CASE REPORT

Fatal methotrexate toxicity: could it have been avoided?

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SUMMARY

Methotrexate is used judiciously, only when specifically indicated. However, in this case the patient had a fatal outcome after only three doses. A young nulliparous woman diagnosed as having high-risk persistent trophoblastic disease was considered for multidrug chemotherapy. However, because of persistent low-grade fever it was decided to give only single agent, methotrexate. She developed severe toxicity which proved fatal, even before the first course could be completed. Analysing causes of this rare, unexpected outcome of methotrexate administration, suggested that estimation of serum levels can be a useful tool in monitoring patients showing hypersensitivity but this facility is rarely available especially in low-resource countries. Pharmacogenetical analysis of blood/tissue sample may be useful to help in identifying patients likely to show hypersensitivity reaction.

BACKGROUND

Methotrexate, a folate analogue, is widely used in the treatment of various malignancies and arthritis. We report an unusual situation, in a case of persistent trophoblastic disease (PTD), where only first three doses of methotrexate resulted in fatal pancytopenia and mucositis.

CASE PRESENTATION

A young nulliparous woman was referred to our hospital for suspected choriocarcinoma. She had a history of dilation and curettage 2 months prior to admission for ultrasonographically suspected hydatiform mole. This was followed by irregular bleeding per vaginum for which she had suction evacuation at another clinic, which provoked profuse bleeding and therefore she was referred to our facility with a vaginal pack in situ. Pack was removed shortly after her arrival in our centre as we did not observe any significant bleeding. At the time of hospitalisation, the patient was febrile and had a firm mass arising from pelvis corresponding to 16 weeks gravid uterine size.

INVESTIGATIONS

She underwent a series of investigations which showed haemoglobin was 10 g/dl, total leucocyte count $16\,700/\text{mm}^3$ and platelets $1.11 \times 10^5/\text{mm}^3$. Her renal and liver function tests were within normal limits and serum βHCG was 473 759 IU/l. Ultrasonography showed a large multicystic, infiltrating mass with ill-defined margins involving the lower uterine body extending superiorly in the posterior myometrium with the rest of the uterus filled

with multiple cystic areas showing intense intraleisional vascularity. Metastatic workup revealed left-sided pleural effusion along with bilateral nodules in the lung parenchyma and a lesion in the left kidney, but no evidence of brain metastasis. A diagnosis of high-risk PTD (WHO Prognostic score—8) was made. Other investigations to diagnose the cause of fever did not reveal any positive results.

TREATMENT

The patient was started on intravenous antimicrobials (ceftriaxone 2 g/day and gentamicin 160 mg/day) in view of fever and because of the pack that had been inserted previously. However, the fever continued off and on for which she received symptomatic paracetamol, but without relief. A medical consultation was taken but physicians were also unable to identify the cause of fever and suggested that occasionally malignancies may be associated with low-grade fever.

Considering her scoring, oncologists suggested multidrug regimen but we felt that in view of the persistent low-grade fever it may be more practical to start single-agent chemotherapy which was initiated after obtaining high-risk consent. The chemotherapy was initiated on 20th day after admission. This long interval, despite being sure about the diagnosis, was a cause of great concern to us as treating physicians. However, it was felt that if her condition could be optimised prior to start of chemotherapy the patient would show better outcome. The patient was kept only on symptomatic treatment from 48 h prior to chemotherapy initiation. Methotrexate was initiated in a dose of 50 mg/day intramuscularly on alternate days with rescue of 15 mg folinic acid on intervening days. After the second dose of methotrexate, the patient had ulcerations in the mouth and throat which worsened after the third dose. Third dose of folinic acid was administered and subsequent methotrexate doses withheld. As per our protocol leucocyte counts are done prior to start of chemotherapy and every third day subsequently. The counts had been only minimally elevated ($11\,230/\text{mm}^3$) prior to the start of chemotherapy and started to show downward trend from third day onwards but reached critical levels ($<2500/\text{mm}^3$) only after administration of third dose. She was given symptomatic treatment initially and later shifted to total parenteral nutrition (TPN) as dysphagia and trismus became very pronounced

OUTCOME AND FOLLOW-UP

Despite stopping chemotherapy, her condition worsened and she developed general anasarca and severe pancytopenia. This was managed by blood

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and platelet transfusions and intravenous administration of granulocyte colony stimulating factor, tranexamic acid and antibiotics. On 5th day of TPN, she had vomiting which was followed by sudden cardiac arrest and the patient expired as she could not be resuscitated.

DISCUSSION

This case is highlighted because of the following management dilemmas it presented in a patient who had no previous history of hypersensitivity:

1. High-risk prognostic scoring in this case called for multidrug therapy but the patient had fatal outcome with use of only methotrexate. Was this correct line of management?
2. Should chemotherapy be initiated in the presence of fever? What were the other options?
3. Should methotrexate be stopped after second dose?
4. In presence of severe mucositis and associated pharyngeal and possibly laryngeal oedema, should an elective tracheostomy be considered for the patient despite the fact that the patient was conscious and on TPN?
5. Is it possible to identify patients who are likely to have serious/life-threatening drug reactions?

These questions were debated in retrospect within the unit and literature search was conducted to answer the questions raised. A summary is presented below.

No evidence could be located in literature to answer the question whether we were justified in starting single-agent therapy in the presence of a high-risk disease. Hysterectomy or radiotherapy was not considered as the patient was nulliparous. Methotrexate was chosen as it is the commonest drug used in cases of PTD. Myelosuppression and gastrointestinal mucositis are the primary toxic effects of methotrexate.¹ Generally mucositis appears 3–7 days after drug administration and precedes the pancytopenia by several days. In this patient also, mucositis preceded the myelosuppression but the interval between development of these two complications was very short and the pancytopenia followed a very rapid downward course despite discontinuation of chemotherapy. This could have been due to accumulation and persistence of the cytotoxic drug in the marrow. Early onset pancytopenia has been reported in a patient of rheumatoid arthritis on low-dose methotrexate therapy who had severe pancytopenia, poor kidney functions and abnormal coagulation parameters within 3 days of initiation of treatment.²

Malignancy itself is one of the three most important causes of fever of unknown origin with the other two being infection and collagen vascular disease. Considering the fact that fever can be a symptom of malignancy, we started her on chemotherapy despite her having low-grade fever as no focus of infection could be identified in this HIV-negative woman. In hindsight, the possibility of activation of a latent tubercular infection could have been considered as this is endemic in our country, but chest findings were attributed to trophoblastic disease and there was no prior history suggesting tuberculosis. The pathogenesis of activation of tuberculosis has been postulated to be mediated via immunosuppression occurring concomitantly with the malignancy.³

In this patient, paracetamol was administered prior to chemotherapy for fever. Unexpected severe bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate with non steroidal anti-inflammatory drugs.¹ They have been reported to elevate and prolong the serum concentration by reducing the renal tubular secretion of methotrexate, resulting in deaths due

to severe haematologic and gastrointestinal toxicity¹ but there were not many other alternatives available.

The patient developed oral lesions soon after the second dose of methotrexate. The decision to continue methotrexate was taken despite early appearance of oral ulcers owing to high-risk nature of disease which was considered more dangerous than the side effects of chemotherapy. Total leucocyte count had decreased from prechemotherapy values but the decrease was not of such a magnitude so as to warrant omitting the drug. It was not anticipated that this patient will have a fatal outcome as we frequently treat patients of PTD with methotrexate at our facility and had never encountered any such major problem. However, fatal methotrexate toxicity has been recorded in patients of autoimmune disorders⁴ where it may be attributed to altered cellular response, in parallel to altered immune response, despite the lower drug doses used.

Folinic acid administration has been recommended to diminish the toxicity of methotrexate and this should begin promptly if toxicity occurs as effectiveness of folinic acid in counteracting toxicity decreases as the time interval between methotrexate administration and folinic acid initiation increases.¹ However, this patient was already receiving folinic acid rescue even before the development of toxicity as is the protocol followed in our institution in all patients who are given methotrexate.

Whether an elective tracheostomy could have saved the patient is debatable. There is no evidence in literature to support or refute this decision which is likely to be individualised on the basis of clinical judgement. It was not anticipated that despite discontinuation of chemotherapy and intensive supportive treatment including totally eliminating oral intake, the mucositis would worsen to such an extent as to result in aspiration and choking. Possibly this patient had associated severe degree of oropharyngeal oedema that did not become apparent as the patient was on TPN. A timely tracheostomy may have altered the outcome but even the ENT specialists who had been consulted for nasal bleeding did not recommend it.

Methotrexate has a narrow therapeutic index and plasma level monitoring has been recommended to prevent toxicity. However, despite this recommendation, we have never monitored serum levels in our centre despite the large clinical experience with methotrexate. Later enquiries revealed that none of the major laboratories in India estimate plasma level of methotrexate.

In cases of massive overdosage, hydration and urinary alkalinisation may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules.¹ The possibility of dialysis was never considered during entire treatment course of our patient as her renal function parameters were normal throughout. However, review of literature revealed that high flux dialysis is effective in clearance of methotrexate from the body as neither standard haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination.¹ This maybe relevant in cases showing signs of toxicity, possibly attributable to persistently high serum levels of methotrexate.

It has been suggested that pharmacogenetical mechanisms are responsible for the toxicity of methotrexate as C677T polymorphism has shown a strong association with severe myelotoxicity^{5,6} and methylenetetrahydrofolate reductase polymorphisms were reportedly associated with methotrexate toxicity in Korean patients with rheumatoid arthritis.⁷ No pharmacogenetical studies were conducted for this patient but it may be worthwhile to consider them especially for those patients who have exaggerated toxicity.

It is possibly the identification of 'susceptible patients' that is crucial. However, literature search did not reveal how to

identify this 'susceptible patient' who is more likely to suffer from very severe toxicity and for whom drug level monitoring should be mandatory or an alternative drug therapy considered.

Learning points

- ▶ Methotrexate is widely used in repeated cycles as an effective chemotherapeutic agent despite potential for toxicity.
- ▶ Optimal monitoring and management of these conditions usually enables adequate treatment. It is difficult to quantify the frequency of monitoring which is generally done frequently, that is, twice weekly, monitoring of counts. The specifics may change depending on the patient's condition, for example, daily or alternate day evaluation of blood counts if they are very low ($<1000/\text{mm}^3$) or frequent blood urea evaluation if renal toxicity is suspected in view of oliguria. Very frequent testing is generally decided on case to case basis as warranted by the clinical situation.
- ▶ Plasma level estimation of methotrexate can be a useful tool in monitoring serious adverse effects.
- ▶ If severe untoward reactions occur shortly after initiation of treatment, blood or tissue sample for DNA and pharmacogenetical analysis can be considered.
- ▶ Further research should be conducted to enable a clinician to identify patients prior to initiation of therapy who are susceptible to suffer from hypersensitivity reactions and who may benefit from these specialised investigations.

Contributors RT and YMM are consultants in charge of the case. VV was resident in charge of the case. PKC was consultant pharmacologist whom the authors consulted and also helped in writing about the case.

Competing interests None.

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