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Cannabis-induced acute pancreatitis: a *case report* with comprehensive literature review

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Abstract. – OBJECTIVE: Cannabis is an illegal drug that has been under the spotlight in recent years, due to its vast array of effects on different biological systems. The role of cannabis has been investigated in the management of pain in acute pancreatitis (AP), even though some studies suggest that it may have a causative effect in this pathology and could be considered the underlying etiology in some cases of idiopathic AP. In this case report, we discuss the case of a young man who presented with three different episodes of AP, with apparently no significant history of alcohol and drug consumption, and with no evidence of a biliary, genetic or, autoimmune etiology. During the third episode, in which he had developed a voluminous pseudocyst, treated trough ultrasound (EUS)-guided drainage, he admitted consumption of cannabis daily. The Naranjo score resulted to be 6 (confirming the possible causality), and it was suggested to the patient to avoid cannabis consumption. Since then, he did not develop any other AP episodes. In summary, cannabis should be considered among the possible AP etiologies, as its causative identification and interruption may significantly improve the course of several idiopathic APs.

Key Words:
Acute pancreatitis, Cannabis, Marijuana, Toxin, Peri-pancreatic fluid collection.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas and is associated to a wide spectrum of clinical manifestations, ranging from a mild disease to more severe forms, even requiring intensive care unit hospitalization[1]. The most common causes of AP are chronic alcohol use or abuse, and biliary stones, accounting together for about 70-80% of all cases. Another common cause of AP is represented by drugs (about 2-5%), such as steroids, non-steroid anti-inflammatory drugs (NSAIDs), immunosuppressive agents, mesalazine, diuretics, statins, antipsychotics, anesthetics, chemotherapy agents, and several antibiotics. To date, it is impossible to determine the cause of about 5-10% of all APs, which are thus considered 'idiopathic'. Among idiopathic APs, toxins may sometimes be a possible cause, in particular *Amanita phalloides*, scorpion venom, and others.

Cannabis and its derivatives are increasingly used by young people, mainly for recreational purposes. Their consumption is illegal and associated with various acute and chronic adverse effects on health, often completely ignored by consumers. The link between the consumption of cannabis and AP is often very difficult to establish; as, cannabis consumers tend to hide its use not revealing it when medical history is collected.

To date, only a few reports have pointed out the possible connection between AP and cannabis[2,3]. The first documented case of cannabis-induced AP was described by Grant et al[4] in 2004 in a young adult, who developed an AP after a period of heavy cannabis use. Other cannabis-induced APs have been documented since and marijuana has been included in the group of agents potentially underlying the development of idiopathic AP.

Case Report

A 25-year-old male presented to the Emergency Department of our Center with epigastric pain, abdominal tenderness, and nausea. The patient had no history of chronic diseases, and reportedly did not take drugs. He admitted to a mild and occasional use of red wine during the weekend (<

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2 UA/week), and he did not smoke. At the time of presentation, his blood pressure, pulse, body temperature, and oxygen saturation levels were normal. His hemoglobin level, white blood cell count, alanine aminotransferase, gamma-glutamyltransferase, and bilirubin levels were normal. Amylase and lipase levels were 601 IU/L and 986 IU/L, respectively. C-reactive protein resulted to be 25 mg/dL. He performed an abdominal ultrasound (US) that revealed a normal biliary system and gallbladder, and the presence of a diffuse enlargement of the pancreatic gland, with a mild ectasia of the Wirsung duct. A diagnosis of AP was made according to the Atlanta Criteria[5], the diagnosis of AP was made, and the patient was managed conservatively[1].

Two months later, the patient returned with the same symptoms (epigastric abdominal pain, and nausea) and was yet again admitted to the Emergency Department. The blood exams confirmed the diagnosis of AP with normal values of liver tests and bilirubin. Abdominal contrast-enhanced Computed Tomography (CECT) revealed the presence of a diffusely edematous pancreas with peripancreatic fat stranding and a fluid collection measuring 10 cm of diameter. After 4 days of fasting, the patient's symptoms improved, and he was discharged.

Both AP episodes were apparently not linked to alcohol or drug consumption, while a biliary etiology was ruled out by both blood tests and imaging exams. To exclude autoimmune etiology, we performed serum IgG4 dosage, but resulted normal. Genetic etiology was investigated analyzing SPINK1, PRSS1, and CFTR genes, but also in this case no alterations were found.

During the following 4 months the patient remained healthy, but he then developed a new bout of abdominal pain and nausea and was hospitalized again. A magnetic resonance cholangiopancreatography revealed the presence of a pancreatic pseudocyst measuring about 15 cm of diameter; the Wirsung duct was not dilated and gallbladder and biliary system were normal (Figure 1). The patient presented persistent nausea and abdominal tenderness, particularly after each meal, so an endoscopic ultrasound (EUS)-guided drainage of the pancreatic pseudocyst was performed, with the placement of two cysto-gastric plastic pigtails. Three days after the procedure, an abdominal US was performed, revealing a reduction in the pseudocyst's dimensions. Patient's conditions quickly improved, and he was discharged.

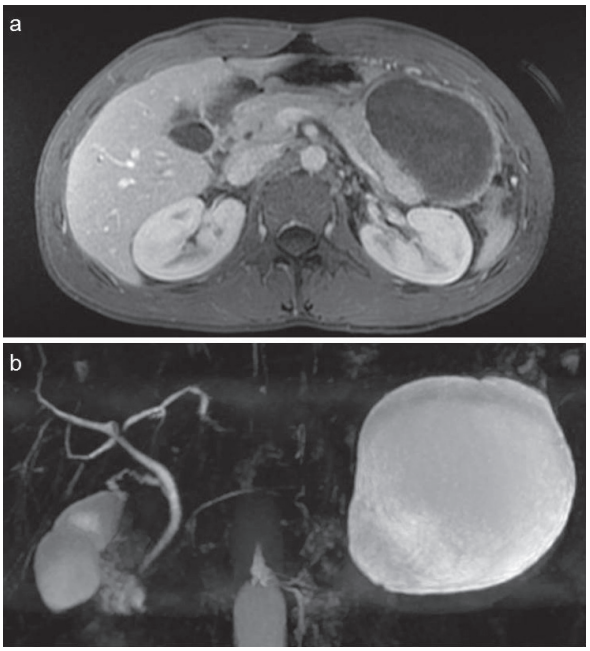

Figure 1. Imaging findings of a case of cannabis-induced acute pancreatitis. A 25-year-old male with recurrent episodes of acute pancreatitis (AP). Axial T1-LAVA MRI **(a)** revealed the presence of a pancreatic pseudocyst measuring 15 cm of diameter with a normal gallbladder and biliary system; the Wirsung duct was not dilated at Magnetic Resonance Cholangio-Pancreatography (MRCP) **(b)**. The patient presented persistent nausea and abdominal pain, so an endoscopic ultrasound (EUS)-guided drainage of the pancreatic pseudocyst was performed, with the placement of two cysto-gastric plastic pigtails. All the AP episodes were considered idiopathic, as alcoholic, biliary, autoimmune, genetic, and drug-related etiologies were excluded. Yet, after further interviewing the patient, he revealed a daily use of cannabis for recreational purposes. Thus, the diagnosis of cannabis-induced AP was made.

All three AP episodes were considered idiopathic, as alcoholic, biliary, autoimmune, genetic, and drug-related etiologies were excluded. Yet, after further interviewing the patient, he revealed a daily use of cannabis for recreational purposes. During the 3 episodes of AP, the patient had continued to consume cannabis. The Naranjo Nomogram for Adverse Drug Reaction Assessment (Naranjo score) resulted in 6, meaning a probable association between cannabis use and the AP episodes. Thus, the diagnosis of cannabis-induced AP was made. The patient stopped consuming cannabis and no further episodes of AP occurred during a 12 months follow-up.

Discussion

Cannabis is an Asian plant belonging to the family of *Cannabaceae*[6]. It is composed by three

different bioactive molecules named flavonoids, terpenoids, and cannabinoids[7]. To date, about 104 cannabinoids have been recognized[8]. The most studied cannabinoids are the delta-9-tetrahydrocannabinol (THC), and cannabidiol (CBD)[9,10]. These substances act binding to specific receptors of the endogenous cannabinoid system, such as cannabinoids receptor type 1 (CB1) and type 2 (CB2), which are both coupled to G-proteins[11]. CB1 receptors can be found prevalently in the central and peripheral nervous system, and they can mediate many of the psychoactive effects of cannabis, while CB2 receptors are mainly present in immune cells and gastrointestinal tract, and they can mediate various effects, such as muscle relaxation, antispasm, and immune modulation. Immunosuppression and anti-inflammatory actions are particularly powerful[7,11,12]. Cannabinoids are involved in a variety of physiological functions, such as metabolism, feeding, behavior, insulin sensitivity, obesity, emotions, pain, memory, mood, and motor coordination[7,13,14]. THC is a partial agonist of CB1 and CB2 receptors with higher affinity for CB1 receptors found in the brain, acting on memory and cognitive functions, possibly mediating also anxiety, and psychotic disorders (i.e., schizophrenia). CBD can reduce the side effects of THC, as it possesses antipsychotic and anti-anxiety proprieties; it also has anti-nausea, anti-bacterial, and anti-fungal effects[7,15,16]. As afore mentioned, CBD is also linked to anti-inflammatory action, through the reduction of pro-inflammatory cytokines, such as IL-6 and IL-10, and the increase of anti-inflammatory cytokines, such as IL-10[15,17].

In the normal pancreas, CB1 and CB2 receptors are weakly expressed and they are mainly located in the islets of Langerhans[18]. Their expression and activation usually increases when the pancreas is inflamed[19]. CB1 receptors are responsible for pancreatic fibrosis, while CB2 receptors may exert anti-fibrotic effects[20]. Consistently, CB1 and CB2 receptors are detected predominantly in the inflamed pancreatic tissue where there is an increase in the pro-fibrotic stellate cells[20].

Some experimental models evaluating the link between cannabis and AP have achieved confounding results[21]. In 2005, Matsuda et al[22] published the results of a murine model of cerulein-induced severe AP, demonstrating that endocannabinoids are associated to a worse course of the disease, and that the administration of an exogeneous CB1 antagonist (AM251) was associated to an amelioration of the disease course. Dembiński et al[23], in a cerulein-induced AP mice model, showed that a natural endogenous ligand for CB1 receptor (anandamide) was associated to an increased severity of AP, with an increased pancreatic edema and inflammatory infiltration; the administration of the exogenous CB1 receptor antagonist AM251 was associated with a reduction of pancreatic tissue inflammation, and it was able to limit the damaging effects of anandamide. On the other hand, in 2007, Michalski et al[24] published the results of a study conducted both in human AP patients and cerulein-induced AP mice. The authors demontrated that AP patients showed an up-regulation of cannabinoid receptors and also an increased levels of endocannabinoids in the pancreas. The administration of a synthetic agonist of CB1 and CB2 receptors (HU210) in the mice with induced AP was able to reduce abdominal pain and also tissue pancreatic inflammation[24]. The latter results would suggest a therapeutic potential for cannabinoids in the treatment of AP-associated pain.

Even though experimental studies regarding the role of cannabinoids and AP do not reach univocal results, there is evidence in clinical practice, suggesting that cannabis use may directly cause AP and may also worse the clinical course of AP patients.

In 2017, Barkin et al[3] published a systematic review including 26 cases of cannabis-induced AP from 16 studies present in the medical literature until May 2016[4,25-36]. These cases mainly referred to young adult males (M/F = 23/3), of age 16-44 years, with heavy use of cannabis from 5 days to 2 weeks before the AP episode, or increased usage during the 2 weeks preceding AP. Cannabis use was assessed by medical history or after urine toxicology. The assessed Naranjo scores ranged from 6 to 9. Several patients presented recurrent episodes of AP. In 7 studies the cessation of cannabis use was associated with the ending of further AP episodes. More recently, Culetto et al[36] in a case-series of about 300 AP patients showed that after first-line investigations, about 50% of cases remained idiopathic, and among these 13% of cases were related to cannabis use.

In 2018, a ten-years evaluation study querying the US Nationwide Inpatient Sample by Njei et al[37] showed that cannabis was associated with an increase in post-endoscopic retrograde cholangiopancreatography pancreatitis.

Sometimes cannabis may be associated with tobacco and alcohol consumption, and, in this context, some reports have shown that canna-

bis may have an intriguing positive role in the modulation of pancreatic inflammation. In 2017, Goyal et al[38] demonstrated indeed that the concomitant use of cannabis and alcohol may reduce the severity of AP through the modulation of the inflammatory effects of alcohol on pancreatic tissue. Also, Adejumo et al[39], showed that the concomitant use of alcohol and cannabis seems to reduce the incidence of AP, in a study analyzing data from 2012 to 2014 of the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample discharge records.

Our case of cannabis-induced AP involved a young male with a moderate daily use of cannabis. However, the first two AP episodes remained idiopathic, because the main known causes of AP were excluded. After the third AP episode associated to the presence of a voluminous pancreatic pseudocyst, further interviewing the patient allowed to discover his history of cannabis consumption. Naranjo score confirmed the hypothesis of cannabis-induced AP. Thus, it was suggested to stop cannabis consumption and no further episodes of AP occurred.

Conclusions

The effects of cannabis use on human health are still not clear and difficult to interpret, because even though several experimental data affirmed that cannabis and its derivatives may limit pancreatic inflammation and reduce AP-related pain, other clinical evidence has shown that cannabis is directly related to the development of AP episodes. Hence, the data we currently have are not enough to confirm the potential therapeutic properties of cannabis in the context of AP (mainly as pain-relief drug), and further studies are necessary to clarify the effects of the administration of cannabinoids on the clinical course of AP. Also, according to the several clinical evidence demonstrating the relation between cannabis and pancreatitis, it is important to contemplate this substance among the possible etiologies of AP, considering that its causative identification and consequent interruption may significantly improve the course of several idiopathic APs.

Conflict of Interest

There are no potential conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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