Clinico-pathological conference

Complications of treatment for cryptosporidial diarrhoea

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Case report (Dr Jane Anderson)

A 26 year old Caucasian, homosexual, male civil servant was found to be HIV antibody positive in November 1988. At that time he reported weight loss, night sweats and a scaling rash over the face and neck. On examination he was thin and weighed 67 kg. He had cervical and axillary lymphadenopathy and a crusting facial rash, and hairy oral leucoplakia. The haemoglobin was 15.9 g/dl, total lymphocyte count $1.5 \times 10^3/l$; a chest radiograph was normal. He was p24 antigen negative. He had no markers of hepatitis B infection despite having had a full course of hepatitis B vaccine in 1986. He was given aqueous cream, Canesten HC (clotrimazole 1% and hydrocortisone 1%) cream and minocycline with good results.

Three weeks later he re-presented with a four day history of cramping abdominal pain and episodic watery, blood-free diarrhoea; cryptosporidium was isolated from the stool. Symptoms persisted over the next five weeks and further stool samples were positive for cryptosporidia. At that point the alkaline phosphatase had risen to 309 IU/l (normal < 28 IU/l) and the AST was elevated at 102 IU/l (normal < 35 IU/l). The other liver function tests, haemoglobin and electrolytes were normal. Oral erythromycin 500 mg qds and loperamide were prescribed. Within two days his condition deteriorated and he was admitted to hospital with constant abdominal pain and 15-20 stools per day. Cryptosporidium was again isolated

from the stool. The erythromycin was discontinued and his symptoms improved gradually. Zidovudine was introduced at a dose of 250 mg qds and he was discharged.

Within four days he was readmitted with vomiting and diarrhoea together with oral candidiasis, and he was unable to eat. Zidovudine was discontinued and he was given liquid food supplements which he tolerated poorly. Several attempts were made to pass a naso-gastric feeding tube without success. Symptom control was achieved with subcutaneous diamorphine, cyclizine and hyoscine via a syringe pump driver. His diarrhoea settled and his vomiting was very much improved. Fluconazole was given for the oral candidiasis and zidovudine was reintroduced at a dose of 100 mg tds, which he tolerated. He was eventually discharged on MST Continus (morphine sulphate sustained release) and oral cyclizine.

Over the next four months he was followed up as an outpatient. He had occasional episodes of nausea and vomiting but very little diarrhoea. Liver function tests returned to normal. Multiple stool cultures remained positive for cryptosporidia and he was able to tolerate zidovudine at a dose of 250 mg qds, and continued on MST Continus. He used metoclopramide and fluconazole intermittently. Towards the end of this period his alkaline phosphatase had risen to 580 IU/l and the AST to 54 IU/l. The other liver function tests and an abdominal ultrasound were normal. Over the next six weeks he developed right upper quadrant pain exacerbated by eating. Further stool cultures were positive for cryptosporidium. He was given oral spiramycin; despite this he deteriorated and was readmitted with increasing right upper quadrant pain and vomiting, but his diarrhoea was well controlled. Liver function tests showed a further deterioration with an alkaline phosphatase of 708 IU/l and an AST of 114 IU/l. A repeat abdominal ultrasound showed marginal enlargement of the liver and spleen. He was given ranitidine and metoclopramide; subcutaneous diamorphine was reintroduced to control his symptoms and he continued on full-dose zidovudine.

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Fig 1 Endoscopic retrograde cholangio-pancreatogram showing dilatation of the common bile duct and multiple irregularities of the intrahepatic ducts.

Dr R F Miller

Endoscopic retrograde cholangio-pancreatography (ERCP) showed dilatation of the common bile duct with irregular mucosa throughout the biliary tree and multiple irregular intrahepatic strictures (fig 1). This was consistent with sclerosing cholangitis and a sphincterotomy was performed, which reduced his pain but the alkaline phosphatase and AST remained grossly elevated.

Dr J Anderson

On discharge from hospital he was managed at home by the Bloomsbury Community Care Team. He continued to have diarrhoea, nausea and vomiting which were controlled with metoclopramide, cyclizine and dexamethasone. Several weeks later he deteriorated and required hospital admission. He was passing 2–3 litres/day of diarrhoea and was vomiting. The liver was found to be smoothly enlarged four fingers breadth below the costal margin. The alkaline phosphatase was 945 IU/l and AST 98 IU/l. Abdominal ultrasound showed an enlarged liver with a dilated common bile duct and intrahepatic ducts consistent with sclerosing cholangitis.

His course in hospital was complicated by a *Haemophilus influenzae* chest infection. A Hickman line was inserted and total parenteral nutrition

(TPN) was instituted. This was complicated by a *Staphylococcus aureus* infection at the Hickman line entry site on the chest wall; the blood cultures taken through the line and from peripheral sites were negative. He was treated with flucloxacillin with good results. Spiramycin given simultaneously by oral and intravenous administration was tried in an attempt to control the cryptosporidial diarrhoea. This made little impact on his symptoms. Somatostatin analogue was tried in an attempt to control the diarrhoea without benefit.

Over the last 2 months of his life he was managed entirely at home and continued to receive TPN, supervised by the Community Care Team. Zidovudine was discontinued but he remained on diamorphine, hyoscine, dexamethasone, metoclopramide and fluconazole. He developed a generalised red macular rash after 2 months on TPN. Terminally he developed polyarthralgia with particular involvement of the left shoulder, a bronchopneumonia and pulmonary oedema. He died 14 months after his original presentation with cryptosporidial diarrhoea.

Discussion (Dr R J D George)

It may seem rather strange for a palliative physician to be managing somebody at home, at the end of their life, with something as "aggressive" as parenteral nutrition. From the patient's point of view, while he was aware of prognosis, the indications justifying this were as follows: both he and his family wanted him to spend his last weeks at home, and there were several important issues to resolve concerning his personal relationships and spiritual integration. To be well enough to deal with these things at home was his absolute priority. From our point of view, to achieve these endpoints, he needed aggressive symptom control. He was unable to tolerate oral fluid, and was severely malnourished and dehydrated. TPN

Fig 2 Support Team Assessment Schedule (STAS) score for the patient during his care by the Bloomsbury Community Care Team. Following insertion of a Hickman line and institution of Total Parenteral Nutrition (TPN) there was a marked fall in the STAS score.

therefore seemed justifiable as a palliative measure. We achieved these goals; TPN made a significant difference to the quality of his life and he was able to complete his remaining agenda.

Do we have any data to justify these statements? As part of continuing clinical audit of team practice in the Bloomsbury Community Care Team, we have established a system which was developed to examine the quality of life in people dying with cancer.¹ This scoring system, the Support Team Assessment Schedule (STAS) goes beyond conventional clinical problems such as pain or symptom control, and quantifies patient and family anxiety and insight, communication, planning, spiritual needs and so on. Each area is scored weekly on a defined five point scale to produce an aggregate reflecting overall quality of life and care being given. By quantifying these parameters, we are able both to understand and track the patterns and interactions of cofactors of importance in clinical and psychosocial care. Figure 2 shows the plot in this case. A high score is bad and the low score is good. The message is clear. You will see that prior to starting TPN the patient's wellbeing was erratic and relatively poor. Poor symptom control characteristically affects other things like anxiety and communication within the social structure and precipitates crisis. The scores reflect this and had he not been admitted, the whole family setup would have collapsed. At the onset of TPN the score dropped dramatically, as the situation was contained. This stability continued to the end of his life when he was scoring 1 or 2 (ie occasional symptoms, no anxiety in him or the family, full communication, spiritual peace and preparedness for death). Given his pathology this was probably optimum.

Another area worth commenting on is the administration of effective symptom control in the face of such extensive pathology. In patients with overwhelming gastrointestinal symptoms, oral or rectal medication is seldom effective because of vomiting, short gut transit times or malabsorption from mucosal disruption. In these cases we have found that parenteral administration is often necessary. Fortunately, most drugs (the main exceptions to this are diazepam, stemetil and chlorpromazine) can be mixed and given subcutaneously using a pocket size syringe driver recharged 12 or 24 hourly. Early on in his history the patient's first severe bout of diarrhoea and vomiting was controlled by subcutaneous diamorphine and metoclopramide and he was then transferred successfully to equivalent oral doses of MST Continus and metoclopramide. In the last 3 months of his life the majority of his medication was given by syringe driver in doses titrated against symptoms.

Some drugs may also serve several purposes. The dexamethasone was initially used for its antiemetic effect, but later its principal value was to suppress the systemic effects of infection, the diamorphine initially

controlled the diarrhoea at doses of about 200 mg/24 h but later increased successfully to 500 mg to suppress cough and breathlessness, and the anticholinergic effect of hyoscine, apart from reducing gut secretion, almost certainly contributed as an antiemetic and dried up the large airway secretions that aggravate cough.

The final point to make is that many of these patients with severe gastrointestinal symptoms require combination antiemetic therapy. It is essential to use adequate doses of each drug, to introduce them one at a time to maximum dose and then to select a representative from another group if symptoms persist. At the end of his life, this patient was receiving 4 antiemetics subcutaneously with additional high dose metoclopramide via his Hickman line to maintain complete control of his vomiting.

Dr I V D Weller

This man presented with persistent generalised lymphadenopathy and a few constitutional symptoms in 1988. I note from the history he failed to respond to hepatitis B vaccine in 1986. In a study carried out here in 1986 it was demonstrated that the response in HIV positive patients is diminished and other studies have confirmed this.^{2,3} This may suggest that he was already HIV infected in 1986 which would fit with the disease course. However, a small proportion of young, healthy individuals do not respond to hepatitis B vaccine either.

As a general comment about the case I am surprised how long this man survived considering he presented with severe cryptosporidial diarrhoea in December 1988. Obviously the palliative care that he received gave him a reasonable quality of life.

One usually sees AIDS sclerosing cholangitis late on in HIV disease.^{4,5} About 65–75% of cases in the literature have been described in association with either cryptosporidial or CMV infection or both. Whether these agents are passengers or pathogens remains to be seen. Other organisms are occasionally found such as various types of bacteria and candida but these may well be secondary infections as a result of the alteration in biliary architecture and not causal.

I was a little surprised by the liver function tests returning to normal but his symptoms and signs also settled during this early period. With later disease one sees fluctuations in liver function tests but they rarely return to normal.

There is something that worries me about this patient and others we have managed with diarrhoea like this. Although we have found cryptosporidium in the stool, we tend not to investigate further as far as other gastrointestinal problems are concerned. CMV disease was not excluded in this case. Even flexible colonoscopy may miss CMV disease in the ascending and transverse colon.

Moving on to the question of treatment of cryptosporidiosis, the short answer is that there is no specific treatment and the long answer is that a large number of treatments have been tried and some have had anecdotal success. I think this man was obviously treated during the phase when we were trying various sorts of agents. Spiramycin and somatostatin are two examples of this. There are also some reports that zidovudine may improve diarrhoea associated with cryptosporidial infection but there are no controlled data on this. Our real problem is that we do not know how cryptosporidium causes diarrhoea. It is hardly invasive. The intermediate form of the parasite sits in the intestinal cells in an intracytoplasmic position but just on the edge covered by the cell membrane. It may be that it releases some form of toxin. The diarrhoea could be mediated by gut hormones or even the immune response to the organism and therefore perhaps even cytokines are involved. These various possibilities are another reason why so many different therapies have been tried. The other drug which we were trying to obtain at the time was diclazoril. This is an agent which is used in veterinary medicine and is active against protozoa in chickens. Again, there have been anecdotal reports of success and a controlled trial is underway in the United States.

With respect to the management of AIDS sclerosing cholangitis you did a sphincterotomy because of pain. Certainly if there is stricture at the lower end of the common bile duct and the patient is experiencing a lot of pain this is worth trying since there have been a number of reports now to show that this procedure can help.⁴ However, it rarely helps the abnormal liver function tests, as one might expect, with such widespread both extra and intrahepatic disease.

His later clinical course shortly before his death reminded me of a number of cases we have seen of disseminated staphylococcal infection with pustular rashes and septic arthritides. This is particularly relevant with him having an indwelling intravenous line.^{6,7} Indeed, staphylococcus was isolated on one occasion from this and he received a short course of flucloxacillin.

In summary, in terms of the management of this man I am sure that to concentrate on palliative care was the most important thing to do. However, coming back to what the necropsy revealed, I return to my comment about continuing to manage patients over a long course once the diagnosis of cryptosporidial disease is made, without further investigating the gastrointestinal tract. So I am worried that our pathologist might tell us that this man had either underlying gastrointestinal disease due to CMV or even perhaps a lymphoma.

Clinical diagnosis: (1) Staphylococcal septicaemia
(2) Cryptosporidial diarrhoea
(3) AIDS sclerosing cholangitis
(4) CMV or lymphoma of gut?

Pathology (Dr S B Lucas)

The macroscopic findings first. He was autopsied 4 days after death and he was emaciated and jaundiced. On the skin were several brown papular seborrhoeic keratoses and a fine macular erythematous rash.

The heart was large and flabby, within the muscle numerous small white spots were visible, he had a myocarditis. There were bilateral pleural effusions and the lungs were large, triple the normal weight. On cutting they were oedematous and bronchopneumonic. In the gastrointestinal tract, the mouth was normal and the tongue did not show oral hairy leucoplakia. The lower oesophagus was ulcerated. The small bowel was greatly distended with brown liquid contents; no focal lesions were seen on the mucosa. The large bowel contained some brownish toothpasty material, and again no focal mucosal lesions. The liver was enlarged and green from cholestasis. The gall bladder appeared normal; but the common bile duct was dilated to over 1 cm in diameter and had a thick and irregular mucosa. The ampulla of Vater looked normal even though he had a papillotomy, probably because of post-mortem autolysis and muscle slackening.

(a)

(b)

Fig 3 (a) Heart muscle showing multiple abscesses some of which are surrounding blood vessels (magnification $\times 20$). (b) High power view of abscess showing it to be composed of polymorphs. A cluster of Gram positive cocci are seen within the abscess (top right) (magnification $\times 40$).

(a)

(b)

Fig 4 (a) Wall of the common bile duct showing considerable thickening. There is distortion of the glands with acute inflammation and fibrosis (magnification $\times 10$). (b) High power view of epithelial surface of the wall of the common bile duct showing many of the cells contain CMV inclusions (magnification $\times 40$).

The kidneys had widespread white spots, like the heart. The spleen was large but appeared unremarkable on section. Lymph nodes from different sites in

the abdomen were just a little larger than the common atrophic nodes found in AIDS cases, but were non-necrotic. The thyroid was firm, and the adrenals atrophic from the steroid therapy. Externally the brain appeared normal, as it did on brain-cutting after fixation. The spinal cord and eyes were not examined.

The histopathology shows that the white spots in the kidneys and heart were abscesses containing gram-positive cocci, consistent with *Staphylococcus aureus*. In the heart there were abscesses under the endothelium, presumably seeding to and from the blood stream (fig 3). There was necrotising bronchopneumonia in the lungs with focal necroses associated with colonies of bacteria.

The atrophic adrenals also contained small bacterial abscesses as did the thyroid (but without sufficient damage to produce hypofunction). The meninges were not inflamed, but throughout the cerebrum, cerebellum and brain stem—white and grey matter—there were small foci of demyelination associated with staphylococcal abscesses. The small arteries had necrotic walls and were obstructed by thrombus adjacent to the staphylococcal colonies. By calculation there were up to fifty thousand of these small abscesses within his brain, surprisingly, as he was said to be mentally normal just before death; probably these abscesses developed terminally.

On the skin, apart from some molluscum contagiosum lesions, the macular rash was due to focal ischaemic lesions caused by staphylococcal pyaemia in the mid and upper dermal blood vessels, causing thrombosis. In some areas the epidermis had small vesicles containing colonies of *Staphylococcus*.

The oesophageal ulceration was not due to CMV or candidiasis, but—again—was caused by staphylococcal pyaemia with infarcted epithelium. Despite the autolysis, the mucosa of the entire small and large bowel was acutely inflamed with polymorphs, associated with numerous CMV inclusions in the endothelium and lamina propria. No cryptosporidium was evident, but that parasite rapidly disappears from gut mucosa after death, so post-mortem histology usually cannot help assess its extent unless autopsy is performed within a few hours of death.

The liver parenchyma was cholestatic with numerous small bile plugs indicating duct obstruction; in the peripheral part sampled the portal tracts are normal without evidence of sclerosing cholangitis. Possibly the liver nearer the hilum may have shown more abnormalities. The wall of the common bile duct was double the normal thickness and was inflamed and fibrosed. The glands were distorted by acute inflammation and fibrosis (fig 4). This was active sclerosing cholangitis. Some of the epithelial cells contained CMV inclusions, but no cryptosporidium could be seen. They may have been present, but autolysis has occurred.

To summarise, the actual causes of death in this man were bronchopneumonia and heart failure due to staphylococcal septicaemia. He also had sclerosing cholangitis and CMV enteritis; cryptosporidial enteric infection was diagnosed during life. As a cause of death, staphylococcal septicaemia is relatively uncommon in most series of AIDS post mortems.^{8,9}

Pathological diagnoses:

1. Staphylococcal septicaemia, with cerebral, cardiac, pulmonary, cutaneous, oesophageal and endocrine abscesses.
2. CMV enteritis.
3. Sclerosing cholangitis associated with CMV infection.

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