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LETTER TO THE EDITOR

Colistin-related thrombocytopenia

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Keywords

Children, colistin, thrombocytopenia

History

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To the editor,

Acute thrombocytopenia occuring due to drugs is a well described but commonly misdiagnosed condition in children. Immune thrombocytopenias are among the most important causes of acquired thrombocytopenias. Probable or definite drug-related thrombocytopenia can be induced by several drugs and may occur because of both decreased production and/or peripheral destruction of thrombocytes [1]. Polymyxins are effective antibiotics for resistant Gram-negative bacteria with a potential adverse effects of nephrotoxicity and neurotoxicity which are often dose-dependent and reversible on discontinuation of treatment [2]. Hematopoietic adverse reactions have not been reported so far in relation with polymyxins. To the best of our knowledge, there is no prior report of colistin-related thrombocytopenia neither in adults nor in children in English medical literature. The present article describes a case of colistin-related thrombocytopenia in a patient treated with colistin. Upon discontinuation of colistin, thrombocytopenia resolved progressively.

A 5-year-old female with a history of chronic renal failure applied with cough and fever that have been present for 1 week. The patient has been on hemodialysis three times in a week for 3 months due to renal insufficiency caused by focal segmental glomerulosclerosis. She was using nifedipine, antiphosphate tablets, enalapril, calcium tablets and erythropoetin. Familiy history was unremarkable. Physical examination findings were normal except for paleness, rales in right lower zone, tachypnea and fever of 38.7 °C. Her blood pressure was 90/60 mmHg. Laboratory findings revealed hemoglobin 8.7 g/dl; hematocrit 25.4%; white blood cell count 14.9×10^6/μl, platelets 165×10^6/μl, and in serum biochemistry blood urea nitrogen was 24 mg/dl and creatinine 1.2 mg/dl with no electrolyte imbalance. Serum procalcitonin was 4.1 ng/ml (0–0.5). Chest X-ray showed pneumonic consolidation in right lower lobe of the lung with a little amount of pleural effusion. She was hospitalized to the General Pediatrics ward of Çukurova University Faculty of Medicine Hospital and meropenem was started empirically. On 3rd day of hospitalization her fever continued and *Klebsiella pneumoniae* was cultured in her blood. Colistin was added to the treatment because of sensitivity to it. The fever of the patient was under control on the 5th day of theatment and procalcitonin started to decrease progressively. On 6th day of treatment an epistaxis emerged and thrombocyte count was found 71×10^6/μl. There were no petechia, purpura, ecchymose on skin or bleeding in other mucous membranes or venous catheter accesses. Blood smear was normal apart from decreased thrombocytes and no mega or micro thrombocyte was seen. Prothrombin time, activated partial thromboplastin time and fibrinogen level were normal. Hemorrhage stopped after thrombocyte transfusion. Thereafter, we determined a gradual decrease in thrombocyte counts (Table I). Etiology of thrombocytopenia was searched. Viral markers for hepatitis A, B, and C, Epstein-Barr virus, cytomegalovirus, parvovirus B-19, rubella and HIV were negative. Autoimmune hepatitis markers and thyroid tests were normal as well. Serum anti-extractable nuclear antigen, anti-nuclear antibody, and anti-DNA were negative. No specific cause was identified to explain the thrombocytopenia. Upon discontinuation of colistin in 14th day of therapy, a gradual increase was observed in platelet counts. On discharge, thrombocytes of the patient were counted as 315×10^6/μl, 6 days after the stopping colistin.

Drug-related thrombocytopenia is a rare condition in childhood that can be associated with numerous drugs. In English medical literature, no prior report of colistin-related thrombocytopenia was found neither in adults nor in children. To our knowledge, this report is the first one describing a relation between colistin and thrombocytopenia. Antibiotic-related thrombocytopenia may occur because of decreased production of megakaryocytes or peripheral destruction of thrombocytes [3]. Peripheral destruction of thrombocytes have been frequently reported in association with the oxazolidinone linezolid [4]. Vancomycin can cause thrombocytopenia and hemorrhage via the production of reactive antibodies and peripheral destruction of platelets [5]. Rifampin, sulfonamides, penicillin and cephalosporin derivatives such as ampicillin, methicillin, cefazolin, and cefoxitin have also been reported to cause thrombocyte destruction [6] Another drug known to induce thrombocytopenia and aplastic anemia is chloramphenicol [7]. Appropriate treatment in such a suspicion of drug-related condition is recognizing and removal of the offending drug urgently. The presence of thrombocytopenia, hemorrhagic complications, and occurence of thrombocytopenia after drug exposure are helpful clues to recognize such a relation. In our patient, epistaxis and

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Table I. Thrombocyte counts of the patient.

Days	Thrombocyte count
Before colistin	165×10^6/μl
3rd day of colistin	71×10^6/μl
6th day of colistin	65×10^6/μl
9th day of colistin	59×10^6/μl
12th day of colistin	60×10^6/μl
14th day of colistin	55×10^6/μl
2nd day without colistin	86×10^6/μl
4th day without colistin	155×10^6/μl
6th day without colistin	315×10^6/μl

subsequently determined thrombocytopenia and a new commenced drug 3 days ago were warning about colistin-related thrombocytopenia.

In suspected drug-related thrombocytopenia other conditions that can cause thrombocytopenia must be excluded [1]. Drug-related thrombocytopenia can be mediated by several drugs and may occur because of both decreased production and/or peripheral destruction of thrombocytes [1,3]. Immune thrombocytopenias are the most important reasons of acquired thrombocytopenias. The clinical condition of our patient is not compatible with acute or chronic idiopathic thrombocytopenic purpura, systemic lupus erythematosus or transfusion reaction. Among non-immune causes of peripheral platelet destruction infections and microangiopathic disorders must be considered. An evidenced but controlled *K. pneumoniae* bacteremia in our case could not have been the causal etiologic agent. On the other hand, we did not determine any hemolytic or thrombotic findings that can be signs of microangiopathies. Disseminated intravascular coagulation was excluded clinically and with normal PT, aPTT and fibrinogen levels. Hemophagocytic syndrome is not thought because of absence of continuing fever, lymphadenopathy and hepatosplenomegaly. Impaired thrombocyte production can be originated from inherited disorders such as Bernard-Soulier syndrome, Wiscott-Aldrich syndrome, and macromegakaryocytes associated with thrombocytopenia. Blood smear and normal morphological appearance of thrombocytes helped to exclude these conditions. In addition there was no splenomegaly nor chronic thrombocytopenia that can be warning for hypersplenism. Because of acute nature and abrupt occurence of thrombocytopenia we did not consider aplastic anemia, myelodisplastic syndrome or bone marrow infiltration and we did not perform bone marrow biopsy. One can suspect from dialysis-related thrombocytopenia. But the patient has been on hemodialysis programme for 3 months and hemodialysis was continued both during and after the colistin therapy.

Antibody testing to confirm drug-related thrombocytopenia and rechallenge test with colistin could be done to further evidence the association between thrombocytopenia and colistin. We planned to perform advanced tests if thrombocytopenia had not resolved after discontinuation of suspected medication and if there was doubt on the clinical diagnosis. In our patient's case, there were no other drug changes or medical conditions that could explain the thrombocytopenia. Moreover, thrombocyte level normalized rapidly after discontinuation of colistin. Drug rechallenge would be unethical and risky in such a suspicion of adverse reaction, especially in case of alternative antibiotics were readily available.

Nowadays, an increase has been reported in infections caused by resistant Gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *K. pneumoniae* and for these bacteria polymyxins are effective alternatives [2]. Nephrotoxicity and neurotoxicity are the most common adverse effects of polymyxins which are often dose-dependent and reversible on discontinuation of treatment. Hematopoietic adverse reactions have not been reported so far in relation with polymyxins. It can be recommended to especially clinicians to be alert about the probable association of colistin and thrombocytopenia.

Declaration of interest

There is no conflicts of interest to disclose.

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