

## AUGMENTIN-INDUCED THROMBOCYTOSIS: A MAIDEN CASE SERIES

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## ABSTRACT

When an infected patient suffers from thrombocytosis, it is very difficult to identify beta-lactam antibiotic-induced cases of the disease and separate those from the possibility that thrombocytosis is an acute-phase reaction in the infected patient. We present 3 cases who were treated with Augmentin for various indications and developed thrombocytosis during the treatment course. The Naranjo probability scale indicates Augmentin as the possible cause of the thrombocytosis in all our patients.

**Keywords:** Amoxicillin/clavulanic acid, Thrombocytosis, Adverse effects, Naranjo's scale.

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## INTRODUCTION

It is very difficult to identify antibiotic-induced thrombocytosis in an infected patient since infection by itself one of the commonest causes of reactive thrombocytosis. Many drugs are implicated in causing reactive thrombocytosis with Adrenaline being the first one discovered to cause reactive thrombocytosis. Other agents include vinca alkaloids, miconazole, and iron preparations. Hence, we present 3 patients (case series) treated with Augmentin for various indications and developed thrombocytosis during the treatment course.

## CASE REPORTS

## Case 1

Informed consent was taken from the patient. A 50-year-old female patient diagnosed of ovarian carcinoma underwent cytoreduction surgery. Post-surgery patient was started on meropenem on September 18, 2016, and later with Augmentin on September 23, 2016. 5 days after starting with Augmentin patient developed elevated platelet counts and counts kept on increasing. On October 4, 2016, platelet counts were high and Augmentin was suspected to be causative agent. All other causes were ruled, and Augmentin was stopped. Intravenous fluid correction was given and she recovered on October 11, 2016 with platelet counts returning to normal levels (Table 1).

## Case 2

Informed consent was taken from patient. A 75-year-old patient diagnosed of malignant melanoma of the right 4<sup>th</sup> toe underwent surgical excision along with right groin lymph node dissection on June 21, 2016. The patient was started on Augmentin on June 21, 2016, and she developed elevated platelet counts on July 4, 2016 and platelet counts continue to elevate till July 9, 2016. Augmentin was stopped on July 5, 2016, and intravenous fluid correction was given (Table 2). The patient slowly recovered back.

## Case 3

Informed consent was taken from the patient. We report a 65-year-old female patient, known case of metastatic adenocarcinoma rectum with bladder infiltration, Stage IV CT4BN2M1B, admitted to the Oncology Department of our hospital with complaints of severe diarrhea for 20 days. Her history revealed that she was an old case of carcinoma endometrium diagnosed in 1999. A complete physical examination revealed pallor and enlarged right inguinal lymph nodes. Per rectal examination revealed an anal growth of 5 cm from the anal verge. Her laboratory parameters revealed mild anemia with leukocytosis.

In view of the above signs and symptoms, patient was taken up for cystoscopy and sigmoidoscopy under the cover of a broad spectrum antibiotic Augmentin (amoxicillin with clavulanic acid) 1 g on July 16<sup>th</sup> 2016. Following the second dose of Augmentin, her laboratory parameters revealed thrombocytosis with a platelet count of about 4,54,000, and the counts kept on increasing to 5,59,000 after 1 week of Augmentin therapy as on 21<sup>st</sup> of July 2016 (Table 3). Others causes of thrombocytosis were ruled out, and Augmentin was stopped on 21<sup>st</sup> and patient platelet counts came down to normal levels.

## DISCUSSION

Thrombocytosis is generally defined as platelets counts above 4,00,000. Patients with systemic inflammation, tumors, bleeding, drugs, trauma, stress, iron deficiency anemia may have elevated platelet counts, a condition called secondary or reactive thrombocytosis.

Antibiotic-induced reactive thrombocytosis is relatively uncommon and extreme thrombocytosis is very rare. There are three major categories of thrombocytosis, namely, secondary or reactive thrombocytosis, hereditary thrombocythemia, and clonal thrombocytosis, including essential thrombocythemia and related myeloproliferative disorders. Many classes of drugs are implicated in causing reactive thrombocytosis such as vinca alkaloids, iron preparations, and also beta-lactam antibiotics. However, antibiotic-induced cases of thrombocytosis are very difficult to interpret due to the possibility of an acute-phase reaction in an infected patient being the actual cause of the thrombocytosis [1].

Amoxicillin originally introduced in the early 1970's for oral use in the United Kingdom was later used in different formulations and combinations to treat various diseases [2]. Amoxicillin/clavulanic acid (Augmentin), is an established combination of a semisynthetic antibacterial agent, amoxicillin and a beta-lactamase inhibitor, clavulanic acid. Penicillin-susceptible strains of *Streptococcus pneumoniae* and beta-lactamase producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* are highly susceptible to Augmentin and penicillin-resistant strains are moderately susceptible to this drug combination. Amoxicillin/clavulanic acid causes many adverse reactions. It includes skin reactions (78%), gastrointestinal (13%), hepatic (4%), hematological toxicity (2%) [3]. There are few case reports of reactive thrombocytosis with beta-lactam and beta-lactamase inhibitor combination [4-6]. Augmentin-induced thrombocytosis is extremely rare with so far only one case report reported as per literature [7].

**Table 1: Case 1 - Platelet counts after Augmentin therapy**

Date	Platelet counts
September 23, 2016	310×10 <sup>3</sup> /UL
September 29, 2016	480×10 <sup>3</sup> /UL
October 04, 2016	785×10 <sup>3</sup> /UL
October 11, 2016	310×10 <sup>3</sup> /UL

**Table 2: Case 2 - Platelet count after Augmentin therapy**

Date	Platelet counts
July 01, 2016	288×10 <sup>3</sup> /UL
July 04, 2016	408×10 <sup>3</sup> /UL
July 09, 2016	785×10 <sup>3</sup> /UL

**Table 3: Case 3 - Platelet count after Augmentin therapy**

Date	Platelet counts
July 13, 2016	344×10 <sup>3</sup> /UL
July 17, 2016	444×10 <sup>3</sup> /UL
July 21, 2016	559×10 <sup>3</sup> /UL

**Table 4: Adverse drug reaction assessment**

Naranjo's scale	Hartwig's scale	Thornton's scale
Probable	Mild severity	Not preventable

In our patient's thrombocytosis developed after starting Augmentin and all patients recovered back to normal after discontinuing the drug. Rechallenge was not done, and other possible causes of reactive thrombocytosis such as infections, Kawasaki disease, inflammatory bowel disease, hemolytic anemias, connective tissue disorders, other drugs such as vinca alkaloids, steroids, antifungals, haloperidol, and iron preparations were ruled out. Mechanisms underlying Augmentin-induced thrombocytosis is not clear yet as per literature evidence, possibility of bone marrow response to thrombopoietin leading to elevated platelet counts is worth a mention here [8].

Causality assessment was done as per Naranjo's scale [9], and a probable causal relationship was established (Table 4). It was also found that the adverse drug reaction was of mild severity and was not preventable as per Hartwig's and Thornton's scale, respectively [9].

## CONCLUSION

Although no obvious complications occurred in most patients, we should pay close attention to the possibility of adverse reactions. Reactive thrombocytosis due to Augmentin should be kept in mind, and it is prudent enough to rule out other causes of secondary thrombocytosis as infection can result in elevated platelet counts. Further prospective studies can be done to find out the incidence of thrombocytosis associated with combination of beta-lactam antibiotics and beta-lactamase inhibitors.

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