Transient visual loss with methotrexate, leucovorin chemotherapy for gestational trophoblastic neoplasia: Happenstance or beyond?

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ABSTRACT

Methotrexate chemotherapy (CT) is a standard for low-risk gestational trophoblastic neoplasia. Its use is associated with minimal toxicities and is chiefly composed of mild nausea and vomiting. Acutely occurring and self-limiting loss of vision has not been reported in the literature as a potential side effect. We discuss such a case with a transient and self-limiting visual loss in a patient on two consecutive courses of the planned CT. We advocate a further in-depth research to find the cause of such an association.

Key words: *Gestational trophoblastic neoplasia, Methotrexate, Oculopathy*

Gestational trophoblastic disease (GTD) is a disease of the proliferative trophoblastic allograft [1]. After uterine evacuation, 80% of hydatidiform mole cases follow spontaneous remission, while 20% progresses to post-molar gestational trophoblastic neoplasm (GTN) [1]. It is more common in some parts of Asia, with reported incidence rates as high as 2 per 1000 pregnancies while the European and North American incidence is usually reported to be <1 per 1000 pregnancies [2]. Chemotherapy (CT) is an essential component of the management of GTN. For low-risk patients, single-agent methotrexate (MTX) or actinomycin-D has been reported to have remission rates of 50–90% [3].

MTX is an antifolate drug which inhibits cell division by interfering with deoxyribonucleic acid replication [4]. The major toxicity is that of hematological, gastrointestinal, and dermatological systems due to the high turnover of cells [5]. Ocular toxicity with high-dose MTX occurs in almost 25% of patients and manifests as periorbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, and decreased reflex tear. We report the case of a rare occurrence of sudden blurring of vision with self-remission in two consecutive courses of low-dose MTX CT for GTN.

CASE REPORT

A 24-year-old female presented to the department of radiation oncology with a history of abortion and profuse vaginal bleeding. She was fit for her age and had no associated comorbidity. The patient had a history of an uneventful pregnancy 2 years back. However, the subsequent pregnancy ended with a spontaneous abortion. She developed profuse vaginal bleeding for which she underwent dilatation and curettage (D and C) on three occasions, but to no relief. The fourth D and C included proper tissue sampling and the histopathological report revealed GTD (Fig. 1). From here, the patient was referred to our department for adjuvant treatment.

At presentation, she was in a good general condition with no systemic abnormalities/comorbidities and an Eastern Cooperative Oncology Group performance score of 1. Her general examination revealed normal range of vital parameters and no abnormality was detected on detailed systemic examination.

Her hemoglobin was 11.0 g%, total leukocyte count was 9700 and platelet count was 210,000/mm^3. Her β-human chorionic gonadotropin (HCG) value was 72,605 mIU/mL. She was stratified as a case of low-risk GTN (age < 40 years, antecedent abortion, no metastases or prior CT) and planned for single-agent CT with injection MTX (1 mg/kg) intramuscular alternating with injection leucovorin (0.1 mg/kg) intravenous for an 8-day cycle.

The patient received three courses of the planned CT uneventfully. However, during the fourth cycle, day 2 of CT (leucovorin), she had a sudden onset diminution of vision in both the eyes. The CT was withheld but after 20–30 min her vision became normal. The patient's case sheet was reviewed for any associated medication, proper premedication as well as the CT drug batch/brand was checked but revealed no notable finding. She was thereafter advised for an ophthalmic consultation and a retinal examination revealed signs of early papilledema with mild hyperemic disc and obliterated cup but no major abnormality. A further exhaustive history regarding any visual problems revealed no previous episode of sudden/gradual blurring of vision. She was continued with her CT and completed the course uneventfully.

Table 1: Modified WHO prognostic scoring system as adapted by FIGO [7]

Scores	0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Antecedent pregnancy from index pregnancy	<4	4–6	7–12	≥13
Pre-treatment serum HCG (Ul/m l)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)		3–<5 cm	≥5 cm	
Site of metastasis	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	0	1–4	5–8	>8
Previous failed CT			Single drug	Two or more drugs

HCG: Human chorionic gonadotropin, CT: Chemotherapy

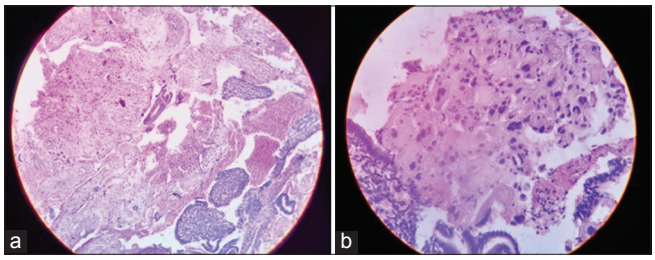

Figure 1: (a) H and E ×10 showing pleomorphic hyperchromatic tumor cells with hemorrhage in background (b) H and E ×40 showing pleomorphic hyperchromatic trophoblastic tumor cells

During the next cycle, again while receiving injection leucovorin, she complained of diminution of vision which resolved in 15–20 min. A repeat ophthalmic examination, however, did not reveal any abnormality. The previous findings of disc edema and disc hyperemia were absent and the margin of a cup was also well appreciated. The patient responded well to the CT as revealed by the beta-HCG levels that reduced to 4.5 mIU/ml. She was doing fine without any ocular or systemic symptom/sign at a 6-month follow-up.

DISCUSSION

The use of MTX includes a variety of cancerous and non-cancerous conditions. In the absence of a contraindication, it is the medical treatment recommended for tubal ectopic pregnancy and constitutes an alternative conservative treatment to laparoscopic salpingotomy for non-complicated tubal ectopic pregnancy with HCG level <5000 UI/L [6]. It is currently used in gynecology to treat disorders arising from trophoblastic tissue, namely ectopic pregnancy and GTN [4].

The World Health Organization has stratified GTN into a low-risk group (score ≤6) intimating single-agent CT and high-risk group (score >6) mandating multiagent CT (Table 1) [7]. Single-agent MTX has revolutionized the treatment of GTN. Previously, women with low-risk disease had to undergo hysterectomy, while those with high-risk disease inevitably died from the condition. MTX has not only replaced surgery as a treatment option but is used to cure almost 100% of women with the low-risk disease and up to 86% of women with high-risk disease in combination CT [4,8,9].

An 8-day multidose MTX protocol with intervening folinic acid (to minimize toxicity) was first suggested by Bagshawe and Wilde, in 1964 [4]. This regimen remains the first-line treatment for low-risk disease and is the most widely used regimen in the world. It achieves remission in 90% of low-risk Stage I patients and 70% of low-risk Stages II–III patients [4]. The toxicity profile of this regimen is low and comprises chiefly of nausea (<15%) and vomiting (<5%), and 2% of patients develop mouth ulcers, sore eyes, or chest or abdominal pain. Rarely, a life-threatening toxicity due to myelosuppression has also been reported in the literature [10]. Treatment is continued until the serum β-HCG normalizes (<5 IU/L) for at least 3 consecutive weeks [4].

MTX preferentially targets rapidly dividing cells; therefore, the hematological, gastrointestinal, and dermatological systems are the most likely to display features of toxicity (neutropenia, myelosuppression, nausea, vomiting, diarrhea, generalized erythema, rash, photosensitivity, and alopecia) [5]. Acute onset, short duration, and self-remitting blurring of vision with low-dose MTX administration have not been reported previously to the best of our knowledge. The literature search reveals a case report describing a reduced full-field electroretinogram in b-wave amplitude in a 13-year-old boy treated with MTX for 8.5 years [11] while in our case, the patient developed symptoms very early. We could not find any literature pertaining to a similar scenario as seen in our patient.

CONCLUSION

We postulate that even in low doses, MTX has the potential to cause ocular toxicity and appears to be a diagnosis of exclusion. Although rare, this is an important consideration to be kept in mind while using MTX and warrants further research to find a safety threshold for MTX use.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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