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RESEARCH ARTICLE

MULTIPLE MANIFESTATIONS OF METHOTREXATE DUE TO OVERDOSING IN CHRONIC PLAQUE PSORIASIS

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ABSTRACT

Background: Methotrexate is the most commonly used immunosuppressive agent used in the treatment of psoriasis owing to its cytoprotective and immunomodulatory effects. However, it is generally safe at lower doses but a cumulative dose has been reported with toxicity manifestations such as Acute Kidney Injury, Bone marrow suppression and pancytopenia. Dermal toxicity is a rare manifestation of methotrexate probably due to overdosing or a result of pharmacological idiosyncrasy.
Case description: A 56-year-old male presented to the dermatology department with complaints of fluid filled lesions on both limbs gradually progressing on face, ears, oral cavity and on whole body. The cutaneous lesions aggravated together with fever with chills, generalized body pains and pedal edema. Skin Biopsy and clinical evidence confirmed methotrexate as an offending drug and was immediately withdrawn and managed accordingly.
Discussion and Evaluation: A Comprehensive clinical, laboratory, histopathogical examination Validated methotrexate induced toxicity. Causality and severity assessment revealed as probable on Naranjo scale and hartwig severity assessment scale assesed as Death.
Conclusion: In this case patient erroneously took a cumulative dose of methotrexate thereby producing multiple toxicity manifestations Early identification and prompt withdrawal of the drug is crucial for impeding further serious morbidity.

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INTRODUCTION

Methotrexate was established in the year 1951 authorized by FDA (Alencar, 2012). It is one of the most extensively used immunosuppressive drug for the management of various skin disorders (Shen et al., 2012; Edmundson, 1958). It is considered as the appropriate antibiotic chosen for the treatment of various autoimmune diseases including Rheumatoid arthritis, psoriasis, atopic eczema and bullous pemphigoid etc (Kalb, 2009). Among all the systemic agents used, methotrexate has substituted aminopterin sodium for the management of plaque psoriasis (Roenigk, 1969) Methotrexate acts as a folate antagonist, it performs by hindering DNA replication of fastly developing cells, obstructing epidermal cell turnover thereby impeding eruption, consequently reducing intra epidermal entrance of multinuclear leukocytes (Agarwal et al., 2008). The starting dose for the management of Psoriasis varies within the range of 7.5 -15mg administered orally,morever the maximum dose not exceeding 25 mg per week (Roenigk, 1998; Yamauchi, 2003).

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We report a case of methotrexate induced toxicity affecting various organ systems thereby leading to pancytopenia, Acute Kidney Injury and cutaneous erosions.

CASE PRESENTATION: A56year-oldmale was admitted in dermatologic department presented with chief complaints of painful pus-filled lesions all over body since4 days. Patient was asymptomatic 4 days back then he developed painful pus filled lesions initially started on both limbs, which progressed to whole body face, mouth, ears associated with fever, chills, rigors, malaise, joint pain ,nausea, ear pain ,pedal edema. He was diagnosed with psoriasis vulgaris beyond 30 years for which he was on topical creams. He had a history of Diabetes mellitus and Hypertension. Prior to its appearance he was prescribed methotrexate 10mg once a week for his psoriasis treatment, he erroneously procured a cummulative dose of 60 mg methotrexate in 3 days, therebyproducing notable toxicity manifestations. Upon admission at the hospital methotrexate was immediately withdrawn and Leucovorin calcium 10 mg was initiated for treatment of overdose. Physical examination revealed multiple asymmetric hyper pigmented plaques of varying size presented all over the body predominantly on lower limbs few erosions have Ulcerations, macerations and oozing from plaques in groin, Hair and nails were found to be Normal.

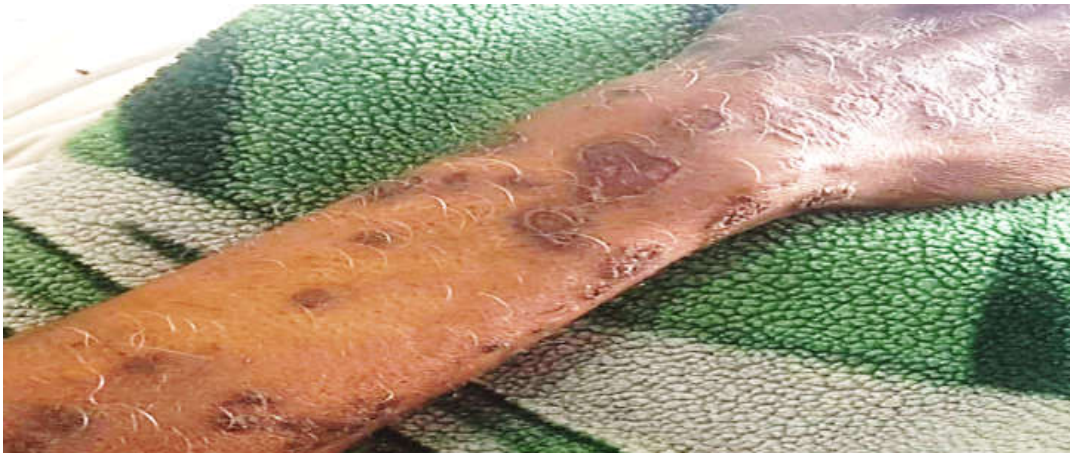

Figure 1. Multiple hyper pigmented Plaques with central erosions progressed on hands

Initially there was a significant improvement in the ulcerations of skin and mucosa However the patient remained unresponsive in spite of supportive therapy. The patient was succumbed to death as the erosions progressed persistently and there was a tremendous decline in blood counts, liver function test thereby leading to septicaemia.

INVESTIGATIONS: The laboratory findings illustrated leucopenia (1.53 10^3/uL) neutropenia (26.0%) accompanied by decreased platelet count. (1.0 lakhs/cumm) Notable alterations were observed in liver function test that includes elevated Total protein (7.2 gms/dl) elevated liver enzymes such as AST (229 U/I), ALT(120U/I) ,Alkaline Phosphatase 80U/I. Furthermore, serum creatinine (2.0 mg/dl), serum uric acid 8.6 mg/dl was found to be elevated. Ultrasound scan of abdomen revealed cholelithiasis. Bacteriology report showed the presence of Pseudomonas aeroginosa grown in culture. A considerable amount of pus cells, epithelial cells, RBC were found in complete urine examination. Skin biopsy exhibited hyperkeratosis, depletion of comparatively atrophic epidermis and apoptotic keratinocytes.

TREATMENT: The patient was managed appropriately with folate supplementation such folic acid 15 mg,Leucovorin calcium for the treatment of overdose. Antiemetic, antihistaminics were prescribed to prevent additional damage to the explicit ulcers in mouth, buccalmucosa. Antipyretics, empirical antibiotics have been used to treat fever, infections. Bone marrow suppression was treated with Leucovorin calcium 15mg twice daily. For treatment of oral mucositis candid mouth paint, Listerine mouth wash, Mucopaine oral gel,Hexi gel, was given. For management of skin infections and healing of erosions fusidic cream, mupirocin ointment was applied topically, liquid paraffin, glymed lotion used as emollients, ciprofloxacin ear drops for ear infections, ursodeoxycholic acid for prevention of further liver damage.

DISCUSSION

Methotrexate is a most extensively used immunosuppressant used for the management of psoriasis owing to its immunosuppressive effects. Concomitant administration of NSAIDS, error in methotrexate dosage are some of the precipitating factors that manifest toxicity (Day, 1995). Day et.al. recommended a classification for ADRs occurring predominantly due to the usage of low frequency methotrexate, it has been divided into four definite levels depending on dosage relation-type A -dose dependent, type B- idiosyncratic, type C cumulative dose, type D-after discontinuation of drug According to Research from previous studies the adverse events are further triggered by accidental overdose or drug interactions. The prevalence of methotrexate induced ulcerations is rarely in occurrence. Methotrexate is the first line of choice in treatment of plaque psoriasis due to its effects and low cost, it is comparatively safe if used within range of 7.5-25mg/week. Exceptionally review of literature suggests its influence on bone marrow, skin, liver, kidneys .overdosing results in manifestations of toxicitysymptoms. The attributable characteristics of toxicity include pancytopenia and bone marrow suppression. IN our presentcase we have noted that patient erroneously took a cumulative dose of methotrexate 60mg for 3 days, thereby leading to numerous toxicities of Acute kidney Injury, pancytopenia, cutaneous ulcerations, oral mucositis, cholelithiasis, bone marrow suppression all of these are probably induced by cumulative dose reaction (type c).Based on clinical and laboratory findings,examining the clinical history of methotrexate intake prior to progression ofpsoriasis, aggravation of symptoms upon methotrexate administration the patient was diagnosed as a case of methotrexate induced toxicity.A Comprehensive clinical, laboratory, histopathogical examination Validated methotrexate induced toxicity. Causality and severity assessment revealed as probable on Naranjo scale and hartwig severity assessment scale assesed as Death.

CONCLUSION

In this case patient erroneously took a cumulative dose of methotrexate thereby producing multiple toxicity manifestations. Early identification and prompt withdrawal of the drug is crucial for impeding further serious morbidity. It is essential that dermatologists should be optimistic about disease progression and its manifestations. In addition, clinicians should provide clear written instructions, emphasizing about daily drug dosage to be used within a week in order to prevent further medication errors.

Abbreviations: FDA-food and drug administration, USG -ultrasonography, CBP -complete Blood picture INR-international normalized ratio, BD -twice daily, AST-aspartate amino transferase, ALT-Alanine Amino transferase, ADR-Adverse drug reaction ,NSAIDS -Nonsteroidal antiinflammatory drug.

Conflict of Interests: The authors proclaim there is no conflict of interest.

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