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Case Report

Acute cutaneous methotrexate toxicity and severe pancytopenia following methotrexate prophylactic chemotherapy for the prevention of post molar gestational trophoblastic neoplasia-a case report

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ABSTRACT

Gestational Trophoblastic Neoplasia is a type of malignancy that develops from a molar gestation and occurs when trophoblastic activity remains following evacuation. Evacuation of retained products of conception is the cornerstone in the management of molar pregnancies however, a subset of patients is at risk to develop post-molar gestational trophoblastic neoplasia. Chemoprophylaxis has been controversial and varies across the guidelines set by local societies. In the Philippines, methotrexate chemoprophylaxis is acceptable for patients who are at high risk developing post molar gestational trophoblastic neoplasia and when post-evacuation surveillance is doubtful. We present a 35-year-old gravid patient who was diagnosed with a partial molar pregnancy who underwent methotrexate chemoprophylaxis after suction curettage. The patient was a candidate for chemoprophylaxis since her baseline B-HCG level was elevated to 1,270,300 mIU/ml. 0.8 ml of methotrexate was given intramuscularly on alternating deltoids for 5 doses on 5 consecutive days. The patient was sent home stable with no complaints after her fifth dose however 5 days after her discharge, the patient presented in our emergency room due to pruritic skin lesions. There were multiple, well-defined, irregularly shaped erythematous to violaceous plaques with whitish scales, some with areas of erosions on the forehead, neck, back, inframammary area, abdomen, periumbilical region, bilateral upper arms, buttocks and lower extremities. Blood work up also revealed severe pancytopenia. Aggressive hydration, urine alkalinization, leucovorin rescue therapy, administration of granulocyte macrophage colony stimulating factor, and transfusion of blood products were strategies done for the successful management of the case. Although rare, the development of severe pancytopenia following MTX-administration is linked to a high incidence of morbidity and mortality and must be treated with the highest-level of care. Clearance of methotrexate from the bloodstream, folinic acid therapy, and organ treatment are 3 cornerstones in the management of methotrexate toxicity.

Keywords: Gestational trophoblastic neoplasia, Methotrexate, Chemoprophylaxis, Molar pregnancy, Methotrexate toxicity

INTRODUCTION

Gestational Trophoblastic Neoplasia (GTN) is a type of malignancy that develops from a molar gestation and occurs when trophoblastic activity remains following evacuation. This is usually demonstrated following a plateau or rise in serial B-human chorionic gonadotrophin (hCG). Certain risk factors are known to increase the risk of developing GTN. The clinical practice guidelines published by the Philippine Society for the study of Trophoblastic Diseases (PSSTD) has enumerated eight risk factors that increases the risk to develop this condition: Advanced maternal age of >/= 40 years old, uterine size that is larger by the computed age of gestation by >/= 5

weeks, markedly elevated serum BHCG of >/= 100,000 mIU/ml, the presence of theca lutein cyst/s >/= 6 cm, presence of one or more medical complications such as preeclampsia, hyperthyroidism, pulmonary embolism and coagulopathies, recurrent molar pregnancy, a documented hydatidiform mole with a coexisting normal twin, and poor follow up.

The cornerstone in the management of molar pregnancy is through the evacuation of retained products of conception (ERPC) usually through suction curettage. In most patients, ERPC provides adequate treatment however a small subset of patients progresses to malignancy. The rate of malignant transformation of high-risk patients was reported to be 30% - 50% compared to patients with molar pregnancy without risk factors.[2] Chemoprophylaxis has been controversial and varies across the guidelines set by local societies. The PSSTD however still recommends the administration of chemoprophylaxis through methotrexate for patients who are at high risk developing post molar gestational trophoblastic neoplasia and when post-evacuation surveillance is doubtful.[4]

CASE REPORT

We present the case of a 35-year-old gravid patient who came in due to vaginal bleeding. A transvaginal ultrasound was done during admission which revealed an enlarged uterus with snow-storm appearance. Baseline BHCG was extracted with a value of 1,270,300 mIU/ml which further strengthened the diagnosis of a molar gestation.

Evacuation of the vesicular tissues was done via suction curettage and specimens were submitted for histopathological examination which eventually revealed a partial molar pregnancy. Due to the patient's markedly elevated B-HCG, chemoprophylaxis with methotrexate was given with a daily dose of 0.4 mg/kg/day administered for 5 days. The computed daily dose administered 0.88 ml but as per the guidelines set by the PSSTD, the maximum daily dose to be given is 0.8 ml/day. Methotrexate was given intramuscularly on alternating deltoids for 5 consecutive days with a cumulative dose of 100 mg total.

Intravenous omeprazole and chlorhexidine gargle three times a day after meals were started. The patient was sent home stable with no complaints after her fifth dose however 5 days after her discharge, the patient presented in our emergency room due to pruritic skin lesions. On examination, there were multiple, well-defined, irregularly shaped erythematous to violaceous plaques with whitish scales, some with areas of erosions on the forehead, neck, back, inframammary area, abdomen, periumbilical region, bilateral upper arms, buttocks and lower extremities (Figure 1).

Serum B-HCG was requested revealing a value of 3911.80 mIU ml demonstrating a 99.6% decrease from baseline of 1,270,300 mIU/ml. CBCPC revealed severe pancytopenia with a hemoglobin of 81 g/l (baseline: 126 g/l), white blood cell count of 1.8×109 (baseline: 9.3×109), and platelet count of 10×109 (baseline: 243×109). Absolute neutrophil count (ANC) was decreased to as low as 612 cells/l. Peripheral blood smear showed microcytic, hypochromic red blood cells with ovalocytes and occasional elliptocytes with no blast cells seen. Serum creatinine was slightly elevated at 98.48 mol/l (reference: 46.92 mol/l) with a computed creatinine clearance of 61 mL/minute. Hypoalbuminemia was also noted with a serum albumin of 27.45 g/l (reference: 35-50 g/l).

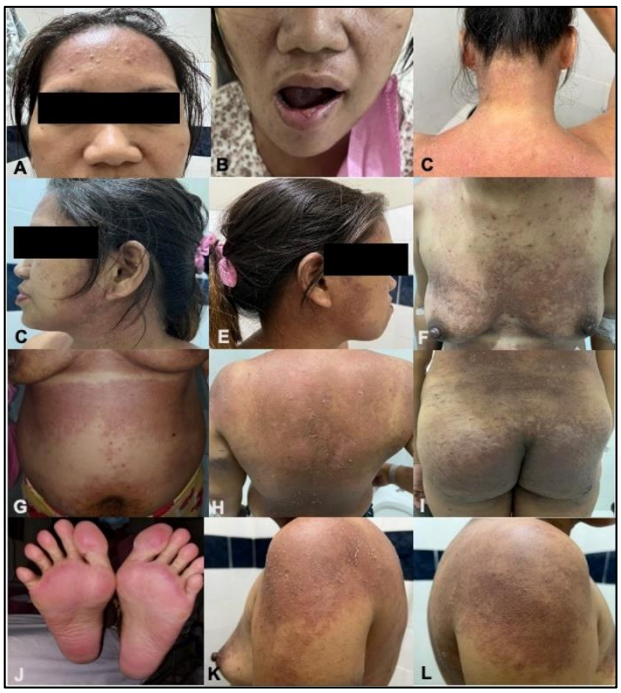

Figure 1 (A-l): Multiple, well-defined, irregularly shaped, erythematous to violaceous plaques with whitish scales, some with areas of erosions on the forehead, neck, back, inframammary area, abdomen, periumbilical region, bilateral upper extremities (deltoids), buttocks and lower extremities.

The patient was referred to the dermatology, allergology and hematology services for co-management. A skin biopsy was done with findings of the stratum corneum showing mounds of parakeratosis. The granular layer was intact and the epidermis showed mild spongiosis with exocytosis of eosinophils. There were many individual dyskeratotic keratinocytes and focal vacuolar interface change. There were superficial perivascular infiltrates of lymphocytes, histiocytes with many eosinophils (Figure 2).

Intravenous hydration was given using 0.9% Sodium Chloride with running rate of 125 cc/hour. Intravenous omeprazole 40 mg OD administration was also initiated. Urine alkalinization was done through oral sodium bicarbonate 650 mg/tab TID. For the oral mucositis, the patient was started with a mouthwash composed of diphenhydramine 12.5 mg/5ml, 160 ml of aluminium chloride and 1 gram of pulverized sucralfate. The patient

was advised to gargle by swallowing 5 ml three times 30 seconds then spit, followed by swallowing 5 m three times a day after meals. For her skin lesions, the patient was started with 50 mg intravenous diphenhydramine every 8 hours and betamethasone lotion to be applied on the affected areas twice a day for one week. Hypoalbuminemia was managed by giving 20% human albumin intravenously.

Anaemia and thrombocytopenia were addressed by transfusing a total of 11 units of platelet concentrate and 2 units of packed red blood cells. For the patient's neutropenia and low ANC count, granulocyte-macrophage-colony-stimulating factor (GM-CSF) was given subcutaneously once a day for a total of 3 doses. Leucoverin (Folinic Acid) was administered intravenously at a dose of 15 mg/m2 every 6 hours and was given for a total of 3 days.

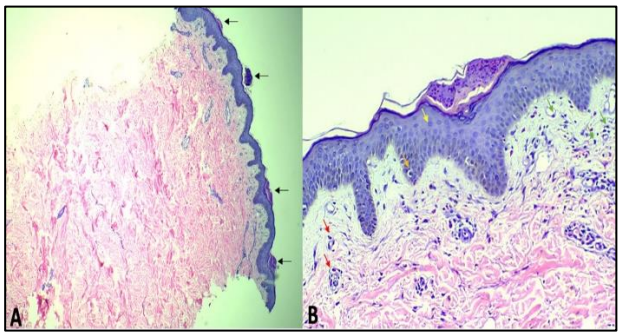

Figure 2: Skin biopsy on haematoxylin and eosin stain. A) Mounds of parakeratosis (Black arrow), B) Dystrophic keratinocytes (red arrow), vaculoar interface change (orange arrow), mild spongiosis of the epidermis (yellow arrow), increased eosinophils (green arrow)

There was noted gradual improvement on the patient's cutaneous lesions with the disappearance of erythema, decrease in scaling but with persistence of hyperpigmentation. Serial monitoring of the patient's complete blood count revealed resolution of anaemia with a haemoglobin of 101 g/l, WBC count of 5.2×109, and platelet count of 108×109. There was also a decrease in creatinine levels and resolution of hypoalbuminemia. The patient was discharged 10 days from readmission stable and was followed up at the outpatient department for B-HCG monitoring.

DISCUSSION

Prophylactic chemotherapy (P-chem) for molar pregnancy was utilized in the management of molar pregnancy starting 1996 and was based on the premise that trophoblastic tumor cells are highly sensitive to certain chemotherapeutic agents such as methotrexate and actinomycin-D, that the development of GTN after the evacuation of a complete hydatidiform mole is biologically predetermined, that the mechanism of malignant transformation is through hematogenous spread, and that high blood levels of cytotoxic agents at the time of molar evacuation should reduce the incidence of both locally invasive and metastatic GTN.[6,7]

Both methotrexate and actinomycin-D are now recognized as first line agents for the prevention of GTN either as single-agent or multi-agent. The course of chemotherapy is still not clearly defined and depends on the guidelines set by local societies.[2] The International Federation on Gynecology and Obstetrics (FIGO) as well as the National Comprehensive Cancer Network (NCCN) has reported that prophylactic chemotherapy can be used in special situations as it has been proven effective in preventing post molar gestational trophoblastic neoplasia (PMGTN) especially in developing countries.[5]

One concern in P-chem is drug resistance to PMGTN however, there is still insufficient evidence to this claim hence chemoprophylaxis is still acceptable especially in economically underdeveloped countries like the Philippines. Another concern is the inherent risk of over-treatment for patients with histologically confirmed non-molar hydropic abortions.[2]

Methotrexate profile

Methotrexate (MTX) is commonly used in the management of GTN. Dosage can be classified into three categories: high dose (500 mg or more) used for malignancies, medium dose for gestational trophoblastic diseases and low dose (up to 50 mg per week) for its anti-inflammatory/ immunomodulatory property for rheumatological and dermatological diseases.[9]

A study by Soriano-Estrella et al, evaluated the efficacy of MTX in preventing PMGTN. A total of 54 high-risk patients were recruited in the study and 31.43% of the patients developed PMGTN. 17 patients received methotrexate chemoprophylaxis through the 5-day MTX regimen however, three patients still developed PMGTN with an incidence rate of 17.65%. Of the 18 patients in the control group, 8 patients developed PMGTN with an incidence rate of 44.44%.

This demonstrated that the use of methotrexate as chemoprophylaxis lowered the incidence of PMGTN.[3] A similar local study by Tan et al, included a total of 123 patients. It concluded that the administration of methotrexate for chemoprophylaxis was effective in a 3-year period of monitoring. All 123 patients received methotrexate chemoprophylaxis using the 5-day regimen and all patients had no occurrence of PMGTD within a 3-year period of monitoring.[4]

Methotrexate toxicity

Frequently seen adverse events following MTX include nausea, vomiting, diarrhea and elevated transaminases.[10] Administration of high-dose methotrexate, can lead to

bone marrow suppression, pulmonary toxicity, nephrotoxicity, and in rare cases, hematologic and dermatologic toxicity.

Hematologic toxicity

Patients who undergo methotrexate therapy can have haematological damage which can include myelosuppression, leukopenia, neutropenia and megaloblastic anaemia. Pancytopenia is a hematologic condition with low levels of RBCs, WBCs and platelets. Pancytopenia is defined as WBC count of <3500 cells/mm3, haemoglobin < 11g/dl and platelet of <150,000 cells/ mm3. Severe pancytopenia on the other hand was defined as WBC <2000 cells/mm3, haemoglobin <10 g/dl and platelet of < 50,000 cells/mm3. It is dose and duration dependent and seen in only 1.0% - 1.4% of the reported side effects of methotrexate.

According to literature, pancytopenia has a female preponderance of about 62.51% with ages greater than 60.[6] It is difficult to prevent since it can appear unexpectedly during therapy.[5] MTX-induced pancytopenia is a potentially fatal complication with mortality rates as high as 17% - 44%.[6] In a case series which included 46 patients with methotrexate induced pancytopenia, 16 patients presented with a severe type and 13 of the 16 patients demised.[10] Most common causes of mortality related to haematological toxicity include septic shock and respiratory failure due to severe pancytopenia.[9]

The exact mechanism of methotrexate induced haematological toxicity is still unknown however hematopoietic toxicity from the use of methotrexate has been linked to the increased levels of unbound extracellular methotrexate. Advanced age causes delayed drug clearance in the elderly, poor nutritional status, presence of infections, folic acid deficiency, and the use concomitant medications. Hypoalbuminemia also gained focus as a possible contributor to the development of pancytopenia as it increases the risk of toxicity due to increased levels of free MTX than albumin-bound MTX. Thrombocytopenia is due increased platelet apoptosis that leads to increased mitochondrial dysfunction.[5] Systemic manifestations of pancytopenia would include fatigue due to low haemoglobin, infections secondary to leukopenia and/or neutropenia, and the presence of bleeding/ ecchymoses due to the decreased platelet counts. Toxicity from methotrexate begins with stomatitis and progresses to pancytopenia and this can occur at any point during the course of treatment.[6]

Dermatologic toxicity

Skin lesions secondary to methotrexate use are rare and most published cases are on patients with pre-existing skin conditions. Currently, there is only a handful of journal articles about cutaneous toxicity following methotrexate administration and there is also no published data yet demonstrating skin toxicity in patients undergoing methotrexate chemoprophylaxis for the prevention of PMGTN. Cutaneous toxicity has been documented following high dose methotrexate therapies and dermatological adverse effects may range from minor to severe. Dermatologic side effects can include nonspecific morbilliform drug rashes which are erythematous, macular, pruritic, and is mainly limited to the neck and trunk.[5]

In the study of Delyon et al, 5 patients were given MTX therapy with cumulative doses ranging from 75 to 2800 mg with prescribed weekly dosage ranging from 12.5 to 40 mg. 3 of the 5 patients had previous skin conditions such as psoriasis and bullous pemphigoid. Cutaneous side effects included ulceration on psoriatic plaques which involved the torso, arms and legs. The skin biopsies revealed subtle abnormalities consistent with a direct toxic effect on the epidermis characterized by severe keratinocyte dystrophy and unevenly arranged enlarged keratinocytes containing clear cytoplasm and variable enlarged nuclei, some having irregular contours.

This is a result of the cytostatic effects of methotrexate causing dysplasia in rapidly renewing tissues which can explain the presence of keratinocyte dystrophy in the epidermis and myelosuppression in the bone marrow.[8] The classic histopathological findings of acute mucocutaneous methotrexate toxicity are acanthosis, epidermal necrolysis, interface dermatitis, and dyskeratosis and some cases with perivascular and interstitial lymphocytic infiltrates with numerous eosinophils.[8]

Treatment

There are 3 cornerstones in the management of MTX toxicity: clearance of MTX from the bloodstream, folinic acid therapy, and organ treatment. Methotrexate is cleared mainly through the kidneys through glomerular filtration and active tubular secretion. Diuresis of 600 mL over six hours through adequate hydration with 0.9% sodium chloride solution must be maintained with a urine output of at least 2 liters per day or until serum MTX levels drop to 0.2 mol/l. Urine alkalinization with 40-50 mEq sodium bicarbonate for every liter of intravenous fluid is also recommended as increasing the urinary pH from 6.0 to 7.0 enhances the solubility of MTX facilitating elimination and prevents crystallization. Methotrexate crystallization can cause crystal nephritis and direct tubular damage.[8]

Ideally, plasma MTX concentrations are monitored especially during high-dose MTX therapy so as to predict possible complications. A plasma concentration greater than 1 mol/l at 48 hours post administration can predispose a patient to develop bone marrow and mucosal toxicities. It is recommended that complete blood count be monitored on days 7, 10 and 14 post-therapy to assess the impact of MTX to the bone marrow. Granulocyte-macrophage-colony-stimulating factor (GM-CSF) is recommended in patients who present with febrile neutropenia and who are at high risk of developing complications and poor outcome

from an infection such as an absolute neutrophil count of <100 cells/l, prolonged neutropenia of >10 days, age of 65 and above, hypotension and multiorgan dysfunction.[10] Leucovorin was first identified in 1948 due to its property of reversing the folate block by antifolate drugs. It is usually given after HD-MTX infusion with the goal of decreasing plasma MTX to less than 0.1 µmol/l. Leucovorin rescue is the standard practice of limiting the adverse effects of high dose methotrexate by administering leucovorin after the initial dose of methotrexate and in cases of diminished MTX elimination.[10]

It is highly beneficial in preventing myelosuppression, gastric toxicity and neurotoxicity following high dose MTX therapy. The dose of leucovorin given for high doses of methotrexate is 10-25 mg/m2 IM or IV every 6 hours and can be increased to 1,000 mg/m2 every 6 hours in patients with compromised renal function. It is acceptable to provide leucovorin therapy for 12-24 doses (3 days) or longer if plasma MTX concentrations are not available.[10]

CONCLUSION

There is a paucity of data on literature demonstrating cutaneous and haematological toxicity following methotrexate use in the field of obstetrics and gynaecology and in the management of gestational trophoblastic disease. Although rare, the development of severe pancytopenia following MTX-administration is linked to a high incidence of morbidity and mortality and must be treated with the highest-level of care. Periodic monitoring of complete blood counts and renal function tests as well as increasing hydration, urine alkalinization so as to facilitate renal elimination and leucovorin rescue are strategies that can be done to prevent the development of severe adverse effects.

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