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Case Report

A Case of Methimazole-Induced Acute Pancreatitis With an HLA Allele Causing Antithyroid Drug-Induced Agranulocytosis

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Abstract

Among the side effects of methimazole (MMI) for the treatment of Graves' disease, MMI-induced acute pancreatitis (MIP) is a rare adverse reaction, with only 7 cases being reported to date. However, 2 large-scale population-based studies recently revealed that the risk of MIP was significantly higher, ranging from 0.02% to 0.56%. Although MIP is common in middle-aged and elderly Asian women, its pathogenesis remains largely unknown. We herein present a case of a 72-year-old Japanese woman with Graves' disease who developed MIP 12 days after the initiation of MMI. The MMI was discontinued, the patient was switched to propylthiouracil (PTU) therapy, and pancreatitis gradually resolved. Serological human leukocyte antigen (HLA) typing identified HLA-DRB1*08:03:02. This HLA allele was previously detected in a patient with MIP and is one of the major risk factors for agranulocytosis induced by antithyroid drugs, including PTU as well as MMI. In cases of MIP, PTU is being considered as an alternative to MMI; however, its safety needs further investigation and patients require close monitoring after the switch to PTU. Further studies are warranted, particularly on the relationship between MIP and the presence of HLA alleles causing antithyroid drug-induced agranulocytosis.

Key Words: methimazole, Graves' disease, acute pancreatitis, human leukocyte antigen

Abbreviations: AP, acute pancreatitis; BNP, brain natriuretic peptide; CRP, C-reactive protein; CT, computed tomography; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; HLA, human leukocyte antigen; IPM/CS, imipenem/cilastatin sodium; IVD, intravenous drip; KI, potassium iodide; MIP, methimazole-induced acute pancreatitis; MMI, methimazole; PTU, propylthiouracil; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TRAb, TSH-receptor antibody; TSH, thyrotropin (thyroid-stimulating hormone); WBC, white blood cell.

Methimazole (MMI) is a thionamide that is used as a first-line treatment for Graves' disease (GD). Mild side effects of MMI include skin rash and liver dysfunction, while the most severe side effect is agranulocytosis. Agranulocytosis most frequently occurs between 2 weeks and 3 months after the initiation of treatment. Other severe side effects include severe hepatotoxicity, vasculitis, and polyarthritis, which are more likely to occur during treatment with the thionamide propylthiouracil (PTU) than with MMI.

MMI-induced acute pancreatitis (MIP) is a rare adverse drug reaction, with only 7 cases being reported to date [1-7]. In 2019, the European Medicines Agency issued a warning about the relationship between MMI and acute pancreatitis (AP) [8]. Two large-scale population-based studies were subsequently performed in Denmark [9] and Italy [10], and the findings obtained revealed a risk of MIP ranging from 0.02% to 0.56%. This risk increased with age but did not differ with sex. Furthermore, MIP generally developed within 3 months of the initiation of MMI.

We herein present a case of MIP and discuss the potential relationship between a specific HLA allele and the development of MIP.

Case Report

A 72-year-old Japanese woman presented to our hospital with palpitations and dyspnea for 1 month and diarrhea for 1 week. The patient had a previous medical history of Sjögren syndrome, but no history of endocrine or hepatobiliary diseases or drug or food allergies. She was a nonsmoker and only consumed a small amount of alcohol on special occasions. There was no family history of endocrine or hepatobiliary disorders. A physical examination revealed tachypnea, orthopnea, excessive sweating, diffuse thyroid enlargement, arrythmia, and pitting edema of the bilateral lower limbs. The results of a laboratory examination were as follows: thyrotropin (TSH) < 0.003 μIU/mL (reference range, 0.50-4.30), free triiodothyronine (FT3) 13.5 pg/mL (2.30-4.10), free

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thyroxine (FT4) 4.17 ng/dL (0.70-1.70), TSH-receptor antibody (TRAb) 27.9 U/L (< 2.0), thyroglobulin antibody (TgAb) 85.0 IU/mL (< 28.0), thyroperoxidase antibody (TPOAb) > 600 IU/mL (< 16.0), and brain natriuretic peptide (BNP) 617.4 pg/mL (≤ 18.4). A thyroid examination with color Doppler ultrasonography revealed a diffusely enlarged thyroid gland with increased blood flow (Fig. 1). Bilateral pleural effusion was observed on chest x-ray. Electrocardiograms showed paroxysmal atrial fibrillation. Echocardiography disclosed abnormal motion of the left ventricular wall and impaired left ventricular systolic function. The concentration of FT3 was not disproportionately elevated, as observed in patients with GD. In addition, TPOAb and TGAb were both positive. Therefore, a differential diagnosis of thyrotoxicosis may include painless thyroiditis underlying Hashimoto disease. However, TPOAb and TGAb are also frequently positive in GD. In the present case, highly positive TRAb together with color Doppler findings on thyroid ultrasound excluded painless thyroiditis, leading to a diagnosis of GD. The patient was admitted for the treatment of GD complicated by acute heart failure, atrial fibrillation, and tachycardia-induced cardiomyopathy.

Fig. 2 summarizes the clinical course of the present case during hospitalization. Treatment for GD was initiated with MMI at 15 mg per day and potassium iodide (KI) at 50 mg per day. Atrial fibrillation was treated daily with apixaban at 5 mg (administration period: from 6 days before admission to post-discharge), diltiazem hydrochloride at 100 mg (from the ninth hospital day to post-discharge), and bisoprolol fumarate at 3.75 mg (from 6 days before admission to post-discharge). Acute heart failure was treated daily with torasemide at 4 mg (from 6 days before admission to post-discharge), digoxin at 0.125 mg (from the sixth to eighteenth hospital day), and tolvaptan at 7.5 mg (from the seventh to eighteenth hospital day). Her FT3 and FT4 levels gradually decreased and symptoms were attenuated.

On the twelfth hospital day, the patient developed a fever of 38.3 °C with acute abdominal pain and diarrhea. Pain was mainly localized to the periumbilical area, and was dull

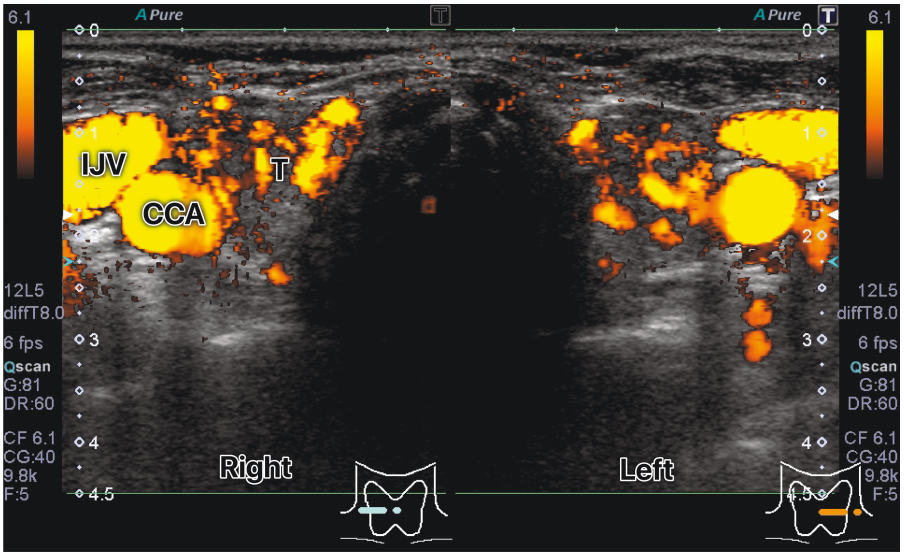

Figure 1. Color Doppler ultrasound findings of the patient on admission. A thyroid examination with color Doppler ultrasonography revealed a diffusely increased blood flow, which is typical of untreated Graves' disease. Abbreviations: IJV, internal jugular vein; CCA, common carotid artery; T, thyroid gland.

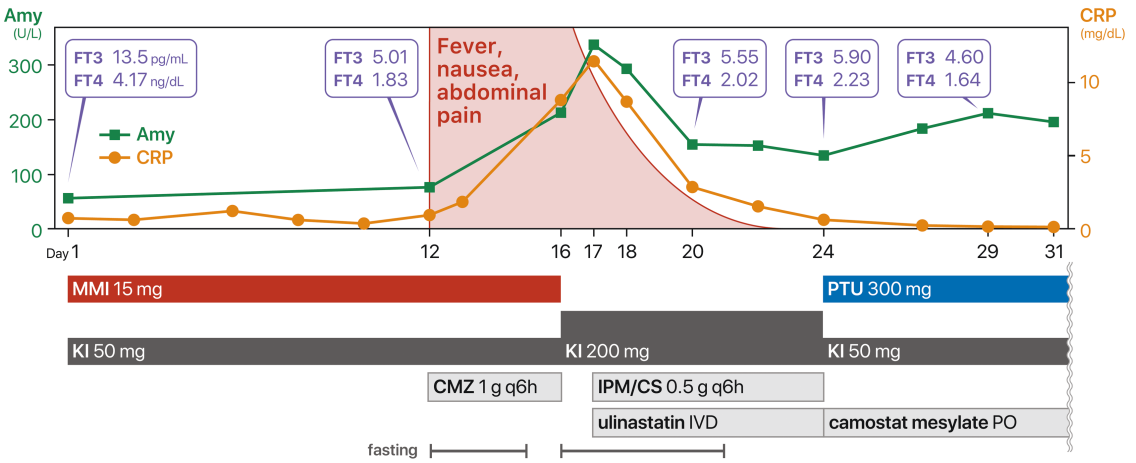

Figure 2. Clinical course during hospitalization. Abbreviations: Amy, amylase; CMZ, cefmetazole; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; IPM/CS, imipenem/cilastatin sodium; IVD, intravenous drip; KI, potassium iodide; MMI, methimazole; PO, *per os*; PTU, propylthiouracil.

in nature, nonradiating, and associated with nausea. There were no notable findings in the laboratory examination, except for a slightly elevated level of C-reactive protein (CRP) (0.98 mg/dL), and the serum level of amylase was normal (76 U/L). FT3 and FT4 levels were 5.01 pg/mL and 1.83 ng/dL, respectively. Abdominal plain computed tomography (CT) showed a relatively high-density area in fat tissues adjacent to the diverticulum of the ascending colon; therefore, diverticulitis was suspected. Empirical treatment with cefmetazole did not ameliorate fever or pain, and a blood culture showed no growth.

On the sixteenth hospital day, a laboratory examination revealed marked increases in the levels of pancreatic enzymes and CRP: amylase, 212 U/L (44-132); lipase, 923 U/L (13-55); elastase-1, 1537 ng/dL (22-221); and CRP, 9.97 mg/dL. The white blood cell (WBC) count was not elevated (4700/μL), with neutrophils accounting for 68.6%. Although the pancreas appeared to be intact on contrast-enhanced CT, based on the clinical presentation and laboratory data, acute pancreatitis was strongly suspected with a bedside index of severity in acute pancreatitis (BISAP) score of 1. The patient had no history of alcohol abuse, smoking, or hypertriglyceridemia (triglyceride level of 68 mg/dL). Furthermore, she was not hypercalcemic (corrected calcium level of 9.8 mg/dL), which ruled out hyperparathyroidism. The level of immunoglobulin G4 (IgG4) (114 mg/dL) did not meet the criterion for autoimmune pancreatitis. The results of abdominal contrast-enhanced CT and ultrasonography, together with the normal levels of the hepatic enzymes, alkaline phosphatase (ALP) and bilirubin, eliminated the possibility of cholelithiasis, biliary sludge, biliary dilatation, and choledocholithiasis. Based on exclusion diagnoses, MIP was suspected. MMI was withdrawn and the dose of KI was increased to 300 mg/day. On the seventeenth hospital day, imipenem/cilastatin sodium (IPM/CS) at 0.5 g every 6 hours (q6h) by an intravenous drip (IVD), ulinastatin IVD, and mild hydration (1500 mL/day) were started. Fever and abdominal pain completely resolved within a few days. The level of CRP returned to within normal ranges after 1 week. The IPM/CS was discontinued on the twenty-fourth hospital day, ulinastatin IVD was replaced by camostat mesylate per oral, and hydration was finished on the twenty-eighth hospital day.

On the twenty-fourth hospital day, a laboratory examination revealed the recurrence of hyperthyroidism (FT3: 5.90 pg/mL, FT4: 2.23 ng/dL). Therefore, PTU (300 mg) was introduced, and the KI was decreased to 50 mg/day. Hyperthyroidism was controlled without the exacerbation of pancreatitis. The patient was discharged on the thirty-second hospital day, and the course after discharge was uneventful. Table 1 summarizes changes in pancreatic enzyme and inflammatory marker levels. Pancreatic enzyme levels began to decrease after the discontinuation of MMI, but only normalized after several months (amylase 26 days, lipase 98 days, elastase-1 161 days). The oral camostat mesylate was discontinued 176 days after admission. Changes in CRP levels were consistent with the course of abdominal pain and pancreatic enzyme levels (Fig. 2). In contrast, WBC and neutrophil counts were not consistently elevated (Table 1).

Since adverse drug reactions correlate with specific human leukocyte antigen (HLA) alleles, serological HLA-DNA typing was performed and identified HLA-A*02:07:01—HLA-A*31:01:02, B*40:01—B*46:01:01, C*01:02—C*03:04:01, and DRB1*08:03:02—DRB1*09:01:02.

Table 1. Changes in pancreatic enzyme and inflammatory marker levels after the development of MIP

	Reference range	Day 12	Day 16	Day 17	Day 18	Day 19	Day 20	Day 22	Day 24	Day 27	Day 29	Day 31	Day 41	Day 50	Day 56	Day 79	Day 93	Day 113	Day 176	Day 239
Amylase	44 – 132 (U/L)	76	**212**	**336**	**292**	**167**	**154**	**152**	**134**	**183**	**211**	**195**	**120**[a]	**131**	**196**	**113**	**97**	**80**	**98**	**100**
Lipase	13 – 55 (U/L)	—	**923**	**1519**	—	—	**252**	**269**	**269**	**331**	—	—	**214**	**248**	**272**	**112**	**94**	**45**[a]	**67**	**64**
Elastase-1	22 – 221 (ng/dL)	—	**1537**	**3133**	—	—	**2194**	**1780**	**1703**	**1986**	—	—	**1050**	**781**	**788**	**285**	**249**	**239**	**162**[a]	**145**
CRP	≤ 0.14 (mg/dL)	0.98	9.97	13.06	9.84	5.12	3.17	1.66	0.61	0.17	0.08	0.05	0.06	1.01	0.17	0.07	0.64	0.79	0.05	0.07
WBC	3300 – 8600 (/μL)	6400	4700	5900	—	—	5500	5300	4300	3700	3500	3800	4400	—	3600	5100	4600	—	—	—
Neutrophils (/μL)		4358	3224	4419	—	—	2915	2380	2296	1258	1103	1273	1597	—	1400	2122	1881	—	—	—
Neutrophils	38.0 – 74.0 (%)	68.1	68.6	74.9	—	—	53.0	44.9	53.4	34.0	31.5	33.5	36.3	—	38.9	41.6	40.9	—	—	—

Serum pancreatic enzyme levels typed in boldface are those that exceeded the reference range.
Abbreviations: CRP, C-reactive protein; WBC, white blood cell.
[a]The first data in the reference range after the onset of acute pancreatitis.

Table 2. Published cases of MIP

Reference	Age/sex	Ethnicity	Diagnosis	Dose (mg)	Interval between start of MMI and development of pancreatitis	Rechallenge dose (mg)	Interval between start of MMI rechallenge and recurrence of pancreatitis	Presentation[a]	Blood examination findings[a]	Interval between elevation and normalization of pancreatic enzyme levels[b]	Acute pancreatitis findings on CT[a]	Alternative to MMI	HLA
Taguchi, 1999 [1]	66/F	Japanese	GD	30	3 weeks	10	3 hours	fever, abdominal pain	WBC 8600/μL, CRP 4.0 mg/dL, amylase 1335 U/L, lipase 2826 U/L	amylase 6 days, lipase 10 days, elastase-1 14 days	N	PTU 300 mg	A:26/-, B: 62/39, C: w3/w7, and DR: 4/14
Marazuela, 2002 [2][c]	33/F	NA	GD	45	1 month	10	24 hours	abdominal pain, weakness, vomiting	WBC 18300/μL, amylase 454 U/L, lipase 2280 U/L	NA	Y	RI	NA
Yang, 2012 [3]	18/F	Chinese	GD	20	4 days	10	a few hours	fever, abdominal pain	WBC normal, amylase 117 U/L, lipase 340 U/L	NA	N	PTU	NA
Abraham, 2012 [4]	80/F	Caucasian	NA	10	12 weeks	—	—	abdominal pain	WBC normal, amylase 371 IU/L, lipase 581 IU/L	lipase 4 days	Y	No alternative	NA
Jung, 2014 [5]	51/M	Korean	GD	20	2 weeks	10	5 hours	fever, chill, abdominal pain	WBC 5460/μL, CRP 4.67 mg/dL, amylase 86 IU/L	amylase 17 days	Y	PTU 150 mg	**DRB1*08:03** and DQB* 06:01
Agito, 2015 [6]	51/F	Caucasian	MNG	10	3 weeks	10	5 days	fever, abdominal pain, diarrhea	lipase 3512 U/mL	lipase 10 days	Y	RI	NA
Kikuchi, 2019 [7]	76/F	Japanese	GD	10	3 weeks	—	—	fever, nausea	WBC 8080/μL, CRP 3.4 mg/dL, amylase 369 IU/L, lipase 1060 U/L	lipase 3 days	Y	KI 200 mg	NA
Current case	72/F	Japanese	GD	15	2 weeks	—	—	fever, abdominal pain, nausea, diarrhea	WBC 6400/μL, CRP 9.97 mg/dL, amylase 212 U/L, lipase 923 U/L, elastase-1 1537 ng/dL	amylase 26 days, lipase 98 days, elastase-1 161 days	N	PTU 300 mg	A*02:07:01 – A*31:01:02, B*40:01 – B*46:01:01, C*01:02 – C*03:04:01, and **DRB1*08:03**:02 – DRB1*09:01:02

Abbreviations: CRP, C-reactive protein; CT, computed tomography; F, female; GD, Graves' disease; HLA, human leukocyte antigen; KI, potassium iodide; M, male; MMI, methimazole; MNG, multinodular goiter; N, no; NA, not available; PTU, propylthiouracil; RI, radioiodine; WBC, white blood cell; Y, yes.
[a]Presentation, blood examination findings, and acute pancreatitis findings on CT at the initial development of MIP.
[b]Interval between the elevation and normalization of pancreatic enzymes at the final development of MIP if patients developed the recurrence of MIP.
[c]In the case reported by Marazuela et al, carbimazole, not MMI was utilized.

Discussion

The diagnosis of drug-induced acute pancreatitis is generally based on the following criteria: (i) the development of pancreatitis during treatment with the drug; (ii) the absence of other likely causes of pancreatitis; (iii) the resolution of pancreatitis upon drug cessation; and (iv) the recurrence of pancreatitis upon the re-administration of the drug [11]. The present case was diagnosed with MIP because the patient fulfilled (i) to (iii); (iv) was not verified because of concerns that the re-administration of MMI may trigger the recurrence of MIP, as previously reported [1-3, 5, 6]. The patient was administered not only MMI, but also apixaban, diltiazem hydrochloride, bisoprolol fumarate, torasemide, digoxin, and tolvaptan at almost the same time as MMI; however, these drugs were not the cause of acute pancreatitis because the amelioration of symptoms was observed during the administration of these drugs. The overproduction of TNF-α plays a vital role in the pathogenesis of acute pancreatitis [12], and calcium channel blockers, such as diltiazem hydrochloride, have been shown to inhibit TNF-α release and improve survival in a rat model of acute pancreatitis [13]. It is important to note that despite the potential protective effects of diltiazem hydrochloride, the patient developed acute pancreatitis, which may be attributed to the potential role of various inflammatory mediators, such as IL-1β and IL-6, in the pathogenesis of acute pancreatitis [14].

Seven cases of MIP have been encountered since the initial case in our hospital in 1999 (Table 2) [1-7]. One of these 7 cases was drug-induced pancreatitis caused by carbimazole, a prodrug of MMI [2]. Most of the cases were middle-aged and elderly Asian women and all recovered after the discontinuation of MMI. The recurrence of MIP was observed in all 4 cases in which MMI was re-administered [1-3, 5, 6]. The interval between the start of MMI and the onset of MIP is generally several weeks, while the re-administration of MMI has been associated with the recurrence of MIP in a short period of time, ranging between several hours and several days. All previously reported cases of MIP were mild at the initial onset, sometimes with the absence of the common indications of acute pancreatitis: abdominal pain [7], an elevated WBC count [1, 2, 5], and acute pancreatitis findings on CT [1, 3]. Acute pancreatitis did not recur in any case after the switch from MMI to PTU. Consistent with these case reports, the present case was also an elderly woman who developed MIP 2 weeks after the initiation of MMI. The patient had typical clinical symptoms, such as abdominal pain, diarrhea, and fever, as well as elevated pancreatic enzymes and CRP; however, her WBC count was normal and CT showed no obvious signs of acute pancreatitis. The amelioration of symptoms was noted after the discontinuation of MMI, and the patient was switched to PTU without relapse.

Based on case reports, the European Medicines Agency issued a warning about the relationship between MMI and acute pancreatitis in 2019 [8]. Three studies on the risk of MIP were subsequently published based on large-scale databases. Two studies performed in Denmark [9] and Italy [10] showed that MMI correlated with an increased risk of AP, ranging from 0.02% to 0.56% [9, 10]. It is important to note that these rates were based on the percentage of new users of MMI who were hospitalized for acute pancreatitis and did not consider whether the cause of acute pancreatitis was MMI. The usage of MMI has been associated with a 56% increase

Table 3. Antithyroid drug-induced adverse reactions associated with specific HLAs as risk factors

	Reference	Drug	Ethnicity	Risk factor	Effect of risk factor
Agranulocytosis	Tamai, 1996 [16]	MMI	Japanese	**HLA-DRB1*08:03:02**	OR = 5.42 (P = 0.002)
	Chen, 2015 [17]	CBZ-MMI-PTU	Chinese	HLA-B*38:02:01	OR = 21.48 (95% CI 11.13 – 41.48, P = 6.28 × 10^-18)
				HLA-DRB1*08:03	OR = 6.13 (95% CI 3.28 – 11.46, P = 1.35 × 10^-8)
	Hallberg, 2016 [18]	CBZ-MMI-PTU	Caucasian	HLA-B*27:05	OR = 3.24 (95% CI 2.31 – 4.55, P = 1.20 × 10^-11)
	Cheung, 2016 [19]	CBZ-MMI	Chinese	HLA-B*38:02	OR = 265.5 (95% CI 27.9 – 2528.0, P = 2.5 × 10^-14)
	He, 2017 [20]	CBZ-MMI-PTU	Chinese	HLA-B*27:05	OR = 66.24 (95% CI 3.54 – 1239.66, P = 9.24 × 10^-5)
				HLA-B*38:02	OR = 7.525 (95% CI 2.294 – 24.68, P = 8.68 × 10^-4)
				HLA-DRB1*08:03	OR = 4.316 (95% CI 1.561 – 11.93, P = 2.8 × 10^-3)
	Nakakura, 2021 [21]	MMI-PTU	Japanese	HLA-B*39:01:01	OR = 3.66 (95% CI 2.41 – 5.57, P = 1.38 × 10^-3)
				HLA-DQB1*06:01:01	OR = 1.80 (95% CI 1.23 – 2.62, P = 1.89 × 10^-3)
				HLA-DQA1*01:03:01	OR = 1.78 (95% CI 1.22 – 2.59, P = 2.12 × 10^-3)
Liver injury	Li, 2019 [22]	MMI	Chinese	HLA-C*03:02	OR = 15.4 (95% CI 1.77 – 133.9, P = 1.1 × 10^-3)

Abbreviations: CBZ, carbimazole; CI, confidence interval; HLA, human leukocyte antigen; MMI, methimazole; OR, odds ratio; PTU, propylthiouracil.

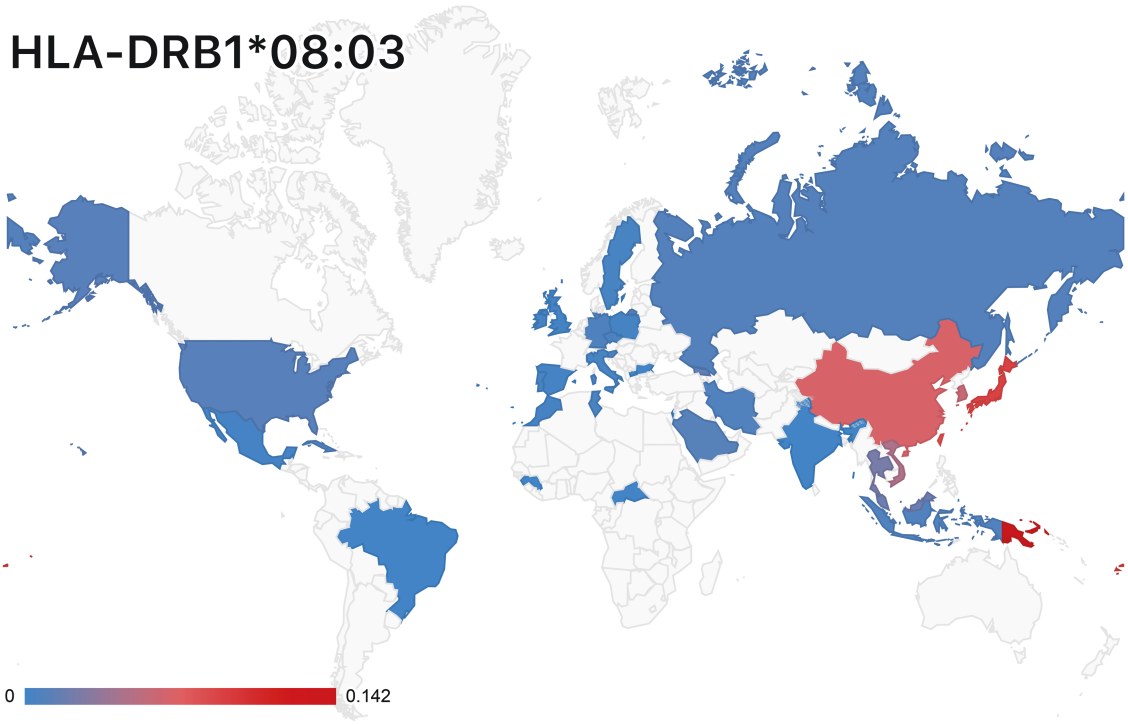

Figure 3. The geographic distribution of the frequency of HLA-DRB1*08:03. The map chart shows the geographic distribution of the frequency of HLA-DRB1*08:03 by country. In "HLA > Allele Frequency Search > Classical" of the Allele Frequency Net Database (http://www.allelefrequencies.net/) [22]), we searched the frequency of HLA-DRB1*08:03 in the following settings: Locus: DRB1, Starting Allele: DRB1*08:03, Ending Allele: DRB1*08:03, Population: All populations, Country: All countries, Source of dataset: Literature, Region: All regions, Type of Study: All Studies, Sort by: Allele, Highest to Lowest Frequency, Population standard: Gold only, Show frequencies. We then compiled allele frequency data by country and drew the map chart. We excluded data from Australia because only Aboriginal people were examined, which did not represent the overall population of the country. Abbreviation: HLA, human leukocyte antigen.

in the risk of being hospitalized due to acute pancreatitis [9]. Among new users of MMI, the risk of acute pancreatitis is higher in older populations and during the first 3 months of treatment initiation [6, 9, 10]. This risk was not associated with sex differences [10] or the cumulative dose-response effect [9]. In contrast, a large case-control study using the national health insurance program database of Taiwan did not show any increase in the risk of acute pancreatitis in MMI users [15]. Since this study did not take into account when patients started MMI, it may not have accurately assessed the risk of MIP, which is more likely to occur in new users of MMI.

The mechanisms underlying drug-induced acute pancreatitis are classified into the intrinsic toxicity of a drug and idiosyncratic reactions in the host. Idiosyncratic reactions are divided into the direct result of hypersensitivity and a secondary reaction to a toxic metabolite of the drug [11]. The clinical course of MIP follows the pattern of patient hypersensitivity [9]. Previous studies demonstrated that organ damage, such as agranulocytosis and liver injury due to hypersensitivity to antithyroid drugs, was associated with specific HLA, as summarized in Table 3 [16-22]. HLA typing in the present case identified DRB1*08:03:02. This allele is a major risk factor for agranulocytosis induced by carbimazole, MMI, and PTU [16-21]. HLA-DRB1*08:03 is also a risk factor for primary biliary cholangitis [23] and systemic lupus erythematosus [24]. Based on the Allele Frequency Net Database (http://www.allelefrequencies.net/) [25], the frequency of HLA-DRB1*08:03 is higher in Asian countries, as shown in Fig. 3. We were unable to validate the correlation between the allele and the risk of MMI due to the insufficient number of case reports of MIP. Nevertheless, the hypothesis that HLA alleles common in Asian populations are risk factors is consistent with the majority of MIP cases reported to date being Asian patients. In addition to the present case, 1 Korean patient had HLA-DRB1*08:03 [5]. Compared to typical cases of MIP or drug-induced AP, the level of pancreatic enzymes in both patients took longer to recover to normal levels after the discontinuation of MMI [26, 27]. The reason for this currently remains unknown. Other than HLA-DRB1*08:03, none of the HLA alleles identified in the present case were associated with GD or MIP in our literature review.

HLA-DRB1*08:03 is a risk factor for agranulocytosis induced not only by MMI, but also by PTU. A switch to PTU is generally contraindicated when agranulocytosis occurs with MMI. Although MIP did not recur in any of the 4 previous case reports, including the present case [3, 5, 16], careful monitoring may be needed after the switch to PTU. On the other hand, if acute pancreatitis is exclusively induced by MMI and not by PTU, MMI-specific factors, such as a reduction reaction by the sulfhydryl (SH) group, may also be involved in the development of MIP. A reduction reaction by the sulfhydryl group of MMI has been shown to play an essential role in the development of insulin autoimmune syndrome. The sulfhydryl group of MMI cleaves the disulfide bond of insulin molecules, leaving the fragment on the α-chain exposed to HLA-DRB1*04:06 on antigen-presenting cells. This fragment binds specifically to HLA-DRB1*04:06 with high affinity, and this binding ac-

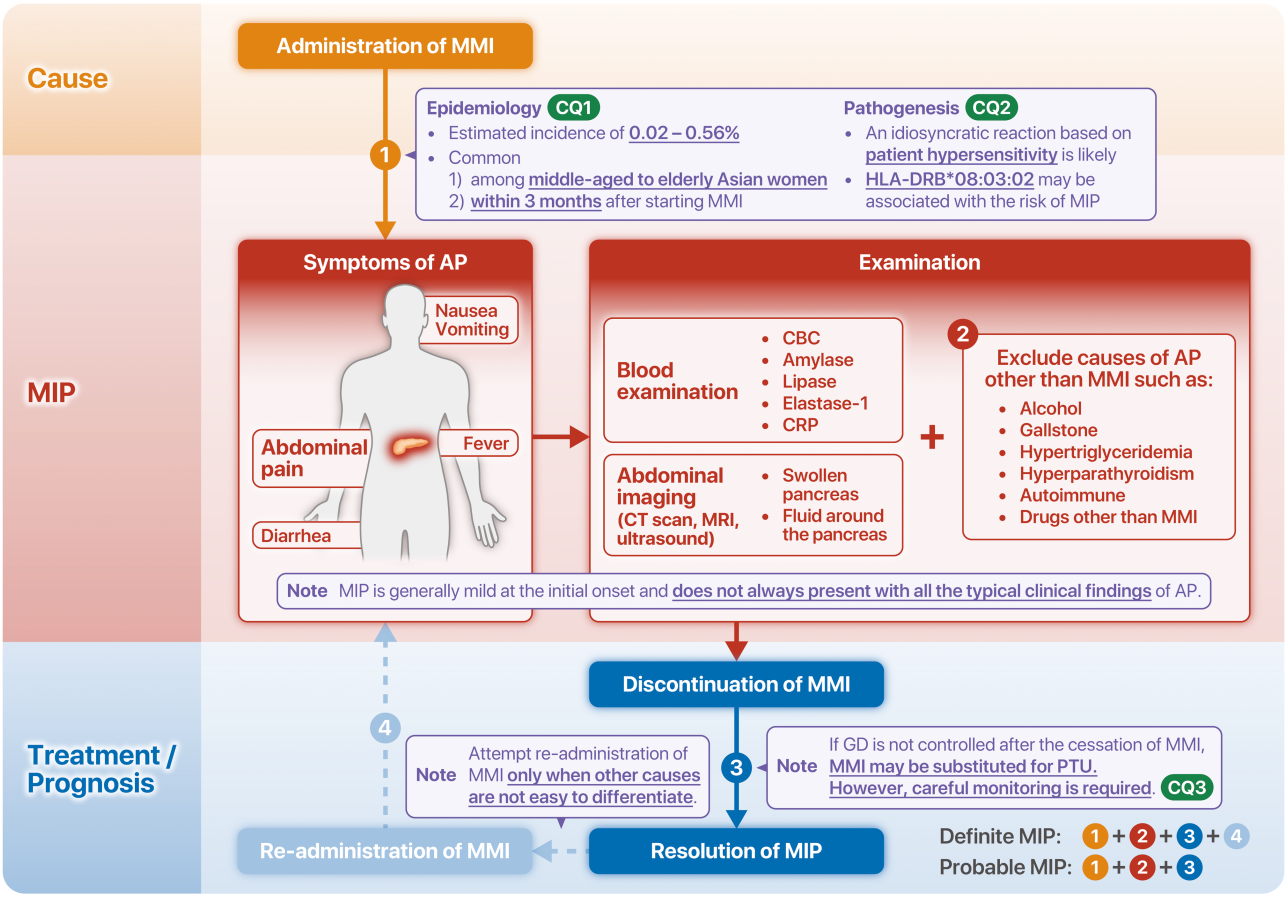

Figure 4. A schematic diagram of current insights and future perspectives on MIP. Abbreviations: AP, acute pancreatitis; CBC, complete blood count; CQ, clinical question; CRP, C-reactive protein; CT, computed tomography; GD, Graves' disease; HLA, human leukocyte antigen; MIP, methimazole-induced acute pancreatitis; MMI, methimazole; MRI, magnetic resonance imaging; PTU, propylthiouracil.

tivates self-insulin-specific T helper cells, leading to insulin autoimmune syndrome [28].

Future Directions and Recommendations

Figure 4 is a schematic diagram of current insights and future perspectives on MIP. When a patient presents with fever and gastrointestinal symptoms with elevated serum pancreatic enzyme levels within 3 months of the initiation of MMI, clinicians need to suspect MIP and consider discontinuing MMI. The frequency of MIP is estimated to range from 0.02% to 0.56%; however, its actual frequency remains unclear because only 8 cases, including the present case, have been reported to date. This is most likely due to the lack of recognition of MIP. MIP may be overlooked because there are cases that do not necessarily exhibit the typical clinical symptoms and findings of AP. The actual incidence of MIP will be clarified by increasing the recognition and number of case reports of MIP (clinical question 1 [CQ1] shown in Fig. 4).

The pathogenesis of MIP remains largely unknown. HLA-DRB1*08:03, one of the major risk factors for antithyroid drug-induced agranulocytosis, was commonly observed in 2 patients, including the present case. Therefore, the relationship between specific HLA alleles and MIP needs to be investigated by accumulating more cases in the future (CQ2).

In previous case reports, as well as in our case, PTU was used as an alternative to MMI without adverse effects when MIP developed. However, in the case of agranulocytosis treated with MMI, a change from MMI to PTU is contraindicated due to the high risk of the recurrence of agranulocytosis due to their cross-reactivity. Since MIP may share specific risk HLA allele(s) with agranulocytosis, careful monitoring is needed after switching to PTU, and its safety warrants further investigation (CQ3).

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Disclosures

The authors have no competing financial interests or conflicts of interest to declare.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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