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SHORT COMMUNICATION

Prolonged accumulation of high-dose methotrexate in a case with large liver cysts

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Abstract Methotrexate (MTX) has been documented to accumulate in "third spaces'' such as pleural effusions or ascitic fluids, resulting in delayed clearance and severe toxicity. We present a case of Burkitt lymphoma possessing large liver cysts, up to the size of 7 × 7 cm, wherein clearance of high-dose MTX was severely delayed, despite normal renal and liver functions. The serum MTX concentration was higher than 0.1 μM on day 12 and remained at toxic levels, higher than 0.01 μM, even on day 25, resulting in severe neutropenia, anorexia, and diarrhea. It was presumed that MTX accumulated in the liver cysts over time and was slowly released back into the serum, resulting into prolonged high serum MTX concentrations. High dose of MTX in patients with large liver cysts induces severe toxicity by virtue of MTX accumulation in the cysts and its subsequent delayed clearance.

Keywords Methotrexate · Accumulation · Delayed clearance · Large liver cyst

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Abbreviations

MTX	Methotrexate
CT	Computed tomography
Ara-C	Cytarabine
LV	Leucovorin
BUN	Blood urea nitrogen

Introduction

Methotrexate (MTX) has been documented to accumulate in "third spaces'' such as pleural effusions or ascitic fluids, resulting in delayed clearance and severe toxicity [1, 2]. We report a case of Burkitt lymphoma possessing large liver cysts, wherein the clearance of high-dose MTX was severely delayed, resulting in toxic serum concentrations even after 25 days, suggesting sequestration of MTX in the liver cysts.

Case report

A 57-year-old Japanese male suffered from dull pain of the left hypochondriac region in June 2006 and experienced body weight loss of 11 kg (14% of his body weight) during the previous 3 months. Computed tomography (CT) revealed an intra-abdominal bulky mass, with a diameter of 14 × 8 cm, originating from the left adrenal gland and extending to the left kidney, perigastric space, and paraaortic area. Furthermore, multiple liver cysts, up to 7 × 7 cm in size were also detected by CT (Fig. 1). Echo-guided needle biopsy diagnosed the bulky mass as Burkitt lymphoma. Besides the intra-abdominal site, all other sites were negative for the disease, indicating a stage IIIA disease, according to the system of Murphy et al. [3]. Since

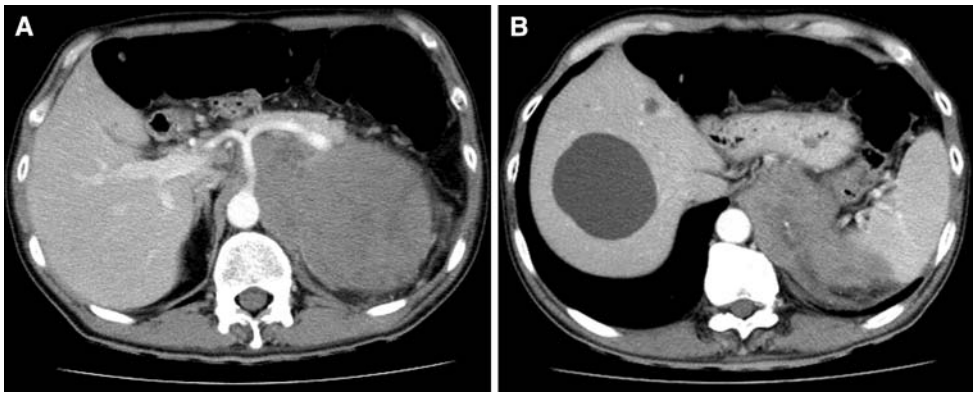

Fig. 1 CT scans of a patient with Burkitt lymphoma. **a** An intra-abdominal bulky mass with diameters of 14 × 8 cm, which originated from the left adrenal gland and extended to the left kidney, perigastric space, and para-aortic area. **b** Multiple liver cysts. The largest size was 7 × 7 cm

the lymphoma was CD20-negative, anti-CD20 monoclonal antibody, Rituximab, was not used for therapy. After the first cycle of hyper-CVAD regimen, consisting of cyclophosphamide 300 mg/m^2 i.v. twice daily on days 1–3, vincristine 1 mg i.v. on day 11, doxorubicin 50 mg/m^2 i.v. on day 4, and dexamethasone 40 mg on days 1–4 and days 11–14, CT revealed that the size of the bulky mass had decreased to 9 × 6 cm [4]. Twenty-seven days after the start of hyper-CVAD therapy, the second cycle of chemotherapy consisting of high-dose MTX and cytarabine (Ara-C) was begun. On day 1, 1 g/m^2 of MTX was administered intravenously. As a loading dose, 200 mg/m^2 of MTX was infused for 2 h and the remaining 800 mg/m^2 was infused over 18 h. Four doses of Ara-C 1.5 g/m^2 i.v. was administered twice daily on days 2 and 3. To promote excretion of MTX, intravenous hydration was performed with 3 l of fluid. For urine alkalinization, 134 meq per day of sodium bicarbonate was continuously infused and 250 mg i.v. acetazolamide was infused twice daily. To adjust urine pH higher than 7, additional doses of sodium bicarbonate and acetazolamide were given if necessary. To reduce MTX toxicity, 50 mg i.v. calcium folinate (Leucovorin, LV) was given 36 h after the start of MTX infusion, followed by 15 mg i.v. administration every 6 h. In most patients receiving high-dose MTX, serum MTX levels are expected to decrease below 1.0 μM in 48 h and 0.1 μM in 72 h, respectively. Also in our case, serum MTX level, which was measured by the fluorescence polarization immunoassay method with 0.02 μM as the lower limit of quantification, decreased to 0.63 μM after 48 h of the start of MTX infusion (day 3) but remained 0.25 μM, which was higher than expected, after 72 h (day 4). The elimination of MTX was further delayed, and its concentration slowly fell to 0.13 μM on day 7. However, it transiently rose to 0.19 μM on day 9. After that, it gradually fell to 0.1 μM on day 12 and below 0.02 μM on day 25 (Fig. 2). The terminal half-life for the decline of serum MTX concentration calculated during the period from 48 h after the start of MTX infusion (days 4–7) was 76.3 h. And the half-life (77.7 h) remained unchanged after day 9. On day 5, when the MTX level was

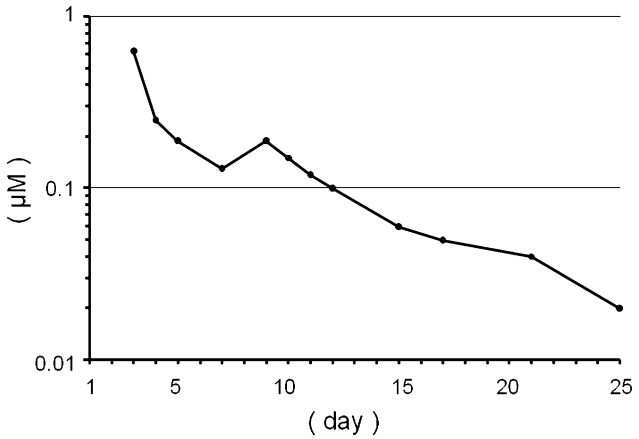

Fig. 2 Time curves of serum methotrexate (MTX) concentrations following 20-h infusion of 1 g/m^2 MTX on day 1 in a Burkitt lymphoma patient with large liver cysts

0.19 μM, the 3 l of intravenous hydration was switched to 1 l of intravenous hyperalimentation to improve the patient's nutrition status. The urine alkalinization with sodium bicarbonate and acetazolamide for promoting excretion of MTX was continued until day 12, when MTX level decreased to 0.1 μM. Mild liver dysfunction, probably due to hyper-CVAD chemotherapy, was observed before MTX infusion (serum levels of ALT and bilirubin were 138 IU/l and 0.45 mg/dl, respectively), but it did not worsen after MTX infusion. Before MTX infusion, serum levels of blood urea nitrogen (BUN) and creatinine were 10.7 and 0.59 mg/dl, respectively, and creatinine clearance was 75.6 ml/min. After MTX infusion, serum levels of BUN and creatinine did not increase to abnormal levels (peak levels were 18.7 and 0.89 mg/dl, respectively). Furthermore, CT revealed no fluid collections such as pleural effusions and ascitic fluids before MTX infusion, and a chest roentgenogram revealed no pleural effusions after MTX infusion. The patient did not suffer from ileus. The delayed clearance of MTX was therefore unexpected. Although LV rescue at the same dose of 15 mg i.v. every 6 h was continued until day 12, when MTX level decreased

to 0.1 μM, the patient subsequently suffered from severe anorexia and diarrhea. Additionally, enterococcal bacteremia occurred during severe neutropenia of less than 100/μl, which persisted for 15 days. And the time to recovery of neutrophil count to more than 500/μl was as long as 27 days, with a median of 17 days [4]. In the later cycles of chemotherapy MTX was omitted, since its toxicity was expected to become very severe. After administration of Ara-C at the same doses as in the second cycle, neutropenia was so mild that the severe neutropenia observed with high-dose MTX and Ara-C was attributed mainly to MTX.

Discussion

Two cases possessing large cysts and receiving systemic MTX therapy have been previously reported. The first case with an ovarian cyst received eight MTX 25 mg i.v. injections, following which the cyst was removed on the same day [5]. The intra-operative MTX level in the removed cyst was higher than that in the serum, 0.31 and 0.16 μM, respectively. The second case with a cystic anaplastic ependymoma received a high-dose MTX 5 g/m^2 i.v. by infusion for 24 h, following which the MTX concentration was monitored both in the serum and in the cystic fluid drained through a catheter in the tumor [6]. Thirty hours after the start of MTX administration, the MTX concentrations in the serum decreased to 0.1 μM but remained higher than 1 μM in the cystic fluid even after 120 h. These two cases demonstrated MTX accumulation and retention in the cysts and suggested a possibility of MTX retention in large liver cysts, such as in our case.

In our present case, high-dose MTX therapy resulted in serum MTX concentrations higher than 0.1 μM until day 12, remaining higher than a toxic level of 0.01 μM, for more than 3 weeks despite normal renal functions [7]. After intravenous infusion, MTX disappearance from plasma is triphasic. The first and second half-lives reflect distribution and renal clearance of MTX, respectively. The terminal half-life, which generally begins 30–48 h after high-dose MTX infusion, has been reported to be 10 h [8, 9]. It reflects the enterohepatic circulation of MTX and has been reported to be prolonged in cases suffering from gastrointestinal obstruction [10]. Furthermore, it has been reported to become longer in cases possessing "third spaces'' such as pleural effusions and ascetic fluids [1, 2]. In our case, the terminal half-life, which was calculated from 48 h after the start of MTX infusion, was severely prolonged to 76.3 h. Since our case revealed only mild elevation of serum ALT levels, no elevation of bilirubin levels, and did not suffer from ileus, the enterohepatic circulation of MTX was considered to be intact. Therefore, a prolonged terminal half-life of MTX in our case suggested the accumulation and retention of MTX in the "third spaces," the liver cysts.

Recently, a case of acute lymphoblastic leukemia that experienced pleural effusions, ascites, and renal failure during the weeks after treatment with high-dose MTX (1.63 g/m^2 i.v. over 24 h) was reported [11]. Following infusion, the plasma MTX concentrations decreased to undetectable levels on day 9 and gradually increased to a peak of 0.72 μM on day 15 as the renal function declined. This unusual phenomenon can be explained by a pharmacokinetic model suggesting the accumulation and retention of MTX in the "third space'' at the time of treatment, followed by subsequent release into the serum, and elimination via the renal system. Also in our case, the MTX levels transiently increased from 0.13 μM on day 7 to 0.19 μM on day 9. However, the half-life of MTX after day 9 (77.7 h) did not change from that before day 9 (76.3 h), indicating that clearance of MTX, which is mainly through the renal system, did not change. Therefore, it was speculated that the release of MTX from the liver cysts into the serum increased between days 7 and 9. CT scan performed on day 32 did not reveal the change of fluid volume in the cysts compared with that before MTX infusion, indicating the changes in diffusion status of MTX into the cysts. However, the detailed mechanism for the changes was unknown.

Liver cysts are common. High-dose MTX therapy can induce severe toxicity if the liver cysts are large, as was seen in this case. Therefore, surgical removal or drainage of large liver cysts should be considered prior to high-dose MTX therapy.

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