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CASE REPORT

Hematology in Clinical Practice
2021, vol. 12, no. 1, 29–32
DOI: 10.5603/HCP.2021.0005

ISSN 2720–1015

Secondary immune thrombocytopenia after *Streptococcus* infection

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Abstract

Immune thrombocytopenia is typically characterized by a decrease in platelet (PLT) count and bleeding diathesis symptoms or increased bleeding risk. In the report, we describe a case of a 19-year-old female patient who suffered from secondary immune thrombocytopenia in the course of streptococcal pharyngitis. After diagnosis, the patient received pharmacotherapy for thrombocytopenia according to Polish standards (intravenous dexamethasone sodium phosphate) which improved the platelet level. However, the change from dexamethasone intravenous to oral prednisone resulted in PLT level decrease. Hematological improvement was observed only after changing prednisone to methylprednisolone.

Key words: immune thrombocytopenia, streptococcal pharyngitis, dexamethasone, prednisone, methylprednisolone

Hematology in Clinical Practice 2021; 12, 1: 29–32

Introduction

Immune thrombocytopenia (IT) is an acquired disease typically characterized by an isolated decrease in platelet count and bleeding diathesis symptoms or increased bleeding risk. Approximately 20–30% of all IT cases are secondary immune thrombocytopenia which may be associated with various causes, such as systemic connective tissue disease, lymphomas, infections, drugs (e.g. heparin, chemotherapeutics) or genetic factors [1, 2]. The literature describes an association between thrombocytopenia and various infections, such as hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Bárr virus (EBV), *Helicobacter pylori*, or cytomegalovirus (CMV) [2, 3]. However, only few cases of IT caused by streptococcal infection were described.

Case report

A 19-years-old female patient was admitted to the hospital's internal ward because of ecchymoses appearing on lower limbs. Several days before admission to the hospital, the patient had streptococcal pharyngitis, treated with oral clarithromycin 500 mg twice per 24 h for five days.

A patient was born from the first pregnancy (Apgar score of 10). In childhood, she had varicella and rubella without complications. The patient did not report spontaneous bleedings from gums, prolonged profuse menstruations, bleedings from mucous membranes (nose, mouths), gastrointestinal tract, lungs or urinary tract. She did not take any drugs, vaccines, and has not been exposed to ionizing radiation prior to hospitalization.

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Investigations

Physical examination on admission revealed: numerous petechiae on skin layers, mottling ecchymoses on lower limbs and inflamed throat mucosa with purulent coating on tonsils. Laboratory examination revealed: thrombocytopenia ($8.76 \times \times 10^9$/L with reference range = 150 to 450), high anti-streptolysin O (ASO) level (1,408 IU/mL with reference value < 200), positive antigen test for PBHA presence (group A hemolytic streptococcal). Anti-HCV and HBS-Ag antibodies were also assessed to exclude hepatitis B and C. Gynecological consultation (to exclude pregnancy), echocardiography with the evaluation of heart valves, abdominal ultrasound with the evaluation of the spleen (no deviations) and hematological consultation with bone marrow biopsy (correct picture of all hematopoietic lines) were carried out during hospitalization. Secondary immune thrombocytopenia in the course of streptococcal pharyngitis was diagnosed based on clinical and laboratory tests (blood morphology, ASO, abdominal ultrasound).

Treatment

According to the Polish standards of *Streptococcal pharyngitis* treatment, the patient was treated with antibiotic therapy, receiving intravenous amoxicillin (1 g) and clavulanic acid (200 mg) 3 times per day. Moreover, following Polish standards of thrombocytopenia treatment, the patient was administered steroid therapy, receiving intravenous dexamethasone sodium phosphate 40 mg per 24 h for five days, which led to increased platelet level (Table 1). After switching from intravenous therapy to oral prednisone at a dose of 1 mg/kg of body mass weight, the platelet level decreased from 66×10^9/L to 11×10^9/L. Hematological improvement was observed on 18th day of hospitalization after changing prednisone to methylprednisolone at a dose of 0.8 mg/kg of body weight.

Outcome and follow-up

The disappearance of purpura and bruises on limbs and normalization of ASO level was observed during the therapy. The patient was discharged home on 25th day of hospitalization with clinical improvement. Steroid therapy with methylprednisolone was maintained in a daily dose of 50 mg with a continuous reduction of 5 mg/week. The patient was also referred to hematological clinic.

Discussion

The most common IT is primary immune thrombocytopenia (ITP), in which the cause of antiplatelet antibody prevalence is unknown. The estimated prevalence is 9.5 per 100,000 adults, while the annual incidence reaches 3.3 per 100,000 [4].

Pathophysiology of immune thrombocytopenia is not fully understood. The principal mechanism relies on the production of antiplatelet antibodies. However, such antibodies are not detected in up to 50% of patients, suggesting the involvement of other mechanisms (e.g. abnormalities in T-cells and decreased number and function of T-regs) [1].

The association between thrombocytopenia and infection is known. In adults, various bacteria and viruses were associated with thrombocytopenia, including streptococcal infections. Thrombocytopenia associated with these factors is chronic, with no tendency to spontaneous remission, and its severity may increase with disease progression [5, 6].

The first cases of thrombocytopenia associated with *Streptococcus* infection were described in 1978 [7]. Six years later, the biopsy-proven case was published [8].

Morrin et al. [9] described a case of thrombotic thrombocytopenic purpura secondary to *Streptococcus* infection, suggesting that it may have followed the development of an inhibitory antibody to metalloprotease which broke down high molecular weight multimers of von Willebrand factor (vWF). Few numbers of cases prevent an accurate understanding of the mechanisms underlying this hematological complication. In the case of thrombocytopenia associated with *Helicobacter pylori* infection, it is assumed that antibodies against bacterial membrane proteins can cross-react with platelet glycoproteins. Another hypothesis reveals the role of increased platelet phagocytosis, induced by the lipopolysaccharide present in the outer membrane of *H. pylori* as well as increased platelet aggregation induced by *H. pylori* binding to vWF [6, 10–13]. As *Streptococcus* can adhere to platelets (binding directly to platelet glycoprotein Ib) it can be hypothesized that a similar mechanism is responsible for thrombocytopenia in case of streptococcal infection [14–16]. However, more studies are required to confirm it.

Current molecular studies revealed that *S. pneumonia* infection induced phosphatidyl-serine exposure in platelets and increased Annexin V (potential factor inhibiting blood coagulation) binding to platelets [17].

A study on the gut microbiome has shown that immune thrombocytopenia can result in the development of dysbiosis (enrichment of *Blautia*, *Streptococcus*, and *Lactobacillus* fecal bacteria) [18].

Table 1. Changes in morphological parameters during hospitalization

Course of therapy	PLT [× 10^9/L] (150–386)	Hb [g/dL] (12.00–15.50)	RBC [T/L] (3.9–5.7)	WBC [× 10^9/L] (3.6–9.6)	MCV [fl] (82–92)	HCT [L/L] (0.36–0.50)
Amoxicillin + clavulanic acid, dexamethasone sodium phosphate from 1st day of hospitalization	7.21	12.12	4.40	10.7	82.9	0.365
4th day	40.7	11.04	4.00	22.3	82.9	0.332
5th day	54.1	10.54	3.69	14.3	82.6	0.305
Prednisone from 6th day of hospitalization	66.9	11.44	4.09	7.94	83.0	0.339
9th day	11.7	12.71	4.58	12.0	83.7	0.383
13th day	15.9	12.68	4.48	15.1	84.1	0.377
Methylprednisolone from 16th day of hospitalization	11.8	12.29	4.54	23.4	83.4	0.379
18th day	13.2	12.41	4.52	27.0	83.2	0.376
21st day	58.9	11.86	4.23	17.2	84.1	0.356
24th day	76.8	12.25	4.67	15.9	82.6	0.386

Reference values range in round brackets; PLT — platelets; Hb — hemoglobin; RBC — red blood cells (erythrocytes); WBC — white blood cells (leukocytes); MCV — mean corpuscular volume; HCT — hematocrit

Observed differences in patient reaction to corticosteroid therapy are another interesting issue. Glucocorticosteroids are used as a first-line treatment of thrombocytopenia; however, their use is associated with many complications (adverse drug reactions and interactions). Prednisone is a prodrug, which requires conversion to an active metabolite (prednisolone) by CYP3A4 enzyme [19]. Dexamethasone and methylprednisolone are administered as active drugs. Inflammation decreases the activity of CYP3A4, which may contribute to a decreased rate of prednisone conversion [20]. The patient could also have genetic variants encoding CYP3A4 with decreased activity; however, no genetic test was carried out to confirm it.

Conflict of interest

The authors declare no conflict of interest.

Financial support

The study received no external funding.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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