

## CASE REPORT

# Case of drug-induced acute pancreatitis produced by horsetail infusions

María del Carmen García-Gavilán, Antonio Moreno-García, José Miguel Rosales-Zabal, José María Navarro-Jarabo and Andrés Sánchez-Cantos

Department of Digestive Diseases. Agencia Sanitaria Costa del Sol. Marbella, Málaga. Spain

### ABSTRACT

**Introduction:** The most frequent causes of acute pancreatitis are biliary stones, alcohol consumption, smoking and tumors. Some of them do not have any established cause, and they are catalogued as idiopathic pancreatitis.

**Case report:** We report the case of a 56-year-old woman with a history of bilateral adrenalectomy on hormone replacement therapy with corticosteroids, who has recurrent episodes of mild acute pancreatitis with an etiologic study (laboratory and imaging tests) without significant findings. A drug-induced etiology was suspected, so corticosteroids were removed and antihypertensive treatment was modified, but the clinical manifestations persisted. Later regular consumption of horsetail infusions was detected, and after their suspension the patient became asymptomatic and has not presented new episodes.

**Discussion:** The drug-induced acute pancreatitis is a strange cause of pancreatitis that is frequently underdiagnosed because of the difficulty to establish a relationship between the drugs and the pancreatitis. Lots of drugs have been related with acute pancreatitis, while the information available for herbal products is limited. They usually present like mild and recurrent episodes, without significant findings in both laboratory and imaging tests (abdominal ultrasound, abdominal computed tomography [CT], cholangiography and endoscopic ultrasound). It is important to detect the origin of this type of pancreatitis to prevent recurrence.

**Key words:** Pancreatitis. Herbal products. Horsetail infusions.

### INTRODUCTION

The most frequent causes of acute pancreatitis are biliary stones, alcohol consumption, smoking and tumors. In the absence of these etiologies, metabolic disorders such as hypertriglyceridemia or hypercalcemia must be excluded. Less frequent causes include anatomical or physiological abnormalities of the pancreas, such as pancreas divisum or sphincter of Oddi dysfunction (1,2), which are present in up to 15% of the population (1). It is important to detect the origin of the pancreatitis to prevent further recurrent

episodes. Although diagnosis is straightforward in most patients, up to 10% of acute pancreatitis and 30% of recurrent pancreatitis do not have a clear origin and are catalogued as idiopathic pancreatitis (2). They are defined as pancreatitis with an unknown cause after the laboratory (including calcium and lipid profile) and imaging tests (abdominal ultrasound, abdominal CT and cholangiography) (1,2). In these cases, it is mandatory to exclude the drug-induced origin.

We report the case of a woman with recurrent mild acute pancreatitis in relation to horsetail infusions.

### CASE REPORT

We present the case of a 56-year-old woman with a history of arterial hypertension, dyslipidemia and bilateral adrenalectomy due to macronodular bilateral hypertrophy of the adrenal glands, in treatment with losartan, hydrochlorothiazide and hormone replacement therapy with hydrocortisone 30 mg/24 hours and fludrocortisone 0.1 mg/24 hours. During nine years she had recurrent episodes of acute pancreatitis presented as mild acute episodes that were self-limited in about 4-5 days with diet and analgesics. During her first admission the laboratory workup showed normal liver function, lipid profile with mildly elevated cholesterol (225 mg/dL) and normal values of triglycerides. The abdominal ultrasound and cholangiography did not show changes in the biliary tract, cholelithiasis and biliary or pancreatic tumors, so it was classified as an idiopathic pancreatitis. Later she presented new episodes, with a frequency between seven months and three years. During this time analytical studies with no abnormalities were performed and imaging tests, including abdominal ultrasound (Fig. 1), cholangiography, abdominal CT (Figs. 2 and 3) and endoscopy ultrasound, without identifying the cause. In the last two years, the frequency of pancreatitis

Received: 18-12-2015  
Accepted: 01-05-2016

Correspondence: María del Carmen García-Gavilán. Department of Digestive Diseases. Agencia Sanitaria Costa del Sol. Autovía A-7, km. 187. 29660 Marbella, Málaga. Spain  
e-mail: marigarciagavilan@hotmail.es

García-Gavilán MC, Moreno-García A, Rosales-Zabal JM, Navarro-Jarabo JM, Sánchez-Cantos A. Case of drug-induced acute pancreatitis produced by horsetail infusions. *Rev Esp Enferm Dig* 2017;109(4):301-304.

DOI: 10.17235/reed.2016.4157/2015

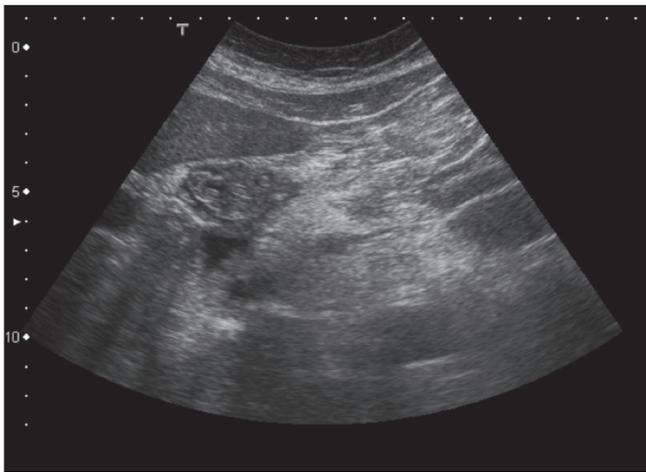


Fig. 1. Abdominal echography with a normal pancreas echostructure without lesions or ductal alterations.

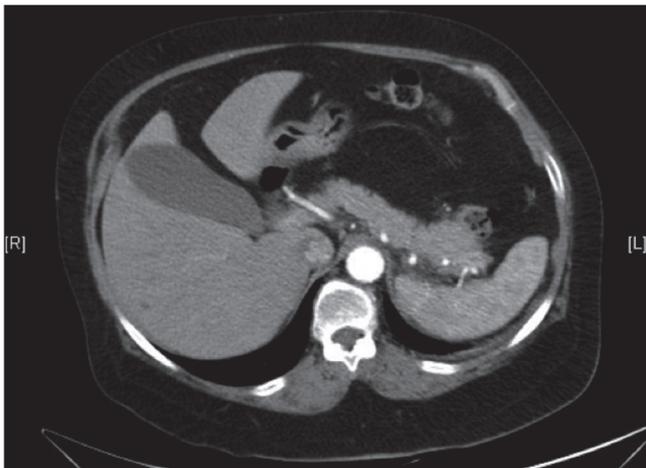


Fig. 2. CT with intravenous contrast, axial section. The pancreas has a normal aspect with no lesions.



Fig. 3. CT with intravenous contrast, coronal section. It shows the uncinate process and the head of the pancreas without lesions.

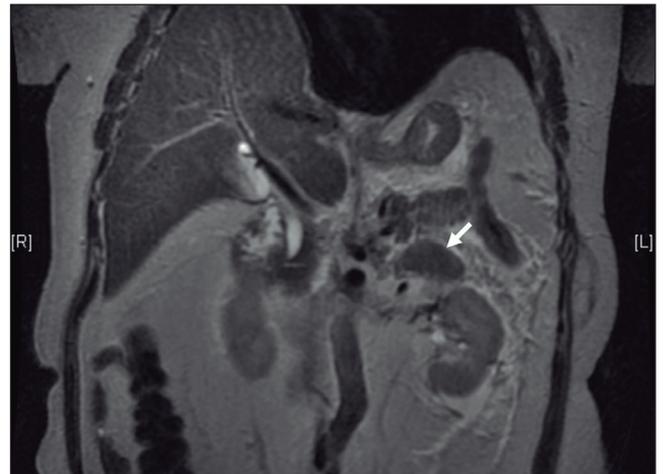


Fig. 4. MRI T1 sequence. The remnant of the left adrenal gland is shown.

decreased, with episodes each 6-7 months, so the whole study was repeated again, and a remnant of the adrenal gland was observed in the cholangiography (Fig. 4). A drug-induced origin secondary to a chronic overproduction of endogenous steroids and hormone replacement treatment with corticosteroids was suspected. The hormonal study showed a level of cortisol about 25.7 mcg/dL and a normal ACTH and 24-hours urine cortisol. The hormone replacement treatment was modified to hydrocortisone 10 mg per day, which was progressively reduced until its suspension. Due to the possibility of a drug-induced pancreatitis, the antihypertensive treatment was changed, from the association of losartan and hydrochlorothiazide to monotherapy with ramipril. The etiology study was completed with IgG4 and ANA that were normal, and the sweat test and genetic test for cystic fibrosis were negative. Six months after treatment modification the patient was admit-

ted again with mild acute pancreatitis. She was interrogated again, and finally confessed the habitual consumption of horsetail infusions. Faced with the possibility of recurrent pancreatitis secondary to the habitual consumption of this infusion, they were completely removed. Fourteen months later, the patient remains asymptomatic with normal ultrasound controls.

## DISCUSSION

Drug-induced pancreatitis are a rare cause of pancreatitis which represents about 3-5% of all causes (3,4), but it is difficult to establish its real incidence because of the lack of prospective studies and the underdiagnosis of this entity. They are more frequent in young patients, women and Crohn's disease (3), the latter being probably related

with the drugs taken for the disease. It represents a diagnostic challenge since quite often the drug is not related to the episode of pancreatitis, which is finally catalogued as an idiopathic pancreatitis (3,4). This difficulty derives from the fact that they are not usually considered in the initial differential diagnosis, and establishing its relationship with the origin of the pancreatitis is difficult. During admission the habitual treatment is withdrawn, the patient improves clinically, and thus its relationship with the cause of the pancreatitis is masked. The problem presents at the time of discharge, when the habitual treatment is reintroduced and the risk of new episodes reappears.

The available information for drug-induced pancreatitis is poor and sometimes it is reduced to series of cases described in the literature. The drugs with further evidence are: mesalazine, azathioprine, 6-mercaptopurine, dexamethasone, fenofibrate, pravastatin, simvastatin, cannabis, carbimazol, codeine, sulfamethoxazole, procainamide, Premarin® (estrogen), enalapril, isoniazid, metronidazole, tetracyclines and valproic acid (3-7). There are also combinations of drugs that increase the risk of pancreatitis; those described with an increased risk include the combination of formoterol + budesonide and ramipril + hydrochlorothiazide.

Badalov et al. published an extensive review of all cases of acute pancreatitis caused by drugs described in the literature, which included 1,214 cases reported between

1955 and 2006. Based on rechallenge, latency, the number of reported cases and the exclusion of other more common causes of pancreatitis, they established a classification based on available evidence, in which the drugs were classified in four categories: a) class I, when there was at least one case described in the literature with rechallenge, being classified as Ia when other etiologies were ruled out (alcohol, hypertriglyceridemia and stones), and Ib when they were not studied; b) class II, when there were at least four cases reported with consistent latency; c) class III, when there were at least two cases described without consistent latency; and d) class IV, with cases that did not fit into the other categories. All drugs described as a cause of pancreatitis were collected and classified into those four categories (5) (Table I). The pathophysiologic cause whereby the damage occurs in the pancreatic parenchyma is still unknown. There is little evidence that an intrinsic toxicity of a drug produces pancreatitis. Only three drugs are described as possible causes of pancreatitis in the context of an overdose: paracetamol, erythromycin and carbamazepine, although the published cases are old and their relationship is not entirely clear. The remaining cases are believed to be idiosyncratic, and depend on the chemical structure of the toxic substance (5). In the case of herbal products or dietary supplements, there is little evidence to relate them with the cause of the pancreatitis, and the mechanism producing the damage is unknown.

**Table I. Drugs related to acute pancreatitis by the Badalov's classification**

| <i>Class Ia</i>      | <i>Class Ib</i>         | <i>Class II</i> | <i>Class III</i>     | <i>Class IV</i>              |                 |
|----------------------|-------------------------|-----------------|----------------------|------------------------------|-----------------|
| $\alpha$ -Mehylidopa | All-trans-retinoic acid | Acetaminophen   | Aledronate           | Adrenocorticotrophic hormone | Mefanamic acid  |
| Azodisalicylate      | Amiodarone              | Chlorothiazide  | Atorvastatin         |                              | Nitrofurantoin  |
| Bezafibrate          | Azathioprine            | Clozapine       | Carbamazepine        | Ampicilin                    | Octreotide      |
| Cannabis             | Clomiphene              | DDI             | Captopril            | Bendroflumethiazole          | Oxyphenbutazone |
| Carbimazole          | Dexamethasone           | Erytromycin     | Ceftriaxone          | Benzapril                    | Penicilin       |
| Codeine              | Isofosfamide            | Estrogen        | Chlorothalidone      | Betamethazone                | Phenophthalein  |
| Cytosine             | Lamivudine              | L-asparaginase  | Cimetidine           | Capecytabine                 | Propoxyphene    |
| Arabinoside          | Losartan                | Pegasparagase   | Clarithromycin       | Cisplatin                    | Ramipril        |
| Dapsone              | Lynesterol/             | Propofol        | Cyclosporin          | Colchicine                   | Ranitidine      |
| Enalapril            | methoxythinyloestradiol | Tamoxifen       | Gold                 | Cyclophosphamide             | Rifampin        |
| Furosemide           | 6-MP                    |                 | Hydrochlorothiazide  | Cyproheptidine               | Risperidone     |
| Isoniazid            | Meglumine               |                 | Indomethacin         | Danazol                      | Ritonovir       |
| Mesalamine           | Methimazole             |                 | Interferon/ribavirin | Diazoxide                    | Roxithromycin   |
| Metronidazole        | Nelfinavir              |                 | Irbesartan           | Diclofenac                   | Rosuvostain     |
| Pentamidine          | Norethindronate/        |                 | Isotretionin         | Difenoxylate                 | Sertaline       |
| Pravastatin          | mestranol               |                 | Ketorolac            | Doxorubicin                  | Strychnine      |
| Procainamide         | Omeprazole              |                 | Lisinopril           | Ethacrinic acid              | Tacrolimus      |
| Pyrotinol            | Premarin                |                 | Metalozone           | Famciclovir                  | Vigabatin/      |
| Simvastatin          | Sulfamethazole          |                 | Mirtazapine          | Finasteride                  | lamotrigine     |
| Stibogluconate       | Trimethoprim-           |                 | Naproxen             | 5-Fluorouracil               | Vincristine     |
| Sulfamethoxazole     | Sulfamethazole          |                 | Paclitaxel           | Fluvastatin                  |                 |
| Sulindac             |                         |                 | Prednisone           | Gemfibrozil                  |                 |
| Tetracycline         |                         |                 | Prednisolone         | Interleukin-2                |                 |
| Valproic acid        |                         |                 |                      | Ketoprofen                   |                 |
|                      |                         |                 |                      | Lovastatin                   |                 |

Only *Harpagophytum* (Devil's claw) and Valeriana® have been associated with episodes of acute pancreatitis in the study of Douros et al., where three cases of each one are described, with an OR (95% IC) of pancreatitis of 12.0 and 10.3 respectively (7). In our case, the episode of pancreatitis was triggered by the infusions of horsetail, which is made from the plant *Equisetum arvense*, commonly called horsetail. It is used for its diuretic effect and to prevent renal colic (8). Its relationship with the production of pancreatitis is totally unknown and any case has been reported in the literature.

Drug-induced pancreatitis is usually edematous type and not clinically severe (3), nor lead to a multiorgan failure (7). It presents like any other pancreatitis with abdominal epigastric pain radiating to the back and amylase above three times its normal value (3,7,9). It is not usually accompanied by rash, lymphadenopathy and/or eosinophilia, as other diseases caused by toxins (5).

It is difficult to establish their etiologic diagnosis because they are not accompanied by typical clinical or laboratory tests, and it has been usually done by excluding other causes and after several recurrent episodes. Initially, the most common causes are ruled out, for which an analytical test with calcium and lipid profile must be done, as well as an abdominal ultrasound to discard cholelithiasis. In the absence of cholelithiasis, a cholangio-NMR or CT is performed (1). In the cases of idiopathic pancreatitis, the endoscopy ultrasound has special interest as it is the most sensitive test to rule out microlithiasis or biliary sludge (10).

Once the most frequent causes are discarded and some toxic substance is thought to be the possible etiologic cause, the cause and effect must be established, as in any other disease caused by toxic agents. In the present case, this would avoid setting the toxic product as the etiological cause when it is actually caused by a gallstone problem (biliary sludge or microlithiasis), which sometimes can be underdiagnosed. For that reason, the relationship is established based on general scientific cause-effect criteria. Following the Bradford Hill criteria, there are nine aspects to be taken into account to establish this relationship with some certainty: strength and consistency of the association, specificity, temporality, biological gradient (dose-response curve), plausibility, coherence, experimentation and analogy (11). In our case, the specificity criterion is met, as the other more frequent causes of pancreatitis were ruled out by appropriate tests and all the drugs the patient was taking were withdrawn, so that she was only exposed to infusions. Temporality and experimentation criteria are met as well, because since her return home the patient took again the infusions and in 6-7 months presented new acute episodes,

remaining asymptomatic without new episodes following the withdrawal of infusions. Finally, it is a plausible and consistent cause because, like all drugs that can lead to a toxic acute pancreatitis, horsetail infusions could also cause them. There is no strength or consistency in this relationship because no other case has been reported in the literature. Therefore, although the nine criteria are not met, there is evidence that in our case horsetail infusions are the cause of the recurrent episodes of pancreatitis in our patient.

The treatment of this type of pancreatitis is the same as in other illnesses produced by toxins: complete removal of the toxic agent and treatment of the acute pancreatitis and its possible complications.

In conclusion, it is recommended that in all idiopathic pancreatitis drugs must be in the initial differential diagnosis, and although the knowledge of herbal products as a cause of pancreatitis is scarce, they should be taken into account as their detection is important to prevent new recurrent episodes.

## REFERENCES

1. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. *Am J Gastroenterol* 2013;108(9):1400-15. DOI: 10.1038/ajg.2013.218
2. Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? *World J Gastroenterol* 2008;14(7):1007-10. DOI: 10.3748/wjg.14.1007
3. Vinklerová I, Procházka M, Procházka V, et al. Incidence, severity, and etiology of drug-induced acute pancreatitis. *Dig Dis Sci* 2010;55(10):2977-81. DOI: 10.1007/s10620-010-1277-3
4. Barreto SG, Tiong L, Williams R. Drug-induced acute pancreatitis in a cohort of 328 patients. A single-centre experience from Australia. *J Pancreas* 2011;12(6):581-5.
5. Badalov N, Baradaran R, Iswara K, et al. Drug-induced acute pancreatitis: An evidence-based review. *Clin Gastroenterol Hepatol* 2007;5(6):648-61. DOI: 10.1016/j.cgh.2006.11.023
6. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: An update. *J Clin Gastroenterol* 2005;39(8):709-16. DOI: 10.1097/01.mcg.0000173929.60115.b4
7. Durous A, Bronder E, Andersohn F, et al. Drug-induced acute pancreatitis: Results from the hospital-based Berlin case-control surveillance study of 102 cases. DOI: 10.1111/apt.12461
8. Cola de caballo. Información del producto. Disponible en: <http://www.coladecaballo.es/para-que-sirva.html>
9. Banks PA, Bollen TL, Dervenis C, et al.; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: Revision of the Atlanta classifications and definitions by international consensus. *Gut* 2013;62:102-11. DOI: 10.1136/gutjnl-2012-302779
10. Smith I, Ramesh J, Kyanam Kabir Baig KR, et al. Emerging role of endoscopic ultrasound in the diagnostic evaluation of idiopathic pancreatitis. *Am J Med Sci* 2015;350(3):229-34. DOI: 10.1097/MAJ.0000000000000541
11. Hill AB. The environment and disease: Association or causation? *Proc R Soc Med* 1965;58:295-300.