Sclerosing cholangitis rapidly following anti-HIV-1 seroconversion

D E Mercey, C Loveday, R F Miller

Abstract
A 22 year old man developed sclerosing cholangitis within two months of documented HIV-1 seroconversion. Sclerosing cholangitis should be included in the differential diagnosis of causes of abdominal pain and raised alkaline phosphatase enzyme levels in HIV-1 antibody positive patients without established CDC stage IV disease.

Introduction
Biliary tract disease is now recognised as a complication of the acquired immunodeficiency syndrome (AIDS). Although the disease is considered rare there appears to be an association between cytomegalovirus (CMV) and/or cryptosporidial infection and changes of acalculous inflammation of the biliary tract which are indistinguishable from the changes seen in primary sclerosing cholangitis/papillary stenosis. Patients present with abdominal pain, nausea and vomiting and elevated alkaline phosphatase enzymes. This disease has been termed AIDS-related sclerosing cholangitis and as the name applies it usually occurs in patients with established human immunodeficiency virus type 1 (HIV-1) infection. We report a case in whom AIDS-related sclerosing cholangitis developed within two months of seroconversion in the absence of CMV or cryptosporidial infection.

Case report
In June 1988 a 22 year old homosexual Caucasian man presented with a three week history of nausea, sore throat, night sweats and lymphadenopathy. Two days previously he had noticed a rash and on the day of presentation he had developed right-sided facial weakness. There was no history of intravenous drug use, nor of excessive alcohol consumption. On examination he was apyrexial with a widespread desquamating rash and signs of a right lower motor neurone seventh cranial nerve palsy and an incomplete right fifth cranial nerve palsy.

Virological investigation for anti-HIV-1 seroconversion was carried out on serial samples before (4 December 1986), during (20 June 1988) and after (19 July 1988, 1 December 1988) the event using the diagnostic criteria applied in our laboratory to all our regional HIV-1 referral cases (fig 1). Samples were initially tested by a competitive enzyme-linked immunosorbent assay (ELISA: Wellcozyme HIV Recombinant, Wellcome Diagnostics) and confirmed by three further divergent assays: the antiglobulin ELISA (Abbott Laboratories), gelatin particle agglutination (Serodia-HIV, Fujirebio Inc) and western blotting (Dupont Ltd) using manufacturers test protocols.

Serum p24 and reverse transcriptase (RT) were measured using in-house antigen assays.23 The p24 antigen assay consisted of incubating the serum samples overnight at 37°C in microtitre wells coated with purified gammaglobulin fraction of high-titre anti-p24 positive human serum. After washing, wells were incubated with rabbit antiserum to recombinant p24 antigen and bound antiserum was then detected using horseradish peroxidase-conjugated swine anti-rabbit IgG. Tetramethyl benzidine (TMB) was used as a substrate.

The RT antigen assay was based upon the same principle; bound rabbit antiserum was detected using alkaline phosphatase-conjugated goat anti-rabbit IgG and RT was demonstrated using a substrate/amplifier system4 in which the alkaline phosphatase substrate NADP was converted to NAD, which in turn activated a strictly NAD-dependent redox cycle leading to the formation of a coloured product.

In both assays dilutions of standard p24 or RT antigens diluted in normal human serum (NHS) were included in each run and results were expressed in pg/ml for values above a cut-off (3 SD from the mean of the negative: 4 pg/ml in the p24 assay and 15 pg/ml in the RT assay) and showing greater than 50% neutralisation with a reference anti-p24 or anti-RT serum.

The virological results showed the patient to be anti-HIV-1 seronegative on 4 December 1986 and to
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be undergoing seroconversion to anti-HIV-1 seropositive on 20 June 1988 with low level reactivity for anti-HIV-1 in the competitive ELISA and the particle agglutination assay, and having p24 and RT antigens present in the serum (14 pg and 80 pg/ml respectively) with indeterminate western blot and negative antoglobulin ELISA results. Subsequent samples (19 July 1988 and 1 December 1988) confirmed increasing reactivity in all anti-HIV-1 assays and loss of serum antigens.

Liver function tests were mildly deranged with an alkaline phosphatase (AP) of 405 IU/l (normal range 100–280) and an alanine transaminase (ALT) of 59 IU/l (normal range 5–40); bilirubin and albumin remained normal. Other negative or normal investigations included a full blood count, erythrocyte sedimentation rate, syphilis serology, hepatitis A and B serology and serum amylase. A chest radiograph and ultrasound of the abdomen were also normal.

His symptoms and signs spontaneously resolved within a few days. During the ensuing 8 weeks he developed right upper quadrant abdominal pain associated with nausea, vomiting and intermittent diarrhoea. His AP and ALT showed further deterioration (fig 2) and repeat hepatitis serology was negative. Multiple stool cultures were negative for cryptosporidia, ova, cysts and parasites, acid fast bacilli, shigella, salmonella and campylobacter. A repeat ultrasound of the abdomen showed no gall stones but an enlarged liver with reduced echogenicity (consistent with hepatitis) and splenomegaly. A screen for auto-antibodies was negative.

An endoscopic retrograde cholangiopancreatogram (ERCP) was performed and demonstrated normal pancreatic ducts and a dilated common bile duct with irregular and dilated intra-hepatic ducts (fig 3), no gall stones were seen. The papilla appeared reddened and swollen and a sphincterotomy was performed. Duodenal biopsy was normal by light and electron microscopy, with no evidence of infection with cryptosporidia or CMV. Liver biopsy showed mild reactive hepatitis with focal necrosis and a mild chronic inflammatory cell infiltrate of the portal tracts consistent with a pericholangitis. Rectal biopsy showed reactive lymphoid follicles with no evidence of inflammatory bowel disease and no cryptosporidia or CMV infection. Cultures of the liver, duodenal and rectal biopsies were all negative.

Immediately following the ERCP the patient’s pain worsened and this was associated with a further rise in AP and ALT (fig 2). A repeat ultrasound scan showed minimal dilatation and irregularity of the intra-hepatic ducts, findings consistent with oedema at the ampulla following sphincterotomy. The pain and abnormal liver function tests subsequently improved over the next four weeks. A 99mTc-HIDA scan (fig 4) performed two months after the ERCP showed rapid concentration of the radioisotope within the liver, rapid excretion into the biliary tree, but considerable pooling within both the intra- and extra-hepatic tree consistent with sclerosing cholangitis.

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**Figure 1** Serological events before, during and after anti-HIV-1 seroconversion. The solid bar indicates the time when the patient was symptomatic. (1) Western blot test known (+) and negative (−) controls are shown on the left with positions of major HIV-1 proteins indicated. INDET = interpretation indeterminate. Figures in brackets for (2) and (3) are normalised optical densities; the ratio of the test cut-off to the patient signal, <1 = negative (NEG); 1 = equivocal (EQUIV); >1 = positive (POS). (4) The highest dilution of serum producing particle agglutination, for (5) and (6) p24 and RT antigen concentrations in pg/ml of serum with test cut-off values indicated below the negative samples.

**Figure 2** Serial liver function tests in the patient following seroconversion. ERCP = Endoscopic Retrograde Cholangiopancreatography.

**Figure 3** ERCP showing a dilated common bile duct (short arrows) and dilated and irregular intrahepatic ducts (long arrows).
Over the subsequent 24 months the patient has remained well with only a single episode of campylobacter enteritis which resolved with erythromycin. As no specific cause had been found for his sclerosing cholangitis it was thought that this possibly represented symptomatic HIV disease and zidovudine 250 mg qds was commenced in December 1988. He has had no further HIV related diagnoses. His most recent liver function tests are normal, his CD4 count is 480/mm$^3$ and p24 antigen is not detectable.

Discussion

We describe a well documented case of anti-HIV-I seroconversion in a 22 year old homosexual man who developed sclerosing cholangitis within eight weeks. Other more common causes of "cholestatic" liver function tests in HIV positive patients include granulomatous hepatitis, secondary to Mycobacterium tuberculosis or drugs such as ketoconazole or sulphonamides, viral hepatitis and intra-hepatic lymphoma.\textsuperscript{5,6} These alternative diagnoses were excluded in our patient by the negative hepatitis serology, negative drug history and negative liver biopsy together with the ERCP findings.

Primary sclerosing cholangitis is closely associated with inflammatory bowel disease, especially ulcerative colitis\textsuperscript{7} and secondary sclerosing cholangitis follows previous biliary surgery, gall stones, suppurative cholangitis, or pancreaticobiliary malignancy.\textsuperscript{7} All these associations were excluded on the basis of a negative history, negative rectal biopsy and absence of pancreatic or gall bladder pathology at ERCP.

In the context of HIV-1 infection, AIDS-related sclerosing cholangitis often occurs in patients with evidence of opportunistic infection of the bowel and biliary tree with CMV and/or cryptosporidia.\textsuperscript{8} In contrast to primary sclerosing cholangitis abdominal pain and dilation of the common bile duct secondary to papillary stenosis are common presenting features.\textsuperscript{1} The symptoms and biochemical abnormalities reflect incomplete biliary obstruction and oedema, fibrosis and spasm account for the radiographic appearances seen on ERCP.\textsuperscript{19}

This case is unusual in that the changes of AIDS-related sclerosing cholangitis were apparent within two months of documented seroconversion. There are only two previous reports of AIDS-related

Figure 4  $^{99}$Tc-HIDA scan (a) 10 minutes post-injection showing rapid uptake of radioisotope in the liver (b) at 15 minutes there is rapid excretion of radioisotope into the biliary tree and some has reached the small bowel (arrows) (c) by 45 minutes there is considerable hold up and pooling of radioisotope in the common bile duct (large arrow) consistent with sclerosing cholangitis.
Sclerosing cholangitis rapidly following anti-HIV-1 seroconversion

Sclerosing cholangitis occurring in HIV-1 antibody positive patients without CDC stage IV disease. Cello et al reported a 40 year old female intravenous drug user with abdominal pain and raised alkaline phosphatase enzyme levels. At ERCP irregular dilated intra- and extra-hepatic ducts were seen. Roulout reported an HIV-1 positive male with culture negative diarrhoea, weight loss and persistent generalised lymphadenopathy; ERCP showed a dilated common bile duct and intra-hepatic bile duct dilatation with irregular strictures. Changes identical to AIDS-related sclerosing cholangitis have also been reported in patients with immunodeficiency from other cause. It may be that development of sclerosing cholangitis is a non-specific occurrence in immunodeficient patients and may not be associated with a specific opportunistic infection.

Both ultrasound and CT have proved useful, both in looking for dilatation and/or wall thickening of the gall bladder or common bile duct and in excluding other diseases that may have similar presentation such as abdominal lymphoma or Kaposi's sarcoma. In our patient CT was not performed and the first ultrasound investigation was normal, it was only with evidence of increased obstruction secondary to oedema following sphincterotomy that abnormalities of the common bile duct were detected by ultrasound. Recently nuclear medicine techniques have been employed to visualise the biliary tree. Despite an adequate sphincterotomy with relief of symptoms and biochemical improvement the 99mTc-HIDA scan showed evidence of more proximal, persistent biliary tree abnormalities. This is in keeping with the observation that the papillotomy would relieve pain and allow adequate biliary drainage but would not influence the disease course of the sclerosing cholangitis.

In conclusion, this case illustrates that changes of sclerosing cholangitis may occur in individuals who have only recently seroconverted and developed antibodies to HIV-1. Clearly AIDS-related sclerosing cholangitis must now be added to the differential diagnosis of causes of abdominal pain and elevated alkaline phosphatase in HIV positive patients without established CDC stage IV disease.

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