Pancreatic abnormalities and AIDS related sclerosing cholangitis

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Objectives: Biliary tract abnormalities are well recognised in AIDS, most frequently related to opportunistic infection with Cryptosporidium, Microsporidium, and cytomegalovirus. We noted a high frequency of pancreatic abnormalities associated with biliary tract disease. To define these further we reviewed the clinical and radiological features in these patients.

Methods: Notes and radiographs were available from two centres for 83 HIV positive patients who had undergone endoscopic retrograde cholangiopancreatography for the investigation of cholestatic liver function tests or abdominal pain.

Results: 56 patients had AIDS related sclerosing cholangitis (ARSC); 86% of these patients had epigastric or right upper quadrant pain and 52% had hepatomegaly. Of the patients with ARSC, 10 had papillary stenosis alone, 11 had intra- and extrahepatic sclerosing cholangitis alone, and 35 had a combination of the two. Ampullary biopsies performed in 24 patients confirmed an opportunistic infection in 16. In 15 patients, intraluminal polyps were noted on the cholangiogram. Pancreatograms were available in 34 of the 45 patients with papillary stenosis, in which 29 (81%) had associated pancreatic duct dilatation, often with associated features of chronic pancreatitis. In the remaining 27 patients, final diagnoses included drug induced liver disease, acalculous cholecystitis, gall bladder empyema, chronic B virus hepatitis, and alcoholic liver disease.

Conclusion: Pancreatic abnormalities are commonly seen with ARSC and may be responsible for some of the pain not relieved by biliary sphincterotomy. The most frequent radiographic biliary abnormality is papillary stenosis combined with ductal sclerosis.

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Introduction
Investigation of HIV infected patients with right upper quadrant pain and obstructive liver function tests led to the recognition of a syndrome termed AIDS related sclerosing cholangitis (ARSC).1,2 Cells1 classified biliary tract abnormalities in a series of 26 patients with AIDS into four distinct radiographic patterns:

1. papillary stenosis alone, with a common bile duct greater than 8 mm in diameter and distal 2–4 mm tapering of the common bile duct,

2. intrahepatic sclerosing cholangitis alone,

3. sclerosing cholangitis in association with papillary stenosis,

4. long extrahepatic bile duct strictures with or without intrahepatic sclerosing cholangitis.

The most common pattern was sclerosing cholangitis in association with papillary stenosis.1 The majority of these biliary abnormalities are associated with cytomegalovirus (CMV) and Cryptosporidium sp infection.3 All 26 patients in this early series1 were noted to have normal pancreatograms. Furthermore pancreatic abnormalities were not reported in a recent larger series of 45 patients.4

Pancreatic disease in human immunodeficiency virus (HIV) infection can be the result of opportunistic infection, neoplasia, drug toxicity or causes unrelated to AIDS such as alcohol abuse or gallstones.5 The spectrum of disease ranges from asymptomatic necropsy findings6 to acute lethal pancreatitis.7

Opportunistic infection is most commonly caused by CMV,7 with 13% of unselected necropsies having evidence of CMV pancreatic involvement. CMV may cause minimal pancreatic inflammation,4 or acute pancreatitis.8 In only one case has pancreatic infection been noted to be associated with hepatobiliary involvement and ARSC.8

We noted the presence of pancreatic abnormalities at endoscopic retrograde cholangiopancreatography (ERCP) performed for the investigation of cholestatic liver function tests and right upper quadrant pain and therefore performed a retrospective analysis of 83 patients to document the prevalence of such changes.

Patients and methods
The study was based at two specialist referral units providing care for HIV positive patients. The case records, laboratory results, radiological findings, and computerised records of patients presenting with obstructive liver function tests or abdominal pain who underwent ERCP between 1989 and July 1995 were analysed retrospectively. The radiographs were then reviewed blindly.

Results
ERCP was performed in a total of 83 patients with obstructive liver function tests, of which 56 were shown to have ARSC. Of the patients
with ARSC, 48 (86%) experienced epigastric or right upper quadrant pain, 37 (66%) had diarrhoea, 30 (53%) had weight loss of > 4 kg, and 13 (24%) had fever. Hepatomegaly, often tender, was seen in 29 (52%). Three patients were asymptomatic.

RADIOLOGICAL FINDINGS
Ten patients had papillary stenosis alone (type I), 11 patients had intra- and extrahepatic sclerosing cholangitis alone (type II), and 35 had a combination of the two (type III). No patient had the fourth type with a long extrahepatic biliary stricture. In the 45 patients with a dilated common bile duct (types I and III), the main pancreatic duct was opacified in 34 patients and found to be dilated in 29. The normal diameter was taken to be 4 mm in the head, 3 mm in the body, and 2 mm in the tail. In 18 the duct was enlarged greater than 6 mm in diameter associated with irregularities of the main duct and side branches similar to the changes seen in idiopathic or alcohol induced chronic pancreatitis (figs 1 and 2). There were no clinical characteristics specific for this group. One of the patients with type I and 11 of the patients with type III ARSC had polypoid filling defects within the biliary tree (fig 3).

Ampullary or biliary biopsy was successful in obtaining a microbiological diagnosis in 16 of 24 patients where performed: CMV in six, Cryptosporidium in six, CMV and Cryptosporidium in one, and one each demonstrated Microsporidium, Mycobacterium avium intracellulare, or fungi. One patient had ampullary non-Hodgkin’s lymphoma. In this patient the cholangiographic findings regressed on treatment of the lymphoma.

Mean survival for patients with ARSC was 6–8 months (range 2 days to 24 months).

BIOCHEMICAL FINDINGS
There were no significant differences in biochemical indices between any of the patient subgroups (table).

In the 27 patients who did not have ARSC on cholangiography, it can be seen that the biochemical values differed little. Clinical symptoms and signs were also similar with abdominal pain present in 23 (85%), diarrhoea in 10 (38%), weight loss in 12 (45%), hepatomegaly in 17 (63%), and fever in seven (28%). Final diagnoses in this group included hepatic non-Hodgkin’s lymphoma (two), cholecystitis (one), acalculus cholecystitis (two), gall bladder empyema (one), ampullary Kaposi’s sarcoma (one), drug induced liver disease (two), chronic hepatitis B virus induced liver disease (three), choledocholithiasis (one), CMV colitis (one), and alcoholic liver disease. The final diagnosis or reason for the ERCP was unclear in the remainder.
Discussion

This series represents the largest reported of ARSC. It also appears to be the first time that the association of pancreatic abnormalities with ARSC has been described.

In keeping with previous series, the most common form of ARSC was type III—papillary stenosis in association with sclerosing cholangitis. In an earlier series the presence of intraluminal polypoidal filling defects was noted and we noted these in almost a third of cases, particularly in association with type III ARSC. Since the polyps are seen with diffuse, severe biliary inflammation their aetiology may be similar to pseudopolyps found in ulcerative colitis.

Opportunistic infections that most commonly cause ARSC include CMV, Cryptosporidium sp, and less commonly Mycobacterium avium intracellulare and Microsporidium. In addition to these organisms, pancreatic disease in HIV infected patients may also be caused by Cryptosporidium neoformans, Pneumocystis carinii, Toxoplasma gondii, and Mycobacterium tuberculosis. CMV and Cryptosporidium are responsible for 45% of infective causes of pancreatitis. As many patients with ARSC have intestinal infection with cytomegalovirus or Cryptosporidium at the time of diagnosis, it can be postulated that ARSC is a result of either ascending biliary infection for the protozoal infections, or systemic bloodborne infection for CMV and other opportunistic infections. This may explain the common association between ARSC and pancreatic abnormalities, with the organisms able to colonise both the pancreas and biliary tree.

In the same way that infection causes stenosis of the biliary sphincter, we postulate that a similar process affects the pancreatic sphincter causing the ductal dilatation. The pancreatic abnormalities that we have detected may give rise to some of the abdominal pain that is a feature of ARSC and explain why biliary sphincterotomy is not always useful in relieving the pain.

The results of our study support the important diagnostic role of ERCP in patients suspected of having ARSC and support the use of ampullary biopsy for microbiological diagnosis of infective causes. In addition the frequent finding of pancreatic abnormalities suggests an additional mechanism for the pain of the condition.

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