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CASE REPORT

Can cannabinoids contribute to cholecystitis – a case of gangrenous acalculous cholecystitis

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Summary
Cannabis legalisation continues to grow globally and its effects on the vascular system have been scrutinized.[1] Cannabis has become recognised as a contributor to cardiovascular, cerebrovascular and peripheral vascular disease.[2,3] This case report highlights the case of a young male patient presenting with atypical symptoms following cannabis use who developed gangrenous cholecystitis (GC) following vasospasm of his cystic artery. We believe that this is the first-ever case, shared with the anticipation of stimulating more research and prompting recognition of vascular events in this group of patients as our knowledge on the effects of cannabis continues to grow.
Keywords: gangrenous cholecystitis, cannabinoids, vasospasm, illicit drugs, acalculous

Case report

A 26-year-old male presented to our emergency department complaining of abdominal pain and vomiting for three days. He was previously well, with no known comorbidities, HIV negative, and the only other significant history was cannabis use that had continued until the day that his symptoms began. He further admitted to daily cannabis use for the past 6 months. He had stable vitals on arrival with a blood pressure of 126/91 and a heart rate of 88 bpm. His abdomen was generally tender but soft with no guarding and all other systems were normal on examination. His X-rays revealed no abnormalities either and he was assessed as an acute gastritis, given a stat dose of a proton pump inhibitor and analgesia after which his symptoms improved. He was subsequently discharged with advice given to return if his symptoms reoccurred.

He returned to the emergency department the following day with worsening epigastric pain and intractable vomiting. He denied further cannabis or any other drug use. His vitals revealed a blood pressure (BP) of 100/62 and a heart rate (HR) of 78 bpm. His blood results were a white cell count (WCC) of 15.3 and c-reactive protein (CRP) of 181 with a lactate of 1 on an arterial blood gas. His abdomen was peritonitic and he was thus booked for an emergency explorative laparotomy. Biliary peritonitis was found on opening with a gangrenous gallbladder, and a cholecystectomy was performed. He had distended bowel loops secondary to an ileus and his nasogastric tube drained 2.5 L during the procedure. The patient remained stable intraoperatively but aspirated upon

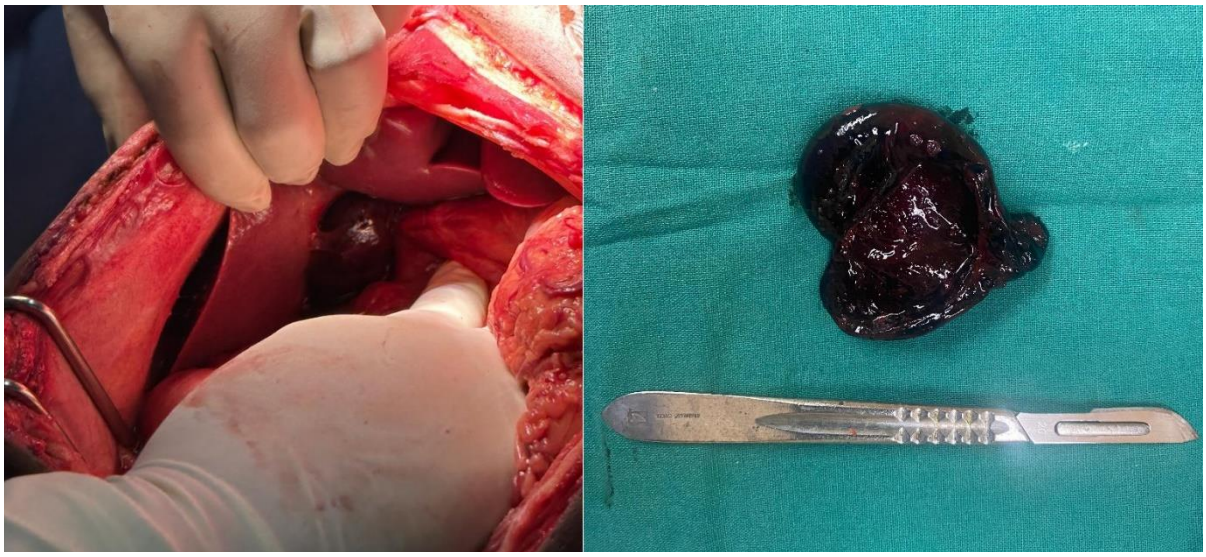

Figure 1a: Intraoperative view of gallbladder, 1b: Gallbladder specimen on removal

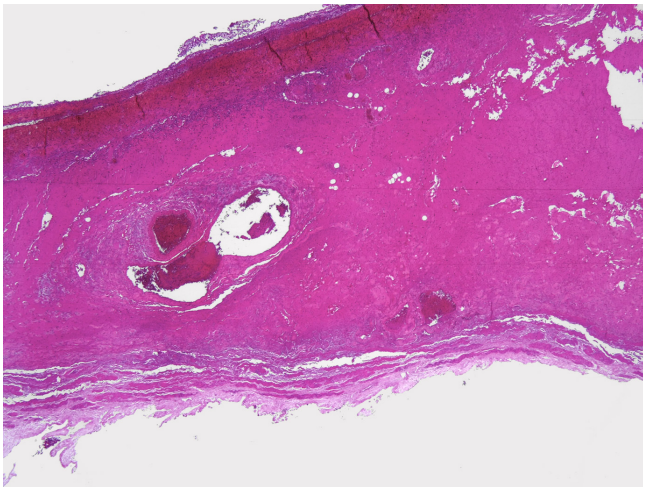

Figure 2: H&E at low power (2X magnification) showing full thickness gangrenous necrosis of the gallbladder wall. Vessels within the muscularis propria show partial occlusion by thrombi.

extubation, requiring re-intubation and intensive care (ICU) admission for further ventilation.

He had worsening respiratory compromise in ICU despite ventilatory optimisation as well as proning and demised 5 days later as a result of the aspiration pneumonia. An abdominal ultrasound excluded any further abdominal pathology as a contributing factor to his demise.

On opening the gallbladder, no polyps, gallstones or tumours were identified, and histological analysis of the gallbladder revealed a vasculitis with several subserosal vessels showing occlusive and non-occlusive thrombi.

Discussion

Cannabis sativa commonly known as marijuana, weed, zol or dagga is the most commonly used illicit substance in South Africa with particularly high use found amongst its youth.[1] Not indigenous to South Africa, cannabis was introduced by European colonialists after which its use became widespread.[2] South Africa is now the world's third largest producer of cannabis.[1] Globally there is a trend toward more liberal cannabis legislation, and in South Africa recreational use amongst adolescents and adults is likely to increase after private production and consumption were legalised in 2018. Public use and sale, however, is still prohibited, although these laws are infrequently enforced.[1,2]

Gangrenous acalculous cholecystitis is defined as necrosis and ultimately perforation of the gallbladder wall secondary to ischaemia following progressive vascular insufficiency.[3] Men are the more commonly affected sex and a delay in hospital treatment as seen in this patient is a recognised risk factor.[4] Classically, the pathogenesis of gangrenous cholecystitis (GC) follows persistent cystic duct obstruction which results in increased gallbladder wall tension with ensuing epithelial injury and vascular insufficiency. Phospholipases are released secondary to the epithelial injury and initiate a massive inflammatory response.[3] Its association with diabetes and cardiovascular disease, however, has a slightly different pathogenesis in that the primary pathology is believed to lie in the cystic artery itself. Microvascular disease or atherosclerosis contribute to ensuing vascular insufficiency.[5] Other purported risk factors include illicit drug use.[6-7]

Compounds in the cannabis plant are called phytocannabinoids, which produce many naturally occurring chemicals. One of the most abundant chemicals is THC (Δ^9-tetrahydrocannabinol) which has a psychotropic effect responsible for the "high" that is described by its users.[8] While the neurological and anti-emetic effects have been well described, research has broadened to look at its effects on the vascular system.[9] These vascular and cardiac effects can be mediated via the two cannabinoid receptors that have been identified, the CB1 and CB2 receptors, or independently of them.[10] These receptors can be found in peripheral tissue as well as in the heart and vasculature. The most notable effects are a significant decrease in cardiac contractility and arterial blood pressure.[10]

In humans, acute cannabis use is associated with an increase in heart rate with no profound blood pressure disruption, however, chronic use has been shown to produce a long-lasting decrease in heart rate and blood pressure.[10] This patient presented with a biliary peritonitis, yet his vitals and HR were within the normal range possibly as a result of his chronic cannabis use. Further studies in rats have shown the bradycardic response to be associated with vasoconstriction of other organ beds – most notably the renal and mesenteric systems.[10] Its effect on the hepatic blood supply and cystic artery are not well described.

A number of pathophysiological mechanisms have been proposed in cannabis use and vascular disease. Cannabis arteritis, vasospasm and platelet aggregation are the most widely recognised effects.[9] The first report of cannabis arteritis was in 1960 by Sterne and Ducastaing.[8] It is a recognised cause of peripheral vascular disease, and the pathogenesis is complex and is at least partly due to THC, which is proven to have a vasoconstrictor effect.[9] Recent literature has also shown an association between chronic cannabis use and cerebrovascular events, with vasospasm and atherosclerosis as the purported mechanisms.[3]

In the context of the GC, it is difficult to ascertain whether the vasculitis and thrombi observed within the gallbladder serosa as seen on this histological specimen represent a primary vasculitis or, alternatively, is a consequence of the GC and therefore a secondary vasculitis. However, as no mechanical cause was found for obstruction on opening the specimen, it is believed that primary pathology of the cystic artery has resulted in GC in this patient, and thus cannabis should be considered as a risk factor.

As cannabis legalisation continues to grow globally, we need to consider the treatment implications as the full significance and consequences of the drug's effects unfold. Its effects on the vascular and hepatobiliary system remain incompletely understood but it seems prudent to keep in mind and investigate its arterial manifestations with a high index of suspicion as a delay or missed diagnosis can have dire consequences and a high mortality.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) Ref: R14/49.

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