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

Yusuke Yoshimura,† Keita Tatsushima,† Yukiko Goshima,† Yoshitomo Hoshino,† Saki Nakashima,† Tatsuro Inaba,† Sara Ikeda,† Daisuke Hattori,‡ Rikako Koyama,‡ Tsunao Imamura,‡ Akira Takeshita,†,* and Yasuhiro Takeuchi†

†Department of Endocrinology and Metabolism, Toranomon Hospital, Minato-ku, Tokyo 105-8470, Japan; ‡Department of Gastroenterology, Toranomon Hospital, Minato-ku, Tokyo 105-8470, Japan; and †Okinaka Memorial Institute for Medical Research, Minato-ku, Tokyo 105-8470, Japan.

Correspondence: Akira Takeshita, MD, PhD, Department of Endocrinology and Metabolism, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo, 105-8470, Japan. Email: coactivator@mac.com.

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, arrhythmia, and pitting edema of the bilateral lower limbs. The results of a laboratory examination were as follows: thyrotropin (TSH) < 0.003 µU/mL (reference range, 0.50-4.30), free triiodothyronine (FT3) 13.5 pg/mL (2.30-4.10), free

Received: 18 January 2022. Editorial Decision: 6 March 2022. Corrected and Typeset: 7 April 2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the Endocrine Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Advance access publication 10 March 2022
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 after the development of MIP.

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    | 334    | 211    | 195    | 120    | 131    | 196    | 113    | 97     | 80     | 98     | 100    | 64     | 64     |
| Lipase         | 13–55 (U/L)  | —      | 923    | 2194   | 1780   | 1793   | 1986   | —      | 214    | 298    | 272    | 112    | 94     | 62     | 67     | 64     | 64     |
| Elastase-1     | 22–221 (ng/dL) | —     | 1537   | 3133   | —      | 2194   | 3133   | —      | —      | 317    | 1.66   | 0.61   | 0.17   | 0.08   | 0.05   | 0.07   | 0.07   | 0.07   |
| CRP            | ≤ 0.14 (mg/dL) | 0.98  | 9.97   | 13.06  | 8.94   | 5.12   | 3.17   | 1.66   | 0.61   | 0.17   | 0.08   | 0.05   | 0.06   | 0.10   | 0.07   | 0.07   | 0.07   | 0.07   |
| WBC            | 3300–8600 (/µL) | 4538  | 3247   | 4538   | 3247   | 4494   | 3185   | 1881   | 1400   | 1288   | 1103   | 3700   | 3500   | 3800   | 4400   | 4000   | 4000   | 4000   |
| Neutrophils    | 5500–8500 (/µL) | —    | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   | 5500   |
| Neutrophils (%)| 38.0–74.0 (%)  | 68.1  | 57.0   | 44.9   | 41.6   | 38.9   | 36.3   | 38.9   | 36.3   | 38.9   | 36.3   | 38.9   | 36.3   | 38.9   | 36.3   | 38.9   | 36.3   | 38.9   |

Serum pancreatic enzyme levels typed in boldface are those that exceeded the reference range.

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 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 | Blood examination findings | Interval between elevation and normalization of pancreatic enzyme levels | Acute pancreatitis findings on CT | 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*26:01, B*62/39, C* w3/w7, and DR: 4/14 |
| Marazuela, 2002 [2] | 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 447 U/L, lipase 340 U/L | N | PTU | NA |
| Abraham, 2012 [4] | 80/F | Caucasian | NA | 10 | 12 weeks | — | — | abdominal pain | WBC normal, amylase 571 U/L, lipase 581 U/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 U/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 | WBC 8080/µL, CRP 3.4 mg/dL, amylase 369 IU/L, lipase 1060 U/L | 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*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.

1Interval between the elevation and normalization of pancreatic enzymes at the final development of MIP if patients developed the recurrence of MIP.

2Presentation, blood examination findings, and acute pancreatitis findings on CT at the initial development of MIP.

3In 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
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 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.](http://www.allelefrequencies.net/)
activates 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).

Funding

This work was supported by the Okinaka Memorial Institute for Medical Research to A.T.

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.

References

1. Taguchi M, Yokota M, Koyano H, Endo Y, Ozawa Y. Acute pancreatitis and parotitis induced by methimazole in a patient with Graves’ disease. Clin Endocrinol (Oxf). 1999;51(5):667-670. doi:10.1046/j.1365-2265.1999.00888.x
2. Marazuela M, Sanchez de Paco G, Jimenez I, et al. Acute pancreatitis, hepatic cholestasis, and erythema nodosum induced by carbimazole treatment for Graves’ disease. Endocr J. 2002;49(3):315-318. doi:10.1507/endocrj.49.315
3. Yang M, Qu H, Deng HC. Acute pancreatitis induced by methimazole in a patient with Graves’ disease. Thyroid. 2012;22(1):94-96. doi:10.1089/thy.2011.0210.
4. Abraham A, Raghavan P, Patel R, Rajan D, Singh J, Mustacchia P. Acute pancreatitis induced by methimazole therapy. Case Rep Gastroenterol. 2012;6(2):223-231. doi:10.1159/000338352
5. Jung JH, Hahn JR, Jung J, et al. Acute pancreatitis induced by methimazole treatment in a 51-year-old Korean man: a case report. J Korean Med Sci. 2014;29(8):1170-1173. doi:10.3346/jkms.2014.29.8.1170
6. Agito K, Manni A. Acute pancreatitis induced by methimazole in a patient with subclinical hyperthyroidism. J Investig Med High Impact Case Rep. 2015;3(2):1-4. doi:10.1177/2324709615592229
7. Kikuchi I, Miyata N, Yoshimura Y, Miyamoto K, Tachikawa N. Methimazole-induced acute pancreatitis: a case report. Clin J Gastroenterol. 2019;12(3):239-242. doi:10.1007/s12328-018-0926-5
8. European Medicines Agency. PRAC recommendations on signals. 2019. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-26-29-november-2018-prac-meeting_en.pdf
9. Brix TH, Lund LC, Henriksen DP, et al. Methimazole and risk of acute pancreatitis. Lancet Diabetes Endocrinol. 2020;8(3):187-189.
10. Pecere A, Caputo M, Sarro A, et al. Methimazole treatment and risk of acute pancreatitis: a population-based cohort study. J Clin Endocrinol Metab. 2020;105(12):e4527-e4530. doi:10.1210/clinem/dgaa544
11. McArthur KE. Review article: drug-induced pancreatitis. Aliment PharmacolTher. 1996;10(1):23-38. doi:10.1111/j.1365-2036.1996.tb00174.x
12. Malleo G, Mazzon E, Siriwardena AK, Cuzzocrea S. TNF-alpha as a therapeutic target in acute pancreatitis—lessons from experimental models. Sci World J. 2007;7:431-448. doi:10.1100/ tsw.2007.98
13. Hughes CB, el-Din AB, Kotb M, Gaber LW, Gaber AO. Calcium channel blockade inhibits release of TNF alpha and improves survival in a rat model of acute pancreatitis. Pancreas. 1996;13(1):22-28. doi:10.1097/00006676-199607000-00003
14. Bhatia M, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J. Inflammatory mediators in acute pancreatitis. J Pathol. 2000;190(2):117-125. doi:10.1002/(SICI)1096-9866(200002)190:2<117::AID-PATH494>3.0.CO;2-K
15. Guo J-Y, Chang C-L, Chen C-C. Association between thionamides and acute pancreatitis: a case-control study. Thyroid. 2020;30(11):1574-1578. doi:10.1089/thy.2019.0589
16. Tamai H, Sudo T, Kimura A, et al. Association between the DRB1*08032 histocompatibility antigen and methimazole-induced agranulocytosis in Japanese patients with Graves disease. Ann Intern Med. 1996;124(5):490-494. doi:10.7326/0003-4819-124-5-19960310-00005
17. Chen PL, Shih SR, Wang PW, et al. Genetic determinants of antithyroid drug-induced agranulocytosis by human leukocyte antigen genotyping and genome-wide association study. Nat Commun. 2015;6:7633. doi:10.1038/ncomms8633
18. Hallberg P, Eriksson N, Ibañez L, et al. Genetic variants associated with antithyroid drug-induced agranulocytosis: a genome-wide association study in a European population. Lancet Diabetes Endocrinol. 2016;4(6):507-516. doi:10.1016/S2213-8587(16)00113-3
19. Cheung CL, Sing CW, Tang CSM, et al. HLA-B*38:02:01 predicts carbimazole/methimazole-induced agranulocytosis. Clin Pharmacol Ther. 2016;99(5):555-561. doi:10.1002/cpt.309
20. He Y, Zheng J, Zhang Q, et al. Association of HLA-B and HLA-DRB1 polymorphisms with antithyroid drug-induced agranulocytosis in a Han population from northern China. Sci Rep. 2017;7(1):11950. doi:10.1038/s41598-017-12350-2
21. Nakakura S, Hosomichi K, Uchino S, et al. HLA-B*39:01:01 is a novel risk factor for antithyroid drug-induced agranulocytosis in Japanese population. Pharmacogenomics J. 2021;21(1):94-101. doi:10.1038/s41397-020-00187-4
22. Li X, Jin S, Fan Y, et al. Association of HLA-C*03:02 with methimazole-induced liver injury in Graves’ disease patients. Biomed Pharmacother. 2019;117:109095. doi:10.1016/j.biopha.2019.109095
23. Onishi S, Sakamaki T, Maca T, et al. DNA typing of HLA class II genes; DRB1*0803 increases the susceptibility of Japanese to primary biliary cirrhosis. J Hepatol. 1994;21(6):1053-1060. doi:10.1016/s0168-8278(05)80617-8
24. Morimoto S, Hashimoto H, Yamanaka K, et al. Multicenter cooperative study of HLA class II alleles in Japanese patients with systemic lupus erythematosus. Mod Rheumatol. 2000;10(4):235-239. doi:10.3109/10496180001317009
25. Gonzalez-Galarza FF, McCabe A, Santos EJMD, et al. Allele frequency net database (AFND) 2020 update: Gold-standard data classification, open access genotype data and new query tools. Nucleic Acids Res. 2020;48(D1):D783-D788. doi:10.1093/nar/gkz1029
26. Ticktin HE, Trujillo NP, Evans PF, Roe JH. Diagnostic value of a new serum lipase method. Gastroenterology. 2016;48(1):12-17.
27. Zieve L. Clinical value of determinations of various pancreatic enzymes in serum. Gastroenterology, 1964;46:62-67.
28. Matsushita S, Takahashi K, Motoki M, Komoriya K, Ikagawa S, Nishimura Y. Allele specificity of structural requirement for peptides bound to HLA-DRB1*0405 and -DRB1*0406 complexes: implication for the HLA-associated susceptibility to methimazole-induced insulin autoimmune syndrome. J Exp Med. 1994;180(3):873-883. doi:10.1084/jem.180.3.873