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CASE REPORT

Methimazole-induced acute pancreatitis: a case report

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Abstract
A 76-year-old Japanese woman was diagnosed with Graves' disease and was administered methimazole (MMI) 10 mg and potassium iodide 50 mg. After 19 days of the drug regime, she developed high-grade fever and nausea and was admitted to our hospital. Blood test results showed elevated pancreatic enzymes and C-reactive protein levels. Abdominal computed tomography showed swollen pancreas, and she was diagnosed with acute pancreatitis. These abnormalities improved after discontinuation of MMI. Five similar cases have been reported, but this is the first case report without abdominal pain. When acute pancreatitis is observed after the initiation of MMI, drug-induced pancreatitis should be considered as the possible etiology.

Keywords Methimazole · Drug-induced pancreatitis · Acute pancreatitis

Introduction

Methimazole (MMI) is widely used in the treatment for Graves' disease. According to the drug interview form of MMI, side effects, including hypersensitivity (5.6%), leukocyte reduction (3.14%), digestive symptoms (1.91%), agranulocytosis (0.68%), and liver dysfunction (0.27%), were observed in 11.3% of patients using MMI. We have previously experienced a case of drug-induced pancreatitis caused by MMI. Acute pancreatitis was not described in the interview form as a side effect of MMI. Literature research showed five case studies of drug-induced pancreatitis caused by MMI. These reports described drug-induced pancreatitis accompanied by abdominal pain. We have reported here a rare case study of painless acute pancreatitis caused by MMI.

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Case report

In 2017, a 76-year-old Japanese woman with hand tremors visited our hospital. An enlarged thyroid gland was observed on the cervical echo images. Blood test results showed high free T4 level (2.8 ng/dL), low thyroid-stimulating hormone level (< 0.11 μIU/mL), and positive TSH-stimulating receptor antibodies (735%). She was diagnosed with Graves' disease, and a drug regime of 10 mg MMI and 50 mg potassium iodide was initiated. After 19 days of MMI administration, the patient developed nausea and fever (39.1 °C), and she visited our hospital again. Blood test results showed no major abnormality, including those with respect to white blood cell count (8.08×10^3/μL) and neutrophil count (4.61×10^3/μL). We continued MMI because her condition was stable. After 24 days of MMI administration, the patient was hospitalized because the fever had continued for 6 days.

The patient's medical history showed no allergies, history of autoimmune diseases, regular alcohol intake, or other drug use. She had no history of surgery or trauma and an unremarkable family medical history. Her height, weight, and body mass index were 144.8 cm, 28.6 kg, and 13.6 kg/m^2, respectively, on admission. She had a fever of 37.8 °C and increased respiration rate (24 times/min), but other vital signs were within the normal range. Physical examination including that of the abdomen, revealed no abnormalities. Blood test results showed elevated levels of C-reactive protein (CRP; 3.4 mg/dL), amylase (369 IU/L), and lipase

Table 1 Laboratory data on admission

Blood count		*Biochemistry*			
WBC	7000/μL	T-Bil	0.8 mg/dL	CRP	3.4 mg/dL
Neutro	74%	AST	44 L/U	Na	138 meq/L
Lymph	22%	ALT	65 L/U	K	4.2 meq/L
Mono	4%	ALP	1330 L/U	Cl	105 meq/L
Eosino	0.0%	γ-GTP	197 L/U	TSH	< 0.01 μ IU/mL
Baso	0.0%	BUN	11.5 mg/dL	fT3	4.3 pg/mL
RBC	4.57×10^6/μL	CRE	0.5 mg/dL	fT4	1.2 ng/dL
Hb	13.2 g/dL	T-CHO	161 mg/dL	IgG	1367 mg/dL
Plt	20.1×10^4/μL	HDL-CHO	62.9 mg/dL	IgM	42 mg/dL
		LDL-CHO	72 mg/dL	IgA	256 mg/dL
		TG	69 mg/dL	IgG4	38 mg/dL
		AMY	369 IU/L	CEA	2.4 ng/mL
		LYPASE	1060 U/L	CA19-9	< 2.0 U/mL
				DU-PAN	44 U/mL

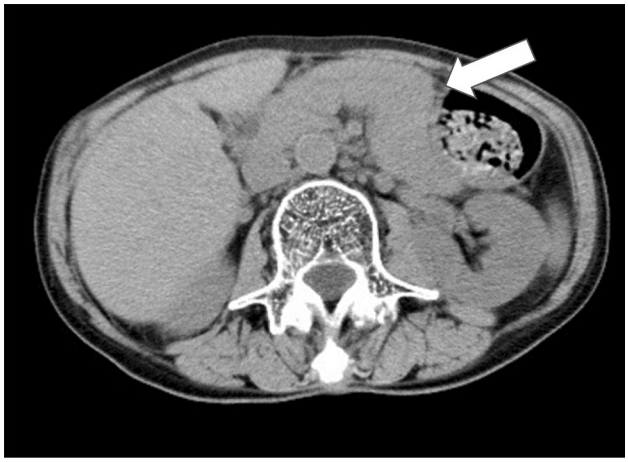

Fig. 1 CT on admission. It showed swollen pancreas

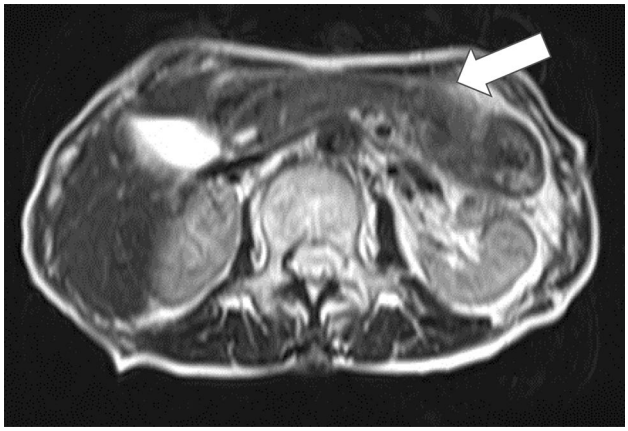

Fig. 2 MRI on admission. In the T2-wieghted image of MRI, the pancreas was swollen

(1060 U/L) (Table 1). Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) showed that the pancreas was swollen (Figs. 1, 2). And the CT showed no increased fat density around the pancreas.

We considered the condition to be acute pancreatitis and further investigated for its cause. Blood test results showed that immunoglobulins, including IgG4, lipids, and tumor markers were in the normal range. In the abdominal CT, no stones and tumors in the bile duct were observed. In the MRI the signal intensity of the pancreas was uniform, and no abnormal tumor signals were observed. In addition, coating-like structure, irregularity, stenosis, and expansion of the main pancreatic duct are well observed in IgG4-related pancreatitis, but these were not observed in this case.

Therefore, we hypothesized that the drug-induced pancreatitis was caused by MMI. MMI administration was immediately discontinued, and fluids and nutrition were provided intravenously. Three days after discontinuation of MMI, her fever rapidly decreased, and CRP and lipase levels also returned to normal. The swollen pancreas returned to normal size at the 1-month follow-up CT scan (Fig. 3). We did not re-administer MMI and we changed the drug to 200 mg potassium iodide. Afterward, no exacerbation was seen. Her clinical course is shown in Fig. 4.

Discussion

In this case, pancreatitis was more likely to be drug-induced because other causes of acute pancreatitis listed in the guidelines were less possible [1]. The diagnosis of drug-induced pancreatitis usually hinges on the following four criteria: (1) acute pancreatitis occurring during drug administration, (2) all other common causes of acute pancreatitis being excluded, (3) symptoms of acute pancreatitis disappearing after drug withdrawal, and (4) symptoms recurring after

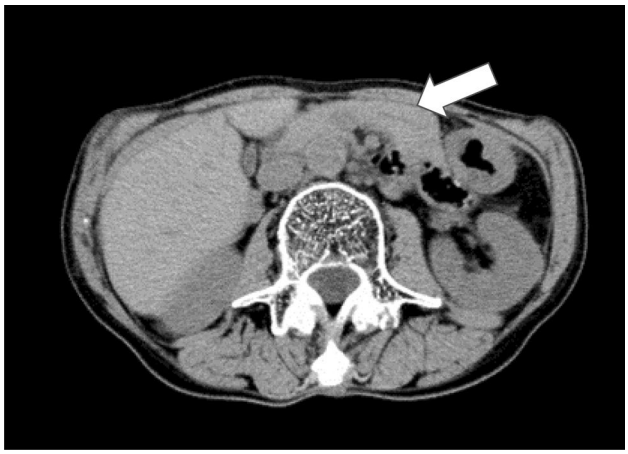

Fig. 3 The 1-month follow-up CT. The swollen pancreas returned to normal size

re-administration of the suspected drug [2]. She had been diagnosed with suspected drug-induced pancreatitis because this patient was not re-administered with MMI.

Anti-epileptic drugs (valproic acid, WHO reported 534 cases in 1968–2001), anti-HIV drugs (didanosine, WHO reported 304 cases in 1968–2001), 5-aminosalicylic acid drugs (mesalazine, WHO reported 201 cases in 1968–2001), and other drugs have been reported to induce drug-associated pancreatitis. However, reports on the drug-induced pancreatitis caused by MMI are rare. Acute pancreatitis was not mentioned as a side effect of MMI in the interview form. In PubMed, we searched for "pancreatitis" and "methimazole" or "methylmercaptoimmidazole", but there were only five reports of drug-induced pancreatitis caused by MMI from 1987 to 2017 [3–7]. We have summarized the previous five reports and this case in Table 2. Of the five patients, three were Asian women, and most patients had taken MMI for 2–3 weeks following which drug-induced pancreatitis had developed. There were four reports of reproducibility, and two, including our case, were not tested

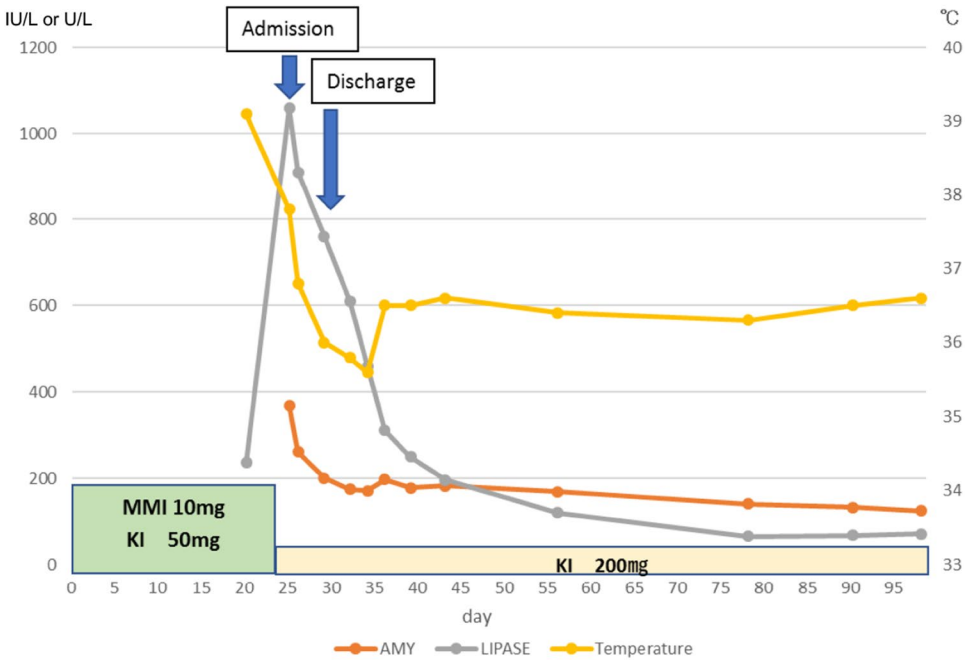

Fig. 4 Clinical course after admission of MMI (day 0). Fever and pancreatic enzymes elevation were improved quickly after discontinuation of MMI. MMI: thiamazole, KI: potassium iodide. The reference range of amylase and lipase are 29–116 IU/L and 16–88 U/L, respectively. Amylase was not measured on day 20

Table 2 Reported cases

References	Publised year	Country	Age	Sex	Time of symptoms onset	Abdominal pain	CT	Reproducibility
[3]	1998	Japan	66	Female	3 weeks	Yes	Normal	Yes
[4]	2001	China	18	Female	4 days	Yes	Normal	Yes
[5]	2012	USA	80	Female	3 months	Yes	PS, IF	Not tried
[6]	2014	Korea	51	Male	2 weeks	Yes	PS, IF	Yes
[7]	2015	USA	51	Female	3 weeks	Yes	PS, IF	Yes
This case	2017	Japan	76	Female	19 days	No	PS	Not tried

PS pancreas swelling, *IF* increased fat around woven concentration

for reproducibility. In addition, all the six patients' symptoms and examination findings improved after discontinuation of MMI. In the previous five reports, all patients had abdominal pain and acute pancreatitis was diagnosed based on abdominal pain and increased pancreatic enzyme levels or imaging findings, this was different from the diagnosis of the present case. According to Takeda, acute pancreatitis without abdominal pain is reported in approximately 5–10% patients [8]. Durr reported the frequency of painless acute pancreatitis in 3.5–22% patients [9]. In such cases, acute pancreatitis cannot be diagnosed if the blood test and imaging are not performed. Absence of abdominal pain in this case made the diagnosis more difficult. Based on literature, causes of painlessness acute pancreatitis include a decline in sensitivity to pain and expressive power of pain due to being elderly, awareness disorders due to diabetic coma, and neurological disorders in the pancreas [10, 11]. In this case study, the aspect of aging is consistent, but the obvious cause is unclear.

In addition, high-grade fever was observed in this case. According to a nationwide survey of acute pancreatitis, high-grade fever is observed in 5.7% patient of acute pancreatitis patients and 7.3% patient of severe acute pancreatitis patients [12]. In general, when patient with acute pancreatitis have high-grade fever, it is necessary to think about the possibility of the infection in the necrotic tissue of the pancreas. In the previous five case reports, three cases developed high-grade fever and two cases did not. Therefore, MMI-induced acute pancreatitis, even without necrosis, might cause high-grade fever more frequently than typical acute pancreatitis.

Lai et al. reported that the relationship between MMI and acute pancreatitis was not proven statistically in a population-based case–control study using national health insurance program of Taiwan [13]. However, as the authors pointed out, this study might be difficult to show the relationship, because only 0.68% of patients with acute pancreatitis and 0.56% of the control group took MMI in the study. The prevalence of Graves' disease is 0.5–1.0%, and MMI is the first choice of oral treatment of Graves' disease [14]. It is estimated that a large number of people have taken MMI. To prove the relationship, there is a need for much more cases to be compared.

Side effects of MMI include hypersensitivity, leukocyte reduction, digestive symptoms, agranulocytosis, and liver dysfunction. However, when the patient develops abdominal pain and/or fever after the administration of MMI, we should consider the possibility of drug-induced pancreatitis.

We experienced a case of painless acute pancreatitis induced by MMI. Clinicians prescribing MMI should be aware of this rare but important side effect.

Compliance with ethical standards

Conflict of interest Itsuka Kikuchi, Nobuyuki Miyata, Yukihiro Yoshimura, Kazunori Miyamoto and Natuo Tachikawa declare that they have no conflict of interest.

Research involving human and/or animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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