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Case Study

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A CASE REPORT ON METHOTREXATE INDUCED PANCYTOPENIA

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ABSTRACT

Pancytopenia is a hematologic condition characterized by a decrease in all three peripheral blood cell lines. It is characterized by the hemoglobin of less than 12 g/dL in women and 13 g/dL in men, platelets of less than 150,000 per mcL, and leukocytes of less than 4000 per ml (or absolute neutrophil count of less than 1800 per ml). However these thresholds largely dependend on age, sex, race as well as varying clinical scenarios. The condition is not a disease in itself but a common pathway caused by a multitude of different etiologies that can be infectious, autoimmune, genetic, nutritional, and/or malignant. Multiple conditions can present with pancytopenia. Bone marrow disorders such as aplastic anemia, myelodysplastic syndrome, acute leukemia, myelofibrosis, megaloblastic anemia, paroxysmal nocturnal hemoglobinuria, and Fanconi's anemia can present with pancytopenia. Methotrexate is a type of disease-modifying anti-rheumatic drug (DMARD). It's used to reduce activity of the immune system for people who have certain conditions. The immune system normally protects the body from infections by causing inflammation to fight them. Inflammation can cause swelling, heat, redness and pain. Methotrexate can sometimes cause side effects, which may include, feeling sick, headaches, vomiting, diarrhea, shortness of breath, mouth ulcers, minor hair loss and hair thinning and rashes.

KEYWORDS: Pancytopenia, Dmard, Methotrexate, Bone Marrow Disorders, MTX.

INTRODUCTION

Pancytopenia is a medical condition in which there is significant reduction in the number of almost all blood cells (red blood cells, white blood cells, platelets, monocytes, lymphocytes, etc.).Iatrogenic causes of pancytopenia include chemotherapy for malignancies if the drug or drugs used cause bone marrow suppression. Rarely, drugs (antibiotics, blood pressure medication, heart medication) can cause pancytopenia. Rarely, pancytopenia may have other causes, such as mononucleosis or other viral diseases. Increasingly, HIV is itself a cause of pancytopenia. Familial hemophagocytic syndrome, Aplastic anemia, Gaucher's disease, Metastatic carcinoma bone, MultipleMyeloma, Overwhelm Infections, Lymphoma, Myelofibrosis Dyskeratosis congenita Myelodysplastic syndrome are some of the causes for pancytopenia. Pancytopenia usually requires a bone marrow biopsy in order to distinguish among different causes.

- Anemia: hemoglobin < 13.5 g/dL (male) or < 12 g/dL (female).
- Leukopenia: total white cell count < 4.0 x 10^9/L. Decrease in all types of white blood cells (revealed by doing a differential count).
- Thrombocytopenia: platelet count < 150×10^9/L.

To tide over immediate crisis Blood transfusion with packed red blood cells (PRBC) or platelet transfusion may be done.

Methotrexate is an antineoplastic agent used in the treatment of a wide variety of cancers as well as severe psoriasis, severe rheumatoid arthritis, and juvenile rheumatoid arthritis. Methotrexate is a folate derivative that inhibits several enzymes responsible for nucleotide synthesis.[1] This inhibition leads to suppression of inflammation as well as prevention of cell division.[1] Because of these effects, methotrexate is often used to treat inflammation caused by arthritis or to control cell division in neoplastic diseases such as breast cancer and non-Hodgkin's lymphoma.[1,4,5,6,7]Due to the toxic effects of methotrexate, it is indicated for treatment of some forms of arthritis and severe psoriasis only if first line treatment has failed or patients are intolerant of those treatments. Methotrexate oral solution is indicated for pediatric acute lymphoblastic leukemia and pediatric polyarticular juvenile idiopathic arthritis. Methotrexate injections for subcutaneous use are indicated for severe active rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and severe, recalcitrant, disabling psoriasis. Other formulations are indicated to treat gestational choriocarcinoma, chorioadenoma destruens, hydatidiform mole, breast cancer, epidermoid cancer of the head and neck, advanced mycosis fungoides, lung

cancer, and advanced non-Hodgkin's lymphoma. Symptoms of overdose include hematologic and gastrointestinal reactions like leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, and gastrointestinalbleeding.

CASE REPORT

A 54 year old male, k/c/o Arthritis on treatment with Methotrexate, now admitted with c/o sudden onset of painfullesions over oral mucosa with painful swallowing, skin lesions on nape of neck, dorsum of hand and foot with blistering for 7-8 days. No fever/ vomiting/ loose stools. He was on treatment for arthritis from outside hospital for 4-5 years (details of treatment not known). Recently the dose of MTX had been increased (records not available).On the time of admission all the vitals found to be normal and on local examination Skin shows Erosive crusted and scaly plaques on nape of neck, dorsum of hand and foot and Neck shows Erosive crusted andscaly plaques on nape of neck. On evaluation he had leucopenia and thrombocytopenia, severe oral mucositis and skin lesions, possibly due to Methotrexate overdose. On his clood routine examination shows Total Leucocyte Count 3300 /µL (4000 - 11000), Hb 12.20 g/dL (12 - 16), RBC Count 3.84 Million (4.3 - 5.6),Packed Cell Volume 35.40 % (38 - 48), MCV 92.3 fL (80 - 100), Platelets Count 0.79Lakhs/microlitre. Peripheral blood smear report shows RBCs: Normocytic normochromic rbc, WBC: Leukopenia, Platelets: Thrombocytopenia.4 pints of blood were transfused as a result of decreased blood counts. The offending drug intake (methotrexate) were stopped. He was immediately initiated on IV Leucovorin and received colony stimulating factors. He was treated with following drugs T. FOLIC ACID 5 mg 1-0-0 x to continue T. NUROKIND OD 1500mcg 1-0-0, T. FLUCONAZOLE 100mg T. VITAMIN C 500mg 1-0-1T. ZINCOVIT 1 tab 0-0-1, CANDID MOUTH PAINT L/A 1-1-1, XYLOCAINE VISCOUS Gargle
L/A 1-1-1. At the time of discharge patient was found to be symptomatically better.

DISCUSSION

Bone marrow suppression also known as myelotoxicity or myelosuppression, is the decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes). Bone marrow suppression is a serious side effect of chemotherapy and certain drugs affecting the immune system such as azathioprine. Many other drugs including common antibiotics may cause bone marrow suppression. Unlike chemotherapy the effects may not be due to direct destruction of stem cells but the results may be equally serious. The treatment may mirror that of chemotherapy-induced myelosuppression or may be to change to an alternate drug or to temporarily suspend treatment. Because the bone marrow is the manufacturing center of blood cells, the suppression of bone marrow activity causes a deficiency of blood cells. This condition can rapidly lead to life-threatening infection, as the body cannot produce leukocytes in response to invading bacteria and viruses, as well as leading to anemia due to a lack of red blood cells and spontaneous severe bleeding due to deficiency of platelets.

Pancytopenia is a condition in which there is a lower-than-normal number of red and white blood cells and platelets in the blood. Pancytopenia occurs when there is a problem with the blood-forming stem cells in the bone marrow. Signs and symptoms include fatigue, weakness, dizziness, trouble breathing, fast heartbeat, fever, pale skin, purple or red spots on the skin, rash, easy bruising, and abnormal bleeding. Pancytopenia may be caused by certain autoimmune, bonemarrow, or genetic disorders. It may also be caused by infection, poor nutrition, pregnancy, cancer treatment (such as chemotherapy or radiation therapy), or exposure to certain toxins, chemicals, or medicines. The underlying pathophysiology depends on the cause of pancytopenia. The pathophysiology of aplastic anemia is an autoimmune-mediated T cell activation, which leads to the destruction of the hematopoietic stem cells. Bone marrow suppression is also caused by direct cytotoxic effects of medications such as methotrexate, anticonvulsants, andchemotherapeutic agents. Ineffective hematopoiesis is seen in the bone marrow of myelodysplastic syndrome. Peripheral blood smear can show abnormal cells such as blasts, dysplastic leukocytes, and immature cells. The workup should also include vitamin B12 and folate levels, liver chemistry, lactate dehydrogenase. Infectious workup should be done as pancytopenia can be associated with infections such as HIV, malaria, and tuberculosis. Bone marrow aspiration and biopsy can be done if no specific etiology is found to evaluate the status of the bone marrow stem cells. Bone marrow aspiration establishes the diagnosis for pancytopenia in 75% of cases. The most common etiologies found are hypoplastic marrow, followed by megaloblastic anemia and hematological malignancies. Pathological examination of the bone marrow biopsy is helpful in malignant etiologies. It can show a clonal population of cells, primary/secondary malignant cells, acellular marrow, fibroblasts, granulomas from tuberculosis, sarcoidosis, or fungal infections. Treatment is based on the underlying etiology for pancytopenia. Nutritional deficiencies should be corrected. Any offending drug should be discontinued. Treatment for infections such as HIV or tuberculosis should be started immediately. If an autoimmune condition or malignancy is diagnosed, it should be treated. Aplastic anemia secondary to viral infections such as parvovirus is transient and symptomatic treatment should suffice. For patients with severe aplastic anemia, treatment options could include hematopoietic stem cell transplant and immunosuppression.

Methotrexate (MTX) is an anti-metabolite most

commonly used in chemotherapy and immunosuppressant in auto-immune diseases. This activity describes the indications, action, and contraindications for Methotrexate as a valuable agent in treating a wide variety of neoplastic diseases. Methotrexate is an FDA-approved folic acid antagonist indicated for the treatment of rheumatoid arthritis because of its high potency and efficacy in such patients; it can also be useful in patients with juvenile idiopathic arthritis. It acts by Inhibits dihydrofolic acid reductase; inhibits purine and thymidylic acid synthesis, which in turn interferes with DNA synthesis, repair, and cellular replication; cell cycle specific for S phase of cycle and may inhibit rapid proliferation of epithelial cells in skin. In autoimmune diseases, different mechanisms have involvement in choosing methotrexate as a drug of choice. It inhibits enzyme AICAR transformylase, leading to hindrance in Adenosine and Guanine metabolism, Adenosine accumulation; and due to anti-inflammatory action of adenosine, leads to repression of T-cell activation, down-regulation of B-cells, increasing activated CD-95 T cells sensitivity; and repression of methyltransferase activity, inhibition of the binding of beta-1 interleukin to its cell surface receptor. The most common adverse effects are gastrointestinal manifestations such as nausea, vomiting, mucosal ulcers, loss of appetite. These are noted in most of the patients and are easily managed. The major adverse effect of methotrexate is hepatotoxicity. These side effects are similar to folate deficiency and can be prevented by supplementation of methotrexate with folic acid. When prescribing this treatment to any female of the reproductive age group, the patient must be made aware of its potential for teratogenesis, and double contraception is mandatory. With high doses, Patients may also experience mucosal ulceration. It may also be a sign of impending methotrexate toxicity. Alopecia, fatigue, fever, increased risk of infection, low white cell count, GI bleeding, pancreatitis, bone marrow suppression (aplastic anemia), malignancy (lymphoproliferative disorders), infections, interstitial pneumonitis, and renal failure are other potentially life-threatening side effects. Patients taking methotrexate should undergo monitoring of CBC, serum creatinine, transaminases is recommended weekly for the first four weeks and then at least bimonthly. A complete list of the current medications should be revised to avoid any possible drug interactions before prescribing methotrexate. Liver function tests (monitoring serum AST, ALT, serum albumin levels), liver biopsy can also be done in cases of hepatotoxicity. Creatinine clearance requires monitoring (50 ml/min is necessary before prescribing methotrexate) to avoid possible nephrotoxicity. Monitoring for pulmonary toxicity is also required as the patients may have a dry cough, fever, dyspnoea. baseline chest radiographs recommended to detect interstitial, and alveolar infiltrates, hilar adenopathy, pleural effusions, and pulmonary fibrosis. Methotrexate may also cause reactivation of tuberculosis in endemic countries, so tests to eliminate the presence of tuberculosis are required. Also, monitoring for Bone marrow toxicity as myelosuppression can occur due to folate deficiency. High-dose methotrexate (HDMTX) is the term for doses higher than 500 mg/ml. Patients may experience nausea, mucosal ulceration, alopecia, fatigue, fever, increased risk of infection, leukopenia, GI bleeding, pancreatitis, cirrhosis, aplastic anemia, malignancy (lymphoproliferative disorders), infections, interstitial pneumonitis, renal impairment, and teratogenesis. To manage MTX toxicity: immediate leucovorin administration. The three antidotes used for MTX toxicity are leucovorin, thymidine, and glucarpidase. Leucovorin is the reduced active form of folic acid. It rescues normal cells from the toxic effects caused by MTX's inhibition of reduced folates. Leucovorin is particularly effective in preventing myelosuppression, gastrointestinal toxicity, and neurotoxicity during methotrexate treatment. Thymidine rescues cells from the cytotoxic effects of MTX; however, its use is still under investigation and is always given together with the other drugs. Glucarpidase converts methotrexate into DAMPA and glutamate, two nontoxic metabolites, thus rapidly removing methotrexate in patients with renal dysfunction. Glucarpidase, in combination with leucovorin, is a common therapy for MTX toxicity. A single dose of glucarpidase reduces plasma methotrexate concentrations by 97% or more within 15 minutes. Hydration and urine alkalinization is also continued in patients requiring glucarpidase. Leucovorin therapy should continue for 48 hours after glucarpidase administration. Hemodialysis and hemoperfusion can also lower MTX levels.

CONCLUSION

Pancytopenia is one of the major adverse event of Disease modifying antirheumatic drug.Hence ,physicians should evaluate the patient's condition inorder to prevent the progression of the adverse event.Although the patient gets recovered after stopping the offending agent and need follow up whether any recurrence.

CONFLICTS OF INTEREST

The authors have obtained the necessary patient consent forms where the patients have given their approval for participation in the investigation, followed by representation in the concerned article. The patients do understand that the authors will ensure that their identities won't be revealed.

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