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CASE REPORT

Isoniazid-Induced Recurrent Pancreatitis

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ABSTRACT

Context Drug induced pancreatitis are rare but potentially serious. Thus, drug withdrawal is warranted. **Case report** A 79-year-old woman who was treated with antituberculosis therapy for 5 weeks was admitted to our unit for pancreatitis. Usual etiologies of pancreatitis were eliminated. Because of vomiting, antituberculosis therapy was withdrawn and symptoms disappeared. Eight days later, the same treatment was reintroduced and the patient presented recurrent pancreatitis; thus, treatment was withheld again followed by disappearance of clinical and biological abnormalities. Two days later, a treatment without isoniazid was reintroduced and no recurrence of symptoms was observed. **Conclusions** We have experienced a case of isoniazid induced pancreatitis. This is a rare cause of pancreatitis but potentially fatal thus recognition of drug induced pancreatitis and definitive withdrawal of the drug is required.

INTRODUCTION

Drugs are a relatively rare cause of pancreatitis. Nevertheless drug-induced pancreatitis is potentially serious so, early recognition and drug withdrawal are warranted for rapid improvement. Isoniazid is a first-line agent used in treatment and chemoprophylaxis of tuberculosis. Its main adverse effects are hepatitis and peripheral neuropathy [1]. Herein we present a case of recurrent episodes of acute pancreatitis caused by isoniazid and a review of the literature.

CASE REPORT

A 79-year-old woman presented to the emergency department due to vomiting for two weeks, weight loss and low potassium levels (2.4 mmol/L; reference range: 3.5-4.5 mmol/L).
Her past medical history included hypertension, dyslipidemia, thyroid nodule, migraine headache and no history of gallbladder disease. Three weeks before her symptoms started, a diagnosis of pulmonary tuberculosis was done and a combination of antituberculosis drugs including ethambutol, rifampicin and isoniazid was started. Her usual treatment included long-term therapy with atenolol, hydrochlorothiazide, candesartan, simvastatin, vitamin D, calcium and magnesium, progesterone and estrogen supplementation. There was no history of alcohol abuse, self-medication or phytotherapy.
Laboratory investigations revealed elevation in serum lipase levels (1,026 IU/L; 3.4 x upper reference limit (URL)), with normal liver function tests and white cell count. Her serum triglyceride level was in normal range as well as calcium level. Abdominal ultrasonography and CT-scan showed normal pancreas and normal biliary tract. A MRCP performed later showed normal biliary system and no abnormalities of the pancreatic duct. Endoscopic ultrasonography was not performed due to patient's age.
Antituberculosis therapy was withdrawn. Symptoms and biological abnormalities decreased quickly and normalized within a week. Antituberculosis therapy was resumed eight days later. Vomiting recurred one hour later and lipase levels rose to 3.5 x URL. Treatment was withheld again followed by disappearance of clinical and biological abnormalities. Isoniazid was suspected as the cause of recurrent pancreatitis and definitely stopped. Two days later, a different combination of antituberculosis drugs including ethambutol, rifampicin, pyrazinamide and moxifloxacin was initiated. She was followed up to 2 months without recurrence of pancreatitis.

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DISCUSSION

Drug-related acute pancreatitis is uncommon, with a prevalence probably between 0.1-2% according to Nitsche *et al*. [2]. Since its discovery in 1952, isoniazid has remained a first-line drug in treatment and chemoprophylaxis of tuberculosis. Rifampicin, as well as isoniazid, has been rarely implicated as a cause of acute pancreatitis. Reviewing international literature (www.biourtox.com) we found 25 and 11 case reports of pancreatitis attributed to rifampicin and izoniazid, respectively (Table 1). Usually, causal relationship based on anecdotal case reports is a matter of controversy. Nevertheless, in our case acute pancreatitis is clearly attributed to isoniazid because pancreatitis resolved after antituberculosis therapy discontinuation, pancreatitis recurred quickly after resuming antituberculosis therapy and resolved again after its cessation and finally pancreatitis did not recurred after resuming a new antituberculosis regimen without isoniazid. According to the 11 case reports reviewed in the literature [3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13] (Table 1), acute pancreatitis associated with isoniazid develops within a median onset of 16 days (range: 0.5-35 days) after starting administration and consistently recurs earlier with a median onset of 9.4 days, (range: 1 h - 56 days) after rechallenge. In our case, pancreatitis was diagnosed 35 days after starting antituberculosis therapy. Most cases of drug- induced pancreatitis showed mild or moderate severity [2]. In isoniazid-induced pancreatitis, the outcome is usually favorable; indeed, clinical and biological abnormalities disappear after 2 hours to 2 weeks after discontinuation of isoniazid treatment [3], even after rechallenge. Nevertheless in one published case, outcome was fatal [4], probably because isoniazid was not quickly withdrawn after recurrence of pancreatitis due to rechallenge. Thereby, isoniazid should be definitely avoided if it is suspected reasonably as the cause of acute pancreatitis. Sometimes, the notion of drug-induced pancreatitis should be forgotten over the following years. Indeed, in the case reported by Chow *et al*. [5] a man who developed a first episode of pancreatitis after isoniazid treatment of genitourinary

Table 1. Main characteristics of the 11 reported cases of isoniazid-induced acute pancreatitis.

Case	Reference	Age/sex	Diagnosis	Daily isoniazid dose	Serum amylase (IU/L)	Serum lipase (IU/L)
#1	Chow *et al*. 2004 [5]	25/Male	Genitourinary TB	200 mg (5.5 mg/kg/day)	2,071 (16.2 URL)	-
#2	Chan *et al*. 1994 [6]	31/Male	Pulmonary TB	300 mg (5.4 mg/kg/day)	1,672	-
#3	Izzedine *et al*. 2001 [3]	80/Male	Spondylitis TB	300 mg	782 (6.5 URL)	180 (3 URL)
#4	Stephenson *et al*. 2001 [7]	42/Male	Spondylitis TB	300 mg	645	-
#5	Jin, Sable 2001 [8]	28/Female	Latent TB	-	292	550
#6	Sanchez, Boken 2004 [9]	53/Female	Latent TB	300 mg	243 (2.2 URL)	1,338 (4.5 URL)
#7	Rabassa *et al*. 1994 [10]	31/Male	Gastrointestinal TB	300 mg	758	-
#8	Dickson 1956 [4]	48/Female	Pulmonary TB	250 mg	-	-
#9	Mendoza *et al*. 1998 [11]	68/Male	Urinary TB	300 mg	487	1,837
#10	Briongos-Figuero *et al*. 2007 [12]	91/Female	TB, osteitis	250 mg	314	2,476
#11	Pandey, Surana 2011 [13]	20/Female	Lymph node TB	-	1,168 (13.6 URL)	15,460 (51.5 URL)
#12	Our case	79/Female	Pulmonary TB	300 mg	-	1,026 (3.4 URL)

TB: tuberculosis; URL: upper reference limit

Table 1. Continued.

Case	Time for acute pancreatitis after first isoniazid intake (day)	Time for acute pancreatitis after isoniazid rechallenge (day)	Evolution
#1	21	21	Favorable after withdrawal
#2	21	5	Favorable after withdrawal (in 7 and 5 days after the 1st challenge and the rechallenge, respectively)
#3	2	No rechallenge	Favorable after withdrawal (within a week)
#4	11	0.33	Favorable after withdrawal (over 5 days after withdrawal at 1st challenge)
#5	21	No rechallenge	Favorable after withdrawal
#6	21	No rechallenge	Favorable after withdrawal (within 2 days)
#7	14	0.25	Favorable after withdrawal
#8	12	0.5	Though recurrence of symptoms at rechallenge isoniazid was continued and patient died 9 days later. Post-mortem examination showed acute pancreatitis with necrosis
#9	0.5	No rechallenge	Favorable after withdrawal
#10	7	4	Favorable after withdrawal
#11	18	56	Favorable after withdrawal
#12	35	0.04	Favorable after withdrawal

tuberculosis with favorable outcome after isoniazid withdrawal but pancreatitis recurred 12 years later after rechallenging isoniazid for pulmonary tuberculosis.

It can be noticed that symptoms presented in our case report is quite uncommon. Nevertheless, pain can be absent in 5 to 10% of pancreatitis [14].

In conclusion, our case and the review of the international literature strongly suggest that isoniazid can induce rarely acute pancreatitis. It is expected that a larger number of patients with isoniazid-induced adverse reactions would be seen due to its increased use in the treatment and mostly for chemoprophylaxis (i.e., related to the growing use of biotherapy) of *Mycobacterium tuberculosis* infection. So, cases of isoniazid-induced pancreatitis would become more frequent. Isoniazid-induced pancreatitis is potentially fatal but usually reversible. Hence, the early recognition of pancreatitis and the quick withdrawal of isoniazid can avoid disastrous consequences.

Conflict of interest Authors have no conflicts of interest to declare

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