Antithyroid treatment improves thrombocytopenia in a young patient with Graves’ disease

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Summary. Autoimmune thyroid disorders, including Graves’ disease and Hashimoto’s thyroiditis, have been reported in patients with primary immune thrombocytopenia (ITP). Several etiopathogenetic mechanisms connecting thyroid diseases and thrombocytopenia have been described. Thrombocytopenia is often documented in patients with Graves’ disease, due to reduced platelet life span in hyperthyroidism, immune dysregulation and genetic predisposition (HLA B8 presence). We present the case of a 14-years old girl, who was referred to our Pediatrics Unit, because of contemporary appearance of weight loss, profuse sweating and episodes of recurrent epistaxis. A complete health team, made up of hematologists and endocrinologists, met in consultation in order to reach a diagnosis. A suppression of serum Thyroid-stimulating hormone (TSH) concentrations, the presence of anti-TSH receptor antibodies, and at the same time an immune thrombocytopenia with positive anti-platelet antibodies, have been detected. Furthermore, a positive direct and indirect Coombs test without hemolytic anemia, antinuclear antibodies (ANA) positivity, and a C4 consumption have been documented. The patient started treatment with thiamazole with progressive improvement of thyroid function and thrombocytopenia, requiring only an intravenous immunoglobulin infusion on one time. A multidisciplinary follow-up has been scheduled, in order to monitor the multi-organ immune dysregulation. This report documents a significant improvement of thrombocytopenia after antithyroid treatment in a young subject affected with Graves' disease. (www.actabiomedica.it)

Keywords: Thrombocytopenia, Graves’ Disease, antithyroid treatment, immune dysregulation, adolescent

Introduction

Immune thrombocytopenic purpura (ITP), also known as idiopathic thrombocytopenic purpura, is an immune-mediated acquired disease characterized by transient or persistent decrease of the platelet count, and increased risk of bleeding (1). The incidence of ITP ranges from 2 to 5 per 100,000 children younger than 15 years. It presents as isolated thrombocytopenia (platelet count < 100 x 10⁹/L), commonly called primary ITP, or as secondary ITP which includes forms caused by underlying diseases such as infections, vaccine administrations, altered immune states, and lymphoproliferative disorders (1,2). The pathophysiology of ITP involves a complex dysregulation of the immune system including antibodies, cytokines, antigen-presenting cells, co-stimulatory molecules, T and B lymphocytes (including T-helper, T-cytotoxic and T-regulatory lymphocytes) (3,4). The prevalent view of the pathogenesis of thrombocytopenia has shifted from increased platelet destruction mediated by autoantibodies to more complex mechanisms where both impaired platelet production and T-cell–mediated effects play a role (5). Generally, newly diagnosed and persistent ITP are the result of a dysregulation of the immune system secondary to an infection and, therefore, transient. Instead, the dysregulation of the immune system is prevalent in chronic forms of ITP, and can also be the index of the onset of other autoimmune diseases (6).
The association between ITP and other organ or not-organ specific autoimmune disorders has been widely reported. One of the associated diseases is the autoimmune thyroid disease (AITD), the most common form of thyroiditis in pediatric age, which can manifest in many clinical forms such as Hashimoto Thyroiditis (HT) and Graves’ disease (GD), also in syndromic subjects (6-9).

Children with ITP are prone to develop AITD, with a prevalence ranging from 11.6-36%, definitely higher than general pediatric population (10). In particular, antithyroid antibodies have been detected in 11.6% of pediatric patients with chronic ITP, significantly higher than in the pediatric general population (1.2%-1.3%) (10). The relation between positivity for antithyroid antibodies and development of a subsequent autoimmune thyroiditis, is still unclear as well as the possible influence on the outcome of ITP (10).

Graves’ disease is the most frequent form of hyperthyroidism in children (11). The disorder can occur at any age, with a peak in prevalence during adolescence. Graves’ disease is more common in children with other autoimmune diseases, such as ITP, and in children with a family history of autoimmune thyroid disease. Inherited forms account for 15 to 20% of cases (11). Kurata et al. reported that 43% of patients with untreated hyperthyroidism have platelet counts less than 150000/uL (12). Several etiopathogenetic mechanisms connecting thyroid diseases and thrombocytopenia have been described: a reduced platelet life span in hyperthyroidism, an increased reticuloendothelial phagocytic activity by the thyroid hormones, an immune dysregulation, a genetic predisposition, an increased expression of T-lymphocyte-associated antigen 4 (CTLA4), and a T-cell surface molecule involved in the control of T cell proliferation (13,14).

The combination of autoimmune thyroid disease and ITP could reflect a more significant defect in the immune self-tolerance of these patients compared with those who have primary ITP alone. When hyperthyroidism and ITP are simultaneously present, it has been reported that the improvement of thyroid function can determine a spontaneous recovery of the platelet count in adult subjects, confirming that the two disorders are probably related to the same pathogenesis (15-17).

In this paper, we describe a young subject with a simultaneous onset of ITP and Grave’s disease, in which anti-thyroid therapy has considerably corrected the platelet count. Signed informed consent has been acquired from the patient’s parents for the publication of this case report and any potentially identifying information was removed.

Case presentation

We present the case of a Caucasian 14-years old female patient, who was born at term from caesarean section, after a physiological pregnancy. Birth weight was 3290 g. She was the third child of an unrelated couple. Family history was positive for thyroid diseases. The main stages of psychomotor development were normal. She was referred to our Pediatrics Unit, because of the contemporary appearance of weight loss, profuse sweating and episodes of recurrent epistaxis for about a month. A complete health team, made up of hematologists and endocrinologists, met in consultation in order to reach a diagnosis. The peripheral blood count revealed thrombocytopenia (34 × 10^9/L) with positive anti-platelet antibodies tested with an immunoenzymatic assay, and a normal red and white blood cells count. Secondary causes of thrombocytopenia (TORCH complex, Mycoplasma, Parvovirus, Hepatotropic viruses infections) have been investigated and excluded. The search for Helicobacter antigen on stool was negative. Reuma-test was negative. A thrombotic thrombocytopenia was also excluded because there was not hemolytic anemia, but only a positivity to Coombs test, and there were no other manifestations (renal, cerebral, gastroenteric). Hyperthyroidism was documented: a raised free T4 (6.27 ng/dl; normal range: 0.76-1.46) and suppressed Thyroid-stimulating hormone (TSH) level (<0.01 mU/l; normal range: 0.36-3.74), both assessed by Luminescent oxygen channeling assay-LOCITM, with positive anti-Thyroglobulin (anti-TG) antibodies: 772 U/ml; normal range: 10-115; assessed by Electrochemiluminescence)
and anti-TSH receptor antibodies: 24.7 UI/l; normal range: <0.10; assessed by Chemiluminescence), in line with a diagnosis of Graves’ disease. Thyroid ultrasound showed an increased thyroid volume, with an inhomogeneous echostructure and an increased signal of vascular flow pattern. Abdomen ultrasound showed splenomegaly (spleen longitudinal diameter: 14 cm). The bone marrow smear was normal, excluding oncological pathologies. Furthermore, a state of multi-organ immune dysregulation has been reported: positive direct and indirect Coombs test without hemolytic anemia, antinuclear antibodies (ANA) positivity with speckled nuclear pattern and granular cytoplasmic pattern (1/160), positive anti-neutrophil cytoplasmic antibodies (p-ANCA) and a C4 consumption (0.07 g/l) have been documented. The search of anti-Thyroperoxidase (anti-TPO), anti-parietal cell, anti- intrinsic factor, anti-transglutaminase, anti-adrenal, anti-smooth muscle, anti-mitochondrial, anti-liver and kidney microsomes (anti-LKM), anti-liver cytosol type 1 (anti-LC1) and anti-soluble liver antigen/liver pancreas (anti-SLA/LP) antibodies was negative. The patient started treatment with thiamazole 0.3 mg/kg/die (15 mg/die) in three doses with a progressive improvement of thyroid function and a significant recovery of the platelets count, requiring only an intravenous immunoglobulin infusion on one occasion (Figure 1).

Intravenous immunoglobulin therapy was administered according to the guidelines (1), at a dosage of 0.8 g/kg when the platelet counts became 20 ×10⁹/L and the patient manifested simultaneous exacerbation of bleeding episodes (severe epistaxis, skin and mucous petechiae). After administration of single dose of immunoglobulins, a prompt rise in platelet count was observed. Anti-thyroid treatment dose was gradually titrated up to 0.12 mg/kg/die (5 mg/die) obtaining a normalization of free T4 and TSH (Figure 2).

Three months after the start of anti-thyroid therapy, the platelet count was 90×10⁹/L, and the thyroid function has been normalized. A multidisciplinary follow-up (endocrinological, hematological and rheumatological) has been scheduled, in order to monitor the multi-organ immune dysregulation.

**Discussion**

Data of the literature reported an association between autoimmune thyroid disease and ITP. The first case report of hyperthyroidism and thrombocytopenia was published in 1931. Since then, more than 160 cases of hyperthyroidism associated with ITP have been reported (18). In all these case reports, the age at diagnosis of hyperthyroidism and ITP was >18 years. In many cases the patients had other autoimmune disorders such as myasthenia gravis, Guillain-Barre syndrome, systemic lupus erythematosus, scleroderma-dermatomyositis, Evans syndrome and autoimmune hemolytic anemia, probably as expression of a defect in immune self-tolerance (18-21). The clinical course of thyroid disease and ITP are usually separated at the time of onset and expression, and it can be variable from months to years. Our patient manifested simultaneously bleeding symptoms (recurrent episodes of

![Figure 1](image_url). Progressive recovery of the platelets count after starting antithyroid treatment, requiring a single dose of intravenous immunoglobulin (T1).
epistaxis) and symptoms suggestive of hyperthyroidism (sweating, cardiopalmus, weight loss). Blood tests showed an increase in thyroid function, with anti-thyroid positive antibodies (anti-TSH receptor and anti-TG) and thrombocytopenia. Several reports have reported that the treatment of hyperthyroidism has either resulted in a complete hematologic remission of ITP or an improved response to standard ITP therapy (15-17). These reports deal with adult patients, since the co-presence of immune thrombocytopenia and Graves’ disease is not common in children, even more if we consider a contemporary onset of the two disorders. Only a report describes a case of a 10-year-old Chinese girl with not-contemporary onset of thrombocytopenia and Graves’s disease (thyroiditis onset 6 months after thrombocytopenia), in which platelets count improves with antithyroid therapy (17). Our report confirms what is described in literature about antithyroid treatment, and deals with a pediatric patient with a contemporary onset of the two disorders. The therapy with thiamazole has determined a progressive improvement in thyroid function (with a reduction in free T4 and a rise in serum TSH), and at the same time a significant recovery of the platelet count. At three months of antithyroid treatment, the platelet count is stably 90×10⁹/L. According to the guidelines (1), our patient has been treated on one occasion with intravenous immunoglobulin administration, when platelet count became about 20×10⁹/L and the patient presented hemorrhagic manifestations. The patient also started a follow-up (endocrinological, hematological and rheumatological), aimed at investigating the appearance of further autoimmune disorders, in order to monitor the evolution towards a form of Autoimmune Polyglandular Syndrome III (APS III), in which thyroid diseases is mandatory, and the preferential age of clinical onset is adolescence and early adulthood (22). This report documents a significant improvement in thrombocytopenia, following the administration of antithyroid treatment, in a young subject suffering from Graves’ disease. The peculiarities of our clinical case were: - the contemporary onset of ITP and Graves’s disease in a pediatric patient; - the long-term recovery of platelet count achieved only with antithyroid

![Progressive thiamazole dose titration](image)

**Figure 2.** Antithyroid treatment dose titration, based on progressive normalization of thyroid function.
Thrombocitopenia and Graves’ disease

therapy, without further specific therapies for ITP, if not the administration of a single dose of intravenous immunoglobulins.

Conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Author Contributions

MFF designed the study and prepared the first draft of the paper. She is guarantor. VVP, MC and GL search literature data and collaborate to write the manuscript. PG revised the final draft. All authors revised the paper critically for intellectual content and approved the final version.

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