One Mistake, One Life at Stake: A Case of Methotrexate Toxicity in A 57-Year Old Male Presenting with Painful Plaques with Erosions*

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Abstract

Introduction: Methotrexate is being given by dermatologists in only extreme cases of skin disorders such as in severe Psoriasis Vulgaris. Strict precautionary measures are done to avoid its well-known adverse effects. An early but less common sign of its toxicity are painful erosions on plaques. Methotrexate is an effective but potentially toxic treatment for different severe dermatologic disorders such as in severe Psoriasis Vulgaris. Meticulous and complete history-taking, physical examination and laboratory work-up to come up with a correct diagnosis as well as, knowledge of indications for treatment, proper dosing, folate supplementation, monitoring, proper referral and early detection of its toxicity are important in order to avoid cutaneous and systemic adverse effects including death.

Case Report: A case of a 57-year old male with a 2-day history of painful erosions on plaques on both upper and lower extremities after eleven days of taking Methotrexate 2.5mg/tablet one tablet three times a day without folate supplementation. He was then being treated by a general physician as a case of Psoriasis Vulgaris. He was subsequently admitted under the Internal Medicine service due to epigastric pain, nausea, anorexia, generalized body weakness and passage of black tarry stools. He was referred to the Department of Dermatology for the painful erosions on plaques. He expired two days after admission due to Acute Respiratory Failure. Post-mortem Skin punch biopsy was done and revealed chronic eczematous dermatitis consistent with Lichen Simplex Chronicus with superimposed drug induced hypersensitivity reaction.

Keywords: Methotrexate toxicity, painful erosions on plaques, Lichen Simplex Chronicus, Psoriasis Vulgaris, folate supplementation

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INTRODUCTION

Methotrexate is being given by dermatologists in only extreme cases of skin disorders such as in severe Psoriasis Vulgaris. Strict adherence to proper guidelines with regards to the indications and proper dosing of this potentially toxic drug is definitely a must in order to avoid its adverse effects. Although the incidence of this condition is unknown, a study by Olsen, Elise, et al in 1991 reported that in Duke University Medical Center, they have recorded 64 cases from 1951 to 1991 [1]. In our department, this was the first case seen and managed. An early but less common sign of methotrexate toxicity are painful erosions on plaques. In this report, we present a case of a 57- year old male who was referred to the Dermatology Service of a tertiary training institution due to painful erosions on plaques over both upper and lower extremities as well as on the abdominal area while taking 120 mgs worth of prescribed oral methotrexate by a general physician in a span of 16 days. This case report stresses the importance of doing complete history-taking, physical examination and laboratory work-up in order to obtain the correct diagnosis as well as the adherence to the proper guidelines to avoid methotrexate's toxic effects. Furthermore, it also aims to increase awareness of the different clinical manifestations of its toxicity in order to have early detection and prevent further deterioration of the patient's health and ultimately, demise.

CASE REPORT

The patient is F.V., 57 year old male, Filipino, from Quezon City, Philippines was referred to our service due to painful erosions on plaques. One year and four months prior to referral, he noted the appearance of these pruritic thin erythematous plaques over the lower third of both legs extending down to the dorsum of the feet associated with pruritus. Consult was done to his company physician wherein assessment was not disclosed. Sessions with intralesional triamcinolone injection was done and Betamethasone valerate with occlusion at night was started. The patient noted flattening of lesions and relief of pruritus after only two months of compliance with medications. He was not able to follow-up due to financial constraints.

On interval history, the patient noted recurrence of pruritic plaques over both upper extremities. Patient self-medicated with topical Fluocinonide cream which provided temporary improvement but lesions would eventually recur few weeks after the discontinuation of the topical medications.

Three weeks prior to referral, the patient noted progression of erythematous thick plaques with minimal whitish fine scales over both upper extremities now with new hyperpigmented patches over the abdomen. Consult was done to a private physician wherein assessment was Psoriasis Vulgaris. No skin punch biopsy was done on patient. He was then started on Methotrexate 2.5mg per tablet, three times a day which the patient continuously took for sixteen (16) days.

On the second day of intake of methotrexate, (cumulative dose of 15 mg) the patient noted generalized dryness of the skin. While on the third day of intake of Methotrexate (cumulative dose of 22.5 mg), the patient noted plaques which became more erythematous to violaceous while some forming moist blackish central eschars and crusts associated with pain over both upper and lower extremities. At this point, there were no consults done, no pain relievers nor other medications taken or applied.

Two days prior to referral (16th day of methotrexate treatment with a cumulative dose of 120 mg), persistence of lesions now accompanied by epigastric pain, nausea, anorexia, fever, generalized body weakness, and passage of black tarry stools prompted consult at the emergency room and subsequently referred by the primary service (Internal Medicine) to the Dermatology service for further evaluation and management.

The patient is hypertensive for already three years and is maintained with on Amlodipine 10mg/tab once a day. He had no history of allergies, asthma, previous surgeries or hospitalizations as well as other systemic diseases such as lung, kidney, and liver diseases. He noted that his father also had hypertension but did not note any other diseases in the family. There was no note of Psoriasis Vulgaris in the patient's family history. The patient is a 25-pack year smoker and an occasional alcoholic beverage drinker. He noted drinking only during special occasions like office parties or holidays at least once a week. He said he can consume three bottles of beer. He denied illicit drug use. The patient worked as a supervisor at a local newspaper company.

Upon seeing the patient, we noted that the patient is awake alert, speaks in phrases and is stretcher-borne. He was normotensive, with regular heart rate and rhythm, afebrile but tachypneic (respiratory rate at 30 breaths per minute). Others

systemic findings were unremarkable although we noted crackles over both lung fields. On cutaneous examination, we noted, multiple, ill-defined, irregularly shaped erythematous to violaceous patches and hyperpigmented lichenified plaques with central blackish eschars and areas of erosions over the upper and lower extremities as well as in the extremities (Figures 1). The initial consideration for this case was 1) Multiple organ methotrexate toxicity 2) Lichen simplex chronicus vs. Psoriasis Vulgaris For the initial workup for the following diagnosis, we requested for: Complete Blood Count, Urinalysis, BUN/creatinine, SGOT, SGPT, PTT, aPTT, Clotting time and bleeding time, Chest X-ray and Skin punch biopsy (once with normal blood parameters). The laboratory results revealed pancytopenia with a very low WBC (1.3 x 10^9/L), hemoglobin 75 g/L, hematocrit (0.221) as well as the platelet count (25 x 10^9/L) although her peripheral blood smear results revealed normocytic and normochromic red blood cells which helped us ruled out anaplastic anemia. He has also prolonged prothrombin time (21) increased BUN (10.4 mmol/L), with a decreased creatinine clearance (74.2 ml/min), hyponatremia (121 mmol/L) and slightly increased AST (36 U/L) and ALT (69 U/L). Upper endoscopy report done by gastroenterology service revealed erosive esophagitis and multiple gastric as well as duodenal ulcers.

The Dermatology Service suggested Folic acid supplementation. Also, Clobetasol propionate ointment + vaselina blanca, mix well (1:1), and apply over the lesions 2x a day (trunk and four extremities), Mupirocin ointment, apply over the eroded areas 2x/ day and PNSS compress 2x a day for 20 minutes over moist eroded areas, Chlorphenamine maleate, 4mg/tab, 1 tab 3x a day as needed for itch and advised mild soap for bathing. Gastroenterology, Hematology, and Toxicology referrals were also done for further evaluation and management.

On the second day referral day the patient was noted to have desaturations, and progressive dyspnea and decrease in sensorium**.** The patient expired and the Internal Medicine service made their final working impression as: 1) Acute Respiratory Failure 2) Hospital Acquired Pneumonia, early onset, and immunosuppression secondary to methotrexate toxicity. Skin punch biopsy by the Dermatology service on the left forearm on post mortem which revealed chronic eczematous dermatitis such as Lichen simplex Chronicus. The possibility of superimposed drug induced hypersensitivity reaction cannot be entirely excluded. The final diagnosis of our service is 1) Multiple Organ Methotrexate Toxicity 2) Lichen Simplex Chronicus.

DISCUSSION

Although the incidence of methotrexate toxicity is unknown Olsen, Elise, et al in 1991 reported that in Duke University Medical Center, they have recorded 64 cases from 1951 to 1991[1]. In our records at the East Avenue Medical Center Department of dermatology, this is the first case of methotrexate toxicity. Although, according to the census, there were five cases of hypersensitivity reaction from methotrexate. There are cases from the Obstetrics and Gynecology service whose patients were undertaking methotrexate therapy for Hydatidiform Mole and other gynecologic related malignancies.

Methotrexate is an analog of folate that competitively and irreversibly inhibits dihydrofolate reductase. It also inhibits thymidylate synthetase. Through the inhibition of these processes, methotrexate decreased the availability of reduced folate and thymidilate necessary for RNA as well as DNA synthesis. Furthermore. Methotrexate-polyglutamate increases the local tissue concentration of adenosine, which has potent anti-inflammatory action [2].

Oral methotrexate is absorbed rapidly through the gastrointestinal tract. The mean bioavailability is 67%. While the Peak Plasma Levels occur 1-3 hours after administration. The half-life of methotrexate is Half-life: 4-5 hours. It is important to note that dosages of greater 25mg/week of methotrexate makes the gastrointestinal absorption erratic and recommends intramuscular dosing. Elimination of methotrexate is primarily done by the kidneys. Therefore, Decrease in Glomerular filtration Rate leads to Methotrexate toxicity.[3]

Since methotrexate is primarily given to cancer patients especially those suffering from Acute Lymphoblastic Anemia (ALL), Oncologic doses (100-250 mg/m2/week) for these usual cases.[2] On the other hand, in Dermatology, Methotrexate are only used in cases of, Severe psoriasis +/- psoriatic arthritis and Mycosis fungoides +/- advanced disease but there are also "Off-label" uses such as Dermatomyositis, Cutaneous lupus erythematosus, Scleroderma, Pemphigus vulgaris, Bullouos pemphigoid, Sarcoidosis, Severe atopic dermatitis, PLEVA and Pityriasis Rubra Pilaris Immunomodulatory dose will be (7.5- 25 mg/week)[3]. It is important to note that in our market, methotrexate is available at Preparation: 2.5mg/tab and methotrexate liquid (25mg/ml) [4]. According to Ahmed et. Al (2013), it is better to give Single weekly dose or in divided doses (usually 3 divided doses separated by

12 hours) [5]. Although it is much better to give equal efficacy but split dose since it may increase tolerance by minimizing gastrointestinal upset. It is important to take note, that methotrexate should never be given on a daily dose basis because it promotes toxicity such as in the case of our patient. It is important to remember that before initiating methotrexate therapy, it is important to have a thorough history and physical examination, have exclusion criteria and equip oneself with proper knowledge of the indications as well as the exclusion criteria.[2]

Laboratory Monitoring:

CBC with platelet count as well as liver function should be done weekly for 2 to 4 weeks gradually increase to every 3-4 months with time and perform 5 -6 days after any dose escalation. Renal function should be done once or twice a year of if suspicion of renal problems are at hand. Liver biopsy should also be performed after 1.5 g (cumulative dose) if there are no risk factors and then repeat biopsy every 1 g thereafter. One can perform pre-treatment if there are risk factors involved in our patient. In the case of our patient, no pre-treatment laboratory work-up were done.[6, 9]

Initiating Therapy

If all laboratory results showed normal results and the patient does not have any risk factors for toxicity, then we could start with Single 5-10 mg test done**,** after which**,** Repeat laboratory studies, skin examination and review of systems after 1 week**.** The dose may be increased to 2.5-5.0 mg every 2-4 weeks and taper at the same dose depending on the response. If there is no response in 20-25mg/week, the dermatologist might as well open its options to UVB Phototherapy or Oral retinoids.[6]

Indications

Since methotrexate is prone to toxicities here are the absolute as well as the relative contraindications:

Absolute: Pregnant and lactating women. Methotrexate is a known teratogen that causes oligospermia, although it is not a mutagen, current recommendations are that both women and men take measures to avoid either pregnant or impregnating their partner during therapy and 3 months for women and 1 month for men after discontinuation.

Relative: Renal dysfunction, hematologic diseases, hepatic diseases such as hepatitis, excessive alcohol intake diabetes mellitus or obesity, active infection, HIV-VIRUS- Men or women contemplating or impending conception.[5]

Adverse Effects:

BONE marrow, gastrointerstinal mucosa, hair and skin are vulnerable to adverse effects of methotrexate secondary to their high rate of turn over

GI: Nausea, vomiting and mucositis, hepatotoxicity,

Bone Marrow: Myelosuppression

SKIN: alopecia; painful skin eruptions

Kidney: decreased creatinine clearance

Lung: non-productive cough, fever, malaise and dyspnea.

Nervous: Intrathecal administration (headache, meningeal signs)

Eye: Ocular burning

In the case of our patient, he experienced mucositis, hepatotoxicity, myelosuppression, painful skin eruptions, decreased creatinine clearance, and dyspnea.[7,8]

In one case report on the erosion of psoriatic plaques as an early sign of methotrexate toxicity by Hannah Pearce MD (1996), noted two cases of methotrexate toxicity which manifested as bone marrow suppressions, gastrointestinal ulceration and painful erosions of psoriatic plaque which were also experienced by our case index. [8] Like our patient, they weren't able to administer folinic acid as antidote for the said toxicity because the golden period of 24-36 hours after the administration of methotrexate toxicity.

According to Review of the prevention and management of high dose methotrexate toxicity by Ahmed Yasar et al (2013) and Folate supplementation during methotrexate therapy for patient with psoriasis article on by Strober BE, MD (2005) Folic acid is used as a Daily supplementation with 1-5mg/folate reduces nausea, vomiting, stomatitis, ulceration, elevated AST, and mild myelosuppression.[5,6] It can be taken with methotrexate without decreasing its efficacy and

it's considered as a 1st line folate supplement: Lower cost and comparable efficacy with folinic acid, while folinic acid (Leucoverin) should be given 1st 24-36 hours after overdose, which prevents myelosuppression, gastrointestinal toxicity and neurotoxicity. This should not be given on same days as methotrexate dosing because it competes with Methotrexate for cellular uptake. Usual dosing will be15-25mg of folinic acid by mouth every 6 hours for 6-10 doses and is considered first choice of treatment of methotrexate overdose.

In summary, methotrexate can be used not only in severe cases of skin problems but also in other systemic diseases. What important is to know the right indication, the complete and proper management and monitoring as well as having folic acid supplementation Early detection of its toxicity is important in order to give the rescue dose of folinic acid to prevent further deterioration and demise.

CONCLUSION

This case report is done to increase awareness of the importance of strict adherence of proper guidelines in prescribing medications. Methotrexate is an effective but potentially toxic treatment for different severe dermatologic disorders such as in severe Psoriasis Vulgaris. Meticulous and complete history-taking, physical examination and laboratory work-up to come up with a correct diagnosis as well as, knowledge of indications for treatment, proper dosing, folate supplementation, monitoring, proper referral and early detection of its toxicity are important in order to avoid cutaneous and systemic adverse effects including death.

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FIGURES

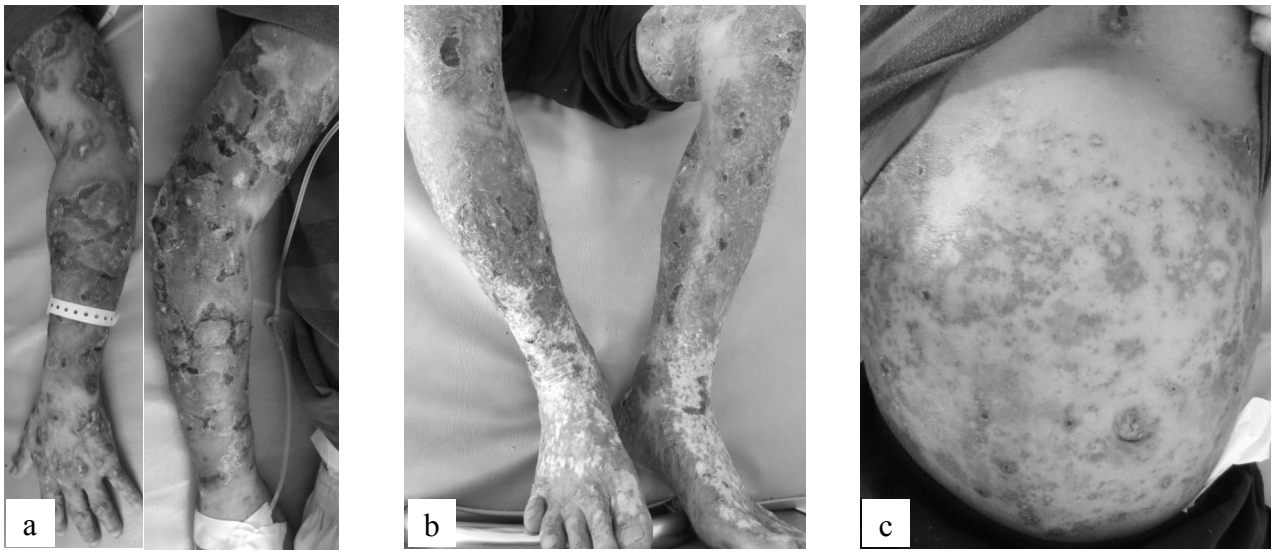

Figure 1
Multiple erythematous to violaceous patches and hyperpigmented lichenified plaques with central blackish eschars and areas of erosions over the a) upper extremities, b) lower extremities, c) abdomen

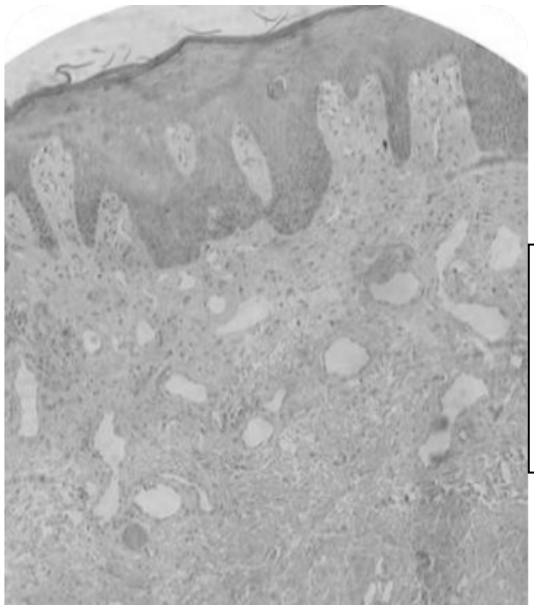

FIGURE 2:
Section from the right leg revealed **psoriasiform dermatitis.** This is more consistent with chronicus eczematous dermatitis such as **LICHEN SIMPLEX CHRONICUS**