

## BRIEF REPORT

# Successful Rescue by Oral Cholestyramine of a Patient With Methotrexate Nephrotoxicity: Nonrenal Excretion of Serum Methotrexate

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High dose methotrexate (MTX) therapy is routinely used and is an effective treatment for osteosarcoma [1]; high serum concentrations have been related to a good prognosis [2]. Simultaneous administration of anti-inflammatory drugs and antibiotics can inhibit the renal elimination of MTX [3], and repeated chemotherapy also causes elevation due to renal dysfunction [4,5]. However, persistent high serum concentrations of MTX because of delayed elimination of the drug on initial treatment for osteosarcoma is very rare. Our experience with such a problem and its successful control with oral cholestyramine is therefore of interest.

Our patient was an eleven-year-old boy who was referred to our hospital complaining of pain in his right knee joint in October, 1998. Plain roentgenograms showed an osteoblastic lesion in the proximal metaphysis of the tibia, and the serum alkaline phosphatase level was elevated to twice the normal level. Other laboratory data including renal function were uniformly unremarkable. Exploratory surgery was performed in October 1998, and the histology was of an osteoblastic type osteosarcoma. Fourteen grams of high dose methotrexate (MTX) therapy (12g/m<sup>2</sup>) combined with 1.2mg of vincristine (VCR) were administered one week after the operation. The combined use of MTX and VCR was based on the fact that VCR augments MTX transport into tumor cells [1]. The urine pH decreased to 6.5 for a few hours after the administration of MTX. No problems were seen regarding urine pH or volume after that time. However, the serum MTX concentration at 48 hours after the administration was 222.2μmol/L. Laboratory data revealed glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase and serum creatinine to be extremely elevated with hypertension of >150mmHg systolic and >110mmHg diastolic pressure, respectively (Fig. 1A and B). We immediately started massive rescue with initial 600mg of leucovorin every three hours maintaining more than 100ml of urine volume and urine alkalization. The dosage of leucovorin

was decided on the basis of the serum MTX level and was continued until this dropped below 0.1μmol/L [2]. Since the concentration after 72 hours was still 103.2μmol/L, oral cholestyramine (2g q. 6 hours) was also given. This depressed the serum concentration of MTX smoothly to 12.9μmol/L at 125 hours (Fig. 2). However, due to the prolonged high level of serum MTX, the level of consciousness was low and the patient suffered slight convulsions of the upper extremities on day 5 (125 hours). A plasma exchange was performed to help lower the serum MTX (concentrations before and after plasma exchange were 12.9 and 8.6μmol/L, respectively). A 200ml blood transfusion was performed on day 10 because the Hb was 7g/dl. Fourteen days after the MTX administration, the serum MTX level had decreased 0.21μmol/L and his general condition had improved except for incipient ileus due to cholestyramine. Both cholestyramine and leucovorin rescue were stopped 17 and 24 days after the MTX administration, respectively, since the serum MTX level had dropped to below 0.1μmol/L on day 15 (Fig. 2). MTX could not be detected in the serum 30 days after it was first administered. Urine volume had been kept at more than 100ml per hour and urine pH was alkaline during the entire treatment period. Chemotherapy could not be continued after sur-

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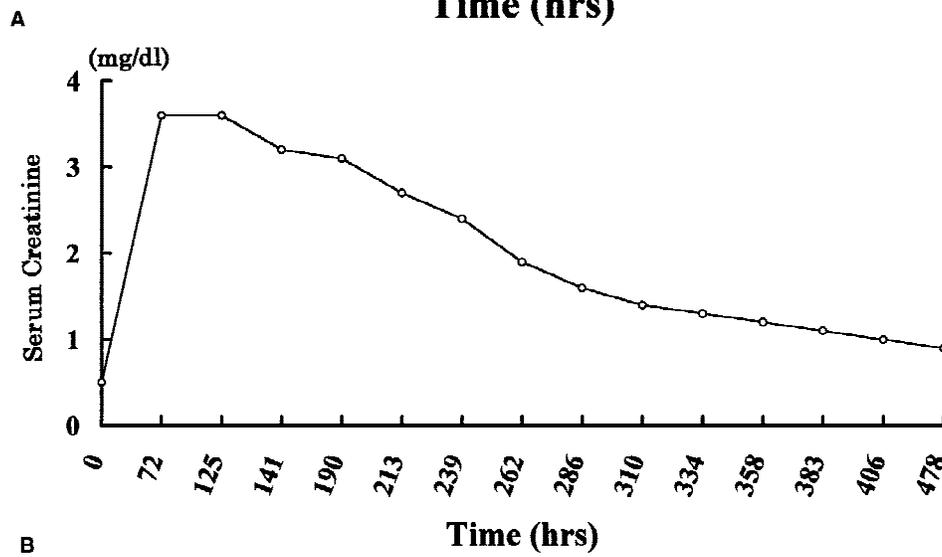
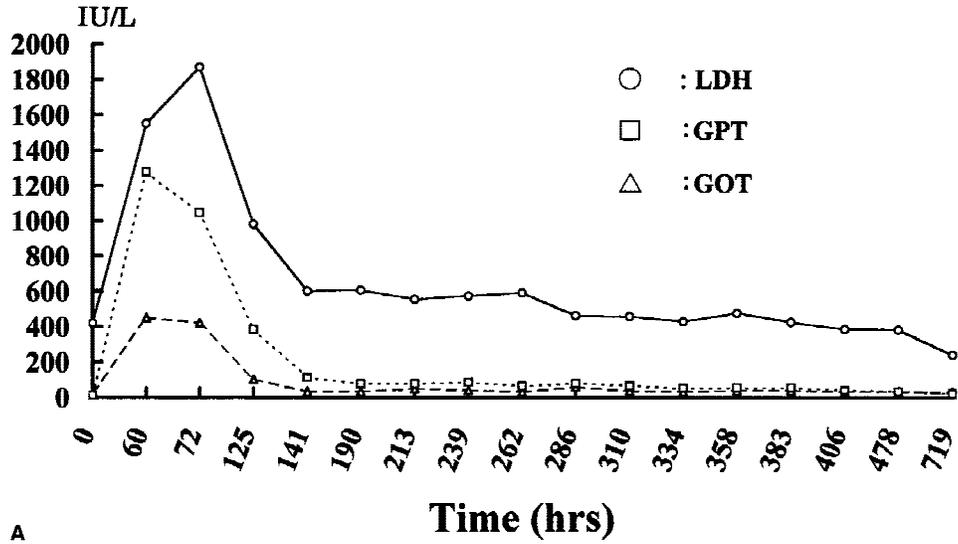


Fig. 1. Biochemical data throughout the treatment course. A: Liver function, B: Renal function. ○: LDH, □: GPT, △: GOT

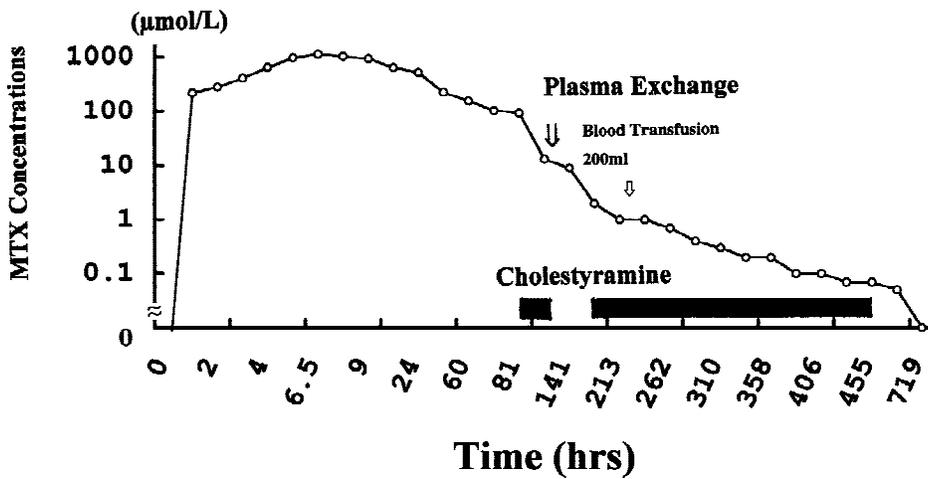


Fig. 2. Serum MTX concentrations throughout the treatment course.

gery in December 1998 because permission could not be obtained from the family. No residual problems have been encountered in the six months since the operation when this report was prepared.

### Discussion

As the serum MTX concentration increases, renal MTX clearance decreases [3]. Based on this fact, the greater the dose administered, the longer drug elimination may be delayed. This is the case even if no intrinsic renal dysfunction exists, or even if other drugs that inhibit the renal excretion of MTX are not co-administered [4]. Our patient exhibited urinary acidosis for a few hours just after high dose MTX was infused. There were no other complicating factors. However, the 222.2  $\mu\text{mol/L}$  serum MTX concentration observed 48 hours after infusion was extremely high compared to values in previous reports [5-8]. Thus some other factors also might have affected the elimination of MTX in our patient, although what they might have been remains unclear.

Little decrease of serum MTX concentration is seen in MTX-induced nephrotoxic conditions, since the kidney is the main elimination organ [4,5]. Hemodialysis or plasma exchange (PE) are then necessary to eliminate the drug from the serum. However, these approaches are not without controversy [5,6,8]. In our case, MTX concentrations before and after PE were 12.9 and 8.6  $\mu\text{mol/L}$ , respectively; so that the effect was minimal.

Bile MTX concentrations in patients receiving high dose therapy are much higher than those in the serum [5]. Enterohepatic circulation is therefore a second elimination pathway [5,7]. Cholestyramine is an anion exchange resin that binds MTX in vitro [7], and when given orally also in the enterohepatic circulation, thus facilitating MTX excretion [7]. As demonstrated in our patient (Fig. 2), cholestyramine can dramatically reduce serum MTX concentrations without any side effects. This treatment is

therefore a simple, useful means of controlling serum MTX under nephrotoxic conditions. As was done here, administration of high dose leucovorin also plays an important role in achieving successful rescue [7]. Clearly, regular measurement of serum MTX to concentrations is very important to prevent lethal side effects and measures allow strenuous rescue to be commenced as soon as toxic conditions become manifest.

### ACKNOWLEDGMENTS

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