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Between Infection and Malignancy: Key Clues to Distinguish Osteosarcoma from Osteomyelitis

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ABSTRACT
Introduction and aim: Osteosarcoma (OS) is a primary malignant bone tumor of youth, while osteomyelitis (OM) is an inflammatory bone infection. Despite of different etiologies, OS and OM can present with overlapping clinical and radiologic features. This paper aims to review the pathophysiology of OS and OM, indicating their clinical similarities, discuss difficulties in diagnosing and differentiating them.
Material and methods of research: A thorough literature review was performed using PubMed, Web of Science and Embase.
State of Knowledge: Osteosarcoma derives from mesenchymal osteoblast precursors and is characterized by malignant osteoid production [1]. It predominantly affects adolescents, often near the metaphyses of long bones, with rapid bone turnover [1]. Osteomyelitis is a bone infection that triggers an inflammatory cascade causing bone destruction, necrosis, and reactive new bone formation [3]. Clinically, both OS and OM cause localized bone pain, swelling and systemic signs, which can lead to one being mistaken for the other [7]. Radiologically, both may show bone lysis, periosteal reaction, and soft-tissue changes, compounding the diagnostic dilemma [6]. Because symptoms and imaging findings can overlap, misdiagnoses occur.
Conclusions: OS and OM have distinct pathophysiologies – one neoplastic, one infectious – yet they can mirror each other clinically and radiographically. Proper diagnosis is critical as treatments diverge.

Key words: *osteosarcoma, osteomyelitis, bone tumor, bone sarcoma*

1. Introduction

Bone tumors and bone infections can present diagnostic dilemmas in clinical practice. Osteosarcoma (OS) is the most common primary malignant bone tumor (excluding hematologic malignancies) and accounts for about 20% of all primary bone cancers [1]. It typically arises in adolescents and young adults during periods of rapid growth, often in the metaphyseal region of long bones (especially around the knee) [1]. Osteomyelitis (OM), in contrast, is an infection of bone, most often caused by pyogenic bacteria such as Staphylococcus aureus. It can occur at any age and in various skeletal locations, originating from hematogenous spread, contiguous infection from nearby tissue, or direct inoculation (trauma or surgery) [4].

Despite their very different etiologies, OS and OM can produce remarkably similar clinical symptoms (bone pain, swelling, reduced function) and imaging findings (bone destruction, periosteal new bone formation). Such overlap can lead to misdiagnosis – for example, a malignancy mistaken as a “refractory infection” and treated with antibiotics, or an infection misidentified as a tumor [7]. Delayed or incorrect diagnosis has serious consequences: untreated OS can metastasize and become life-threatening, while missing an OM diagnosis can lead to chronic infection, sepsis, or unnecessary oncologic treatments. Therefore, understanding the nuanced differences between OS and OM is critical for clinicians to plan appropriate management.

This review synthesizes current knowledge on the pathophysiology of osteosarcoma and osteomyelitis, examines their clinical and radiological similarities, discusses the challenges in distinguishing between them, and outlines available and emerging methods for accurate differentiation. By analyzing literature from the past 15 years (with older foundational studies for context), we aim to elucidate potential pathophysiological links between chronic inflammation and malignancy in bone, and to provide a comprehensive resource on distinguishing these two conditions.

2. Descpription of state of knowledge

2.1 Pathophysiology of Osteosarcoma

Osteosarcoma is a malignant tumor originating from primitive bone-forming mesenchymal cells. The hallmark of OS is the production of osteoid (unmineralized bone matrix) by the malignant cells [1]. OS most commonly arises in the metaphyses of long bones (distal femur, proximal tibia, proximal humerus), correlating with sites of rapid bone growth in adolescence [1]. The median age at diagnosis is in the second decade of life, and there is a slight male predominance [1]. A smaller second incidence peak occurs in older adults, often in the setting of pre-existing conditions (Paget's disease of bone, bone infarcts, or prior irradiation) – so-called secondary osteosarcomas [27].

Genetic and Molecular Factors:

Osteosarcoma development is driven by a collection of genetic abnormalities. In most cases, there is no single identifiable cause, but several key pathways have been implicated. Inactivation of the tumor suppressor genes TP53 (coding p53) and RB1 (retinoblastoma protein) is observed in a large proportion of osteosarcomas [27]. Germline mutations in these genes underlie cancer predisposition syndromes (Li-Fraumeni syndrome for TP53, hereditary retinoblastoma for RB1) that dramatically increase OS risk [27]. Experimentally, mesenchymal stem cells lacking p53 and Rb form OS-like tumors, highlighting the critical role of these pathways in osteosarcomagenesis [27]. Other molecular abnormalities frequently found in OS include alterations in the Wnt/β-catenin pathway, overexpression of oncogenes like c-MYC, and dysregulation of cell cycle regulators and kinase signaling cascades [27]. The tumor microenvironment in OS is highly complex – it contains osteoblasts, osteoclasts, immune cells, and vascular elements. OS cells often induce osteoclast-mediated bone resorption (contributing to lytic areas of bone destruction) by secreting factors such as RANKL, and they interact with surrounding stromal cells to promote tumor growth and invasion [21, 2]. In response, the body sometimes lays down reactive bone at the periphery of the tumor, which appears as sclerosis on imaging. High levels of alkaline phosphatase (ALP) in the serum can be seen in OS patients, reflecting the tumor's bone-forming activity; elevated ALP and lactate dehydrogenase (LDH) are associated with higher tumor burden and worse prognosis [1].

Growth and Spread:

Osteosarcoma is usually high-grade and aggressive. It typically grows rapidly within bone, destroying trabecular architecture from the inside. The tumor often breaks through the cortex into surrounding soft tissues early, provoking a periosteal reaction. Classic periosteal responses in OS include the "sunburst" pattern (spiculated new bone radiating outward) and Codman's triangle (an angle of lifted periosteum at the tumor margin) [1]. These occur due to fast tumor growth lifting the periosteum and prompting reactive bone formation at the edges. OS frequently metastasizes, with the lungs being the most common site of metastasis. At diagnosis, about 15–20% of patients have detectable pulmonary metastases, and an even higher proportion have micro-metastatic disease. This propensity for early hematogenous spread is a major reason systemic chemotherapy is a standard part of OS treatment. Locally, OS can also spread within the bone marrow (skip lesions) and across joint spaces if not limited by physes or other barriers [1].

2.2 Pathophysiology of Osteomyelitis

Osteomyelitis is fundamentally an infectious and inflammatory process in bone. The "pathophysiological hallmark" of osteomyelitis is the coexistence of bone necrosis and new bone formation as the host attempts to contain and eradicate the infection [3]. The most frequent causative agents are pyogenic bacteria, particularly Staphylococcus aureus, which possess specialized adhesins to bind bone matrix and evasion tactics to survive within the host [22]. However, a wide variety of organisms can cause OM (including streptococci, gram-negative rods, mycobacteria, and fungi), especially in specific clinical contexts (e.g. Salmonella in sickle cell disease, Pseudomonas in IV drug users) [4].

Routes of Infection: There are three main routes by which microbes reach bone [4]:

- Hematogenous spread: Bacteria in the bloodstream (from transient bacteremia or distant infection) lodge in bone. In children, the metaphysis of long bones is particularly susceptible due to its rich but slow blood flow and discontinuous capillary endothelium, which allows organisms to exit vessels into bone tissue [4]. In infants and adults, transphyseal vessels or vertebral end-arteries can transmit infection to epiphyses or vertebral bodies, respectively. Hematogenous osteomyelitis typically presents in the metaphyses of long bones in children and in the vertebrae in adults.
- Contiguous spread: Infection spreads to bone from an adjacent infected site, such as a soft tissue abscess, decubitus ulcer, or septic joint [4]. This is common in polymicrobial osteomyelitis associated with chronic wounds (e.g. diabetic foot ulcers) or surgical site infections. Compromised local vascularity (as in diabetes or peripheral arterial disease) increases susceptibility.

- Direct inoculation: Trauma (open fractures, penetrating injuries) or orthopedic surgery can introduce organisms directly into bone [4]. Orthopedic hardware (plates, rods, prostheses) can also seed infection on the bone-implant interface, often involving biofilm-forming bacteria that are difficult to eradicate [4].

Acute Osteomyelitis:

Once bacteria establish in bone, an acute inflammatory response ensues. In the early (acute) stage of osteomyelitis, pus begins to accumulate in the bone marrow space. The body attempts to wall off the infection: granulation tissue forms around the collection of pus, and osteoblasts lay down new bone at the periphery, creating an intraosseous abscess cavity [4]. This early abscess is classically called a Brodie's abscess when it is small and subacute, often in metaphyses. As pressure builds within the marrow from the expanding purulence, the rigid cortical bone cannot accommodate swelling like soft tissue can. Eventually, the intramedullary pus dissects through the haversian canals to the cortex, elevating the periosteum. The pressure may rupture through the cortex itself, producing a cortical defect known as a cloaca [4]. Through the cloaca, pus can drain out of the bone into the subperiosteal space and surrounding soft tissues [4]. The periosteum, lifted by the underlying abscess, reacts by forming new bone – an acute periostitis visible on imaging as periosteal elevation or layering [4]. If the abscess finds a path to the skin surface, a sinus tract can form, venting pus externally. In summary, acute OM is characterized by suppurative inflammation within bone (osteitis), rising intramedullary pressure, local ischemia from compromised blood flow, and the initial attempts at repair and containment (granulation and reactive bone). Clinically, this corresponds to severe bone pain, fever, and often an acute systemic illness.

Chronic Osteomyelitis:

If the infection is not cleared in the acute phase, osteomyelitis transitions into a chronic phase, which can smolder for months or years. Chronic OM is defined by the presence of devitalized bone that has separated from viable bone, ongoing suppuration, and episodes of quiescence and flare-ups. The key pathologic features are:

- Sequestrum: a fragment of necrotic bone that has become separated from the surrounding living bone. On imaging, a sequestrum appears as a piece of sclerotic (dense) bone often encircled by a radiolucent halo (the granulation tissue) [4]. Sequestra form because the infection compromises the blood supply to a portion of bone, causing it to die. The body cannot easily resorb this dead bone due to its avascularity and the presence of bacteria shielding within it.
- Involucrum: reactive new bone formed by the periosteum that encases the infected area [4]. The involucrum is basically the bone's attempt to wall off and contain the infection. It appears as thickened, irregular cortex surrounding the original bone. In chronic OM, one might see a thick bony collar (involucrum) around an area where the original cortex has been destroyed.
- Sinus tracts: chronically draining tracts from the infected bone to the skin surface. These tracts can heal and reopen, and their presence is a clinical hallmark of chronic OM. Sinography (injecting contrast into a sinus tract) can delineate the tract's course and its communication with bone abscesses [5].
- Persistent infection and inflammation: Histologically, chronic OM shows granulation tissue, fibrosis, and pockets of pus. Bacteria often survive inside biofilms on dead bone or foreign material, evading immune clearance and antibiotics. The chronic inflammation can wax and wane, leading to periods of low-grade symptoms punctuated by acute exacerbations if the bacteria re-activate or the sequestrum causes irritation.

Chronic OM can last decades if not properly treated, and it imposes ongoing inflammatory stress on the bone and surrounding tissues.

Biofilms and Immune Evasion:

A significant aspect of chronic osteomyelitis pathophysiology is bacterial biofilm formation. Bacteria such as S. aureus can form colonies encased in a protective extracellular matrix on bone surfaces or hardware. In this biofilm state, bacteria become dramatically less susceptible to antibiotics and host immunity [3]. This is why chronic OM often requires surgical debridement – to physically remove biofilm-coated sequestra – in addition to prolonged antibiotics. Chronic OM also skews the local immune response: macrophages and neutrophils are persistently activated, producing cytokines (IL-1, IL-6, TNFα) and proteolytic enzymes that contribute to tissue damage. These inflammatory mediators stimulate osteoclasts, causing bone resorption, while the periosteal irritation stimulates osteoblasts to form new bone (involucrum). Hence, chronic OM is an active balance of bone destruction and formation.

Aseptic Osteomyelitis:

It is worth noting a non-infectious chronic osteomyelitis variant: Chronic Recurrent Multifocal Osteomyelitis (CRMO), an autoinflammatory disorder in children [4]. In CRMO, the lesions are sterile (no organism) but cause similar bone inflammation. While CRMO is beyond this review's scope, it underscores that chronic inflammation alone (even without bacteria) can produce osteomyelitis-like pathology.

In summary, osteomyelitis pathophysiology involves an interplay between invading organisms and the host bone's response. The outcome is a spectrum from an acute, potentially curable infection to a chronic, indolent

disease characterized by dead bone and persistent inflammation. This chronic inflammatory microenvironment has implications for oncogenesis, as discussed later.

2.3 Clinical Similarities and Overlapping Features

Despite their different causes, osteosarcoma and osteomyelitis share many clinical features that can make initial differentiation difficult. Both conditions primarily affect the long bones (especially around the knee region) in adolescents and young adults – a demographic overlap that can confuse the clinical picture. Key similarities include:

- Localized Pain: Pain is the most common presenting symptom of both OS and OM. In osteosarcoma, pain often gradually increases over weeks to months; it may initially be intermittent and mistaken for "growing pains" or sports injury. Similarly, in subacute or chronic osteomyelitis, pain can be insidious and chronic. In acute osteomyelitis, pain onset is more rapid and severe, but in an indolent infection, the pain may be milder and protracted. In both diseases, the pain tends to be localized to the affected bone and often worsens with activity or at night. Because bone pain in a young person could suggest either a tumor or an infection, this symptom alone is non-discriminatory [6].
- Swelling and Mass: Both OS and OM can present with swelling of the affected area. In osteosarcoma, a firm, often tender mass may be palpated if the tumor extends into soft tissue. Overlying skin may be warm due to increased blood flow, and superficial veins can be distended in large tumors. In osteomyelitis, especially chronic, there can be an inflammatory swelling of the soft tissues. Chronic OM can cause an enlargement of bone contour due to involucrum formation, and a fluctuant swelling might be present if an abscess tracks near the surface. In one comparative series, local swelling was reported in about half of osteomyelitis cases and two-thirds of Ewing's sarcoma (a bone tumor) cases, indicating substantial overlap [6]. Thus, the presence of a swollen, enlarged area over a bone could be either an infected periosteum or a tumor mass.
- Tenderness: On examination, both conditions typically cause point tenderness over the involved bone. The pain on palpation can be severe in both cases. Guarding and limited range of motion in adjacent joints are common to both OS and OM when the metaphysis near a joint is involved.
- Fever and Systemic Symptoms: Classically, osteomyelitis (especially acute hematogenous OM) presents with fever, chills, and systemic illness, whereas osteosarcoma is not usually associated with high fever. However, this distinction is not absolute. Low-grade fever and malaise can occur in patients with large osteosarcomas, possibly related to cytokine release or tumor necrosis. Conversely, subacute or chronic osteomyelitis may present with minimal or no fever, particularly in adults or if partially treated with antibiotics. In the study by McCarville et al.comparing osteomyelitis and Ewing sarcoma, fever was present in 23% of osteomyelitis cases and 41% of Ewing sarcoma cases – not a statistically significant difference [6]. This surprising finding underscores that tumors (especially Ewing's sarcoma and rarely OS) can provoke fever, while infections can sometimes smolder without systemic signs. Other systemic markers like weight loss or night sweats are uncommon in both, but both conditions can cause fatigue and decreased appetite in chronic cases.
- Laboratory Findings: Both OS and OM may elevate certain laboratory markers, but again with overlap. Osteomyelitis often elevates acute phase reactants: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually high in acute OM and may remain mildly elevated in chronic OM. Leukocytosis (high white blood cell count) is common in acute OM, though it may be mild or absent in chronic cases. Osteosarcoma can also cause elevated ESR or CRP in some patients, due to tumor-induced inflammation. In fact, one study found no significant difference in mean ESR or CRP between patients with Ewing sarcoma and osteomyelitis [6]. The WBC count in OS is usually normal, but it can be elevated if there is tumor necrosis or accompanying stress response [6]. Both OS and OM can cause anemia of chronic disease in prolonged cases. Distinct lab clues do exist (e.g. extremely high CRP is more suggestive of infection, while elevated ALP or LDH favors OS), but these are trends, not definitive tests [6]. In summary, routine labs are often inconclusive: one must consider the whole picture rather than any single lab result.
- Imaging Findings (Overview): Clinically, if an X-ray of a painful swollen limb in a teenager shows a destructive bone lesion with periosteal reaction, the differential automatically includes osteomyelitis and osteosarcoma (among other entities). Both conditions show what radiologists term an "aggressive" bone lesion pattern: poorly defined margins (wide zone of transition between normal and abnormal bone), cortical destruction, and periosteal new bone formation [6]. These similarities on plain radiographs account for many initial diagnostic dilemmas. Both can also show a mixture of osteolysis (bone loss) and reactive sclerosis. Although certain radiographic features favor one diagnosis or the other (discussed in the next section), it often requires advanced imaging and biopsy to be sure.

Because of these overlapping clinical features, a careful and often multidisciplinary approach is required when a patient presents with signs that could indicate either diagnosis. Clinical context can provide hints: for example,

an acute onset of symptoms following trauma or surgery might point toward osteomyelitis, whereas a few months of progressive pain in an otherwise healthy teen might more strongly suggest a tumor. A history of antecedent infection (like a boil or tooth abscess leading to bacteremia) might raise suspicion for hematogenous osteomyelitis. Conversely, a history of familial cancers or retinoblastoma could heighten concern for osteosarcoma. Physical exam may reveal clues like a draining sinus (pathognomonic of chronic OM) or a very firm fixed mass (more typical of a solid tumor). Yet, none of these alone is definitive.

In practice, any substantial bone lesion in a patient (especially a child or adolescent) is often investigated for both possibilities. Oncologists and orthopedists often collaborate, and empiric antibiotics should generally be avoided unless infection is confirmed, since partially treated osteomyelitis can further confound the picture. Conversely, one must be cautious not to dismiss a true infection as "just tumor inflammation." The interplay of these clinical aspects makes the diagnostic process challenging and necessitates a thorough evaluation with appropriate investigations.

2.4 Diagnostic Challenges in Distinguishing Osteosarcoma and Osteomyelitis

Distinguishing osteosarcoma from osteomyelitis can be challenging even for experienced clinicians due to the overlapping features described. Several studies in the literature highlight the pitfalls and delays in diagnosis that can occur:

- Misdiagnosis and Delayed Diagnosis: It is well documented that osteosarcomas have been misdiagnosed as osteomyelitis, leading to delays in proper cancer therapy. Patients have been subjected to repeated courses of antibiotics and even surgical debridements for an assumed infection, while the tumor continued to grow. Conversely, there are cases of chronic infections mistaken for malignancies, with patients undergoing unnecessary biopsies or being monitored for "tumor" when they actually needed antimicrobial treatment. Jung et al. (2022) explicitly state that OS is "often misdiagnosed as osteomyelitis due to the nonspecificity of its symptoms" at initial presentation [7]. Such misdiagnoses are especially common when a lesion presents with atypical features – e.g., an osteosarcoma with an accompanying fever and elevated CRP, or an osteomyelitis that on imaging has a large soft-tissue component or aggressive periosteal reaction. The cost of misdiagnosis is high: for OS, a delay can mean progression to metastatic disease (which drastically lowers survival rates), and for OM, a delay can mean progression to chronic infection or sepsis.
- Biopsy Considerations: Obtaining a definitive diagnosis via biopsy can itself be fraught with difficulty. In osteomyelitis, culture of a biopsy sample can be negative (so-called "culture-negative osteomyelitis") in a significant subset of cases due to prior antibiotics or intracellular bacteria. In osteosarcoma, a biopsy could be non-diagnostic if the sample is not representative (e.g., sampling reactive bone instead of the tumor). Moreover, when infection and tumor coexist or one masquerades as the other, biopsy interpretation can be tricky. There are instances of "sterile abscesses" within osteosarcomas – cystic tumor areas that can be mistaken for infection on imaging and even yield neutrophils on pathology. On the flip side, chronic OM can cause atypical fibroblastic and reactive changes in tissue that a pathologist might initially wonder about neoplasm. McCarville et al. examined the accuracy of needle versus open biopsy in patients suspected of Ewing sarcoma vs osteomyelitis. They found that percutaneous needle biopsy was significantly less reliable for diagnosing osteomyelitis (only ~58% yielded the correct diagnosis) whereas open surgical biopsy was 100% accurate for OM in their series [6]. The lower yield of needle biopsy in OM is often due to insufficient or non-representative tissue (missing a sequestrum or not getting enough sample for culture and histology). Thus, one challenge is that even after a biopsy, the distinction might remain unclear if results are inconclusive, necessitating repeat or open biopsy.
- Imaging Ambiguities: While modern imaging has improved lesion characterization, certain scenarios are notoriously ambiguous. For example, a lytic lesion in the metaphysis of a child with surrounding edema on MRI might represent subacute osteomyelitis (Brodie abscess) or an osteoid osteoma or even an osteosarcoma of telangiectatic type – all very different diagnoses. Telangiectatic osteosarcoma is a variant of OS that is mostly lytic and can present as a fluid-filled cavity in bone (sometimes with fluid levels on MRI), mimicking an abscess radiologically. Conversely, chronic osteomyelitis can cause such extensive sclerosis and periosteal bone that it forms a mass-like lesion (sometimes termed Garre's osteomyelitis, or proliferative periostitis) which can resemble a surface osteosarcoma. In imaging studies, radiologists use certain criteria to suggest one over the other (discussed below), but none are foolproof. McCarville's study noted that individually, features like a Codman triangle or soft tissue mass on X-ray suggested Ewing sarcoma, whereas a sequestrum or draining sinus on imaging would indicate osteomyelitis – yet many patients lacked pathognomonic signs [6, 4]. They concluded that a combination of clinical, lab, and imaging findings had to be considered together, and even then a biopsy was often needed [6].
- Laboratory Pitfalls: If a patient presents with fever and high inflammatory markers, clinicians may be biased toward an infection diagnosis. While this is often correct, there are pitfalls: Ewing sarcoma (and

rarely OS) can present with fever and an inflammatory response that mimics infection (sometimes termed "tumor fever"). Such patients might be started on antibiotics for presumed OM, only to have no improvement. Conversely, in an afebrile patient with a normal WBC, one might lean toward tumor – but certain chronic low-grade infections (e.g., tubercular osteomyelitis or fungal osteomyelitis) can present without leukocytosis or fever. A specific example is tuberculous osteomyelitis (Pott's disease in the spine or TB of long bones), which often has a indolent course and can create a lytic lesion with mild systemic signs, potentially confused with a neoplasm like Langerhans cell histiocytosis or metastatic cancer. Thus, relying solely on the presence or absence of systemic inflammation can be misleading.

- Overlap of Infection and Tumor: In some cases, both processes coexist, further complicating diagnosis. An osteosarcoma can become secondarily infected, especially if it has ulcerated through the skin or after a pathologic fracture. Alternatively, chronic osteomyelitis (particularly with long-standing sinus tracts) can rarely undergo malignant transformation (typically to squamous cell carcinoma of the skin or a sarcoma in scar tissue) [23]. In a patient with decades of chronic osteomyelitis and a sudden worsening or new mass, one must consider that an OS (or other malignancy) could arise in that environment. The incidence of malignant transformation in chronic OM has been reported between ~1.6% and 23% in older series, most often after a very long latency (average ~30 years of infection) [11, 12]. While usually this results in carcinoma, there are case reports of sarcomas on a background of OM. Therefore, a bone biopsy in chronic OM should always be examined carefully for any malignant cells. When infection and tumor coincide, diagnostic tests can yield mixed results (e.g., positive cultures and malignant histology), requiring a multidisciplinary interpretation.
- Experience and Resources: In some settings, lack of advanced imaging or expert pathology can make distinction harder. For example, in resource-limited regions, a child with a bone lesion might get an X-ray and maybe an aspirate. If the aspirate shows neutrophils but no organisms, one could misinterpret it. Access to MRI, nuclear medicine, or specialized microbiology (for atypical organisms) improves diagnostic accuracy, but not all centers have these readily. Even the experience of the radiologist or pathologist matters – musculoskeletal tumors are relatively rare, and distinguishing reactive atypia from malignancy in bone biopsies is a subspecialty skill.

Given these challenges, standard of care for an undiagnosed destructive bone lesion often involves a combined approach: imaging (plain radiographs, MRI, possibly bone scan), laboratory tests (CBC, inflammatory markers, sometimes alkaline phosphatase, etc.), and a tissue biopsy for histology and culture. Orthopedic oncologists often emphasize performing the biopsy in a controlled manner (ensuring proper tract placement in case it is a tumor that will need wide resection) but also obtaining adequate material for cultures (in case it is infection). Only through this comprehensive approach can the diagnostic ambiguity be resolved in most cases [6]. It is also crucial to communicate to the radiologist and pathologist the full clinical picture and differential, so they can specifically look for features favoring OM vs OS.

In summary, distinguishing OS from OM is challenging because each can masquerade as the other. High clinical suspicion, awareness of the subtleties, and timely use of diagnostic tools are necessary to avoid misdiagnosis. The following section will delve into specific methods and findings that help differentiate the two conditions, highlighting both classical approaches and newer techniques.

2.5 Methods of Differentiation and Latest Diagnostic Techniques

Accurately differentiating osteosarcoma from osteomyelitis requires integration of clinical information with multiple diagnostic modalities. Here we outline the key methods and findings used to distinguish the two, ranging from classical imaging signs to cutting-edge techniques:

Clinical Clues and Laboratory Tests

While, as noted, clinical and lab features alone are not definitive, they do provide important clues when interpreted in context:

- Time Course: An acute, fulminant course with high fever and toxicity strongly suggests osteomyelitis (especially acute hematogenous OM) rather than osteosarcoma, which usually has a more insidious onset. On the other hand, a chronic, indolent course with symptoms over months could be either chronic OM or OS; one pitfall is that chronic OM can have a relapsing-remitting pattern (flare-ups of pain and drainage) whereas OS pain generally steadily progresses. If empirical antibiotics lead to improvement of symptoms (and especially if inflammatory markers drop), that supports an infectious etiology, although one must be cautious interpreting a partial response (OS will not truly improve on antibiotics, but some tumors might have waxing symptoms).
- Physical Exam: The presence of a sinus tract with purulent drainage is virtually pathognomonic for chronic osteomyelitis, not osteosarcoma. Any visible pus from the bone or an ulcer over a chronic lesion favors infection. In contrast, a hard, non-mobile mass attached to bone (without signs of infection) is

more indicative of a tumor. Lymph node involvement may also differ: reactive lymphadenopathy can occur in infection; in OS, regional lymph node metastasis is rare (except in certain small cell variants).

- Blood Tests: Markedly elevated inflammatory markers (ESR > 50 mm/hr, CRP > 10 mg/dL) and leukocytosis (WBC > 12,000/μL) are more common in acute osteomyelitis [6]. If blood cultures are positive (growing bacteria), that essentially confirms an infectious process. In osteosarcoma, blood cultures would be sterile. Serum ALP and LDH tend to be elevated in many OS cases due to bone formation and high cell turnover [1], whereas in osteomyelitis these enzymes are usually normal (unless there's extensive bone remodeling in chronic OM). Thus, a high ALP in a destructive bone lesion leans toward OS, while a high CRP and WBC lean toward OM – but none of these is absolute. Additionally, pediatric patients with Ewing sarcoma often have elevated LDH and sometimes anemia, which could mimic infection labs.
- Microbiological Tests: If a bone aspirate or biopsy yields a microorganism on Gram stain or culture, it points to osteomyelitis. For example, finding gram-positive cocci and subsequently growing S. aureus from a bone aspirate is definitive for OM. However, negative cultures do not rule out infection (culture-negative OM is common after prior antibiotics). Modern techniques like broad-range 16S ribosomal DNA PCR or sequencing can detect bacterial DNA in tissue and have improved sensitivity for diagnosing OM, especially in cases where conventional cultures are negative or slow-growing organisms (e.g. mycobacteria, Brucella) are involved. In a differentiation context, demonstration of bacteria in a lesion virtually rules out a pure osteosarcoma (though one must consider possibility of a secondary infection superimposed on a tumor).
- Biopsy Histology: Histopathology remains the gold standard. An adequate biopsy, examined by an experienced musculoskeletal pathologist, will usually make the distinction. Osteosarcoma is characterized by malignant tumor cells producing osteoid matrix [1]. The biopsy will show atypical mesenchymal cells (often with high mitotic activity) and unmineralized bone matrix (eosinophilic "lace-like" osteoid) deposition. In contrast, osteomyelitis biopsy will show necrotic bone fragments (sequestra) devoid of osteocytes, inflammatory cells (neutrophils in acute, mixed inflammatory and fibrous tissue in chronic), and possibly bacterial colonies. Granulation tissue with plasma cells and lymphocytes is common in chronic OM. There is no clonal atypia in purely infectious lesions – except perhaps reactive fibroblasts – and no malignant osteoid. However, one must be vigilant for concurrent malignancy (like squamous cell carcinoma arising from a sinus tract) in chronic OM specimens; any dysplastic or carcinoma cells should prompt additional sampling. Another nuance: small round cell tumors like Ewing sarcoma can resemble inflammation (lots of necrosis and reactive changes) but immunohistochemical stains and molecular tests (like EWSR1 gene translocation analysis) help identify them. Similarly, chronic OM can cause reactive bone formation that might mimic low-grade osteosarcoma, but immunostains and the bland nature of cells will differentiate it. Therefore, when in doubt, special diagnostic tests (like FISH for gene rearrangements in tumors, or Gram stains for bacteria in biopsy) are used.

Imaging Modalities

Plain Radiography: The first-line imaging for bone lesions is the X-ray. Several radiographic features help distinguish OS and OM:

- Location: OS typically arises in the metaphysis of long bones [1], while hematogenous OM in children also favors metaphyses. However, OM can also occur in diaphyses (especially chronic or in adults with vascular insufficiency) or vertebrae (in adults), whereas primary OS of the spine or foot is exceedingly rare. If a lesion is in an unusual location (e.g., mid-diaphysis of tibia in a child), Ewing sarcoma or infection might be more likely than conventional OS (which is metaphyseal ~90% of the time [1]). Location must be interpreted with other signs.
- Bone destruction pattern: Osteosarcoma often shows a mixed lytic and blastic pattern – areas of bone destruction with adjacent regions of tumor new bone formation [1]. In some cases OS can be predominantly osteoblastic (dense sclerosis) or predominantly lytic. Osteomyelitis, especially acute, usually causes purely lytic lesions due to bone necrosis; chronic OM can show sclerosis, but it tends to be peripheral involucrum rather than internal tumor bone. A classical teaching is that a sequestrum in chronic OM appears as a piece of sclerotic bone separated from surrounding lucent infection (sometimes described radiographically as a "button sequestrum" – a central opacity with a lucent rim) [4]. This appearance is uncommon in tumors; it strongly favors OM..
- Periosteal reaction: Both processes cause periosteal new bone formation, but the pattern can differ. OS, due to aggressive rapid growth, classically shows a "sunburst" periosteal reaction – thin spicules of bone radiating outward – or amorphous cloud-like mineralization in the soft tissue mass [1]. A Codman's triangle (triangular elevation of periosteum at the tumor margin) is another OS-associated finding [1]. Osteomyelitis can also lift the periosteum; in acute OM, the periosteal reaction might be lamellated ("onion-skin" layers) or modest. Chronic OM often leads to thick, solid periosteal reaction (involucrum)

rather than the delicate spiculation of OS. One study found that a visible Codman's triangle on X-ray was significantly more common in Ewing sarcoma than in osteomyelitis [6]. However, onion-skin periosteal reaction can be seen in Ewing's sarcoma and in OM (especially subperiosteal abscess in children). Thus, while periosteal patterns are suggestive, they are not foolproof. Generally, a complex, interrupted periosteal reaction with a large soft tissue component raises more suspicion for tumor [6].

- Soft tissue involvement: On X-ray, the presence of a large soft-tissue mass with calcifications is characteristic of osteosarcoma [1]. Osteomyelitis can cause soft tissue swelling or abscess, but usually not a massive calcified soft tissue tumor. If one sees tumor bone extending into soft tissue (cloud-like densities beyond the cortex), that indicates OS producing osteoid in soft tissue [1]. Soft tissue abscesses in OM typically appear as non-calcified masses (visible as soft tissue shadow, possibly with gas if anaerobes). Gas in the lesion (radiolucent bubbles on X-ray) is a red flag for infection, as certain bacteria (like Clostridium or other gas-formers) produce gas, and tumors do not.
- Joint involvement: OS rarely crosses joint spaces (it usually stops at the epiphyseal plate in adolescents, though it can occasionally invade an epiphysis and joint in advanced cases). Osteomyelitis, especially if chronic or in young infants (with transphyseal vessels), can spread into adjacent joints causing septic arthritis, or spread across physes. If imaging shows clear evidence of infection in a joint along with bone changes, osteomyelitis (with secondary arthritis) is likely, not a primary bone tumor. McCarville et al. noted joint involvement was more often seen with osteomyelitis than Ewing sarcoma on imaging [6], reflecting the fact that infection can track through natural pathways into joints.

Magnetic Resonance Imaging (MRI):

MRI is extremely useful for both entities, providing detailed information on marrow, cortical bone, and soft tissue:

- On MRI, osteosarcoma typically shows a bulky intramedullary tumor with low signal on T1-weighted images and heterogeneous high signal on T2 or fluid-sensitive sequences due to tumor matrix and necrosis. Gadolinium contrast enhancement is usually robust and heterogeneous in OS, reflecting the tumor's vascularity (necrotic areas may not enhance). MRI defines the intraosseous extent (skip lesions, transphyseal spread) and the soft tissue mass very clearly [1]. OS often has a soft tissue component with enhancement extending through cortical breaches.
- Osteomyelitis on MRI classically shows bone marrow edema: low signal on T1 and high signal on T2/STIR in the affected marrow, often with enhancement after contrast [4]. In acute OM, this marrow edema can be diffuse; there may be an abscess which appears as a fluid pocket (T2 bright, T1 low) with a rim of enhancement (the granulation tissue "ring enhancement"). A helpful sign for subacute OM (Brodie abscess) is the penumbra sign – on T1 images, a Brodie abscess sometimes shows a thin rim of slightly higher signal intensity around the abscess cavity, representing proteinaceous granulation tissue [6, 4]. This penumbra sign is quite specific for a bone abscess and is usually not seen in tumors [6]. Chronic OM MRI might show a sequestrum as a dark void (low on both T1 and T2) within the marrow, surrounded by enhancing inflammatory tissue [4]. Sinus tracts, if present, will enhance and can often be traced from bone to skin on MRI [4].
- Comparative MRI features: A study by Kaim et al. (noted in other sources) suggested that a well-defined border between normal and abnormal marrow on T1 (a sharp transition) favors osteomyelitis, whereas a more infiltrative indistinct marrow replacement favors tumor. Additionally, the presence of a sizable soft tissue mass with relatively little marrow edema points to tumor. In McCarville's analysis, MRI findings of cortical destruction with a large soft-tissue mass were strongly associated with Ewing sarcoma, whereas a combination of multiple small abscesses or the penumbra sign pointed to OM [6].
- One limitation is that both infection and tumor can cause reactive edema in neighboring tissues; for instance, both can have peri-lesional edema in muscle and both can extend to the growth plate region. Therefore, while MRI greatly delineates the lesion, certain advanced MRI techniques have been explored to improve differentiation. Diffusion-weighted MRI (DWI) can provide insights: abscess fluid often has very high signal on DWI (restricted diffusion) due to pus, whereas tumor tissue may have intermediate diffusion restriction; still, the overlap is significant. Dynamic contrast enhancement (DCE) might show different perfusion kinetics – infections might enhance in a rim pattern and wash out quickly, whereas tumors often have neoangiogenic patterns – but again, not definitive.
- It's worth noting spinal lesions: differentiating vertebral osteomyelitis/discitis from metastatic tumor can be tricky on MRI. Clues there include disc space involvement (infection often destroys the disc, whereas metastases usually spare discs). For OS vs OM in long bones, this is less relevant as OS rarely involves discs.

Computed Tomography (CT):

CT is excellent for visualizing bone architecture and detecting small sequestra or calcifications:

- In osteosarcoma, CT can better show matrix mineralization within the lesion (cloud-like osteoid calcifications). It also helps in characterizing cortical destruction and any ossification in soft tissue. CT

of the chest is mandatory in OS for detecting lung metastases [1], but for local diagnosis, MRI is usually preferred over CT. However, if MRI is contraindicated, CT can help differentiate a bone abscess (which might show a fluid cavity ± gas and an intact or expanded cortex) from a tumor (irregular osteoid mineralization and permeative cortical erosion).

- In osteomyelitis, CT is superb at identifying sequestra, cloacae, and involucrum in chronic cases [4]. A tiny sequestrum is seen as a fragment of dense bone separated by a lucent boundary from normal bone – CT can pick this up better than MRI (where the sequestrum is just a signal void) [4]. CT can also show intramedullary gas, which, if present, confirms infection. For complex anatomical regions (e.g., pelvis, sternum), CT can be very helpful to map the infection.
- CT-guided biopsy is often used to obtain samples from bone lesions. Under CT, one can target a specific area (like the center of an abscess or the most lytic part of a tumor). This improves diagnostic yield when distinguishing OS vs OM by allowing precise sampling (e.g., hitting the sequestrum for cultures, or getting viable tumor tissue).

Nuclear Medicine and PET:

Radionuclide imaging provides functional information:

- Three-phase bone scan (Tc-99m MDP): Both osteomyelitis and osteosarcoma will generally show increased uptake on bone scintigraphy due to high bone turnover. A classic three-phase bone scan can sometimes differentiate cellulitis (soft tissue infection) from osteomyelitis but is less specific between OM and tumor – both will be hot on blood pool and delayed phases if bone is involved [5]. However, diffuse uptake in an entire bone segment might lean toward infection if it corresponds to an anatomic vascular pattern, whereas a more focal intense uptake might be tumor. In multifocal disease, bone scan can identify multiple hotspots: multifocal uptake could mean metastatic OS (which is rare at presentation except for lung metastases which bone scan wouldn't show) or multifocal OM (like in bacteremia or CRMO). Thus, bone scan is sensitive but not specific for the cause of increased uptake [5].
- Gallium-67 scan: Gallium accumulates in areas of infection and some tumors but has some preference for inflammation. It can sometimes help – gallium uptake in a bone lesion, in conjunction with bone scan, was traditionally used to distinguish infection (high gallium and technetium uptake) from tumor (high technetium, lower gallium). In practice, this is rarely used now, supplanted by labeled leukocyte scans and FDG-PET.
- Indium-111 or Tc-99m labeled white blood cell (WBC) scan: In suspected infection, a patient's WBCs can be labeled and re-injected to see if they home to the lesion. Osteomyelitis will typically show WBC uptake in the bone, whereas a malignancy will not accumulate WBCs (unless there's secondary inflammation). A WBC scan combined with a bone scan is a highly specific test for osteomyelitis. If a bone scan is hot but the WBC scan is not, it suggests tumor or another non-infectious process. WBC scans are most useful in cases of suspected OM with hardware or difficult anatomy, but they can be applied to differentiating tumor vs infection as well.
- FDG-PET/CT (Fluorodeoxyglucose Positron Emission Tomography): Both tumors and infections are usually hypermetabolic and will show uptake of FDG. Thus, PET is very sensitive for detecting an abnormality but not specific to distinguish them. An FDG-PET may show a high standardized uptake value (SUV) in an osteosarcoma – but acute OM can have SUVs in a similar range. Some studies have tried to look at patterns: tumors may have more localized uptake, whereas infection might have a more diffuse uptake and adjacent soft tissue uptake. But generally, FDG-PET on its own cannot reliably tell infection from tumor. It is more useful in ensuring you're not missing additional sites (like metastases or multifocal infection). Because of this limitation, research has turned to other tracers or techniques (e.g., radiolabeled bacteria-specific tracers, or combining PET with MRI).
- PET/MRI with USPIO (Ferumoxytol): A novel approach currently under investigation is using ferumoxytol (an iron oxide nanoparticle) as an MRI contrast agent and PET tracer surrogate to differentiate infection vs tumor. Ferumoxytol is taken up by macrophages in areas of inflammation. In an infection, there is typically a strong macrophage presence (especially chronic OM with granulomas or abscess walls), whereas in a malignant tumor the distribution of macrophages (tumor-associated macrophages) may be different. Early pilot trials (Stanford University, etc.) are assessing whether ferumoxytol-enhanced MRI can highlight inflammatory uptake that would be higher in OM compared to OS [24]. While results are not yet conclusive, this represents the kind of cutting-edge diagnostic innovation being explored.

Advanced and Adjunct Techniques:

- Histological and Molecular Analysis: Beyond standard histology, ancillary tests can aid differentiation. For example, if small round blue cells are seen on biopsy, immunohistochemical stains for Langerin, cytokeratins, CD99, desmin, etc., can distinguish Ewing sarcoma, lymphoma, eosinophilic granuloma, or osteomyelitis with granulomas. PCR can detect Mycobacterium tuberculosis in a granulomatous lesion, clinching tubercular osteomyelitis rather than, say, Ewing sarcoma. Conversely, finding a genetic

mutation or fusion (like EWS-FLI1 in Ewing, or MDM2 amplification in parosteal OS) would confirm a tumor diagnosis. These molecular tools are increasingly available and can be crucial when the histology is confusing due to overlapping features.

- Fractal and Texture Analysis: As demonstrated by Jung et al. (2022), radiographic texture analysis might pick up subtle differences in bone microarchitecture caused by OS vs OM [7]. In their study on jaw lesions, OS-affected bone had a higher degree of isotropy (more uniform trabecular pattern disruption) compared to OM, which had a slightly different anisotropy in trabecular architecture [7]. Such computational analysis of X-rays or MRI (radiomics) could become an adjunct in borderline cases, potentially via an AI algorithm trained to classify lesions.
- Infrared or Spectroscopic Techniques: Experimental methods like Fourier-transform infrared (FTIR) spectroscopy of bone samples have shown that the chemical composition changes in infected bone vs tumor are detectable in spectral patterns [25]. These are currently research tools, but they highlight the broader attempt to "fingerprint" a lesion's nature via non-morphological data.

In clinical practice, multidisciplinary discussion is key. Radiologists will often give a differential (e.g., "findings are more suggestive of osteomyelitis, consider biopsy and cultures" or "aggressive features concerning for osteosarcoma"). If uncertainty remains, an orthopedic surgeon or interventional radiologist will obtain a biopsy. Infectious disease specialists may be involved if OM is likely, to manage cultures and antibiotic strategy, while oncology teams will get involved if OS is diagnosed.

3. Summary:

Osteosarcoma and osteomyelitis are distinctly different diseases – one a malignant bone-forming tumor, the other an infectious/inflammatory bone destruction – yet they can present with strikingly similar clinical and radiographic pictures. Osteosarcoma's pathophysiology centers on genetic mutations in bone progenitor cells (commonly TP53 and RB1), leading to uncontrolled osteoid production and aggressive growth [27, 1]. Osteomyelitis's pathophysiology revolves around microbial invasion of bone, eliciting acute inflammation, pus formation, and a chronic cycle of bone necrosis (sequestrum) and repair (involucrum) [3, 4]. Clinically, both may manifest as bone pain, swelling, and even fever, and both can produce an "aggressive" bone lesion on imaging with periosteal reaction and bone destruction [6]. These overlaps create diagnostic challenges, risking misdiagnosis and inappropriate treatment if one is mistaken for the other [7].

Differentiation requires a careful, multimodal approach. Key discriminators include certain imaging hallmarks (e.g., tumor-type periosteal reactions like sunburst and Codman's triangle in OS [1] vs. sequestra and sinus tracts in OM [4], or a penumbra MRI sign in OM [6] vs. large solid soft-tissue mass in OS), laboratory patterns (e.g., positive cultures, high CRP in OM vs. elevated ALP/LDH in OS), and ultimately biopsy analysis. New diagnostic techniques and research are augmenting our abilities – from advanced MRI contrasts and PET tracers to computational analysis of bone structure – offering improved accuracy in distinguishing infection from malignancy.

4. Conclusions:

Distinguishing osteosarcoma from osteomyelitis is critical, as their management diverges radically: OS demands oncologic therapy (chemotherapy and limb-salvage or amputation surgery), whereas OM requires antimicrobial therapy and often surgical debridement. A missed osteosarcoma treated as "osteomyelitis" delays proper cancer care, potentially reducing survival, while treating an infection as "presumed tumor" delays needed antibiotics and can lead to unnecessary morbid procedures. Clinicians should maintain a high index of suspicion for both in any atypical bone lesion and systematically employ imaging and biopsy to secure a diagnosis. Multidisciplinary teamwork – involving radiology, orthopedics, pathology, infectious disease, and oncology – is often the best strategy in ambiguous cases.

AUTHOR'S CONTRIBUTIONS

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