CASE REPORT

Reversible khat-induced hepatitis: two case reports and review of the literature

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ABSTRACT

Recreational chewing of *Catha edulis* (khat) leaves is part of the ethnic culture of Somali, Yemeni and other East African societies for its stimulant properties. With increasing emigration, khat use has become common in these ethnic groups once they move to other areas such as Europe and the USA; one-third of the UK Somali population report khat use within the last month. Cathinone, the active component of the khat leaves, is controlled under the UK Misuse of Drugs Act, but the use of the khat plant and its leaves remains not subject to control in the UK. There have been several previous reports of acute hepatitis related to chronic use of khat leading to acute liver failure, and resulting in transplantation or death. We report two cases with severe acute khat-related hepatitis that resolved on cessation of khat use initially, but relapsed with further use, reinforcing the importance of permanent khat cessation to prevent progression to liver failure. With reference to the current literature, we also consider the difficult diagnosis of this disorder, then go on to consider the pathophysiology, mechanisms of liver injury and potential future areas of research.

BACKGROUND

Recreational chewing of *Catha edulis* (khat) leaves is part of the ethnic culture of Somali, Yemeni and other East African societies for its stimulant properties.¹ With increasing emigration, khat use has become common in these ethnic groups once they move to other areas such as Europe and the USA; one-third of the UK Somali population report khat use within the last month.²

Cathinone, the active component of the khat leaves, is controlled under the UK Misuse of Drugs Act when extracted

from the leaves or synthesised, but the use of the khat plant and its leaves remains not subject to control in the UK. There have been several previous reports of acute hepatitis related to chronic use of khat leading to acute liver failure, and resulting transplantation or death.^{3–8} We report two cases with severe acute khat-related hepatitis that resolved on cessation of khat use initially, but relapsed with further use, reinforcing the importance of permanent khat cessation to prevent progression to liver failure.

With reference to the current literature, we also consider the difficult diagnosis of this disorder, then go on to consider the pathophysiology, mechanisms of liver injury and potential future areas of research.

CASE REPORT

Case one

A 49-year-old Somali male was referred to the liver clinic with a 4-week history of non-specific abdominal pain and abnormal liver function tests. He was previously well with no significant past medical or family history, and there was no history of alcohol use, no regular or over-the-counter medications or use of other alternative remedies, and he did not report any illicit drug; risk factors for infection. His initial blood results on presentation to hospital: alanine transaminase (ALT) 893 IU/l, bilirubin 100 µmol/l, alkaline phosphatase (ALP) 159 IU/l, gamma glutamyl transpeptidase (GGT) 212 IU/l, albumin 38 g/l and international normalised ratio (INR) 1.0. A comprehensive liver screen was negative for viral hepatitis (A, B, C and E) and antinuclear, antismooth muscle, gastric parietal cell, mitochondrial and liver/

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kidney microsomal autoantibodies. Serum caeruloplasmin, ferritin and α -1-antritypsin levels were all normal. Liver ultrasound was unremarkable.

Further detailed history revealed that the patient had been chewing an unknown amount of khat regularly for several years for recreational purposes. A liver biopsy showed a severe acute hepatitis, thought to be secondary to khat as no other aetiological factors could be identified (figure 1). He was advised to abstain from chewing khat, and his LFTs significantly improved within 7–10 days of abstinence, and he remained well for the next 3 years.

Three years later he re-presented to his general practitioner with a 2-week history of right upper quadrant pain, having restarted chewing khat 2 weeks before. LFTs were again abnormal, ALT 1032 IU/l, bilirubin 79 μ mol/l, ALP 173 IU/l, GGT 224 IU/l, albumin 37 g/l, INR 1.0. An ultrasound scan of the liver with portal vein Doppler study, and a repeat full liver screen were negative. He was once again advised to abstain from khat and his LFTs improved gradually over 8 weeks, returning to normal in 6 months. His LFTs have remained normal over the subsequent 7 years, with continued khat abstinence.

Case two

A 39-year-old Somali male presented to the emergency department with a 7-day history of jaundice and dark urine, preceded by 3 weeks of intermittent right upper quadrant pain. He was previously well

with no significant past medical and family history, and there was no history of alcohol use, no regular or over-the-counter medications or use of other alternative remedies, and he did not report any illicit drug use; there were no risk factors for infection. He worked nights as a taxi driver and had used khat daily, over 2 h at a time, for 3–4 years as a stimulant.

Examination revealed jaundice and right upper quadrant tenderness; initial blood tests were ALT 1318 IU/l, bilirubin 101 μ mol/l, ALP 199 IU/l, GGT 171 IU/l, albumin 37 g/l, INR 1.4. A comprehensive liver screen for acute infection (including hepatitis, cytomegalovirus, toxoplasma, EBV), autoantibodies, metabolic pathology and ultrasound were negative. MRI scan showed focal fibrosis of the left lobe of the liver.

A liver biopsy showed acute hepatitis with periportal collapse, lobular and portal inflammation and some features of interface hepatitis with eosinophils (figure 2). His serum eosinophil count at $0.2 \text{ cells} \times 10^9$ was in normal range (0.0–0.4).

His symptoms resolved and liver function tests improved over 7–10 days following abstinence from khat use. A final diagnosis of acute hepatitis secondary to khat use was made. He re-presented 5 months later with another acute hepatitis, initial ALT 748 IU/l, bilirubin 227 μ mol/l, albumin 39 g/l, and INR 1.5, liver screen negative. He underwent liver MRI which showed further reduction in size of left lobe of liver with new fibrosis in the right lobe. This episode was

Figure 1 Liver histology case 1: H&E staining showing (a) acute severe hepatitis, (b) swollen hepatocytes with ballooning degeneration and heavy lymphocytic infiltrate of portal tracts with no fibrosis.

Figure 2 Liver histology case 2: H&E staining showing (a) acute hepatitis, (b) lymphocytic infiltrate of portal tract and interface hepatitis.

self-resolving and likely due to underlying khat usage.

DISCUSSION

The active components of khat are cathinone and cathine (norpseudoephedrine), both of which are structurally similar to phenylethylamines; cathinone is the beta-keto derivative of amphetamine.⁹ Cathinone and cathine are released into saliva when khat leaves are chewed; they cause presynaptic release and reuptake inhibition of dopamine from the caudate nucleus and release of serotonin from the striatum, producing two-thirds the effect of amphetamine in laboratory studies.¹⁰

Khat causes mild, stimulant, amphetamine-like features including increased alertness, euphoria and hypertension.⁹ More significant acute effects are rare, but psychosis, acute coronary syndrome and stroke have been reported.^{3, 9} A recent review of global data reported 111 cases associating death with use of khat.⁴

There are a number of previous reports of khat-related acute hepatitis.^{5-8, 11} The first report was in 2005 from the UK and described a case of acute hepatitis in a 35-year-old East African man with regular, daily, khat use, which resolved with supportive treatment and cessation of khat chewing.⁵ Subsequently, there have been further reports from the UK^{6, 7} and The Netherlands.^{8, 11}

In 2010, Chapman *et al* published a series of six patients with chronic khat use that was associated with severe acute hepatitis that resulted in death (1 patient) or liver transplantation (five patients).⁶ Histopathological findings in all cases included multilobular necrosis, and cathinone was identified in the liver biopsy from one patient 3 weeks after last use of khat. Similar to our first patient, five of the six patients in this series, at the pretransplantation stage, had recurrence of liver damage when they restarted khat.

Peevers *et al*⁷ reported seven Somali men, all regular khat users, four of whom presented with acute, and three with acute-on-chronic hepatitis. They had jaundice with a predominantly hepatocellular derangement. Three had evidence of severe liver injury with prolongation of INR. Other causes of liver disease were excluded. Of the three men presenting acutely who had a liver biopsy, none had fibrosis. However, of those with an acute-on-chronic presentation, two were cirrhotic, and the one remaining patient had portal fibrosis (stage 3/6) suggesting khat can cause repeated episodes of subclinical hepatitis leading to fibrosis and cirrhosis. Four were treated conservatively, with resolution of jaundice and liver function abnormalities following khat cessation. In two patients, severe liver injury was observed, and immunosuppression was unsuccessful suggesting that mechanism of khat injury may not be immunogenic. One underwent successful liver transplantation and

one cirrhotic patient died following variceal haemorrhage.

The first report of khat-associated liver disease from outside the UK was reported from The Netherlands in 2011; this described a 26-year-old East African man who developed acute liver failure secondary to khat-induced necrotic hepatitis requiring liver transplantation.⁸ Stuyt *et al*¹¹ reported six cases of long-term khat users who migrated from East Africa to The Netherlands who presented with liver injury. Four presented with jaundice and hepatitis; one of these and two others had variceal bleeding and hepatic encephalopathy; two had clinical ascites. Other causes of liver disease were excluded. Three patients died from spontaneous bilateral peritonitis, sepsis and one case receiving liver transplant died post-transplantation.

In most of these cases, the characteristic clinical picture is of acute or subacute hepatitis that resolves on cessation of khat use. It is essential that other causes for liver disease be ruled out, including viral hepatitis, autoimmune hepatitis, drug-induced liver injury (DILI), non-alcoholic fatty liver disease (NAFLD), Wilson's disease, primary biliary cirrhosis and primary sclerosing cholangitis. Liver histology and presence of antismooth muscle antibodies in some of the reported cases of khat-related hepatotoxicity suggests that khat may trigger an autoimmune hepatitis,^{11, 12} however, in the above cases where immunosuppression was trialled, it did not alter the natural history.

Khat causes lobular hepatitis which explains the ALT:alkaline phosphatase ratio. The marked raise in ALT is typical of a drug-related lobular hepatitis or seronegative hepatitis. The histological features seen in khat-related liver disease are similar to any acute hepatitis with ballooning degeneration of hepatocytes and lymphocytic infiltrate in the portal tracts. There may sometimes be an interface hepatitis with eosinophils (figure 1), but this is non-specific and non-diagnostic; fibrosis and cirrhosis have also been reported.

The mechanism of khat-related hepatotoxicity remains to be elucidated. Animal studies have demonstrated that khat can cause an acute hepatitis,¹³ and that long-term khat exposure in rats is associated with chronic active hepatitis and fibrotic liver disease.¹⁴ Studies on leukaemic cell lines have shown that khat induces mitochondrial damage and enhances autophagy.¹⁵ This study also showed that use of cycloheximide and caspase inhibitors (Z-VAD-fmk) were effective in inhibiting khat-induced cell death that is induced by cleavage of procaspase-3. Procaspase-3 is thought to be the main effector caspase during the execution phase of apoptosis.^{16, 17} This is one possible area for consideration of further research into the effect on hepatic mitochondrial activity and antiapoptotic function.

CONCLUSION

The UK Advisory Council on the Misuse of Drugs is currently reviewing the evidence for harm associated with khat, with a view to advising the UK government. Our cases, together with those previously reported, highlight the potential for chronic khat use to cause severe, potentially life-threatening hepatotoxicity, in addition to its acute stimulant adverse effects.

It is important that clinicians investigating patients with abnormal liver function take a good history covering not just therapeutic, over-the-counter and therapeutic drugs, but also use of recreational drugs; this should include khat (particularly if the patient is from the Somali, Ethiopian, Yemeni or other East African community). If khat is the cause of abnormal liver function, it is important that the patient is advised to stop the use of khat, as it appears that in many cases liver function will return to normal on cessation of its use.

Contributors MJ, RH, KM, TY, DMW, PID and TW were involved in the clinical care of these patients and, hence, the case write ups. Histopathology and interpretation was provided by SL and UM. MJ, RH and KM undertook the literature review, with additional support from PID and TW.

Competing interests PID is a member of the UK Advisory Council on the Misuse of Drugs (ACMD). All other authors have nothing to declare.

Patient consent Obtained.

Ethics approval This was a case review of two patients whose consent was obtained to provide the histories and images provided. This was retrospective, hence, no ethical approval was required.

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