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CASE REPORT

Recurrent acute pancreatitis after isoniazid

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ABSTRACT

Drug-induced acute pancreatitis should be in the differential diagnosis of acute abdomen occurring soon after initiation of tuberculosis treatment and chemoprophylaxis. Isoniazid-induced pancreatitis is potentially reversible; early recognition and drug withdrawal are warranted in the appropriate clinical setting. We present a case of reversible acute pancreatitis after isoniazid treatment of genitourinary tuberculosis, followed by recurrence of pancreatitis 12 years later when the patient received isoniazid again for pulmonary tuberculosis. Isoniazid-induced pancreatitis, if highly suspicious or confirmed with re-challenge test, mandates permanent avoidance of the drug.

INTRODUCTION

Isoniazid has been used for treatment of *Mycobacterium tuberculosis* for over 50 years. Although it was initially considered to be free of serious side effects, the potential adverse effect of isoniazid hepatotoxicity has now become evident. Furthermore, as our experience with isoniazid accumulates, there have been more reports of isoniazid-induced pancreatitis in post-marketing surveillance. This category of adverse effect, albeit less frequent than hepatotoxicity, should be promptly recognised because development of acute pancreatitis mandates drug withdrawal and permanent isoniazid avoidance as illustrated in our case.

CASE REPORT

A 25-year-old Chinese patient with a history of systemic lupus erythematosus presented with malaise and progressive uraemic symptoms. There was no history of alcohol abuse. Plasma creatinine was 18.0 mg/dl (normal range, 0.6 to 1.4 mg/dl). Urinary sediment was unremarkable except for sterile pyuria. Advanced renal failure with quiescent lupus nephritis was diagnosed, followed by identification of acid-fast bacilli in the early morning urine. Intermittent peritoneal dialysis was commenced after Tenckhoff catheter insertion, together with implementation of quadruple tuberculosis treatment consisting of isoniazid 200 mg daily (5.5 mg/kg/day), rifampicin, pyrazinamide and ethambutol.

The patient developed acute severe pain in the epigastrium region three weeks after initiation of tuberculosis therapy, before the scheduled date for continuous ambulatory peritoneal dialysis training. Examination revealed diffuse abdominal tenderness. His serum and peritoneal dialysate amylase levels were 2071 U/l (normal range, 44-128 U/l) and 1478 U/l, respectively. An erect chest radiograph demonstrated right apical granuloma only. Abdominal sonography and computed tomographic imaging showed an oedematous pancreas, in the absence of biliary tract disease. The clinical picture of acute pancreatitis resolved with conservative management and withdrawal of isoniazid therapy. There were no other identifiable causes of acute pancreatitis.

Subsequent cadaveric kidney transplantation was complicated by progressive allograft dysfunction secondary to chronic rejection. Twelve years later, reactivation of tuber-

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culosis occurred with pulmonary involvement. When isoniazid 200 mg daily, rifampicin and levofloxacin were started, his plasma creatinine was 6.7 mg/dl with an estimated glomerular filtration rate of 12 ml/min/1.73 m^2.

After three weeks of tuberculosis therapy, the patient presented acutely with marked epigastric tenderness. The serum amylase level rose from 429 U/l to 2100 U/l within five days. He had been receiving prednisolone, cyclosporin and azathioprine for more than ten years, and the serum amylase levels were normal in between the two attacks. Ultrasound imaging confirmed the clinical impression of acute nonbiliary pancreatitis. Again, the pain resolved 72 hours after discontinuation of isoniazid, accompanied by biochemical and radiological evidence of improvement. No further bouts of pancreatitis were encountered thereafter.

DISCUSSION

Drug-related acute pancreatitis is uncommon.[1] As always, causal relationship based on anecdotal case report(s) has been a matter of controversy. Theoretically, it should be clearly documented that pancreatitis developed during treatment with the implicated drug, was reversed by withdrawal of the drug, and recurred when the drug was reintroduced.[2]
We have previously reported another end-stage renal disease patient with isoniazid-induced pancreatitis, which was supported by means of re-challenge test.[1] In case of tuberculosis therapy, controlled re-challenge with the drug suspected of causing pancreatitis is deemed necessary in view of the limited range of drugs available for *Mycobacterium tuberculosis* infection as well as the confounding drug culprit rifampicin.[3] Now considered the first-line essential antituberculous drug, isoniazid should be included in all tuberculosis treatment regimens unless contraindicated.

According to the case reports in literature,[1,4-9] acute pancreatitis associated with isoniazid develops within three weeks after drug administration and consistently recurs, with a much earlier onset, if re-challenged soon after resolution of pancreatitis (*table 1*). The role of concurrent rifampicin may not be directly contributory since this complication has been documented in several cases of isoniazid monotherapy (mostly chemoprophylaxis therapy).[4,6,9]
It remains unclear whether the reaction of isoniazid-induced pancreatitis occurs in a dose-dependent manner or in the setting of a hypersensitivity syndrome to isoniazid.

Given the short time lapse (i.e. hours between re-challenge and occurrence of pancreatitis (*table 1*), the latter is most likely. The current case allows us to evaluate recurrence of pancreatitis as isoniazid was re-introduced 12 years after the initial episode. Irrespective of the mechanisms of isoniazid-induced pancreatitis,[1] the message here is clear: isoniazid should be permanently avoided once it has been documented to cause acute pancreatitis.

Table 1
Well-documented case reports of isoniazid-induced acute pancreatitis

REFERENCE	SUBJECT SEX/AGE	ESRD	DAILY TREATMENT DOSE (MG)	DIAGNOSIS	AMYLASE IN SERUM (U/L)	ONSET (DAY(S)) OF PANCREATITIS AFTER START OF ISONIAZID	ONSET OF PANCREATITIS AFTER RE-CHALLENGE
4	F/43	-	300	Chemoprophylaxis, sarcoidosis	Not done	4	2 hours
5	M/31	-	300	Gastrointestinal tuberculosis	758	14	6 hours
6	M/68	-	300	Urinary bladder treatment	458	0.5	No re-challenge
1	M/31	+	300	Pulmonary tuberculosis, IgA nephropathy	1672	21	5 days
7	M/80	+	300	Tuberculous spondylitis, ischaemic nephropathy	782	2	No re-challenge
8	M/42	-	300	Tuberculous spondylitis	645	11	8 hours
9	F/28	-	300	Chemoprophylaxis	356	21	No re-challenge
Our case report	M/25	+	200	Genitourinary tuberculosis, systemic lupus erythematosus	2071	21	21 days

ESRD = end-stage renal disease, F = female, M = male.

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