

Non-neoplastic Orthopedic Pathology – A Systematic Review

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Learning Point of the Article:

Accurate distinction of non-neoplastic bone lesions from neoplastic mimics requires integrated clinicoradiological–pathological correlation to avoid overtreatment.

Abstract

Introduction: From inflammatory to neoplastic disorders, a variety of pathological bone lesions can manifest. Only 0.5% of all cancer kinds are bone tumors, making them comparatively rare. Cartilaginous, osteoid, fibrous, and bone marrow components make up bone. Benign or malignant tumors can develop in any tissue. Most of the current research focuses on uncommon tumors and their even less frequent molecular events, even though the ordinary surgical pathologist evaluates significantly more non-neoplastic orthopedic pathology on a regular basis. Our observations from concentrated seminars and consultations strongly suggest that a knowledge and diagnosis gap still exists in certain non-neoplastic orthopedic disorders. Revision arthroplasty and the assessment of infection in periprosthetic joints are among the most common intraoperative consultations conducted in the United States, both in academic and private facilities. In this technique, pathologists are essential because they assist in evaluating intraoperatively whether patients need antibiotic spacers before reimplantation. Since they (and their surgeons) wrongly think that a thorough pathological evaluation yields little therapeutically important information, several pathology departments have stopped examining arthroplasty specimens. Bone tumor-like lesions are those that resemble tumors in appearance and cytogenetics but exhibit clinical behavior that suggests they are not malignant. Tumor-like bony lesions are significant because they are widespread and resemble real bone tumors, including malignant lesions, on radiographs.

Materials and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to non-neoplastic orthopedic pathology updates: Common problems and pitfalls and how to avoid them.

Results: Six original research scientific articles dated between 2020 and 2024 pertaining to mentioned topic were highlighted.

Conclusion: Although primary musculoskeletal neoplasms account for <1% of all musculoskeletal surgical pathology cases, they are disproportionately emphasized in the surgical pathology literature compared to non-neoplastic orthopedic pathology. Detailed information regarding the non-neoplastic orthopedic pathology updates: common problems and pitfalls and how to avoid them is discussed in this systematic review.

Keywords: Musculoskeletal, tumors, bone tumors, diagnostic imaging, histopathology, non-neoplastic lesions.

Introduction

According to a review of Global Burden of Disease 2019 data, musculoskeletal disorders affect 1.71 billion people globally and

are the leading cause of disability and the requirement for rehabilitation. Of the 570 million common cases of musculoskeletal disorders globally, low back pain is the primary

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cause, resulting from a variety of traumas and illnesses, including bone diseases. Although they can affect people of any age, bone-related diseases are more common as people age. Osteoporosis is linked to cardiovascular disease and arterial calcifications, osteoarthritis (OA) to sarcopenia, and both to disability, reduced quality of life, morbidity, and mortality. These conditions frequently coexist with other non-communicable diseases and raise the chance of developing additional comorbidities. Bone fractures, OA, rheumatoid arthritis, spondyloarthritis, benign or malignant primary bone tumors, and bone cancer metastases can all cause bone-related discomfort. Bone pain is also linked to rare and inherited bone and joint conditions that afflict children and young adults, such as fibrous dysplasia and osteogenesis imperfecta. A diverse group of neoplasms known as bone tumors can develop directly from the bone (primary tumors) or spread to the bone from other parts of the body (secondary or metastatic cancers). Benign and malignant kinds of primary bone tumors are further classified, and each exhibits distinct biological characteristics, clinical symptoms, and treatment responses. Understanding the intricacy of these circumstances and creating effective management plans depends on this classification. Osteosarcoma is the most prevalent primary malignant bone tumor, especially in young adults and adolescents during periods of fast growth. The formation of osteoid tissue or immature bone by malignant cells is a characteristic of this tumor type. Bone tumors are rare, and histological analysis is essential for the precise diagnosis and treatment of bone lesions. In many respects, the pathologist's role is like a lens that focuses several light beams on a single place. The most relevant final diagnosis can be obtained by tempering microscopic findings by superimposing imaging results, clinical information, and the surgeon's personal impression, both before and after surgery, on the glass slide.

Materials and Methods

“Non-neoplastic” AND “bone” AND “pathology” were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 and 2024. The result was 58 articles, out of which we selected 6 articles based in the inclusion criteria. Inclusion criteria were case studies and scientific literature between 2020 and 2024. Exclusion criteria were those of scientific literature irrelevant to the specific search. This systematic review was conducted to determine the importance of non-neoplastic orthopedic pathology updates: Common problems and pitfalls, and how to avoid them following the guidelines of the Preferred Reporting Items for systematic reviews and meta-analyses PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of

electronic databases. The search strategy used Boolean operators (AND and OR): (ALL [“non-neoplastic”] AND [bone OR musculoskeletal OR pathology OR histopathology OR diagnostics] AND [incidence]). The following data were collected: First author, year, country of study, type of study and outcome. The quality of studies was assessed using the Strengthening the Reporting of Observational Studies checklist.

Results

Six articles were included in this systematic review based on the selection criteria. We analyzed and mentioned in the six articles reviewed. This included only relevant research articles and excluded articles pertaining to non-specific search terms (Table 1).

Discussion

Bone tumors represent a heterogeneous collection of neoplasms that originate either directly from the bone or metastasize to the bone from other sites in the body [1].

Understanding the prevalence and distribution of bone tumors is crucial for healthcare providers to develop effective screening, diagnostic, and treatment strategies [2].

The surveillance, epidemiology, and end results (SEER) database, maintained by the National Cancer Institute, collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S population [3].

Techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography scans have significantly enhanced the ability to detect and diagnose bone tumors at earlier stages [4].

The incidence rates of bone tumors vary widely across different populations and regions. According to the SEER database, the overall incidence rate of primary malignant bone tumors is approximately 0.9/100,000 individuals [5].

Osteosarcoma accounts for about 35% of all primary malignant bone tumors, followed by chondrosarcoma (30%) and Ewing's sarcoma (16%) [6].

Globally, the incidence rates show significant variability. For instance, the incidence of osteosarcoma is higher in some Asian countries compared to Western countries [7].

Several risk factors have been identified for the development of bone tumors. Age is a significant risk factor, with certain types of tumors being more prevalent in specific age groups. Gender also plays a role, with some tumors common in males than females [8].

Genetic predispositions, such as hereditary retinoblastoma and Li-Fraumeni syndrome, increase the risk of developing bone tumors. In addition, exposure to radiation and certain chemicals has been linked to an increased risk of bone tumors [9].

Biopsy is the gold standard for diagnosing bone tumors, as it allows for histopathological examination of the tumor tissue. Molecular and genetic testing can also provide valuable information for diagnosis and treatment planning [10].

Bone incidentalomas are not uncommonly found on radiographs and increasingly, CT or MRI performed for other clinical reasons, typically pain or injury at a bony site [11].

Although mostly asymptomatic, the incidental bone lesions detected on imaging may be developmental or acquired, be regarded as normal variants, or even be normal, that is, pseudolesions [12].

Anatomically, long bones include femur; flat bones include pelvis; short bones include hand and feet, and irregular bones include wrist, ankle and spine [13].

The human bone is affected by various pathological conditions, which comprise; degenerative diseases, inflammatory diseases, metabolic diseases and neoplastic lesions. Neoplastic lesions constitute; benign, malignant and metastatic lesions [14].

Diagnosis of bone lesions is a great challenge to a practicing pathologist and requires a comprehensive support of clinical, laboratory, radiological and histopathological correlation [15].

The need for accurate demographic details, such as age, gender and the affected site, becomes important, for the simple reason that many benign lesions mimic malignant lesions [16].

Age-related fractures are projected to exceed over 3 million in 2025. The prevalence of degenerative joint disease (DJD)/OA worldwide is 7%, affecting almost 500 million people [17].

There are approximately 719,000 total knee arthroplasties and 332,000 total hip arthroplasties annually, and these numbers do not reflect total shoulder replacements and other similar surgeries in the hands and feet [18].

Additional non-neoplastic specimens likely to be encountered, often due to non-healing ulcers, gangrene, or osteomyelitis, non-osteochondroma exostoses, entheses, trigger finger and carpal tunnel syndrome (CTS) biopsies, and loose bodies [19].

DJD/OA is the most common form of joint disease worldwide. It is a disease of articular cartilage, characterised by progressive erosion and loss of the articular cartilage surface with secondary changes [20].

DJD/OA may be a primary disorder or occur secondary to other pre-existing conditions, including trauma, inflammation, crystal deposition disease, osteonecrosis, and congenital

abnormalities [21].

Most arise as a primary condition, possibly related to ageing and overuse, with most patients older than 60 years of age, and some have suggested that underutilization may be an even greater risk factor [22].

Clinical symptoms include joint pain, often worse in the morning, stiffness and reduced the range of motion. Patients with secondary DJD/OA report similar symptoms but often present at an earlier age [23].

Significant chronic lymphoplasmacytic inflammation, especially if accompanied by synovial hyperplasia and surface fibrin/fibrinoid necrosis, should raise the possibility of inflammatory arthritis [24].

The most common “loose body” is the osteocartilaginous loose bodies (OLB) associated with severe DJD/OA. OLB displays concentric layering, composed of variable amounts of viable proliferating cartilage and necrotic bone [25].

OLB should be distinguished from the far less common synovial chondromatosis (SC), a benign but locally aggressive hyaline cartilage neoplasm occurring within the synovium, bursa and/ or tendon sheaths surrounding joints [26].

Compared with OLB, the “loose bodies” of SC are typically more uniform in size and shape, occur in the absence of DJD/OA and typically involve the large joints of younger patients, between 30 and 50 years of age, with males affected twice as often as females [27].

Avascular necrosis (AVN), also known as aseptic necrosis, may occur in any bone and can be traumatic or atraumatic but, especially in the hip, is pathologically defined as subchondral osteonecrosis in the absence of hip dislocation/fracture and infection [28].

Risk factors include trauma, chronic steroid use, autoimmune disease, especially systemic lupus erythematosus, decompression sickness, radiation, alcohol use, organ transplant particularly kidney, sickle cell anemia, leukemia, and Gaucher's disease [29].

Reliable recognition of the condition is important as patients with AVN have an increased risk (at least 50%) of developing the disease in the contralateral hip as well as other bone sites [30].

An important differential diagnosis to consider for both DJD/OA with secondary osteonecrosis and AVN is subchondral insufficiency fracture (SIF). It is a small fracture/microfractures occurring due to deficient elastic resistance underneath the articular cartilage [31].

Classic clinical setting is elderly women with osteoporosis; however, it may also affect younger adults, particularly active

Table 1: An overview

| Author | Title | Journal | Outcome |
|--|--|--|---|
| Sebnem Örgüç , Remide Arkun | Tumor-like lesions of bone and soft tissues and imaging tips for differential diagnosis | Örgüç S, Arkun R. Tumor-like lesions of bone and soft tissues and imaging tips for differential diagnosis. In <i>Seminars in Musculoskeletal Radiology</i> 2020 Dec (Vol. 24, No. 06, pp. 613-626). Thieme Medical Publishers, Inc. doi: 10.1055/s-0040-1721378 | Spectrum of entities mimicking tumors of bone and soft tissues that include various non-neoplastic diseases and anatomical variants |
| Faheem Ahmed Malik, Snehanish RoyChaudhary, Nathan Edwards, Raja Bhaskara Rajasekaran, Basavaraj Chari | Non-neoplastic pathologies mimicking sarcoma – Experience from a tertiary referral center multidisciplinary team | Malik FA, Chaudhary SR, Edwards N, Rajasekaran RB, Chari B. Non-neoplastic pathologies mimicking sarcoma—Experience from a tertiary referral center multidisciplinary team. European Journal of Radiology. 2022 Nov 1;156:110510. doi: 10.1016/j.ejrad.2022.110510. | A significant proportion of pathologies referred to a tertiary center sarcoma multidisciplinary team are non-neoplastic in nature |
| Alberto Di Martino , Davide Pederiva, Barbara Bordini , Gabriele DiCarlo , Alessandro Panciera, Giuseppe Geraci , Niccolò Stefanini , Cesare Faldini | Proximal femoral replacement for non-neoplastic conditions: a systematic review on current outcomes | Di Martino A, Pederiva D, Bordini B, Di Carlo G, Panciera A, Geraci G, Stefanini N, Faldini C. Proximal femoral replacement for non-neoplastic conditions: a systematic review on current outcomes. <i>Journal of orthopedics and traumatology: official journal of the Italian Society of Orthopedics and Traumatology</i> . 2022 Mar 29;23(1):18. doi: 10.1186/s10195-022-00632-z. | The use of proximal femoral replacement in non-neoplastic conditions associated with low direct mortality and high complication rates |
| Nuttaya Pattamapasong , Wilfred Cg Peh | Benign incidental do-not-touch bone lesions | Pattamapasong N, Peh WC. Benign incidental do-not-touch bone lesions. <i>The British Journal of Radiology</i> . 2023 Jan 1;96(1142):20211334. doi: 10.1259/bjr.20211334. | Benign bone lesions may occasionally be incidentally detected on radiographs and are also increasingly found |
| Michael J Klein | Non-neoplastic bone, joint, and soft-tissue pathology: What every pathologist should know | Klein MJ. Non-neoplastic bone, joint, and soft-tissue pathology: What every pathologist should know. <i>Human Pathology</i> . 2024 May 1;147:15-57. doi: 10.1016/j.humpath.2024.01.001. | The alterations of bones, joints, and to a lesser extent soft tissues that are encountered in the practice |
| Diana Expósito , José Martel , Beatriz Alvarez de Sierra , Angel Bueno, Cristina Vilanova , Joan C Vilanova | Neoplastic and Non-neoplastic Bone Lesions of the Knee | Expósito D, Martel J, de Sierra BA, Bueno A, Vilanova C, Vilanova JC. Neoplastic and Non-neoplastic Bone Lesions of the Knee. In <i>Seminars in Musculoskeletal Radiology</i> 2024 Jun (Vol. 28, No. 03, pp. 225-247). Thieme Medical Publishers, Inc. doi: 10.1055/s-0044-1781471. | The radiologic characteristics of tumor and non-tumor lesions that may appear around the knee to make a correct diagnosis and avoid unnecessary complementary |

and obese males. Other risk factors include renal and kidney transplant and systemic lupus erythematosus [32].

Unlike DJD/OA and AVN, SIF patients report acute onset pain usually because of minor injury such as twisting or long walks with heavy bags [33].

With progression, a “healing” linear fracture callus may replace the initial acute fracture. A subset appears to resolve with conservative therapy, but other cases undergo rapid progression and collapse, leading to destructive arthropathy [34].

Rapidly progressive/rapidly destructive arthritis represents a rapidly progressive and non-infectious degenerative change, occurring over a short period of time, culminating in femoral head collapse [35].

There is significant overlap with so-called neuropathic joint; however, underlying mechanisms remain unclear. The disease occurs mostly in elderly women, involving unilateral or bilateral hip joints with progressive destruction of the joint [36].

Radiologically, rapid loss of articular surface with joint space

narrowing is characteristic, and collapse of the femoral head may be appreciated. Osteophytes are not formed due to the short time interval [37].

Sequential radiographs illustrating rapid loss of articular surface with joint space narrowing are characteristic, and complete collapse of the femoral head may be appreciated [38].

Gout has plagued humanity for more than 4500 years; Population studies reveal a pooled global range of prevalence of <1–6.8% and an incidence of 0.58–2.89/1000 person-years [39].

It is caused by persistent chronic hyperuricemia resulting in deposition of monosodium urate crystals in soft tissues and joints, excess dietary purine or underexcretion [40].

Regardless of etiology, the clinical manifestations of gouty arthritis encompass four distinct syndromes – asymptomatic hyperuricemia, nephrolithiasis, acute gouty arthritis and chronic tophaceous gout; the latter two are of primary concern to the pathologist [41].



The most common clinical manifestation is a painful arthritis, frequently monoarticular and most often afflicting, at least initially, the first metatarsophalangeal joint, generally resolving within days to weeks, only to recur later [42].

Overall, treatment involves relieving the pain of acute gout, using non-steroidal anti-inflammatory drugs, as well as the prevention of future attacks with colchicine and/or allopurinol [43].

Like gouty arthritis, calcium pyrophosphate deposition (CPPD) deposition disease is a form of arthritis characterized by crystal deposition within the joints. The clinical features of CPPD deposition disease vary quite considerably, ranging from asymptomatic, incidental joint calcifications (chondrocalcinosis) to acute arthritis, closely resembling gout (pseudogout) [44].

Amyloidosis (AL) in carpal tunnel release AL represents a group of disorders involving protein misfolding, which results in aggregates of extracellular deposits of amyloid fibrils, leading eventually to organ dysfunction [45].

CTS represents the most common peripheral neuropathy of the upper extremity. Indeed, it is even more frequently observed in systemic AL, and the vast majority have bilateral symptoms [46].

Pathological fractures result from local or generalized bone disorder leading to qualitative reduction in bone strength, and disorders of production, resorption, remodeling and local bone destruction are chief causes of pathological fractures [47].

Various causes lead to abnormal bone quality, leading to pathological fracture, and primary factors of causation are the load pattern and altered strength of the bone. The pattern, clinical profile and management data are essential to know the burden of the problem [48].

Regarding an already fractured bone, surgical fixation has been linked to better function and improved quality of life. A multidisciplinary approach is advocated for the management [49].

As tumors like lesions of the bone are not neoplasms, they need not be treated as aggressively as other bone tumors. Most of the cases can be left alone. They need to be treated only if they are symptomatic or likely to produce a pathological fracture [50].

Conclusion

A crucial area of oncology, bone tumors are distinguished by their distinct epidemiological characteristics and substantial effects on afflicted patients. This systematic study provides important information about the incidence rates, survival rates, and risk factors related to various types of bone tumors. Given that patients with localized disease had substantially higher survival rates than those with metastatic disease, the review emphasizes the significance of early detection and therapy intervention. The need for specialized treatment approaches is highlighted by the observed differences in survival rates among various tumor forms. Growth patterns, environmental exposures, and genetic predispositions are key risk factors that have been identified and can inform targeted screening procedures for high-risk groups. The growing identification of bone cancers, made possible by improvements in imaging methods and increased consciousness among medical practitioners, points to a promising trend in early diagnosis. Bone tumor-like lesions are those that resemble tumors in appearance and cytogenetics but exhibit clinical behavior that suggests they are not malignant. The tumor-like bony lesions are significant because they are highly prevalent and resemble real bone tumors, including malignant lesions, on radiographs. Bone lesions that resemble tumors might be aggressive, like aneurysmal bone cysts, active, like simple bone cysts, or latent, like non-ossifying fibromas. For their management, there are no clear rules available. Unlike other bone tumors, they do not require the same level of rigorous treatment.

Clinical Message

Non-neoplastic bone lesions often mimic malignancy on imaging and histology. Careful clinicoradiological correlation is essential to avoid misdiagnosis and unnecessary aggressive treatment. Most lesions require conservative management rather than oncologic intervention.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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