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Lymphedema and Paget's Disease: beyond the nipple

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Abstract

Lymphedema praecox is a rare lymphatic vascular anomaly diagnosed before the age of 35, presenting with unilateral involvement of the lower extremities. Paget's Disease of Bone (PDB) is also a rare osteometabolic disorder characterized by an accelerated rate of bone remodeling, and diagnosis of the disease is challenging. Here, we report a 49-year-old woman with primary lymphedema since the age of 33, who presented with pain and swelling in her right leg. Although the volume of the extremity diminished after complete decongestive therapy, the pain continued. Further evaluation with X-ray, bone scan, and biochemical markers supported the diagnosis of PDB. Following the zoledronic acid infusion, the pain score improved. However, there is no published association between these two diseases. Both lymphedema and PDB are associated with vascular disease and have a genetic background. This is the first case reporting the coexistence of lymphedema and PDB in the same extremity.

Introduction

Lymphedema is caused by impaired lymphatic function, which may result from primary or secondary causes. It manifests as swelling in an extremity due to the accumulation of lymphatic fluid in the interstitial space, leading to subsequent inflammation, adipose tissue hypertrophy, and fibrosis. Primary lymphedema is a rare disorder caused by intrinsic damage to the lymphatics, either by a genetic disorder of the lymphatic vessels or lymph nodes or a dysfunction in the lymphatic system.[1] It is classified as congenital (present at birth), praecox (before the age of 35 or around puberty), or *tarda* (onset after 35 years) according to the age of onset.[1] Lymphedema praecox is the most common form of primary lymphedema, and the classic presentation is unilateral involvement of the lower extremities. Although lymphedema is a clinical diagnosis and diagnostic tests are typically not required, lymphoscintigraphy is the method of choice to assess lymphatic function. Complete Decongestive Therapy (CDT) is considered the gold standard treatment, which is an intensive program that combines various treatment approaches, including bandaging, compression garments, manual lymphatic drainage, exercise, and self-care.

Paget's Disease of Bone (PDB), also known as *osteitis deformans*, is a uni- or multifocal osteometabolic disorder characterized by an accelerated rate of bone remodeling, resulting in overgrowth or disruption of the affected bone's integrity, or a combination of these changes due to a balance of osteoblast and osteoclast overactivity.[2,3] It is inherited in an autosomal dominant pattern with incomplete penetrance and variable expression of the responsible genes in the

condition of familial Paget's disease. Alternatively, it can be influenced by environmental conditions, including viral infection, animal contact, and pesticides.[4] PDB is a rare disease with a male predominance over the age of 50.[2,] Diagnosis of the disease is challenging and is mostly based on the appearance of the affected bone on standard X-rays; rarely, a bone biopsy is necessary. The primary indication for bone scanning is to detect and accurately define the extent of metabolically active PDB, but it is not indicated for the initial diagnosis.[5] Biochemical markers of bone turnover are used to assess the activity and extent of PDB.[6] Intravenous 5 mg zoledronate, which provides rapid normalization of bone turnover markers and relieves pain, is the current first-line treatment for individuals with active disease or those at risk of complications.

Lymphedema and PDB are both chronic progressive diseases. The association of these two conditions reminds us of Paget's disease of the nipple, which is more commonly linked with lymphedema, as previously reported in the literature.[7] However, this is the first case reporting the coexistence of lymphedema and PDB in the same extremity.

Case Report

A 49-year-old woman with primary lymphedema since the age of 33 presented to our lymphedema clinic with pain, swelling, and heaviness in her right leg. She had no related risk factors, including surgical, traumatic, or family history. Her Body Mass Index (BMI) was calculated as 31,61 kg/m^2,

with a weight of 74 kg and a height of 153 cm. During the physical examination, the right lower extremity was noticeably larger than the left side. Concomitantly, non-pitting edema, fibrosis, and a positive Stemmer's sign supported a diagnosis of primary grade 3 lymphedema.

The patient's diagnosis, initially established at another medical center where previous examination records were unavailable upon presentation to our clinic, was ultimately confirmed by Tc-99m non-albumin subcutaneous injection lymphoscintigraphy revealing a delayed lymphatic drainage obstruction in the right leg. Subsequent to the diagnosis, the patient was hospitalized to initiate a rehabilitation program, including complete decongestive therapy. The CDT program, which has proven efficacy in the treatment of lymphedema, was applied regularly by a trained physiotherapist, and although there was a notable decrease in limb measurements (Table 1), no significant improvement in leg pain was observed. The patient was re-evaluated after 10 sessions of CDT for right leg pain and rated her pain as 9 out of 10 according to the Numeric Rating Scale (NRS).

Given that lymphedema itself was not a source of pain in this patient, a plain X-ray of the knee was planned. The X-ray of the lower extremities revealed lytic and sclerotic bone changes, cortical thickening, and osteophytic enlargement around the right knee (Figure 1). Based on these findings, the presence of PDB affecting the same extremity as lymphedema was suspected. To support the diagnosis of Paget's disease of bone and determine the degree of activity and involvement, a whole-body bone scan was performed.

The images showed intense increased involvement starting from the right iliac bone and extending along the right femur, patella, tibia, and fibula, involving all bones of the right foot. On the left foot, the 3rd, 4th, and 5th metatarsal bones, calcaneus, and cuboid showed increased heterogeneous uptake. Wrists and metacarpal bones also exhibited increased uptake (Figure 2). These findings were evaluated in favor of Paget's disease of bone as the primary concern.

Laboratory findings included the erythrocyte sedimentation rate of 75 mm/h (0-20 mm/h) and the C-reactive protein of 18,12 mg/L (0-5 mg/L). Hemoglobin was 10,9 g/dL (12-15,5g/dL), and the parathormone level was 47,08 pg/mL (19,8-74,9 pg/mL), the 25-hydroxyvitamin D (25-(OH)D) level was 12,34 ng/mL (20-50ng/mL), calcium level was 8,44 mg/dL (reference range, 8,8-10 mg/dL), phosphor level was 3,1mg/dL (2,5-4,5 mg/dL). The Alkaline Phosphatase (ALP) level was 98 U/L (35-104 U/L), and bone fraction of ALP was 9,61 mcg/L (<22.4 mcg/L) with 174 mg of 24-hour urine calcium level (150-300 mg). The N- telopeptide (NTx) in 24-hour urine was >2350 nM Bone Collagen Equivalent/mM kreatinin (26-124 nM BCE/mM kreatinin), and Beta-crossLaps (b-CTx) was 0,56 (0-0,556).

A bone biopsy was not considered necessary in the presence of typical biochemical and radiographic findings of PDB. Zoledronic acid 5 mg/year was chosen as the bisphosphonate for treatment. However, due to a low serum 25-(OH)D level, vitamin D replacement therapy was provided for 6 weeks before the infusion. Following the replacement, zoledronic acid infusion was

administered without any reported side effects. Three months after treatment, the NRS score of the patient improved from 9 to 4.

Discussion

Lymphedema is a rare, chronic, progressive, disabling, and incurable but treatable disease that poses significant challenges in terms of diagnosis, requiring specialized expertise for both diagnosis and treatment follow-up. The most common symptoms of lower extremity lymphedema include tightness (16%), pain/tenderness (23%), and heaviness (15%). Substantial reductions in volume and symptoms, along with an increase in functionality, have been reported following CDT.[1,8] In the presence of new symptoms or persistent pain despite treatment, patients should undergo a detailed re-evaluation, involving advanced imaging modalities and laboratory examinations. Osteoarthritis (OA), often attributed to low-grade inflammatory reactions, is the most common cause of knee pain associated with aging and overweight. However, in patients with lymphedema, OA is exacerbated due to the impairment of the synovial lymphatic system, which is responsible for transferring inflammatory macromolecules from the joint cavity, significantly intensifying OA progression.[9] Therefore, the initial investigation for knee pain in this population should involve an X-ray, as we requested in our case.[10]

While the prevalence and incidence of PDB have been steadily decreasing, recent studies report a prevalence of less than 1% in the population aged 45 years and older, even in the United Kingdom, which has a notably high prevalence of PDB.[11] X-rays remain the primary imaging tool for PDB diagnosis. Changes in long bones, such as progressive osteolysis extending toward the diaphysis and focal bone sclerosis at the epiphysis and metaphysis, are often pathognomonic. However, 13-25% of PDB patients are asymptomatic, often diagnosed incidentally during radiologic evaluations for other reasons. Notably, clinical manifestations such as pain and secondary osteoarthritis, as in this case, along with pathologic fractures and deformities in long bones, can occur. Complications and symptoms of PDB depend on the affected part of the skeleton, with the pelvis (58%), spine (55%), femur (32%), tibia (20%), skull (19%), and hip (12%) being the most affected areas.[3]

Davie *et al*. reported pain as the predominant symptom in their 7-year follow-up study, and a case-control study using the UK General Practice Research Database found a significant increase in osteoarthritis in PDB patients (70%).[3] Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are useful in differentiating these changes from other possible causes and in evaluating complications.

Histopathologic features of PDB include three phases: osteolytic, mixed, and osteosclerotic.[12] During the osteolytic phase, intense osteoclastic activity replaces the normal marrow with a highly vascular fibrocellular stroma, leading to localized disruption of bone architecture, potentially resulting in significant weakening of the bone, deformity, and associated complications.[3,13]

However, most patients present in the mixed phase, characterized by decreased osteoclastic activity and increased osteoblastic activity, notable for having all four cardinal features of the disease, as found in this case's X-ray.[14]

The most useful biochemical marker for PDB is serum ALP, although its normal level does not rule out the disease. This is because serum ALP is an indicator of overall disease activity rather than the activity of individual lesions that can be evaluated scintigraphically.[15] In some cases, bone-specific ALP is elevated more accurately and with lower variability than total serum ALP, particularly in patients with limited disease. In instances where common markers like ALP are normal, as in this case, serum and urine assays for type 1 collagen N-telopeptide and C-telopeptide, which more specifically indicate bone resorption, are used for assessment.[5]

The etiology of PDB and lymphedema involves multifactorial interplays between genetic predispositions, epigenetic modifications, and environmental factors.[16] As far as we know, no specific genetic mutation has been identified that directly links PDB and lymphedema. However, both conditions have genetic components, and ongoing research is underway to understand their genetic basis better. PDB has been associated with mutations in genes such as SQSTM1, TNFRSF11A, and VCP, which are involved in bone remodeling pathways.[11] Likewise, lymphedema can result from mutations in genes related to lymphatic development or function, including VEGFR3, FOXC2, and GJC2.[17] Given the potential genetic basis of these conditions, genetic consultation emerges as a crucial aspect of patient care. Genetic counseling provides

valuable information about an individual's genetic risk factors, facilitates informed decision-making regarding diagnostic tests, and guides management, such as the development of new therapies that target epigenetic abnormalities that cause Paget's disease and help prevent disease progression, and surveillance of these complex conditions.

PDB is effectively treated with Bisphosphonates (BPs) to suppress accelerated bone turnover. BPs result in a reduction in disease activity, symptomatic improvement, and normalization of serum bone turnover markers.[4] Denosumab, an alternative therapy, inhibits bone resorption by blocking Receptor Activators of Nuclear Factor Kappa-B Ligand (RANKL), elevated in PDB patients.[18] Although patients treated with denosumab achieve normalization of biochemical indices, the response may not be sustained. However, denosumab remains an option for patients intolerant to BP treatment.[19] Intravenous 5 mg zoledronic acid is the preferred treatment according to recent guidelines. Studies show that patients respond more rapidly to zoledronic acid than oral BPs, with a complete and sustained response.[20] Therefore, zoledronic acid was administered as the first choice in this case, achieving a significant reduction in pain within a short time.

Conclusions

The proposed etiologic conditions of Paget's disease include vascular diseases, genetic diseases, immunologic or metabolic disorders, or it is considered a true neoplastic process.[16] Primary lymphedema is a rare developmental lymphatic vascular anomaly caused by genetic mutations,

and it can manifest as an isolated disease or be part of a complex syndrome. Considering the etiologies of these diseases, both lymphedema and Paget's disease of bone are associated with vascular disease and have a genetic background. However, although there have been some reported cases of Paget's disease of the nipple with secondary lymphedema due to axillary lymph node resection, Paget's disease of the bone and lymphedema are not medically related and there are no published associations between these two diseases in the literature. Nevertheless, genetic consultation serves as an important component of comprehensive care, providing personalized approaches to diagnosis, treatment, and genetic risk assessment for affected individuals and their families.

This case reminds us of the importance of careful management for patients with lymphedema, especially if they experience unresponsive pain. To the best of our knowledge, this is the first reported case of Paget's disease of bone and primary lymphedema occurring together.

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Table 1. Lower extremity circumference measurement (cm)

	Before CDT			After CDT		
	Right	**Left**	**Differences**	**Right**	**Left**	**Differences**
Metatarsal joints	29	24	5	26.5	24	2.5
Ankle	30	25.5	4.5	28	25	3
Greatest calf circumference	44	37	7	43.5	37	6.5
Mid patella with slight knee flexion	52	38.5	3.5	51	38.5	2.5
Mid-thigh	67	57	10	62	56	6

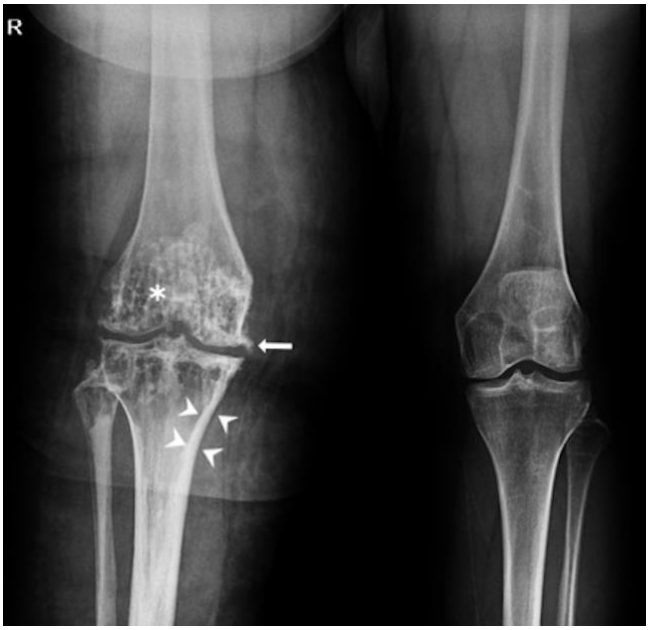

Figure 1. Plain anteroposterior lower extremities radiography demonstrating osteolytic (star) and sclerotic changes, osteophyte (arrow), and cortical thickening (arrowheads) in the femur, tibia, patella, and fibula.

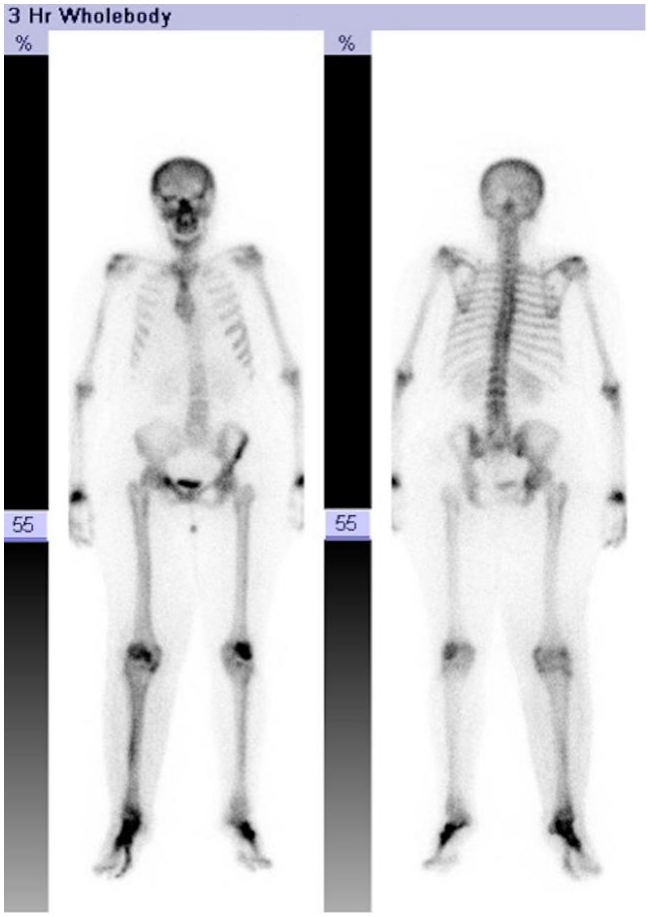

Figure 2. Anterior and posterior view of a whole-body bone scan shows an intense increased uptake starting from the right iliac bone and radiating throughout the right femur, patella, tibia, and fibula and involving all bones of the right foot. On the left foot 3., 4. and 5. metatars, calcaneus, and cuboid have increased heterogeneous uptake. Wrists and metacarpal bones also show an increased uptake.