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Commentary

The Vitiated Ossein-Bacterial Osteomyelitis

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Received: October 16, 2021; **Published:** October 29, 2021

Preface

Infection and inflammation of the bone, initially designated as osteomyelitis by Auguste Nelaton in 1844, occurs due to diverse pyogenic organisms, bacteria, fungi and mycobacteria. The infection may extend to encompassing tissue and occurs as an acute or chronic inflammation. Osteomyelitis is categorized into acute osteomyelitis, subacute osteomyelitis or chronic osteomyelitis contingent to clinical duration of disease.

Bacterial infection induces pyogenic osteomyelitis, a variant which is exceptionally delineated with the advent of contemporary antibiotics. Following the articulation of a sinus tract, an enlarged epidermal inclusion cyst layered with stratified squamous epithelium may be configured within the incriminated bone. Infrequently, the lining epithelium metamorphoses into well differentiated squamous cell carcinoma, a malignancy which is accompanied by a superior prognosis.

Disease characteristics

Significant bacterial ingress due to trauma, ischemia or foreign bodies with adherent microorganisms may infiltrate sites of exposed bone and engender osteomyelitis. An estimated 50% instances may occur due to unknown bacteria [1,2].

Osteomyelitis is generally detected between 2 years to 12 years although no age of disease emergence is exempt. A male predominance is exhibited with a male to female proportion of 3:1 [1,2].

Frequently the lower extremities, vertebral column, radial styloid and sacroiliac joints are incriminated. Location of infection is contingent to age of incriminated individual as altered vascularization is enunciated in diverse bone segments. Commonly, metaphysis or epiphysis in neonates, metaphyseal region in children and epiphyses or subchondral region of adult subjects are implicated. Distal and proximal femur, proximal tibia, humerus and distal radius are commonly implicated in children [1,2]. Of undefined incidence, osteomyelitis displays an enhanced prevalence in male subjects of increasing age associated with comorbid conditions such as diabetes mellitus and peripheral vascular disease. Individuals with traumatic aetiology, bacterial dissemination, endocarditis, intravenous drug abusers and open fractures exhibit an enhanced possible occurrence of osteomyelitis [1,2].

Also, peripheral vascular disease, peripheral neuropathy, orthopaedic implants, chronic or inadequately healed wounds occurring in diabetes mellitus enunciate an enhanced possibility of osteomyelitis [1,2].

Disease pathogenesis

Bacterial proliferation occurring within bone may engender inflammation and necrosis which disseminates through the Haversian system or medullary canal within the bone shaft and involves the periosteum. Sub-periosteal abscess may impair vascular perfusion, thereby inducing additional necrosis and draining sinuses [3,4].

Acute and chronic osteomyelitis can be classified contingent to duration of illness or mechanism of infection as haematogenous dissemination or contiguous infection [3,4].

Bone infection may ensue through the haematogenous route with distant bacteria infiltrating the bone wherein osteomyelitis is essentially engendered from a singular microorganism. Haematogenous osteomyelitis is frequently discerned within metaphyseal region of long bones in children or flat bones or vertebral column in adults [3,4].

Direct inoculation of bone may be traumatic or iatrogenic and appears with ulceration or surgical inoculation. Osteomyelitis engendered with direct bacterial inoculation is delineated with open fractures, bone reconstructive surgery or with insertion of orthopaedic implants [3,4].

Bacterial dissemination in contiguous osteomyelitis ensues from joints or circumscribing soft tissue and may incriminate the vertebral column in adults. Contiguous osteomyelitis is infrequent and may be induced by singular or multiple micro-organisms. Contiguous infection is subdivided according to presence or absence of associated vascular insufficiency [3,4].

Contiguous osteomyelitis arising due to trauma, surgical intervention, immune deficiency or intravenous drug abuse occurs in young adults. Contiguous osteomyelitis occurring due to trauma is associated with infected, exposed soft tissue and cutaneous surfaces [3,4].

Decubitus ulcer, urinary tract infection, diabetes and infected joint arthroplasty may engender contiguous osteomyelitis in older individuals. Contiguous osteomyelitis frequently appears in debilitated, wheelchair or bedbound subjects prone to pressure-sores or cutaneous ulceration [3,4].

Lesions are commonly discerned in the sacrum, gluteal region and heel.

Frequently, osteomyelitis occurs due to vascular insufficiency in concurrence with diabetes mellitus. Diabetic subjects depict compromised vascular perfusion within the lower extremities which impairs local immunity and healing of cutaneous wounds and stimulates dissemination of infection. Sensory neuropathy engenders cutaneous ulceration in diabetes mellitus, thus aggravating bacterial influx. Typically, poly-microbial flora from cutaneous surfaces or gastrointestinal tract accumulate within the ulcers wherein soft tissue infection may rapidly disseminate to underlying bone [3,4].

Staphylococcus aureus can thrive within intracellular environment, manifests receptors such as adhesins and may adhere to bone matrix constituents as laminin, collagen, fibronectin or bone sialoglycoprotein [3,4].

Staphylococcus aureus formulates collagen-binding adhesin which initiates adherence to bone cartilage. Also, fibronectin-binding adhesion aids bacterial attachment to surgical implants. Bacteria may be layered within a protective biofilm coating the underlying surface. Aforesaid features of bacterial adherence contribute to phenotypic resistance towards antibiotic therapy and aid intracellular survival with persistence of bone infections and consequent failure of short-term antibiotic therapy [5,6]. Osteomyelitis engendering pathogens are contingent to age of incriminated individual. *Staphylococcus aureus, Brucella* or *Salmonella* spp may contribute to acute haematogenous osteomyelitis arising in adults and children [5,6].

Also, methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative *Staphylococci*, beta-haemolytic *Streptococci, Enterococci*, aerobic gram-negative bacilli such as *Enterobacter* spp, *Pseudomonas* spp, *Escherichia coli, Klebsiella* spp, *Haemophilus influenza, Treponema, Listeria* spp and anaerobic gram-negative bacilli such as *Peptostreptococcus, Clostridium* spp, *Bacteroides* may engender from osteomyelitis [5,6].

Infrequently, pathogens such as *Bartonella henselae, Mycobacterium tuberculosis*, nontuberculous mycobacteria as *Mycobacterium avium* intracellulare, fungi such as *Candida* spp, *Blastomyces, Coccidiodes*, *Cryptococcus* and *Aspergillus* may induce osteomyelitis, especially in immunocompromised individuals [5,6].

Inoculation with *Actinomyces* or *Sporothrix* occurs with trauma. *Pasteurella multocida* or *Eikenella corrodens* are isolated from human or animal bites. Occasionally, osteomyelitis may be associated with malakoplakia [5,6].

Clinical elucidation

Anatomic subcategories of osteomyelitis are

- Stage I where osteomyelitis is confined to bone medulla
- Stage II with superficial disease
- Stage III with localized disease
- Stage IV with diffuse osteomyelitis [5,6].

Associated comorbidities exemplifying compromised host immunity are malnutrition, renal or hepatic failure, diabetes mellitus, chronic hypoxia, neoplasia and immunodeficiency disorders [5,6].

Localized factors contributing to decimated immunity are chronic lymphedema, venous stasis, vascular disease implicating major or miniature blood vessels, arteritis, peripheral neuropathy and tobacco consumption [5,6].

Clinical representation of osteomyelitis is contingent to disease aetiology. Acute osteomyelitis manifests gradually within few days to two weeks. Localized symptoms such as erythema, swelling, warmth upon incriminated site, dull pain at rest or upon mobility and constitutional symptoms as fever or chills may appear. Acute osteomyelitis may enunciate septic arthritis, especially of bone metaphysis impacted within infected joint capsule. Septic arthritis of elbow, shoulder and hip joint may complicate osteomyelitis arising within proximal radius, humerus or femur [5,6].

Deep-seated, extensive, non-healing ulcers may be discerned despite appropriate therapy, especially in diabetics or debilitated subjects [6].

Histological elucidation

Upon gross examination, infants depict permanent joint and epiphyseal deterioration with exclusion of metaphysis and diaphysis whereas young children display metaphyseal damage with joint exclusion. Adults demonstrate joint infection with extensive incrimination of bone [7,8].

Acute osteomyelitis exemplifies dissemination of inflammatory exudate through the bone with periosteal elevation. An attenuated rim of reactive, periosteal bone encompasses the centric, necrotic bone trabeculae. Neonates demonstrate significant sub-periosteal accumulation of inflammatory exudate [7,8].

Initially, bacterial propagation triggers a localized inflammatory reaction engendering limited cellular demise. Gradually, infection is segregated by peripheral granulation tissue and deposition of new bone [7,8].

As bone metaphysis is well perfused and depicts minimal proportion of functioning phagocytes, metaphysis remains a common site of infection in haematogenous osteomyelitis of long bones [7,8].

Sluggish vascular perfusion of metaphysis contributes to microbial accumulation and infection. Enzymes from incipient phagocytes lyse bone and circumvent microbial dissemination, thereby initiating an inflammatory response which configures pus or a protein-rich exudate constituted of necrotic phagocytes, tissue debris and microorganisms [7,8].

The inflammatory exudate elevates intramedullary pressure and may rupture through bone cortex or periosteum [8].

Upon microscopy, a significant neutrophilic exudate is observed along with lymphocytes and plasma cells. Foci of bone necrosis are delineated along with configuration of reactive, new bone. Capillary proliferation is accompanied by fibrosis. Bone marrow space may be replaced by inflammatory cells and exudate [7,8]. Infection with *Salmonella* may demonstrate tuberculoid, epithelioid cell granulomas with variable, centric necrosis [8].

Discontinuity of periosteum impairs periosteal vascular perfusion with consequent bone ischemia and necrosis. Necrotic bone is designated as "sequestrum", is segregated from viable bone by granulation tissue and may infrequently depict accumulation of inflammatory exudate [8].

New bone deposited upon injured periosteum is denominated as "involucrum" and it may partially circumscribe the sequestrum. Exudate discharging from sequestrum may configure a sinus tract, layered with stratified squamous epithelium [7,8].

On microscopy, acute bacterial osteomyelitis exhibits accumulated microorganisms, congested or thrombosed vascular articulations and neutrophilic infiltration [7,8].

Contingent to histological manifestations, osteomyelitis is categorized as

- Acute osteomyelitis which indicates bone infection preceding genesis of sequestrum and usually appears within two weeks of disease onset.
- Chronic osteomyelitis denominates the development of necrotic bone and sequestrum [7,8].

Differential diagnosis

Osteomyelitis requires a segregation from conditions such as Charcot's arthropathy, SAPHO syndrome constituted of synovitis, acne, pustulosis, hyperostosis and osteitis, arthritis or rheumatoid arthritis, metastatic bone disease with primary malignancy arising from Ewing's sarcoma, osteosarcoma, lymphoma, multiple myeloma, pathological fracture or stress fracture, gout, avascular necrosis of bone, Langerhans cell histiocytosis (LCH), bursitis or sickle cell vaso-occlusive pain crises [1,2].

Investigative assay

Competent clinical history and physical examination is essential and beneficial. Physical examination necessitates detection of an infective nidus and evaluation of sensory function or peripheral vasculature. Ulcer may extend to the bone and may be discerned by radiographic imaging or cogent bone biopsy [8,9].

Biochemical or haematological parameters are usually nonspecific and leukocytosis, elevated erythrocyte sedimentation rate (ESR) or augmented c-reactive protein (CRP) may or may not be enunciated in osteomyelitis. c-reactive protein (CRP) is concurrent to and beneficial in monitoring response to therapy. Haematogenous osteomyelitis of the vertebrae, clavicle or pubic bone may be detected with appropriate blood cultures [8,9].

Employment of sensitive imaging techniques such as magnetic resonance imaging (MRI) and bone scintigraphy ameliorates diagnostic precision and possible categorization of infection [8,9].

Radiographic imaging is mandatory for evaluating suspected osteomyelitis. Additionally, plain radiographs, magnetic resonance imaging (MRI) and technetium-99 bone scintigraphy are beneficial. Plain radiography is the initial imaging modality demonstrating features indicative of osteomyelitis in around 2 weeks. Also, features of bone metastasis or fractures due to osteoporosis may be identified [7,8].

Upon plain radiography, preliminary modifications are discerned as swelling within adjacent soft tissue and skeletal muscle along with absence or blurring of adipose tissue planes. Adjacent joint may depict effusion [8,9].

Alterations appearing within two weeks are comprised of regional osteopenia, periosteal reaction, periostitis, configuration of Codman's triangle, focal bone or cortical lysis, endosteal scalloping, decimation of trabecular bone, configuration of new bone and ultimately, peripheral sclerosis with articulation of sequestrum, involucrum or cloaca [7,9].

Typically, soft tissue swelling, osteopenia, osteolysis, bone destruction and nonspecific periosteal reaction are observed [9].

As plain radiographs depict lytic lesions following decimation of around 50% of bone matrix, the modality is relatively inadequate for discerning preliminary bone disease. Imaging at delayed stage demonstrates a prominent periosteal reaction [7,9].

Ultrasonography is a rapid, inexpensive technique for assessing soft tissue, joints and guiding evacuation of inflammatory exudate although the manoeuver is inadequate for evaluating osteomyelitis as bone penetration is unsatisfactory. Also, assessment of soft tissue abscess, foci of cellulitis, accumulated sub-periosteal pus, joint effusion and extra-osseous component of orthopaedic implants may be possible [7,9].

Computerized tomography (CT) is an expensive, sensitive technique for assessing integrity of bone cortex and trabeculae, periosteal reaction, gas within intraosseous and soft tissue, expanse of sinus tract and necrotic bone fragments. Computerized tomography (CT) is optimal for discerning bone perimeter or identification of sequestrum or involucrum. The technique is recommended for determining ensuing bone destruction and guiding accruement of incriminated bone and soft tissue samples [7,9].

Currently, magnetic resonance imaging (MRI) depicts enhanced sensitivity and specificity for appropriately discerning osteomyelitis. Preliminary lesions or bone infection can be detected within 3 days to 5 days of disease onset. However, infection induced by orthopaedic or surgical implants may not be appropriately detected [7,9].

MRI may be normal in preliminary instances exhibiting clinical symptoms for nearly a week. MRI is optimal in detecting bone marrow oedema appearing in preliminary acute osteomyelitis. Soft tissue and joint complications can be identified. Upon MRI, T1 signal intensity is minimal to intermediate in the centric component with reduced signal intensity of circumscribing, oedematous bone marrow and destroyed cortical bone.

T2 signal intensity is enhanced due to centric fluid component and bone marrow oedema [7,9].

Administration of intravenous contrast aids distinction between phlegmon, necrotic tissue and abscess. Post contrast imaging depicts enhancement of bone marrow, abscess perimeter, periosteum and aggregated, adjoining soft tissue [7,9].

Although minimally specific, nuclear imaging is a sensitive technique for detecting preliminary bone disease and can be beneficially adopted in instances where MRI is circumvented due to orthopaedic implants. Three phase technetium-99m bone scan and tagged white blood cell scan are generally employed [7,9].

Alternatively, imaging modalities such as positron emission tomography (PET), leukocyte scintigraphy and gallium scan can be adopted to assess osteomyelitis [7,9].

Bone scintigraphy with technetium- 99m (Tc-99m) scan is a sensitive technique which depicts enhanced osteoblastic activity with elevated radiotracer uptake within the circumscribing bone [6,7].

Indium-111 labelled white blood cell (WBC) scintigraphy is recommended in evaluation of diabetic osteomyelitis, orthopaedic implants, vertebral osteomyelitis or ulceration in immobilized subjects with potential osteomyelitis [6,7].

Gallium-67 scintigraphy with exposure to radioactive gallium demonstrates enhanced isotope uptake in conditions with infection or sterile inflammatory conditions and malignant metamorphoses [6,7].

Positron emission computerized tomography (PET-CT) is a contemporary, precise modality for diagnosing chronic osteomyelitis.

Bone tissue samples may be obtained percutaneously or with open technique [6,7].

Tissue sampling is essential for morphological confirmation of osteomyelitis, identification of pathogens and assessing susceptibility to diverse antibiotics in order to ensure pertinent therapy. Superficial wound culture, needle puncture material or tissue extracted from sinus tract is unsatisfactory for histological confirmation [6,7].

Percutaneous tissue samples are preferably obtained through intact cutaneous surface, prior to commencement of antibiotics with guidance from computerized tomography (CT) or fluoroscopy. The samples may be utilized for histological assessment, gram's stain, culture and sensitivity. Open bone biopsy is recommended, in contrast to percutaneous tissue sampling [6,7].

Therapeutic options

Osteomyelitis is appropriately treated with surgical confinement of infection and antibiotic therapy for extended duration [8,9].

Surgical debridement of infected, necrotic bone and soft tissue is required as impregnation of antibiotics into infected fluid, abscess or injured, necrotic bone is inadequate [8,9].

Osteomyelitis associated with prosthetic joints necessitates eradication of implants. However, susceptible organisms such as streptococci may be satisfactorily managed with extended antibiotic therapy with the implanted device in place. Vacuum-assisted wound closure devices may be employed for repairing enlarged, deep wounds following extensive debridement of necrotic tissue [8,9].

Control of associated comorbidities, revascularization of implicated limb and decimation of contributing host factors which impede wound healing such as consumption of tobacco, malnutrition, chronic hypoxia, immunodeficiency, chronic lymphedema and peripheral neuropathy is necessitated prior to surgical intervention [8,9].

Prolonged antibiotic therapy is recommended contingent to culture and sensitivity or as empirical, broad-spectrum antibiotics applicable to gram-positive and gram-negative organisms, such as cloxacillin, nafcillin, vancomycin, ceftriaxone, piperacillin or tazobactam. Antibiotic levels in bone may be decimated [8,9].

Disease sites challenging to treat, as with pelvic osteomyelitis may be subjected to several months of extended antibiotic therapy. Frequently, intravenous antibiotics may be extensively employed. Accumulation of inflammatory exudate, sequestrum or involucrum can be managed with surgical drainage or debridement [8,9].

Amputation is a manoeuver applicable to instances of unsuccessful medical therapy or life threatening infection [8,9].

Hyperbaric oxygen therapy is not generally recommended for treating osteomyelitis [8,9].

Initiation of preliminary, aggressive treatment strategies ensure a superior prognosis of acute osteomyelitis. However, reoccurrence of infection may ensue [8,9].

Complications associated with untreated or inadequately treated osteomyelitis are septic arthritis, pathological fracture, configuration of sinus tract, squamous cell carcinoma, secondary sarcoma, bone abscess, bone deformity, systemic infection, contiguous soft tissue infection and exceptionally, secondary amyloidosis [8,9].

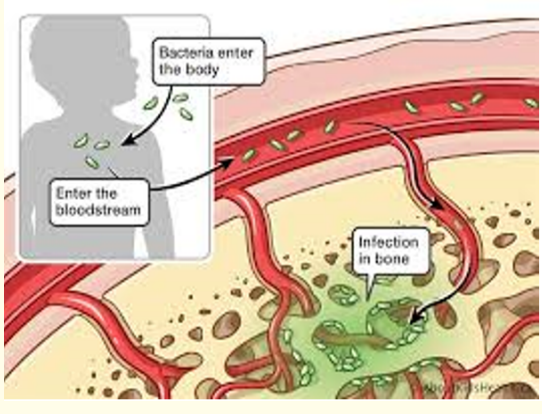

Figure 1: *Osteomyelitis with the frequently discerned haematogenous bacterial dissemination encountered in children [10].*

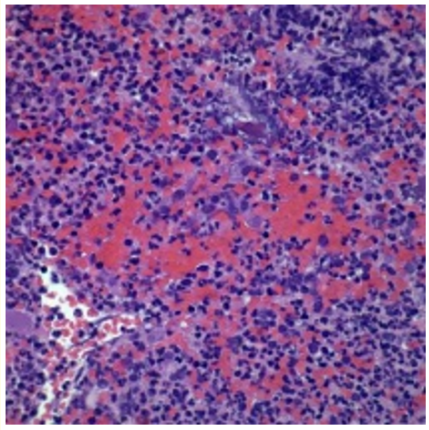

Figure 2: *Osteomyelitis depicting dissemination of neutrophils and lymphocytes commingled with foci of necrotic bone [11].*

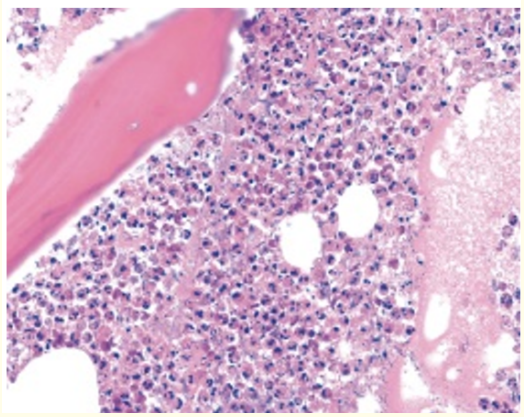

Figure 3: *Osteomyelitis delineating scattered neutrophils and marrow spaces intermingled with foci of osteonecrosis [12].*

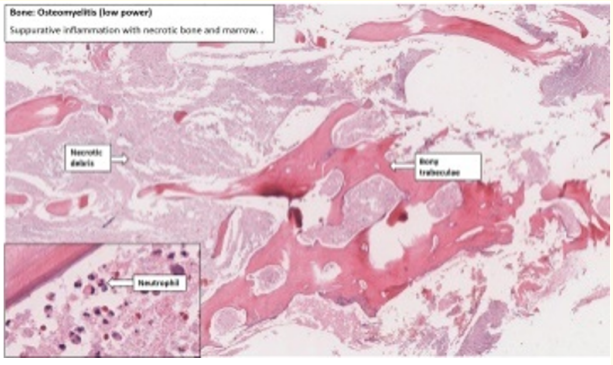

Figure 4: *Osteomyelitis enunciating sequestrum, inflammatory cells and exudate admixed with necrotic debris [13].*

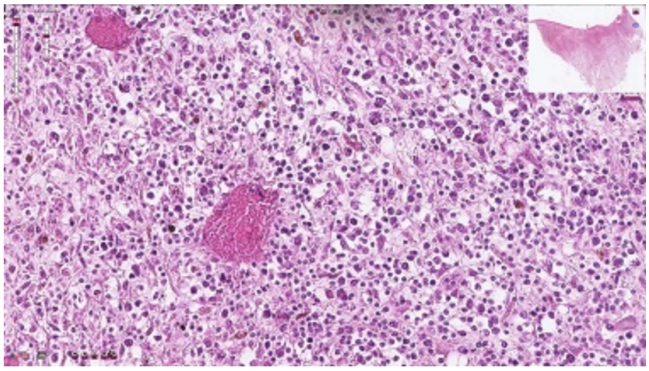

Figure 5: *Osteomyelitis exemplifying dissemination of neutrophils and lymphocytes with fragments of necrotic bone [14].*

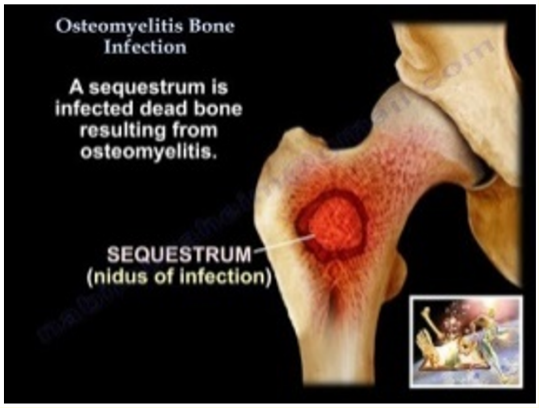

Figure 6:*Osteomyelitis depicting configuration of a sequestrum at the nidus of infection [14].*

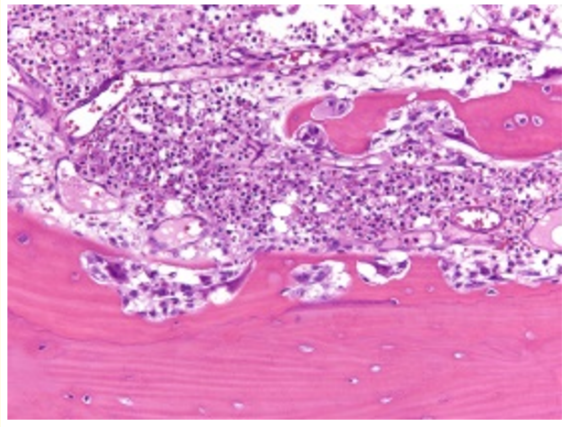

Figure 7:*Osteomyelitis exhibiting aggregates of neutrophils and lymphocytes intermixed with foci of dead bone [15].*

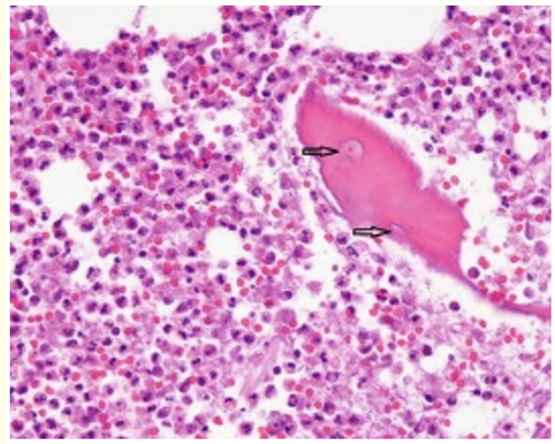

Figure 8:*Osteomyelitis demonstrating aggregates of acute inflammatory cells as neutrophils and lymphocytes admixed with necrotic bone and red cell extravasation [16].*

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10. Image 1 Courtesy: About Kids Health.
11. Image 2 Courtesy: Orthobullets.com.
12. Image 3 Courtesy: Pathology outlines.
13. Image 4 Courtesy: medicine.nus.sdu.sg.com.
14. Image 5 and 6 Courtesy: You tube.
15. Image 7 Courtesy: Diagnostic Histopathology.
16. Image 8 Courtesy: Springer link.

Volume 20 Issue 11 November 2021