Piperacillin/tazobactem induced epistaxis- A case report

Sir,

Thrombocytopenia is a rare side effect associated with beta-lactam antibiotic therapy,[1] and isolated thrombocytopenia induced by ureidopenicillins seems to be not so uncommon nowadays in clinical practice.[2] We describe a patient who was treated with piperacillin/tazobactam and developed antibodies to platelets, resulting in uncontrolled epistaxis related to severe thrombocytopenia, after taking consent from the patient and the Institutional Review Board.

A 51-kg, 50-year-old woman with past medical history of bronchial asthma, on bronchodilator therapy, presented with chief complaints of dry cough and breathlessness for the last 4–5 months. Complete blood cells (CBC) revealed a white blood cell count of 15,000/mm with a left shift, and values for red blood cells and platelets were within normal limits. Results of serum chemistry studies, blood gas evaluation, and urinalysis were normal, except the findings on a chest radiograph suggestive of right middle and lower lobe opacification and consolidation. She was advised to go for sputum examination for acid-fast bacilli (AFB) using Gram's stain and KOH mount, but they came out to be negative. She was further investigated by chest computed tomography scan to rule out allergic bronchopulmonary aspergillosis (ABPA), which showed centrilobular bronchiectasis. She was later admitted in medical intensive care unit on day 3. Therapy was initiated with intravenous 4 g of piperacillin plus 0.5 g of tazobactam TID, ranitidine 150 mg OD, and dexamethasone 4 mg BID. On high suspicion of ABPA, absolute eosinophil count was done which was found to be raised (620/mm^3). Further respiratory medicine consultation was sought in view of aspergillosis. She was again advised to go for bronchoalveolar lavage (BAL) after repeated AFB-KOH mount stain which was negative again. BAL findings were insignificant except the post-procedure mild epistaxis that came to notice when she used to cough out the bloody sputum, but it was ignored as a part of ordinary post-procedure complication. Next day, the isolated epistaxis persisted without bleeding from other sites of the body and CBC count was repeated that showed a platelet count of 16,000/mm^3. Dengue serology was sought due to it being the endemic regional seasonal infection. But the results were negative on serum NS1 antigen and antibody titer (IgM, IgG). Peripheral smear was reviewed by hematologists, who confirmed the negative dengue infection as suggested by the absence of relative lymphocytosis, increased hematocrit, and erythrocyte sedimentation rate (ESR) level. Epistaxis could not be controlled by general measures and anterior nasal packings. Four units of platelet-rich plasma were transfused so as to check the unusual complication that was previously presumed to be an aftermath of fiberoptic BAL. After 12 h, the platelet count was just 9000/mm^3. Next day morning, the platelet count dropped to 1000/mm^3, but there were no signs of any spontaneous bleeding from the body other than the minor concealed bleeding from nose as post-nasal drip. After review of literature and present treatment, and in consultation with the physician and intensivist, it was decided to withhold the drugs (piperacillin, tazobactam, and ranitidine) causing thrombocytopenia on a high suspicion. Serology was advised for antibodies (IgG and IgM) against the drug piperacillin–tazobactam, which were found to be positive, thereby confirming our diagnosis. Following this, the patient's platelet count showed a transient upward trend, and the repeat platelet count 12 h later was 3000/mm^3. Bleeding was under control by the next day morning, and the platelet count progressively increased to 45,000/mm^3. Next day, her CBC counts increased to within normal limits (platelets were 150,000/mm^3).

Acute, unexpected thrombocytopenia in a patient hospitalized for multiple medical problems has multiple potential etiologies. It is of primary concern to monitor the platelet count besides routine hemogram and total leukocyte counts taken regularly during hospitalization (other than medical or surgical ICU) and on subsequent follow-up visits, even after the most probable etiology has been identified or the most likely causative drug has been withdrawn. In a patient being treated for infection and at risk for additional infectious complications, sepsis must be the initial consideration because of the risk for sudden, critical deterioration. In a patient on multiple medications, drug-induced thrombocytopenia (DITP) is the other principal consideration. Our patient had isolated thrombocytopenia, without any evidence of microangiopathic hemolysis, consistent with both of these etiologies. The absence of evidence of microangiopathic hemolysis [no schistocytes (fragmented red blood cells)] was seen on examination of the peripheral blood smear, and serum lactate dehydrogenase (LDH) was normal which excluded the consideration of thrombotic thrombocytopenic purpura. The risk of thrombocytopenia with any single drug is rare, but bleeding complications in the affected patients can be severe, and may even be fatal.

Our patient represents an uncommon case of antibiotic (in particular, piperacillin/tazobactam)-induced severe immune thrombocytopenia that resulted in epistaxis. Both IgG and

Table 1: Clinical criteria and levels of evidence for evaluation of patients with suspected drug induced thrombocytopenia[2]

Clinical criteria
Drug administration preceded thrombocytopenia; recovery from thrombocytopenia complete and sustained after drug discontinued
Other drugs administered prior to thrombocytopenia were continued or reintroduced after discontinuation of the suspected drug
Other etiologies of thrombocytopenia excluded
Re-exposure to the drug resulted in recurrent thrombocytopenia
Levels of evidence
Definite: all 4 criteria met
Probable: Criteria 1–3 met
Possible: Criterion 1 met
Unlikely: Criterion 1 not met

Adapted from www.ouhsc.edu/platelets and Ref. [2]

IgM antibodies specific for piperacillin against platelets were positive as confirmed by immunoprecipitation and flow cytometry studies, further ascertaining the etiology and the diagnosis. DITP typically occurs within 1–2 weeks of daily treatment with a new drug or after intermittent use for a longer time. Piperacillin as the etiology of the thrombocytopenia in our patient was confirmed by documentation of piperacillin-dependent platelet-reactive antibodies and by the absence of tazobactam-dependent platelet-reactive antibodies.[3,4]

When DITP is suspected, the foremost step is to take a complete history of all drugs that the patient is taking, including not only the prescribed drugs that are used regularly but also the occasionally used over-the-counter medicines, including herbal remedies[5,6] and quinine-containing beverages. The next step is to evaluate the particular drug among the multiple medications that the patient is taking, which may have triggered DITP [Table 1]. It is equally important to confirm the etiology of the DITP by testing for the presence of a drug-dependent platelet-reactive antibody.[7]

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