5 **White AJ**. Mitochondrial toxicity and HIV therapy. *Sex Transm Inf* 2001;**77**:158–73.
- 6 **Churchill DR**, Mann D, Coker RJ, *et al.* Fatal haemorrhage following liver biopsy in patients with HIV infection. *Genitourin Med* 1996;**72**:62–4.
- 7 **Loneragan JT**, Behling C, Pfander H, *et al.* Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis* 2000;**31**:162–6.
- 8 **Carr A**, Morey A, Mallon P, *et al.* Fatal portal hypertension, liver failure and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia. *Lancet* 2001;**357**:1412–14.