Graves’ Disease Presenting as Autoimmune Hemolytic Anemia

Patient: Female, 29-year-old
Final Diagnosis: Graves’ disease
Symptoms: General malaise
Medication: —
Clinical Procedure: Laboratory checkup
Specialty: Endocrinology and Metabolism • Hematology

Objective: Unusual clinical course
Background: Atypical manifestations of Graves’ disease (GD) such as anemia have been noticed in the last decades. Anemia is present in up to 34% of patients with GD, yielding various anemia types such as GD anemia, pernicious anemia, iron deficiency anemia, and autoimmune hemolytic anemia (AIHA). So far, AIHA is the rarest manifestation of anemia in GD.

Case Report: We report a case of 29-year-old woman with initial presentation of typical anemia. Further findings revealed GD signs and symptoms such as orbitopathy, increased appetite along with loss of weight, and hand tremors. Laboratory findings showed very low hemoglobin (3.9 g/dL), reticulocytosis, elevated indirect bilirubin, and positive direct Coomb’s test. Later, thyroid function testing showed decreased TSH, elevated fT4, and positive TrAb. The diagnosis of GD was made, with AIHA as initial presenting manifestation. The patient was treated using corticosteroids followed by anti-thyroid without any blood transfusion and responded well.

Conclusions: In this case, typical AIHA was the initial presenting manifestation of GD and should not be overlooked since delayed diagnosis increases morbidity and mortality. Thyroid function assessment may be needed to search for etiologies of AIHA. Regardless of the exact underlying pathophysiology, AIHA under GD generally responds well to anti-thyroid and steroid treatment.

Keywords: Anemia, Hemolytic, Autoimmune • Graves Disease • Thyroid Diseases

Abbreviations: AIHA – autoimmune hemolytic anemia; ANA – antinuclear antibodies; BMI – body mass index; CLL – chronic lymphocytic leukemia; CTLA-4 – cytotoxic T-lymphocyte-associated protein 4; ER – Emergency Room; FcγR – Fc-gamma receptors; fT4 – free thyroxine; GD – Graves’ disease; Hb – hemoglobin; RBC – red blood cell; RES – reticuloendothelial system; RF – rheumatoid factor; SLE – systemic lupus erythematosus; TrAb – TSH receptor autoantibodies; TsAb – thyroid stimulating antibody; TSH – thyroid stimulating hormone; TSI – thyroid stimulating immunoglobulin

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### Background

Hyperthyroidism is logically associated with elevated number of red blood cells since there is elevated tissue oxygen demand, hence erythropoietin secretion increases [1]. However, in up to 33% of cases, anemia was found as an atypical hematologic manifestation in GD patients. The anemia is of various types: GD anemia, pernicious anemia, iron deficiency anemia, and autoimmune hemolytic anemia (AIHA). Of these type, AIHA is the rarest type, with only 4 reported cases [2]. It appears that an association exists between hyperthyroidism and autoimmunity; the hypothesis had been reported, but not proven.

Here, we report the case of a GD patient with the initial manifestation of AIHA. Anti-thyroid therapy and steroid treatment effectively relieved symptoms and increased hemoglobin levels without blood transfusions. The scarcity of pure AIHA manifestations in GD potentially delays diagnosis or leads to unnecessary performance of examinations that negatively impact patient outcomes.

### Case Report

A 29-year-old woman came to the ER with complaints of weakness since 2 months and worsened in the last 1 week before being admitted to the hospital. Symptoms of anemia (palpitations and pallor) were identified without any mucocutaneous bleeding. The patient denied previous weakness and menstrual disorders. The patient reported loss of weight (10 kilograms) along with increase in appetite in the past year. Symptoms of chronic liver and kidney diseases were not identified. The typical lupus complaint was also denied.

The patient was hospitalized 1 month ago with diagnosis of GD and received additional therapy of methimazole 10 mg/day. After 2 days of hospitalization, patient complaints were relieved along with increased hemoglobin level (6.1 g/dL). Thyroid function tests showed reduced TSH, elevated fT4 levels, along with positive TrAb and negative ANA test (Table 1). Thyroid ultrasound revealed bilateral diffuse goiter with normal parenchymal echo intensity, right lobe dimensions was 1.7×1.8×3.4 cm, while the left lobe was 1.8×1.3×3.4 cm. The patient was then diagnosed with GD and received additional therapy of methimazole 10 mg/day.

Improvements in hemoglobin level were recorded during discharge (7.2 g/dL) and 1-week follow-up (9.2 g/dL), presented in Figure 1. Additionally, oral propranolol was added to the previous therapy (oral methylprednisolone and methimazole) since the heart rate was 110 bpm, despite improved hemoglobin (9.2 g/dL). Unfortunately, the patient did not attend outpatient care because of the pandemic.

### Laboratory findings during hospitalization.

| Lab test            | Admission | Normal range* | Lab test | Day 2  | Normal range* |
|---------------------|-----------|---------------|----------|--------|---------------|
| Hemoglobin          | 3.9 g/dL  | 11.0-14.7 g/dL| Hemoglobin| 6.1 g/dL| 11.0-14.7 g/dL|
| Reticulocyte (%)    | 32.77%    | 0.80-2.21%    | TSH      | 0.005 mU/L| 0.55-4.78 mU/L|
| Reticulocyte# (10^9/uL) | 0.16     | 0.034-0.100.10^9/uL | fT4 | 2.03 ng/dL | 0.89-1.76 ng/dL |
| Direct bilirubin    | 0.92 mg/dL | <0.20 mg/dL  | TrAb     | 4.82 IU/L | <1.75 IU/L |
| Total bilirubin     | 1.86 mg/dL | 0.2-1.0 mg/dL | ANA      | 28.57 AU/mL | <40 AU/mL |
| Urobilin urine      | 2.0       | <1.0          | C3       | 49.2 mg/dL | 50-120 mg/dL |
|                     |           |               | C4       | 11.1 mg/dL | 20-50 mg/dL |

* Based on local laboratory references.
GD is hyperthyroidism caused by thyroid stimulating immunoglobulin (TSI) or thyroid stimulating antibody (TSAb) which is synthesized by B lymphocytes in the thyroid gland and partly in the bone marrow and lymph nodes [3]. Signs and symptoms of GD usually are similar to any cause of thyrotoxicosis as well as those specific to Graves’ disease (orbitopathy and dermopathy). These clinical presentations depend on age, disease duration, severity, and individual susceptibility to thyroid hormone excess [4]. It may be cost-effective to use diagnostic indexes such as Wayne’s and Newcastle index to limit the number of investigations required [5,6].

Hyperthyroidism is associated with increased tissue oxygen demand, followed by increased erythropoietin secretion. Therefore, an increased number of circulating erythrocytes is logically plausible [4]. Interestingly, anemia was found in up to 34% of hyperthyroid cases and is considered an atypical hematologic manifestation [2]. This phenomenon is hypothesized to be due to altered iron metabolism, hemolysis, and oxidative stress leading to enhanced osmotic fragility of erythrocytes and lipid peroxidation, and hence shortened erythrocyte survival [1].

In GD, anemia has been reported in 33% of cases [7]. It is postulated that decreased erythrocyte circulation time and autoimmune mechanisms are responsible for anemia in GD [8]. It is quite challenging to detect GD if it is clinically presented as anemia since both conditions have overlapping symptoms. However, some specific types of anemia are directly or indirectly associated with GD, such as pernicious anemia, iron deficiency anemia due to celiac disease, and AIHA [9]. In addition, an unclassified type of anemia that occurs in GD which improves after anti-thyroid treatment is termed GD anemia [7].

AIHA is by far the rarest form of GD-related anemia. AIHA is a heterogenous disorder characterized by destruction of RBC through antibodies. AIHA is further classified based on autoantibody type or the underlying disease. Warm AIHA accounts for 48-70% of patients with AIHA. Warm autoantibodies are dominated by IgG that strongly react toward erythrocytes at a temperature of 37°C, causing extravascular hemolysis through FcyRIII or C3b receptors on macrophages [10]. These autoantibodies are invariably polyclonal and flawed during T-cell regulation of humoral immune system; therefore, distinction function between self and non-self is defective. Gene polymorphism for signal substance CTLA-4, which activates regulatory T cells (Treg cells), increases risk of autoimmunity [11]. Therefore, it is not surprising that half of warm AIHA cases were secondary to lymphoproliferative disease (chronic lymphocytic leukemia) and other autoimmune-based conditions, particularly ulcerative colitis, rheumatoid arthritis, and systemic lupus erythematosus and GD [10].

Some patients develop signs and symptoms of anemia, while others with compensated hemolysis or mild anemia do not. Diagnosis includes evidence of hemolysis which includes reticulocytosis, elevated indirect bilirubin, elevated conditions lactate dehydrogenase (LDH) levels, decreased haptoglobin, and increased urinary urobilinogen. DAT testing is vital, preferably monospecific DAT, to further determine the autoantibody iso-types or complement [10].

According to Hegazi [2], only 4 cases of GD with AIHA have been reported. The exact pathophysiology of AIHA in GD is not fully understood, yet autoimmunity and hyperthyroidism might play major roles. One hypothesis is that the TSH receptor autoantibodies cross-react with the red blood cell surface, resulting in AIHA, mainly because the warm-type reactive antibody is the IgG antibody and possibly this occurs by polymorphism of the CTLA-4 gene [12]. In some cases, AIHA in Graves’ disease has been successfully treated with anti-thyroid without glucocorticoids, which emphasizes the role of hyperthyroidism [13,14]. Yet, in other cases, AIHA occurs in a euthyroid condition, leading to autoimmune processes as a possible mechanism [15].

Previous research concluded that anti-thyroid alone can reduce microsomal and TSH receptor antibodies. Methimazole regulates autoantibody levels, possibly through a direct effect on autoantibody synthesis and independent of serum thyroxine levels [16]. Meanwhile, another study emphasized the use of glucocorticoids as first-line agents for the treatment of idopathic warm-type AIHA [17] and appears to be effective in GD as well. Naji et al observed a dramatic increase of hemoglobin in GD patients with AIHA during 3 weeks on glucocorticoid and methimazole treatment without blood transfusions, similar to this case [5].
Conclusions

This report describes a rare case of GD with AIHA manifestations. It is important to always identified etiologies of AIHA through thyroid function assessment. Regardless of the exact underlying pathophysiology, GD with AIHA generally responds well to anti-thyroid treatment and steroids.

References:

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