

Osteomalacia mimicking skeletal metastasis induced by antacid and sucralfate: An interesting image on bone scintigraphy

Y-W Chuang^{1#}, H-P Chan², C-Y Lin¹, Y-F Huang^{1,3}, C-C Hsu⁴, C-C Chang^{1,5#},
D. H-Y Shen², K-P Chuang⁶, M-H Yang^{7,8*}, Y-C Tyan^{3,6,9*}

¹Department of Nuclear Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan

²Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

³Department of Medical Imaging and Radiological Sciences, Kaohsiung Medical University, Kaohsiung 807, Taiwan

⁴Department of Nuclear Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung 833, Taiwan

⁵School of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan

⁶Graduate Institute of Animal Vaccine Technology, College of Veterinary Medicine, National Pingtung University of Science and Technology, Pingtung, 912, Taiwan

⁷Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

⁸Center of General Education, Shu-Zen Junior College of Medicine and Management, Kaohsiung 821, Taiwan

⁹Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan

► Case report

ABSTRACT

*Corresponding authors:

Dr. Ming-Hui Yang,

E-mail: mhyang@vghks.gov.tw

Dr. Yu-Chang Tyan,

E-mail: yctyan@kmu.edu.tw

Received: April 2022

Final revised: August 2022

Accepted: October 2022

Int. J. Radiat. Res., January 2023;
21(1): 173-176

DOI: [10.52547/ijrr.21.1.25](https://doi.org/10.52547/ijrr.21.1.25)

Keywords: Bone scan, antacid, sucralfate, hypophosphatemic osteomalacia.

#These authors contributed equally as the first author to this work.

Phosphate absorption can be blocked by over-the-counter antacids, such as calcium- magnesium-, and aluminum-containing products. Although it is rare to see hypophosphatemia induced by aluminum-containing antacids, the combination treatment using two kinds of aluminum-containing agents may significantly increase the risk of hypophosphatemia in clinical settings. We present a case of hepatocellular carcinoma, showing multiple hot spots while being investigated for metastatic cancer in a routine bone scan. Initial laboratory studies showed hypophosphatemia. Long-term treatment for upper gastrointestinal bleeding with antacids and sucralfate was remarkable in the patient's past history. Compared with corresponding radiographic findings, multiple areas of increased uptake on the bone scan are consistent with osteomalacia and microfractures. This case demonstrates that antacid and sucralfate-induced osteomalacia can mimic bony metastasis in a hepatocellular carcinoma patient on bone scintigraphy. Additional imaging modality, laboratory surveillance or follow-up bone scintigraphy may be recommended for accurate diagnosis or an appropriate treatment plan for the patient.

INTRODUCTION

Phosphorous, a important mineral found in human bones, promotes strong and healthy bones and body. Hypophosphatemia (with clinical low serum phosphorus concentration < 0.8 mmol/l or 2.5 mg/dl) can cause health challenges, including osteomalacia (softening or weakening of the bones), respiratory failure, heart problems, muscle weakness/ muscle pain/ depletion of muscles, numbness, seizures, or even coma. It may result from a multifactorial etiology, including acute and chronic presentations. Acute hypophosphatemia is usually seen in severe clinical settings, including recovery from diabetic ketoacidosis, chronic alcoholism,

burns and respiratory alkalosis. Chronic hypophosphatemia, however, typically occurs by conditions with the kidneys and renal function related to phosphorus absorption, including malnutrition/ semistarvation, hyperparathyroidism, hormonal conditions (e.g., Cushing syndrome), vitamin D deficiency, electrolyte imbalance, and medications. The hypophosphatemia-relationship to drug-treatment may be caused by several kinds of medication, e.g. long-term usage of diuretics and antacids. Medication-related hypophosphatemia is commonly observed in the hospitalized patient. It is usually mild for clinical manifestations, however, sometimes it may be severe and potentially life-threatening (1-4).

Clinically, patients with osteomalacia may present symptoms of dull and aching pain in which most affects the rib cages, lower back, pelvis, hips and the legs. The sensation of pain may get worse when the affected bone bears the pressure or at night, and is rarely completely relieved by rest. Moreover, leg weakness caused by the decreased muscle tone can cause a waddling gait and make walking slower and with difficulty. Osteomalacia is most often diagnosed through x-ray imaging, blood tests, or a bone biopsy. Nuclear medicine bone scintigraphy for this clinical condition has rarely been reported in previous articles ⁽⁵⁻⁹⁾. However, pseudofractures are common in patients with osteomalacia, and increased uptake of the fracture sites on bone scans may mimic metastatic bone lesions of patients presenting for a cancer work-up.

Herein, we present a patient with hepatocellular carcinoma who reported chest pain with antacid and sucralfate-induced osteomalacia. There are multiple abnormal radiotracer-accumulated foci which mimic bony metastasis on the whole-body bone scintigraphy. It reminded us of the importance of chart review for past medical history when documenting the examination report.

Case report

The case described is a female patient (age: 78) who has multinodular type hepatocellular carcinoma (with clinical staging T2N0M0, stage II) after transcatheter arterial chemoembolization (TACE) and radiotherapy. She did not have antecedent trauma, but present with chest pain. She was referred from another hospital for detection of bone metastasis. The whole-body bone scan for the patient was performed (Discovery NM/CT 670, GE Medical System, France) around 3 hours after the intravenous injection of 740MBq (20 mCi) Technetium-99m methylene diphosphonate (Tc-99m MDP, Global Medical Solutions, Taiwan). In the routine bone scan, it was found the uptake increased in multiple areas caused confusion with malignant metastatic disease (figure 1). But these blurred and linearly-arrayed hot spots reminded us of insufficiency fractures in a metabolic bone disorder (figure 2). The chest plain film only showed nonspecific osteopenia (figure 3), and the abdominal computed tomography (CT) showed fractures of ribs and typical looser zones: wide linear transverse lucencies (pseudofractures) (figure 4). These findings were not pointed out on the first interpretation of the abdominal CT without knowing the result of the bone scan. No characteristic advanced tumor invasion or bone destruction was detectable in these radiographic findings. In the laboratory finding, it was noted the low serum level of phosphorus (2.1 mg/dl) may due to the hypophosphatemia after prolonged ingestion of antacids and sucralfate for the bleeding of upper gastrointestinal. Esophagogastroduodenoscopy (EGD) revealed angiodysplasia with active oozing

at the antrum to duodenal bulb and hemorrhagic gastritis. Antacid and sucralfate-induced hypophosphatemic osteomalacia seems most likely, due to the combined course of treatment with drugs and features of available imaging findings. It is recommended to withdrawal of antacids and sucralfate, then treatment with phosphate for the underlying cause of drug-induced hypophosphatemia. However, it is regrettable that the follow-up and final results of therapy were not available.

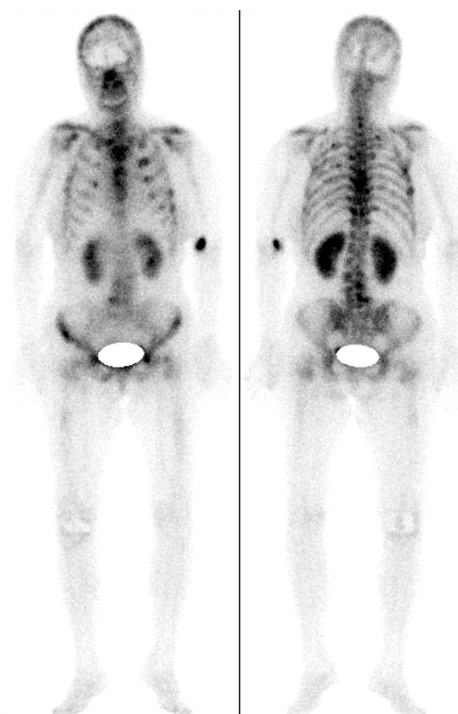


Figure 1. On the whole-body Tc-99m MDP bone scintigraphy, there are multiple hot and warm spots scattered in the skeleton (including thoracic, lumbar spine and bilateral rib cages) except for the 4 limbs. The appearance is difficult to be distinguished from metastatic bony disease.

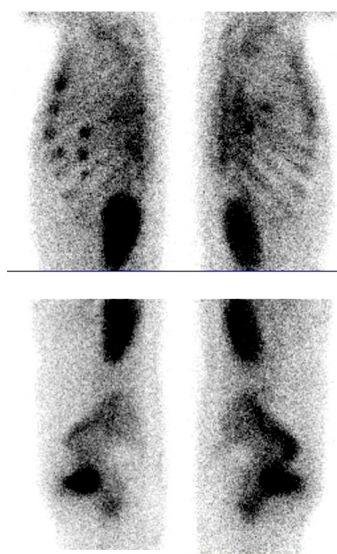


Figure 2. Blurred and linearly-arrayed hot spots in bilateral rib cages revealed on the lateral views suggest insufficiency fractures commonly noted in the metabolic bone disorder.

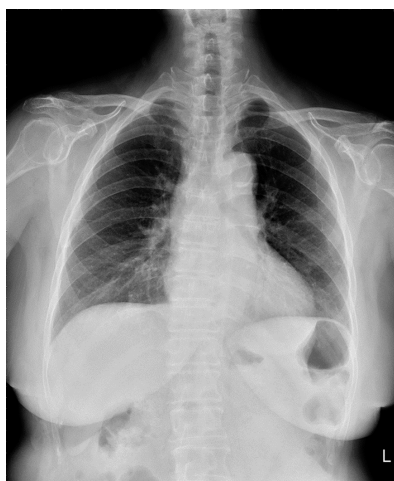


Figure 3. The posterior-anterior chest plain film shows nonspecific finding regarding the bony structures.

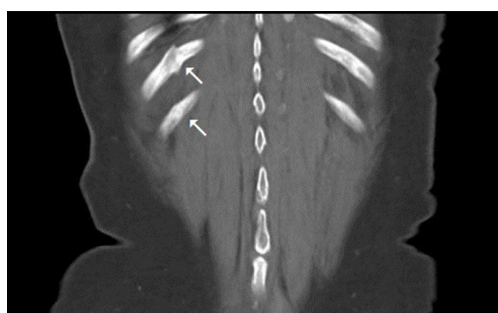


Figure 4. The coronal view of abdominal CT at the level of the lower thoracic to lumbar spine shows pathologic fractures of ribs (tend to be transverse), and typical looser zones: wide linear transverse lucencies (pseudofractures).

DISCUSSION

The clinical manifestations of osteomalacia are usually progressive generalized bone pain, pseudofractures, hypocalcemia, muscle weakness, and a waddling gait in the late stages. It is most commonly caused by mineralization defect, including hypophosphatemia, serum alkaline phosphatase level elevation, and low/normal active vitamin D status that is related to reduction of bone mineral density⁽¹⁰⁾. Another rare cause of osteomalacia that was induced by tumor cell is seen in recent articles⁽¹¹⁻¹³⁾. Tumour-induced osteomalacia (TIO) is one of the paraneoplastic syndromes. The patients with TIO were presented with symptoms such as low serum phosphate, phosphaturia, low/normal levels of serum calcitriol, and normal or elevated levels of fibroblast growth factor-23 (FGF23) or other phosphatonins⁽¹⁴⁾. This disease is commonly induced by small, benign mesenchymal tumors with somatostatin receptors (SSTR) expression and the level of FGF23 increasing. TIO can be detected by ⁶⁸Ga-DOTA-TATE PET/CT in nuclear medicine that currently is considered the most sensitive imaging modality for tumor detection⁽¹⁵⁾. We did not have histological evidence or a positive ⁶⁸Ga-DOTA-TATE PET/CT result for confirmation of TIO for our patient.

However, hypophosphatemia can be a multifactorial etiology due to the treatment with drugs used in every-day clinical practice, such as diuretics and bisphosphonates. Thus, the drug-induced hypophosphatemic osteomalacia has been often not diagnosed promptly in susceptible patients and may be due to physicians who are not sufficiently aware of this rare condition⁽¹⁶⁻¹⁸⁾.

It has been regarded as a sensitive tool to use standard bone scanning for the investigation of bony metastases. However, the Tc-99m MDP is not a tumor-specific agent. It is the primarily uptake tracer and represents the osteoblastic response elicited by a skeletal lesion. This response is nonspecific and may occur in several benign bony pathologies, such as infection, trauma, degenerative and some benign bone disease. It may present similar on the bone scan in a variety of conditions⁽¹⁹⁾. In some cases, on a Tc-99m MDP bone scan, osteomalacia shows the focally increased radioactivity, which may cause the difficult differential diagnosis from bone metastasis. This case report illustrates potential pitfalls of unexpected drug-induced hypophosphatemic osteomalacia misdiagnosed as stage-changing bone metastases. The most typical radiographic finding in plain film and CT are lucent, smudgy, coarsened, demineralized trabecula, nonspecific osteopenia, and pathologic fractures in looser zones. MRI findings are useful for non-radiographically apparent fractures, and to evaluate soft tissues for ligament rupture⁽²⁰⁾.

In this study, we also review the clinical information of hypophosphatemia associated with specific drug treatment and discuss the underlying pathophysiology. The combined clinical features and imaging findings are the best diagnostic clue. The misinterpretation of the bone scan in the present case has finally been clarified from what appeared to be bone metastases.

CONCLUSIONS

The careful medical review or imaging approach regarding the evolution of bone metastasis in the patient's cancer work-up is important. Identification of the false-positive uptake in the bone scan may avoid unnecessary workup and therapy. In this report, the appearance of sucralfate-induced osteomalacia mimicking bony metastasis in a hepatocellular carcinoma may present in the clinical routine. Additional imaging modality or laboratory surveillance may be recommended for accurate diagnosis or an appropriate treatment plan for the patient.

ACKNOWLEDGMENTS

The authors thank S. Sheldon MT (ASCP, Retired) of Oklahoma University Medical Center Edmond for fruitful discussions and editorial assistance.

Funding: This work was supported by research grants: MOST 109-2221-E-037-001-MY3 from the Ministry of Science and Technology, and the Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

Institutional review board statement: This study was performed in accordance with the Declaration of Helsinki and local laws. The study design was approved by the Institutional Review Board KMHIRB-E(I)-20220019.

Conflicts of Interest: The authors declare no conflict of interest. All persons who made significant contributions to this study and the manuscript are included in the author list. The first draft of the manuscript was written by Ya-Wen Chuang, Ming-Hui Yang, and Yu-Chang Tyan, and no other honoraria, grants, or other forms of payment were given to anyone to produce the manuscript.

Author contributions: Conceptualization, Y.-W.C. and C.-Y.L.; methodology, H.-P.C., Y.-F.H. and C.-C. C.; validation, C.-C. H., D.H.-Y.S., and C.-C.C.; writing-original draft preparation, Y.-W.C., C.-Y.L. and H.-P.C.; writing-review and editing, K.-P. C., M.-H.Y. and Y.-C.T.; supervision, Y.-C.T.; All authors have read and agreed to the published version of the manuscript.

REFERENCES

- Liamis G, Milionis HJ, Elisaf M (2010) Medication-induced hypophosphatemia: a review. *QJM*, **103**(7): 449-459.
- Herzog P and Holtermüller KH (1982) Antacid therapy--changes in mineral metabolism. *Scand J Gastroenterol Suppl*, **75**: 56-62.
- Megapanou E, Florentin M, Milionis H, Elisaf M, Liamis G (2020) Drug-Induced Hypophosphatemia: Current Insights. *Drug Saf*, **43**(3): 197-210.
- Serna J and Bergwitz C (2020) Importance of Dietary Phosphorus for Bone Metabolism and Healthy Aging. *Nutrients*, **12**(10): 3001.
- Cooke N, Teitelbaum S, Avioli LV (1978) Antacid-induced osteomalacia and nephrolithiasis. *Arch Intern Med*, **138**(6): 1007-1009.
- Boutsen Y, Devogelaer JP, Malghem J, Noel H, Nagant de Deuxchaisnes C (1996) Antacid-induced osteomalacia. *Clin Rheumatol*, **15**(1): 75-80.
- Chines A and Pacifici R (1990) Antacid and sucralfate-induced hypophosphatemic osteomalacia: a case report and review of the literature. *Calcif Tissue Int*, **47**(5): 291-295.
- Kassem M, Eriksen EF, Melsen F, Mosekilde L (1991) Antacid-induced osteomalacia: a case report with a histomorphometric analysis. *J Intern Med*, **229**(3): 275-279.
- Woodson GC (1998) An interesting case of osteomalacia due to antacid use associated with stainable bone aluminum in a patient with normal renal function. *Bone*, **22**(6): 695-698.
- Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, Collins MT (2017) Tumour-induced osteomalacia. *Nat Rev Dis Primers*, **3**: 17044.
- Aligail K, Dave JA, Ross IL (2022) Tumor-induced osteomalacia: a case report. *J Med Case Rep*, **16**(1): 22.
- Yin Z, Du J, Yu F, Xia W (2018) Tumor-induced osteomalacia. *Osteoporos Sarcopenia*, **4**(4): 119-127.
- Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, Collins MT (2017) Tumour-induced osteomalacia. *Nat Rev Dis Primers*, **3**: 17044.
- Velazquez-Navarro JA, Loya-Teruel E, Rios-Gomez M, Montes-Ramirez JE (2022) Tumor-Induced Osteomalacia With Normal Fibroblast Growth Factor-23 (FGF23) and Idiopathic Hypercalcemia. *Cureus*, **14**(1): e20893.
- Beil FT, Stürznickel J, Rolvien T, Amling M, Oheim R (2022) Tumor localization and treatment of tumor-induced osteomalacia. *Z Rheumatol*, **81**(3): 182-188.
- Ukinc K (2009) Severe osteomalacia presenting with multiple vertebral fractures: a case report and review of the literature. *Endocrine*, **36**(1): 30-36.
- Kim SH, Won KS, Song BI, Jo I, Zeon SK (2013) Low-dose adefovir-induced hypophosphatemic osteomalacia on whole-body bone scintigraphy. *Nucl Med Mol Imaging*, **47**(4): 294-296.
- Tanaka M, Setoguchi T, Ishidou Y, Arishima Y, Hirotsu M, Saitoh Y, et al. (2012) Pathological femoral fractures due to osteomalacia associated with adefovir dipivoxil treatment for hepatitis B: a case report. *Diagn Pathol*, **7**: 108.
- Sood A, Agarwal K, Shukla J, Goel R, Dhir V, Bhattacharya A, Rai Mittal B (2013) Bone scintigraphic patterns in patients of tumor induced osteomalacia. *Indian J Nucl Med*, **28**(3): 173-5.
- Sadineni RT, Pasumarthy A, Bellapa NC, Velicheti S (2015) Imaging Patterns in MRI in Recent Bone Injuries Following Negative or Inconclusive Plain Radiographs. *J Clin Diagn Res*, **9**(10): TC10-TC13.