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Severe methotrexate hypersensitivity during treatment for Gestational trophoblastic Neoplasia: Case Report and considerations for management

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1. Introduction

Gestational trophoblastic disease (GTD) is a group of benign and malignant tumors that develop from placental tissue. The incidence of GTD in the United States is approximately 1 in 1,000 pregnancies. The most common form of GTD is hydatidiform mole, encompassing 80 % of GTD. Malignant forms of GTD are classified as gestational trophoblastic neoplasia (GTN), which include invasive moles, choriocarcinomas, epithelioid trophoblastic tumors, and placental site trophoblastic tumors. The most common type of GTN is invasive mole, accounting for about 15 % of all GTD (Brown et al., 2017).

A large majority of GTD is due to abnormal fertilization. Hydatidiform moles (HM) can be either partial or complete based on karyotype, histology, and malignant potential. Invasive mole or choriocarcinoma after HM occur in 15–20 % of complete moles but only 1–5 % of partial moles (Abu-Rustum et al., 2019). The reported incidence of GTN after molar pregnancy is 18 % to 29 % (Lurain, 2010). Invasive moles develop from molar extension into the myometrium and can metastasize to local structures in addition to the lung and brain. Choriocarcinoma, epithelioid trophoblastic tumors, and placental site trophoblastic tumors can occur after HM or other pregnancy-related events. Staging is based on the International Federation of Obstetrics and Gynecology (FIGO) criteria with additional risk factor assessment by World Health Organization (WHO) criteria to guide treatment planning.

Cure rates are greater than 90 %, making GTN one of the most curable gynecologic malignancies (Seckl et al., 2010). First line, single-agent treatment options for low-risk GTN include dactinomycin, a RNA transcription inhibitor or methotrexate (MTX), a folic acid antagonist. The side effect profile of dactinomycin includes alopecia, which can be concerning for the patient population that is typically affected by GTN, as well as most commonly myelosuppression, nausea, or vomiting. Most commonly (>10 %), patients experience mucositis, gastrointestinal upset (nausea, vomiting, diarrhea), renal or hepatotoxicity, dizziness, and headache when on MTX (Solomon et al., 2020). Contraindications to MTX include intended pregnancy, blood dyscrasias, liver disease, and renal impairment, in which cases, dactinomycin can be utilized. Meta-analyses have suggested that while dactinomycin may be more effective, the side effect profile of MTX is associated with generally less severe toxicity, thus making it likely more widely used in practice (Hao et al., 2021).

Adverse drug reactions include type A reactions which are predictable reactions from the known pharmacologic properties of the drug and type B reactions which are hypersensitivity reactions. Additionally, there are four types of hypersensitivity reactions. Type I is immediate (within minutes to hours of exposure) and IgE mediated, where symptoms are attributed to the release of vasoactive mediators by mast cells and basophils. Types II-IV are delayed and are either due to IgG mediated cell destruction, IgG and drug immune complex deposition and complement activation, or T-cell mediated, respectively.

Methotrexate hypersensitivity is overall rare and there are few cases reported in the literature with both low and high-dose treatment regimens for non-gynecologic pathologies and largely in pediatric populations (Dilley et al., 2017). Both IgE-mediated and less well-delineated immunologic mechanisms have been hypothesized as mediators of methotrexate hypersensitivity. Table 1 summarizes reported cases of methotrexate hypersensitivity in adults. With the incidence of carboplatin reactions approaching 10–30 %, gynecologic oncologists are well-versed in managing hypersensitivity in platinum agents (Garcia et al.,

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2019). However, MTX hypersensitivity has not been reported in our population or in our dosage regimens. Given the effectiveness and favorable side effect profile of methotrexate, it is important to delineate how to approach and manage methotrexate hypersensitivity and what factors increase risk of a hypersensitivity reaction. We present a case of a 27-year-old female found to have a complete hydatidiform mole with subsequent progression to GTN who had an atypical hypersensitivity reaction to MTX. The patient provided consent to present her case.

2. Case Report

A 27-year-old G5P2022 female presented to the emergency room as a transfer from outside hospital (OSH) for concern for ectopic pregnancy on transvaginal ultrasound with beta-HCG (bHCG) of 195,422 mIU/mL. She initially presented to the OSH with complaints of heavy vaginal bleeding for three days and right shoulder pain.

On physical exam, mild abdominal tenderness to palpation was noted without rebound or guarding, as well as an enlarged, retroverted uterus. No significant or active bleeding was noted on the speculum exam. On bedside ultrasound, there was no evidence of an intrauterine pregnancy and OSH ultrasound reported right cystic lesion in right adnexa. bHCG was 114,343 mIU/mL on admission. Given that the patient was requiring intravenous opioids for pain control and had a significantly elevated bHCG without evidence of intrauterine pregnancy, she was admitted for management of a possible ruptured ectopic pregnancy and the patient provided consent for an emergent exam under anesthesia, diagnostic laparoscopy, possible salpingectomy, possible dilation and curettage.

Operative findings included a small amount of hemoperitoneum without clear intra-abdominal source but otherwise normal abdominal and pelvic survey. Uterus was enlarged but bilateral ovaries and fallopian tubes were grossly normal appearing. Suction dilation and curettage was completed without complication. Pathology later confirmed a complete hydatidiform mole. Immediately postoperatively, bHCG declined appropriately to 60,146 and the plan at the time of discharge included close follow up and serial bHCG measurements.

Initially, weekly bHCG measurements revealed a downtrend with nadir to 249 mIU/mL. However, on postoperative day 20, bHCG began to rise inappropriately, with an 117 % increase in bHCG over one week. At this point, the patient was referred to gynecologic oncology given high suspicion for GTN. CT chest, abdomen, and pelvis revealed pulmonary nodules, consistent with FIGO Stage III GTN, with a final pretreatment WHO risk score of 2. The patient was then started on a 5-day regimen of MTX (0.4 mg/kg/day) given every 2 weeks as per NCCN guidelines and tolerated the first two days of the first cycle well. On cycle 1 day 3, the patient developed chest pain, lightheadedness, chills, diaphoresis, and drowsiness during the infusion. Erythema was noted on the patient's chest and throat, however vital signs remained stable throughout and point of care glucose was 133. Methotrexate was discontinued and the patient was evaluated in the emergency room. The initial episode resolved within fifteen minutes, but she had two additional episodes in the emergency room. She eventually stabilized and did not require inpatient admission.

The patient was then pre-medicated with Tylenol, Decadron, Benadryl, Pepcid, and Zofran prior to the fourth dose of methotrexate and tolerated cycle 1 day 4 without issues. However later at home, she experienced two episodes of stuttering, headache, difficulty keeping her eyes open, shaking, diaphoresis, and dizziness. She then arrived for cycle 1 day 5 premedicated with Benadryl, Hydrocortisone, and Pepcid. However, she had another episode prior to methotrexate infusion, and thus was admitted for observation. The allergy team was consulted; they determined that the patient's reactions to methotrexate were more consistent with an intolerance than an IgE-mediated hypersensitivity reaction. Tryptase was normal at the time of the initial episode, reducing suspicion for an IgE-mediated response. No other etiology was found for these episodes, as neurologic and infectious work up revealed normal findings.

Given persistent reactions to methotrexate, the patient was then switched to dactinomycin, which she tolerated well with mild alopecia and completed two cycles past normalization of her bHCG. We have continued monthly bHCG measurement for twelve months since diagnosis and all have remained undetectable. The patient preferred Depo-Provera for contraception.

3. Discussion

Methotrexate hypersensitivity, while rare, can impact the treatment and management of GTN, ectopic pregnancy, and various rheumatologic and oncologic conditions. When a hypersensitivity reaction is encountered, immediate discontinuation of the offending agent and management of resultant symptoms is required. If premedication prior to methotrexate administration does not resolve hypersensitivity reactions, consultation with an allergist could be considered especially in patients who strongly wish to avoid side effects that may affect their physical appearance, like alopecia or hyperpigmentation. In the case above, premedication failed, and an allergist was consulted in the emergency room to assist with work-up.

When administering chemotherapy, patients can either have an infusion reaction, which is likely secondary to cytokine release, or true anaphylactic reaction. Typical work up for suspected type I hypersensitivity reactions include a tryptase level to discern between intolerance, infusion reaction, or IgE-mediated reactions. In IgE-mediated reactions, mast cells degranulate and release tryptase. Therefore, an elevated tryptase level can be indicative of anaphylaxis. However, mast cell degranulation can also be secondary to recent opiate or NSAID use, history of disorders with mast cell activation (systemic mastocytosis,

Table 1
MTX Hypersensitivity: Reported Cases in Adults.

Author & Year	Study Type	Journal	Patient Age & Sex	Indication	MTX Dose	Reaction Type/Symptoms
Cazaña et al., 1994 (Cazaña et al., 1994)	Case Report	Journal of Allergy and Clinical Immunology	60/F	Breast Cancer	75 mg IV	Itching in palms and soles, and a generalized rash, hypotension, loss of consciousness, and cardiopulmonary arrest after 7th cycle, within the first few minutes
Davis et al., 2003 (Davis et al., 2003)	Case Report	Annals of Allergy, Asthma & Immunology	22/M	Osteosarcoma	12 g/m^2 IV	Diffuse urticaria, facial swelling, cough, and chest tightness after 1st cycle, within 5 min
Alkins et al, 1996 (Alkins et al., 1996)	Case Series	Cancer	30/M	Osteosarcoma	12 g/m^2 IV	Generalized pruritus, urticaria, angioedema, and pharyngeal edema after 1st cycle, within 15 min
			23/M	Osteosarcoma	12 g/m^2 IV	Pruritus and generalized urticaria after 1st cycle, within 30 min
Fernando, 2013 (Fernando, 2013)	Case Report	Rheumatology	57/F	Rheumatoid arthritis	20 mg PO daily	Generalized urticaria, angioedema, throat constriction and abdominal cramping after 5 weeks
Joychan et al., 2017 (Joychan et al., 2017)	Case Report	Annals of Allergy, Asthma & Immunology	20/M	Anaplastic large cell lymphoma	60 mg/m^2 IV	Burning sensation in throat, emesis, generalized urticaria, left eyelid swelling, and throat clearing within 15 min after previous exposure to both IV and intrathecal MTX

hereditary alpha-tryptasemia, acute myeloid leukemia, myelodysplastic disorders), and severe renal failure (may be secondary to impaired metabolism of tryptase or mast cell activation) (Sirvent et al., 2010). To characterize the type of reaction most accurately, tryptase levels should be drawn within ninety minutes of symptom onset. Skin testing can also be pursued for further work up in the outpatient setting with an allergist (at least two to four weeks after initial reaction to reduce the risk of false negatives) depending on the length of treatment and other clinical considerations. While many drugs are not validated or reliable for use in skin testing, methotrexate skin testing has been reported in mostly pediatric populations (Dilley et al., 2017; Cazaña et al., 1994).

MTX hypersensitivity is typically encountered when higher doses of methotrexate are administered for the treatment of other malignancies. Per our literature review, there have been no reported cases of MTX hypersensitivity in the setting of treatment of GTN and very few cases of MTX hypersensitivity in the treatment of other pathologies with typically higher dose protocols (Table 1). Fortunately, dactinomycin is an alternative to MTX for the treatment of GTN. When comparing dactinomycin to MTX, there are different considerations to make in terms of efficacy and toxicity. Meta-analyses have found that while MTX is associated with less toxicity, dactinomycin seems to be more efficacious (Hao et al., 2021). Primary remission rates for MTX range between 74 and 93 % whereas for dactinomycin, remission rates range from 69 to 94 % depending on dosing (Abu-Rustum et al., 2019). Additionally, there is only one reported case of a dactinomycin hypersensitivity reaction in the treatment of pediatric orbital embryonal rhabdomyosarcoma (Cappelli et al., 2001). Given this, if MTX is not well tolerated or a hypersensitivity reaction is encountered, dactinomycin is an appropriate alternative.

It is difficult to predict whether a patient will have a hypersensitivity reaction or infusion reaction to a chemotherapeutic agent. Some risk factors include intravenous versus oral administration, history of atopic disorders, multiple exposures (like in the case of platinum containing agents), prior infusion reaction, or a history of multiple drug reactions, regardless of drug class. If a patient is deemed to be at higher risk, dactinomycin could be considered first line, as opposed to methotrexate, to potentially avoid a hypersensitivity reaction. Further study is required to ascertain the overall risk of MTX hypersensitivity and risk factors for developing a reaction.

CRediT authorship contribution statement

Ayesha Kar: Writing – original draft, Data curation. **Kathryn A. Mills:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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