Radiologically Equivocal Bone Lesions Finally Diagnosed By Bone Scan

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Abstract

Bone scintigraphy remains the second highest volume procedure in nuclear medicine laboratories with diverse applications. Bone scans are highly sensitive and can detect abnormalities much earlier than conventional X-rays. They provide a full-body image, allowing for the assessment of multiple bone sites simultaneously. They can also show specific patterns associated with specific diseases, eliminating ambiguity in diagnosis and establishing a specific diagnosis. Bone scan may be the final station to confirm the diagnosis of certain bone lesions that appear equivocal on other imaging modalities. There are some conditions where bone scans can be considered accurate and guide precise diagnosis, particularly when interpreted in conjunction with clinical findings and/or other imaging modalities as bone metastases, myositis ossificans, osteomyelitis, discitis, avascular necrosis, metabolic bone disease, fibrous dysplasia, osteopetrosis, stress fractures, Rheumatoid arthritis, reflex sympathetic dystrophy, transient migratory osteoporosis, hypertrophic osteoarthropathy, osteoid osteoma, condylar hyperplasia and osteopoikilosis.

Keywords: *bone scan, equivocal bone lesions, accurate diagnosis*

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Introduction

Bone scan, also known as bone scintigraphy, is a specialized imaging technique used to diagnose and monitor various bone-related conditions. Bone scan was first used in the late 1950s and early 1960s [1]. The development of bone scanning is closely tied to the advancements in nuclear medicine, particularly the use of radioactive isotopes. One of the earliest and most significant contributions to bone scanning came from George de Hevesy, who is credited with pioneering the use of radioactive tracers in biological systems [2]. However, the bone scan as we recognize it today, using technetium-99m, became more established in clinical practice in the late 1960s and early 1970s [3]. Bone scintigraphy remains the second highest volume procedure in nuclear medicine laboratories with diverse applications. Continuing improvement in gamma camera hardware and software with the addition of single photon emission computed tomography (SPECT) and, more recently, hybrid SPECT/CT, has maintained and moved the role of nuclear medicine modalities in bone disease to the next level [4].

Bone scans are used to identify various bone conditions such as fractures, infections, primary bone tumors, bone metastases and metabolic disorders. When the cause of unexplained bone pain is unclear, a bone scan can help pinpoint the problem. Bone scans are highly sensitive and can detect abnormalities much earlier than conventional X-rays [5]. They provide a full-body image, allowing for the assessment of multiple bone sites simultaneously. It is a safe technique and the amount of radiation exposure is relatively low, comparable to other diagnostic imaging procedures [6].

Although bone scans are highly sensitive imaging techniques used to detect various bone conditions, they can also show specific patterns associated with specific diseases, eliminating ambiguity in diagnosis and establishing a specific diagnosis [6]. Bone scan may be the final station to confirm the dia-

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gnosis of certain bone lesions that appear equivocal on other imaging modalities [5]. Here are some conditions where bone scans can be considered more accurate, particularly when interpreted in conjunction with clinical findings and/or other imaging modalities.

Bone Metastases

Bone metastases commonly occur in advanced stages of various cancers, particularly breast, prostate, lung, and kidney cancers. Such cancer thus termed osteotropic [7]. Cancer cells typically spread to the bones via the bloodstream. The most common sites for bone metastases are the spine, pelvis, ribs, skull, and long bones such as the femur and humerus [7]. The process of selective deposition and proliferation of malignant cells disseminated within the skeleton is related to the "seed and soil" hypothesis in tumor biology developed by Stephen Paget in the late 19th century. According to this hypothesis, the bone environment represents a "fertile soil", and some types of cancer cells (seeds) can flourish [8].

Bone remodeling disruption results in osteolytic lesions which result from the activation of osteoclasts by cancer cells, leading to bone resorption and weakening of the bone, osteoblastic lesions which are caused by the stimulation of osteoblasts, resulting in abnormal bone formation [7].

The prognosis of bone metastases depends on the primary cancer type, extent of metastatic disease, and response to treatment. Early detection and appropriate management can improve symptoms and quality of life, although bone metastases often indicate advanced-stage cancer [9].

Bone scans (using technetium-99m MDP) can identify areas of increased osteoblastic activity, which appear as “hot spots” on the scan. Their findings, when combined with other imaging modalities, clinical evaluation, and laboratory tests, provide a comprehensive approach to diagnosing and treating bone metastases [6].

Bone scans are highly sensitive for detecting bone metastases, with reported sensitivity rates typically ranging from 85% to 100% [10]. This means they are very good at identifying areas of increased bone turnover, which is common in metastatic disease. They can detect early metastatic lesions before they become apparent on plain radiographs, as they can pick up subtle changes in bone metabolism. The specificity of bone scans for detecting bone metastases is moderate, usually reported between 65% and 85% [10]. This is because increased uptake on a bone scan can also occur in benign conditions such as fractures, infections, and degenerative bone diseases. Bone scans have a high negative predictive value, meaning that a negative scan strongly suggests the absence of bone metastases. This is particularly useful for ruling out metastatic disease in patients with low or intermediate risk [6].

Patterns of uptake that are almost characteristic for metastases include; diffuse skeletal uptake: In advanced prostate cancer with widespread osteoblastic metastases, a “superscan” appearance can occur, where there is diffuse skeletal uptake with minimal renal visualization and the multiple focal hot spots scattered throughout the skeleton [11]. Primarily destructive bone lesions with marked surrounding osteoblastic reaction may give the characteristic donut-shape pattern [12], but lytic lesions with limited reactive osteoblastic reaction, such as renal cell carcinoma or thyroid cancer metastases, are problematic because they typically show low or absent tracer accumulation leading to a false-negative result [13]. Bone marrow-based lesions cannot be ideally detected by static bone scan, however tumors that tend to give diffuse bone marrow-based lesions such as neuroblastoma may present a pattern of diffusely non-uniform enhanced uptake involving the axial skeleton and shafts of long bones with hyperemia consistent with diffusely activated bone marrow on early blood pool images [14] **(Figure 1)**.

Some malignancies may be also associated with paraneoplastic syndromes which are a group of rare disorders, but not due to direct tumor invasion or metastasis [15]. In the context of a bone scan, paraneoplastic syndromes might lead to a variety of features [15]. Paraneoplastic syndromes can cause diffuse metabolic changes in bone, sometimes leading to an increase in uptake throughout the skeleton, giving the bone scan a "super scan" appearance. This can occur without evidence of bony metastases. Some paraneoplastic syndromes, particularly those associated with lung cancer, can lead to hypertrophic osteoarthropathy [16]. This is characterized by periosteal new bone formation, which can cause increased uptake in

the long bones. Some paraneoplastic syndromes may induce bone marrow changes, which can appear on bone scans as areas of altered uptake, though bone marrow scans (using labeled white blood cells or specific marrow agents) are more sensitive to these findings [17]. In some cases, cancer-associated syndromes (such as hyperparathyroidism in paraneoplastic contexts) may lead to bone

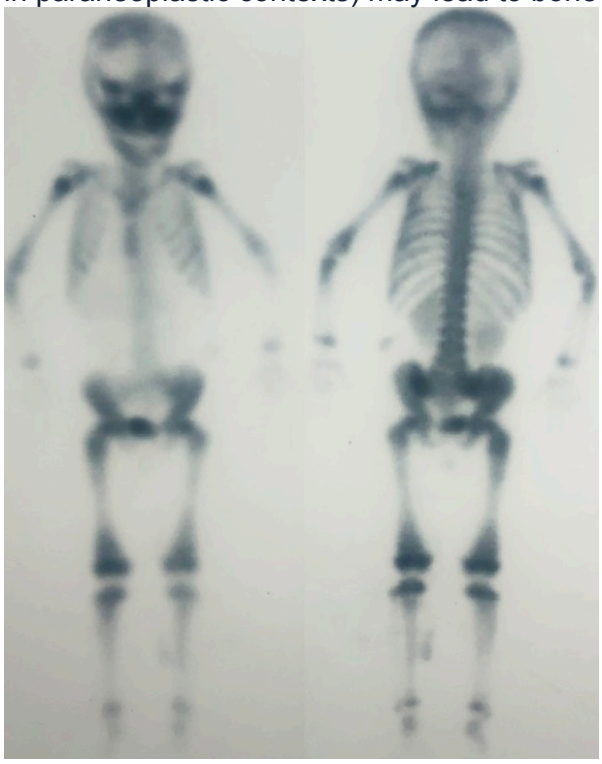

Figure 1: *a 6-year-old child diagnosed with neuroblastoma. Bone scan revealed diffuse heterogenous tracer uptake over axial and appendicular skeleton impressive for disseminated bone marrow-based neuroblastoma infiltrates that was also proven by bone marrow biopsy.*

weakness, resulting in pathologic fractures or generalized osteopenia, which may manifest as focal areas of increased uptake on a bone scan [17]. Paraneoplastic endocrine syndromes, such as those causing hypercalcemia or hypophosphatemia, may cause metabolic changes in bone [16]. This could lead to abnormal patterns of uptake that might resemble metastatic disease or metabolic bone disorders or possibly a combination of both [17].

Extraskeletal soft tissue uptake on a bone scan in the context of paraneoplastic syndrome is an unusual finding but can occur in certain scenarios [18]. The mechanisms underlying this uptake are usually related to calcium deposition or abnormal metabolic activity in soft tissues. Paraneoplastic syndromes, especially those associated with certain malignancies (e.g., lung, breast, or renal cancers), may cause hypercalcemia, leading to metastatic calcifications in soft tissues [18]. These calcifications can be seen as areas of increased uptake on a bone scan, often in locations such as the lungs, kidneys, blood vessels, myocardium, and skin **(Figure 2)**.

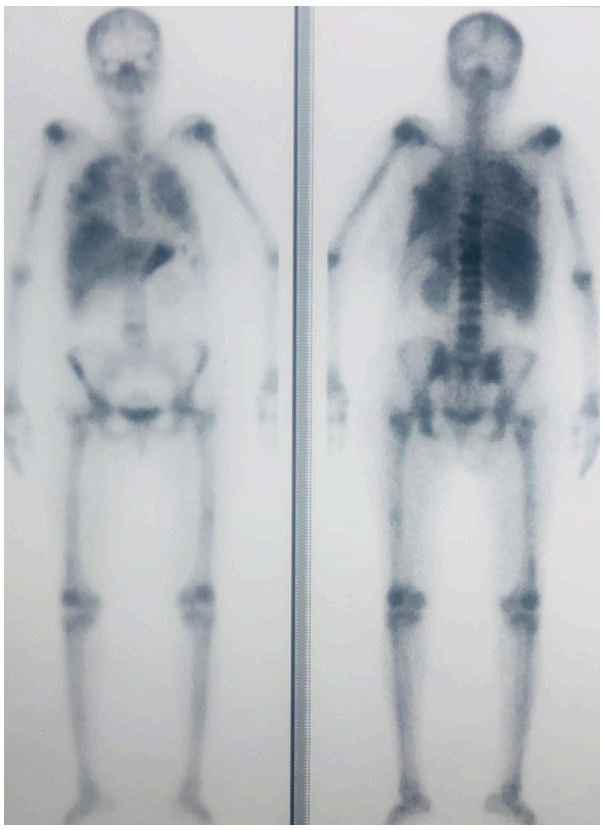

Figure 2: *36-years- old female with pathologically proven breast cancer. Bone scan revealed multiple metastatic bone lesions involving axial and appendicular skeletal bones with extra-skeletal tracer localization involving both lungs and stomach, features impressive for associating paraneoplastic syndrome.*

Paraneoplastic dermatomyositis, which is associated with certain cancers, can also lead to soft tissue calcification, particularly in muscles and subcutaneous tissues [19] **(Figure 3)**.

Tumor-induced osteomalacia, a rare paraneoplastic syndrome associated with mesenchymal tumors, may cause abnormal phosphorus metabolism, which can lead to calcifications or uptake in soft tissues [20]. Some paraneoplastic syndromes result in ectopic calcifications due to metabolic imbalances (e.g., hyperparathyroidism secondary to malignancy). These can involve soft tissues such as tendons, ligaments, or other connective tissues, which may demonstrate increased tracer uptake [15]. Myositis Ossifi-

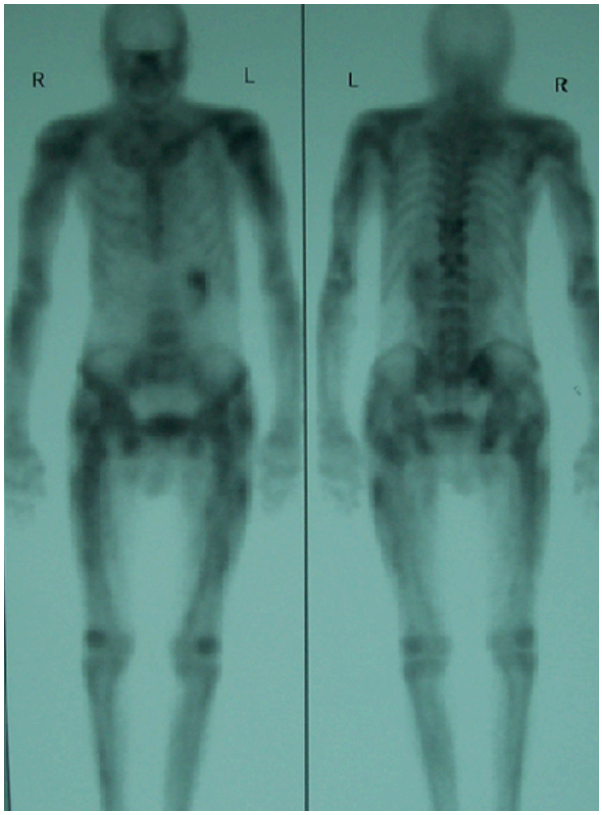

Figure 3: *A 63-year-old male patient with non-small cell lung cancer. On follow-up, he developed bone and muscle pain. Bone scan revealed multiple dominant lytic bone metastases evident in the spine and pelvis, however, there was a striking feature of diffusely increased uptake of radiotracer by almost all skeletal muscle, the picture was impressive for paraneoplastic dermatomyositis that was proven clinically.*

cans sometimes seen as part of a paraneoplastic syndrome, involves the abnormal formation of bone tissue within muscles or other soft tissues. It shows increased uptake on bone scans in the affected areas, mimicking bone involvement but located in the soft tissues [17]. In some cases, malignancy-associated hypercalcemia may cause vascular calcifications, especially in larger arteries or around the heart (coronary arteries). These can be visible as linear areas of uptake on bone scans along the path of blood vessels [15].

Myositis ossificans

Myositis ossificans is a condition in which bone tissue forms inside muscle or other soft tissues following trauma or injury [21]. It is a type of heterotopic ossification. The condition usually develops after an acute injury, but it can also occur from repetitive trauma, surgical procedures, or even spontaneously in some rare cases [21]. Myositis ossificans is generally a benign and self-limiting condition, but early recognition and proper management can prevent complications like long-term loss of function or mobility [21].

Stages of Myositis Ossificans include Early Stage (1–4 weeks): involves the formation of a soft tissue mass due to inflammation and hematoma formation after trauma [22]. Patients experience swelling, pain, and decreased range of motion in the affected area. Intermediate Stage (4–8 weeks): Gradual calcification begins within the soft tissue, and the lesion starts to mature [22]. Pain and swelling may decrease as the mass becomes more organized. Late Stage (8 weeks and beyond): The calcified mass matures and solidifies into bone [22]. Over time, the bone may fuse with nearby skeletal structures if severe, but in most cases, it remains isolated. The mainstay of treatment involves rest, immobilization, and gradual return to activity. Physical therapy helps maintain the range of motion and prevents muscle atrophy [23]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can help reduce pain and

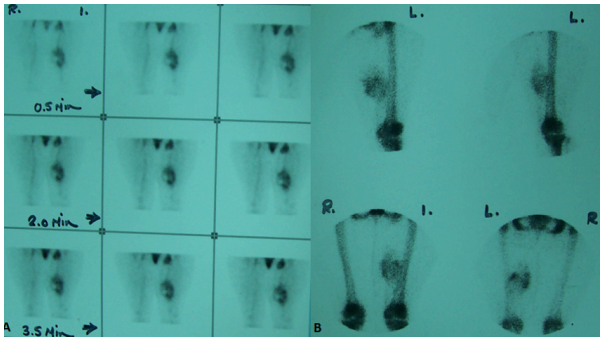

Figure 4: *images A; represent dynamic flow images of bone scan that revealed focal soft tissue hyperemia at the mid medial aspect of the left thigh. Images B; represent delayed static bone images that revealed extra-skeletal tracer localization at anatomical site of the adductor group of left thigh muscles denoting active phase of myositis ossificans.*

inflammation. In some cases, bisphosphonates or radiation therapy may be used to prevent further bone formation [23]. Surgical removal of the ossified mass is considered if it causes significant pain, limits function, or compresses nerves or blood vessels [23]. Surgery is generally delayed until the bone mass has matured (at least 6–12 months), as early intervention can result in recurrence. X-rays are the most common initial imaging modality [24]. In the early stages, it may not show much, but over time (usually after 2–4 weeks), it shows calcification within the soft tissue [22]. The most important role for bone scan encompasses detecting early ossifica-

tion and active bone formation. If surgery is required to remove the ossified tissue, bone scans can help assess the activity of the lesion and the optimal timing for surgery. Surgery is typically delayed until the bone formation has stabilized to avoid recurrence [25]. **(Figure 4).**

Osteomyelitis

Osteomyelitis is an infection of the bone that can be acute or chronic. It often results from a bacterial infection, most commonly caused by Staphylococcus aureus, although other bacteria, fungi, and mycobacteria can also be responsible [26]. The infection can reach a bone through the bloodstream, from nearby tissue, or directly from an injury or surgical procedure [26].

The prognosis for osteomyelitis varies depending on the type, cause, and timeliness of treatment. Acute osteomyelitis often responds well to treatment if caught early, while chronic osteomyelitis can be more challenging to treat and may require prolonged medical and surgical management [27].

Bone scans can detect osteomyelitis earlier than plain X-rays. Within 48 to 72 hours of infection onset, a bone scan can show increased uptake of the tracer in the affected bone, indicating inflammation and infection [28] **(Figure 5)**. Bone scans are highly sensitive, meaning they are good at identifying areas of bone involvement. This makes them useful for ruling out osteomyelitis in

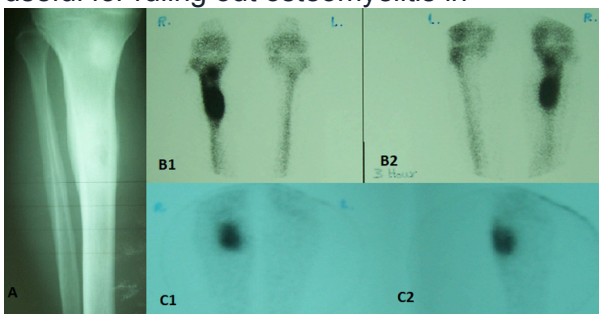

Figure 5: *image A, represent plain X ray showing proximal periosteal reaction in right tibia. Images B (1 and 2 anterior and posterior views respectively); represent bone scan showing focal intense increased tracer uptake at proximal right tibia. Images C; represent Galium 67 scan (1 and 2 anterior and posterior views respectively) confirm presence of active bone infection "osteomyleitis".*

cases where the diagnosis is uncertain [28]. A bone scan can help localize the site of infection, which is particularly useful in complex anatomical regions like the spine or in cases where multiple bones might be involved [29]. Bone scans provide an overview of the entire skeleton, allowing physicians to assess the extent of infection and identify any additional sites of involvement that may not be clinically apparent [29].

In cases of suspected bone infection, localized increased uptake on a bone scan can indicate osteomyelitis. Focal increased uptake in the area of infection, often corresponding with clinical signs such as localized pain, hotness , swelling, and systemic signs of infection [30].

To improve specificity, bone scans are often combined with other imaging modalities and clinical information. For example: Triphasic Bone Scan: involves taking images at three different phases; blood flow phase, blood pool phase, and delayed phase. This can help differentiate between infection and other causes of increased bone activity [28]. Single Photon Emission Computed Tomography (SPECT): provides more detailed 3D images and can help localize the infection more precisely. Combination with MRI or CT Scans: provides detailed anatomical information and can help confirm the diagnosis [28].

Bone scans are highly sensitive for detecting osteomyelitis, with reported sensitivity rates typically ranging from 80% to 100% [31, 32]. This means they are very good at identifying cases where osteomyelitis is present, even in the early stages of infection. The specificity of bone scans is lower, generally reported between 40% and 70% [31, 32].

There are several factors affecting diagnostic performance of bone scan in detection of osteomyelitis includes type of bone scan: as single-phase bone scan primarily shows the distribution of the tracer after several hours, highlighting areas of increased bone metabolism while triphasic bone scan includes three phases [32]. This can help distinguish between different causes of increased tracer uptake, such as distinguishing infection from other inflammatory processes. Also, the performance of bone scans may vary depending on the patient population. For example, in diabetic patients with foot ulcers, the specificity might be lower due to the presence of non-infectious inflammatory changes [33]. The accuracy of bone scans can also depend on the anatomic site of suspected osteomyelitis. For instance, diagnosing osteomyelitis in the spine can be more challenging compared to long bones [29].

Septic arthritis is also a serious infection in a joint, usually caused by bacteria, although viruses and fungi can also be responsible [34]. It requires urgent medical attention, as the infection can rapidly destroy the joint and

lead to systemic complications if not treated promptly [34]. X-rays may show joint space narrowing or signs of joint damage but are usually normal early on. Bone scans are often used alongside other imaging methods (like MRI or ultrasound) and joint aspiration (arthrocentesis) with microbiological analysis for definitive diagnosis of septic arthritis [35] **(Figure 6).**

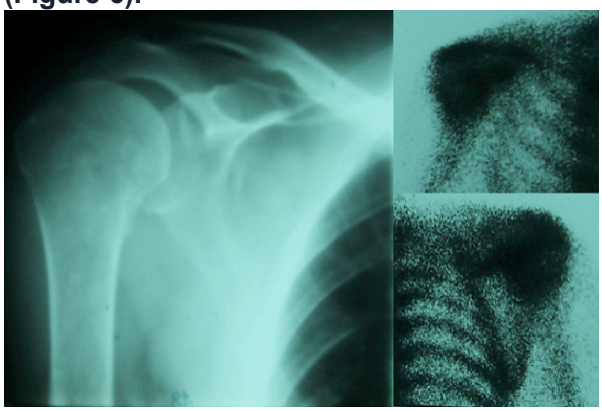

Figure 6: *A male patient with right shoulder pain and movement limitation. Xray (on the right) was performed did not reveal gross changes and excluded arthritis. Bone scan (on the left) revealed marked increased tracer uptake by the right shoulder bones, such findings together with the clinico-laboratory findings, were suggestive of septic arthritis.*

Discitis

Discitis refers to an infection or inflammation of the intervertebral disc space, most commonly caused by bacterial infection, although it can also result from viral or fungal agents [36]. It can lead to severe back pain, spinal instability, and neurological complications if not treated promptly [36]. MRI is the gold standard imaging modality, showing early inflammatory changes in the disc and adjacent vertebrae (vertebral osteomyelitis) [37]. However, in some cases, septic discitis may mimic a destructive neoplastic process on MRI, in which case a bone scan combined with clinical data can resolve this dilemma [38,39]. On bone scan, the two opposing vertebrae are closely approximated together, obliterating the intervertebral disc space between them and appearing as a single block with increased diffuse tracer uptake and corresponding hyperemia on early dynamic images and a blood pool [38, 39] **(Figure 7)**.

Avascular Necrosis (AVN)

Avascular necrosis (AVN), also known as osteonecrosis or bone infarction, is a condition that occurs when there is a loss of blood supply to a bone [40]. Without adequate blood flow, the bone tissue dies and can lead to the collapse of the bone structure [40]. AVN most commonly affects the ends (epiphyses) of long bones, such as the femur, but it can also affect other bones like the humerus, knees, shoulders, and ankles. [41] AVN can result from various

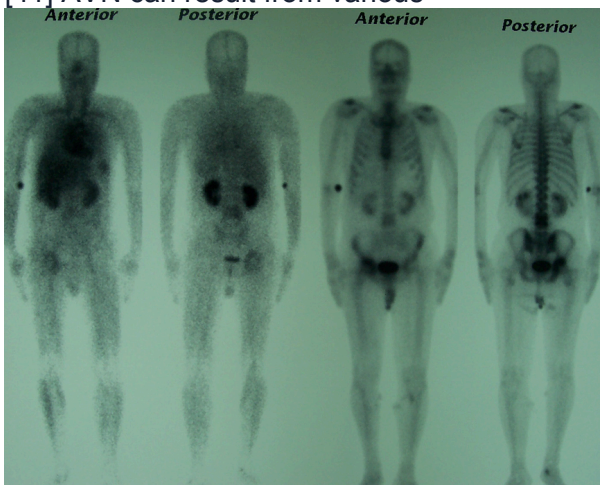

Figure 7: *A 38-year-old male patient presented with bone pain and no history of malignancy. Bone scans showed diffuse increased tracer uptake over L3/L4 vertebrae and their intervening disc space (block-like) as well as the right hip area with corresponding moderate hyperemia on early blood pool images. This case was reported as being suggestive of septic discitis and right hip arthritis. This was confirmed by clinical findings and hip aspiration which revealed tuberculosis.*

factors that interrupt the blood supply to the bone, including: Trauma, alcoholism, steroid use, diseases such as sickle cell anemia, lupus, and Gaucher's disease can lead to AVN, conditions that increase the risk of blood clots can impede blood flow to bones, radiation therapy and decompression sickness [40, 41].

AVN is a serious condition that requires timely diagnosis and appropriate treatment to prevent bone collapse and joint dysfunction [42]. A multidisciplinary approach involving medication, lifestyle changes, physical therapy, and possibly surgery can help manage symptoms and improve outcomes [42].

The prognosis for AVN varies depending on the stage at which it is diagnosed and the effectiveness of treatment [42]. Early detection and intervention can help preserve bone structure and joint function, while advanced stages may require more extensive surgical procedures [40, 42].

Bone scans can detect AVN early in its course, sometimes before changes are visible on X-rays [43]. This early detection is critical for timely intervention to prevent further bone damage. Bone scans are sensi-

tive in identifying AVN. They can detect changes in bone metabolism that occur due to impaired blood flow [43]. The characteristic pattern of AVN on a bone scan includes "cold spots" in the affected areas due to decreased blood flow and "hot spots" surrounding these areas due to reactive bone formation [44].

Bone scans are generally highly sensitive for detecting AVN, particularly in the early stages of the disease. Sensitivity rates are reported with SPECT to be around 85% to 100% [45,46]. This means that bone scans are effective in identifying cases of AVN, even before significant structural damage occurs. The specificity of bone scans with SPECT in AVN is lower, typically ranging from 50% to 80% [45, 47, 48, 49]. The accuracy of bone scans can depend on the stage of AVN. In early stages, bone scans may show a photopenic (cold) area due to the lack of blood flow **(Figure 8)**.

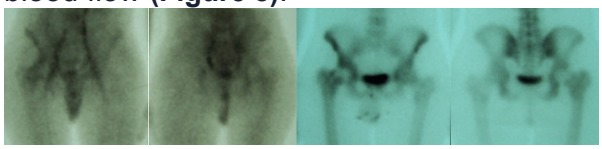

Figure 8: *Blood pool and delayed static spot images of bone scan revealed right femoral head photon deficient area surrounded by active mildly hyperemic margin impressive for acute AVN.*

In later stages, as the bone begins to collapse and repair processes start, increased uptake may be observed, which can complicate interpretation [45]. Due to its high sensitivity, a bone scan can be useful for initial screening, particularly in patients with risk factors for AVN, such as those on long-term steroid therapy or with a history of trauma [49].

Bone marrow infarction is also a well-recognized complication of sickle cell disease. Bone scan typically shows area of suppressed tracer uptake representing the infarcted areas in the early stage [43]. Hyperactive marrow (surrounding the area of infarction) represented by increased tracer uptake shortly follow the acute stage of bone marrow infarction and is a more common presentation [43] **(Figure 8)**.

Metabolic bone disease

Metabolic bone diseases are a group of disorders that affect the strength and structure of bones, typically due to abnormalities in the metabolism of minerals such as calcium, phosphorus, or vitamin D [50]. These conditions can lead to bones becoming weak, brittle, or deformed, making them more susceptible to fractures and other complications [50].

Metabolic Bone Diseases include:

Hyperparathyroidism: an overactivity of the parathyroid glands resulting in excess production of parathyroid hormone (PTH), which causes increased bone resorption and, in severe cases, leads to bone weakening and fractures [51].

Osteomalacia: softening of the bones due to inadequate mineralization, often caused by severe vitamin D deficiency. In children, this condition is known as rickets, leading to bone deformities and growth disturbances [52].

Osteoporosis: characterized by reduced bone density and deterioration of bone tissue, leading to increased fragility and risk of fractures.Commonly affects postmenopausal women, older adults, and individuals with certain medical conditions or on long-term corticosteroid therapy [53].

Paget's Disease of Bone: a chronic disorder characterized by abnormal bone remodeling, where excessive bone resorption is followed by disorganized bone formation. Leads to bones that are enlarged, misshapen, and weak, particularly in the pelvis, skull, spine, and legs [54].

Renal Osteodystrophy: a type of bone disease that occurs in patients with chronic kidney disease (CKD) [55]. It involves a complex interplay of factors, including impaired vitamin D metabolism, phosphate retention, and secondary hyperparathyroidism, leading to bone pain, deformities, and fractures [55].

Osteogenesis Imperfecta: a genetic disorder characterized by brittle bones that fracture easily due to defects in collagen production. There are several types, ranging from mild to severe, with varying degrees of bone fragility and other complications [56].

Hypophosphatasia: a rare genetic disorder caused by mutations affecting the enzyme alkaline phosphatase, leading to defective bone mineralization. Results in soft, weak bones and can present in infancy, childhood, or adulthood [57].

General Role of Bone Scans in Metabolic Bone Diseases include; detection of bone abnormalities: bone scans can detect changes in bone metabolism that may not be visible on standard X-rays [58]. This is particularly useful for identifying early or subtle changes in bone structure or activity. Assessing bone turnover: in metabolic bone diseases, bone scans can help assess the

level of bone turnover [58]. Areas of increased uptake ("hot spots") indicate higher bone metabolism, which can occur in conditions like Paget's disease or hyperparathyroidism. Whole-Body imaging: bone scans provide an overview of the entire skeleton, allowing for the identification of multiple affected sites, which is crucial in diseases that involve widespread bone involvement [59]. Monitoring disease progression and treatment response: bone scans can be used to monitor the progression of metabolic bone diseases and assess the effectiveness of treatments. Changes in the pattern of tracer uptake over time can indicate whether the disease is stabilizing, improving, or worsening [59].

Specific Roles in Different Metabolic Bone Diseases include

· **Hyperparathyroidism:** leads to increased bone turnover, which is reflected in bone scans by increased uptake of the radiotracer. This is particularly notable in the areas of subperiosteal bone resorption, commonly seen in the phalanges (fingers), clavicles, and other long bones [51]. This pattern reflects areas of increased and decreased bone density due to abnormal bone resorption. Hyperparathyroidism can lead to a severe form of bone disease known as osteitis fibrosa cystica, characterized by bone cysts and brown tumors (localized bone lesions) [60]. Bone scans can detect these lesions, which show up as areas of increased tracer uptake due to the active bone remodeling occurring within them [60]. Bone scans can be used to monitor the activity of bone disease in hyperparathyroidism over time, helping to assess the effectiveness of treatment, such as surgical removal of the overactive parathyroid gland(s) [61]. After parathyroidectomy, a bone scan can be used to monitor the normalization of bone metabolism [61] **(Figure 9)**.

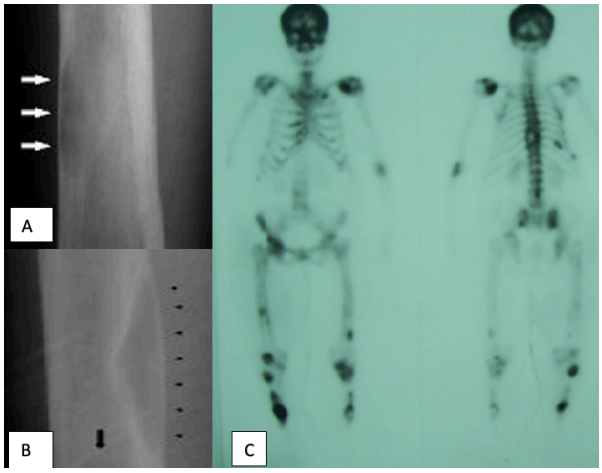

Figure 9: *image A: plain x ray revealed radiolucent lesion at mid right femur and image B revealed radiolucent lesion at proximal right tibia. These lesions were suspicious for metastatic nature on basis of plain X ray only. Image C: bone scan revealed active and lytic bone lesions corresponding to those detected at X ray with additional ones, in addition the whole-body scan revealed features of metabolic superscan attributed to hyperparathyroidism and the focal lesions were interpreted as brown tumors. Further laboratory assessment revealed markedly elevated parathormone level and Tc 99m MIBI scan was performed showed right inferior metabolically active parathyroid adenoma.*

· **Osteomalacia:** One of the hallmark features of osteomalacia on bone scans is the presence of Looser's zones, also known as pseudofractures [62]. These are areas of incomplete fractures, usually found in locations like the ribs, pelvis, and long bones [62]. On a bone scan, these areas show up as regions of increased radiotracer uptake due to the ongoing attempt of the body to repair these stress fractures [58]. Bone scans can detect multiple pseudofractures simultaneously, providing a comprehensive view of the extent of the disease, which might be challenging to assess with standard X-rays [58]. Osteomalacia is associated with increased bone turnover, which can manifest as a diffuse increase in tracer uptake across the skeleton on a bone scan. This increased uptake is due to the active but abnormal bone remodeling process occurring as the body attempts to compensate for defective mineralization [63] **(Figure 10)**.

· **Osteoporosis:** in osteoporosis, the most common application of a bone scan is in the detection of insufficiency fractures, which are fractures that occur with minimal or no trauma due to weakened bones [64]. These fractures often occur in weight-bearing bones like the spine, pelvis, and femur. On a bone scan, these fractures appear as areas of increased radiotracer uptake due to the bone's repair activity [64,65]. Bone scans can detect fractures that may not be visible on standard X-rays, particularly in the early stages. This is especially useful in elderly patients or those with unexplained bone pain where fractures are suspected but not clearly identifiable through other imaging modalities [64,65].

· **Paget's Disease of Bone:** in Paget's disease, affected bones show a marked increase in radiotracer uptake on a bone scan due to the high metabolic activity associated with both bone resorption and formation [66].

Bone scans can detect Paget's disease at an early stage, sometimes before the patient becomes symptomatic or

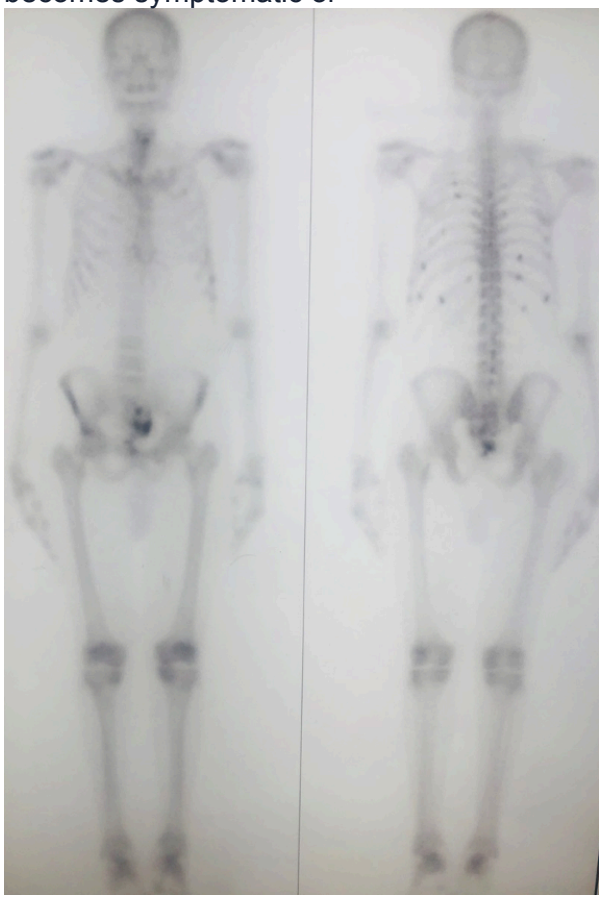

Figure 10: *Bone scan revealed diffusely enhanced tracer uptake allover the axial skeleton and shafts of long bone with increased bone to soft tissue ratio and non-visualized kidneys, picture impressive for metabolic super-scan. Moreover, multiple active tracer avid foci scattered at bilateral ribs representing looser zones and the whole case was impressive for osteomalacia and was confirmed clinic-laboratory.*

before changes are visible on standard X-rays [66]. This early detection is crucial for initiating treatment to prevent complications. Paget's disease typically presents with characteristic findings on a bone scan. Diffuse and intense uptake in affected bones, often described as a "cotton wool" appearance in radiographs [67]. **(Figure 11)**

Fibrous dysplasia

Fibrous dysplasia (FD) is a rare, non-cancerous (benign) bone disorder where normal bone is replaced by abnormal fibrous tissue [68]. This can cause the affected bone to become weak and deformed, and it may lead to fractures, pain, or other complications [68]. FD can affect one bone (monostotic) or multiple bones (polyostotic). FD results from a mutation in the GNAS gene, which leads to abnormal bone formation [69]. The fibrous tissue, made up of immature bone cells, does not harden properly, resulting in weakened bone structure [69].

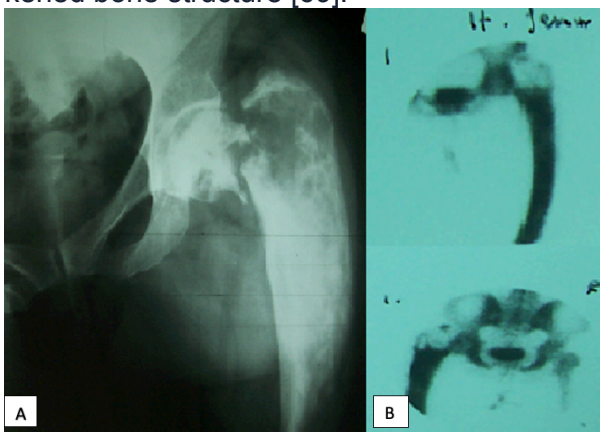

Figure 11: *Image A: Plain X-ray revealed left femur bone expansion and sclerosis apart from lytic changes at the greater trochanter region. Image B: Bone scan revealed diffuse intense active tracer uptake involving the left femur that also appears expanded with photon deficient area at the greater trochanter impressive for malignant transformation on top of Paget's bone disease that was histopathologically proven.*

A bone scan plays an important role in diagnosing and assessing FD. It helps visualize bone metabolism by detecting areas of increased or abnormal bone activity, which is typical in FD due to abnormal fibrous tissue replacing normal bone [70]. It can identify asymptomatic lesions in areas that are not currently causing symptoms, helping in the early diagnosis of FD in multiple bones [70].

In polyostotic FD, a bone scan is especially valuable for mapping the extent of the disease. It highlights all the affected bones throughout the body, even if those bones aren't causing any symptoms yet [71]. This is particularly useful for planning treatment, as it provides a full picture of the skeletal involvement. A bone scan helps differentiate FD from other bone disorders such as metastatic bone disease, infections, or other bone lesions. FD typically shows areas of increased uptake but has a characteristic pattern that aids in its differentiation from more aggressive conditions like cancer [71, 72] **(Figure 12)**.

Bone scans can be used to monitor the progression of the disease over time, especially in cases of polyostotic FD. After treatments like bisphosphonates, bone scans can be used to assess how the lesions are responding and if the therapy is effec-tively reducing abnormal bone activity [72].

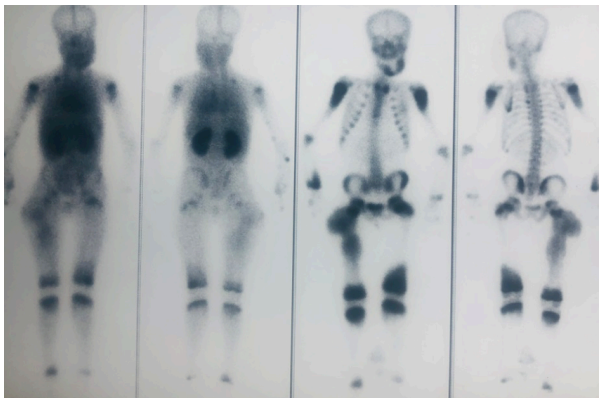

Figure 12: *Blood pool and static Bone scan images revealed multiple areas of intense active tracer uptake with bone deformity, picture impressive for polyostotic fibrous dysplasia.*

Osteopetrosis

"Marble bone disease," also known as osteopetrosis, is a rare genetic disorder that affects bone metabolism [73]. It is characterized by the excessive density and abnormal structure of bones, making them more brittle and prone to fractures [73]. The name "marble bone" comes from the fact that the bones in people with this condition appear dense and stone-like on X-rays, similar to marble [74]. In osteopetrosis, a bone scan plays a supportive role in diagnosis, monitoring disease progression, and evaluating complications [75]. Although X-rays are more commonly used for initial diagnosis due to the characteristic dense, "marble-like" appearance of bones, bone scans can provide additional insights [75]. In osteopetrosis, bone resorption is defective, but bone formation can still occur, leading to abnormal patterns on the scan **(Figure 13)**. Osteopetrosis makes bones brittle despite their increased density, leading to frequent fractures [73,74]. A bone scan can detect occult fractures that may not be visible on routine X-rays [75]. This is important because fractures in osteopetrosis can be hard to diagnose due to the density of the bone and overlapping structures on X-rays. Bone scans can be used over time to track changes in bone metabolism and structure [75]. This is especially useful in patients undergoing treatments, such as bone marrow transplants or medication therapy, to observe how the bones are responding to interventions. In rare cases, osteopetrosis can predispose patients to osteomyelitis, particularly in areas like the jaw [73-75]. A bone scan can help detect signs of infection by identifying areas of abnormal bone activity and inflammation [75].

Stress Fractures

Stress fractures are small cracks or severe bruising within a bone, typically caused by repetitive force or overuse [76]. Unlike acute fractures, stress fractures develop over time with gradually worsening pain. The pain usually starts as a dull ache during activity and may progress to persistent pain even at rest. The pain from a stress fracture is typically localized to the site of the fracture [76].

Stress fractures most commonly occur in weight-bearing bones. While X-rays are usually the first imaging test ordered, they may not show a stress fracture until several weeks after symptoms begin, once new bone formation occurs [77]. Bone scans are more sensitive than X-rays with reported sensitivity often exceeding 90-100% and can detect stress fractures earlier [78].

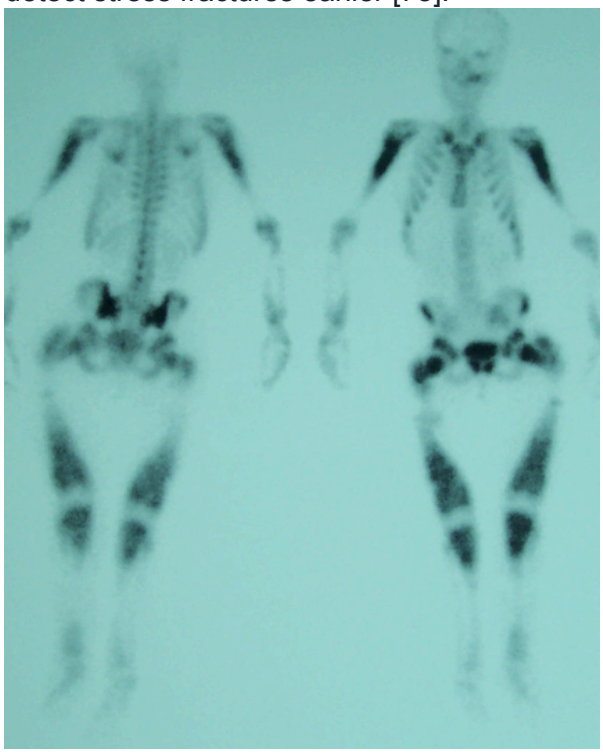

Figure 13: *Bone scan showed significant tracer localization at shafts of long bones mainly periarticular with abnormal bones configuration and expansion. This patient with histopathologically proven to have Marble bone disease.*

Though lower reported specificity, however bone scan is highly accurate when it comes to detecting stress fractures in the absence of confounding conditions [79]. A bone scan shows increased uptake of the radiotracer at the site of the stress fracture, indicating increased bone activity and repair [80]. Three-Phase Bone Scan is especially useful

for early detection: Phase 1 (Flow Phase) shows increased blood flow to the affected area, which is common in the early stages of stress fractures due to increased vascularity. Phase 2 (Blood Pool Phase): reflects increased blood pooling and inflammation in the soft tissues surrounding the bone, indicating an inflammatory response associated with the stress fracture. Phase 3 (Delayed Phase): displays bone uptake of the radiotracer, which is useful for detecting the actual stress fracture [80] **(Figure 14)**. Increased uptake in the periarticular regions or along the bone cortex is characteristic of stress fractures [79,80].

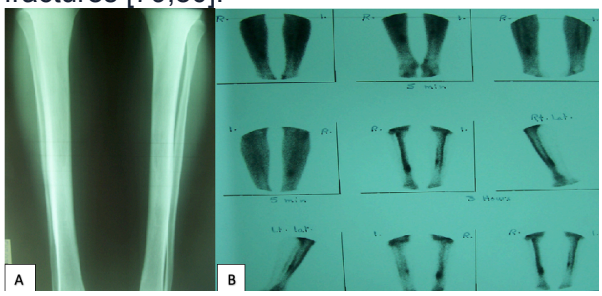

Figure 14: *21-years old male patient with marked right leg pain. Image A: plain X ray on both legs was normal. Image B: Bone scan was performed and revealed hyperemic focal fusiform tracer uptake at right tibia impressive for stress fracture.*

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that primarily affects the joints, leading to inflammation, pain, and eventual joint damage.

It can also have systemic effects on other organs and tissues [81]. Key features of rheumatoid arthritis include symmetric polyarthritis, morning stiffness, swelling and tenderness [81].

Bone scans are highly sensitive, particularly with three-phase bone scanning, to detecting areas of increased bone metabolism, which can occur in inflamed joints due to RA [82,83].

They can identify active inflammation earlier than X-rays, as they detect increased radiotracer uptake indicative of inflammation and increased blood flow [82]. Bone scans are also useful for monitoring disease activity over time and can show increased uptake at sites of chronic inflammation or erosion [83]. Increased uptake in the affected joints can indicate active disease or flare-ups, and a reduction in uptake may reflect a response to treatment [82,83].

Though they are less commonly used for routine monitoring compared to MRI and ultrasound.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD), now more commonly referred to as Complex Regional Pain Syndrome Type I (CRPS I), is a chronic pain condition that typically affects an arm or leg. It often occurs after an injury, surgery, heart attack, or stroke, but the pain experienced is out of proportion to the initial injury [84].

Key Features of CRPS I are pain as the pain in CRPS I is typically severe, persistent, and burning or throbbing in nature [85]. It can be triggered by a minor injury or no apparent cause. There is often an exaggerated response to touch or pain (hyperalgesia) and sensitivity to stimuli that wouldn't normally cause pain (allodynia). Over time, the affected limb may develop osteoporosis due to disuse and the chronic nature of the disease [85].

Diagnosing CRPS I is primarily clinical, based on history, symptoms, and physical examination [85]. However, imaging and other diagnostic tests can support the diagnosis and help rule out other conditions. Bone scans, particularly three-phase bone scintigraphy, play an important role in the diagnosis and evaluation of CRPS I [86]. Bone scans are highly sensitive in detecting the early changes associated with RSD/CRPS I, even before these changes become evident on standard X-rays [86]. The early phase of RSD is characterized by increased bone turnover and vascular changes, which are effectively captured on a bone scan [86,87]. Three-Phase Bone Scintigraphy: Phase 1 (Flow Phase): there may be increased blood flow, indicating hyperemia. Phase 2 (Blood Pool Phase): increased uptake in the soft tissues suggests inflammation or vascular changes, which are common in CRPS I. Phase 3 (Delayed Phase): there may be increased uptake in the periarticular region (around joints) of the affected limb, which is indicative of bone changes and increased bone turnover [87, 88,89]. This finding supports the diagnosis of CRPS I. A positive bone scan can help confirm a suspected diagnosis of CRPS I, especially when clinical symptoms are ambiguous or in the early stages of the disease when other imaging may not show abnormalities [89]. Bone scans can be used to monitor the progression of CRPS I. As the disease progresses, the bone scan may

show reduced uptake in the chronic stage, reflecting decreased bone activity and potential bone loss (osteoporosis) [87,90]. Serial bone scans can help evaluate the response to treatment. Improvement in clinical symptoms often correlates with normalization of the bone scan findings [90]. Bone scans can help differentiate CRPS I from other conditions that cause chronic pain and swelling, such as osteomyelitis, arthritis, or fractures. The pattern of uptake in CRPS I is typically distinct and can aid in the exclusion of these conditions [88].
The findings on a bone scan, especially the extent and intensity of radiotracer uptake, can have prognostic implications. For example, significant uptake in the early phase might correlate with a more aggressive disease course, necessitating more intensive treatment [87,88,89].

Transient Migratory Osteoporosis (Bone marrow oedema syndrome)

It is considered to be a form of reflex sympathetic dystrophy differing in that a history of trauma is rare. It usually affects middle aged males [91]. There is consecutive involvement of the bones around major joints, specially the hips and knees. Symptoms (pain) usually resolve spontaneously within 4 - 10 months [91]. Scintigraphic changes are those of increased hyperaemia on early images with diffuse increased uptake on the delayed image [92] **(Figure 15)**. Sometimes the delayed uptake may be intensely focal with less active diffuse area peripherally. This may be miss diagnosed as AVN. Most common sites are the femoral head and the femoral condyles [92].

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is a medical condition characterized by a combination of periostitis, digital clubbing, and arthritis [93]. HOA can occur as a primary condition, but it is more commonly secondary to various underlying diseases, especially those involving the lungs [93]. Primary Hypertrophic Osteoarthropathy (Pachydermoperiostosis): this rare, hereditary form of HOA is characterized by digital clubbing, skin thickening (pachydermia), and periostitis. It usually presents in adolescence and progresses slowly. There is no underlying systemic disease [94].

Secondary Hypertrophic Osteoarthropathy: this more common form of HOA is associated with a variety of diseases, most notably: chronic lung diseases, such as lung cancer,

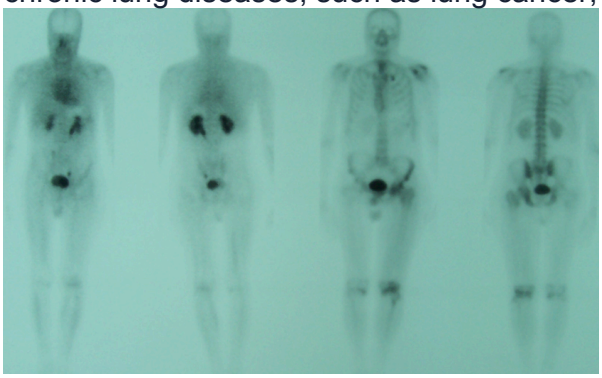

Figure 15: *45-years old male patient complained of sudden onset of left hip pain. Dual phase bone scan revealed warm diffuse tracer uptake involving left femoral head and extending downwards to involve neck, trochanteric region and proximal shaft of left femur with mild hyperemia on early blood pool images, picture impressive for left femoral transient migratory osteoporosis.*

chronic obstructive pulmonary disease (COPD), and interstitial lung disease, are the most frequent causes [95]. Cyanotic congenital heart disease is another significant cause of secondary HOA. Some cases are linked to inflammatory bowel disease, liver cirrhosis, or other gastrointestinal conditions. Rarely, HOA can be associated with other systemic conditions like thyroid disease or certain cancers outside of the lungs [95].
Bone scans are highly sensitive in detecting the periosteal reaction that is characteristic of HOA [96]. The bone scan shows increased uptake of the radiotracer in the periosteum, often described as a "linear" or "tramline" pattern along the shafts of the long bones [96]. Bone scans can detect HOA at a very early stage, even before clinical symptoms like joint pain or digital clubbing become apparent [97]. This makes bone scintigraphy a valuable tool for early diagnosis. HOA typically affects the long bones in a symmetrical fashion, which can be clearly visualized on a bone scan [97]. The distribution pattern seen on the scan can help differentiate HOA from other conditions that may cause bone pain or periostitis. While both HOA and metastatic bone disease can cause increased uptake on bone scans, the patterns differ. In HOA, the uptake is more diffuse and linear along the long bones, whereas in metastatic disease, the uptake is typically more focal and irregular [98] **(Fig. 16)**. Bone scans can help distinguish HOA

from other conditions that present with similar symptoms, such as rheumatoid arthritis, osteomyelitis, or other bone-related disorders. The characteristic pattern of uptake in HOA is usually distinct enough to aid in this differentiation [97,98].

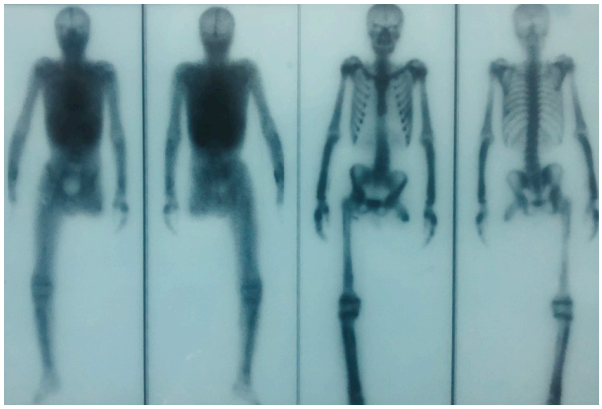

Figure 16: *18-years-old male patient underwent left above knee amputation for osteosarcoma. He gave a history of heavy smoking. On Follow-up bone scan was performed to rule out metastases and it revealed diffuse increased tracer uptake along shafts of long bones with "tram-track sign", picture impressive for hypertrophic osteoarthropathy.*

Osteoid osteoma

Osteoid osteoma is a benign bone tumor that typically affects children and young adults. It is characterized by a small, painful lesion that produces an excessive amount of prostaglandins, leading to pain [99]. Commonly affects individuals between 10 and 30 years old. More prevalent in males than females [99]. Typically found in the long bones of the lower limb but can occur in any bone [100]. Less frequently, it can affect the spine, leading to scoliosis. The hallmark symptom is localized pain that is typically worse at night and relieved by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen [100]. Imaging studies, especially CT scans and bone scans, are crucial for identifying the nidus and planning treatment [101]. While conservative management with NSAIDs can be sufficient for some, minimally invasive procedures like radiofrequency ablation offer high success rates and are often preferred for definitive treatment [99, 100].

Bone scintigraphy plays a significant role in the diagnosis and management of osteoid osteoma. Bone scans are highly sensitive and can detect increased metabolic activity associated with osteoid osteomas [102]. This is particularly useful when the lesion is not clearly visible on X-rays.It helps in localizing the site of the osteoid osteoma, especially in cases where the pain is diffuse or the exact location is uncertain [102]. The hallmark of an osteoid osteoma on a bone scan is intense focal uptake of the radiotracer at the site of the lesion. This "hot spot" is due to the increased osteoblastic activity and bone turnover associated with the nidus [103]. In some cases, a double density sign can be observed, where the nidus shows a central area of intense uptake surrounded by a less intense area, representing reactive bone sclerosis [103]. The characteristic intense focal uptake and, in some cases, the double density sign, when correlated with clinical symptoms, provide a reasonably high specificity for diagnosing osteoid osteoma often cited as being between 80-100% [99] **(Figure 17)**.

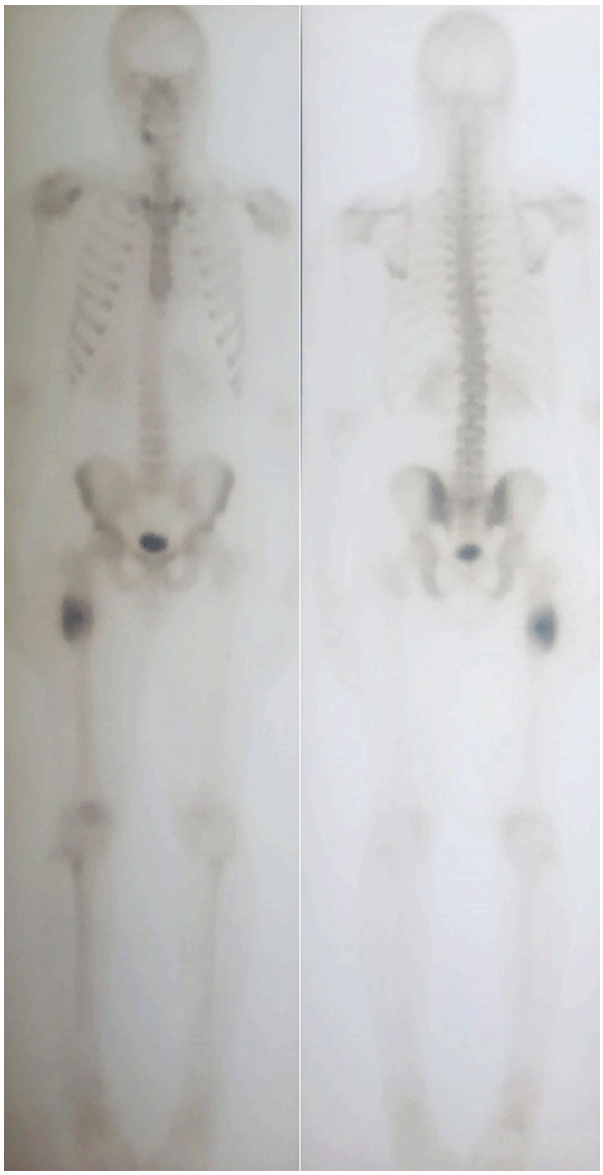

Figure 17: *20-years old male patient with nocturnal pain at right lower limb. Bone scan revealed the characteristic double density sign for osteoid osteoma at the right femur.*

Bone scan can easily confirm the diagnosis provisionally suggested by plain X-rays or CT and oftenly detected the active nidus. Also, by accurately localizing the lesion, bone scans can prevent unnecessary procedures and focus subsequent imaging and interventions on the correct area [104]. Bone scans can be used to evaluate the effectiveness of treatment, such as radiofrequency ablation (RFA) or surgical excision [103,104]. A follow-up bone scan may show reduced or absent uptake at the treatment site, indicating successful intervention. If symptoms persist or recur after treatment, a bone scan can help detect residual or recurrent disease [104].

Condylar hyperplasia

Condylar hyperplasia is a rare condition involving excessive growth of the mandibular condyle [105]. This overgrowth can cause facial asymmetry, jaw misalignment, and functional issues like malocclusion, temporomandibular joint dysfunction, and speech or chewing difficulties [105]. Bone scan with SPECT plays a critical role in evaluating condylar hyperplasia [106]. Bone scans can determine whether condylar hyperplasia is active or inactive by evaluating uptake levels. Increased uptake in the affected condyle indicates active growth, suggesting that the condition may progress if untreated [106]. Active condylar hyperplasia often requires surgical intervention, such as condylectomy or orthognathic surgery, to prevent asymmetry from worsening [107]. Inactive cases, on the other hand, may only need corrective orthodontics or orthognathic surgery without removing the condyle [107]. By conducting

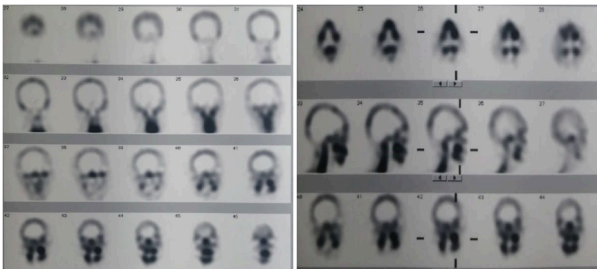

Figure 18: *Bone SPECT coronal, axial and sagital images for a case of active left condylar hyperplasia.*

serial bone scans, clinicians can monitor the progression or stabilization of condylar hyperplasia. Reduced uptake over time suggests that growth has stabilized, while sustained uptake might indicate ongoing hyperplasia [106]. SPECT/CT allows for quantification of tracer uptake, providing a more precise assessment of activity levels. This quantification can help in deciding whether the hyperplasia is actively progressing or has stabilized, influencing the choice between condylectomy and orthognathic surgery alone [106] **(Figure 18)**.

Osteopoikilosis

Osteopoikilosis is a rare, benign bone condition characterized by the presence of multiple small, rounded, radiopaque lesions scattered throughout the bones [108]. These lesions are typically asymptomatic and are often discovered incidentally during imaging studies performed for other reasons [108].
On X-ray images, osteopoikilosis is characterized by multiple small, well-defined, radiopaque foci in the trabecular bone [109]. These lesions are often described as "bone islands" or "sclerotic lesions". The lesions are usually found in the long bones, pelvis, and sometimes in the ribs. They are typically scattered and do not follow a specific pattern" [109].

Osteopoikilosis is usually asymptomatic and does not cause any pain or functional impairment. Most individuals with osteopoikilosis are unaware of the condition until an imaging study is performed for another reason [110]. Bone scans can help differentiate osteopoikilosis from other conditions that might present with similar radiological findings, such as metastatic bone disease [111]. In osteopoikilosis, the bone scan typically shows normal radiotracer uptake patterns, which can help rule out metastases or other pathologies that might cause abnormal uptake and can confirm the benign nature of the lesions [111].

Discussion

Bone scans are used to identify various bone conditions such as fractures, infections, primary bone tumors, bone metastases and metabolic disorders. When the cause of unexplained bone pain is unclear, a bone scan can help pinpoint the problem. Bone scans are highly sensitive and can detect abnormalities much earlier than conventional X-rays [5]. They provide a full-body image, allowing for the assessment of multiple bone sites simultaneously. It is a safe technique and the amount of radiation exposure is

relatively low, comparable to other diagnostic imaging procedures [6].

Conclusion

Bone scan may be the final station to confirm the diagnosis of certain bone lesions that appear equivocal on other imaging modalities [5]. Here are some conditions where bone scans can be considered more accurate, particularly when interpreted in conjunction with clinical findings and/or other imaging modalities.

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Declarations

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