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Isotretinoin-induced pancreatitis: is it time to definitely recognize it: a case report

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Abstract

Background Although often overlooked, drug-induced pancreatitis is a frequent cause of pancreatitis. Pancreatic drug toxicity is defined according to the classification by Mallory *et al*. and Trivedi *et al*. Isotretinoin is only classified as possibly toxic to the pancreas (class 3). We report the first case of recurrence of pancreatitis after rechallenge, which argues for a modification of the classification of drug-induced pancreatitis.

Case presentation We present here the case of a 20-year-old Belgian man who suffered several episodes of acute pancreatitis for which no etiology could be identified despite an exhaustive assessment. Eventually, as a precaution, isotretinoin was discontinued and there was no recurrence until it was reintroduced.

Conclusion This is the 25th case described in the literature, but the first with a positive rechallenge on two occasions. This case therefore implies that isotretinoin should definitely be considered a class 1 toxic drug for the pancreas and should be incriminated in acute pancreatitis in patients treated with this drug.

Keywords Case report, Recurrent acute pancreatitis, Isotretinoin, Drug-induced pancreatitis

Introduction

Acute pancreatitis is characterized by an inflammatory reaction of the pancreas manifested clinically by abdominal pain associated with elevated serum pancreatic enzymes [1]. The pathogenesis of acute pancreatitis is still controversial, and seems to depend on the etiology [2].

In almost all of Europe, the most common cause of acute pancreatitis is gallstone impacting the distal common bile-pancreatic duct [3]. The other well-known causes are, non-exhaustively, alcohol abuse, hypertriglyceridemia (>1000 mg/dL), hypercalcemia, trauma, infections, autoimmune diseases, endoscopic retrograde cholangiopancreatography, and, in an increasing way, drugs.

More than 100 drugs have been alleged to cause acute pancreatitis, but in many case reports the association is ambiguous, mostly because the pancreatitis may develop within a few weeks after beginning a drug with an immunologically mediated adverse reaction, but it can also appear after several months of use due to the chronic accumulation of toxic metabolic products. This is also made difficult by the fact that it is mostly impossible to rule out all the other possible etiologies, as there are so many. Moreover, although drug-induced pancreatitis is a well-accepted precipitant, it is often neglected by the clinician, even though 42% of patients admitted for a first episode of acute pancreatitis take pancreaticotoxic drugs [4].

Isotretinoin, also known as 13-cis-retinoic acid, is a retinoid (related to vitamin A), used as medication to treat severe acne, but also to prevent squamous cell carcinoma [5] and in the treatment of other cancers. More rarely, it is used to treat harlequin-type ichthyosis and lamellar ichthyosis [6].

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Isotretinoin was patented in 1969 and approved for medical use in 1982. It has multiple well-known adverse effects: cheilitis, dry and fragile skin, photosensibility, myalgias, headaches, hyperostosis and premature epiphyseal closure, psychiatric disorders, and mainly due to the close resemblance to retinoic acid, birth defects [7]. However, acute pancreatitis is not part of the list of main side effects and isotretinoin is only recognized as a possibly pancreatic toxic drug (class III according to Mallory *et al*. [8]).

Case presentation

A 20-year-old Belgian male without personal history or familial history of pancreatitis came to the emergency department for transfixing abdominal pain that had appeared a few hours ago. Parameters and clinical examination were reassuring. There was a notion of minor alcohol consumption a few days before (approximately 5–6 beers). The only medication he took was oral isotretinoin 10 mg/day for acne.

Blood biology and an abdominopelvic scan were performed, highlighting grade D acute edematous pancreatitis. The patient was hospitalized for hydration and analgesia.

An abdominal ultrasound and blood test in search of an obstructive, metabolic (hypertriglyceridemia, hypercalcemia), or autoimmune (antinuclear antibodies, Antineutrophil cystoplasmic antibodies (ANCA), anti-saccharomyces cerevisiae antibodies (ASCA), and immunoglobulin G4 (IgG4)) cause was carried out, without any findings. Finally, acute pancreatitis on recent alcoholic consumption was retained and the patient left the hospital 3 days later with a follow-up in gastroenterology. Without being suspected as being responsible for this episode of acute pancreatitis, the isotretinoin was stopped spontaneously by the patient.

Then 1 month later, an upper digestive echoendoscopy was performed and found to be unremarkable. Due to the excellent evolution, no additional exploration was performed and the gastroenterological follow-up was discontinued.

The patient presented to the emergency department again 2.5 years later for abdominal pain that he identified as similar to his previous episode of pancreatitis. Parameters and clinical examination were reassuring. He was again under oral isotretinoin 10 mg/day for almost 1.5 years. This time he had not had any alcohol for several weeks. Blood test showed hyperlipasemia more than three times than normal, motivating the patient's hospitalization for acute pancreatitis.

New explorations were carried out with abdominopelvic scanner, abdominal ultrasound, and echoendoscopy. All radiologic examinations were normal without sign of pancreatitis.

At the biological level, many analyses were carried out to exclude metabolic, infectious, autoimmune (ANCA, ASCA, antinuclear antibodies, IgG4), autoinflammatory, neoplastic, and even genetic causes (with search for mutations in the *CFTR, CTRC, PSTI, SPINK1, CaSR, CLDN2, CPA1 and PRSS1*). The search for porphyria and angioneurotic edema was also negative.

Because of his good evolution, the patient was allowed to leave the hospital after 3 days. The isotretinoin was stopped since in the absence of any other cause, drug-induced pancreatitis was suspected.

In the following weeks, a MRI of the pancreas with secretin stimulation was performed and found no pancreas divisum or other abnormality. The patient was seen again at 3 months and then at 6 months and continued to evolve quite favorably without any new episode of pancreatitis.

The patient decided, due to severe acne 2 years later and after discussion with his attending physician, to resume treatment with isotretinoin at the same dosage but topical this time. He presented himself 15 days later at the emergency department for a new episode of pancreatitis. Again there was no other precipitant, such as consumption of alcohol or drugs.

An abdominopelvic scan was performed 48 hours after onset of symptoms and showed grade B acute pancreatitis without other anomalies. At the biological level, given the recent reintroduction of isotretinoin, only a basic assessment was carried out to exclude metabolic, infectious, autoimmune, and autoinflammatory causes. The evolution was favorable and the patient was authorized to leave the service 48 hours later. He was told never to resume isotretinoin again.

The patient was seen again at 3 months, 6 months, and 12 months and continued to evolve quite favorably without any new episode of pancreatitis. The patient's medical history is summarized in Fig. 1.

Discussion

Isotretinoin-induced pancreatitis is a rare condition. There are 15 papers describing 30 cases of pancreatitis associated with isotretinoin reported in the literature (search strategy using MEDLINE, Embase, and grey literature) from 1960 to January 2023. In these papers, there are as many cases of isotretinoin-related pancreatitis in men as in women (sex ratio 1). The mean duration of isotretinoin use after which pancreatitis occurred was 3.39 months, and the mean dose at which pancreatitis occurred was 34.29 mg/day; five of these cases were

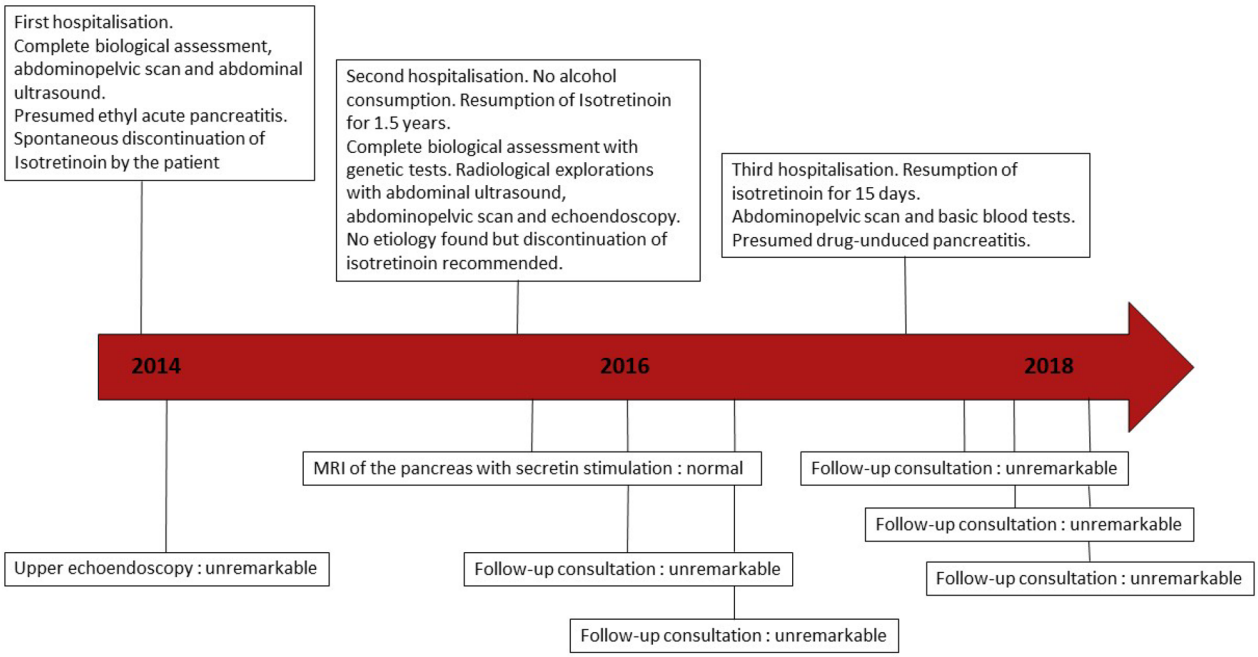

Fig. 1 Timeline representation of the patient's medical history

likely due to hypertriglyceridemia. No cases of pancreatitis resulted in death or presented complications.

These articles are summarized in Table 1.

It would seem that acute pancreatitis can develop according to two mechanisms: (1) rarely associated with hypertriglyceridemia and (2) more frequent, caused by an idiosyncratic reaction, sometimes remote from the introduction of the drug.

Despite this large number of reported cases, isotretinoin is still a class III drug in the drug-induced pancreatitis classification.

This is a new case of isotretinoin-induced pancreatitis without hypertriglyceridemia, with a positive rechallenge twice, with no other cause of acute pancreatitis demonstrated despite numerous and multiple biological and radiological explorations. Moreover, this is the first documented case of acute pancreatitis associated with the topical use of isotretinoin.

The classification of pancreatoxic drugs can be defined by the classification of Mallory *et al.*, established in 1980, which is based on four criteria:

1. Pancreatitis develops during treatment with the drug
2. The absence of other causes of pancreatitis
3. Pancreatitis resolves with drug discontinuation
4. Pancreatitis recurs with reintroduction of the drug.

The drug is then classified according to these criteria into three categories: definite, probable, or possible association with pancreatitis. A definite association implies that all four criteria are met. A probable association requires that all criteria be met except for reexposure. The association is possible when there are only incomplete or contradictory levels of evidence. In this case, isotretinoin would therefore be classified as class I.

More recently, Trivedi *et al.* [9] proposed a new classification into three classes according to the number of cases reported in the literature:

> Class 1: More than 20 cases reported in the literature and more than one case with positive reexposure
> Class 2: More than 10 but less than 20 cases reported in the literature with or without positive reexposure
> Class 3: Less than 10 cases reported in the literature

Again, isotretinoin is recognized as a class 1 pancreatic toxic drug according to this new classification.

Conclusion

Drug-induced pancreatitis is becoming increasingly common, and it is essential to keep classifications up to date to be able to warn patients and clinicians and properly assess the benefit/risk balance when introducing a new drug. Isotretinoin should definitely be recognized as a class I pancreaticotoxic drug. This change would raise clinicians' awareness of this not-so-rare complication (Table 1).

Table 1 Summary of the reported cases of acute pancreatitis linked to isotretinoin

Study	Type of report	Indication of treatment	Sex	Age	Isotretinoin dose	Time on isotretinoin	Confounding factor	Peak triglyceride level	Triglyceride associated	Complications	Outcome
Flynn 1987 [10]	Case report	Acne	F	41	40 mg twice a day (1 mg/kg/day)	7 weeks	Estrogen intake, hypertriglyceridemia	7380 mg/dL	Yes	No	Resolved
McCarter 1992 [11]	Case report	Acne	F	30	40 mg daily (0.5 mg/kg/day)	6 weeks	Gestational hypertriglyceridemia	5940 mg/dL	Yes	No	Resolved
Anrousseau 1995 [12]	Case report	Acne	M	17	10 mg twice a day first, then 20 mg daily	15 days first, then 10 days	Cholelithiasis	57 mg/dL	No	No	Resolved
Bourantas 1995 [13]	Cohort study	Myelodysplasic syndrom	F	78	20 mg daily	1 year	Cholelithiasis	NC	No	No	Resolved
Jamshidi 2002 [14]	Case report	Hidradenitis	F	43	40 mg twice a day	6 months	Prednisone and tetracyclines intake, hypertriglyceridemia	884 mg/dL	Yes	No	Resolved
Fine 2004 [15]	Cohort study	Dystrophic epidermolysis bullosa	NC	>15	0.1 mg/kg/day	NC	NC	<350 mg/dL	No	No	Resolved
Tsimberidou 2004 [16]	Cohort study	Lymphoïd malignancy	NC	NC	1 mg/kg/day	NC	Interferon alpha intake	NC	No	No	Death
See 2004 [17]	Cohort study	Recurrent glioblastoma	NC	NC	100–200 mg/m^2/day	NC	Hypertriglyceridemia	NC	Possibly	No	Resolved
Greene 2006 [18]	Case report	Acne	F	19	60 mg daily	2 months	Estradiol and sertralin intake	351 mg/dL	No	No	Resolved
Pillai 2014 [19]	Cohort study	Small cell lung cancer	NC	NC	1 mg/kg twice a week for 6 weeks	NC	Interferon alpha and paclitaxel intake	NC	No	No	Death
Bataille 2014 [20]	Case series	NC	10H/6F	Mean 19 (min. 14, max. 30)	NC	Mean 3 months (min. 15 days, max. 15 months)	Oral contraceptive (two people)/alcohol intake (one person)	<350 mg/dL	No	No	Resolved
Tejedor 2019 [21]	Case report	Acne	M	14	30 mg daily	3 months	No	<175 mg/dL	No	No	Resolved
Atiq 2019 [22]	Case report	Acne	M	29	30 mg twice a day	NC	No	<175 mg/dL	No	No	Resolved

Table 1 (continued)

Study	Type of report	Indication of treatment	Sex	Age	Isotretinoin dose	Time on isotretinoin	Confounding factor	Peak triglyceride level	Triglyceride associated	Complications	Outcome
Ashraf 2020 [23]	Case report	Acne	F	55	NC	1 month	Hypertriglyceri-demia	1300 mg/dL	Yes	No	Resolved
Dhattarwal 2022 [24]	Case report	Acne	F	18	20 mg daily	15 days	No	< 500 mg/dL	No	No	Resolved

NC non-communicated, *M* male, *F* female

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Not applicable.

Declarations

Ethical approval and consent to participate
Written informed consent was obtained from the patient for the publication of this case report, including the clinical information. The authors confirm that all efforts were made to preserve the patient's anonymity, and no identifying information is included in the manuscript. The study adheres to the ethical standards outlined by the Declaration of Helsinki.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
Not applicable.

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