Case Study

Unraveling the Consequences; Methotrexate Induced Abnormal Uterine Bleeding: A New Case Report

Abhirami Rajasekhar[1], Adithyan R S[2], Dhanya Dharman[3], Shashikala[4], Shaiju S Dharan[5]

[1],[2]Pharm. D Intern, Ezhuthachan College of Pharmaceutical Sciences, [3]Professor, Department of Pharmacy Practice, Dr Moopens college of Pharmacy, Naseera Nagar, Meppadi, Wayanad, [4]Clinician, Obstetrics and Gynaecology, NIMS Medicity, Aralumoodu, Neyyattinkara, Thiruvananthapuram, Kerala, India, [5]Principal, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences.

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Abstract

A 49-year-old female patient was admitted in a tertiary care hospital with complaints of heavy menstrual bleeding and breathlessness on exertion and fatigue. The personal history was 15-20 pads/day fully soaked/ clots+ 5-6 days. She had past medical history of Rheumatoid Arthritis for 2 years and was taking Disease- Modifying Antirheumatic Drugs (DMARDs). Ultra sound abdomen showed bulky uterus. Due to improper dosing and monitoring of DMARDs ,it led to alteration in progesterone/ estrogen levels, resulting in abdominal uterine bleeding. Plan of care was primarily to withhold DMARDs, and perform Hysteroscopy guided with Polypectomy, D and C (dilation and curettage). At the time of discharge the patient was stable and wanted to consult rheumatologist outside.

Keywords: DMARDs, Abdominal Uterine Bleeding, Hysteroscopy, Polypectomy, Rheumatoid Arthritis.

Introduction

Abnormal Uterine Bleeding (AUB) is a broad term that defines irregularities in menstrual cycle including frequency, regularity, duration and volume of flow outside of pregnancy. A normal menstrual cycle lasts 2 to 7 days with 5 to 80 millimeters of blood loss of frequency about 24 to 38 days. differences in any of these parameters constitute Abnormal uterine bleeding.

In 2011 the Federation International de Gynecologie et d'Obstetrique (FIGO) described etiology of AUB with the help of acronym PALMCOEIN. PALM represents structural causes: Polyp, Adenomyosis, Leiomyoma, Malignancy. COIEN represents non- structural causes: Coagulopathy, Ovulatory disorders, Endometrial, Iatrogenic and Not otherwise classified. Any structural derangement in uterus, or to the clotting pathways or disruption of the hypothalamic-pituitary- ovarian axis can affect menstruation which lead to AUB.[1,2,3]

Corresponding Author: Dhanya Dharman, Professor, Department of Pharmacy Practice, Dr Moopens college of Pharmacy, Naseera Nagar, Meppadi, Wayanad.

E-mail: dhanyadharman07@gmail.com

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Disease- Modifying Antirheumatic Drugs (DMARDs) are class of drugs used for the treatment of especially inflammatory arthritis including Rheumatoid Arthritis, Psoriatic arthritis, Ankylosing Spondylitis and also for connective tissue diseases like Systemic Sclerosis, Systemic Lupus Erythematosus, Sjogren Syndrome. Mostly used conventional DMARDs include Methotrexate, Leflunomide, Hydroxychloroquine and Sulfasalazine. Biological agents include Infliximab, Adalimumab, Etanercept, Rituximab, Abatacept, Tocilizumab, Tofacitinib.[4]

Here we are reporting a case of wrong dosage form and monitoring of DMARDs induced Abdominal Uterine Bleeding with endometrial polyp followed by severe anemia.

Case Report

A49 year old female patient was admitted to Obstetrics and Gynaecology department with the complaints of fatigue, heavy menstrual bleeding and breathlessness on exertion. She had an OBG history of three full term normal vaginal delivery and last child birth was 30 years back. Her menstruation history for the last 2 to 3 months was 15- 20 pads per day fully soaked with clots about 5 to 6 days. The patient had past medical history of Rheumatoid Arthritis for 2 years, and managed with T. METHOTREXATE 10mg P/O 1-0-1, T. HYDROXYCHLOROQUINE 400mg P/O 1-0-0, T. CEFEXIME 200mg P/O 1-0-0, T. CALCIUM + VITAMIN D 500mg P/O 1-0-0, T. METHYL PREDNISOLONE 4mg P/O 1-0-0, T. LEFLUNOMIDE 20mg P/O 0-0-1, T. PANTOPRAZOLE 40mg P/O 1-0-0.

The patient was conscious, oriented with pallor, heart sounds were heard, chest was clear, was able to move all limbs and GI was non-tender. During admission, she had a Pulse Rate of 72 beats/min, Respiratory Rate of 20 breaths/min, Blood Pressure of 120/80mmHg. Her laboratory investigation showed an elevation in RBC distribution width (21.4%), MCHC (25.6%), RBS (154mg/dL), Triglycerides (219mg/dL) and decline in Hemoglobin (6.5, 8.1g/dL), PCV (17.6%), RBS (2.07 million/cmm), Urea (10mg/dL), Serum Iron (10µg/dL), Transferrin Saturation (2.70%),. The liver parameters were Total Protein (5.9g/dL), T. Bilirubin (0.37mg/dL), D. Bilirubin (0.13mg/dL), I. Bilirubin (0.24mg/dL), AST (20U/L), ALT (24U/L), ALP (55.0U/L), Serum Albumin (3.4g/dL), Serum Globulin (2.4g/dL) Ultra sound abdomen and pelvis suggested bulky uterus with a focal solid cystic lesion in fundus of uterus close to endometrial cavity, diffuse mild fatty change in liver and diffuse thickening of wall of urinary bladder.

At first the patient's initial medication regimen was withheld. INJ. CEFOTAXIME SODIUM 1g IV 1-0-1 was given for prevention of infection, INJ. PANTOPRAZOLE 40mg IV 1-0-1 for prevention of gastric irritation, INJ. TRANEXAMIC ACID 500mg IV 1-0-1 for prevention of bleeding and T. MEFENAMIC ACID + DICYCLOMINE HYDROCHLORIDE 250mg/10mg P/O 1-0-1 for pain. On day 3, patient had undergone Hysreroscopy guided Polypectomy with D and C. For that INJ. METOCLOPRAMIDE HYDROCHLORIDE 10 mg IV was given for prevention of nausea, vomiting and INJ. MISOPROSTOL 400mg IV was given to soften the cervix. On day 2, 20 PRBC were given, on day 3, 30 PRBC were given, on day 4, 20 PRBC were given to treat severe anemic condition. Finally the patient was stable with no active bleeding but had C/O cough and was discharged with SYP. BROMHEXINE HYDROCHLORIDE + TERBUTALINE SULPHATE + GUAIPHENESIN + MENTHOL 5ml P/O 1-1-1, T. CEFIXIME 200mg P/O 1-0-1, T. PANTOPRAZOLE 40mg P/O 1-0-1 for 5 days, T. FERROUS ASCORBATE + FOLIC ACID P/O 1-0-0 for 30 days and C. B- COMPLEX FORTE + VITAMIN C P/O 0-1-0 for 7 days. Patient wanted to continue treatment of Rheumatoid Arthritis from outside and denied consultation from current hospital.

Discussion

Methotrexate is an FDA approved folic acid antagonist indicated for treatment of Rheumatoid Arthritis. Methotrexate toxicity occurs when the drug, commonly used in the treatment of various cancers, autoimmune diseases, and inflammatory disorders, reaches harmful levels in the body. This can result in a range of adverse effects due to its mechanism of inhibiting folic acid metabolism, which is essential for DNA synthesis and cellular division. Acute toxicity may manifest as gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, while chronic toxicity can lead to more serious complications, including bone marrow suppression, liver damage, pulmonary

toxicity, and renal dysfunction. High doses or prolonged use of methotrexate can exacerbate these risks, making close monitoring of serum levels and organ function essential, especially in patients with pre-existing conditions or those taking other medications that affect renal or hepatic function. The onset of toxicity can be subtle and may require aggressive management, including drug cessation, folinic acid rescue therapy, or other supportive treatments. Preventive measures, such as proper patient education, routine monitoring, and dose adjustments, are crucial in minimizing the risk of methotrexate toxicity. Usual oral dose is as weekly as single dose or three divided doses over 8 hourly in 24 hours in a week. Folate supplementation with 1mg per day 5 to 7mg once weekly should be taken to prevent bone marrow suppression. The peak serum levels are achievable within 1 to 2 hours and oral absorption depends on dose taken. Methotrexate will affect in corpus luteum and results in less support in the production of progesterone leading to menstruation complication. The usual dosing is weekly once but here it was administered twice daily.[5,6]

Other drugs in DMARDs suppresses immune system and thereby results in abnormality for endocrine system.[7,8] T. CEFEXIME was unnecessary for Rheumatoid Arthritis[9]. The standard treatment for Rheumatoid Arthritis are shown in table 1.1[10,11]

Table 1: Treatment of Rheumatoid Arthritis

DRUGS	DOSE	MECHANISM	SIDE EFFECT	CONTRAINDICATION
DMARDS METHOTREXATE	Oral or IM 7.5-15mg/week	Inhibit cytokine production and purine biosynthesis and stimulate adenosine release all of which leads to inflammatory property.	Stomatitis Indigestion Nausea Vomiting	Pregnency, chronic liver diseases, leukopenia
LEFLUNOMIDE	Oral 100mg daily for 3 days then 10 – 20mg daily without loading dose	It inhibit pyramidine synthesis which reduces lymphocyte proliferation and modulation of inflammation.	Diarrhoea, Headache, Nausea, Leukopenia, Thrombocytopenia	Liver diseases,Pregnency
HYDROXY CHLOROQUINE	Oral 200-300 mg twice daily after 1-2 month may decrease to 200mg once or twice daily	Regulate the activity of immune system which may be over active in some condition it can modify the underline disease process rather than simply treaing symptoms	Rashes, Graying of hair, myopathy, neuropathy	Anaemia, low blood sugar, low amount of potassium, and magnesium
SULFASALASINE	Oral: 500mg twice daily, then the 1g twice daily	Work by the reducing swelling, this keep in reduce the symptoms of inflammatory condition like rheumatoid arthritis	Neutropenia, thrombocytopenia	Asthma, liver problem, G6PD Defiency
MINOCYCLINE	Oral:100-200mg daily	It inhibit metaloproteases active in damaging articular cartilage it may be an alternative for patient with mild diseases and without feature of poor prognosis	Photosensitivity Dizziness Vomiting Itching Diarrhoea	Pregnency, Lactation, decrease kidney function, liver diseases

TOFACTINIB	Oral: twice daily Oral XR: 11mg once daily	It is a JAK B and JAK 1 kinase inhibitor, interface with JAK-STAT signaling pathway and DNA transcription production of inflammatory mediators and release of cytokine is inhibited	Headache, insomnia, diarrhea, hypertension	Anemia, cancer
NSAIDS ASPIRIN	Adult 2.6-5.2g Children 60-100mg	It inhibit the activity of of the enzyme called cyclo oxygenase which leads to the formation of prostaglandin that causes swelling, pain, fever, inflammation	Heartburn, nausea, stomach, bleeding	Active bleeding, hemorrhagic disorder
INDOMETHACIN	50-200mg – adult 2-4 mg children	It produce potent anti-inflammatory effect with antipyretic action	Vomiting, Nausea, Bleeding, edema	Asthma, allergic reaction
DICLOFENAC	Adult- 150-200mg	Inhibition of prostaglandin by inhibiting COX1 and COX2	Loss of appetite Vomiting Stomach ulcer Heart burn Nausea	Edema, Hepatotoxicity, Gastrointestinal Bleeding, Anaphylaxis
CORTICOSTE-ROID PREDNISOLONE	7.5mg per day	It modulates the gene expression by blocking the glucocorticoid receptor they promote the upregulation of anti-inflammatory gene	High BP Stomach upset Fluid retension	Osteoporosis Glaucoma Systemic fungal infection
TRIAMCINO-LONE	10mg /ml or 40 mg/ml injection			

Here it is the first case representing the condition. The prescription error in DMARDs is the significant cause of reaction. The regimen was not according to standard therapeutic guidelines. The improper monitoring and irregular follow ups paved the condition. Methotrexate can disrupt hormonal balance, affecting follicular development and ovulation, leading to irregular bleeding. It may also cause bone marrow suppression, reducing red blood cells and platelets, which can contribute to bleeding or clotting disorders. Additionally, methotrexate may directly affect the endometrial lining, causing abnormal bleeding. Other DMARDs, by suppressing the immune system, can disrupt endocrine function, particularly estrogen and progesterone, further contributing to uterine bleeding.The Naranjo adverse drug reaction probability scale was 5 that represents probable. According to WHO classification of adverse drug reaction, the condition belongs to Type C (Continuous) that is usually dose related and due to long term use of drug. According to Hartwig severity assessment scale, classified as Severe Level 5 (The adverse reaction cause permanent damage to the patient).

Conclusion

A new case of methotrexate-induced abnormal uterine bleeding has been reported. The condition was confirmed through both subjective and objective evidence and resolved upon withholding the drug and implementing appropriate management. However, it was not further confirmed through methods like serum drug concentration testing or therapeutic drug monitoring. Depending on its severity, this reaction can be classified as a severe adverse drug reaction, potentially life-threatening,

with the possibility of causing permanent damage and requiring intensive medical treatment. The lack of patient education and failure in management contributed to the adverse reaction. For preventing the condition, standard algorithm of Rheumatoid Arthritis should be obtained from consultant with regular follow ups and monitoring.

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