

A case of imipramine-associated immune thrombocytopenia

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SUMMARY: Aksoy A, Erduran E, Gedik Y. A case of imipramine-associated immune thrombocytopenia. *Turk J Pediatr* 2009; 51: 275-278.

Drug-induced immune thrombocytopenia (DITP), excluding heparin-induced thrombocytopenia, is relatively uncommon. It is characterized by drug-dependent antibodies that bind to the platelets and cause their destruction when the responsible drug is ingested or injected. Imipramine is a tricyclic antidepressant drug that is one of those used widely for primary enuresis nocturna, attention deficit hyperactivity disorder, depression, and anxiety disorder in children and adolescents. Imipramine rarely causes hematological abnormalities. A five-year-old boy with imipramine-associated antiglobulin-positive immune thrombocytopenia is reported herein, and we also discuss the possible pathogenesis of drug-associated thrombocytopenia.

Key words: imipramine, immune thrombocytopenia.

Tricyclic antidepressant (TCA) drugs are widely used in children and adolescents. The many adverse effects of these drugs are well known, in addition to their therapeutic activities, for disorders such as enuresis nocturna, attention deficit hyperactivity disorder (ADHD), depression, and anxiety disorder¹. TCA drugs affect muscarinic, adrenergic, and serotonergic receptors. The adverse effects of TCA drugs are gastrointestinal discomfort, blood pressure alterations, lightheadedness, and anticholinergic effects on vision². Imipramine is a TCA drug that is metabolized almost exclusively in the liver, undergoing oxidation by microsomal enzymes, followed by conjugation with glucuronic acid. Imipramine is mainly metabolized by the cytochrome P450 pathway (CYP2D6), which changes imipramine to its active metabolites 2-hydroxyimipramine and 2-hydroxydesipramine^{2,3}.

Drug-induced hematological disorders are rarely seen but can sometimes cause a life-threatening critical course. According to the previous studies, their frequency is estimated as one or two cases per 100,000 subjects annually, and the mortality rate fluctuates between 8 and 17%. TCA drugs producing the most frequent hematologic side effects are imipramine, mianserin and nomifensine. The most common adverse effects of imipramine are predominantly on

the endocrine, cardiovascular, autonomic, and central nervous systems. Imipramine rarely causes hematological abnormalities^{1,3}.

To our knowledge, immune thrombocytopenia caused by the imipramine metabolite, desipramine, was first reported by Rachmilewitz et al.⁴ The authors stated that the antibodies against desipramine were characterized as 7S-IgG types and that these antibodies were responsible for the desipramine-induced thrombocytopenia⁴. Herein, we report a child with antiglobulin-positive immune thrombocytopenia due to imipramine treatment, and we discuss the pathogenesis of drug-induced immune thrombocytopenia (DITP).

Case Report

A five-year-old boy was treated with imipramine at a dose of 10 mg/day for ADHD by the Department of Child Psychiatry. The patient's family history and past medical history were unremarkable, and his motor and mental development was normal.

When the patient with specific language impairment was admitted to the Department of Child Neurology, he had been taking imipramine for one week. On physical examination, petechiae were detected on his legs. There were no other remarkable physical findings.

Several weeks before the current admission, his platelet count was 288,000/ μ l and other cell counts were within normal limits. When the patient was admitted to the hospital, the laboratory findings were hemoglobin: 13.1 g/dl, platelets: 18,000/ μ l, reticulocyte count: 1%, and white blood cell count: 11,400/ μ l, with differential count of 70% neutrophils and 30% lymphocytes. Rare platelets with normal appearance were seen on the peripheral blood smear. The peripheral blood smear did not show any evidence of hemolytic anemia such as red blood cell fragmentation, microspherocytes, polychromasia or normoblasts. Erythrocyte sedimentation rate was 5 mm/h. The results of the biochemical analyses were within the normal limits. Increased megakaryocytes were seen on the bone marrow aspiration smear. Direct antiglobulin test was (+3) positive and indirect antiglobulin test was (+1) positive. Prothrombin time, activated partial thromboplastin time and complement factors (C₃ and C₄) were normal. The autoimmunity test results were as follows: rheumatoid factor, antinuclear antibody, anti-double stranded DNA antibody, anticardiolipin IgM and IgG antibodies, antinuclear cytoplasmic antibody, antithyroglobulin antibody, lupus anticoagulants (the mixing test) and lupus erythematosus (LE) cell were negative. The serologic test results revealed HBs antigen, anti-HBs antibody, anti-HBc IgM antibody, human immunodeficiency virus antibody, antinuclear cold agglutinin, Epstein-Barr virus IgM antibody, cytomegalovirus IgM and IgG antibodies, toxoplasmosis IgM and IgG antibodies, and rubella IgM and IgG antibodies as negative. The throat swab culture did not show any pathologic organisms.

The imipramine therapy was urgently discontinued and he was treated with mega-dose methylprednisolone (MDMP) (30 mg/kg/d for 3 days, 20 mg/kg/d for 4 days, 10 mg/kg/d for 7 days, 5 mg/kg/d for 7 days, and 1 mg/kg/d for 15 days) as first described by Özsoylu⁵. On the seventh day of the treatment, his platelet count reached 391,000 cells/ μ l. The platelet counts were between 225,000 and 461,000 cells/ μ l during MDMP. The steroid dose was decreased gradually and discontinued five weeks after the initiation. Indirect antiglobulin test was negative five weeks later, and direct antiglobulin test was negative in four months following the initiation of MDMP. No adverse

effects such as hypertension, hyperglycemia, gastric discomfort, or cushingoid appearance were observed during MDMP. We observed no psychiatric or behavioral side effects related to MDMP. The patient has been followed on an outpatient basis for seven months without thrombocytopenia.

Discussion

Classic immune thrombocytopenia can be induced by some drugs that trigger anti-platelet antibodies indistinguishable from the platelet autoantibodies found in autoimmune thrombocytopenia⁶. The important diagnostic issue is to distinguish the difference between DITP and idiopathic thrombocytopenic purpura (ITP), because the latter diagnosis requires the exclusion of other causes of thrombocytopenia. Both DITP and ITP are immune thrombocytopenias and the treatment of non-drug-induced ITP is not different from that of DITP. ITP in childhood is a heterogeneous clinical disorder characterized by immune-mediated platelet destruction. The responsible factor for ITP is the immunoglobulin G (IgG) antibodies that increased against platelet glycoprotein (GP)^{7,8}.

Quinine and quinidine were among the first reported causes of DITP by Grandjean⁹. DITP has developed following the use of many medications, including heparin, sulfonamides and other antibiotics, especially vancomycin, rifampicin, cephalosporins, and nonsteroidal antiinflammatory drugs¹⁰. DITP is a challenging clinical problem in a patient taking several medications. We diagnosed direct antiglobulin-positive imipramine associated with the thrombocytopenia in our patient who received imipramine treatment for ADHD for seven days before being admitted to the pediatric clinic. Although antiplatelet antibodies due to imipramine could not be determined, imipramine-associated immune thrombocytopenia was diagnosed in the patient.

Drug-induced immune thrombocytopenia can develop via several mechanisms. The majority of cases of thrombocytopenia with current drugs are believed to be idiosyncratic, immunologically mediated, and almost always caused by the increase in the platelet destruction. Though some drugs cause thrombocytopenia by suppressing the bone marrow production, this

mechanism is not relevant to the platelet GP antagonists^{11,12}. Increased platelet destruction is caused by an increased platelet-associated IgG resulting in accelerated platelet clearance by the reticuloendothelial system. The drug is first bound by an IgG antibody. This drug-antibody complex subsequently binds to the membrane receptors on the platelet¹¹. Drug-induced antibodies cause platelet destruction by a number of different mechanisms. The pathogenetic mechanisms of DITP consist of hapten-induced antibody, "quinine-type" thrombocytopenia, ligand mimetic GPIIb/IIIa inhibitor, drug-specific antibody, drug-induced antibody, and immune complex^{13,14}.

Drug-induced and drug-dependent immune thrombocytopenias are induced by antibodies recognizing an epitope on platelet GP formed after binding of a drug to a platelet GP. How the drug provides the stimulus for production of such antibodies is also unknown. These antibodies especially react with monomorphic epitopes on platelet GP. Not only the drug itself but also its metabolites are responsible for the immune response in the patients. Drug-dependent antibodies bind to platelets via their Fab fragments and are usually recognized on the GP complex Ib/IX, IIb/IIIa, GPV and platelet-endothelial cell adhesion molecule-1^{6,12}. However, there are no standard assays for drug-dependent antiplatelet antibodies, no standard criteria for distinguishing the positive from the negative results, and no data on the sensitivity and specificity of these assays based on the clinical criteria for the causal relation. Mirtazapine is one of the tetracyclic antidepressant drugs used widely for the treatment of depression. Binding of the antibodies with the platelet GP IIb/IIIa complex was shown by a flow cytometry in a patient with mirtazapine-induced immune thrombocytopenia¹². However, we could not measure drug-dependent antibodies against our patient's platelets. We think that the underlying mechanism is completely uncertain, but hapten-dependent antibodies, platelet reactive autoantibodies, and drug-dependent antibodies might play a role in the development of the antiglobulin-positive immune thrombocytopenia caused by imipramine. Evans syndrome, systemic lupus erythematosus (SLE) and autoimmune lymphoproliferative syndrome (ALPS) may overlap with DITP¹⁵. These diseases were

excluded in the patient because the peripheral smear evidence, laboratory tests and physical examination findings did not indicate Evans syndrome, SLE or ALPS. Nevertheless, the patient will be followed for Evans syndrome and SLE on an outpatient basis.

The standard treatment for DITP has not been reported. An algorithm is recommended for ITP by the American Society of Hematology based on the presence or the absence of bleeding, the timing of thrombocytopenia and the degree of thrombocytopenia. It is recommended that the drug responsible for thrombocytopenia be withdrawn at once. Severe thrombocytopenia (platelet count $\leq 20,000/\mu\text{l}$) or thrombocytopenia associated with minor to moderate bleeding (including mucous membrane) may require an administration of platelet transfusions, reverse heparin with protamine, warfarin with vitamin K, intravenous (IV) steroids and IgG. In case of immune-mediated thrombocytopenia, the administration of steroids and IV IgG may be considered^{5,11,16-18}. We used MDMP in our patient with antiglobulin-positive immune thrombocytopenia, and we consider it to be effective in the treatment of DITP.

We think that imipramine-associated direct antiglobulin-positive thrombocytopenia developed in this patient in view of its emergence after seven days of imipramine treatment, although antiplatelet antibodies due to imipramine could not be determined. We describe a child with immune thrombocytopenia to stress that physicians should be aware of this rare and most unusual adverse effect of the imipramine. Further researches are needed to analyze the mechanisms responsible for imipramine-associated immune thrombocytopenia.

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