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Sulfamethoxazole-Trimethoprim Induced Neutropenia After Posterior Spinal Fusion in a Patient with Congenital Scoliosis: A Case Report

Open Access **Case Report**

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Abstract

Neutropenia is a condition characterized by a significant reduction in neutrophils. Increased risk for infection remains to be its main complication. Apart from its manifestation in many systemic conditions, it may arise as a result of exposure to certain medications. Sulfamethaxozole-Trimethoprim (SMX-TMP), a common antibiotic prescribed for various infections is one of the typical drugs which can cause neutropenia. This report is a case of an 11 year old female who presented with methicillin resistant staphylococcus aureus infection after posterior spinal fusion for congenital scoliosis secondary to SMX-TMP induced neutropenia. Prompt referral to appropriate specialty led to the early diagnosis of the condition and immediate discontinuation of the causative drug. Significant improvement in her blood parameters was observed thereafter, preventing severe complications such as systemic infections.

Keywords: Neutropenia; Sulfamethoxazole-trimethoprim; Congenital scoliosis

Introduction

Drug-induced neutropenia is a serious complication of therapy with many different medications.1Neutropenia is defined as an absolute neutrophil count (ANC) of <1500 cells/mm^3 for most adults and children. ANC is the product of the total leucocyte count and the percentage of neutrophils and band cells observed in the peripheral blood by a differential leucocyte count. Neutropenia can be graded as mild, moderate, and severe, corresponding respectively to ANC values of 1000-1500 cells/mm^3, 500-1000 cells/ mm^3, and <500 cells/ mm^3. Neutropenia related to causative drugs may be immune mediated or due to direct inhibition of the bone marrow precursors. Recently, due to wide use of chemotherapy, febrile neutropenia has become a common and devastating problem *[2]*. A variety of therapeutic agents have been associated with drug induced neutropenia. One of the drugs associated with this condition is SMX-TMP. In a study by Andres, et al., majority of the cases with drug induced neutropenia were caused by antibiotics (49.3%), especially Beta-lactams and Co-Trimoxazole (SMX-TMP) *[3]*. Introduced in 1968, SMX-TMP remains a popular antibiotic because of its low cost, effectiveness and familiarity among clinicians *[4]*. It remains to be a vital inclusion in the armamentarium for soft tissue infections associated with methicillin resistant staphylococcus aureus (MRSA). Although this drug is well tolerated by many patients, it is associated with several potentially serious adverse reactions. Several uncommon, but potentially serious blood dyscrasias have been reported following the use of SMX-TMP. In 1979, a 10-yr nation-wide study in Sweden indicated that the incidence of drug-induced neutropenia was 1 case/million population/yr. An international study in 1991 yielded an incidence of 3-4 cases/million population/yr *[2]*. A relatively rare disorder but with catastrophic outcomes if undiagnosed. Here, we report a case of an 11 year old female who developed febrile neutropenia after exposure to SMX-TMP. Presented is the patient's clinical and hematologic profile as well as ancillary procedures leading to the diagnosis of the disease. Based on our experience with successful management, recommendations are suggested**.**

Case Report

An 11 year old female (ht.142.4cm & wt. 38kg) presented with fever with no other associated symptoms after 20 days of exposure to SMX-TMP with dosage of 400mg/80mg qid. Review of systems was unremarkable. On further evaluation of her past medical and surgical history, patient is a known case of Holt-Oram Syndrome with Congenital scoliosis *(Figure 1)*.

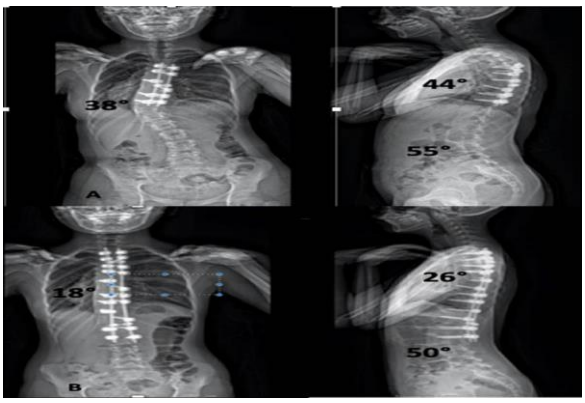

Figure 1: Preoperative and postoperative radiographs (anterior-posterior and lateral). She underwent posterior spinal fusion (T2-L2) due to the progression of postoperative congenital scoliosis.

At 4 years old, she underwent cast and brace treatment, at 9 years old underwent posterior spinal fixation T4-T10 and right T6 hemivertebrectomy (Figure 2) and at 11 years old, because of curve progression, underwent T2-L2 posterior spinal fusion *(Figure 3).*

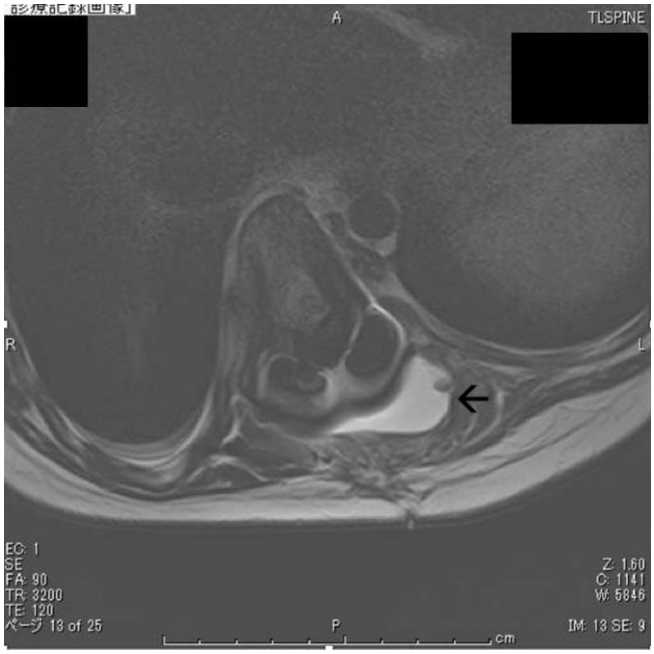

Figure 2: MRI T2 image showing abscess around implant (arrow).

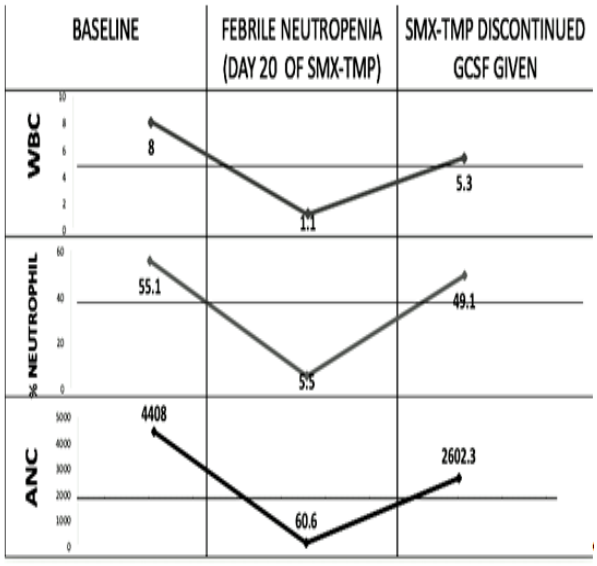

Figure 3: Summary of patient's hematologic profile

One week post surgery, she developed fever. CBC revealed leukocytosis of 12.6% neutrophils of 79.5 and increase in CRP of 3.67. MRI was done and revealed an abscess around implant *(Figure 4).*

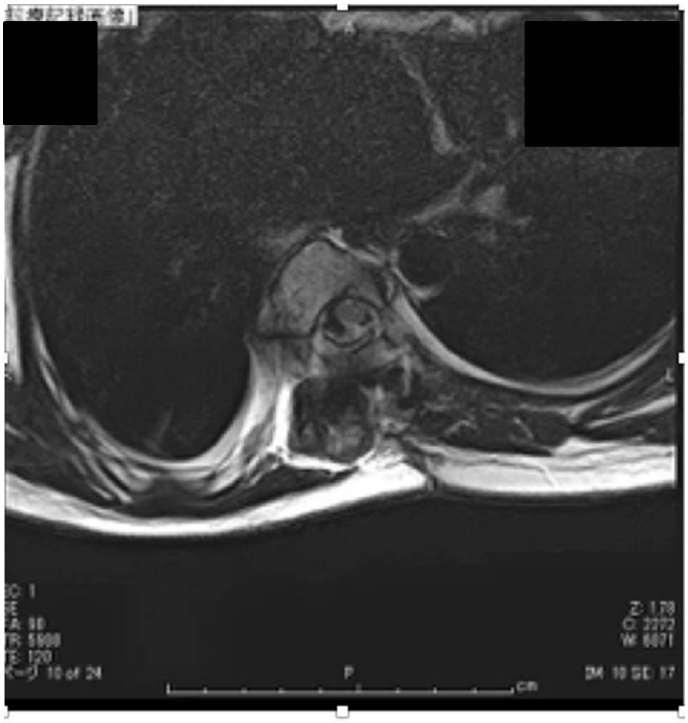

Figure 4: MRI T2 image showing no abscess recurrence around implant.

Immediate debridement was done, abscess was drained and culture revealed MRSA. Vancomycin was started and shifted to Linezolid. On day 30 of Linezolid, it was shifted to SMX-TMP. Laboratory data at this time revealed normal WBC count and CRP which was consistent with the improvement of the surgical site infection. On day 10 of SMX-TMP antibiotic therapy, she was discharged improved. Patient had no known drug allergies and denied any nonprescription or herbal supplement use and claimed full adherence to the SMX-TMP regimen prescribed. On initial presentation, the patient had a high grade fever of 38.6°C. Physical examination revealed a well healed scar with no signs of surgical site infection. Examination of other organ systems was essentially normal. Laboratory tests performed revealed a WBC count of 1.1% neutrophil of 23.4 and an ANC of 257.4 cells/μL *(Graph 1).* In addition, MRI T2 image revealed negative for recurrence of abscess *(Figure 5).* Impression at this time was a blood dyscrasia, for which she was referred to pediatric hematology. Bone marrow biopsy was requested and revealed hypoplastic bone marrow with reduced myeloid cells *(Figure 6*). Genetic testing was also done and showed normal result. She was then diagnosed with drug induced neutropenia. Consequently, SMX-TMP was immediately discontinued and granulocyte colony stimulating factor (G-CSF) was administered. Repeat

labs showed recovery of the WBC to 5.3% neutrophil to 59.1 with ANC of 2603.3 *(Graph 1).* She was discharged improved and on regular follow-up showed normal labs.

Discussion

The pattern of neutropenia observed in our patient was consistent with other reported cases. Our patient developed neutropenia after 20 days of SMX-TMP therapy and had recovery of ANC 8 days after it was discontinued (Graph1). In a study by Prinicipi et al., it was reported that late neutropenia (evident after 10 days of treatment) appeared in co-trimoxazole (SMX-TMP) treated children (p value less than 0.05). No superimposed bacterial infection was demonstrated in any case. Late neutropenia seems to be strictly related to the sequential blockage of folinic acid metabolism and can be prevented by the concomitant administration of folinic acid *[5]*. The mean and median durations of haematological recovery (from initial neutropenia documentation to neutrophil count >/=1.5 $x10^9$/L) were 7.8 and 6 days (range: 2-10), respectively. The mean and median durations for neutrophil count >/=0.5x 10^9/L were 6.8 and 5 days (range: 1-24), respectively *[3]*. Furthermore, our patient presented with a high-grade fever (38.6°C) at the time of admission. These findings are consistent with results reported in the literature which states that isolated fever (unknown origin) as the main clinical presentation during hospitalization (Table 1)*[3]*. Diagnosis of drug induced neutropenia in our patient was arrived based on exposure to SMP-TMX drug, presence of febrile neutropenia and bone marrow finding of myeloid hypocellularity with neutrophilic maturation arrest. In accordance with studies on the condition, diagnosis was suggested during or immediately following drug exposure, the occurrence of febrile neutropenia with decreased classic signs of inflammation, reduced absolute neutrophil count, and bone marrow findings of myeloid hypocellularity, neutrophilic maturation arrest, or hypercellularity with increased myeloid precursors and little maturation *[2]*. Immediate cessation of the drug was done and G-CSF was administered once patient was diagnosed. Consistent with measures to manage drug-induced neutropenia presented in research which include the following treatment: Discontinuation of the offending drug or presumed causative agent. Recombinant human granulocyte colony-stimulating factor (rG-CSF). G-CSF is the major cytokine that stimulates the growth and development of neutrophils in the bone marrow. It increases the activation, proliferation, and differentiation of neutrophil progenitor cells and enhances the function of mature neutrophils. It results in increased granulopoiesis without reducing the half-life of neutrophils. Consequently, it produces dose-dependent increases in the ANC and is associated with decreased incidence, duration, and severity of neutropenia *[2]*. Prevention and risk reduction of such condition is vital in deterring the more severe complications of neutropenia. Clinicians should be cognizant of the potential consequences of prescribing SMX-TMP, monitor patients for adverse events during therapy or use an alternate antibiotic when appropriate *[4]*. Literature regarding patient monitoring on SMX-TMP antibiotic regimen is scarce. However, some studies suggest periodic monitoring of the CBC in patients receiving a high dose of SMX-TMP for extended periods *[4]*. In addition, children treated with SMX-TMP should be followed up with biweekly leukocyte and platelet counts *[6]*.

Conclusion

Although SMX-TMP is a popular, effective and inexpensive drug with a long history of use, it is associated with a range of adverse effects, some with fatal outcomes *[4]*. Clinicians should be aware that drug induced neutropenia may ensue after exposure to SMX-TMP drug. Febrile neutropenia with no other associated symptoms is the usual presentation. As such, regular monitoring of CBC and platelet is necessary to identify the disease early and administer immediate and appropriate management. Moreover, prompt referral to appropriate medical specialty is vital in preventing severe complications.

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

MT Velasco, R Tauchi, and N Kawakami wrote and prepared the manuscript. All of the authors participated in the study design. All authors have read, and approved the article.

IRB Approval

The institutional review board at our Hospital approved this study.

Acknowledgment

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Informed Consent

Informed consent was obtained by patient and her parents in this study.

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