COMPARATIVE ANALYSIS OF CLINICAL AND VISUAL CHARACTERISTICS OF OSTEOMALACIA AND SPONDYLOARTHRITIS

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Objective: To compare the clinical and radiological characteristics of osteomalacia and spondyloarthritis/ ankylosing spondylitis (SpA /AS) for differential diagnosis.

Methods: a retrospective analysis of patients diagnosed with osteomalacia was carried out at the Traumatology Center 260 Hospital (Samarkand, Uzbekistan) from January 2018 to January 2022. Clinical and radiological data of all patients were collected; at the same time, age and sex matched patients with SpA /AS were selected for comparison.

Results. We enrolled a total of 62 patients, 28 with osteomalacia and 26 with SpA /AS. The mean age in the two groups was 44.6 ± 14.9 years and 44.8 ± 9.7 years, respectively ($P > 0.05$). SpA /AS was misdiagnosed in 65.8% of patients with osteomalacia (n = 23) . In the osteomalacia and SpA /AS groups, there were 29 and 30 patients with low back pain, 20 and 10 patients with peripheral arthralgia, and 12 and 2 patients with heel pain, respectively. Alkaline phosphatase (AP) levels were significantly higher in the osteomalacia group than in the SpA /AS group ($P < 0.05$). Serum phosphorus levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and bone mineral density (BMD) were significantly lower in the osteomalacia group than in the SpA /AS group ($P<0.05$). Twenty-five patients in the osteomalacia group underwent sacroiliac joint magnetic resonance imaging (SIJ-MRI); abnormalities were found in 10 of these patients, seven of whom met the 2009 International Spondyloarthritis Assessment Society (ASAS) definition of positive CRPS-MRI. All seven had bilateral sacral lesions. Logistic -regression analysis showed that the odds ratio (OR) for assessing bone erosion was 0.551; the higher this figure, the lower the likelihood of osteomalacia.

Conclusion: Clinical and radiological manifestations in patients with osteomalacia may strongly mimic those in patients with spondyloarthritis; identifying differences between the two diseases can effectively reduce the rate of misdiagnosis.

Introduction

Bone is a hard tissue formed by hydroxyapatite [Ca10(PO 4)6(OH)2] crystals deposited on a matrix protein produced by osteoblasts. With rickets, an increase in non-mineralized bone matrix occurs , osteomalacia develops due to a violation of the mineralization of matrix proteins. Among them, rickets occurs in children, and osteomalacia is a disease in adulthood. Osteomalacia is a rare disease.

Patients may complain of bone pain, myasthenia gravis, arthralgia, and/or scoliosis. Clinical and even radiological manifestations of osteomalacia can mimic those of spondyloarthritis, but the two diseases are distinct. Patients with early stage osteomalacia may make a full recovery, while untreated patients may become completely bedridden due to severe bone pain. However, there are still no uniform international criteria for diagnosing osteomalacia, which leads to misdiagnosis and, as a result, a delay in the treatment of some patients. In this article, we summarize osteomalacia patients treated in our hospital over the past 5 years. Our results showed that 78% of them had previously been misdiagnosed with spondyloarthritis/ ankylosing spondylitis (SpA /AS). Therefore, here we compare the clinical, laboratory, and radiographic characteristics of this patient cohort with corresponding SpA /AS patients in order to reduce misdiagnosis in patients with osteomalacia and improve their outcomes.

Subjects and methods. The study included patients diagnosed with osteomalacia at the Trauma Center of Hospital 260 (Samarkand, Uzbekistan) from January 2017 to January 2022. The diagnosis of osteomalacia is defined as: (1) hypophosphatemia or hypocalcemia ; (2) high ALP; (3) clinical presentation of myasthenia gravis or bone pain; (4) BMD <80% of the normal level for the age group of patients; (5) bone scan showing multiple metabolic abnormalities, or x-ray showing multiple osteoporotic lesions. A definitive diagnosis of osteomalacia can be made if criteria 1–5 are met. Subjects without clinical symptoms, low BMD, and radiological abnormalities may have osteomalacia. At the same time, we also selected patients with SpA /AS of appropriate age and gender, and all patients with SpA met the ASAS 2009 classification criteria for axial spondyloarthritis.

Methods. We obtained and recorded patient gender, age, clinical presentation data, biochemical markers [blood phosphorus, blood calcium, serum creatinine (sCr) and serum alkaline phosphatase (ALP)], bone mineral density (BMD) and sacroiliac bone . Results of joint magnetic resonance imaging (CPS-MRI). BMD was represented by a T-score in the L1-L4 spine. The Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system was used to evaluate CPS-MRI results. This study was carried out with the approval of the Ethics Committee of the First Medical Center of the PLA General Hospital (Samarkand, Uzbekistan). All participants provided written informed consent prior to the start of this study.

Statistical analysis. SPSS version 19.2 (IBM Corp. , Armonk , NY, USA) was used for statistical data processing. Quantitative data were expressed as mean ± standard deviation (SD) and qualitative data were described using frequency (percentage). For statistical analysis, Student's t-test or rank sum test was used. We used logistic regression analysis to identify risk markers for osteomalacia.

Results. A total of 35 patients with osteomalacia were included; 14 cases were associated with the use of adefovir , 13 were associated with tumors, and eight were of unknown etiology. At the same time, we selected 38 patients with SpA /AS

of the corresponding age and sex for comparison (Table 1). The results showed no significant difference in mean age or gender between the two groups. However, the mean duration of disease in patients with osteomalacia was shorter than in patients with SpA /AS.

Table 1. General information about patients in both groups.

	Osteomalacia	Spa /AC	P
Age	44.62 ± 14.90	44.85 ± 9.76	0.934
Gender (M/F)	25/13	29/9	0.312
Illness duration (months)	34.37 ± 47.12	195.45 ± 116.88	0.000

Comparison of clinical symptoms between the two groups

The main clinical symptoms in patients with osteomalacia and SpA /AS were lumbago, peripheral arthralgia, and hip pain. Lumbago and hip pain did not differ between patients with osteomalacia and SpA /AS. More patients with osteomalacia developed peripheral arthralgia than those with SpA /AS. Heel pain and fractures were significantly less common in patients with SpA /AS than in patients with osteomalacia. In addition, patients with osteomalacia, but not with SpA /AS, experienced generalized pain and myasthenia gravis (Table 2).

Table 2. Clinical symptoms of patients in both groups.

	Osteomalacia	Spa /AS	P
Lumbago	31	33	0.529
peripheral arthralgia	22	13	0.038
Pain in the hip	3	5	0.455
Heel pain	13	3	0.028
fractures	9	1	0.007
generalized pain	8	0	-
myasthenia gravis	6	0	-

Comparison of blood test results between two groups

Serum ALP was significantly higher in patients with osteomalacia than in patients with SpA /AS (P <0.01). Serum phosphorus levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, positivity rates for human leukocyte antigen (HLA)-B27, and lumbar and femoral neck BMD were significantly lower in osteomalacia than in patients with SpA . /AS (P <0.05; table 3).

Table 3. Results of laboratory studies of patients in both groups.

	Osteomalacia	Spa /AC	P
AKP (μmol /l)	418.47 ± 326.25	86.72 ± 45.43	0.000
Serum Phosphorus	0.47 ± 0.14	1.29 ± 0.6	0.000
Serum calcium	2.18 ± 0.20	2.27 ± 0.09	0.248
creatinine	82.52 ± 33.88	73.89 ± 16.00	0.151
25-hydroxyvitamin D3 (ng /ml)	17.47 ± 10.04	21.83 ± 6.04	0.295
Erythrocyte sedimentation rate	5.50 ± 6.19	21.66 ± 20.22	0.002
SRP	0.74 ± 0.02	2.26 ± 2.58	0.016
HLA-B27 (n)	0.03% (1)	97.37% (37)	0.000
Bone mineral density of the lumbar vertebrae	−3.23 ± 1.44	−1.81 ± 0.92	0.000
Bone mineral density of the femoral neck	−3.45 ± 0.91	−1.38 ± 0.63	0.000

Comparison of SIJ-MRI anomalies between two groups

Of the osteomalacia and SpA /AS groups, 25 and 33 patients, respectively, underwent SIJ MRI; Abnormal manifestations were found in 40% (n = 10) and 54.5% (n = 18) of patients, respectively. There was no significant difference between the two groups (P = 0.272).

Comparison of CPS-MRI scores between two groups

We compared patients with SIJ abnormalities on MRI between two groups (10 in the osteomalacia group and 18 in the SpA /AS group). In the osteomalacia group, seven patients met the 2009 ASAS definition of positive CRPS-MRI showing bilateral sacral involvement, and three (3/7) had bone erosion. There was no significant difference in SIJ-MRI bone marrow edema (BME) signal scores between the two groups. However, the bone erosion score was lower in the osteomalacia group than in the SpA /AS group.

Comparison of SIJ participation between two groups

The site of injury in patients with osteomalacia was bilateral sacrum; iliac bone involvement was absent in all 10 patients. Table 4 shows the participation statuses of the two groups. Both tended to involve the SIJ bilaterally, but the abnormal changes in the osteomalacia group tended to focus on the sacrum, while sacral and iliac involvement was present in SpA/AS patients . There was a significant difference between the two groups.

Table 4. Distribution of SIJ lesions in patients of both groups.

	Osteomalacia		Spa /AS	
	Two -sided	Unilateral	Bilateral	Unilateral
	10	0	16	2
sacred participation	10*	0	1	1
iliac involvement	0	0	2	0
Involvement of the sacrum/ilium	0	0	13*	1

Prognostic value of CPS-MRI for osteomalacia

Ten patients in the osteomalacia group and 18 in the SpA /AS group had abnormal SIJ MRI findings. We performed a logistic regression analysis of SIJ-MRI abnormalities (i.e., BME and bone erosion) in both groups. The ORs were 0.995 (CI: 0.939–1.088) and 0.551 (CI: 0.3250–0.934), respectively, with corresponding P values of 0.921 and 0.027. In other words, the higher the bone erosion score, the lower the likelihood of osteomalacia. We performed a receiver performance curve (ROC) analysis of bone erosion and found an area under the curve (AUC) of 0.736 (CI: 0.557–0.914;). With a bone erosion score of 3.5, the sensitivity and specificity of diagnosing osteomalacia were 80.0 and 61.9%, respectively.

Discussion. Osteomalacia is classified as a metabolic bone disease, but endocrinologists do not consider it an endocrine disease. History shows that vitamin D deficiency causes rickets and osteomalacia, which is extremely important in clinical practice. Research on vitamin D deficiency has led to the identification of 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1, 25(OH)2D]. Subsequently, etiologies of osteomalacia have been identified, including drug-induced and tumor-induced osteomalacia. In our study, we included 17 patients with drug-induced osteomalacia (adefovir) and 13 patients with tumor-induced osteomalacia. Thyroid and parathyroid function tests were performed on all patients after osteomalacia was considered, but no significant abnormalities were found. Thus, we could not exclude tumor-induced osteomalacia in eight patients with unknown etiology. The spread of such tumors is nonspecific, and the tumors themselves are not easy to detect. The most common manifestations of osteomalacia are chronic lumbago, peripheral arthralgia, generalized pain, and myasthenia gravis.

At an early stage of SpA /AS, only chronic back pain, bone pain, and peripheral joint damage are noted, which are difficult to distinguish from osteomalacia by clinical manifestations. In this study, we included 38 patients with osteomalacia, predominantly involving the sacroiliac joint and axial, with a mean age of 44.62 ± 14.90 years. One patient was HLA-B27 + 31 patients experienced lumbago, 22 peripheral arthralgia and 13 heel pain. These symptoms are very similar to those of SpA /AS, so 65.79% (25/38) of our patients with osteomalacia were misdiagnosed with SpA /AS. To compare the clinical and radiological differences between the two diseases, we selected patients with SpA /AS matched in gender and age to the osteomalacia group. The results showed that the duration of the disease in these patients was significantly longer than in patients with osteomalacia. This could be due to the fact that SpA /AS mainly occurs in young people aged 20–30 years, while the average age of the patients we selected was 44.85 ± 9.7 years. Abnormalities in blood tests, such as ALP, phosphorus, ESR, and serum CRP levels, in patients with SpA /AS with a long course of the disease may differ from those in patients with an early stage, since the former may develop osteoporosis. Studies show that the incidence of osteoporosis in SpA /AS is 11.7–34.4% (5) . Our study also revealed a decrease in BMD in patients with SpA /AS. However, the reduction in BMD was more significant in patients with osteomalacia (Table 3).

Figure 1. Man, 32 years old, bilateral hip pain for 7 months and lumbago for 2 months. C-reactive protein, rheumatoid factor, and human leukocyte antigen-B27 were all negative. Alkaline phosphatase 347 IU / l. Inorganic phosphorus 0.49 mmol / l. No overt anomalies were observed in the sacroiliac joint (SIJ) repair and T1 magnetic resonance imaging [T1W, (A)] and short tau inversion [STIR, (B)] sequences. Computed tomography shows that the left SIJ is rough rather than smooth (C).

We also found that radiographic abnormalities were another major cause of misdiagnosis, in addition to clinical symptoms. Five patients in our study were misdiagnosed with SpA /AS due to abnormalities in the rhsi-computed tomography (CT)/X-ray. Anomalies in traditional radiology are mainly manifested as a rough SIJ with no smooth bone (Fig. 3) . Ten patients were misdiagnosed due to MRI SIRS abnormalities, seven of which met the definition of positive SIJ on MRI for patients with SpA . In 2019, the ASAS-MRI working group revised the definition of SIJ-MRI anomalies. The panel believed that even though the CRPS-MRI pattern may be

indicative of SpA , clinical presentation, laboratory tests, and other markers need to be combined. Thus, osteoarthritis, infections, trauma, tumors, and artefacts in osteomalacia may mimic the MRI findings of patients with SpA . In our current study, we found that patients with osteomalacia may develop BME, but the OR of this finding was 0.995 (CI: 0.939–1.088). Therefore, BME on MRI has a small risk of osteomalacia. However, the assessment of bone erosion in osteomalacia was significantly lower than in SpA /AS; his OR was 0.551 (CI: 0.325–0.934) and the area under the ROC curve was 0.736 (CI: 0.557–0.914). Therefore, the higher the bone erosion score, the lower the risk of osteomalacia, but the sensitivity and specificity of this finding were not high. The longer disease duration in the SpA /AS patients included in our study may be responsible for the higher bone erosion score. Moreover, erosions themselves in the sacroiliac joints can occur in many clinical situations and be observed in osteomalacia as a decrease in BMD. Therefore, this marker may not be suitable for differentiating patients with osteomalacia and early SpA . It should be noted that fatty infiltration occurred only in one patient in the osteomalacia group, and joint fusion in this group did not occur at all. Because fatty infiltration is not a specific radiographic finding in SpA /AS patients, while SIJ fusion is one of the most specific manifestations of advanced AS, and because our SpA /AS patients had a median disease duration of ≥16 years, many of these patients suffered from spinal fusion . To rule out this effect, we did not include these two measures in this study. We also found that MRI anomalies in patients with osteomalacia were mainly focused on the sacrum, and there was a bilateral symmetrical lesion present. In contrast, although bilateral involvement was also found in SpA /AS patients , involvement of both the sacrum and the ilium was occasionally present. This was the largest difference in SIJ MRI findings between the two groups (Table 4). Therefore, we suggest that the location of SIJ abnormalities on MRI may be of greater importance in the diagnosis of osteomalacia than in the diagnosis of SpA /AS. We also found that SIJ-MRI abnormalities mainly occur in tumor-induced osteomalacia and rarely in drug-induced osteomalacia. A recent study showed that fibroblast growth factor 23 (FGF23) is a bone-produced phosphatonin that, when overexposed, causes many types of hypophosphatemic rickets and osteomalacia. This may be the pathological basis of tumor-induced osteomalacia, as well as the greater propensity for radiological abnormalities associated with this etiology. In addition, errors in the interpretation of images by both radiologists and rheumatologists should not be overlooked, and their errors occurred due to insufficient experience in performing CPS-MRI.

Currently, no laboratory test can demonstrate the presence of osteomalacia. However, patients with osteomalacia often have high ALP levels and either hypophosphatemia or hypocalcemia ; we saw similar results in this study (Table 3). In addition, we did not find a significant difference in 25-hydroxyvitamin D3 levels between the two groups, but ESR and CRP were significantly lower in the osteomalacia group than in the SpA /AS group. This showed that osteomalacia was a non-inflammatory lesion. Hypophosphatemia or hypocalcemia and a high ALP level are now thought to be necessary to diagnose or suspect osteomalacia. However,

their importance in such diagnostics, especially in differential diagnostics, has not yet been widely recognized. Currently, there is no single standard for diagnosing osteomalacia in the world. The Japanese study defined the diagnosis of osteomalacia and we also adopted these diagnostic criteria as inclusion criteria, but this study also indicated that osteomalacia should be distinguished from SpA /AS in addition to other endocrine diseases.

This study has some strengths and limitations. As a strength, the importance of differential diagnosis between these conditions is highlighted due to the overlap of clinical manifestations of osteomalacia and SpA /AS. However, all retrospective clinical studies, including this study, are subject to data collection errors. In addition, there are no comments in this study on imaging data on the presence or absence of syndesmophytes and examination of the spine. Finally, this study did not take into account different therapies and SpA disease activity index . Prolonged illness and low disease activity secondary to therapeutic modalities or controlled disease may be associated with a smaller reduction in the CJB BME gap between groups.

Conclusions. Osteomalacia is a rare disease but can seriously affect the quality of life of patients. Untreated patients with osteomalacia can become completely bedridden due to severe myasthenia gravis and bone pain. However, those in the early stage can make a full recovery. The absence of specific clinical, laboratory and radiological abnormalities, as well as unified diagnostic criteria, poses the problem of early and accurate diagnosis for clinicians. Our study showed that the clinical manifestations of patients with osteomalacia are largely similar to those in SpA /AS, but only patients with osteomalacia developed generalized pain and myasthenia gravis. At the same time, inflammatory markers in patients with osteomalacia were not elevated. Radiographic abnormalities, especially SIJ abnormalities on MRI, have been one of the main reasons why osteomalacia was misdiagnosed as SpA /AS. The presentation of osteomalacia on CPS-MRI may correspond to the definition of positive MRI in patients with SpA /AS proposed by the ASAS-MRI task force, but lesions in patients with osteomalacia mainly occur on the sacrum. Low serum phosphorus and serum calcium levels and high ALP levels can help clinicians effectively distinguish between the two diseases. Therefore, we recommend that all patients with lumbago or suspected SpA /AS undergo testing for serum phosphorus, serum calcium, and ALP. These simple serological tests can effectively reduce the risk of misdiagnosis of osteomalacia , but lesions in patients with osteomalacia mostly occur on the sacrum. Low serum phosphorus and serum calcium levels and high ALP levels can help clinicians effectively distinguish between the two diseases. Therefore, we recommend that all patients with lumbago or suspected SpA /AS undergo testing for serum phosphorus, serum calcium, and ALP. These simple serological tests can effectively reduce the risk of misdiagnosis of osteomalacia , but lesions in patients with osteomalacia mostly occur on the sacrum. Low serum phosphorus and serum calcium levels and high ALP levels can help clinicians effectively distinguish between the two diseases. Therefore, we recommend that all patients with lumbago or suspected SpA /AS

undergo testing for serum phosphorus, serum calcium, and ALP. These simple serological tests can effectively reduce the risk of misdiagnosis of osteomalacia.

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