



Retrospective Study

Adult-onset hypophosphatemic osteomalacia as a cause of widespread musculoskeletal pain: A retrospective case series of single center experience

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dang SS, China

Received: October 4, 2023

Peer-review started: October 4, 2023

First decision: October 9, 2023

Revised: October 14, 2023

Accepted: October 30, 2023

Article in press: October 30, 2023

Published online: November 16, 2023



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Abstract

BACKGROUND

Osteomalacia (OM) is frequently confused with various musculoskeletal or other rheumatic diseases, especially in patients with adult-onset widespread musculoskeletal pain because of its low prevalence and non-specific manifestations.

AIM

To facilitate the early diagnosis and etiology-specific treatment of adult-onset hypophosphatemic OM.

METHODS

A retrospective review of medical records was performed to screen adult patients who visited a physiatry locomotive medicine clinic (spine and musculoskeletal pain clinic) primarily presenting with widespread musculoskeletal pain at a single tertiary hospital between January 2011 and December 2019. We enrolled patients with hypophosphatemia, high serum bone-specific alkaline phosphatase levels, and at least one imaging finding suggestive of OM.

RESULTS

Eight patients with adult-onset hypophosphatemic OM were included. The back was the most common site of pain. Proximal dominant symmetric muscle weakness was observed in more than half of the patients. Bone scintigraphy was the most useful imaging modality for diagnosing OM because radiotracer uptake in OM showed characteristic patterns. Six patients were diagnosed with adefovir (ADV)-induced Fanconi syndrome, and the other two patients were diagnosed with tumor-induced OM and light-chain nephropathy, respectively. After phosphorus and vitamin D supplementation and treatment for the underlying etiologies, improvements in pain, muscle strength, and gait were observed in all patients.

CONCLUSION

Mechanical pain characteristics, hypophosphatemia, and distinctive bone scintigraphy patterns are the initial diagnostic indicators of adult-onset hypophosphatemic OM. ADV-induced Fanconi syndrome is the most common etiology of hypophosphatemic OM in hepatitis B virus-endemic countries.

Key Words: Hypophosphatemia; Osteomalacia; Widespread musculoskeletal pain; Bone scintigraphy; Hepatitis B virus; Phosphaturic mesenchymal tumor

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Core Tip: This retrospective study assessed the clinical manifestations as well as laboratory, and imaging findings of patients with adult-onset hypophosphatemic osteomalacia (OM) to highlight the importance of early diagnosis and etiology-specific treatment. Physicians should consider OM as a possible cause of widespread musculoskeletal pain in adult patients. Mechanical pain characteristics, insufficiency fracture sites, distribution of muscle weakness, hypophosphatemia, and distinctive patterns on bone scintigraphy can be the initial diagnostic indicators. Adefovir-induced Fanconi syndrome, phosphaturic mesenchymal tumors, and light-chain nephropathy can cause hypophosphatemic OM.

Citation: Kim S, Kim SW, Lee BC, Kim DH, Sung DH. Adult-onset hypophosphatemic osteomalacia as a cause of widespread musculoskeletal pain: A retrospective case series of single center experience. *World J Clin Cases* 2023; 11(32): 7785-7794

URL: <https://www.wjgnet.com/2307-8960/full/v11/i32/7785.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i32.7785>

INTRODUCTION

Osteomalacia (OM) is characterized by bone matrix hypomineralization, and its histological hallmarks include hyperostoidosis and delayed mineralization[1]. The symptoms of OM include widespread musculoskeletal pain due to multiple bone fractures, arthralgia, skeletal deformities, height loss, and muscle weakness[2-4]. Most patients complain of generalized or localized bone pain, which usually occurs in the axial skeleton, rib cage, shoulder/pelvic girdle, and weight-bearing bones, particularly patients with adult-onset disease. Hence, patients with adult-onset OM commonly visit physiatric or musculoskeletal pain clinics rather than endocrinology or rheumatology clinics. Owing to variable clinical manifestations, non-specific radiological findings, and non-characteristic routine biochemical changes, adult-onset OM is often confused with various musculoskeletal diseases or other rheumatic diseases, and a high clinical index of suspicion is essential for diagnosing OM[4-7].

The etiologies of OM include vitamin D deficiency or resistance, calcium deficiency, hypophosphatemic disorders, and mineralization inhibitors. Although the most common cause of OM is vitamin D deficiency due to lack of exposure to the sun and inadequate intake, which results in secondary hyperparathyroidism, hypophosphatemic OM of various etiologies other than vitamin D deficiency is yet another important cause of OM[2,3,8-11].

This study assessed the clinical manifestations and laboratory and imaging findings of patients with adult-onset hypophosphatemic OM and summarized the points differentiating this disease from other musculoskeletal or rheumatic diseases. We focused on the imaging findings of the skeletal system and etiologies of hypophosphatemia to facilitate the early diagnosis of this rare, but treatable and, even curable cause of widespread musculoskeletal pain.

MATERIALS AND METHODS

Participants

We retrospectively analyzed the databases of a physiatry locomotive medicine clinic (spine and musculoskeletal pain clinics) at a single tertiary hospital between January 2011 and December 2019. Patients with clinical, laboratory, and radiological findings consistent with adult-onset hypophosphatemic OM were included. As the diagnosis was not confirmed by bone biopsy, we set the inclusion criteria based on those reported in previous studies[8,12]. We included

adult patients presenting with widespread musculoskeletal pain, hypophosphatemia, high serum bone-specific alkaline phosphatase, and at least one of the following imaging findings suggestive of OM: Looser's zone/pseudo-fracture or codfish vertebrae on radiography, and costochondral junction beading ("rachitic rosary" appearance) on bone scintigraphy[13].

Data collection

The data on patient demographics, clinical histories, physical examination findings of the skeletal system, and results of laboratory tests, electromyographic studies, and imaging studies [plain radiographs, bone scintigraphy using technetium 99m-methyl diphosphonate, dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging, and ⁶⁸Ga-DOTATOC positron-emission tomography/CT (PET/CT)] were extracted. In particular, we evaluated the presence of typical bone scintigraphy findings of OM, such as the "adult rachitic rosary" appearance, pseudo-reactivation of the growth plate, and the "tie sign" of the sternum[13-15].

Differential diagnosis of hypophosphatemia

The diagnostic approach for patients with hypophosphatemia in our clinic was based on previous reports on the differential diagnosis of various causes of hypophosphatemia[3,8,10]. Initially, we determined whether the hypophosphatemia was renal or extrarenal based on the renal tubular reabsorption rate of phosphate in the patient. Within these categories, a specific diagnosis was made based on the family history, medical history, dietary history, nutritional status, medication history, and serum parathyroid hormone, and vitamin D {25-hydroxyvitamin D [25(OH)D]} levels. The serum fibroblast growth factor (FGF)-23 levels were measured only when the etiology was not found in the above two steps and FGF23-related causes were suspected. Finally, serum/urine protein electrophoresis with light chain analysis or ⁶⁸Ga-DOTATOC PET/CT was performed when light-chain nephropathy or tumor-induced OM (TIO) was suspected.

RESULTS

Eight patients with adult-onset hypophosphatemic OM, comprising three men and five women, were identified. Of the eight patients, one and seven patients were classified as having possible and definite OM, respectively, according to the Japanese diagnostic criteria[8]. The average age at diagnosis was 62 years (range, 52-76 years), and the average interval between symptom onset and diagnosis of OM was 23.8 mo (range, 6-61 mo). Two cases (patients #2 and #7) had been described in our previous case report, and these cases provided insights on the suspicion and diagnosis of OM in adult patients presenting with widespread musculoskeletal pain[15].

Clinical features

The most common site of pain was the back, followed by the shoulders, chest wall, and lower extremities. The pain characteristics corresponded to the mechanical pain patterns (aggravation with movement and relief with rest). Five patients were misdiagnosed and treated for other diseases before the OM diagnosis. Seven patients had a history of fractures; however, the majority of fractures were atraumatic. Height loss after the development of widespread pain was observed in seven patients. Physical examination revealed focal tenderness over the bony regions in six patients. Significant deformities of the skeleton, such as bowing or varus/valgus deformities of the long bones, were not observed, and hypertrophy of the costochondral junctions was not detected upon palpation. Signs of joint inflammation were absent in all the patients (Table 1).

Neuromuscular examination showed symmetric muscular weakness of the proximal limb girdle in five patients, including two with shoulder and pelvic girdle muscle weakness and three with only pelvic girdle muscle weakness. Bilateral compensated Trendelenburg gait (waddling gait) was observed in all five patients, four of whom showed a positive Gower sign. The muscle strength of the hip abductors was grade 0-4 (Medical Research Council scale) and that of the hip flexors or knee extensors was grade 4. However, knee jerk was preserved in all patients (Table 1).

Laboratory tests and electromyographic test

All patients showed low tubular reabsorption of phosphate and a low ratio of tubular maximum reabsorption of phosphate to the glomerular filtration rate, indicating renal tubular phosphate wasting. Two patients had decreased serum calcium levels; however, normal ionized calcium levels were observed. None of the patients had severe vitamin D deficiency [serum 25(OH)D concentration < 30 nmol/12 ng/mL]. FGF23 levels, assessed in two patients without a history of antiviral treatment for hepatitis B virus (HBV) infection, were within the normal range. Despite evidence of proximal girdle muscle weakness, denervation, myopathic evidence on needle electromyography, and elevated serum creatine kinase (CK) levels, were not found in any patient (Supplementary Table 1).

Imaging studies of the skeletal system

On bone scintigraphy, multiple hot uptakes were observed in all patients (Table 2). The most common sites of involvement were the thoracic vertebrae, costochondral junctions, costovertebral/costotransverse process joints, and arc of the ribs. The uptakes were not necessarily symmetric. Multiple hot uptakes at the bilateral costochondral junctions revealed a characteristic "adult rachitic rosary" appearance in five patients (Figure 1A). Pseudoreactivation of the growth plate was observed in the distal femur (two patients) and proximal tibia (three patients) (Figure 1B). None of the patients showed the "tie sign" of the sternum. Chest CT in patient #2 confirmed the fractures of the neck and tubercle of the ribs,

Table 1 Clinical features of patients with adult-onset hypophosphatemic osteomalacia

	Sex/age	Location of pain	Previous misdiagnosis before OM diagnosis	Weakness (MRC grade)	Gait	Gower sign	Height loss (cm)
1	F/52	Low back, left scapula and chest wall, bilateral mid-thigh	N/A	Hip flexor - 4 Hip abductor - 3	Bilateral compensated Trendelenburg gait	(-)	(-)
2	M/62	Thoracic back, bilateral chest wall and knee	N/A	Negative	Normal	(-)	170 to 166
3	F/55	Thoracic and low back, bilateral flank, left shoulder	Osteoporotic compression fracture	Negative	Normal	(-)	159 to 153
4	F/76	Low back, right shoulder, left knee	Pathological scapular fracture	Negative	Normal	(-)	145 to 143
5	M/62	Low back, bilateral chest wall buttock, and flank, left heel	Polymyalgia rheumatica. Osteoporosis	NT	Bilateral compensated Trendelenburg gait	(+)	164 to 161
6	F/74	Neck, low back, bilateral shoulder, ASIS, knee, and ankle	Polymyalgia rheumatica. Somatization syndrome	U/E proximal - 4 L/E proximal - 4	Bilateral compensated Trendelenburg gait	(+)	150 to 144
7	M/54	Low back, bilateral chest wall, right hip, thigh, and knee	Stress fracture of tibia. Osteoporotic compression fracture	L/E proximal - 4	Bilateral compensated Trendelenburg gait	(+)	171 to 165
8	M/61	Low back, bilateral thigh and calf	N/A	U/E proximal - 3 L/E proximal - (hip abductor - 0, hip flexor, knee extensor, knee flexor - 4) L/E distal - 4	Bilateral compensated Trendelenburg gait	(+)	158 to 151

F: Female; M: Male; OM: Osteomalacia; MRC: Medical Research Council; N/A: Not applicable; NT: Not tested; ASIS: Anterior superior iliac spine; U/E: Upper extremity; L/E: Lower extremity.

where multiple hot radiotracer uptakes of the costovertebral/costotransverse process joints were observed on bone scintigraphy (Figure 1C). CT in patient #8 confirmed an insufficiency fracture at the sites of pseudo-reactivation of the growth plate on bone scintigraphy and the calcaneus (Figures 1D and E). Looser's zones (pseudo-fractures) or overt fractures on plain radiographs or CT scans were observed in all patients, which correlated with the hot-uptake sites on bone scintigraphy (Figures 1F and G). Typical "codfish vertebrae" findings due to multiple compression fractures of the vertebrae were observed in only one patient. According to the DEXA scans of the lumbar spine and femoral neck, four patients were in the osteoporotic range, whereas the other four were in the osteopenic range.

Etiology of hypophosphatemia

Six patients were diagnosed with adefovir (ADV)-induced Fanconi syndrome because they had a history of long-term ADV use and improved after ADV discontinuation or switching to other antiviral agents. Five of the six patients were taking regular doses (10 mg/d); however, the dose was unknown in the other patient because the antiviral medications were prescribed at other hospitals. The duration of ADV use before OM diagnosis was 4-11 years (Table 3).

The other two patients (patients #1 and #6) had no history of surgery or medications that could cause OM, and their dietary history was not remarkable. In patient #1, ⁶⁸Ga-DOTATOC PET/CT was conducted to identify the culprit lesion of the phosphaturic mesenchymal tumor (PMT) and revealed hot uptake of the radiotracer in the right temporal bone of the calvarium (Figure 1H). Histological examination of the surgically excised tumor showed spindle- to ovoid-shaped tumor cell infiltration with a well-developed, rich capillary network and prominent osteoid deposition. Two days after tumor removal, the serum phosphate levels normalized. The patient was diagnosed with TIO secondary to a PMT. In patient #6, protein electrophoresis revealed monoclonal protein in the serum and the free light chain ratio (Kappa/Lambda) increased to 11.7. A subsequent bone marrow biopsy revealed an increased proportion of monoclonal plasma cells (15%). Therefore, the patient was diagnosed with multiple myeloma (MM), and Fanconi syndrome due to light-chain nephropathy was the cause of the hypophosphatemic OM. There was no family history to suspect the hereditary origin of OM in all patients (Table 3).

Treatment and prognosis

All patients received phosphorus supplements (500-1240 mg/d), and calcitriol was administered in six patients (0.25-0.5 µg/d). Three of the six patients with ADV-induced Fanconi syndrome changed the drug to entecavir, one patient was changed to tenofovir alafenamide fumarate, and one patient discontinued the medication altogether. Patient #2 had a history of jaundice after ADV discontinuation; therefore, ADV treatment was continued with simultaneous phosphate

Table 2 Sites of increased radiotracer uptake on bone scintigraphy

	Spine				Girdles		Long bone (focal)			Long bone (pseudo-reactivation of the growth plate)			Hand and Foot				Rib cage		Others			
	C	T	L	S	Scapula	Pelvis	Humerus	Femur	Tibia	Patella	Femur	Tibia	Carpals	Calcaneus	Mid tarsals	Meta tarsals	CV/CT JT	CC jnc	Rosary	Arc	Mandible	Sternum
1		•	•		•		•	•	•	•				•			•	•	•	•	•	
2	•	•		•								•	•	•		•	•	•	•	•		•
3		•		•														•				
4		•	•		•			•	•		•	•		•	•		•	•		•		
5	•	•	•	•		•	•							•	•	•	•	•	•	•		
6	•	•	•		•		•	•	•	•				•			•	•	•	•	•	
7		•	•	•	•	•		•	•						•		•	•		•		•
8		•	•		•			•	•		•	•	•	•	•		•	•	•	•		

C: Cervical; T: Thoracic; L: Lumbar; S: Sacral; CV/CT JT: Costovertebral/costotransverse joint; CC jnc: Costochondral junction.

and calcitriol supplementation. After supplementation and treatment for causes (when possible), improvements in pain, muscle strength, and gait were observed in all patients within 1 wk to 3 mo. In six patients, the serum phosphate levels normalized within 2 d to 9 mo. Although patient #2 was continuously taking ADV, there was a significant improvement in the symptoms after phosphorus supplementation, and the phosphate level remained low for 3 years. In patient #6 with light-chain nephropathy, the serum phosphate level did not normalize because the smoldering MM was not treated with chemotherapeutic agents. However, after a month of phosphorus supplementation, the pain and muscle strength improved.

DISCUSSION

We summarized the characteristics of eight patients with adult-onset hypophosphatemic OM of various etiologies. The most common cause was ADV-induced Fanconi syndrome, whereas the other two rare causes of renal tubular phosphate wasting were PMT and light-chain nephropathy. The most important indicators of OM suspected as a cause of widespread musculoskeletal pain are low serum phosphate levels and characteristic findings on bone scintigraphy. Since the most common symptom of OM is widespread skeletal pain, it can mimic various musculoskeletal or rheumatic diseases, such as osteoporosis, myofascial pain syndrome, degenerative spondylosis, fibromyalgia, polymyalgia rheumatica (PMR), spondyloarthritis (SpA), and inflammatory myositis; hence, it may be easily misdiagnosed or underdiagnosed[3,5-7,16]. Adult-onset OM should be differentiated from inflammatory rheumatic diseases, such as PMR or SpA. Two of our patients were initially suspected of having PMR before visiting our clinic. As the

Table 3 Etiology, treatment, and outcome of adult-onset hypophosphatemic osteomalacia

	Etiology	Onset to diagnosis (mo)	ADV dose (mg/d)	ADV duration (yr)	Medication change	Time to symptom improvement (mo)	Time to normalization of phosphate (mo)
1	Tumor-induced osteomalacia	25	N/A	N/A	N/A	7 d	2 d
2	ADV-induced nephropathy	25	10	6	Keep ADV	3	Never
3	ADV-induced nephropathy	24	10	11	Change to ETV	0.5	3.5
4	ADV-induced nephropathy	6	10	10	Discontinuation of ADV	3	3
5	ADV-induced nephropathy	9	Unknown	11	Change to ETV	2	8
6	Light-chain nephropathy due to multiple myeloma	14	N/A	N/A	N/A	1	Never
7	ADV-induced nephropathy	27	10	4	Change to ETV	2	9
8	ADV-induced nephropathy	61	10	7	Change to TAF	1	1

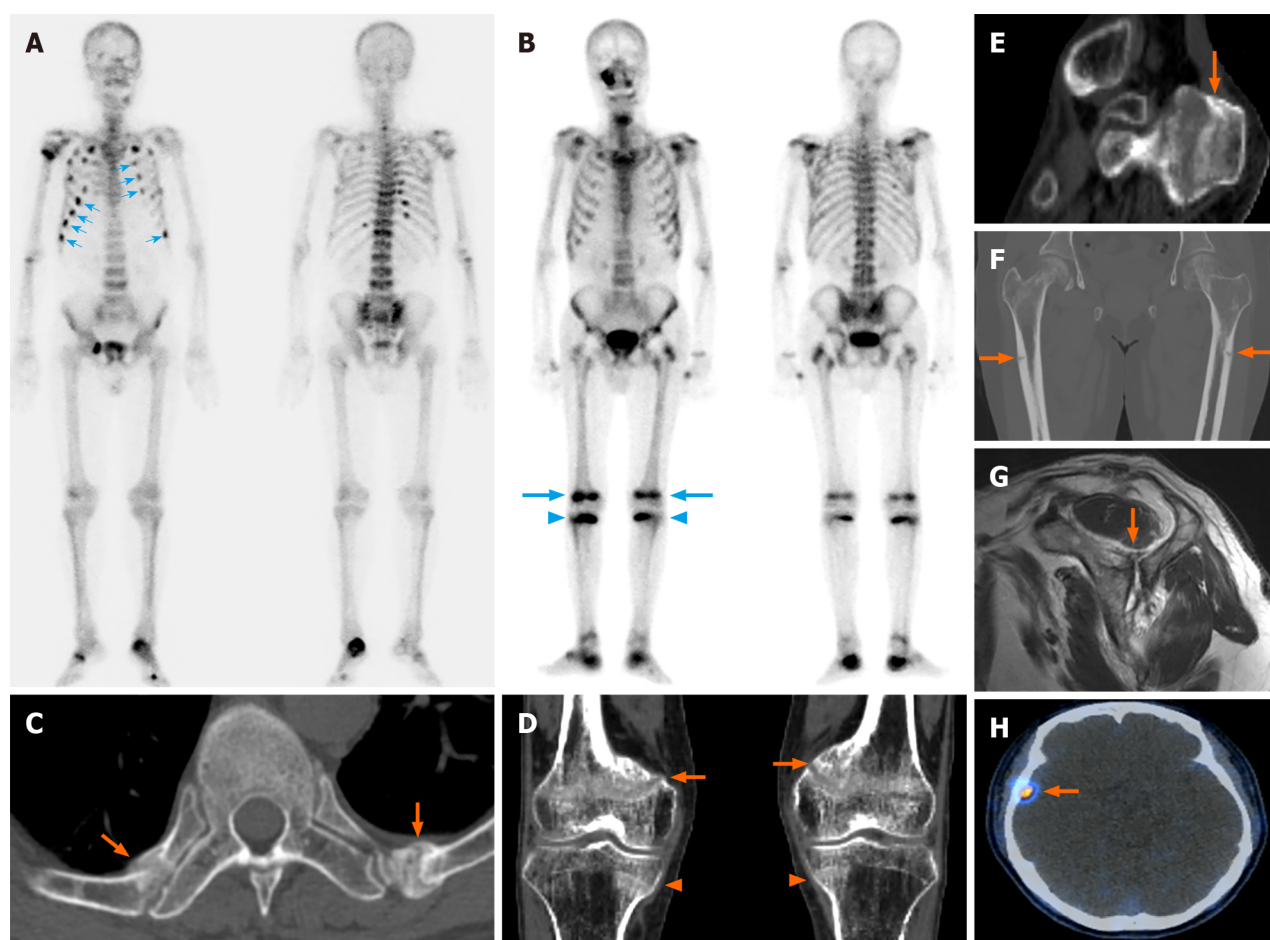
N/A: Not applicable; ADV: Adefovir; ETV: Entecavir; TAF: Tenofovir alafenamide fumarate.

prominent features of PMR and SpA are periarticular and articular inflammation, their pain presented with inflammatory pain characteristics[17]. In contrast, pain in OM presents with mechanical pain characteristics because fractures due to weak bone strength are the source of pain. Thus, pain characteristics in a patient's history are vital for differentiating between OM and inflammatory rheumatic diseases. OM may also be misdiagnosed as osteoporosis owing to the accompanying multiple fractures. Unlike osteoporotic fractures, which usually involve the neck of the femur, vertebral bodies, and wrists, OM fractures mainly involve the ribs, shoulder/pelvic girdle, spine, and long bones[3,4]. In our case series, insufficiency fractures occurred mainly in the neck/tubercle of the ribs, long bones of the lower extremities, sacral ala, calcaneus, and vertebral bodies. The accompanying muscle weakness and biochemical abnormalities in OM, especially hypophosphatemia and alkaline phosphatase elevation, could also be crucial for differential diagnoses.

More than half of the patients in this study showed evidence of proximal muscle weakness in the lower extremities. Osteomalacic myopathy usually involves the proximal muscles around the shoulder and pelvic girdles, causing gait disturbance, difficulty in sit-to-stand, and difficulty in climbing up and down stairs; when properly treated, it has a good prognosis and is rapidly reversible[1,3,4,18-20]. Although proximal muscle weakness in OM may lead to misdiagnosis as a primary muscle disease, such as inflammatory myositis, normal CK levels and characteristic findings on bone scintigraphy can easily differentiate OM from inflammatory myositis. The pathophysiological mechanism of proximal weakness in OM is assumed to be multifactorial; however, no clear mechanism for muscle weakness has been identified in OM[20]. In our patient, electromyography did not reveal evidence of denervation or myopathic motor unit action potential, and serum CK levels were within the normal range. These findings suggest that muscle weakness in OM is not caused by denervation or muscle cell death but by disturbed energy metabolism of muscle cell contraction, probably due to phosphorus deficiency. In an animal study, significant muscle force reduction occurred only when vitamin D deficiency was accompanied by hypophosphatemia[21]. Thus, muscle weakness in OM can be reversed with appropriate treatments. The early improvement (within 3 mo after treatment) in muscle strength and disappearance of the waddling gait in our cases support this hypothesis.

Bone scintigraphy is the most useful imaging modality for diagnosing OM, or at least one type of metabolic bone disease. This is because it permits the examination of the whole skeleton at a glance, and the patterns of uptake in OM are distinct from those of other skeletal diseases, such as metastatic bone disease and osteoporosis. In our cases, "adult rachitic rosary" appearance at the chest cage or pseudo-reactivation of the growth plate at the distal femur/proximal tibia was noted in all patients, except two. Thus, these two characteristics are highly suggestive of, but not specific to OM. A characteristic finding of OM on plain radiographs is a pseudofracture or Looser's zone, which is a radiolucent line through one cortical plate, often with sclerosis at the margins. This insufficiency fracture is usually observed prior to the occurrence of other radiologic changes in OM[22]. In the present case series, it was commonly observed in the long bones, pelvic rami, scapula, and posterior arcs of the ribs. However, standard plain radiography did not reveal definite cortical disruption at any site.

Previously, vitamin D deficiency was considered the most common cause of OM. However, with improvements in the nutritional status, hypophosphatemic OM due to other causes has become more common. There have been several reports of adult-onset hypophosphatemic OM and renal Fanconi syndrome induced by regular doses (10 mg/d) of ADV after long-term use (mostly for 2-7 years) since 2000, especially in HBV-endemic areas[15,16,23]. In the present case series, ADV-induced Fanconi syndrome was the most common cause of hypophosphatemic OM. Therefore, when hypophos-



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Figure 1 Bone scintigraphic and radiologic findings of adult-onset hypophosphatemic osteomalacia. A: Bone scintigraphy of patient #5 shows multiple foci of increased radiotracer uptake in multiple costovertebral/costotransverse joints, bilateral costochondral junctions (blue thin arrows: Costochondral beading or "adult rachitic rosary" appearance), arc of the ribs, cervicothoracolumbar vertebral bodies, sacrum, right humerus, left calcaneus, and right midtarsal bone; B: Bone scintigraphy of patient #8 shows multiple foci of increased radiotracer uptake in the thoracolumbar vertebral bodies, costovertebral junctions, costochondral junctions, posterior arc of the ribs, bilateral scapula, sacrum, pelvic bone, bilateral distal femur and proximal tibia (blue arrows and arrowheads: Pseudo-reactivation of the growth plate), bilateral calcaneus, right distal tibia, and right midtarsal bone; C: Axial computed tomography (CT) image of patient #2 shows insufficiency fracture of the neck and tubercle of the ribs (thick orange arrows); D and E: Coronal and sagittal CT images of patient #8 reveals insufficiency fracture of bilateral distal femur (thick orange arrows in D, proximal tibia (orange arrowheads in D), and left calcaneus (thick orange arrow in E)); F: CT of patient #1 shows transverse linear radiolucency on the lateral aspects of the subtrochanteric area of both femurs (Looser's zone or pseudo-fracture) (thick orange arrows); G: Magnetic resonance imaging of the shoulder of patient #4 shows overt fracture of the right scapula (thick orange arrow); H: Axial image of ^{68}Ga -DOTATOC positron emission tomography/CT of patient #1 shows small, focal increased radiotracer uptake on the inner surface of the right temporal bone (thick orange arrow).

phatemic OM is suspected to be the cause of widespread musculoskeletal pain, careful history taking for the use of anti-HBV medications is imperative. Regular monitoring of serum phosphate levels is also recommended for the early detection of hypophosphatemia in patients taking ADV for hepatitis B.

Although rare, light-chain nephropathy or PMT can cause adult-onset hypophosphatemic OM when there is no history of causative medications that induce OM. Light-chain nephropathy causes hypophosphatemic OM due to proximal tubular dysfunction caused by crystal deposition in the proximal tubule cells[24,25]. Therefore, latent MM should be considered in patients with acquired hypophosphatemic OM. In TIO, the tumor secretes a factor called phosphatonin, which causes phosphaturia and hypophosphatemia. The tumors were morphologically distinct and classified as a single histopathological entity named PMT[26]. As PMTs are often small and exist within the bone, they are difficult to locate. The recent development of somatostatin-receptor functional scintigraphy and PET/CT using ^{68}Ga -radiolabeled DOTA-conjugated peptides has helped in diagnosis[6,10,13]. Although serum FGF23 levels in blood samples from the antecubital vein of one patient with TIO in this case series were within the normal range, ^{68}Ga -DOTATOC PET/CT detected the culprit lesion for PMT. Although autosomal dominant hypophosphatemic rickets (ADHR) is one of the causes of adult-onset hypophosphatemic OM because it is characterized by variability in the age of the clinically evident disease, genetic studies for ADHR were not performed because other causes of hypophosphatemia were clearly identified in our cases.

The treatment of OM requires the management of the underlying disease or drugs that cause it, along with simultaneous phosphate and vitamin D supplementation. In our cases, the bone pain improved within a short period when appropriate treatment was administered. In some of our patients, the symptoms tended to improve even if the

phosphorus level was not completely normalized. This can be explained by the inaccuracy of serum phosphate levels in predicting total phosphorus levels in the body[27]. The favorable prognosis in our cases emphasizes the importance of the early diagnosis of hypophosphatemic OM in adult-onset patients presenting with multiple musculoskeletal pain.

Our study had some limitations. The most crucial limitation was the lack of a pathological diagnosis of OM. However, a bone biopsy is rarely performed at our institute for the diagnosis of OM because of its invasiveness. We attempted to include highly compatible patients using the criteria set by a thorough review of the literature. All patients presented with a clear etiology of OM. Another limitation was the inherent bias due to the retrospective nature of the study and the relatively small number of patients recruited in a single center. Larger prospective multi-centered cohort studies are needed to establish a more precise clinical picture of the disease entity. Additionally, ADV has been used as a drug of choice for treating HBV infection for years. However, after the introduction of other anti-HBV medications with better efficacy including entecavir and tenofovir, ADV is not recommended for the treatment of chronic HBV infection in European and Korean clinical guidelines[28,29]. Thus, our conclusion that ADV-induced Fanconi syndrome is the most common etiology of adult-onset hypophosphatemic OM in HBV-endemic countries may have little clinical significance in the future. However, as a considerable number of patients continue to receive ADV for their long-term maintenance therapy, physicians in HBV-endemic countries should be aware of this clinical entity.

CONCLUSION

Therefore, physicians should consider the possibility of adult-onset hypophosphatemic OM as a cause of widespread musculoskeletal pain. Although it is not a common disease, the quality of life of affected patients can be severely compromised if the diagnosis is delayed. Once the correct diagnosis is made, there is dramatic improvement with proper treatment. The mechanical pain characteristics, hypophosphatemia, and distinctive patterns on bone scintigraphy may be initial diagnostic indicators. When hypophosphatemic OM is confirmed, a diagnostic work-up based on the proposed diagnostic algorithm is necessary. Drugs, such as antiviral agents for hepatitis B, may be the most common etiology of adult-onset hypophosphatemic OM in HBV-endemic countries.

ARTICLE HIGHLIGHTS

Research background

Adult-onset hypophosphatemic osteomalacia (OM) is a rare disorder primarily presenting with widespread musculoskeletal pain.

Research motivation

As the most common symptom of OM is widespread skeletal pain, it can be easily misdiagnosed as other musculoskeletal or rheumatic diseases.

Research objectives

This study aimed to facilitate the early diagnosis and etiology-specific treatment of adult-onset hypophosphatemic OM.

Research methods

This retrospective study included patients diagnosed with adult-onset hypophosphatemic OM at a single tertiary hospital between January 2011 and December 2019. Clinical features, diagnostic test results, treatments and prognosis of the patients were reviewed.

Research results

Eight patients with adult-onset hypophosphatemic OM were included, and five patients were misdiagnosed and treated for other diseases. Six patients were diagnosed with adefovir-induced Fanconi syndrome, and the other two patients were diagnosed with tumor-induced OM and light-chain nephropathy, respectively.

Research conclusions

Mechanical pain characteristics, hypophosphatemia, and distinctive bone scintigraphy patterns are the initial diagnostic indicators of adult-onset hypophosphatemic OM.

Research perspectives

Physicians should consider the possibility of adult-onset hypophosphatemic OM as a cause of widespread musculoskeletal pain because it is rare, but treatable disorder.

FOOTNOTES

Author contributions: Kim SW, Kim DH and Sung DH contributed to the conceptualization of this study; Kim S, Lee BC, and Kim SW involved in the investigation and data curation of this manuscript; Kim S and Kim SW wrote the original draft; Lee BC, Kim DH, and Sung DH participated to the writing - review & editing; and all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional review board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments. This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2020-09-027-001).

Informed consent statement: Informed consent was waived by the Institutional Review Board because of the retrospective nature of the study and the analysis used anonymous clinical data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated for this study are available on request to the corresponding author.

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Country/Territory of origin: South Korea

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Yu HG

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