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【 ORIGINAL ARTICLE 】

Clinical Studies on Potassium Iodide-induced Painless Thyroiditis in 11 Graves' Disease Patients

Keiichi Kamijo

Abstract:

Objective Painless thyroiditis (PT) is characterized by transient hyperthyroidism with a low ^{99m}Tc uptake. We herein describe 11 cases of PT that occurred during treatment with potassium iodide (KI) for Graves' disease (GD).

Methods From August 2016 to December 2018, 11 women with GD who developed PT during treatment with KI were enrolled. Of these patients, 10 discontinued antithyroid drug (ATD) because of side effects and began KI, and 1 patient switched from thiamazole to KI because she was planning a pregnancy. The mean patient age was 40.1 years old. Thyroid function tests, thyroid autoantibodies including anti thyroglobulin antibody (TgAb), anti-thyroperoxidase antibody (TPOAb), and M22-TRAb, and the ^{99m}Tc uptake were evaluated at the time of PT.

Results All 11 women patients presented with transient thyrotoxicosis in which ^{99m}Tc scans revealed a low uptake of 0.34±0.15% (normal 0.70-1.02%). M22-TRAb was absent in all cases except for one (2.4 IU/L), whereas TgAb and TPOAb were present in 10 and 6 cases, respectively. Ten patients returned to a euthyroid status without passing through the post-hypothyroid phase, and one patient underwent total thyroidectomy during the euthyroid phase of PT. Only four patients require beta-blocker therapy. All patients with KI-induced PT except 1 displayed GD remission during a mean observation period of 23.3 months, and 1 patient had recurrence of GD after PT.

Conclusion We encountered 11 GD patients who developed PT during treatment with KI, which was initiated after ATD had been discontinued due to side effects.

Key words: painless thyroiditis, potassium iodide, Graves' disease

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Introduction

The administration of stable iodine to hyperthyroid patients provides a clinical benefit (1-3). In Japan, where the iodine intake is sufficient, among hyperthyroid patients with antithyroid drug (ATD)-associated side effects, potassium iodide (KI) therapy is effective in two-thirds of cases, and about 40% of patients experience remission after KI therapy alone (4). In patients with mild Graves' disease (GD), KI is a possible alternative initial treatment for this condition (5).

Painless thyroiditis (PT also called silent thyroiditis) can be subclassified into the sporadic type (unrelated to pregnancy), postpartum thyroiditis, gestational PT (6), exogenous PT, and others.

We herein report cases of KI-induced PT that occurred during treatment for GD, mostly after the cessation of ATD due to side effects.

Materials and Methods

From August 2016 to December 2018, 11 patients who met the eligibility criteria and gave their written informed consent were enrolled in the study. The study cohort comprised 11 women who developed PT during treatment with KI at 50 mg or 100 mg daily (50 mg KI is equivalent to 38.2 mg inorganic iodide; Nichiiko, Tokyo, Japan) for GD. These patients were outpatients of the Kamijo Thyroid

Department of Internal Medicine, Kamijo Thyroid Clinic, Japan
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Correspondence to Dr. Keiichi Kamijo, katt@cocoa.ocn.ne.jp

Table 1. Summary of the Clinical and Laboratory Findings and Thyroid Tests at the Diagnosis of PT in 11 Patients with KI-induced PT.

Case No.	Age (years)	Reason for use of KI	KI dose (mg)	FT4 levels (N: 0.80-1.90 ng/dL)	FT3 levels (N: 2.00-4.40 pg/mL)	TSH levels (N: 0.45-4.50 μU/mL)	Thyroid weight (10-25 g)	^{99m}Tc uptake (N: 0.70-1.02%)	M22-TRAb (N: ≤2.0 IU/L)	TPOAb (N: <30 IU/mL)	TgAb (N:<40 IU/mL)
1	29	Side effect of PTU	38.2	2.74	6.51	<0.01	26	0.59	0.3	597.1	775
2	21	Side effect of MMI	76.4	3.81	10.34	<0.01	43	0.27	0.5	92.2	72.7
3	38	Side effect of MMI	38.2	3.06	8.53	<0.01	36	0.21	2.4	17.4	2,023
4	55	Side effect of MMI	76.4	2.04	6.67	<0.01	25	0.30	0.3	<5.0	301.4
5	56	Side effect of MMI	38.2	2.34	4.5	<0.01	23	0.33	0.7	126.2	1,035
6	53	Side effect of MMI	38.2	4.74	14.77	<0.01	35	0.65	0.3	600	496.3
7	37	Side effect of MMI and PTU	38.2	4.64	10.63	<0.01	34	0.26	1.3	14.6	68.3
8	38	Planning a pregnancy	38.2	2.34	5.73	<0.01	33	0.29	0.3	<5.0	301.4
9	34	Side effect of MMI	76.4	2.77	6.55	<0.01	36	0.21	0.6	536.3	684.4
10	52	Side effect of MMI	38.2	2.51	5.51	<0.01	34	0.39	0.3	119.7	4,000
11	28	Side effect of MMI	76.4	2.01	5.05	<0.01	50	0.20	1.9	12.8	19.5
		Mean±standard deviation	52.1±19.3	3.00±0.98	7.71±3.10		34.1±7.0	0.34±0.15			
		Range	38.2-76.4	2.01-4.74	4.50-14.77		23-50	0.20-0.65			

PT: painless thyroiditis, KI: potassium iodide, PTU: propylthiouracil, MMI: methylmercaptoimidazole, TPOAb: anti-thyroperoxidase antibody, TgAb: anti-thyroglobulin antibody

Clinic, and the median age at the diagnosis was 40 years old (range, 21-56 years old). Ten GD patients discontinued thionamide due to side effects and began to take KI. The remaining patient discontinued methylmercaptoimidazole (MMI) and switched to KI because she was planning a pregnancy.

Tests (normal ranges in parentheses) were performed with an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) for free thyroxine (FT4) (0.80 to 1.90 ng/dL), free triiodothyronine (FT3) (2.00-4.40 pg/mL), and thyrotropin (TSH) (0.45-4.50 μU/mL). The thyroid weight was estimated by the previously reported method (7). The normal range of female thyroid weight is 15 to 25 g. The cut-off values of anti-thyroperoxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) were 30 and 40 IU/L, respectively, and the values were calculated by a receiver operating characteristic (ROC) analysis based on patients with Hashimoto's disease and normal controls pathologically diagnosed according to resected tissue (data not shown). The M22-TRAb levels were measured with the inhibition assay kit Elecsys anti-TSH receptor assay (Roche Diagnostic) according to the manufacturer's instructions (8). This assay detects M22-TRAb via the inhibition of a monoclonal antibody (M22), which binds to the extracellular domain of porcine TSH receptor. M22-TRAb was considered present when the value exceeded 2.0 IU/L (8). The intra- and inter-assay coefficients of variation for M22-TRAb in 4 different serum samples ranged from 0.8-9.4% and 1.3-22.0%, respectively. The 20-minute uptake of ^{99m}Tc pertechnetate was assessed immediately after thyrotoxicosis was diagnosed. According to the ROC analysis with untreated GD (n=1,234) and PT (n=679), the ^{99m}Tc uptake cut-off value was to be 1.02%. The sensitivity and specificity of the optimal cut-off value were 99.8% and 100%, respectively. When the ^{99m}Tc uptake is <0.70%, all thyrotoxic patients are considered to have PT. Thus, the reference range is 0.70% to 1.02%.

The diagnosis of PT was based on 1) a transient increase in FT3 and FT4 with suppressed TSH (<0.01 μU/mL), 2) a painless thyroid gland, and 3) a marked decrease in the thyroid ^{99m}Tc uptake. In all cases, PT occurred during treatment with KI. None of the 11 patients were using levothyroxine or amiodarone at the time of the diagnosis.

Results

Enrollment and characteristics of patients with KI-induced PT

Table 1 summarizes the clinical and laboratory findings of

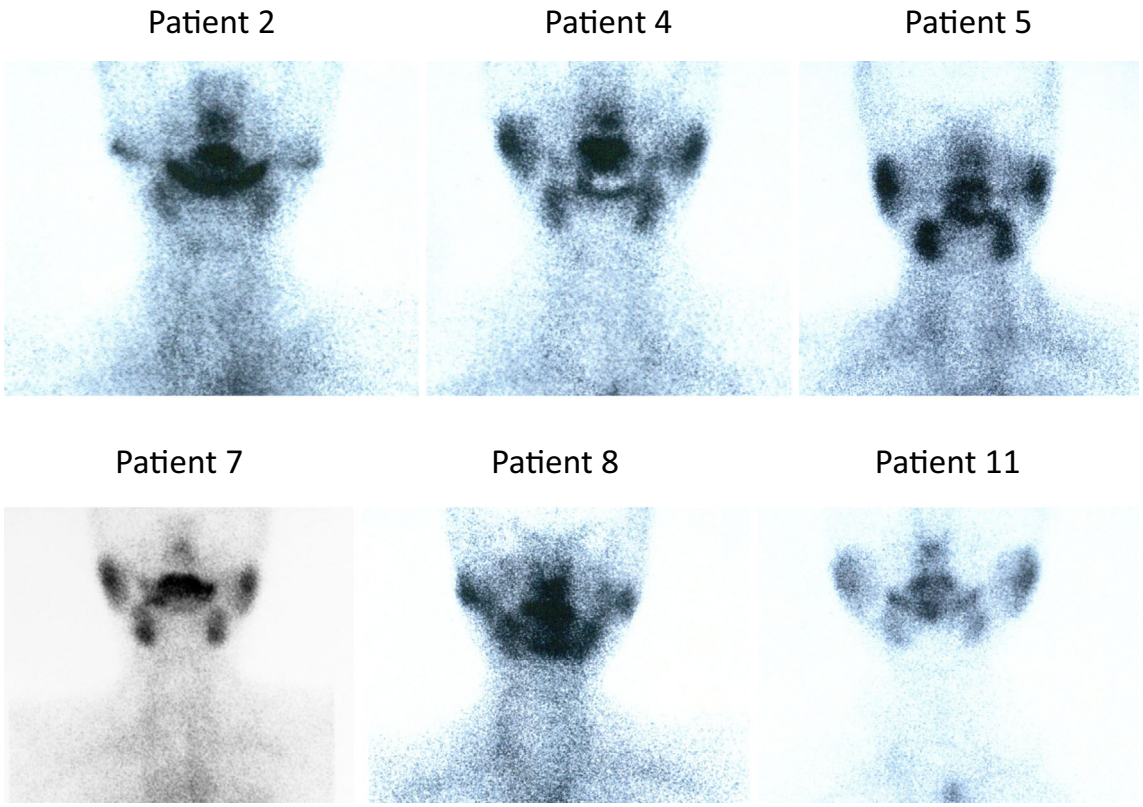

Figure 1. **^{99m}Tc thyroid scan showing an extremely diminished uptake by the thyroid, although a dark structure is visible in the salivary glands.**

the 11 patients. The dose of KI at the diagnosis of PT was 52.1±19.3 (mean±standard deviation) mg daily (range, 38.2-76.4). Routine blood work detected evidence of thyrotoxicosis approximately 18.5±14.5 months (range, 2.0-45.0) after the initiation of KI therapy.

Blood tests revealed suppressed TSH (<0.01 μU/mL) along with elevated FT4 (3.00±0.98 ng/dL (mean±standard deviation) (normal, 0.80-1.90 ng/dL) and FT3 (7.71±3.10 pg/mL (normal, 2.00-4.40 pg/mL). During the thyrotoxic phase, serologic tests and a thyroid scan with ^{99m}Tc were performed in all 11 patients. M22-TRAb was negative except in 1 patient whose value (2.4 IU/L) was just above the reference range (normal: <2.0 IU/L). Six patients (54.5%) had elevated TPOAb (>30 IU/mL), and 10 (90.9%) had elevated TgAb (>40 IU/mL). The thyroid weights were mildly enlarged [34.1±7.0 g (normal, 15-25g)]. A thyroid scan with ^{99m}Tc revealed a decreased uptake at 0.34±0.15% (reference range, 0.80-1.20%). The thyroid images obtained by ^{99m}Tc scan in all patients with KI-induced PT showed an extremely diminished uptake by the thyroid, although a dark structure was visible in the salivary glands, consistent with PT, as shown in Fig. 1.

KI treatment was promptly discontinued after the diagnosis of PT in all patients. During the thyrotoxic phase, 8 patients (73%) were symptomatic, with palpitations being the most common symptom, followed by shortness of breath, tremors, perspiration, heat intolerance, and fatigue. Four patients required temporary β-blocker therapy. No specific therapeutic intervention was required for these patients because their thyroid dysfunction resolved spontaneously.

Timeline of PT

The details of the clinical course and prognosis of the 11 patients are shown in Table 2. The mean period from thyrotoxicosis to euthyroidism was 72.7±45.9 days (range, 34-174 days). The FT4 levels at 100.4±30.0 days prior to PT were normal at 1.43±0.22 ng/dL (range, 1.00-1.70 ng/dL). The euthyroid condition remained in 9 patients for 315.2±44.1 days (range, 84-558 days) after PT. No hypothyroidism following thyrotoxicosis was observed.

In case 5 only, GD recurred 49 days after PT, as shown in Table 2. Case 1 who was planning a pregnancy underwent total thyroidectomy immediately after recovery from PT, as described in detail below.

Pathological findings

Case 1 stopped propylthiouracil (PTU) because of myeloperoxidase-anti-neutrophil cytoplasmic antibody [MPO-ANCA: 14.3 IU/mL (normal, <3.5)]-associated general arthralgia and started KI (50 mg daily). Seventy-seven days after the initiation of KI, she developed PT. The patient received no therapy, and 54 days later she was clinically euthyroid with FT3 2.31 pg/mL, FT4 0.98 ng/dL, and TSH <0.01 μU/mL. She therefore underwent total thyroidectomy 71 days later, as previously decided. The histology of the resected thyroid showed cells in the papillary folds that ex-

Table 2. The Clinical Course and Prognosis of KI-induced PT.

Case No.	FT4 value (months: mos) prior to PT	Months to PT from KI initiation	FT4 values at PT	β-blocker	Days to spontaneous normalization	FT4 values at normalization	Hypothyroid phase	Prognosis after PT
1	1.56 (2 mos)	2	2.74	Not	54	0.98	no	Total thyroidectomy immediately after recovery from PT
2	1.53 (2 mos)	24	3.81	Pr	132	1.51	no	GD remission for 14 mos
3	1.53 (2 mos)	6	3.06	Not	41	1.49	no	GD remission for 24 mos
4	1.06 (2 mos)	36	2.04	Not	34	1.00	no	GD remission for 24 mos
5	1.58 (4 mos)	12	2.34	Not	41	1.30	no	GD recurred 49 days after recovery from PT
6	1.23 (3 mos)	10	4.74	Not	48	0.81	no	GD remission for 26 mos
7	1.29 (3 mos)	45	4.64	Not	45	1.67	no	GD remission for 34 mos
8	1.31 (4 mos)	36	6.89	Pr	84	1.22	no	GD remission for 22 mos
9	1.78 (4 mos)	16	2.77	Not	108	1.53	no	GD remission for 22 mos
10	1.26 (4 mos)	9	2.51	Pr	44	1.31	no	GD remission for 36 mos
11	1.70 (2 mos)	12	2.01	Pr	174	0.94	no	GD remission for 8 mos
Mean± standard deviation	1.44±0.22 (2.9±0.9)	18.9±14.0	3.41±1.49		73.2±46.1	1.25±0.29		
Range	1.06-1.78 (2.0-4.0)	2.0-45.0	(2.01-6.89)		(34-174)	(0.81-1.67)		

KI: potassium iodide, PT: painless thyroiditis, Pr: prescribed, Not: not prescribed, GD: Graves' disease

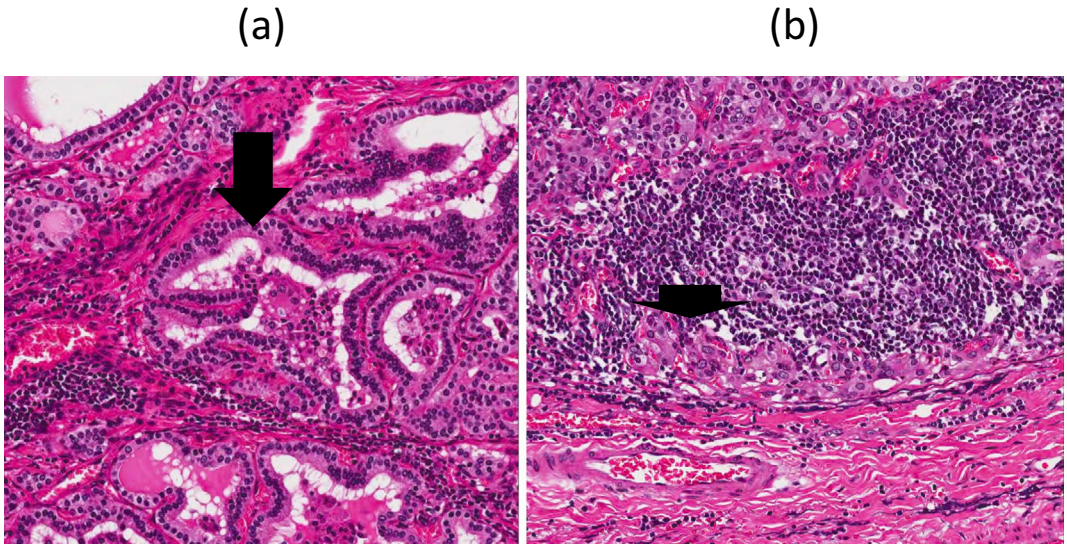

Figure 2. Pathology of the resected thyroid gland in a 29-year-old female Graves' disease patient with KI-induced painless thyroiditis. The cells are present in the papillary folds and extend into the lumen of the follicles [arrow in (a)] and (b) disrupted follicles [arrowhead in (b)] (Hematoxylin and Eosin staining, ×20).

tended into the lumen of the follicles (Fig. 2a), consistent with GD and disrupted thyroid follicles (Fig. 2b). No oxyphilia or evidence of granulomatous thyroiditis was seen.

Discussion

To our knowledge, the present study is the first case study of patients who developed PT during treatment with KI for GD. Ten patients started KI because of discontinuation of ATD due to side effects. At the diagnosis of the thyrotoxic phase of PT, the mean ^{99m}Tc scintigram was 0.34% (range 0.20-0.60%), and all patients spontaneously achieved clinical and biochemical euthyroidism, consistent with PT. In this study, no hypothyroidism following thyrotoxicosis was observed. More recently in 2020, outside of our observation period, two patients with KI-induced PT showed spontaneous resolution with subsequent hypothyroidism. One of these two patients is currently receiving levothyroxine (data unshown).

Interestingly, 60.7% of cases of PT that occurred in GD patients, directly recovered to a euthyroid status without passing through the hypothyroid phase, in contrast with 40%

of cases of PT in Hashimoto's thyroiditis patients (6). Regarding the spontaneous remission of GD, Codaccioni et al. (9) reported that treatment of patients with hyperthyroid GD with β-adrenergic antagonist drugs was followed by remission of hyperthyroidism in 30.8% of cases. Their patients showed a homogeneous thyroid ^{99m}Tc uptake and 62% of them were positive for TSAb at the diagnosis of GD. In contrast, our reported cases showed an extremely diminished thyroid ^{99m}Tc uptake, although the dark structures were visible in the salivary gland. These finding were consistent with PT, that occurred in Hashimoto's thyroiditis patients.

In our experience, ^{99m}Tc uptake was not significantly different between PT occurring in GD remission (n=163) and KI-induced PT (n=11) (0.38±0.19% vs 0.34±0.15%; p= 0.4785). However, Hays and Wesselossky (10) reported that Lugol's solution induced the suppression of the ^{99m}Tc thyroid uptake. In fact, Hamada et al. (11) reported two patients with mild GD who were misdiagnosed as PT because of low ^{99m}Tc uptake during KI therapy. However, they also emphasized that, aside from two cases, the ^{99m}Tc uptake could be used to differentiate PT from GD in most of patients with GD receiving KI therapy. Further studies will be needed to establish the effect of iodine on the ^{99m}Tc uptake.

In our study, only 1 patient showed relapse of GD 49 days after PT, and another patient underwent a total thyroidectomy with recovery of euthyroidism as previously decided because she was planning a pregnancy. The mechanism underlying the high remission rates of GD after KI-induced PT remained unclear. However, there was a case report of spontaneous remission of GD preceded by PT (12), suggesting that PT might have some effect on the prognosis of GD.

Physiologically, iodine is an indispensable constituent of thyroid hormones, and the recommended daily adult iodine intake is 150 μg. The thyroid gland has intrinsic regulatory mechanisms that maintain normal thyroid function even in the presence of iodine excess (13). Wolff and Chaikoff (14) reported that the organic binding of iodide in the rat thyroid is blocked when the plasma iodide level reaches a critical threshold. This acute inhibitory effect of iodide on thyroid hormone synthesis is called the acute Wolf-Chaikoff effect and is due to increased intrathyroid iodine concentration. They next demonstrated that this inhibitory effect of excess iodide is transient, lasting approximately 48 hours, which was known as escape from the acute Wolff-Chaikoff effect. Eng et al. demonstrated the escape from it was caused by a decrease in Na^+/I^- symporter mRNA with a resultant decreased iodide transport into the thyroid (15).

In addition to this physiological action of iodide, the administration of stable iodine to hyperthyroid patients produces clinical benefits by inhibiting the release of thyroid hormone (16) and its synthesis due to a decrease in TPO mRNA (12). Historically, iodine was used to treat toxic goiter as early as 1840 by von Basedow, who reported an improvement in all clinical symptoms by iodine administration in one woman (17). From Japan, Okamura et al. (4) reported that KI therapy was effective in two-thirds of patients who discontinued ATD because of side effects, and about 40% of patients experienced remission after KI therapy alone.

In the present study, we prescribed KI for the treatment of GD patients who discontinued ATD because of adverse effects. Unexpectedly, we found that 11 patients developed PT during KI therapy.

Amiodarone is a benzofuranic derivative that contains approximately 37% iodine by weight. The amount of iodine released is approximately 6 mg/day for each 200-mg tablet. Interestingly, amiodarone also leads to destructive thyrotoxicosis, known as Type 2 amiodarone-induced thyrotoxicosis in the normal thyroid (18). Chiovato et al. (19) demonstrated in an *in vitro* study that amiodarone has a cytotoxic effect on FRTL-5 cells, CHO cells, and human thyroid follicles obtained from nontoxic goiters at surgery.

In contrast, KI has a cytotoxic effect on only human thyroid follicles that is abolished by MMI. Furthermore, Xu et al. (20) showed a cytotoxic effect due to KI by demonstrating that excess iodine contributes to autophagy suppression and apoptosis of thyroid follicular cells using a cell line of human thyroid follicular epithelial cells. The pathogenesis of KI-induced PT is unclear but may be related to this cytotoxic effect of KI. In addition, because 10 of the 11 patients in our current study with KI-induced PT were positive for TgAb and/or TPOAb, an autoimmune mechanism may be involved in this process.

Finally, we emphasize that clinicians who manage GD patients who received KI after discontinuing ATD due to side effects., should be alert for KI-induce PT.

Study limitations

The present study was limited by the fact that only patients treated for KI for GD after discontinuing ATD due to side effects were evaluated. Future studies should confirm whether or not untreated patients with GD who received initial therapy of KI similarly develop PT.

Conclusion

We herein report for the first time that 11 patients with GD developed PT during treatment with KI following ATD treatment cessation due to side effects.

The author states that he has no Conflict of Interest (COI).

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