CASE REPORT

Concomitant AIDS cholangiopathy and Fanconi syndrome as complications of HIV in a single patient

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SUMMARY

We describe the case of a 50-year-old woman presenting to our acute medicine department with generalised non-specific symptoms on a background of HIV managed on triple therapy (tenofovir, lamivudine and zidovudine). On admission, she was noted to be acidotic with proteinuria, glycosuria, hypophosphataemia and generalised body pain, and was diagnosed with Fanconi's renotubular syndrome secondary to tenofovir. It was also noted that she had elevated liver dysfunction markers, and an MRI of the liver revealed a focal stricture near the ampulla of Vater, resulting in a diagnosis of AIDS cholangiopathy. These two diagnoses are rare complications of HIV, and the presence of both these pathologies in a single patient has never been reported in the literature before, and we therefore believe that this case is the first of its kind.

BACKGROUND

While clinicians often seek all-encompassing diagnoses, this case shows the importance of following the clinical picture and multidisciplinary collaboration, with successful management to the point of discharge only achievable through the input of acute medicine, genitourinary medicine, renal medicine and gastroenterology specialists. We hope that increased awareness about both these rare conditions, their diagnosis and management will lead to their earlier diagnosis and more comprehensive management, when they present separately or, as in our case, together.

CASE PRESENTATION

A 50-year-old woman with a background of HIV on highly active antiretroviral therapy (HAART)

presented, on return from a trip to Uganda, with a 6-month history of generalised body and joint pain leading to decreased mobility. This was associated with significant unintentional weight loss. Of note, she reported no fever. Full examination was unremarkable and her vital signs were all within normal limits. Urine dipstick was positive for protein, glucose and ketones. Her arterial blood gas showed metabolic acidosis. Review of her medical history showed that at time of HIV diagnosis 2 years previously, her baseline viral load was 1410 and her CD4 count was 37. She had been started on tenofovir, lamivudine and zidovudine, with a more recent CD4 count of 104 and undetectable viral load. She had previously been treated for pulmonary tuberculosis at time of HIV diagnosis.

INVESTIGATIONS

Routine haematological indices were unremarkable and malaria screen showed no malaria parasites, while the renal profile revealed a creatinine level of $150\mu\text{mol/L}$, associated with serum urea of 7.9mmol/L and a phosphate level of 0.43 . Albumin, calcium and magnesium were within normal limits. Further to this, an albumin:creatinine ratio was done, which was high at 21.6, as well as a urine protein:creatinine ratio, which was also high at 118.9. MRI of the renal tract showed no abnormalities.

In light of the metabolic acidosis, proteinuria, glycosuria, hypophosphataemia and generalised body pain, a diagnosis of Fanconi's renotubular syndrome was made, thought, most likely, to be secondary to tenofovir.

Furthermore, her liver profile showed a raised alkaline phosphatase (ALP) ($349\mu\text{L}$) and gamma glutaryltransferase ($72\mu\text{L}$). Alanine Transaminase (ALT) and bilirubin were within normal limits. Liver autoimmune and viral screens were performed, being unremarkable with the exception of the presence of hepatitis A total antibody and cytomegalovirus (CMV) IgG.

An ultrasound scan (USS) of the abdomen showed a dilated common bile duct (CBD) measuring 7.5 mm to the distal CBD, where it appeared to be obstructed by sludge; however, magnetic resonance cholangiopancreatography (MRCP) showed that 3.7 cm of the lower CBD was narrowed relative to the proximal CBD (figure 1). An endoscopic retrograde cholangiopancreatography (ERCP) was not felt to be justified at this point due its associated risks, necessitating an MRI liver with hepatobiliary contrast; this showed a subtle focal 1.7 cm stricture

Figure 1 Magnetic resonance cholangiopancreatography showing 37 mm of the lower common bile duct (CBD) narrowed relative to the proximal CBD.

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Figure 2 MRI of the liver with contrast showing focal 17 mm stricture near the ampulla.

near the ampulla (figure 2). This collection of results and symptoms led to a diagnosis of AIDS cholangiopathy.

TREATMENT

The patient's HAART was changed to darunavir, ritonavir and raltegravir, and with assistance from physiotherapy and occupational therapy her mobility improved and she was discharged home. Treatment was not instituted at this point for AIDS cholangiopathy as the patient was asymptomatic, with a plan made to follow up and consider intervention if she became symptomatic or had significant worsening of her Liver Function Tests (LFTs.)

OUTCOME AND FOLLOW-UP

She was reviewed in renal outpatient 3 months later when her creatinine was noted to be 120, suggesting she had developed chronic kidney disease. Her liver function tests were stable and not significantly improved.

DISCUSSION

Literature review could not identify any other case of patients presenting with these two conditions together.

Fanconi syndrome

Initially described by Lignac in 1924 and then Fanconi in 1936,¹ Fanconi syndrome (FS) is characterised by a defect in proximal renal tubular function, leading to aminoaciduria, hypophosphataemia, hypokalaemia and hyperchloraemia.² This leads to a clinical picture of polyuria, polydipsia and glycosuria in the presence of normal serum glucose, as well as rickets (children) or osteomalacia (adults). These occur due to failure of effective reabsorption in the proximal renal tubule, possibly due to failure of Na-K-ATPase pump of proximal tubular cells or increased permeability of the proximal tubule, resulting in a persistent metabolic acidosis.

The condition can be inherited or acquired. Congenital FS is an autosomal recessive condition, and can be associated with cystinosis, galactosaemia and Wilson's disease.

Multiple myeloma is the most common cause of acquired FS, with other causes including renal transplantation and medications. Indeed, drug toxicity is a significant problem, limiting the usability of otherwise suitable medication, especially in viral conditions such as HIV and hepatitis B.¹² In the case described, FS was most likely secondary to tenofovir, a known iatrogenic cause.

Other antiretrovirals causing FS include nucleotide reverse transcriptase inhibitors (NtRTIs) adefovir and cidofovir, and nucleoside analogue reverse transcriptase inhibitors (NARTIs) didanosine and stavudine. NtRTIs have been shown to result

in higher incidences of FS compared with NARTIs, and this is thought to be secondary to high levels of uptake of the drugs into the cells of the proximal renal tubule via organic anion transporters.³ Among the NtRTIs, tenofovir is the more widespread used than the other NtRTIs due to its lower nephrotoxic profile in initial safety trials.⁴⁵ However, several cases have been reported recently showing FS induced secondary to tenofovir usage.¹⁶⁷ In these cases, patients reportedly had normal renal function prior to commencement, with a slight rise in serum creatinine following commencement. This was however disregarded until patients presented with acute kidney injury, metabolic acidosis and exhibiting other signs of FS. The symptoms and renal function gradually improved following discontinuation of tenofovir, much like our patient.

This is unfortunate, as tenofovir is a key part of first-line treatment guidelines for HIV, although the prodrug formulation, tenofovir alafenamide (TAF), which achieves high intracellular tenofovir concentrations and low serum levels, has recently been found to have reduced adverse effects, particularly renal toxicity and bone mineral density loss, when compared with the older prodrug, tenofovir disoproxil (TDF), while maintaining similar efficacy against the virus, immune activation and systemic inflammation. Thus, guidelines have migrated towards encouraging this formulation, particularly as longer term studies have become available and TAF becomes more affordable to low-income and middle-income countries.^{8–10}

Tenofovir is also recommended, internationally, for pre-exposure prophylaxis (PrEP), for example, between serodiscordant couples, with the Truvada formulation, a combination of TDF and emtricitabine (a nucleoside reverse transcriptase inhibitor), approved and in use for over 5 years now.^{11 12} Indeed, there have been few cases of FS related to tenofovir-based PrEP,¹³ with guidelines suggesting avoidance in patients with new onset or worsening renal impairment.^{14–16} This paucity of FS cases is also true of patients receiving tenofovir as postexposure prophylaxis.¹⁷ However, it is suggested that the risk of FS is very small in these groups, with a majority of the clinical trials not identifying any patients with FS,^{11 12 15 16} although it is important to note that initial trials for tenofovir in HIV also underestimated the risk of FS, stressing the importance of ongoing safety monitoring and real-world studies.

AIDS cholangiopathy

AIDS cholangiopathy is a syndrome of biliary duct anomalies seen typically in patients with advanced HIV disease—usually those with a CD4 T lymphocyte count of less than 100 cells/mm³—although it has been known to be a presenting problem in those previously undiagnosed.^{18 19} Highly active antiretroviral agent (HAART) has led to a reduction in the incidence of AIDS cholangiopathy, with contemporary studies placing it at 0.9%—down from 26%—although it is still thought to be high in areas with limited access to healthcare.^{20 21}

The exact pathogenesis of AIDS cholangiopathy has yet to be elucidated, but it is believed that the biliary abnormalities are a result of opportunistic infections of the biliary tree in the immunocompromised. Multiple micro-organisms have been isolated from endoscopic biopsies, but the two the most common organisms identified are *Cryptosporidium parvum* and CMV.^{18 22} In one study, it was revealed that *C. parvum* is capable of exerting direct cytopathic effects on biliary epithelial cells by inducing apoptosis.²³

The majority of patients present with right upper quadrant (RUQ) abdominal pain,^{18 20} varying in severity based on site(s)

of involvement seen on endoscopy. Asymptomatic patients make up the second most common presentation.²⁴ Other symptomatic patients present with fever or diarrhoea, which is a manifestation of small bowel involvement by the microbe. Jaundice is uncommon and is only reported in 10%–20% of cases and may be related to cholangitis. Physical examination may be unremarkable, as in the case of our patient, or show hepatomegaly, and less often, splenomegaly.²⁰

Characteristically, most of the patients will have a markedly elevated serum ALP level.¹⁸ Gamma Glutamyl Transferase (GGT) is usually only modestly raised, as are liver transaminases if raised at all. Serum bilirubin typically lies in the normal range or is only slightly raised.¹⁹ Rarely, the condition is associated with pancreatitis, with up to fivefold increase in pancreatic enzymes, although this can also be iatrogenic, from instrumentation of the biliary tract in ERCP.²⁰

Diagnosis is based on medical history, biochemical markers as well as radiological features. The cornerstone of making an accurate diagnosis used to be with the ERCP, which also allows for therapeutic interventions to be performed if necessary. Endoscopy is also useful for classification, with Cello and Rogers¹⁸ categorising AIDS cholangiopathy into four different variants based on endoscopy, which is still used²⁰:

1. Papillary stenosis in about 30% and is associated with severe abdominal pain.
2. Papillary stenosis and sclerosing cholangitis, which is the most common variant (>40%).
3. Sclerosing cholangitis.
4. Long extrahepatic bile duct stricture.

Despite that, the go-to screening tool for patients presenting with RUQ pain and cholestasis is still USS. It has been shown that USS is 98% accurate in anticipating correctly ERCP outcomes, with a sensitivity of 97% and specificity of 100%.²⁵ However, it is not helpful in distinguishing AIDS cholangiopathy from its differentials; thus, one must have an index of suspicion and consider ERCP or MRCP when encountering an HIV-positive patient presenting with some, or all, of the above clinical features.

MRCP is currently favoured due to its significantly reduced cost and side effects when compared with ERCP, with technological advances in recent years allowing shortened acquisition times and improved image quality, such that MRCP has sensitivity of 85%–100% and specificity of 92%–100%.¹⁹

Therapeutic ERCP is effective in providing symptomatic relief and improving pathological biliary changes but does not influence overall survival of patients with AIDS cholangiopathy. Indeed, endoscopic sphincterotomy has been shown to provide lasting pain relief for those who suffer from papillary stenosis.^{18 24 26} Biliary stents may be inserted to overcome biliary strictures.

It has also been shown that focused therapy with single or combination antimicrobials against causative micro-organisms is futile in producing symptomatic relief or altering biliary anomalies. The use of HAART is associated with improved survival perhaps because it allows for reconstitution of immunity, which is essential for warding off opportunistic infections.²⁷

Previously, even with HAART, the prognosis of patients with AIDS cholangiopathy is poor, as most patients were diagnosed in the late stages of HIV. One study concluded that 1-year and 2-year survival rates were 41% and 8%, respectively.¹⁹ Another showed that mean survival time from diagnosis of AIDS cholangiopathy to death was 9 months, with prognosis made worse with concomitant opportunistic infections of various bodily systems at the time of diagnosis of AIDS cholangiopathy. Additionally,

markedly raised ALP has been shown to be associated with shorter lifespan.²⁷ However, contemporary studies have shown median survival to be up to 34 months, perhaps resulting from improved holistic care of patients with HIV and treatment of opportunistic infections.^{19 20}

Learning points

- This patient presented with two rare conditions that have not been previously documented to occur together.
- Although rare, Fanconi syndrome has become a recognised side effect of tenofovir since the initial clinical trials and necessitates a change of treatment regimen to mitigate and potentially reverse damage to the renal tubules.
- Equally, if not, rarer, AIDS cholangiopathy is a marker of poor prognosis and has no curative management strategy, although therapeutic endoscopic retrograde cholangiopancreatography may confer symptomatic relief.
- The case indicates the complexities of AIDS care in patients with low CD4 counts.
- This case also reflects the importance of the multidisciplinary team in the management of the patient, both in the diagnoses and the management and subsequent follow-up of the patient.

Contributors RM and SA treated the patient. JK, RM and SL performed the literature search and wrote the manuscript. SA edited the manuscript.

Competing interests None declared.

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