Periodic Granulocyte Count Measuring Is Useful for Detecting Asymptomatic Agranulocytosis in Antithyroid Drug-Treated Patients with Graves' Disease

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Key Words

Agranulocytosis · Antithyroid drug · Granulocytopenia · Graves' disease

Abstract

Objective: Finding agranulocytosis (AG) at an early stage is important to improve outcome, but periodic granulocyte count monitoring is not generally recommended for patients with Graves' disease, because AG develops suddenly. **Method:** At the Kuma Hospital, Graves' patients under antithyroid drug (ATD) treatment in an outpatient clinic have a granulocyte count examination during each visit, and if it is $<1,000/\mu\text{l}$, a warning is immediately sent to the patient's physician. We evaluated the usefulness of this system. **Results:** We investigated 25 AG and 33 granulocytopenia (GP) cases over a recent 5-year period, excluding patients who developed AG or GP at another hospital and were referred to us for treatment. Among the 25 AG patients, 16 patients (64%; 9 asymptomatic and 7 very mild symptomatic cases) were discovered by the periodic granulocyte count examination at an outpatient clinic. The remaining 9 patients visited the Kuma Hospital or other hospitals because of infection symptoms. Most of the AG patients were given granulocyte colony-stimulating factor injections immediately and

were admitted if a prompt increase in granulocytes could not be obtained. The final treatments for Graves' disease were ^{131}I -radioisotope therapy (19 patients), thyroidectomy (2 patients), inorganic iodine (1 patient), or another ATD (1 patient). Among the 33 GP patients, 31 (94%), including 20 asymptomatic cases, were discovered during periodic granulocyte count monitoring. Most of them stopped ATD, and other treatments for Graves' disease were selected. **Conclusion:** Periodic monitoring of granulocyte counts is useful for identifying AG and GP patients with no or minimum infection symptoms.

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Introduction

Agranulocytosis (AG) is one of the most serious complications of antithyroid drug (ATD) therapy for Graves' disease. It is rare, but if its discovery is delayed and severe infection develops, a lethal outcome can happen [1]. In fact, our recent analysis of 754 cases of ATD-induced AG over a 30-year period in Japan included 30 fatal cases, and most of them died after a few months of struggle with serious infections [2]. To avoid such critical outcomes, it is impor-

tant to find AG at an early stage, especially before the onset of infection symptoms, and stop ATD therapy immediately. However, finding asymptomatic AG patients is considered difficult, since AG develops suddenly. Periodic monitoring of the white blood cell (WBC) count is generally considered useless and not recommendable. The American Thyroid Association guidelines and some review articles recommend against regular monitoring [3–5].

Twenty-five years ago, Tajiri et al. [6] reported that they found 43 of 55 patients with ATD-induced AG (78%) in an asymptomatic state by checking WBC counts every 2 weeks during the first 2 months of medication and once every month thereafter. They concluded that routine WBC monitoring could be the most effective way of detecting ATD-induced AG. To our knowledge, however, there has been no report to confirm their finding, and their recommendation of routine WBC monitoring has been criticized based on skepticism about its benefit and the complications as well as costs of instituting the monitoring [7, 8].

In Japan, the methimazole (MMI) and propylthiouracil (PTU) package inserts recommend the checking of blood counts every 2 weeks for the first 2 months of medication. Our institute, the Kuma Hospital, has maintained a unique system for a decade in which every Graves' patient under ATD treatment undergoes a granulocyte count measurement together with the measurement of serum thyroid hormone levels as part of each follow-up at an outpatient clinic, and when the granulocyte count is $<1,000/\mu\text{l}$, a warning is immediately sent from the testing laboratory to the patient's physician. Here, we retrospectively reviewed the cases of Graves' disease with $<1,000/\mu\text{l}$ granulocytes over a recent 5-year period and evaluated the usefulness of this system.

Subjects and Methods

AG and GP Cases at the Kuma Hospital

We reviewed the cases of AG (defined as a granulocyte count $<500/\mu\text{l}$) and GP (defined as a granulocyte count $\geq 500/\mu\text{l}$ but $<1,000/\mu\text{l}$) between April 2009 and March 2014 at the Kuma Hospital. During this period, there were 10,410 patients with Graves' disease (8,555 females and 1,855 males) on ATD therapy (9,190 with MMI, 1,732 with PTU, and 512 with both), and we found 25 patients with AG (AG patients treated before April 2011 were included in our previous analysis of 745 AG cases [2]) and 33 cases (among 30 patients) of GP. Patients who developed AG or GP at other clinics or hospitals and were referred to the Kuma Hospital for treatment were excluded. We analyzed the patient profiles, characteristics of Graves' disease, ATD therapy, onset situations of AG or GP, the treatment for hematological complications, and the outcomes in these patients.

The Kuma Hospital System for Finding AG and GP at Outpatient Clinics

For patients who visit the Kuma Hospital for the first time, a physician sees the patient first and orders the necessary examinations. The patient goes to an examination room, where the patient's blood is sampled and other scheduled examinations, such as ultrasonography, chest X-ray, and/or electrocardiography, are performed. Patients who are returning to the Kuma Hospital with preordered examinations go to an examination room directly before seeing a physician. After the examinations and availability of the results, the patient is called in for a consultation with a physician. If the patient's granulocyte count on that day is found to be $<1,000/\mu\text{l}$, a warning is sent immediately from the testing laboratory to the physician, and the physician sees the patient without delay, prescribing all the necessary treatments.

Laboratory Investigations

The Kuma Hospital system involves complete blood cell counts with an automated hematology analyzer (XN-2000; Sysmex Corp.). When the granulocyte count is $<1,000/\mu\text{l}$, the sample is reexamined using another unit of the same analyzer (the hospital has two XN-2000 units), and then a laboratory technician measures the differential leukocyte counts visually again before sending a warning to the physician. Serum thyroid-stimulating hormone (TSH), free T_4 (fT_4) and free T_3 (fT_3) concentrations are measured by chemiluminescent immunoassays (Architect TSH, Architect fT_4 , and Architect fT_3 , respectively; Abbott Japan Co., Tokyo, Japan). The normal ranges are 0.4–4.5 $\mu\text{IU/ml}$ for TSH, 0.7–1.4 ng/dl for fT_4 , and 1.8–3.5 pg/ml for fT_3 . Serum anti-TSH receptor antibody (TRAb) is measured with a third-generation electrochemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany). The upper cutoff of TRAb is 1.9 IU/l.

Results

AG Patients

For a recent 5-year period, we had 25 patients (all of them were female) who developed AG. The incidence of AG is 0.24% (25/10,410 patients). Sixteen of the 25 AG patients (64%) were discovered in a routine blood count tests during regular follow-ups at an outpatient clinic (group A; fig. 1). Nine patients in group A were asymptomatic at the time of diagnosis (group A0), and 7 patients had very mild symptoms such as slight fever and/or slight sore throat, but they did not care about these minor symptoms (group A1). Among the 9 asymptomatic patients, 6 patients remained completely asymptomatic (group A00), and the other 3 patients exhibited some infection symptoms later (group A01).

The remaining 9 AG patients (36%) had infection symptoms such as high fever and/or acute pharyngitis and came to the Kuma Hospital or went to see a physician at nearby clinics or hospitals (group B). In 1 patient (No.

Fig. 1. Flowchart of the 25 AG patients; 16 patients were discovered by periodic monitoring of granulocyte counts during regular follow-ups at outpatient clinics (group A), while 9 patients presented at the Kuma Hospital or other hospitals because of high fever and pharyngitis (group B). Nine of the 16 patients were asymptomatic at the time of diagnosis (group A0), and 6 of them remained completely asymptomatic (group A00), while the remaining 3 patients exhibited later some infection symptoms (group A01). Seven pa-

tients in group A had mild symptoms, such as slight fever and/or mild sore throat, but they did not care about these minor symptoms (group A1). The final treatment for Graves' disease is shown. OPC = Outpatient clinic; OP = surgical operation; KI = inorganic iodine (38 mg iodine daily); another ATD = change to MMI from PTU. * The OP patient died suddenly at home from an unknown cause just a few days before the scheduled total thyroidectomy.

12; table 1), the granulocyte count was 255/ μ l despite a normal WBC count (5,100/ μ l).

At the time of AG discovery, 17 patients were being treated with MMI (2.5–30 mg/day, average: 15 mg/day) and 8 patients with PTU (50–600 mg/day, average: 219 mg/day) (table 1). The duration between the initiation of ATD therapy and the onset of AG ranged from 0.5 to 46 months. The precise duration time was uncertain in 2 patients (No. 2 and 9) because data from the clinics where they had been treated earlier were not available. Drug compliance was poor in patients who had a long history of treatment, including patients No. 2 and 9. More than one third of the patients (9/25 patients) had a history of relapse of Graves' disease.

When AG was found, most of the patients (88%) immediately received an injection of 100 μ g of granulocyte

colony-stimulating factor (G-CSF). Patients No. 4 and 13 had granulocyte counts of 494 and 551/ μ l, respectively, at diagnosis and were given only antibiotics. However, 2 days later, the granulocyte count of patient No. 13 fell to 274/ μ l and the patient was admitted to the Kuma Hospital. Of the 25 AG patients, 21 (84%) were admitted to hospital; 3 patients who showed a prompt increase in the granulocyte count after G-CSF injection (No. 2, 5, and 6) and 1 asymptomatic patient with a granulocyte count of 494/ μ l (No. 4) were not hospitalized. Three patients (No. 16, 20, and 21) were transferred for treatment to a hospital near their homes on their own wish. Another 3 patients (No. 1, 23, and 25) were admitted to the Kuma Hospital first but transferred to the hematological department of another general hospital several days later for further AG treatment in a clean room, because their gran-

Table 1. AG patients

No.	Group	Age, years	Sex	ATD (mg/day)	Duration, months	Compliance	Course	Granulocyte counts at diagn. (nadir)	Symptoms		G-CSF	Admission	Final treatment
									at diagn.	subsequent			
1	A00	68	F	MMI (15)	2		after relapse	240 (0)	none	none	+	+ transferred to other hospital	RI
2	A00	13	F	MMI (2.5)	?	poor		440	none	none	+	–	RI
3	A00	28	F	PTU (100)	29		after relapse	60	none	none	+	+	RI
4	A00	15	F	PTU (200)	27			494	none	none	–	–	KI
5	A00	39	F	PTU (200)	0.5		after relapse	362	none	none	+	–	MMI
6	A00	40	F	PTU (50)	14			442	none	none	+	–	OP
7	A01	58	F	MMI (10)	2		after relapse	48 (33)	none	(next day) fever, stomatitis	+	+	RI
8	A01	36	F	MMI (15)	9.5			538 (13)	none	(5th day) high fever	+	+	KI
9	A01	44	F	PTU (600)	?	poor		350	none	(4th day) high fever	+	+	sudden death before OP
10	A1	60	F	MMI (15)	2.5			161	slight fever	fever	+	+	RI
11	A1	30	F	MMI (15)	2		after relapse	186	fever	fever, stomatitis	+	+	RI
12	A1	22	F	MMI (15)	1			255 (WBC: 5,100)	fever, pharyngitis	fever, pharyngitis	+	+	RI
13	A1	38	F	MMI (5)	11		after relapse	551 (274)	fever, slight pharyngitis	fever, slight pharyngitis	–	+	RI
14	A1	55	F	PTU (200)	2			90	pharyngitis	pharyngitis	+	+	RI
15	A1	42	F	PTU (200)	0.7			256	fever, pharyngitis	fever, pharyngitis	+	+	RI
16	A1	26	F	PTU (200)	10.5			211	fever	fever, pharyngitis	–	+	RI
												(other hospital)	
17	B	34	F	MMI (15)	46	poor		17	fever, pharyngitis	fever, pharyngitis	+	+	RI
18	B	44	F	MMI (15)	1			12 (0)	fever, pharyngitis	fever, pharyngitis	+	+	RI
19	B	36	F	MMI (10)	2.7			10 (0)	fever, pharyngitis	fever, pharyngitis	+	+	RI
20	B	54	F	MMI (10)	1.5		after relapse	18	fever, pharyngitis	fever, pharyngitis	+	+	RI
												(other hospital)	
21	B	48	F	MMI (10)	3.3		after relapse	405	fever, pharyngitis	fever, pharyngitis	+	+	RI
												(other hospital)	
22	B	54	F	MMI (15)	1		after relapse	136	fever, pharyngitis	fever, pharyngitis	+	+	OP
23	B	48	F	MMI (15)	26	poor		0	fever, pharyngitis	fever, pharyngitis	+	+	RI
												transferred to other hospital	
24	B	42	F	MMI (15)	2.4			174 (0)	fever, pharyngitis	fever, pharyngitis	+	+	RI
25	B	54	F	MMI (30)	1.3			0	fever, pharyngitis	fever, pharyngitis	+	+	RI
												transferred to other hospital	

See figure 1 for groups. Sixteen of the 25 AG patients (64%) were discovered by routine blood monitoring during the patients' regular visits to an outpatient clinic (group A). Nine patients (group A0) were asymptomatic at the time of diagnosis, and 7 patients (group A1) had very mild symptoms such as slight fever and/or slight sore throat, but they did not care about these minor symptoms. Among the 9 asymptomatic patients, 6 patients remained completely asymptomatic (group A00), and the other 3 patients (group A01) later exhibited some infection symptoms. The remainder (n = 9) of the 25 AG patients (group B) had infection symptoms such as high fever and/or acute pharyngitis and visited the Kuma Hospital or other hospitals to see a doctor. OP = Surgical operation; KI = inorganic iodine; ? = duration unclear (treated by another clinic).

ulocyte counts were deteriorating despite G-CSF treatment.

The final treatments for Graves' disease were ¹³¹I-radioisotope (RI) therapy in 19 patients, surgical resection in 2 patients, inorganic iodine administration in 1 pa-

tient, and another ATD (from PTU to MMI) therapy in 1 patient. No patient succumbed except for 1 patient (No. 9) who died suddenly at home from an unknown cause just a few days before a scheduled total thyroidectomy.

Fig. 2. Flowchart of the 33 cases in 30 patients with GP. Thirty-one of the 33 cases were discovered at routine outpatient clinic examinations. Among them, 20 cases in 17 patients were asymptomatic and 11 patients had infection symptoms, although most of the symptomatic patients complained of cough, nasal discharge, and/or sputum in addition to sore throat and/or fever, suggesting their

GP might be more likely related to viral infection rather than ATD use. Only 2 patients visited the Kuma Hospital directly for high fever. The final treatment for Graves' disease is shown. OPC = Outpatient clinic; OP = surgical operation; KI = inorganic iodine (38 mg iodine daily); another ATD = change to MMI from PTU or vice versa; same ATD = the same PTU was continued.

A Representative AG Case (No. 1)

A 64-year-old female patient visited the Kuma Hospital for easy fatigability at 6 months after cessation of the 1-year MMI treatment for Graves' disease. Her thyroid function test showed a hyperthyroid state (fT_4 2.14 ng/dl, fT_3 6.53 pg/ml, TSH <0.003 IU/l, and TRAb 2.0 IU/l). She was diagnosed with recurrent Graves' disease and given MMI 15 mg/day with information about the potential risks of AG.

On her second regular visit to an outpatient clinic, 2 months after starting the above-described MMI, she was found to have only 240 granulocytes/ μ l (WBC 1,600/ μ l, red blood cells 455×10^4 / μ l, and platelets 18.8×10^4 / μ l), although she felt well without any symptoms. Her thyroid hormones were within the normal ranges. A close examination did not reveal any signs or symptoms of infections. Her blood cell counts were completely normal prior to this time. AG was diagnosed and G-CSF (100 μ g s.c.) was immediately injected, but the granulocyte count showed no increase 4 h later. She was admitted to the Kuma Hospital, MMI was discontinued, and broad-spec-

trum antibiotics were administered prophylactically. Her granulocytes decreased to null on the 3rd day despite another G-CSF injection, and she was transferred to a hematological division of another general hospital, where she underwent intensive treatment with antimicrobial chemotherapy and G-CSF in a clean room. Although her granulocytes kept null for several days, she recovered without any infectious problems. She had been asymptomatic during the entire period. One month later, she underwent RI therapy with 13 mCi.

GP Patients

There were 33 GP cases among 30 patients. All patients except for 1 case were female. Two patients experienced GP episodes more than once. In 31 of the 33 cases (94%), GP was identified during a routine follow-up in an outpatient clinic (fig. 2). Twenty of the 31 cases (64.5%) were asymptomatic, and 11 had infection symptoms. Many of the symptomatic patients, however, complained of cough, nasal discharge, and/or sputum in addition to sore throat and/or fever, and therefore their GP condition might be

more likely related to viral infection rather than the ATD used. Two asymptomatic patients were also uncertain whether GP was induced by the ATD because their granulocyte counts were sometimes $<1,000/\mu\text{l}$ even after MMI was completely stopped. There were only 2 patients who visited the Kuma Hospital directly for high fever. Both of them did not reveal a causal factor except for the initiation of MMI at 15 mg/day about 2 weeks earlier, suggesting that GP might be related to the ATD treatment. Similarly to patient No. 12 in table 1, the WBC count was normal ($4,520 \text{ WBC}/\mu\text{l}$ and $542 \text{ granulocytes}/\mu\text{l}$) in 1 GP patient.

Although it was unclear whether GP had been caused by ATD in some patients, the treatment with the same ATD was discontinued in all but 1 GP patient, and they underwent RI (15 patients), surgical (4 patients), inorganic iodine (5 patients), or a different ATD therapy for Graves' disease (fig. 2). One patient whose GP was judged to be virus related continued the same PTU therapy without any further problems.

Discussion

Discovering AG before symptoms of infection occur is important to prevent disease progression and a fatal outcome. When AG is identified at an asymptomatic stage via a blood cell count examination and ATD is immediately stopped and intensive infection control measures are started immediately, even a patient with severe AG such as patient No. 1, a representative case whose granulocyte count remained null for several days, can recover without any serious problems.

Routine monitoring of blood cell counts is, however, generally believed not useful because of the sudden onset of AG. It is true that AG develops quite abruptly in many patients. In patients with sudden onset of AG, e.g. those described in our previous study [2] who developed AG 1 day after a normal hematological test result, routine monitoring is never meaningful. However, AG may develop more slowly in other patients [2]. There are two possible types of AG pathogenesis: an immune-mediated process and direct or indirect drug intoxication [9]. The existence of circulating complement-dependent IgM antibodies against granulocytes and antibodies against differentiated granulocytes, monocytes, and myeloid/erythroid progenitor cells, for example, has been reported in patients receiving ATD [10–12]. The immune-mediated destruction of circulating granulocytes or the suppression of granulopoiesis results in rapid onset of severe neutrope-

nia, whereas AG due to the toxic effects of a drug or its metabolites on bone marrow cells is considered to progress more slowly, taking a couple of weeks. Routine monitoring of granulocyte counts may not be useful for sudden-onset AG, but it can be useful for the slowly progressive type. Based on the results of the study by Tajiri et al. [6] and our present analysis, which showed that periodic granulocyte monitoring discovered 16 of 25 AG patients (64%), including 9 asymptomatic patients, the slowly progressive type of AG seems to account for at least half of all AG cases.

When it comes to the effectiveness of routine monitoring of granulocyte counts, the cost-benefit relationship is an issue to be considered. The cost-effectiveness depends on the expense of the testing and the incidence of AG. The cost of a complete blood cell count examination is as low as only a half dollar in Japan, though it differs from country to country. Regarding the frequency of AG in Japan, it was 0.24% at the Kuma Hospital in the present analysis, which is quite compatible with the 0.22% in our previous study in our Institute [13]. Other large-scale studies in Japan reported approximately 0.3% [14] and 0.4% [6]. We estimated the incidence of AG in whole Japan as 0.1–0.15% with the assumption that 40–50 cases of AG occur annually among 35,000 Graves' patients newly treated with an ATD [2]. Since there may be a sizable number of unreported AG cases, the actual incidence of AG is estimated as 0.2–0.4%, which suggests that approximately 100 Graves' patients develop AG annually in Japan [2]. Considering that just a half-dollar examination can identify half of all AG cases, routine monitoring of granulocyte counts is very useful and recommendable at least in Japan.

During the preparation of this article, a retrospective analysis of 114 ATD-induced cases from China was published [15]. The result was well compatible with that of our previous study in general [2], though the incidence of AG was much higher than that in Japan (1.2 vs. 0.2–0.4%). Very interestingly, of the total of 114 AG cases, 20 patients were detected under asymptomatic condition by routine WBC monitoring. Unfortunately, details about the monitoring system was not described, and how often WBC/granulocyte counts were measured is unclear.

It is critically important to provide adequate information about AG to every ATD-treated patient: the early signs and symptoms of AG and what to do when AG is suspected. Knowledge about AG among Graves' patients remains still inadequate, as reported recently [16]. In addition, although in approximately 85% of the cases AG presents within 3 months after the start of ATD therapy [2], continued vigilance against AG is important, espe-

cially for patients with poor drug compliance, since some of the patients in the present study developed AG near or after 1 year. In the present study, patient No. 12 and 1 GP patient showed normal WBC counts, similarly to the report on 12 AG patients with normal WBC counts by Tajiri and Noguchi [17], which indicates that monitoring of granulocytes, and not only WBC, is necessary [18].

The present study revealed 33 cases of GP, but it is not clear whether they were all caused by the ATD therapy. Instead, several symptomatic cases might be related to viral infection. However, all but 2 of the present cases stopped ATD treatment and selected other treatment strategies for Graves' disease, even though the etiology of GP was uncertain. There might be the risk of overdiagnosis of ATD-induced GP, but the physicians' anxiety and hesitation to continue the same ATD medication are understandable. Their clinical attitude could be acceptable in view of the risk of AG progression.

Limitations of this study derive from its retrospective nature. Since the visits to outpatient clinics were completely dependent on each patient, we could not obtain the patients' granulocyte counts before AG onset at uniform intervals. It was difficult to analyze whether the granulocyte counts decreased gradually or abruptly. Although there is a common policy in the Kuma Hospital regarding the management of AG patients, specific management strategies, such as a G-CSF administration, hospitalization, and final treatment for Graves' disease, for example, depend on each physician's judgment. It was difficult to identify the best strategy for the management of AG from this study. In addition, whether an abnormal drop in the granulocyte count was truly caused by an ATD was not clearly evident in some GP cases.

Recently, human leukocyte antigen (HLA) genotyping and a genome-wide association study (GWAS) have revealed genetic determinants of ATD-induced AG. Chen et al. [19] demonstrated HLA-B*38:02 and HLA-DRB1*08:03 as independent susceptibility loci in Tai-

wanese patients. The odds ratio for carriers of both HLA-B*38:02 and HLA-DRB1*08:03 to noncarriers is as high as 48.41. A similar study has been just reported from Hong Kong, China. Cheung et al. [20] identified HLA-B*38:02:01 as the susceptibility locus of carbimazole-/MMI-induced AG, whereas the association with HLA-DRB1*08:03 did not reach significance. On the other hand, Hallberg et al. [21] performed a GWAS in 234 European patients with nonchemotherapeutic-induced AG, including 39 ATD-induced AG, and found an association with HLA-B*27:05 and other single nucleotide polymorphisms on chromosome 6. To date, there has been no study on genetic determinants of ATD-induced AG in the Japanese population, but Okada et al. [22] applied HLA imputation to GWAS and reported that multiple HLA genes independently contribute to the risk of Graves' disease in Japanese patients. These recent studies have clearly indicated that the population-specific genetic markers for ATD-induced AG are at hand and that the carriers of these variants could be placed under intensified monitoring.

In conclusion, periodic monitoring of granulocyte counts in Graves' patients on ATD at outpatient clinics is useful, since it is able to identify AG or GP patients with no or only minimal infection symptoms very efficiently. Regular monitoring can be recommended especially during the first 3 months of ATD therapy.

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Disclosure Statement

The authors have nothing to declare.

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