

Leading article

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There are a number of urgent problems facing gastroenterologists in relationship to the epidemic caused by the human immunodeficiency virus (HIV). First, an assessment of the scale of the problem; second, the recognition and treatment of gut related HIV problems and third, the impact that HIV infection has on endoscopic techniques.

The epidemic of HIV disease in the United Kingdom at present is patchy and most gastroenterologists have not yet seen their first case. Over the next few years it is likely that we shall all see large numbers of such patients and will need to give advice not just on the gastroenterological complications, but also on general medical manifestations and on the changes in lifestyle necessary to improve health and reduce the risks of cross infection. Although HIV disease has produced a global pandemic of tragic proportions, it is also a fascinating condition offering potential insights into a range of gut disease, including the influence of gut immunity on infection, the subtle interplay of host resistance and virulence of organisms and the mechanism and production of diarrhoea and weight loss. These fundamental problems have not yet been addressed and remain a rewarding area for research.

Background

After the first reports of the acquired immunodeficiency syndrome (AIDS) in 1981 among homosexuals in San Francisco,¹ an infectious aetiology was suspected, because other groups at no obvious risk were infected after blood transfusion and sexual and vertical transmission was demonstrated. The first description of the AIDS virus (HIV) in 1983² was followed by its more thorough classification in 1984 and confirmation of its aetiological importance by culturing the virus from a significant proportion of AIDS sufferers. Human immunodeficiency virus is known to infect cells displaying the T4 antigen on their surface (helper cells and macrophages) and produces a profound immune deficit by lysis of cells and by functional inhibition.³ B-cells and monocytes are non-specifically activated, but are unable to respond appropriately when presented with new antigens.

The origin of the virus remains unknown. It bears closest similarities to the retrolente viruses of the visna group and no close similarity to any known primate virus. A more recently discovered virus (HIV2) which can also produce AIDS found predominantly in West Africa, is closely related to simian immune deficiency virus (SIV).⁴ Although initial work seemed to indicate an origin in Africa: the earliest evidence of HIV sero-positivity was found there, doubt has now been cast on this concept, because of the difficulty of interpreting HIV antibody testing in Africans who have notoriously 'sticky' serum.

The discovery of the virus led rapidly to the development of antibody tests which have a remarkably high specificity and sensitivity. A much wider range of people are infected with the virus than those who have opportunistic infections or unusual tumours (Kaposi's sarcoma), allowing a diagnosis of AIDS to be made. Although the original definition of AIDS has been robust in epidemiological terms, it has led to too much emphasis on the terminal phases of this illness. Perhaps 100 times as many people are infected with the virus and a proportion of these are seriously ill (ARC/AIDS related complex).

Antibody studies have also produced a much clearer understanding of viral transmission. The main routes of spread are undoubtedly sexual and parenteral; there is no evidence for casual contagion, or a marked risk amongst health care workers.⁵ Of over 1000 patients suffering needlestick injuries, only four have seroconverted. Recent reports indicated three patients in whom massive skin exposure to blood may have been responsible for seroconversion, but this is not a common mode of spread.⁶ How far general medical and surgical procedures should be adapted to cater for this minor risk is a moot point.

In the United Kingdom and most of the Western world the predominant groups of infected patients at present are homosexuals, or drug addicts. A major outbreak of HIV disease in heterosexuals is awaited, but plotting its development and impact on healthcare is at present hampered by controversy surrounding the widespread testing of well individuals.

Gastroenterological problems

A wide range of infections which are venereally acquired by homosexuals whether HIV antibody positive or not, has been well reviewed recently and emphasises the need to be aware of the sexual preferences of any patients presenting with colonic pathology.⁷ Approximately 50% of the patients infected with HIV present with gastrointestinal abnormalities and they virtually all develop gut complications during the course of the disease.

The mouth

Candidiasis is a very common manifestation of immune deficiency and over 50% of HIV antibody positive patients with oral infection will develop full blown AIDS within two years.⁸ Some patients do respond to local nystatin or amphotericin, but in most ketoconazole is needed for complete eradication; the relapse rate is high. Fortunately hepatotoxicity with ketoconazole, which is mainly confined to middle aged women, has not been described in this group of patients.⁹

Hairy leucoplakia which is unique to HIV infection and may be found anywhere in the mouth, but has a predilection for the side of the tongue, is also a stronger predictor of AIDS, as 80% will have developed the full syndrome within one year.¹⁰ The condition is usually asymptomatic, rarely requires treatment and is not usually biopsied as the appearances are so typical.

Kaposi's sarcoma of the palate is common and indicative of more widespread involvement of the gut in three quarters of the patients.¹¹

Aphthous ulceration of the mouth is common in HIV patients, although

no prevalence studies are available. Thalidomide has been successfully used to treat the buccal ulceration of Bechets disease and equally satisfactory results have been obtained in HIV positive patients.¹² Dental problems are also common in HIV infected patients with gum retraction, gingivitis and dental abscesses.¹³

Weight loss

Loss of more than 10% of ideal body weight is present in about half AIDS patients at presentation and occurs in most during the illness. At the time AIDS was first recognised in Africa, 'slim disease' also appeared in Uganda. This condition, with massive weight loss and diarrhoea, is undoubtedly caused by the HIV and often associated with an opportunist infection, such as cryptosporidium.¹⁴ The impact of weight loss is likely to be severe, but the importance of trace element deficiency remains to be worked out.

The cause of weight loss is often obscure. Gut infection leading to anorexia is common, and half the patients have accompanying diarrhoea. The importance of malabsorption is uncertain. Abnormalities of small intestine mucosa do occur, and are occasionally severe¹⁵ but usually the changes are mild and non-specific.¹⁶ Although abnormalities of carbohydrate and fat absorption are common, they may not be severe enough to account for weight loss. Although malabsorption is easy to document, in our experience and that of others, it is usually secondary to infection with CMV, cryptosporidium, or mycobacterium avium intracellulare (MAI).¹⁷ Mycobacterium avium intracellulare infection of the small bowel may produce foamy macrophages, similar to those in Whipple's disease, at the tips of the villi.¹⁸ The association of pigmentation and lymphadenopathy may strengthen this erroneous diagnosis.

The importance of direct HIV infection of the gut producing weight loss is unknown. Although widespread inflammation of the whole GI tract in AIDS can be shown histologically in those with, or without gut symptoms, HIV infection of epithelial cells of the gut mucosa has not been demonstrated. Success with DNA hybridisation has recently been achieved, with localisation of HIV infection in Paneth cells.¹⁹ It would not be surprising to find HIV in T lymphocytes and macrophages within the mucosa, but this is the first demonstration of infection of cell types which did not have the surface T4 antigen. Paneth cells originate from neural crest tissue and controversy continues as to which cells in the brain are capable of being infected by HIV. It remains to be seen whether HIV infection is commonplace in the gut, is found in association with other infection, or is present predominantly in those patients with no other cause for weight loss or diarrhoea.

Oesophageal symptoms

Dysphagia or pain on swallowing (oesophagodynia) is the presenting feature of AIDS in some 10% of patients; it develops during the course of the illness in a further 20%. The most common cause is candidiasis, which is included within the CDC definition of AIDS and is virtually always associated with buccal infection. Occasionally oesophageal candidiasis has been described in asymptomatic individuals, but this is unusual.²⁰ Treatment with

ketoconazole is rapidly successful, with frequent relapse after drug withdrawal. In our experience candida oesophagitis carries a grave prognosis, with an average survival of only five months.

Other causes of dysphagia are associated with oesophageal ulceration. The appearance of CMV which produces linear ulcers, herpes producing small vesicles and aphthous ulcers with superficial spreading ulceration are all different. Histological confirmation may be difficult, because of small oesophageal biopsy samples. This is a particular problem with CMV infection, where the normal antibody responses may not occur in AIDS patients, and where a high proportion of homosexuals carry CMV virus in body tissues without evidence of disease. Thus treatment of CMV may need to start empirically. It is now possible with two experimental agents: phosphonformate, a pyrophosphate analogue, and ganciclovir, a guanine derivate similar to acyclovir. Both have been used successfully for the treatment of CMV infection after bone marrow and renal transplantation, and have also been used extensively in AIDS, although controlled trials are lacking.²² These agents appear effective in the treatment of CMV retinitis and CMV ulceration of the gullet.

Herpetic infection of the oesophagus is uncommon and always associated with peri oral or buccal ulceration. Although islands of inflamed mucosa are described in herpetic oesophagitis, in our experience vesicles similar to those on the skin are common. As with other extensive herpetic infections, intravenous acyclovir treatment is probably required, although subsequent oral treatment is sufficient to maintain remission.

Aphthous ulceration of the gullet also produces painful dysphagia and may respond to treatment with thalidomide.

Diarrhoea

Most HIV antibody positive patients with diarrhoea have an infective cause, particularly if they have full blown AIDS. The numbers with no infective cause are greater in third world countries with poor laboratory facilities, and in patients with ARC. If patients with diarrhoea are repeatedly re-investigated, a potential infectious agent often emerges. There are a small core of patients without an apparent pathogen, and it remains to be determined whether in this group malabsorption is important, HIV infection of the gut itself is the cause, or there is another, as yet undescribed infecting agent.

Cryptosporidiosis

This agent was first shown to produce diarrhoea in man in 1976²³ and has since emerged as a common cause of travellers diarrhoea.²⁴ It is the most frequent pathogen in HIV antibody positive patients with diarrhoea and the diagnosis of AIDS is confirmed, if the infection lasts for longer than three weeks. Cryptosporidium infection often produces a high volume watery stool, but the mechanism is unknown. Stool volumes of up to 24 l a day are described, but more commonly 2–3 l a day are passed.²⁵ The protozoan appears to be attached to the mucosa and may be surrounded by a host cell membrane, but there is no evidence of invasion or tissue reaction. Abdominal pain is rare; vomiting occurs in the terminal phase.

Uncommonly right upper quadrant pain and vomiting does occur, often associated with a very high alkaline phosphatase. In these patients endoscopic retrograde pancreatography may show ampullary stenosis and changes of sclerosing cholangitis with thickening of the gall bladder wall. Cryptosporidia may be found attached to the biliary epithelium in these patients, often in association with CMV infection.

The diagnosis of cryptosporidiosis is most efficiently made by a stool flotation method with subsequent staining by a modified Ziehl-Neelsen technique which shows the spores.²⁶ Although the various forms in the life cycle may be observed by light microscopy within the brush border of the rectal mucosa and occasionally on duodenal biopsies, rectal histology has a low sensitivity for the diagnosis. Cryptosporidium is a zoonosis, although human to human transmission has been described. As all phases of the life cycle are observed in the human host, auto-reinfection may also occur.²⁷

Treatment consisting of fluid replacement and simple antidiarrhoeal agents is worthwhile, as many patients live a year or more after diagnosis. Macrolide antibiotics like erythromycin, spiramycin and clindamycin will reduce the load of cryptosporidia in the gut and may produce transient improvement in stool volume, but eradication of the organism is not possible. Azidothymidine will often produce dramatic improvement in diarrhoea and with this drug the organisms may no longer be found in the stool.²⁸

Isosporidia infection

Isospora belli is a coccidian parasite very similar to cryptosporidium, but the oocyst seen in the stools is much larger at 20–30 μm (cf 2–5 μm). It produces attacks of diarrhoea in institutions and is endemic in South America. Human immunodeficiency virus antibody positive and negative homosexuals have diarrhoea associated with this organism with very similar symptoms to cryptosporidium, except that the condition responds to treatment with cotrimoxazole or metronidazole.

Herpes

Herpes simplex virus may cause diarrhoea usually by extension from perianal infection. This usually produces proctitic low volume stools,²⁹ but occasionally the inflammation extends a considerable distance up the bowel producing higher volume stools. Treatment with intravenous acyclovir usually produces prompt resolution of the symptoms.

Cytomegalovirus infection

Cytomegalovirus may infect the liver, eyes, lung, brain or the bowel. About 10% of AIDS patients with diarrhoea have CMV colitis.³⁰ They are often febrile, wasted, generally look unwell and may have rebound abdominal tenderness. Ulceration of the large bowel may mimic Crohn's disease, or produce fine ulceration with radiographic changes similar to ulcerative colitis.³¹ The difficulty in diagnosing CMV colitis is less than in oesophagitis, as biopsies are bigger. Vasculitis may be associated with CMV infection and perforation may occur. As with other infections of the colon toxic dilation

also occurs, but may resolve spontaneously without surgical intervention. In our experience ganciclovir appears to be more effective than phosphonformate in treating the diarrhoea induced by CMV, but this infection tends to occur late in the time course of AIDS and is associated with a poor ultimate prognosis.

Mycobacterium avium intracellulare

Virtually 100% of necropsies of patients with AIDS show these organisms within the body, but with little tissue reaction and their importance remains uncertain. MAI may cause fever and anaemia associated with an abnormal bone marrow,³² and in 5% of AIDS patients with diarrhoea the organism is cultured from the stool and occasionally seen in rectal biopsy samples.³³ Although MAI is sensitive *in vitro* to a range of new antituberculous drugs including amikacin and ceftazidime³³ responses *in vivo* have been very disappointing and thus the acid test of a response in stool volumes to an effective therapy is unavailable to determine if MAI is pathogenic in this situation.

Microsporidia

There are a few case reports of microsporidia causing diarrhoea in AIDS, particularly from Holland. Although these organisms have not been encountered in the United Kingdom they are difficult to diagnose by light microscopy.¹⁷ It is unlikely that they are a major cause of diarrhoea.

Bacteriological and non-opportunistic protozoal infections

Salmonella typhi may produce a very serious illness in AIDS patients and may require long term treatment, but is uncommon. *Salmonella typhi murium* an intracellular organism, produces a devastating systemic infection in AIDS patients, who lack a cellular immune response.³⁴ Shigella is also venereally transmitted in homosexuals and may produce a pseudo-membranous colitis appearance of the rectal mucosa. Giardia is common in homosexuals and in AIDS patients can produce discrete ulceration of the colon. In view of the difficulties of confirming a diagnosis a course of metronidazole would seem sensible at the outset of a diarrhoeal illness. Campylobacter like organisms are often seen in stools of AIDS patients,³⁵ but whether they are pathogenic is uncertain. Although various species of amoeba are commonly encountered in AIDS patients, their pathogenicity is in doubt, because of the types of amoeba identified by zymodene analysis and because of lack of responsiveness to appropriate therapy.³⁶

Kaposi's sarcoma

Kaposi's sarcoma (KS) is an unusual neoplasm which is thought not to metastasise, but to represent a field change in the blood vessel endothelium, perhaps partly induced by a venereally transmitted coinfection such as CMV. Immune suppression is also important in its genesis and the tumour may regress if the immune system recovers. Although KS may produce protein losing enteropathy, diarrhoea, severe bleeding or perforation,

involvement of the gut is more often asymptomatic.¹¹ The prognosis of KS which is closely related to visceral involvement, is less than six months with gut KS, compared with two years when the only skin is involved. Although classical KS is an indolent tumour sensitive to both chemotherapy and radiotherapy, the treatment of AIDS related disease is controversial, as further immunosuppression is associated with rapid development of opportunistic infection and no trial has shown prolongation of survival.

Endoscopy and radiology

Although the appearances of candidiasis of the gullet are characteristic radiologically, barium swallow will be normal in at least half the patients. Ulceration in the gullet produced by various opportunists is only seen in about half the radiographs undertaken. Although endoscopy is valuable in confirming the diagnosis, this can often be inferred from other physical signs, as virtually all the patients with candidiasis, herpetic ulceration or Kaposi's sarcoma will have buccal involvement, and half the cases of CMV will have evidence of infection elsewhere.

In our experience with patients with diarrhoea, rectal biopsy, repeated stool cultures and sigmoidoscopy diagnose virtually all the causes of diarrhoea and little additional information is gained by colonoscopy or barium enema. Abnormalities in most patients with CMV colitis or Kaposi's sarcoma are visible at sigmoidoscopy and in the majority of other patients with diarrhoea barium enema or colonoscopy is normal. Endoscopy involves a potential risk to health care workers and potential transmission of virus from one patient to another. The risks to health care workers are low, but protective clothing, gloves and a mask should be worn. Aerosol transmission of HIV virus has not been demonstrated, but as other viruses do gain access through the eye, the wearing of goggles is also recommended.

To prevent transmission of HIV from patient to patient adequate disinfection of the endoscope is needed. Although the virus is delicate and withstands heat and detergents very poorly, it may live for long periods when frozen or dried.³⁷ The most important part of any disinfection process is thorough washing. After this, a four minute immersion in 2% gluteraldehyde, or two minutes in a quaternary ammonium chloride (Dettol) followed by four minutes in 70% alcohol is sufficient to kill HIV. It should be noted that although these recommendations are not in line with present Department of Health policy, they are contained within the recent British Society of Gastroenterology guide lines.³⁸

Two tier procedures with different precautions used in known risk patients are not recommended by microbiologists. This is particularly true in HIV infection, where the most infectious patients (well carriers), are often unsuspected.³⁹ An ideal method of conducting an endoscopy list is to use two totally immerseable scopes with an automatic washing machine. Such an approach has enormous cost implications if adopted throughout the country, and at present the HIV prevalence rate in most communities is extremely low.

Another problem with endoscopy procedures is the potential transmission of opportunistic infection from one immunosuppressed patient to another. This may be a particular problem with cryptosporidium, but because there is no animal model of infection the risks are unknown.⁴⁰

Sporulating organisms need a much longer period of immersion in disinfectant for eradication. Thus it is recommended that a known immunosuppressed patient is placed at the end of a routine endoscopy list and following this the instrument should be immersed for three hours in glutaraldehyde.

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