Diffuse Hepatic Uptake of Technetium-99m Methylene Diphosphonate in a Patient Receiving High Dose Methotrexate

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A child with diffuse accumulation of [^{99m}Tc]MDP in the liver on a bone scan, at the time of study the patient had a severe, but reversible, hepatic dysfunction on the basis of methotrexate toxicity. Visualization of the liver on skeletal scintigrams can be a consequence of high-dose methotrexate therapy, as there was no other explanation for this unusual finding.

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Although an unusual phenomenon, hepatic uptake of technetium-99m- (^{99m}Tc) labeled bone scanning agents has been reported in hepatic metastases (*1,2*), hypercalcemic states (*3,4*), hepatic necrosis (*5-8*), amyloidosis (*9*) and secondary to faulty radiopharmaceuticals. In the present case we describe a patient that does not appear to fit into any of the above categories. The phenomenon occurred in the setting of transient severe hepatic dysfunction.

CASE REPORT

The patient was a 9-yr-old, 24 kg girl. Thirteen months prior to the current study she had undergone an amputation above the right knee for osteosarcoma of the femur. A bone scan had been performed 5 mo after surgery, this did not show either focal skeletal abnormalities or evidence of tracer uptake in the right upper quadrant (Fig. 1). The patient had received postoperative adjuvant chemotherapy comprising bleomycin, cyclophosphamide, dactinomycin, cisplatinum and methotrexate.

On the day prior to study, blood was drawn for CBC, serum chemistry and liver function tests (Table 1). The patient received 11.4 g (475 mg/kg) of i.v. methotrexate with allopurinol. At the time of bone scanning the next day the patient had symptoms of methotrexate toxicity with fever and nausea. The bone scan on this occasion while not demonstrating evidence of bony metastases showed diffuse hepatic uptake (Fig. 2).

Serial liver function tests demonstrated marked hepatic dysfunction associated with a doubling of serum creatinine, an initial leucocytosis followed by a degree of leukopenia.

The patient was given folinic acid and over 10 days the liver function returned to normal and she was able to be discharged.

DISCUSSION

The patients' clinical course and laboratory results indicate a period of severe, reversible hepatic dysfunction. This is an expected consequence of high-dose methotrexate therapy. Liver atrophy, necrosis, fatty change, and periportal fibrosis have all been reported secondary to this agent (*10*). Given intravenously, methotrexate peak serum levels occur within 30-60 min. Our patient received 200-400 times the previous standard methotrexate dosage. The rationale for the use of these regimes is to overcome deficiencies of carrier mediated membrane transport thereby achieving an excess of intracellular unbound drug. Polyglutamation of methotrexate in the liver increased its polarity and accounts for the prolonged retention of the drug in hepatocytes after a single dose. These polyglutamated forms have substantially greater affinity for enzymes such as thymidylate synthetase than does the monoglutamated form. The inhibition of protein synthesis by methotrexate leads to depressed cellular respiration. The cell membrane loses its functional integrity (*11*) as energy stores are depleted, this allows the passive egress of K^+ and the passive ingress of Na^+ and Ca^{2+}. The intracellular Ca^{2+} forms complexes in the mitrochondria, this is a possible explanation for MDP localization in tissue necrosis and lesser degrees of cellular injury.

Diffuse hepatic uptake of bone scanning agents has

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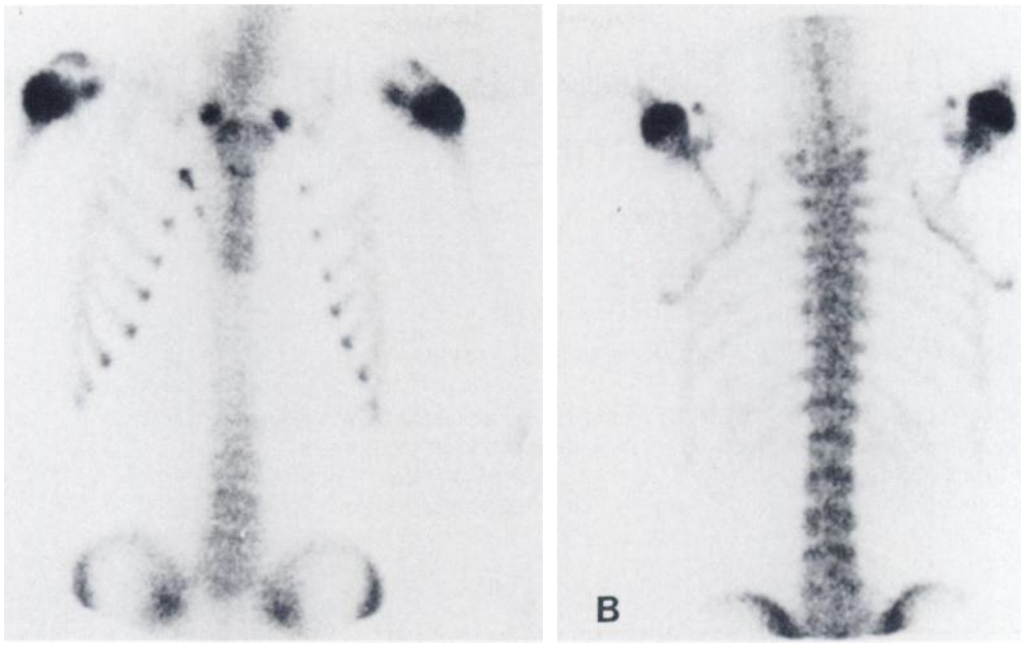

FIGURE 1
A, B: Anterior and posterior images of thorax and abdomen. On this occasion no hepatic uptake was demonstrated. The activity in Fig. 1A in the region of the second right costal cartilage indicates the injection site.

been described in acute massive liver necrosis. Of the four cases we found in the literature, three involved pyrophosphate and the last [^{99m}Tc]hydroxymethylene diphosphonate. In all four cases uptake was associated with a fatal outcome. Indeed, Hakim et al. concluded that hepatic uptake equated with necrosis and had, therefore, a grave prognosis. Our patient indicates that this is not necessarily the case.

In a large review (*1*) of diffuse thoracoabdominal activity on bone scanning, eighteen cases were found in 1,100 cases reviewed. Seven of these were due to metastatic liver disease—in each case from a primary colonic tumor, six were due to accumulation in pleural effusions and two cases were due to metastatic lung tumors, one to spleen and the other to the chest wall. The three remaining cases were due to defective radiopharmaceuticals with resultant formation of colloidal substances. While we did not perform chromatography on the agent we used, two other patients had bone scans performed on the day the subject of this report was studied. All three doses were drawn from the same vial, the other two patients did not demonstrate hepatic uptake.

TABLE 1
Laboratory Values Obtained During Admission*

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 8
WBC (×10^3 perml.)	8.9	26.9	22.2	4.7	2.8	
Ca^{2+} 9–11 mg%	8.9	8.6		9.3	9.6	
Po_4^{3-} (3.5–4.5 mg%)	2.4	3.5		3.5	3.5	
Creat (0.5–0.8 mg%)	0.7		1.4	1.4	1.5	1.2
Total bili (0–1.3 mg%)	0.3		2.4	2.2	1.3	
SGOT (2-21 mU/ml)	24			213	134	
SGPT (2-22 mU/ml)	25		779	153	125	
LDH (0-88 mU/ml)	123					
SAP (50-125 mU/ml)	206		266	270	272	

* Serial laboratory values demonstrating evidence of acute hepatic, renal and bone marrow toxicity secondary to methotrexate therapy.

Conceivably, extensive metastatic disease of liver could give rise to diffuse hepatic uptake and we did not exclude this in our patient. However, the near normal initial liver function tests in our patient (Table 1) make extensive metastatic replacement unlikely.

Soft-tissue uptake of bone scanning agents is well accepted in local and generalized hypercalcemic and/or hyperphosphatemic states (*3,4,11*). In our patient the serum calcium and phosphate levels were not elevated and the pretreatment renal function was within normal limits.

Amyloid has been reported to accumulate [^{99m}Tc] methylene diphosphonate (MDP) (*9*). In the absence of a liver biopsy we cannot exclude this as an explanation for our patient's findings. It seems, however, unlikely that an indolent process such as amyloidosis could progress from no uptake (Fig. 1) to diffuse hepatic uptake (Fig. 2) over a period of 8 mo.

The use of high-dose methotrexate regimes is a recent development. If, as seems likely, reversible hepatic dysfunction secondary to methotrexate toxicity was responsible for the abnormal uptake seen in our patient, nuclear medicine physicians should be aware of this possibility. If high-dose regimes become routine, the phenomenon may be seen more frequently.

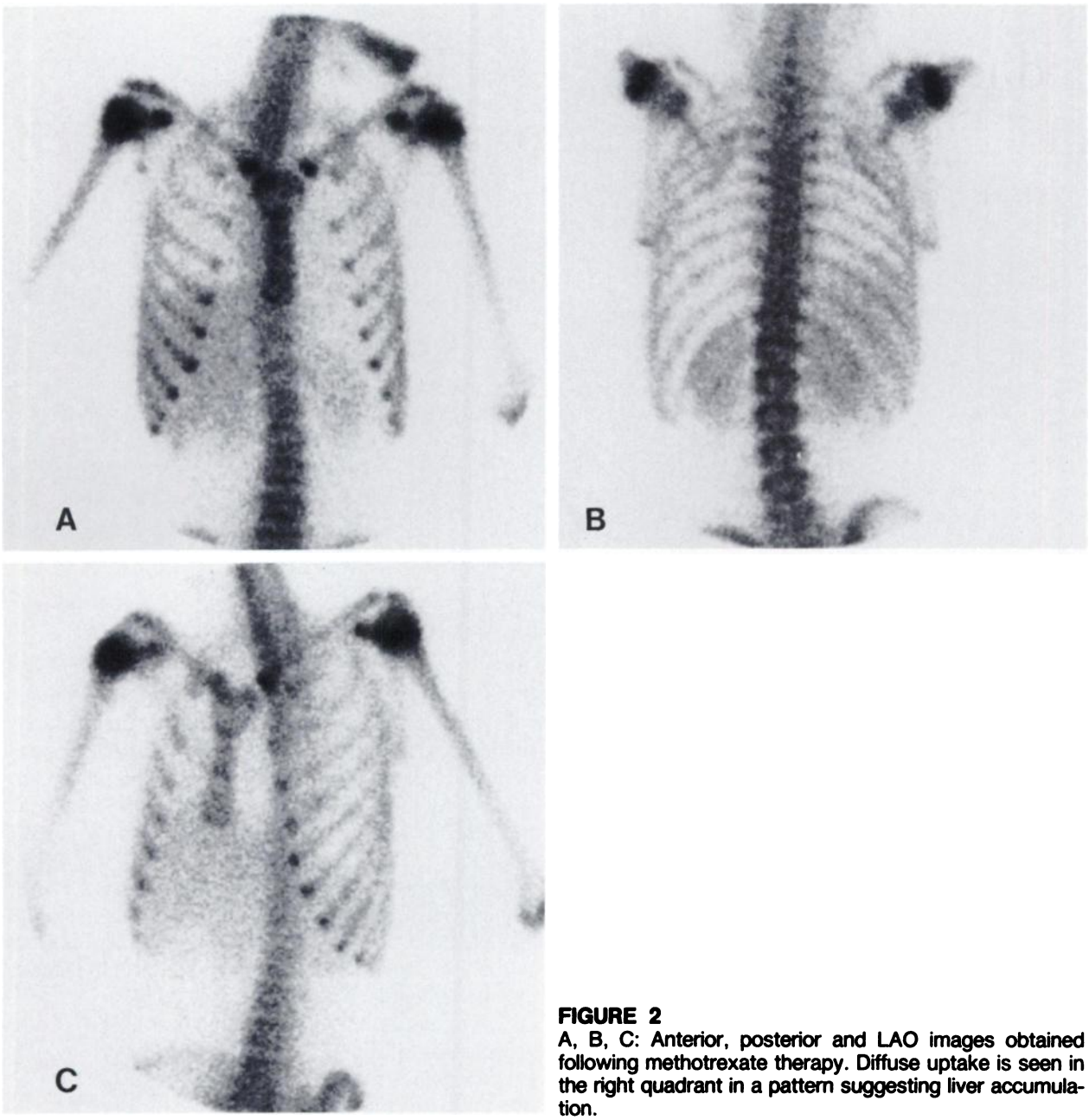

FIGURE 2
A, B, C: Anterior, posterior and LAO images obtained following methotrexate therapy. Diffuse uptake is seen in the right quadrant in a pattern suggesting liver accumulation.

REFERENCES

1. Shih WJ, Coupal JJ, Domstad PA, et al. Diffuse thoracoabdominal radioactivity seen in bone imaging. *Clin Nucl Med* 1986; 11:254–257.
2. Shih WJ, Domstad PA, Lieber A, et al. Localization of 99m-Tc-HMDP in hepatic metastases from colonic carcinoma. *Am J Roentgenol* 1986; 146:333–336.
3. Dudezak R, Angelberger P, Kletter K, et al. Transient accumulation of 99m-Tc-MDP in the liver. *Eur J Nucl Med* 1980; 5:189–191.
4. Heck LL. Extra-osseous localization of phosphate bone agents. *Semin Nucl Med* 1980; 10:311–313.
5. Hakim S, Kwang GJ, Baevmler GR. Visualization of acute hepatic necrosis with a bone imaging agent. *Clin Nucl Med* 1985; 10:697–698.
6. Hansen S, Stadalnik RD. Liver uptake of 99m-Tc-pyrophosphate. *Semin Nucl Med* 1982; 7:89–90.
7. Guiberteau MJ, Potsaid MS, Mckusick KA. Accumulation of 99m-Tc-diphosphonate in four patients with hepatic neoplasm. *J Nucl Med* 1976; 17:1060–1061.
8. Lyons KP, Kuperus J, Green HW. Localization of 99m-Tc-pyrophosphate in the liver due to massive liver necrosis. *J Nucl Med* 1977; 18:550–552.
9. Varek JA, Bukowski RM. Hepatic uptake of 99m-Tc labelled diphosphonate in amyloidosis. *J Nucl Med* 1977; 18:1086–1088.
10. *The pharmaceutical basis of therapeutics.* Goodman LS, Gilman AG, Rall TW, et al., eds. New York: Macmillan, 1985: 1263–1266.
11. *Pathologic basis of disease.* Robbins SL, Cotran RS, Kumar V, eds. Philadelphia: Saunders, 1984: 13–14.
12. Larsen MJ, Adcock KA, Satterlee WG. Dermal uptake of technetium—99m-MDP in calcinosis cutis. *Clin Nucl Med* 1985; 10:780–782.