Antithyroid Drug Contributed to Non-Agranulocytosis, Predominantly Severe Anemia: A Case Report and Review of Literature

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Abstract

Agranulocytosis is a serious, though rare, side effect of antithyroid drugs (ATD) treatment. Pancytopenia, aplastic anemia and hemolytic anemia are even rarer than agranulocytosis. Predominantly severe anemia without agranulocytosis contributed by ATD has been very seldom reported before. A 39-year-old man with hyperthyroidism was found to have severe anemia, mild thrombocytopenia and mild leukopenia without agranulocytosis after treatment with methimazole (MMI) and propranolol for 29 days. The predominantly severe anemia, pancytopenia improved in one week after discontinuation of MMI and propranolol treatment. This patient was later found to have concomitant vitamin B12 deficiency. This case of severe anemia not associated with agranulocytosis was likely contributed by MMI treatment. Both discontinuation of ATD therapy and search for other etiologies of anemia should be made without delay. Any other etiologies of anemia should also be corrected. (J Intern Med Taiwan 2015; 26: 39-47)

Key Words: Antithyroid drugs, Agranulocytosis, Aplastic anemia, Non-agranulocytosis anemia

Introduction

Hyperthyroidism is a common problem in general internal medicine practice. Current treatments of hyperthyroidism involve antithyroid medications, radioactive iodine (RAI) therapy and thyroidectomy. The thionamide group, including carbimazole (CMZ), methimazole (MMI) and propylthiouracil (PTU), have been used for the control of hyperthyroidism since the 1940s[1]. These medications are usually prescribed to control thyroid function in the initial stage of treatment of hyperthyroidism before definitive therapy with RAI treatment or surgery. These drugs are also used for long-term control of hyperthyroidism in children, adolescents, and pregnant women and for those patients who reject to accept RAI treatment or thyroid surgery[2]. RAI treatment is not available in most of the local or community medical institutes in Taiwan. Therefore, antithyroid drugs (ATD) have been widely used as a first-line therapy, and usually also used for chronic control of hyperthyroidism.

Adverse effects of ATD treatment such as skin rash, fever, urticaria, or arthralgia are not rare, with an incidence rate of about 1-5%. Serious adverse effects include agranulocytosis, aplastic anemia or hepatitis. Agranulocytosis is rare and occurs in 0.2-0.5% of patients taking ATD[3]. Aplastic anemia

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(AA) is a pathologic condition with both pancytopenia in the peripheral blood and hypocellularity in the bone marrow. ATD-induced pancytopenia and AA are even more rarely reported than ATD-induced agranulocytosis. Until 2008, besides the two cases of aplastic anemia reported by Thomas D, et al., their review found only another 34 cases of ATD-induced AA published in the literature. All these 36 cases had concomitant agranulocytosis[4]. ATD-induced hemolytic anemia (HA) was also very seldom reported. To our knowledge, only 7 cases of HA due to ATD treatment have been reported[5,6,7,8,9]. One of the 7 HA cases also had mild neutropenia (1000/μL) and mild thrombocytopenia (141 × 10^3 / μL)[8]. Here we present a case that was found to have non-agranulocytosis, predominantly severe anemia which developed in the course of treatment of hyperthyroidism with MMI and propranolol.

Definition of Severity of Cytopenia

In this report, the following values are adopted to define the severity of cytopenia of blood cells.

Anemia: In men with age of 15 years and above, a hemoglobin (Hb) level 11.0-12.9 g/dL is mild anemia, 8.0-10.9 g/dL is moderate anemia, less than 8.0 g/dL is severe anemia[10].

Leukopenia: Total leucocyte count (TLC) below 4000/μL .

Neutropenia: An absolute neutrophil count (ANC) of 1000-1500/μL is mild neutropenia, an ANC of 500-1000/μL is moderate neutropenia, an ANC less than 500/μL is agranulocytosis (severe neutropenia)[11].

Thrombocytopenia: Mild if a platelet count is between 70 and 150 × 10^3 /μL, moderate if a count is between 20 and 70 × 10^3 /μL and severe if a count less than 20 × 10^3 per/μL[12].

Pancytopenia: a condition combined with anemia, leukopenia and thrombocytopenia.

Case report

A 39 years old male visited our Department of Internal Medicine on November 6, 2013. He brought a report of red blood cell (RBC) count of 1.98 × 10^6/μL, which RBC count was performed for his regular occupational health examination offered by the factory he was working in. He denied any chillness, fever, sore throat, skin pruritus and arthralgia which might hint an infection or immune reaction. He also denied tarry stool or bloody stool. Physically, his conjunctiva was pale, sclera was not icteric and thyroid gland was diffusely enlarged. Other significantly abnormal signs were not noted.

This patient was offered a set of health examination every year by the factory. He had not been informed to have anemia in the previous examinations until this examination was performed. To his knowledge, none of his workmates were also informed to have anemia after the examinations of this year. He was being treated with MMI and propranolol which were prescribed by this hospital for his hyperthyroidism. He denied taking other drugs, herbs or health supplements concomitantly.

Immediate complete cell count (CBC) showed an Hb level of 6.7 g/dL (normal range 13.5-17.5 g/dL), RBC count 1.71 × 10^6/μL (normal range 4.50-5.90× 10^6/μL) , mean corpuscular volume (MCV) of RBC 112.3 fL (normal range 80.0-100.0 fL), mean corpuscular hemoglobin (MCH) 39.2 pg (normal range 27.0-34.0 pg), mean corpuscular hemoglobin concentration (MCHC) 34.9 g/dL (normal range 31.0-37.0 g/dL), white blood cell (WBC) 3.13× 10^3 / μL (normal range 3.90-10.60 × 10^3/μL), ANC 1.84 × 10^3/μL, platelet 75× 10^3/μL (normal range 150-400 × 10^3/μL). Other examinations showed random serum glucose 99 mg/dL (normal range 70-120 mg/dL), creatinine 0.6 mg/dL (normal range 0.8-1.5 mg/dL), alanine aminotransferase 20 IU/L (normal range 6-34 IU/L).

Review of history revealed that this patient was

first noted to have hyperthyroidism 10 years ago. In October 2004, a laboratory examination showed a serum T4 level 17.02 μg/dL (normal range 6.09-12.23 μg/dL), serum T3 level 281 ng/dL (normal range 50-220 ng/dL), serum thyroid-stimulating hormone (TSH) 0.02 μIU/mL (normal range 0.34-5.6μIU/mL). Thereafter, he was irregularly treated with PTU 100 mg twice daily. He had prescriptions of PTU for 28 days in February 2005, 28 days in April 2005, 28 days in July 2005, and a consecutive course of treatment for another 168 days from October 6, 2005 onto March 23, 2006. After that, he had not received any treatment until October 1, 2013 when he visited our department of General Surgery with a complaint of palpitation. Laboratory investigations showed a serum T4 level 15.46 μg/dL (normal range 4.87-11.72 μg/dL), serum T3 level 231.92 ng/dL (normal range 58-159 ng/dL), serum TSH level < 0.038 μIU/mL (normal range 0.350-4.940 μIU/mL). He received MMI 5 mg and propranolol 10 mg three times daily from October 8, 2013 and continued to November 6, 2013 when his anemia was found.

Though this patient did not have agranulocytosis, however, he had pancytopenia with not only predominantly severe anemia but also mild thrombocytopenia and leukopenia. With the serious concern that he might deteriorate to aplastic anemia, he was advised to discontinue MMI and propranolol treatment promptly and also advised to visit a medical center as soon as possible. Examinations for serum levels of vitamin B12 and folic acid were requested at this occasion for the increased MCV, MCH of RBC. Tests of serum iron, total iron binding capacity (TIBC) and ferritin were also requested for fear of mixed causes of anemia. He re-visited our clinic one week later. According to the statement of the patient at this second visit: he visited the out-patient clinic of a medical center one time as our recommendation, there he was not given any drug treatment except some blood tests performed. At this second visit to our clinic, repeated CBC showed an Hb 9.0 g/dL, RBC count 2.25 × 10^6/μL, MCV of RBC 115.6 fL, MCH 40.0 pg, MCHC 34.6 g/dL, WBC 4.93 × 10^3/μL, ANC 3.12 × 10^3/μL, platelet 133× 10^3/μL. Laboratory examination results also available at this occasion included serum vitamin B12 level 127.0 pg/mL (normal range 247.0-911.0 pg/mL) and serum folic acid level 10.19 ng/mL (normal > 5.38 ng/mL), serum iron 118 μg/dL (normal range 30-170 μg/dL), TIBC 167 μg/dL (normal range 200-340 μg/dL) and ferritin 360.8 ng/mL (normal range 22.0-322.0 ng/mL). Oral vitamin B12 was prescribed. For the contraindication of ATD treatment, further definite treatment of hyperthyroidism with RAI therapy or thyroidectomy at a medical center was recommended.

Discussion

Reappraisal of Approach to Anemia in This Patient

Our patient presented with pancytopenia. His leukopenia did not further fulfill the definition of neutropenia. The etiologies of pancytopenia are very vast which include hypersplenism, infections, myelosuppressants, megaloblastosis, hypoplastic/aplastic anemia, immune pancytopenia, etc[13,14]. Because of the severity of anemia, it was the primary problem to focus on. Besides detailed history taking and physical examination, approach to anemia should include CBC, reticulocyte count, MCV, MCH, MCHC, RBC distribution width, WBC differential count and peripheral blood smear. A reticulocyte count is very helpful in directing the next step of differential diagnosis of anemia. A corrected reticulocyte count > 2% favors diagnoses in the arm of blood loss or hemolytic anemia, which should be followed by peripheral blood smear for morphologic evaluation of RBC and other specific diagnostic tests as appropriate, such as direct antiglobulin test, osmotic fragility test, serology for infections, etc. On the other hand, a corrected reticulocyte count < 2% leads to the diagnostic

categories of hypoproliferative anemia. Choice of examinations for differential diagnosis of hypoproliferative anemia can base on MCV, MCH, RBC distribution width and peripheral blood smear. The specific tests as appropriate for hypoproliferative anemia include iron studies, folate and vitamin B12 levels and erythropoietin level, etc. If the diagnosis of anemia remains unclear, then proceed to bone marrow examination[15].

For our patient, recent significant gastrointestinal blood loss was not favored by the absence of black stool or bloody stool. Chronic iron deficiency state could be rejected by the normal level of serum iron, decreased TIBC, and increased ferritin. With a normal serum creatinine level, end state renal disease was also not likely. Owing to our limited clinical experiences in hematologic medicine, we only performed a CBC examination with MCV, MCH, MCHC and WBC differential count. We did not request a reticulocyte count, peripheral blood smear, serum bilirubin, lactate dehydrogenase (LDH), haptoglobin and antiglobulin test at the first on site examinations. These tests would be helpful in suggesting hemolysis in an anemic patient. Therefore, the diagnosis of pancytopenia/severe anemia in this patient, mainly a differentiation between ATD-contributed hypoproliferative state in bone marrow and ATD-contributed hemolysis, was difficult. Although the absence of jaundice in this severe anemic patient and the lack of symptoms such as arthralgia, fever, etc. made us less in favor of the diagnosis of hemolysis.

Pancytopenia Induced by Infections, Drugs or Environmental Exposures

Numerous infections, such as Epstein-Barr (E-B) virus, hepatitis, human immunodeficiency virus (HIV), parvovirus, septicemia, typhoid fever, etc., are reported to cause pancytopenia[13,16]. Drugs, including chloramphenicol, nonsteroidal anti-inflammatory drugs, ATD, corticosteroids, penicillamine, allopurinol, and gold, etc., have been shown to be associated with the development of pancytopenia and even AA[16]. In the controlled epidemiologic study Thai NHLBI Aplastic Anemia Study performed in Bangkok and a northeast rural region of Thailand in the 1990s, benzene and pesticides (organophosphates, dichloro-diphenyl-trichloroethane (DDT), carbamates) were significantly associated with AA[17]. Our patient was requested to visit our clinic by the staff of the health office of the factory after being found to have anemia at routine examination offered by the factory. He did not have symptoms and signs suggesting infections. Although comprehensive examinations such as blood cultures, serologic tests for typhoid fever, HIV, E-B virus, parvovirus, etc., were not performed; the absence of jaundice and a normal alanine aminotransferase level suggested that hepatitis was not likely for this patient. Except MMI and propranolol, he denied taking any other drugs, herbs or health supplements concomitantly. A comprehensive search for environmental factors this patient being exposed was out of our capability. However, to the knowledge of this patient, none of his workmates were also informed to have anemia after this yearly health examination. He also kept on working in his factory in the following week after being informed to have anemia, meanwhile he discontinued MMI and propranolol, also in this same week his leukopenia recovered to normal range, thrombocytopenia recovered to nearly normal range and his severe anemia recovered moderately. Considering all these phenomena together, we rationally suggested that his hematologic derangement was not likely contributed significantly by infections, drugs except MMI or propranolol, or factors from his environment.

Antithyroid Drugs, Propranolol and Hematologic Damage

When this patient was noted to have pancytopenia/severe anemia, he had been taking MMI and

propranolol for 29 days. This patient denied taking other drugs, health supplements or herbs concomitantly. The risks of agranulocytosis and aplastic anemia in relation to the use of cardiovascular drugs were estimated in a population-based case-control study conducted in Israel and Europe (total population, 23 million)[18]. Propranolol, dipyridamole, digoxin, and acetyldigoxin were significantly associated with agranulocytosis and not associated with AA. The excess risks of agranulocytosis attributable to propranolol, dipyridamole, digoxin, and acetyldigoxin ranged from one to three cases per 10 million persons exposed for up to 1 week. Though either MMI or propranolol might be implicated as the cause of agranulocytosis, in this very large population study, propranolol was not found to associate with AA. Our patient had pancytopenia/severe anemia without agranulocytosis, based on this report, we could only think subjectively that the pancytopenia/severe anemia of this patient was far more likely to be contributed by MMI rather than by propranolol.

In the report and review of ATD-induced AA by Thomas D, et al., all 36 cases had agranulocytosis[4]. In another retrospective Japanese cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Graves' disease between January 1983 and December 2002, there were fifty-five patients with documented hematopoietic damage, 50 had agranulocytosis and 5 had pancytopenia. All of these patients received ATD, either MMI (n = 51) or PTU (n = 4). Seven of the 50 patients with agranulocytosis also had either anemia or thrombocytopenia, none had both anemia and thrombocytopenia. In four of the five patients with pancytopenia, development of agranulocytosis preceded the development of pancytopenia. Only the fifth patient displayed thrombocytopenia at the onset of agranulocytosis. The median value and range (in parentheses) of cell counts at the onset of pancytopenia in the five pancytopenic patients were WBC 900/μL (200-2700 /μL), granulocyte 4/μL (0-108/μL), Hb 9.3 g/dL (9.1-11.0 g/dL) and platelet 89 × 10^3 /μL (36-100 × 10^3 /μL)[19]. The anemia of these pancytopenic cases were only mild to moderate in severity. In this report all cases with anemia also had agranulocytosis.

Two large studies about ATD-induced agranulocytosis in Taiwan were reported. Of 5653 hyperthyroid patients treated with ATD at National Taiwan University Hospital between January 1987 and December 1997, 13 (0.23%) developed agranulocytosis[20]. In another report by Huang et al. of Chang Gung Hospital also found thirteen patients with agranulocytosis from 7,466 patients with hyperthyroidism while they were being treated with ATD from July 1989 to November 2003[21]. There were not any cases of anemia mentioned in these two reports.

Among the 7 cases of HA due to ATD treatment that have ever been reported, two cases were PTU-related, four cases CMZ-related and one case MMI-related. The first PTU-related HA was confirmed by re-challenge of small dose of PTU[5]. The second case, who had been first treated irregularly with CMZ, developed HA in the course of treatment with PTU[6]. However, the HA of this case persisted for 19 months after discontinuation of PTU. The phenomenon of persistence of HA after discontinuation of PTU probably made the causal effect of HA and PTU in this case somewhat doubtful. In the four cases of CMZ-related HA, CMZ-dependent antibodies which bound to RBC only when CMZ was present were detectable in the sera of all patients[7,8]. Carbimazole is a pro-drug and is rapidly hydrolyzed to MMI and only MMI is detectable in plasma after oral administration of CMZ[22]. However, unlike the results of using CMZ in the test, no antibody binding to RBC was observed using either MMI or urine containing CMZ metabolites of these CMZ-treating patients. These cases all recovered after discontinuation of CMZ. In the report of a case of MMI-related HA, pruritus and arthralgia developed after 2 weeks of MMI treatment and these symptoms were unresponsive to the replacement of MMI with CMZ. The

diagnosis of HA was supported by scleral jaundice, hemoglobin decreased from 14.7 g/dL (baseline) to 13 g/dL, increased reticulocytes, increased total bilirubin with increased unconjugated bilirubin[9]. However, the development of HA after sequential exposure to MMI first and CMZ second in this case made the claim that this case of HA was associated solely with MMI somewhat uncertain. As this manuscript was being prepared, we could not find reports about HA secondary to taking propranolol. Because our limited experience, we did not perform comprehensive examinations to enable us to have a clear differentiation between states of immune hemolytic anemia/pancytopenia and of hypoproliferative hematopoiesis contributed by MMI.

Hyperthyroidism and Vitamin B12 Deficiency

The etiologies of vitamin B12 deficiency in this patient were not clear. However, Graves' disease (GD) is the most common cause of hyperthyroidism, accounting for 60 to 80 percent of all cases[23]. Graves' disease is an autoimmune disease caused by an antibody that acts against the TSH receptor. Pernicious anemia is also a form of autoimmune diseases that may occur in association with GD[24]. Boelaert et al. reported that the prevalence of pernicious anemia among patients with GD was 1.4% compared to 0.13% in the general population of United Kingdom[25]. Laboratory examinations for diagnosis of pernicious anemia include checking serum vitamin B12 concentration, anti-intrinsic factor antibody, gastric parietal cell antibody and the Schilling test. Except serum vitamin B12 concentration, we did not perform these tests for lack of facilities in our hospital.

Vitamin B12 deficiency per se is not rare in the general population. In 1994, a report from the Framingham Heart Study revealed the prevalence of vitamin B12 deficiency to be 12 percent among 548 community-dwelling older patients[26]. In that report, vitamin B12 deficiency was defined as a serum vitamin B12 level less than 200 pg per mL and elevated levels of serum homocysteine, methylmalonic acid, or both. However, most of these patients with vitamin B12 deficiency did not have hematologic manifestations.

Is The Hematologic Derangement in This Patient Caused by Vitamin B12 Deficiency?

This patient was promptly advised to discontinue MMI on the scene of his severe anemia, mild thrombocytopenia and leukopenia. In only one week after discontinuation of MMI treatment, his Hb level recovered from 6.7 g/dL to 9.0 g/dL; his thrombocytopenia and leukopenia also prominently recovered. Also at this occasion, he was found to have vitamin B12 deficiency. His severe anemia improved moderately in merely one week after discontinuation of MMI before receiving any supplement of vitamin B12. This clinical scenario not only argued against the directly causal relationship between this patient's vitamin B12 deficiency and his severe anemia, but also made us reasonably think that his severe anemia, mild thrombocytopenia and leukopenia was majorly contributed by MMI. Though the macrocytosis of RBC was likely due to vitamin B12 deficiency. However, macrocytosis is an early diagnostic harbinger of serious vitamin B12 deficiency. An increased MCV of RBC may precede the anemia by months or even years[27,28].

More examinations needed to be performed to find the etiologies of his vitamin B12 deficiency. We referred this patient to a medical center for further definite treatment of hyperthyroidism and also for further investigation of his vitamin B12 deficiency.

Choice of Further Treatment of Hyperthyroidism for This Patient

This patient was noted to have pancytopenia/severe anemia after taking MMI and propranolol for 29 days. Current guidelines clearly point out that in patients who develop agranulocytosis or AA while

taking any ATD, further treatment with an ATD is unethical and absolutely contraindicated[2]. However, this patient had taken PTU irregularly for 252 days between Feb, 2005 and Mar, 2006. During this period of PTU treatment, there was not any history suggesting serious side effects of PTU treatment. Is it reasonable to resume PTU therapy for this patient?

Agranulocytosis is a recognized but rare side effect of ATD therapy which usually occurs within the first 3 months of treatment[29]. Cases of delayed ATD-induced HA or agranulocytosis after years of continuous ATD administration have been reported[8,30]. Owing to the risk of cross-reactivity between PTU and MMI[31,32], in a patient with agranulocytosis or other serious side effects while taking any ATD, change from one ATD to the other is absolutely contraindicated[2]. Therefore, only RAI or thyroidectomy is indicated for further treatment of our patient.

Conclusion

We present a case of non-agranulocytosis, predominantly severe anemia contributed by MMI. Lessons learned from this case suggest that MMI-contributed anemia may develop insidiously and, once diagnosed, can recover in several days after discontinuation of MMI. The pattern of recovery of this kind of anemia may be helpful to clinicians while in making decision about blood transfusion therapy in patients with ATD-contributed severe anemia.

For patients with agranulocytosis, a differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking ATD. Routine monitoring of white blood counts is not recommended[2]. With an extreme rare incidence of non-agranulocytosis, severe anemia among patients with ATD treatment, detailed clinical history and physical examination should be performed at every follow up visit for patients with ATD treatment. Regular CBC examination is not recommended and should only be obtained when there are clinical symptoms and signs suggesting anemia.

This patient also concomitantly had macrocytosis of RBC and vitamin B12 deficiency. Besides prompt discontinuation of ATD, other etiologies of pancytopenia/anemia should also be searched as guided by reticulocyte count, MCV, MCH, or finding on peripheral blood smear.

We hope this report would be helpful to the future care of patients of hyperthyroidism and also invite more attention and studies in these fields.

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抗甲狀腺藥物引起之無顆粒白血球缺乏症之重度貧血：一病例報告及文獻回顧

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摘　要

無顆粒白血球缺乏症之重度貧血是甲硫咪唑(methimazole, MMI)的極其罕見的副作用。顆粒白血球缺乏症(agranulocytosis)已知是抗甲狀腺藥物(antithyroid drugs, ATD)引起的罕見但卻是嚴重的副作用。如果全血球減少症(pancytopenia)患者併有骨髓細胞過少即是再生不良性貧血(aplastic anemia)。抗甲狀腺藥物引起之全血球減少症、再生不良性貧血及溶血性貧血比顆粒白血球缺乏症更是罕見，至今文獻上報告只有幾十例由ATD引起的再生不良性貧血及數例溶血性貧血，而且文獻報告之所有由ATD引起的全血球減少症及再生不良性貧血之病例皆有顆粒白血球缺乏症。至今文獻上因ATD引起的無顆粒白血球缺乏症之重度貧血的病例報告非常稀少。一位在例行健康查發現重度貧血(血紅素6.7 gm/dL)的病人。病史顯示他已服用MMI及propranolol二十九天，其貧血雖併有輕度血小板缺乏及輕度白血球缺乏，但並無顆粒白血球缺乏症。此病人於停止服用MMI及propranolol一周後其貧血就已見改善(血紅素9.0 gm/dL)，血小板缺乏及白血球缺乏也明顯改善。這名患者後來也發現有維生素B12缺乏。唯因其貧血於停用MMI及propranolol一周後且未經維生素B12治療即已見改善，推斷MMI治療為其貧血之主要原因。雖然非常罕見，甲狀腺亢進病人於ATD治療中可能發生無顆粒白血球缺乏症之貧血。建議甲狀腺亢進病人於ATD治療中若發生貧血應立即停止ATD治療並尋找貧血之其他原因，並建議病人接受放射碘治療或甲狀腺切除術。貧血之其他原因亦應予以治療。