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Methotrexate Involving Drug-Drug Interaction Causing Myelosuppression: A Case Report

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1. Abstract

Methotrexate is commonly prescribed antimetabolite for rheumatoid arthritis. There are certain side effects at higher doses such as bone marrow suppression, pulmonary toxicity, hematologic toxicity, nephrotoxicity and increased risk of infection. This case reports discuss about the elderly patient who developed a rare presentation about the methotrexate induced pancytopenia. As, patient was on methotrexate since 2 years, leflunomide and etoricoxib, consequently, there can be a possible drug-drug interaction between these three drugs and which may enhance the risk of myelosuppression as well as manifests oral ulcers, diarrhoea, and infection. During the admission to hospital, patient was symptomatically treated with the symptoms of toxicity and also with the antidote of methotrexate, injection leucovorin. Even though the exact mechanism of MTX-induced haematological toxicity remains uncertain but possible cause can be MTX-induced hematopoietic toxicity has been found as excess unbound extracellular MTX.In conclusion, Patients on MTX therapy should be regularly monitored with liver function tests and CBC to identify myelosuppression and avoid the sequelae of pancytopenia.

2. Introduction

Methotrexate (MTX) is antimetabolite commonly used in various doses to treat malignancy, severe psoriasis, and rheumatoid arthritis.[1] MTX is prescribed to more rheumatoid arthritis patients than any other biologic medication now in use. It is the most studied and prescribed medication used in combination with other DMARDs, demonstrating clear additive therapeutic efficacy.[2] MTX has been used to treat rheumatoid arthritis (RA) and psoriasis since 1951. However, MTX therapy for RA was not widely used until the 1980s.[3] Although higher doses of MTX, defined as doses of 500 mg/m2or greater are often more beneficial,oral therapy at doses ≥15 mg/week,as well producing toxicity and side effects such as bone marrowsuppression, pulmonary toxicity, nephrotoxicity, hepatotoxicity,hematologic toxicity, and an increased risk ofinfections. [3] The combination of MTX and either leflunomide or sulphasalazine (DMARDS) in non-responders RA patients reduce the symptoms but tempt an increase in serious ADRs. [4]

3. Case Presentation

A 73 years old male presented with complains severe watery diarrhoea for 3 days, mouth ulcer, back pain and swelling also with blood report of a week ago showing Hb: 8.2, RBCs: 3.42, WBCs: 500 and Platelets: 10,000. On admission, oral mucositis grade II was examined and personal history was suggestive of increase bowel movement, decrease in appetite. Also on systemic examination, generalized mild tenderness in alimentary system was evident.

3.1. Medical and Medication History

Patient had past medical history of right shoulder rheumatoid arthritis for 2 years taking tablet Methotrexate(7.5mg) twice a week, tabletLeflunomide(10mg) once a day, tablet Methylprednisolone (4mg) twice a day, tablet Folic acid (5mg) once a day for 5 days in a week,Etoricoxib (60mg) twice a day, tablet Acetaminophen (650mg) once a day.

Additionally, surgical procedure total Knee replacement on left knee was done 5 years ago.

3.2. Investigation

Besides, Stool culture test resulted to be positive (Table 1).

Table 1: Besides, Stool culture test resulted to be positive.

Parameters	On admission	2nd day	3rd day	4th day	6th day	Last day	Normal Values
Haemoglobin	8.8	7.2	6.6	7.7	8.6	8.9	13.8–17.2 g/dL
RBCs	3.22	2.16	2.42	2.81	3.12	3.12	4.5-5.5 mill/uL
WBCs	250	370	620	650	7360	10340	4000-10000
Platelets	8,000	34,000	21,000	19,000	27,000	67,000	270000-410000
Neutrophils	4	4	28	31	71	69	50-80%
Lymphocytes	52	73	64	72	19	20	20-40%
Eosinophils	44	20	5	9	0	0	00-06%
Monocytes	0	3	3	8	10	10	00-10%
Basophils	0	0	0	0	0	0	00-02%
Platelets	8000	34000	21000	19000	27000	27000	150000-410000
Serum Creatinine	2.18	2.13	--	1.53	1.29	1.28	0.60-1.30
Sodium serum	132	--	140	--	136	135	136-145
Potassium serum	3.1	--	2.05	--	3.87	3.98	3.5-5.1
Serum Bilirubin	3.124	--	--	3.76	--	1.27	0.3-1.2mg/dl
Bilirubin Direct	2.805	--	--	2.98	--	1.02	0.1-0.4mg/dl
Bilirubin Indirect	0.32	--	--	0.78	--	0.25	0.1-0.4mg/dl
SGPT	10.3	--	--	9.2	--	6.9	10-40 U/L
SGOT	10			13		25	10-40U/L
Total Protein serum	5.53	--	--	4.05	--	5	6.0-7.8
Serum Albumin	2.78	--	--	2.03	--	2.18	3.5-4.8
C- reactive protein	--	330.75	--	104.41	89.4	49.3	<10
Methotrexate	--	0.04	--	0.01	--	--	< 0.01 after 48hours of dose

3.3. Diagnosis

Patient was diagnosed with Methotrexate-induced Pancytopenia through suggestive symptoms, drug-drug interaction among past medication and abnormal haematological levels.

3.4. Treatment

On admission patient was treated with prophylacticantibiotics like injection meropenem (1gm) infused with 10cc NS thrice a day (TDS), injectionmetronidazole (400mg) TDS,Injection teicoplanin (400mg) once a day (OD), injectionfluconazole (200mg) OD; supportive therapies such as anti-emetic like injection ondansetron (4mg) TDS, PPI likeinjection pantoprazole (40mg) twice a day (BD), normal saline (100ml/hr);anti-diarrheal like capsule racecadotril (100mg) TDS, capsule rifaximin (400mg) TDS; MTX antidoteinjection leucovorin (50mg with 100cc NS) four times day (QDS).Patient was also transfused with4 units of platelet rich concentration (PRC).

On the 2nd day injection fluconazole was replaced with tablet voriconazole (200mg) twice a day. As well injection romiplostim (500mcg) was given subcutaneously. As stool routine microscopy test resulted positive, injection nitazoxanide was prescribed, injection potassium chloride.On day 3, injection leucovorin was reduce to (25mg) QDS with 100cc NS.Injection PCV (Packed cell volume) was given on 4th day. Additionally, magnesium serum level was found to be 1.58mg/dl, consequently treated with magnesium supplement,and to treat neutropenia injection filgrastim was given subcutaneously.Betadine gargle was suggested to oral mucositis. Besides,methotrexate was omitted and its level were normal to 0.01 on 4th day of admission, also, haematological parameters were normal in 8 days. Patient was discharge with modified prescription for arthritis that is: capsule pantoprazole+ domperidone, capsule rifaximin, tablet voriconazole, tablet folic acid, tablet potassium, tablet acetaminophen.

4. Discussion

Patients treated for Rheumatoid arthritis with MTX may experience haematological damage, such as myelosuppression, leukopenia, neutropenia, and megaloblastic anemia. [3,5]Pancytopenia is one of the MTX toxicities that is challenging to prevent because it might occur suddenly during therapy.[6]Even though the exact mechanism of MTX-induced haematological toxicity remains uncertain, it has been linked to the development of Arthritis. One cause of MTX-induced hematopoietic toxicity has been found as excess unbound extracellular MTX. Along with age, infections,

folic acid insufficiency, hypoalbuminemia, and concomitant drugs are all factors to consider.[3] MTX is a folate antagonist that inhibits dihydrofolate reductase (DHFR), preventing the conversion of dihydrofolate to tetrahydrofolate and thus blocking the synthesis of purines and pyrimidines and, therefore, inhibiting DNA, RNA, and protein synthesis. In addition to inhibiting DHFR, other mechanisms that are thought to be involved in its effect against autoimmune diseases include selective downregulation of B cells, inhibition of T-cell activation, and inhibition of methyltransferase activity.[7] Polyglutamylation of this drug prolongs its intracellular presence form MTX-PG. [8] Therefore, an increase in polyglutamylation increases the risk of toxicity due to direct and prolonged intracellular exposure. Myeloid megakaryocytes and epithelial polyglutamylation elevate the intracellular levels of MTX and consequently the patients may have experienced ulcers. The same is for WBC and RBC, which may manifest as neutropenia, infection, also present in this case.[8,9]The most potential adverse reaction is severe myelosuppression, which causes most of the relatively rare fatalities caused by MTX. [3] Looking at pharmacokinetics of MTX has been reported that 95% of MTX is eliminated through renal excretion within 30hours of administration.MTX and its metabolites 7-hydroxy-methotrexate are eliminated with distal renal tubules with hydrogen ions produced by the hydrogen/potassium ATPase pump in the renal tubules.[10]Moreover, it is rapidly absorbed after oral administration, maximum plasma concentrations (Cmax) being reached within 1.5 hours under fasting conditions and absorbed in the proximal jejunum. Methotrexate binds almost exclusively to the albumin component of plasma proteins. RA patients often have a mean binding percentage of 42-57%.[11]

Apart from this,DDIs are the main contributors to ADRs, especially among the elderly,Marinella Patanè et al says,the combination of MTX and either leflunomide orsulphasalazine in non-responders RA patients reduced pain symptoms but induce serious ADRs. [4]Also, Australia's voluntary adverse drug reaction reporting scheme suggests the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 9 reports of well-documented pancytopenia in patients taking leflunomide. Out of which7 patientswere taking concomitant methotrexate 7.5–12.5 mg/week.[7] The mechanism of interaction between MTX and leflunomide is uncertain. Leflunomide inhibits OAT3, BCRP, and OATP1B1/1B3 transporters that contribute to methotrexate disposition and increases the level of MTX in the cells. [12,13]Besides, Human organic anion transporters hOAT1 (SLC22A6) and hOAT3 (SLC22A8) are thought to be mediate renal tubular uptake of methotrexate, because they are expressed in the basolateral membrane of proximal epithelial cells, and mediate transport of methotrexate. Selective cyclooxyganase-2 likeetoricoxib inhibits methotrexate transport by hOAT3 affecting decreased excretion of MTX with an increase in risk ofAdverse events.[4,11,12] As revealed by the case, medication history of elder patientinforms MTX 7.5mg twice a week, leflunomide 10mg once a day and etoricoxib 60mg twice a day; consequently, there can be a possible drug-drug interaction between these three drugs and which may enhance the risk of myelosuppression as well as manifests oral ulcers, diarrhoea, and infection. For antidote of methotrexate toxicity, MTX works by blocking the synthesis of reduced folates; folinic acid (leucovorin), which is a fully reduced folate, can restore marrow toxicity. Patients receiving methotrexate are already encouraged to notify their healthcare provider immediately if they experience any symptoms suggestive of infection. Furthermore, we recommend that patients discontinue methotrexate immediately if such symptoms occur.[14]

5. Conclusion

It is crucial that primary care physiciansare aware of these complications and recommendations, because the majority of these serious complications can be detected on time and even prevented before any serious consequences. Patients taking MTX therapy should be regularly monitored with liver function tests and CBC to identify myelosuppression and avoid the sequelae of pancytopenia. Also, renal function must be monitored as this drug uses mainly the kidneys for excretion, especially in elderly patient and educating patient on the importance of MTX and its side effect is a vital task of clinical pharmacist.

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