Diffuse Liver Uptake of Technetium-99m-MDP Bone Scan Due to Hepatotoxicity Secondary to Methotrexate Therapy

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Bone scintigraphy is a common and sensitive modality for detecting either primary or secondary bone malignancy. Sometimes additional information could be found besides skeletal abnormalities. An eleven-year-old female who was diagnosed osteogenic sarcoma underwent technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) whole body bone scan to survey the distant metastasis status. Diffuse liver uptake of ^{99m}Tc-MDP was noted incidentally. According to the clinical history, high dose methotrexate was given one day prior to bone scan performed and the laboratory data showed marked elevation of serum alanine aminotransferase (GPT). Therefore, methotrexate-induced hepatotoxicity is considered to be the cause of the diffuse liver uptake of ^{99m}Tc-MDP. The mechanism of extraskeletal uptake of bone-seeking radiopharmaceuticals in damaged, inflamed, neoplastic or necrotic tissues may be due to dystrophic calcification and is associated with cell injury and calcium deposition. Owing to the acute hepatotoxicity corresponding to laboratory and clinical findings, the protocol was adjusted and the neoadjuvant chemotherapy was completed smoothly. This case demonstrates an example of unusual diffuse hepatic uptake of ^{99m}Tc-MDP resulted from the hepatotoxicity and for patients that are receiving chemotherapy, the regimen may need adjustment if the hepatotoxicity is presented.

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Bone scan, commonly used to detect bone metastatsis, sometimes provides additional useful information other than bone lesions. Diffuse liver uptake of bone-seeking radiotracers, which can be due to a variety of etiologies, is one of the unusual patterns of extra-osseous uptake. In the following case, we report an 11-year-old female who was diagnosed osteogenic sarcoma and received neoadjuvant chemotherapy with methotrexate in our hospital. ^{99m}Tc-MDP whole body bone scan performed for distant metastasis survey incidentally showed diffuse liver uptake of ^{99m}Tc-MDP.

Case Report

An 11-year-old female had complained about left knee pain for a month when she visited our hospital. A palpable fixed hard mass was noted at medial aspect below her left knee joint. Prior to hospitalization in our hospital, ostectomy with biopsy was performed at St. Mary's Hospital and osteogenic sarcoma at left proximal tibia was diagnosed. Therefore, the patient was transferred to our hospital for further evaluation and treatment. ^{99m}Tc-MDP whole body bone scan was performed for distant metastasis survey and revealed there was a photopenic area corresponding to the clinically palpable tumor whereas intense diffuse uptake of radioactivity in the liver was also noted (Figure 1). Tracing back to her clinical hospitalization course, preoperative neoadjuvant chemotherapy with methotrexate and leucovorin was planed for treatment of osteogenic sarcoma. Intravenous

drip of methotrexate (12 g/m^2) in D5W was given just one day before the bone scan was performed. Laboratory data showed markedly elevated serum GPT value (3534 U/L) which was within normal limit at the time of admission (16 U/L). Methotrexate serum concentration and GPT value were monitored in the following days (Figure 2) and the GPT value was at its peak with the highest serum concentration of methotrexate and then declined corresponding to the decrease of serum methotrexate concentration. Excluding other common causes of diffuse liver uptake, we impressed that the unusual pattern of diffuse liver uptake was resulted from high-dose methotrexate-induced acute hepatotoxicity. The chemotherapy protocol was then adjusted to using cisplatin plus epirubicin instead of methotrexate in consideration of the acute hepatotoxicity. The first course of the neoadjuvant chemotherapy was finished smoothly and the patient was discharged under stable condition. The tumor was excised two months later with other courses of pre- and post-operative chemotherapy. The patient is 15-year-old now and neither metastasis nor significant abnormal liver function is found.

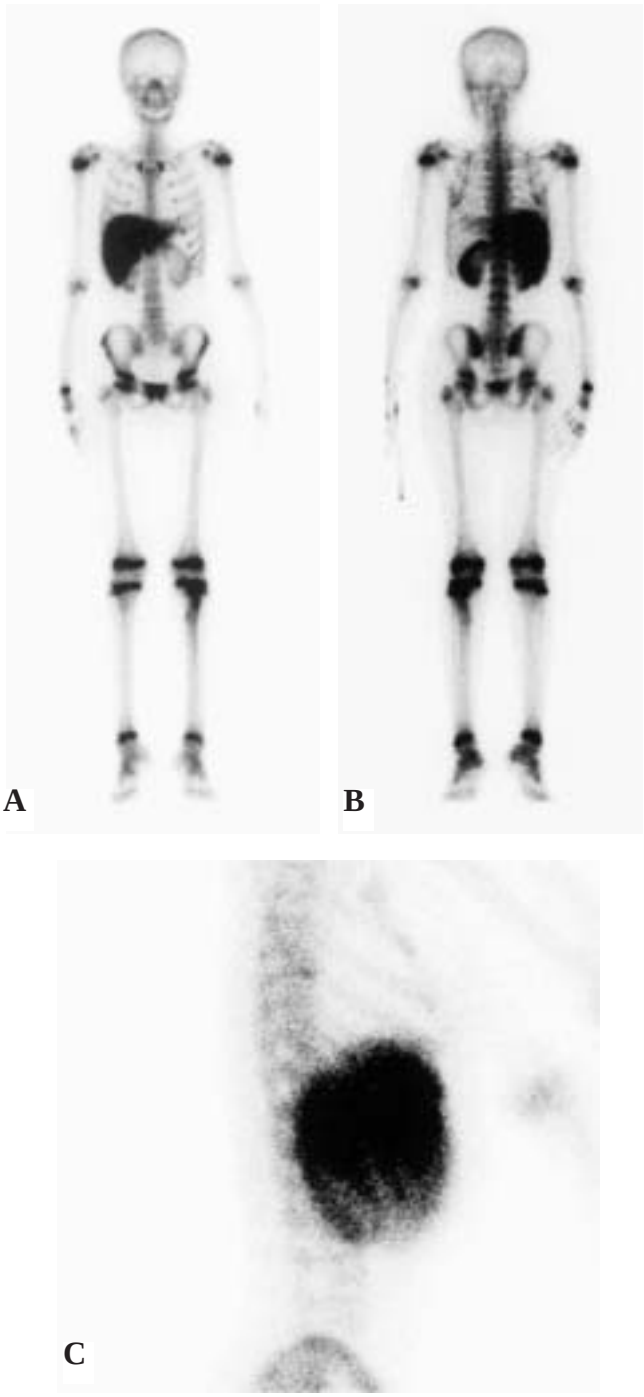
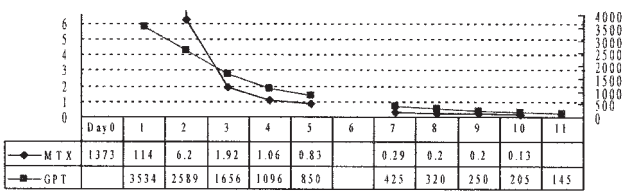


Figure 1. ^{99m}Tc-MDP whole body bone scan: (A) anterior view, (B) posterior view, and (C) right lateral view, shows a photopenic area in the medial aspect of left proximal tibia with mildly increased tracer uptake in the margins with no definite evidence of distant bone metastasis whereas there is intense diffuse uptake of radioactivity in the liver.

Discussion

High dose methotrexate and doxorubin were first used to demonstrate significant regression of osteosarcoma since early 1970s [1]. Preoperative chemotherapy can shrink the tumor size and permit limb-salvage surgery [2]. Our patient was scheduled excision of the tumor at left proximal tibia and neoadjuvant chemotherapy with methotrexate was performed. Methotrexate is a folic analogue, and binds tightly to dihydrofolate reductase, blocking the reduction of dihydrofolate to its active form, tetrahydrofolic acid. Tetrahydrofolic acid is essential for the one carbon transfer reaction required for the synthesis of thymidylate, a precursor to DNA, and the purines adenosine and guanosine, precursors of both DNA



	Day 0	1	2	3	4	5	6	7	8	9	10	11
MTX	1373	114	6.2	1.92	1.06	0.83		0.29	0.2	0.2	0.13	
GPT		3534	2589	1656	1096	850		425	320	250	205	145

Figure 2. Serum methotrexate (MTX) concentration checked statim at finish of MTX administration (day 0) and monitored with GPT value for 10 days. Units: MTX (μmoL/L); GPT (U/L)

and RNA. In standard doses, methotrexate is excreted unchanged in the urine. In high doses, it is partially metabolized by the liver to 7-hydroxymethotrexate [3]. When used in high doses with leucovorin rescue, as our patient was given, methotrexate diffuses into both normal and malignant cells. Leucovorin enters normal cells, blocking the effects of methotrexate. Serum aminotransferases elevation following methotrexate therapy has been reported in treating different kinds of diseases, such as gestational trophoblastic disease [4], acute lymphoblastic leukemia [5], rheumatoid arthritis [6] and a case of osteosarcoma [7] as well. The elevation was transient and reversible as that happened to our patient.

Diffuse liver uptake of ^{99m}Tc-labeled bone scanning agents has been reported in cases of diffuse liver damage due to a variety of etiologies including massive hepatic necrosis associated with Budd-Chiari syndrome [8], amphotericin B toxicity [9], cocaine hepatotoxicity [10], acute hypoxic hepatitis [11], ischemic hepatopathy [12], and osteosarcoma treated with high-dose methotrexate chemotherapy [7]. In the last paper mentioned above, the osteosarcoma patient was also treated with methotrexate, and diffuse liver uptake of ^{99m}Tc-MDP was noted on bone scan performed also one day after methotrexate was given. The authors concluded that it was a consequence of high-dose methotrexate therapy based on clinical course and laboratory data. The abnormal liver function returned to normal after palliative treatment as was seen in our patient. Therefore, reversible transient hepatotoxicity induced by high-dose methotrexate therapy and resulting in diffuse ^{99m}Tc-MDP uptake on bone scan which happened to our case is compatible with the previous study.

Uptake of diphosphonate in hydroxyapatite, in immature collagen and by enzyme receptor binding are the mechanisms of bone uptake. However, extraosseous uptake of diphosphonate can also occurred in dystrophic, metastatic and heterotopic calcification. The dystrophic calcification involves the deposition of calcium in damaged tissues. Accumulation of diphosphate in almost any damaged tissue could be predicted. Diffuse liver uptake of diphosphonate was considered to be resulted from hepatic necrosis and other liver damage owing to different etiologies. Hypothesized mechanisms include that phosphate localizes within the mitochondria of damaged cells in a complex with hydroxyapatite [13,14], phosphate binds to soluble protein resulting from denatured macromolecules [15], deposited with calcium on the mitochondria or attaches to calcium already deposited by replacing other anions [16]. Although the actual mechanism is not certain, the bone-seeking radiopharmaceuticals accumulation in damaged tissues is observed in some reports.

Serum aminotransferases are the most common laboratory data to evaluate the liver function. In our case, the GPT value was normal before methotrexate administration, reached highest peak just after methotrexate was given and declined as the serum concentration went down. Therefore, a reversible, transient hepatotoxicity induced by methotrexate happened to our patient was considered. The bone scan was performed at the next day methotrexate was given, at which time the liver function was most impaired. The diffuse hepatic uptake of ^{99m}Tc-MDP was probably associated with the transient liver hepatotoxicity after methotrexate because other common causes of diffuse liver uptake of diphosphate such as a prior ^{99m}Tc-sulfur colloid scan or radiopharmaceutical preparation problems were excluded and no other factors that could result in diffuse liver uptake were compatible with that in our patient. It seemed the only explanation that the diffuse hepatic uptake of ^{99m}Tc-MDP was resulted from the hepatotoxicity. It is worth noticing that the diffuse liver uptake of ^{99m}Tc-MDP may be seen in various kinds of hepatotoxicity as in this case, secondary to chemotherapy with high-dose methotrexate. In other words, diffuse liver uptake in bone scan may indicate hepatotoxicity and in those who are receiving chemotherapy, the chemotherapeutic agents may necessarily be modified if hepatotoxicity is concerned.

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續發於Methotrexate化學治療的肝毒性導致骨骼掃描廣泛肝臟鎝-99m-MDP攝取

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摘要：骨骼閃爍造影在原發或次發骨癌的診斷是常用且敏感度高的檢查，有時候也額外提供了一些骨骼異常之外的臨床資訊。一位十一歲的女性被診斷出骨肉瘤而做骨骼掃描來評估腫瘤侵犯全身的程度，意外發現了肝臟廣泛的亞甲基二磷酸脂 (MDP) 攝取。跟據臨床病史，在接受骨骼掃描的前一天，病人接受了高劑量的methotrexate治療，實驗數據則顯示相當高的麩胺酸丙酮酸胺基轉化 (GPT)，這可能是造成廣泛性肝臟攝取的原因。在受傷、發炎或壞死的組織常會出現骨外的鎝-99m-MDP攝取，其機制可能跟細胞損傷及鈣的沉澱產生失養性鈣化有關。鑒於與血液及臨床一致的肝功能異常，治療藥物做了調整而術前輔助性的化學治療也平順地完成，這個案例呈現因肝臟損傷導致了不常見的廣泛肝臟MDP攝取，對於接受化學治療的病人，如果有肝毒性產生，其治療藥物也可能需做調整。

關鍵詞：廣泛性肝臟攝取，骨骼掃描，肝毒性，methotrexate，骨肉瘤

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