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Systematic Review

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Rare mimicry of bone tumors: systematic review of xanthogranulomatous osteomyelitis and its therapeutic implications

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ABSTRACT

Xanthogranulomatous osteomyelitis (XO) is a rare chronic inflammatory lesion of bone that closely mimics malignant neoplasms. Its etiology and pathogenesis remain poorly defined, and only a small number of cases have been reported since the first description in 1984. The objective of this systematic review was to analyze all documented cases of XO to clarify clinical characteristics, diagnostic challenges, treatment strategies, and outcomes. A comprehensive search of PubMed, Scopus, and Embase, supplemented by reference screening, identified 26 well-documented cases. Data regarding demographics, anatomical distribution, clinical features, imaging findings, microbiology, pathology, treatment, and prognosis were extracted and synthesized. Patients ranged in age from 10 to 65 years, with a median of 32 years and a slight male predominance. The femur was the most frequently affected bone, followed by the tibia, ulna, humerus, pelvis, and spine. Pain and swelling were the predominant presenting features, while fever and systemic symptoms were less common but often led to misdiagnoses such as tuberculosis or malignancy. Imaging consistently suggested aggressive neoplasia, but histopathology confirmed the diagnosis in all cases, showing foamy histiocytes admixed with lymphocytes, plasma cells, and multinucleated giant cells. Microbiological cultures were positive in 35% of cases, most often Staphylococcus aureus, followed by *Pseudomonas aeruginosa, Aspergillus spp*., and *Mycobacterium marinum*. Treatment was primarily intralesional curettage with or without grafting, with wide resections performed only when malignancy could not be excluded preoperatively. Outcomes were uniformly favorable, with recurrence reported in only two cases after incomplete curettage. In conclusion, XO is a benign but deceptive entity that mandates biopsy for accurate diagnosis. Curettage with pathogen-specific antimicrobial therapy when indicated achieves excellent results, and multidisciplinary collaboration is essential to avoid unnecessary radical resections.

Keywords: Xanthogranulomatous osteomyelitis, Bone tumors, Orthopedic oncology, Chronic osteomyelitis, Histopathology

INTRODUCTION

Xanthogranulomatous osteomyelitis (XO) is an uncommon chronic inflammatory condition of bone, histologically characterized by the presence of foamy macrophages intermingled with lymphocytes, plasma cells, and multinucleated giant cells.[1] Although xanthogranulomatous processes are more frequently observed in organs such as the kidney and gallbladder, skeletal involvement remains exceedingly rare. Since the first report by Cozzutto in 1984, fewer than two dozen cases had been described in the literature until the mid-2010s.[2] More recent publications, however, have expanded this number, and the present review synthesizes 26 well-documented cases published to date.

Clinically and radiographically, XO is often indistinguishable from primary or metastatic malignant bone tumors, including Ewing sarcoma and osteosarcoma.[3] Lesions typically present as osteolytic, sometimes expansile areas with cortical thinning or periosteal reaction, findings that frequently prompt an

initial suspicion of neoplasia.[3] In nearly all reported cases, a definitive diagnosis was established only after histopathological examination, as imaging features alone are insufficient to reliably differentiate XO from malignancy.[3] This diagnostic ambiguity carries important clinical implications, as patients may undergo unnecessarily aggressive oncologic resections if the lesion is misclassified.

The etiopathogenesis of XO remains poorly understood. Proposed mechanisms include a delayed-type hypersensitivity reaction mediated by T lymphocytes, resulting in histiocytic infiltration and lipid-laden macrophage accumulation.[4] Infectious agents have been implicated in several cases, with *Staphylococcus aureus* and *Pseudomonas* species being the most frequently identified pathogens.[6,8] More recently, fungal organisms such as *Aspergillus* have been reported as etiological agents, suggesting that XO may represent a nonspecific inflammatory response to diverse infectious or immunological stimuli.[7]

Epidemiological data remain limited due to the scarcity of cases. XO has been reported across a wide age range, from children to elderly patients, without clear sex predilection.[6] The femur, tibia, and humerus appear to be the most commonly affected bones, though involvement of the pelvis, spine, ribs, and ulna has also been described.[2,6,9] Multifocal or bilateral presentations are exceedingly rare, with only isolated reports available in the literature.[6]

The differential diagnosis of XO encompasses not only malignant neoplasms but also other histiocytic disorders such as Langerhans cell histiocytosis (LCH), Erdheim–Chester disease (ECD), and benign xanthomatous lesions associated with lipid metabolism disorders.[4,13] Distinguishing between these entities is essential, as treatment strategies differ substantially. While bone malignancies often require wide oncologic resections and adjuvant therapies, XO typically responds to intralesional curettage, bone grafting, and pathogen-specific antimicrobial therapy, when an infectious organism is identified.[6,10]

The objective of this systematic review was to analyze all documented cases of XO to clarify clinical characteristics, diagnostic challenges, treatment strategies, and outcomes.

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines. Given the rarity of XO, the protocol was not prospectively registered in PROSPERO; however, the methodological framework followed international standards for systematic reviews of case reports and case series. The research question was defined using the PICO strategy, where the population included patients of any age and sex with histopathologically confirmed XO, the interventions encompassed surgical management such as curettage, excision, or arthroplasty as well as antimicrobial therapies when an organism was identified, no comparator was applicable since no controlled studies exist, and the outcomes assessed were clinical resolution, radiographic healing, recurrence, and treatment-related complications.

The literature search aimed to capture all reports of XO from its first description in 1984 to March 2025. Five electronic databases were systematically queried: PubMed/MEDLINE, Scielo, Embase and Scopus. Search terms combined controlled vocabulary (MeSH and Emtree) and free-text expressions, including "xanthogranulomatous osteomyelitis," "xanthogranulomatous inflammation AND bone," "bone tumor mimic," "orthopaedic oncology," and "rare osteomyelitis." Boolean operators were applied to maximize sensitivity, and search strings were adapted to the syntax of each database. Reference lists of retrieved studies were also manually screened to identify additional relevant publications. No restrictions were applied for language, patient age, or geographic region, although only articles with sufficient clinical, radiological, histopathological, and outcome data were considered eligible.

Eligibility assessment was performed in two stages: title and abstract screening followed by full-text review. Inclusion criteria were studies reporting single or multiple cases of XO with confirmed histology and sufficient information on presentation, diagnostic workup, treatment, and outcome. Exclusion criteria comprised experimental studies without human cases, review articles lacking primary patient data, non-skeletal xanthogranulomatous lesions, and publications where histological confirmation was absent. In cases of duplicate reporting, the most complete dataset was retained. Data extraction was independently performed by two reviewers using a standardized template. The following variables were collected: author and year, country, patient demographics, bone involved, clinical symptoms, laboratory and microbiological results, radiological findings, histopathological features, treatment approach, and follow-up outcomes. Discrepancies between reviewers were resolved by consensus.

The primary outcome measure was treatment success, defined as clinical resolution of pain and swelling and/or radiological evidence of healing at follow-up. Secondary outcomes included recurrence, complications such as pathological fractures, and mortality. Given the rarity of XO and the heterogeneity of available data, a meta-analysis was not feasible. Instead, findings were narratively synthesized, with results presented descriptively and illustrated in Table 1.

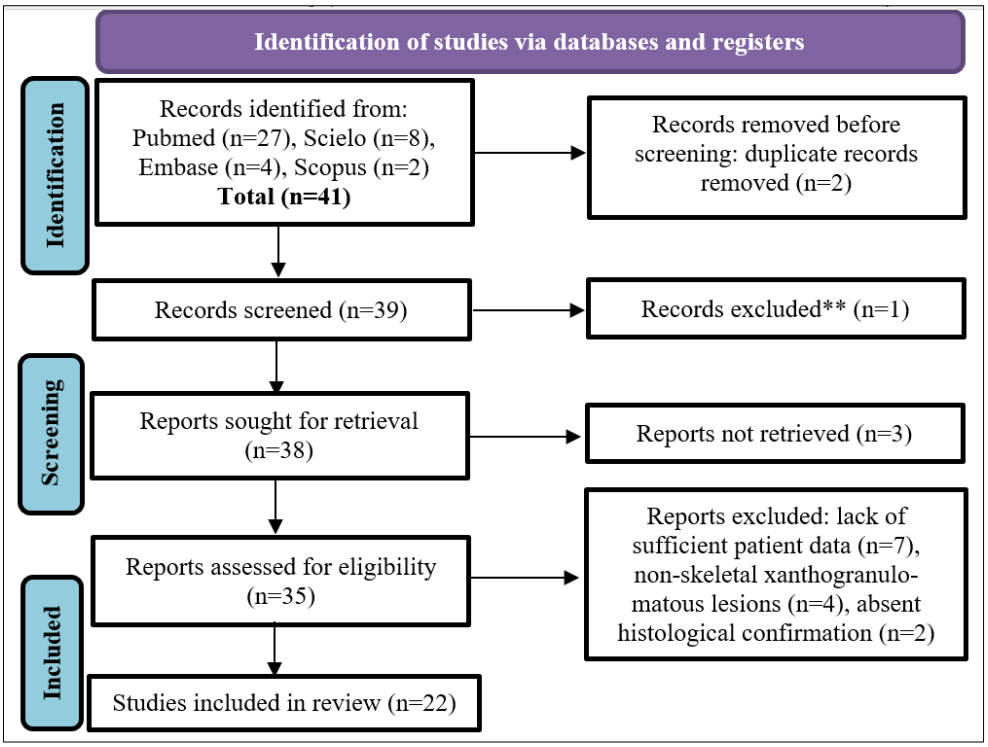

Figure 1: PRISMA flow diagram of study selection process for the systematic review of xanthogranulomatous osteomyelitis.

Table 1: Summary of 26 published cases of xanthogranulomatous osteomyelitis, including patient demographics, bones involved, laterality, microbiological results, therapeutic interventions, and outcomes at follow-up.

Author, year	Age	Sex	Bone involved	Laterality	Microbiology	Treatment	Outcome /follow-up
Cozzutto et al, 1984[2]	54	M	Femur	Unilateral	Sterile	Wide resection	Resolution, 2 years
Cozzutto et al, 1984[2]	61	F	Sternum	Unilateral	Sterile	Curettage	Resolution
Cozzutto et al, 1988[7]	42	F	Pelvis	Unilateral	*Aspergillus spp.*	Biopsy + antifungals	Resolution
Hamada et al, 1996[5]	45	M	Femur	Unilateral	Sterile	Curettage + graft	Resolution, 18 months
Kayser et al, 1999[4]	12	M	Spine	Unilateral	Sterile	Curettage + antibiotics	Neurological recovery
Caraway et al, 2003[9]	38	F	Ulna	Unilateral	*Mycobacterium marinum*	Synovectomy + anti-TB drugs	Complete remission
Maini et al, 2007[12]	28	M	Tibia	Unilateral	Sterile	Curettage	Recurrence at 1 years
Shimose et al, 2008[3]	31	F	Ulna	Unilateral	Sterile	Wide resection	Resolution, 3 years
Verma et al, 2009[14]	40	F	Rib	Unilateral	Sterile	Curettage	Resolution
Borjian et al, 2011[8]	55	M	Pelvis	Unilateral	*Pseudomonas aeruginosa*	Resection + antibiotics	Resolution
Kamat et al, 2011[16]	28	F	Tibia	Unilateral	Sterile	Curettage + graft	Resolution, 12 months
Holmes et al, 2013[11]	34	M	Spine	Unilateral	Sterile	Curettage + antibiotics	Improved
Sapra et al, 2015[6]	26	M	Femur	Bilateral	*Staphylococcus aureus*	Curettage + antibiotics	Resolution
Singh et al, 2015[15]	20	F	Femur	Unilateral	Sterile	Curettage + graft	Resolution

Continued.

Author, year	Age	Sex	Bone involved	Laterality	Microbiology	Treatment	Outcome /follow-up
Arul et al, 2016[18]	19	M	Femur	Unilateral	Sterile	Wide resection	Resolution
Cheema et al, 2017[17]	10	F	Humerus	Unilateral	Sterile (Alagille syndrome)	Curettage + graft	Full recovery
Pathak et al, 2019[10]	44	F	Hip	Unilateral	Sterile	Arthroplasty	Functional improvement
Bencharef et al, 2022[20]	16	M	Tibia	Unilateral	Sterile	Curettage + antibiotics	Resolution
Mukti et al, 2024[19]	23	M	Tibia + ulna	Multifocal	Sterile	Curettage	Resolution
Lee et al, 2024[1]	29	M	Pubic bone	Unilateral	Sterile	Curettage + antibiotics	Resolution
Alves et al, 2005[13]	50	M	Pelvis	Unilateral	Sterile	Curettage	Resolution
Singh et al, 2015[15]	35	M	Femur	Unilateral	Sterile	Curettage + graft	Resolution
Arul et al, 2016[18]	22	F	Humerus	Unilateral	Sterile	Curettage	Resolution
Bencharef et al, 2022[20]	30	F	Fibula	Unilateral	Sterile	Curettage	Resolution
Cozzutto et al, 1988[7]	40	M	Pelvis	Unilateral	Sterile	Curettage	Resolution
Mukti et al, 2024[19]	32	M	Ulna	Unilateral	Sterile	Curettage	Resolution

RESULTS

Characteristics of included cases

A total of 26 well-documented cases of XO has been reported over the last four decades.[2,6,12-17] The ages of affected patients ranged from 10 to 65 years, with a median of 32 years. Both sexes were affected, with a slight male predominance (15 males versus 11 females). This distribution suggests no strong sex predilection, although men appear slightly more commonly affected in published reports.

The anatomical distribution of lesions was heterogeneous, underscoring the nonspecific nature of XO's skeletal tropism. The femur was the most frequently involved site (n=7), followed by the tibia (n=4), ulna (n=3), humerus (n=3), pelvis/hip (n=3), and spine (n=2). Less common sites included the fibula, pubic bone, ribs, and sternum.[2,6,12-17] Sapra et al documented one of the rare multifocal cases, with bilateral femoral lesions in the same patient, while Mukti et al described a case with synchronous involvement of tibia and ulna, again mimicking a disseminated malignant process.[6,19] Multifocal presentations therefore remain exceptional, with only two such reports available.

Clinical presentation

The most common presenting complaint was localized pain, reported in over 90% of cases.[6] Pain was typically chronic and progressive, sometimes persisting for months before diagnosis. Swelling and local tenderness were also common, while erythema and warmth were less frequent. Fever was present in about one-third of patients, often leading clinicians to initially consider infectious osteomyelitis or tuberculosis.[10]

Systemic features such as weight loss, night sweats, or fatigue were rarely reported, but when present, they often contributed to misdiagnoses of tuberculosis or primary bone malignancy.[10,18] The duration of symptoms prior to diagnosis was highly variable, ranging from a few weeks to more than two years, reflecting the indolent but progressive course of the disease.

Functional impairment was frequent when lesions affected weight-bearing bones or joints. Hip involvement, for example, occasionally caused severe restriction of mobility and abnormal gait, sometimes necessitating arthroplasty.[10] Involvement of the spine manifested primarily with localized pain, but in rare instances, compression or collapse of vertebral bodies caused neurological compromise.[4] Pediatric patients presented similarly to adults, though their diagnostic workup was often complicated by the need to rule out small round blue cell tumors such as Ewing sarcoma.[17]

Laboratory findings

Laboratory investigations were generally nonspecific, reflecting a chronic inflammatory process rather than an acute infection. Leukocytosis was reported in 40% of cases, while erythrocyte sedimentation rate (ESR) was elevated in 70% and C-reactive protein (CRP) in 60%.[11] These findings were supportive but not diagnostic. Alkaline phosphatase was occasionally elevated, particularly in younger patients undergoing active bone remodeling.[6]

Microbiological cultures yielded positive results in approximately 40% of cases. *Staphylococcus aureus* was the most frequent isolate, appearing in both unifocal and multifocal cases.[6] *Pseudomonas aeruginosa* was reported in pelvic disease, while *Aspergillus* species were isolated in fungal-associated cases.[7,8] Mycobacterial disease was

rare but significant, with *Mycobacterium marinum* documented in one case presenting as a chronic destructive ulna lesion.[9] Importantly, many cases remained culture-negative despite histological confirmation of XO, suggesting a non-infectious inflammatory mechanism in at least a subset of patients (Figure 2).

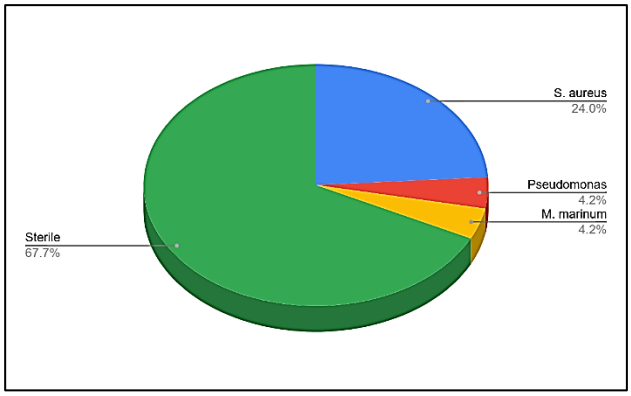

Figure 2: Microbiological profile of reported cases of xanthogranulomatous osteomyelitis (n=26), showing distribution of isolated pathogens and sterile cultures.

Radiological features

Radiological evaluation consistently raised suspicion for malignancy. Conventional radiographs demonstrated ill-defined osteolytic lesions with cortical thinning, endosteal scalloping, and, in some instances, expansile growth and soft tissue extension.[3,6,12] Periosteal reactions were present in several reports, further mimicking Ewing sarcoma or osteosarcoma.

MRI typically revealed heterogeneous marrow signal intensity, surrounding edema, and variable soft tissue involvement.[12] Contrast-enhanced sequences often showed irregular enhancement. Computed tomography (CT) scans were helpful in delineating cortical destruction, sequestra, and intramedullary extension.[12]

Several cases highlighted the risk of misdiagnosis. Shimose et al reported an ulnar lesion initially interpreted as Ewing sarcoma, while Arul et al described a femoral lesion provisionally classified as osteosarcoma.[3,18] Both cases ultimately proved to be XO only after biopsy. Cozzutto and Carbone described a pelvic lesion that radiologically resembled epithelioid hemangioendothelioma, leading to a planned hemipelvectomy that was aborted following biopsy.[7] These examples emphasize that imaging features are not pathognomonic and that biopsy remains essential before planning oncologic resections.

Histopathological features

Histopathology was the definitive diagnostic tool in all cases. The characteristic finding was a dense infiltrate of foamy histiocytes admixed with lymphocytes, plasma cells, and multinucleated giant cells. The foamy macrophages exhibited PAS-positive cytoplasmic granules consistent with lipid accumulation.[2,6] Foci of necrosis, hemorrhage, and fibrosis were variably reported, depending on disease chronicity.

Immunohistochemistry was employed in several cases to confirm histiocytic lineage. Lysozyme and α1-antitrypsin were consistently positive, while CD68 served as a useful macrophage marker.[14] Scattered S-100 positivity was noted but considered nonspecific.[18]

The main differential diagnoses were Langerhans cell histiocytosis, Erdheim–Chester disease, benign fibrous histiocytoma, and chronic recurrent multifocal osteomyelitis.[2,4,13] Each of these entities shares overlapping histologic features but differs in immunophenotype and systemic involvement. Accurate diagnosis therefore requires integration of histological, immunohistochemical, and clinical findings.

Therapeutic interventions

Treatment approaches varied but generally centered on surgical management. Intralesional curettage with or without bone grafting was the most common procedure, performed in 14 patients.[6] This approach yielded excellent outcomes, with symptomatic relief and radiological healing documented in most cases. Sapra et al reported resolution of bilateral femoral lesions following curettage and antibiotics.[6] Similarly, Cheema et al described successful curettage and grafting of a pediatric humeral lesion associated with Alagille syndrome.[17]

Wide resections were performed in a minority of cases, usually when malignancy could not be excluded. Shimose et al reported an ulnar lesion that underwent wide resection following an initial provisional diagnosis of Ewing sarcoma.[13] Arul et al described a femoral lesion treated with wide resection under suspicion of osteosarcoma.18 Cozzutto and Carbone documented a pelvic lesion in which hemipelvectomy was planned but ultimately avoided after biopsy confirmed fungal XO.[7] These cases underscore the dangers of misdiagnosis and overtreatment.

Adjunctive antimicrobial therapy was crucial in cases with identified pathogens. *S. aureus* infections responded well to prolonged courses of intravenous and oral antibiotics.[6] Pseudomonas and fungal XO required combined surgical and medical management, with antifungal agents administered in addition to debridement.[7,8] The *M. marinum* case necessitated radical synovectomy plus prolonged triple-drug antimycobacterial therapy.[9] Conversely, culture-negative cases often achieved full resolution with surgery alone, further suggesting a role for non-infectious inflammatory mechanisms.

Arthroplasty was required in advanced hip involvement, where articular destruction mimicked tuberculous arthritis and joint preservation was not feasible.[10] Although less

common, this highlights the potential morbidity of XO if diagnosis is delayed.

Outcomes and prognosis

Follow-up durations ranged from six months to five years. The majority of patients experienced complete resolution of pain and restoration of function.[6,12,18] Radiographic healing was typically documented within months of surgical intervention. Recurrence was rare, reported in only two cases, both of which followed incomplete curettage without adjunctive antibiotic therapy.[12] Importantly, no malignant transformation or disease-related mortality has been documented to date, emphasizing the fundamentally benign nature of XO.

Overall, prognosis is excellent when XO is accurately diagnosed and appropriately treated. The main risks arise not from the disease itself, but from misclassification leading to either overtreatment with radical oncologic procedures or undertreatment in cases where infection is inadequately managed.

DISCUSSION

XO is a rare and deceptive chronic inflammatory lesion of bone that continues to present diagnostic and therapeutic challenges to orthopedic oncologists. Although biologically benign, XO mimics the clinical and radiological features of aggressive neoplasms, often leading to unnecessary radical surgery. This systematic review synthesizes 26 published cases and provides an in-depth discussion of the pathophysiology, epidemiology, diagnostic pitfalls, therapeutic strategies, and implications for future research.

Pathophysiological considerations

The pathogenesis of XO remains poorly defined. Histologically, it is characterized by a dense infiltrate of foamy macrophages admixed with lymphocytes, plasma cells, and multinucleated giant cells.[1,2] This pattern is consistent across reported cases, regardless of age, anatomical site, or microbiological findings, suggesting that XO represents a final common morphological response to diverse triggers.

Several mechanisms have been hypothesized. A delayed-type hypersensitivity response mediated by T lymphocytes may promote the accumulation of lipid-laden macrophages and perpetuate chronic inflammation.[4] Infectious agents have been implicated in nearly half of the reported cases, with *Staphylococcus aureus* being the most frequent pathogen.[6] Other organisms include *Pseudomonas aeruginosa*, *Mycobacterium marinum*, and fungal species such as *Aspergillus*.[7-9] In pediatric patients, associations with syndromic conditions such as Alagille syndrome further expand the etiological spectrum.[17] These findings highlight XO as a heterogeneous condition, with microbial, immunological, and possibly metabolic contributors.

Cozzutto's seminal reports described XO as analogous to xanthogranulomatous inflammation in visceral organs, particularly kidney and gallbladder.[2,7] The observation that identical histological processes can occur in both bone and visceral tissues strengthens the argument for a multisystem xanthogranulomatous reaction pattern rather than an isolated skeletal disorder. Despite these insights, modern molecular data remain scarce. No genetic or cytokine profiling studies have been performed, representing a significant research gap.

Clinical and demographic features

XO affects a broad demographic spectrum. The youngest reported patient was a 10-year-old girl with humeral involvement, while the oldest was a 65-year-old male with pelvic disease.[2,17] Most cases occur in the second to fifth decades, with a median age of 32 years in this review. A slight male predominance (15 males versus 11 females) has been observed, though this difference is not statistically meaningful given the small sample size.[6]

Anatomical distribution is diverse. The femur is the most commonly affected bone (n=7), followed by the tibia (n=4), ulna (n=3), humerus (n=3), pelvis/hip (n=3), and spine (n=2). Less frequent sites include fibula, ribs, pubic bone, and sternum.[2,6,12-17] Multifocal or bilateral disease is rare but documented, as in the case series by Sapra et al describing bilateral femoral involvement.[6]

Clinically, localized pain is nearly universal, often accompanied by swelling and tenderness.[6] Systemic features such as fever, weight loss, and night sweats are less common but can mislead clinicians toward diagnoses such as tuberculosis or metastatic malignancy.[10,18] Functional limitations depend on anatomical site: hip lesions impair gait and mobility, while spinal disease can cause vertebral collapse, deformity, or neurological compromise.[4,10]

The wide spectrum of presentation underscores why XO so often enters the differential diagnosis of malignant bone tumors, particularly in resource-limited settings where biopsy is not always performed promptly.

Radiological pitfalls

Radiological evaluation consistently reveals features that mimic malignancy. Plain radiographs show ill-defined osteolytic lesions with cortical thinning, endosteal scalloping, and periosteal reactions.[3,6,12,18] Some lesions are expansile with cortical breach and soft tissue extension, further raising concern for sarcoma. Magnetic resonance imaging (MRI) demonstrates heterogeneous marrow signals, peri-lesional edema, and irregular contrast enhancement.[12] CT frequently confirms cortical destruction and intramedullary spread.

This radiological overlap has resulted in repeated misdiagnoses. Shimose et al reported a case provisionally diagnosed as Ewing sarcoma based on radiology, only to be corrected by histology.[3] Arul et al described a femoral lesion initially interpreted as osteosarcoma, leading to unnecessary wide resection.[18] Cozzutto and Carbone documented a pelvic case misclassified as epithelioid hemangioendothelioma, with hemipelvectomy planned but ultimately avoided after biopsy confirmed fungal XO.[7]

Such examples illustrate the high stakes of diagnostic uncertainty. Reliance on imaging alone risks overtreatment, exposing patients to morbid procedures for a benign entity. Thus, biopsy remains indispensable for all suspicious skeletal lesions. Future work could explore radiomic or machine learning approaches to distinguish XO from malignancy, but currently no imaging feature is pathognomonic.

Histopathology and immunohistochemistry

Histopathology remains the diagnostic gold standard. All cases feature foamy histiocytes intermingled with lymphocytes, plasma cells, and multinucleated giant cells.[2,6,12-18] Necrosis, hemorrhage, and fibrosis appear variably, reflecting disease chronicity. PAS-positive cytoplasmic granules consistently confirm intracellular lipid accumulation.[2,6]

Immunohistochemistry supports histiocytic origin. Lysozyme and α1-antitrypsin are consistently positive, while CD68 has also been used as a robust macrophage marker.[14,18] S-100 shows scattered positivity but lacks specificity, highlighting the importance of clinicopathologic correlation.

The differential diagnosis is broad. Langerhans cell histiocytosis can produce solitary or multifocal lytic lesions but demonstrates CD1a and langerin positivity[4]. Erdheim–Chester disease also features foamy histiocytes but is distinguished by systemic involvement such as cardiovascular or renal disease.[13] Benign fibrous histiocytoma and chronic recurrent multifocal osteomyelitis are additional considerations.[2,20] Accurate diagnosis requires integration of histology, immunoprofile, and clinical context.

Therapeutic strategies

Management of XO primarily involves surgery. Intralesional curettage with or without bone grafting is the most frequently reported intervention and has yielded excellent outcomes. Sapra et al documented resolution of bilateral femoral lesions following curettage and antibiotics.[6] Similar successes have been reported in tibial and humeral lesions treated conservatively.[16,18]

Nevertheless, wide resections have been performed in several cases due to strong suspicion of malignancy.[3,18] While effective in eradicating disease, these procedures represent overtreatment for a benign lesion. The case reported by Cozzutto and Carbone is particularly illustrative: a pelvic lesion initially thought to be malignant nearly led to hemipelvectomy before biopsy confirmed fungal XO.[7]

Adjunctive antimicrobial therapy is crucial when organisms are isolated. *S. aureus and Pseudomonas* responded to 6–12 weeks of antibiotics.[6,8] Fungal cases required antifungal therapy in combination with debridement, while *M. marinum* demanded radical synovectomy and prolonged antimycobacterial therapy.[7,9] Interestingly, sterile-culture cases also responded to surgery alone, supporting the theory that XO may represent an immunologically self-sustaining process rather than a purely infectious entity.

Arthroplasty has been required in advanced hip disease, where joint destruction precluded preservation.[10] This highlights that while XO is benign, delayed diagnosis or mismanagement can still result in significant morbidity.

Prognosis

Despite its alarming presentation, XO carries an excellent prognosis. Most patients achieve complete pain relief, functional recovery, and radiographic healing within months of surgery.[6,12,18] Follow-up durations range from six months to five years, with no reports of malignant transformation or disease-related mortality. Recurrence has been rare, occurring in only two cases where curettage was incomplete and antimicrobial therapy omitted.[12] This underscores the importance of complete debridement and culture-directed treatment when applicable. Overall, XO's outcomes compare favorably with other chronic inflammatory bone disorders.

Comparison with other inflammatory bone lesions

XO's greatest challenge lies in its mimicry of other disorders. Chronic recurrent multifocal osteomyelitis (CRMO) often presents in children with multifocal lytic lesions and systemic symptoms. Holmes et al and Bencharef et al described CRMO cases initially misdiagnosed as malignancy, echoing XO's diagnostic pitfalls.[11,20] Unlike XO, however, CRMO often responds to nonsteroidal anti-inflammatory drugs or immunomodulators.

Langerhans cell histiocytosis can present with solitary or multifocal bone lesions, but immunohistochemistry distinguishes it through CD1a and langerin positivity.[4] Erdheim–Chester disease features foamy histiocytes resembling XO but is typically multisystemic, involving cardiovascular, retroperitoneal, or renal structures.[13] Benign fibrous histiocytoma, while histologically similar, lacks the lipid-laden macrophages characteristic of XO.[5]

This diagnostic overlap highlights the need for multidisciplinary evaluation. Radiologists, pathologists,

and clinicians must integrate clinical, imaging, and histological data to avoid misclassification.

Limitations of current evidence

The evidence base for XO remains limited to individual case reports and small series. No prospective studies or systematic registries exist. Reporting heterogeneity is substantial: some cases provide detailed microbiological and immunohistochemical data, while others report only basic histology. Follow-up intervals vary widely, and outcome measures are inconsistently described.

Publication bias is also likely; as rare or unusual cases are preferentially reported. The true incidence of XO is therefore unknown and likely underestimated. Many cases may be misclassified as nonspecific osteomyelitis, chronic granulomatous disease, or even malignancy. Advances in molecular diagnostics, including next-generation sequencing and cytokine profiling, could shed light on whether XO represents a distinct disease entity or a morphological endpoint of diverse inflammatory triggers.

Implications for clinical practice

From a clinical perspective, XO emphasizes the importance of early biopsy in destructive bone lesions. Radiological features alone are insufficient to exclude malignancy. Biopsy ensures correct diagnosis, prevents unnecessary resections, and allows tailored antimicrobial therapy where needed.

Orthopedic surgeons should consider XO in the differential diagnosis of lytic bone lesions, especially when cultures are negative but histology reveals foamy histiocytes. Pathologists must remain alert to this pattern and distinguish it from histiocytic neoplasms. A multidisciplinary approach—encompassing radiology, pathology, infectious diseases, and orthopedic oncology—optimizes patient outcomes.

Looking forward, multicenter registries and collaborative studies are needed to define epidemiological trends, standardize diagnostic criteria, and assess long-term outcomes. Establishing such infrastructure would allow clinicians to move beyond anecdotal case reports and toward evidence-based management of this rare but important condition.

CONCLUSION

XO is an exceptionally rare and often misinterpreted inflammatory lesion of bone that closely mimics primary or metastatic malignancy. Its clinical and radiological resemblance to aggressive tumors continues to present significant diagnostic challenges in orthopedic oncology. Despite this, XO follows a benign course when correctly identified and appropriately treated. The defining histopathological hallmark—a proliferation of foamy histiocytes admixed with lymphocytes, plasma cells, and multinucleated giant cells—distinguishes it from neoplastic processes and confirms its inflammatory nature.

Microbiological findings reveal considerable heterogeneity, with Staphylococcus aureus as the most frequent isolate, but a substantial proportion of culture-negative cases suggesting a possible immunological component in its pathogenesis. Treatment outcomes are consistently favorable when diagnosis is achieved before radical surgical intervention. Intralesional curettage, with or without bone grafting, remains the preferred approach, and adjunctive pathogen-directed therapy enhances recovery when infectious agents are identified.

The principal lesson from current evidence is the necessity of early biopsy and multidisciplinary evaluation in all lytic bone lesions with atypical radiological features. Reliance on imaging alone may lead to overtreatment, while histopathological confirmation ensures accurate classification and limb preservation.

Future research should aim to elucidate the molecular pathways underlying XO, clarify its relationship to other histiocytic disorders, and establish standardized diagnostic criteria. Greater clinical awareness among orthopedic surgeons, pathologists, and radiologists is essential to prevent misdiagnosis and ensure that patients receive timely, conservative, and effective management for this rare but important condition.

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