Case reports and review

Cholangitis in the acquired immunodeficiency syndrome: report of two cases and review of the literature

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SUMMARY We report the cases of one patient with the acquired immunodeficiency syndrome as a result of human immunodeficiency virus type 1/lymphadenopathy associated virus type 1/human T-cell lymphotropic virus type III (HIV-1/LAV-1/HTLV-III) infection and of another patient with AIDS related complex caused by human immunodeficiency virus type 2/lymphadenopathy associated virus type 2 (HIV-2/LAV-2) infection, who were suffering from cholangitis. The manifestations and possible mechanisms for cholangitis in these patients and in 10 previously reported similar cases are reviewed.

Case reports

PATIENT 1

On 10 October 1986, a 47 year old woman was admitted to Hôpital Beaujon for liver and biliary tract evaluation. The patient was born in France and had remained there all her life. There was no history of intravenous drug abuse. Past history was remarkable: (a) several operations, requiring transfusions of blood products, for ovarian cysts and uterine fibroma in 1977, 1980, 1982 and 1983; (b) adenocarcinoma of the breast treated by tumourectomy, radiotherapy and antineoplastic agents from May 1984 to April 1985; (c) asymptomatic chronic non-A, non-B viral hepatitis fortuitously found in May 1984 with compatible liver histologic lesions and negative tests for hepatitis B virus infection and tissue autoantibodies; and (d) acquired immunodeficiency syndrome recognised in June 1985 by the following features: *Pneumocystis carinii* pneumonia, cutaneous Kaposi sarcoma, chronic diarrhoea with *Cryptosporidium* in

stools; cutaneous anergy to candidin, phytohaemagglutinin and tuberculin; lymphopenia ($375/\text{mm}^3$) with low T3, T4 and T8 lymphocyte counts (203, 43 and $142/\text{mm}^3$, respectively) and low T4/T8 ratio (0.3). Antibodies to HIV-1/LAV-1/HTLV-III were detected in the patient's sera by Elisa (ELAVIA, Pasteur Diagnostics, Marnes la Coquette, France) and immunoblot analysis (LAV-BLOT), Pasteur Diagnostics). From June to October 1986, several episodes of severe epigastric pain radiating to the left upper quadrant and low grade fever occurred. Urine amylase was repeatedly found to be raised (from two to 20 times the upper limit of normal). Serum alkaline phosphatase and gammaglutamyltranspeptidase were increased to 17 and 55 the upper limit of normal, respectively; serum bilirubin and transaminases were normal. Cytomegalovirus was found in blood in July and September 1986. On admission, the patient appeared severely ill and emaciated. Liver tests were unchanged. Serum lipase was increased to six times the upper limit of normal. Ultrasound and computed tomography showed normal appearance of liver, bile ducts and pancreas. Microscopic examination of a liver specimen taken by percutaneous needle biopsy showed marked portal fibrosis and polymorphous

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Fig. 1 Endoscopic retrograde cholangiogram in patient 1 showing diffuse beadings of intrahepatic bile ducts. Insert shows the irregularities of the margins of the common bile duct.

inflammatory infiltrates with ductular proliferations; interlobular bile ducts were not seen in the portal tracts; there were no granuloma, or intranuclear inclusion suggesting cytomegalovirus infection, no bacteria, fungi or mycobacteria. Endoscopic retrograde cholangiography showed mild irregularities of the margins of the common bile duct which was of normal calibre (Fig. 1); there was diffuse beadings of the intrahepatic bile ducts (Fig. 1); pancreatic duct could not be cannulated. Transhepatic puncture of the gall bladder was done under ultrasound guidance; examination of a sample of bile allowed identification of *Cryptosporidium* oocysts.

PATIENT 2

On 2 April 1986, a 34 year old man was admitted to Hôpital Beaujon for liver and biliary tract evaluation. He was born in Senegal to Guinean parents. He was raised in Senegal in the vicinity of the Guinea-Bissau border, but had been living in France since 1980. He paid frequent visits to Guinea-Bissau when living in Senegal and France. He denied homosexuality or intravenous drug abuse; there was no history of transfusion of blood or blood products. Since September 1984, he complained of permanent watery diarrhoea and of 20 kg weight loss. In February 1986, he was admitted to another hospital for chills, fever and myalgias. There was diffuse

lymphadenopathy. Blood cultures grew *Salmonella typhimurium*. Stool examinations for pathogens were negative. Liver tests gave the following results: serum alkaline phosphatase 1480 U ($N < 130$), gammaglutamyltranspeptidase 1500 U ($N < 40$), aspartate aminotransferase 118 U ($N < 40$), and bilirubin 10 $\mu\text{mol/l}$. Serum hepatitis B surface antigen was present but IgM antibody to hepatitis B core antigen was absent. The patient was treated with intravenous ampicillin and netilmicin for 14 days and became afebrile within five days after initiation of antimicrobial therapy. *Salmonella typhimurium* septicaemia recurred seven days after the end of the first antibiotic course and was treated with intravenous cefoperazone for 21 days with apparent success. The patient was then referred to Hôpital Beaujon for further evaluation.

On admission, the patient was afebrile. Physical examination and liver tests were unchanged. Peripheral blood cell counts were normal. Ultrasound examination disclosed a dilated (12 mm) and thick walled (5 mm) common bile duct with normal gall bladder. Endoscopic retrograde cholangiography (Fig. 2) showed involvement of both intra- and extrahepatic bile ducts: the duodenal papilla was wide open. The common bile duct was dilated with markedly irregular margins and the intrahepatic bile ducts were affected by focal dilatations and diffuse

Fig. 2 Endoscopic retrograde cholangiogram in patient 2 showing a dilated common bile duct with irregular margins but no stenosis. The intrahepatic bile ducts show focal dilations and diffuse stricturing.

stricturing. Examination and cultures of a sample of bile and of a specimen of mucosa obtained through endoscopic cannulation of the bile duct showed no bacteria, mycobacteria, fungi, or parasites. Specimens of bile duct mucosa were obtained using endoscopic forceps introduced through the duodenal papilla. Histological examination of these specimens (Fig. 3) showed minute erosions of the mucosal lining covered with fibrin and polymorphonuclear exudates. The most striking lesions were seen in the submucosa. There was marked oedema and inflammatory infiltrates consisting of round and polymorphonuclear cells. There was no abscess, granuloma, or intranuclear inclusion suggesting cytomegalovirus infection. Stains for bacteria, fungi and mycobacteria were all negative. Examination of a hepatic specimen obtained by percutaneous needle biopsy (Fig. 4) showed a normal architecture; connective tissue of the portal areas was moderately increased. A few interlobular bile ducts were circumscribed by concentric layers of fibrous tissue, with degenerative epithelial changes and periductular mononuclear cell

infiltrates. A few granuloma consisting of epithelioid and lymphocytic cells were present in the lobules. Endoscopic examination of rectum and colon was normal and specimens of rectal and colonic mucosa were histologically normal.

Serum IgG concentration was high (2660 mg/100 ml). Blood lymphocyte subpopulations counts revealed T3 1899/mm³; T4 297/mm³, T8 1721/mm³; T4/T8 ratio was 0.19. The cutaneous responses to stimulation with multiple skin test antigens (tuberculin, candidin, tetanus, diphtheria, trichophyton) were depressed.

No antibody to HIV-1/LAV-1/HTLV-III could be detected in the patient's sera by Elisa (ELAVIA, Pasteur Diagnostics, France). By immunoblot analysis (LAV-BLOT, Pasteur Diagnostics) sera showed only weak reactivity with protein p34. Radioimmunoprecipitation assay (RIPA) using ³⁵S cystein labelled HIV-1/LAV-1/HTLV-III confirmed the precipitation of only the p34 and no antibody to the gp110, the major envelope glycoprotein of HIV-1/LAV-1/HTLV-III, could be shown by Western Blot (WB) and RIPA.

For isolation of retrovirus the peripheral T-lymphocytes of the patient were cultured as previously described.^{3,4} The reverse transcriptase activity in the supernatant was detectable after 12 days of culture; maximum activity was 15 × 10⁴ cpm which decreased after. Concurrently, a typical cytopathic effect appeared in the infected T-lymphocyte with multinucleated giant cells and cell lysis. The viral RNA from this isolate did not hybridise in stringent conditions with any HIV-1/LAV-1/HTLV-III probe.

Antibodies to HIV-2/LAV-2 were shown in the patient's sera. The immunofluorescence assay conducted with HIV-2/LAV-2 infected MOLT cells showed a very strong fluorescence of the syncytia. Radioimmunoprecipitation using ³⁵S-cystein labelled HIV-2/LAV-2 cultivated on T4-enriched CEM cell line showed precipitation by the patient's sera of the major envelope glycoprotein, gp 140. The sera was not reactive with p26, the major gag protein of HIV-2/LAV-2.

Discussion

Patient 1 was suffering from AIDS as a result of infection with HIV-1/LAV-1/HTLV-III. Patient 2 was afflicted with ARC as documented by the following findings: chronic diarrhoea, marked weight loss, persistent diffuse lymphadenopathy, cutaneous anergy, low T4 lymphocyte level with decreased T4/T8 ratio,^{5,6} and relapsing *Salmonella typhimurium* bacteraemia despite appropriate antibiotic treatment.^{7,8} The ARC was not caused by HIV-1/LAV-1/HTLV-III. Analysis of the patient's serum

Fig. 3 Biopsy specimen of the common bile duct in patient 2. Submucosa is involved by a marked inflammatory infiltrate with numerous polymuclear cells (arrows). (H&E)

with ELISA, Western Blot and RIPA failed to show antibodies to HIV-1/LAV-1/HTLV-III. Infection with a recently identified viral agent, HIV-2/LAV-2, was shown by detection of antibodies to HIV-2/LAV-2 in the patient's serum and by isolation of the virus on the peripheral blood lymphocytes. As in the majority of HIV-1/LAV-1/HTLV-III infections in Africa, the risk factors recognised in Europe and North America were absent in our patient. He was not a homosexual or a drug addict. Moreover, he had been living in Senegal, an area where HIV-1/LAV-1/HTLV-III infection is not endemic. In contrast, LAV-2 was originally identified in AIDS patients from Guinea-Bissau,³ which is the native country of our patient's parents and one which he visited repeatedly.

A remarkable association to AIDS or ARC in our patients was cholangitis. A few similar cases of cholangitis affecting AIDS patients have been recently reported,⁹⁻¹⁵ the main characteristics of which are presented in Table 1. The features of cholangitis associated to ARC or AIDS can be summarised as follows: (a) in the majority of the cases, manifestations of acute symptomatic acalculous cholecystitis led to the recognition of the

asymptomatic cholangitis; (b) the most common abnormality of liver tests was a marked increase in serum alkaline phosphatase; (c) involvement of intrahepatic bile ducts was indistinguishable from that seen in primary sclerosing cholangitis; (d) involvement of the common bile duct was distinct from that seen in primary sclerosing cholangitis and consisted of dilatation with or without stenosis and markedly irregular margins of the duct; (e) liver histology was non-diagnostic; (f) microscopic examination of the wall of the bile ducts and gall bladder usually showed superficial ulcerations, covered with purulent exudates, and subepithelial oedema.

The prevalence of cholangitis in AIDS or ARC patients, although admittedly low, may well be currently underestimated because the condition is usually asymptomatic or associated with non-specific changes in liver tests and liver histology. In a series of nine unselected patients with AIDS, necropsy showed unexplained dilatation of the common bile duct in two of three patients with high alkaline phosphatases.^{15a} Cholangitis must therefore be added to the list of the multiple conditions associated with abnormal liver tests in AIDS patients.¹⁶⁻¹⁹

The cause of cholangitis in our patients as in

Fig. 4 Needle biopsy specimen of the liver in patient 2 showing a bile duct circumscribed by concentric fibrosis (arrows) in a small portal tract. (H&E)

previously reported cases is uncertain. Various infectious agents were identified in bile or in the wall of the gall bladder or bile ducts, and, therefore, might be implicated. As shown in Table 2, cytomegalovirus and *Cryptosporidium* were the most commonly reported species. *Candida albicans* was also reported in few instances of cholangitis^{14 15 20} and cholecystitis^{14 15} affecting patients with AIDS^{14 15} or other forms of immunodeficiency.²⁰ *Cryptococcus neoformans* cholangitis has been described in patients without AIDS.²¹ Surprisingly, *Cryptococcus neoformans* has not been reported hitherto in association with cholangitis in AIDS patients in whom this agent causes a variety of opportunistic infections.²² In patient 2, none of the above mentioned infectious agents could be identified in bile or in a specimen of bile duct mucosa. Therefore, the role of *Salmonella typhimurium* which was isolated from blood in several occasions in this patient may be envisaged to account for cholangitis.

As there are similarities between primary sclerosing cholangitis and AIDS related cholangitis, both conditions might share common aetiological factors. This view is reinforced by several reports of 'primary' sclerosing cholangitis affecting patients with various

forms of underlying immunodeficiency.²⁴⁻²⁸ Indeed, several abnormalities of the immune system have been identified in patients with primary sclerosing cholangitis.²⁹⁻³³ Differences between primary sclerosing cholangitis and AIDS are obvious. In particular, in patients with primary sclerosing cholangitis, the inflammatory cell infiltrates surrounding diseased bile ducts have been found to be rich in T4 lymphocytes,³³ the subpopulation specifically depleted in AIDS patients.

Patient 1 was afflicted with mild chronic pancreatitis as evidenced by recurrent bouts of epigastric pain radiating to the left upper quadrant and by a persistent rise in pancreatic enzymes. We are not aware of any previous report of such a clinical presentation in AIDS patients. Asymptomatic dilatation of the pancreatic duct, however, was noted in a patient with AIDS associated cholangitis.¹⁵ Factors similar to those envisaged in AIDS associated cholangitis might be implicated in our patient's pancreatitis: cytomegalovirus inclusions have been observed in pancreatic acinar cells in AIDS patients¹¹; *Cryptosporidium* in Rhesus monkey has been identified in close vicinity to pancreatic duct lesions.¹⁴ Non-infectious mechanisms might also explain simul-

Table 1 Summary of clinical, radiological and pathological findings in 12 patients with AIDS or ARC and cholangitis

Reference (patient's number)	Clinical manifestations	Serum alkaline phosphatase (xN)	Extra hepatic bile ducts	Intrahepatic bile ducts	Gall bladder	Liver
9 (patient 1)	Right upper quadrant pain, fever, jaundice hepatomegaly	9.5	Dilated with stenosis of the papilla of Vater (ERCP)	NS	Chronically inflamed (cholecystectomy)	Portal triaditis
10 (patient 2)	Abdominal pain, fever, jaundice, hepatomegaly	10.5	Dilated with stenosis of the papilla of Vater (ERCP)	NS	NS	Portal triaditis
11	Fever	7	No gall stone, no stricture (necropsy)	Radiological evidence of dilatation. Dilated; with connective tissue surrounding such ducts thickened and swollen but with minimal inflammatory infiltrates (necropsy)	NS	Normal histology
12	Abdominal pain, fever	95 IU/l	Normal calibre (laparotomy)	NS	Acute gangrenous cholecystitis (US). Mucosal surface flattened and extensively ulcerated (cholecystectomy)	Normal histology
13 (patient 1)	Right upper quadrant pain, Murphy's sign, fever	NS	Severe necrotising cholangitis (necropsy)	Severe necrotising cholangitis (necropsy)	Extensive mucosal necrosis, mucopurulent exudate, no stone (cholecystectomy)	NS
13 (patient 2)	Right upper quadrant pain, Murphy's sign, fever	NS	Dilated (CT)	Dilated (CT)	Haemorrhagic mucosa; ulcers covered by grey-brown exudate, extensive necrotising inflammation (cholecystectomy)	Focal hepatocellular necrosis
14	Right upper quadrant pain, fever	6	Focal irregular dilatations (PTC)	Diffuse stricturing with focal dilatations (PTC)	Stones, thickening due to marked chronic inflammation (cholecystectomy)	Non-specific periportal inflammation
15 (patient 1)	Right upper quadrant pain, fever, jaundice	NS	Dilated up to the level of the ampulla; tapered narrowing of the distal common bile duct with partial obstruction (US, CT, PTC)	NS	No stone, chronic and acute acalculous cholecystitis (cholecystectomy)	NS
	2 weeks later	NS	Serrated common bile duct, normal ampulla (ERCP)	Markedly ectatic (ERCP)		NS
	2 months later	8.5	Coarsely serrated irregularities (ERCP)	Pronounced beadings (ERCP)		Mild cholestasis
15 (patient 2)	Right upper quadrant pain, fever	7.5	Dilated, totally obstructed at the level of the ampulla (laparotomy). Marked ductal wall irregularities and narrowing at the level of the bifurcation of the right and left hepatic ducts (T-tube cholangiogram)	Dilated (US, CT)	No stone, acute and chronic inflammation, oedema, focal epithelial necrosis (cholecystectomy)	Mild chronic portal inflammation, with slight portal fibrosis and cholestasis
15 (patient 3)	Fever	29	Dilated (CT). Distal common bile duct narrowed by some scalloping of the walls in an incomplete rosary head type of configuration (ERCP). Oedematous and dilated throughout with probe patient ampulla of Vater (necropsy) Mild irregularities of the wall	Slightly dilated, focal narrowing of one right Branch (ERCP). Several ulcers covered by fibrous material (necropsy)	Several ulcers covered by fibrous material (necropsy)	NS
Our patient 1	Epigastric pain radiating to the left upper quadrant, fever	17		Focal dilatations and stricturing (ERCP)		Marked portal fibrosis and ductular proliferation. Mild portal inflammatory cell infiltrates. No interlobular bile duct
Our patient 2	Asymptomatic	11	Dilated with markedly irregular margin. Normal ampulla (ERCP). Minute erosions covered with fibrin, oedema, inflammatory cell infiltrates (biopsy)	Focal dilatations and diffuse stricturing (ERCP)		Fibrous layers concentric to bile ducts with epithelial changes and inflammatory cell infiltrates. Lobular granulomas

CT: computed tomography; ERCP: endoscopic retrograde cholangiopancreatography; PTC: percutaneous transhepatic cholangiography; US: ultrasound; NS: not specified.

Table 2 Results of microbiological studies in 11 patients with AIDS or ARC and cholecystitis or cholangitis*

Reference (patient's number)	Infectious agent	Site of identification
9 (patient 1)	Cryptosporidium	Stools, gall bladder wall, stomach, colon, appendix
10 (patient 1)	Cryptosporidium	Stools, bile, colon
11	Cytomegalovirus	Endothelial cells of periductal capillaries, arterioles and venules; degenerative bile duct epithelial cells; endothelial cells of submucosa of gall bladder; duodenum; colon; pancreatic acinar cells
12	Cytomegalovirus	Stools, gall bladder wall and content, stomach, liver
	Cryptosporidium	Stools, gall bladder wall and content, stomach
	<i>Klebsiella pneumoniae</i>	Gall bladder content
	<i>Pseudomonas aeruginosa</i>	Gall bladder content
13 (patient 1)	Cytomegalovirus	Mesenchymal endothelial and epithelial cells of the gall bladder, connective tissue and lumen of common duct and major intrahepatic ducts
13 (patient 2)	Cytomegalovirus	Endothelial and epithelial cells of gall bladder wall
	<i>Candida albicans</i>	Pseudohyphi infiltrating the gall bladder wall
14	Cryptosporidium	Stools, gall bladder epithelial cells
	<i>Candida albicans</i>	Bile
	<i>Klebsiella pneumoniae</i>	Bile
15 (patient 1)	Cryptosporidium	Stools, bile, gall bladder wall
	Enteric bacteria	Bile
15 (patient 2)	Cryptosporidium	Stools, gall bladder epithelium
	Cytomegalovirus	Ampulla of Vater
15 (patient 3)	Cytomegalovirus	Epithelium, lamina propria and muscularis of bile ducts and gall bladder
Our patient 1	Cryptosporidium	Gall bladder content

*In our patient 2, no infectious agent could be identified in bile, or walls of the bile ducts.

taneous disease of bile and pancreatic ducts as involvement of pancreas and/or pancreatic ducts has been known to occur in primary biliary cirrhosis^{35 36} and primary sclerosing cholangitis.³⁷⁻³⁹

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