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Case Report

Khat-induced liver injuries: A report of two cases

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ABSTRACT

Khat is consumed for recreational purposes in many countries, including Yemen, where >50% of adults chew khat leaves regularly. A wide spectrum of khat-induced liver injuries has been reported in the literature.

Herein, we report two patients with khat-induced liver injury. Both patients clinically presented with acute hepatitis, one of whom showed radiological evidence of hepatic outflow obstruction. Based on the histological tests, both patients had acute hepatitis, which indicated drug-induced liver injury (DILI) on a background of chronic hepatitis and portal fibrosis; of the two, one presented with symptoms of immune-mediated liver injury.

Introduction

More than 90% of Yemeni men and 50% of Yemeni women chew khat leaves habitually [1]. The leaves of khat contain the following pyrrolizidine alkaloids: cathine, cathidine, and cathinone [2]. Cathinone, a sympathomimetic amine with similar properties to amphetamine, is responsible for the sense of delight associated with khat consumption [3]. The Yemenis believe that khat chewing can cure impotence and improve stamina [4]. However, this dependence has a wide range of potential adverse effects [5], including hypertension, coronary vasospasm, myocardial infarction, delayed intestinal absorption, and mood disorders [6].

Several case reports have described liver diseases among khat users in several countries [4]. The full spectrum of khat-related liver injury is not fully known, which continues to evolve and increase in incidence. We describe two cases of liver injury in khat users referred to our hospital, and we discuss their clinical and histological features.

Case 1

A 32-year-old man living in Yemen from birth was referred to the National Liver Institute, a tertiary referral centre for liver disease in Egypt, for the management of an acute liver injury. He had no medical history of chronic illness. He reported acute onset of malaise and anorexia for 5 weeks, which was associated with jaundice, dark urine, and pruritus.

He has been chewing khat leaves regularly for 25 years, consuming approximately 100 g daily. He did not report using other herbal products or recreational drugs in the preceding 6 months.

On examination, the patient was found to be underweight (47 kg) and deeply jaundiced with mild right upper abdominal tenderness. The laboratory data are shown in Table 1. The results of the serological assays for the hepatitis viruses (A, B, C, and E), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and herpes simplex virus (HSV) were negative (anti-hepatitis A virus (HAV)-IgM, hepatitis B surface antigen

Abbreviations: DILI, drug-induced liver injury; EBV, Epstein–Barr virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HCV, hepatitis C virus; HEV, hepatitis E virus; PCR, polymerase chain reaction; RUCAM, Roussel Uclaf Causality Assessment Method; TIPS, transjugular intrahepatic portosystemic shunt.

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Table 1
Laboratory data of case 1.

	1 week before admission	Admission labs	Discharge labs
Total bilirubin	5.4	10.2	5.9
Direct bilirubin	2.7	7.06	5.2
Albumin	3.3	2.8	3.2
AST	67	1574	430
ALT	400	723	240
ALP		273	238
GGT		380	277
INR	1.09	1.04	1.04
HG	12.1	11.7	11
WBCs	5.3	7.2	6.1
Differential count	NAD		
Platelets	257	169	165

GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalised ratio; PC, prothrombin concentration; NAD, no abnormality detected; WBCs, white blood cells; HG, haemoglobin.

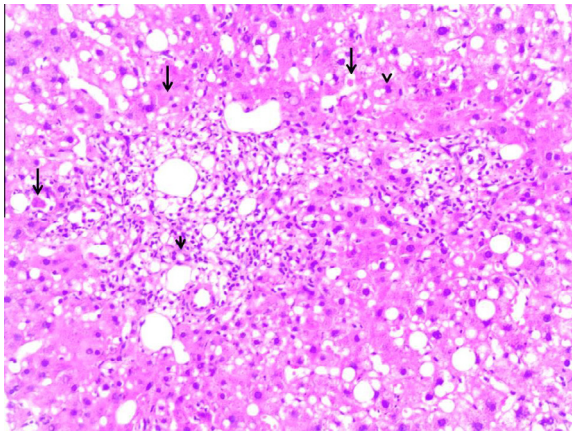

Fig. 1. Liver section from case 1 stained with H&E showing portal tract inflammation, bile duct injury (short arrow), apoptotic bodies (long arrow), and microvesicular steatosis (arrowhead). Original magnification 200×.

(HbsAg), anti-hepatitis B core (HBc)-IgG, anti-HBc-IgM, anti-hepatitis C virus (HCV)-antibody, anti-hepatitis E virus (HEV)-IgM, anti-EBV-IgM, anti-CMV-IgM, anti-HIV-Ab, and anti-HSV-IgM). The results of the polymerase chain reaction (PCR) for HCV-RNA were negative. Hypergammaglobulinaemia was detected (IgG: 3147 mg/dl (normal 700–1600)). However, the results of tests for autoantibodies (antinuclear antibody (ANAs), anti-smooth muscle antibody (ASMA), and anti-liver/kidney microsomal antibody (LKM)) were negative.

The findings on imaging the liver, biliary tree, and hepatic vasculature by ultrasonography and computed tomography were unremarkable. Examination by upper endoscopy revealed severe monilial oesophagitis, for which fluconazole was prescribed for 10 days.

A percutaneous liver biopsy (performed on the fifth day of admission) showed interface hepatitis, cytoplasmic cholestasis, and feathery degeneration with mixed inflammatory infiltrate high in eosinophilic load, indicative of drug-induced liver injury (DILI), as well as portal fibrosis (score of 3/6) with necroinflammation rated 8/18 according to the Ishak score (Fig. 1) [10].

Calculation of the Roussel Uclaf Causality Assessment Method (RUCAM) score of DILI was probable, whereas that of the autoimmune hepatitis score was unlikely [11–13].

The serum levels of bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) decreased in a stepwise pattern, which reflect the slow regression of the condition after khat withdrawal. The patient was discharged and was recommended monthly follow-ups.

Case 2

A 31-year-old man living in Yemen from birth with no history of chronic illness was referred to our hospital due to acute onset of jaundice, dark urine, pain in the right upper quadrant, and pruritus for 8 weeks. He has been chewing fresh khat leaves regularly for 25 years, consuming approximately 100 g daily. He has abstained from khat since the onset of his illness, except one instance a week before admission. The patient had been an alcoholic for several years before abstaining from alcohol 7 years ago.

On examination, the patient was found to have jaundice with mild right upper abdominal tenderness and mild hepatomegaly. The laboratory data are shown in Table 2. The results of the serological assays for HAV, HBV, HCV, HEV, EBV, CMV, HIV, and HSV were negative (anti-HAV-IgM, HBsAg, anti-HBc-IgG, anti-HBc-IgM, anti-HCV-antibody, anti-HEV-IgM, anti-EBV-IgM, anti-CMV-IgM, anti-HIV-Ab, and anti-HSV-IgM), and that of the PCR for HCV-RNA was negative. The patient showed hypergammaglobulinaemia with a serum gammaglobulin level of 2408 mg/dl (normal 700–1600 mg/dl). The patient tested positive for ASMA with a titre of 1/40, but negative for ANA, anti-LKM, and AMA.

Ultrasonographic examination revealed hepatomegaly with an enlarged caudate lobe, completely thrombosed hepatic veins (right, middle, and left), and an enlarged spleen, with no evidence of ascites. Computed tomography and magnetic resonance imaging (MRI) venography confirmed the diagnosis of hepatic vein occlusion, showing the slit-like appearance of the retrohepatic portion of the inferior vena cava.

Coagulation studies revealed normal levels of anti-thrombin III (82%), as well as negative results for anti-cardiolipin IgM and lupus anticoagulant. Negative results were obtained in tests for factor V Leiden, prothrombin gene, and Janus kinase 2 (JAK 2) mutations. A heterozygous mutation of the methylene-tetra-hydro-folate reductase (MTHFR) gene was detected.

A transjugular intrahepatic portosystemic shunt (TIPS) was placed 2 days after admission. One day later, percutaneous liver biopsy was performed. Histopathological examination revealed no evidence of centrilobular congestion or data indicative of veno-occlusive disease. The patient presented with moderate interface hepatitis, spotty and focal confluent necrosis with mixed inflammatory infiltrate rich in plasma cells and eosinophils, which is indicative of an autoimmune-related liver injury associated with a new insult. The histopathological examination also revealed the presence of some microvesicular steatosis, implicating khat in the new acute insult and possibly the chronic features. The fibrosis score was 4/6, and the necroinflammatory activity score was 9/18 according to the Ishak score (Fig. 2) [7].