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Editorial

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Primary Subacute Hematogenous Osteomyelitis in Children

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Editorial

Subacute osteomyelitis is one of the various clinical presentations of pediatric osteomyelitis. It is usually secondary to local inoculation by penetrating trauma and is not associated with systemic symptoms. Factors that may influence the behavior of a septic process in bone depend on the virulence of the infecting bacteria, the immune mechanism of the host and the adequacy of antibiotic therapy. Subacute osteomyelitis represents a favorable host-pathogen response. Any osseous infectious process lasting at least 2 weeks without acute symptomatology can be referred to as subacute osteomyelitis [1,2].

Most reports indicate a decline in the incidence of childhood hematogenous osteomyelitis of the long bones possibly due to the improved standards of living, personal hygiene and general health of the population. However, an increasing incidence of subacute osteomyelitis, which may produce worse results, has been documented since antibiotics have been used to treat osteomyelitis [3-6]. Subacute osteomyelitis is the most common type of osteomyelitis diagnosed in Northern Nigeria and East Africa, where children walk in bare feet, have frequent foot infections following puncture wounds and develop a high resistance to staphylococcal infections [7].

Brodie's lesion is the most common subtype of subacute osteomyelitis. It generally refers to a low-grade pyogenic metaphyseal bone abscess. Brodie's abscess was recognized in 1832 as a cavity of dark-colored pus surrounded by whiter and harder bone whose inner surface appeared to be highly vascular. The Swiss surgeon Carl Garré also described it as a type of chronic osteomyelitis also called proliferative periostitis, periostitis ossificans or Garré's sclerosing osteomyelitis. Phemister presented it in 1929 by the name of chronic fibrous osteomyelitis. However, Billroth in 1881 first coined the term 'subacute' [8-11].

Subacute osteomyelitis may also be secondary to:

1. Acute osteomyelitis that has been modified by inadequate or partial treatment with antibiotics,
2. Chronic osteomyelitis that follows an acute attack, when the virulence of the organism and the resistance of the patient are evenly balanced, and
3. Other diseases, such as the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) [9,12].

On the other hand, true primary subacute osteomyelitis is a distinct entity that occurs through hematogenous dissemination (PSAHO) in children without a history of previous antibiotic treatment. It develops when there is an altered host-pathogen relationship as a result of increased host resistance and decreased bacterial virulence so widespread involvement of the cancellous bone or of the subperiosteal

region has not occurred. A central area of suppurative necrosis becomes enclosed by a wall of fibrous tissue and granulation, the offending organisms are destroyed, and the pus is usually sterile. An occasional history of minor trauma may be noted and may be regarded as a predisposing factor for infection, since it may result in vascular injury and an area of hypoxia in the involved region of bone [13-15].

The causative organism is usually coagulase-positive *Staphylococcus aureus* (30-60%). Other organisms encountered are coagulase-negative Staphylococcus (most likely *Staphylococcus epidermidis*), *Streptococcus, Pneumococcus, Haemophilus influenzae* (much less common after widespread vaccination), *Pseudomonas aeruginosa, Enterococcus faecalis, Klebsiella, Brucella* spp and *Salmonella* spp. An increased prevalence of *Kingella kingae*, a gram-negative coccobacillus, has also been reported, mostly in children younger than 3 years. Patients with sickle cell anemia are predisposed to infections with *Salmonella*. However, in almost 71% of cases of PSAHO, no organism is cultured. Appropriate nucleic amplification assays significantly improve the detection rate of the responsible microorganisms [13, 16-27].

The onset of PSAHO tends to occur in slightly older children than the onset of acute hematogenous osteomyelitis. It has been reported in patients as young as 6 months but it usually appears in children older than 2 years. Sex ratios vary but, in general, males are affected slightly more often than are females. Two distinct forms seem to be distinguished on the basis of patient age and bacteriological etiology. The infantile form affects children aged between 6 months and 4 years and is predominantly due to *Kingella kingae*. The juvenile form involves children older than 4 years and *Staphylococcus aureus* appears to be the main bacteriological etiology [27].

Diagnosis is difficult because the characteristic signs and symptoms of the acute form of the disease are absent; therefore, a diagnostic delay is very likely. It is characterized by insidious onset, mild to moderate intermittent progressive pain, usually described as a persistent ache, and, often, a long delay between the onset of pain and the diagnosis (the most common presenting symptom). Usually, symptoms are present for 2 weeks or longer. The course is generally marked by few or no constitutional symptoms and no known previous acute disease. A systemic reaction is absent and supportive laboratory data are inconsistent, apart from a slightly raised erythrocyte sedimentation rate. Blood cultures are usually negative [28-31].

Radiology plays an important role in the diagnosis. Imaging with standard radiographs, bone scintigraphy and conventional or computed tomography (CT) has been described in the literature. The radiographic diagnosis is easy if the clinical data is known to the radiologist [32,33]. The great majority of PSAHO cases (90%) show benign characteristics on radiologic assessment. These benign findings include medullary lytic lesions with well-defined edges, marginal sclerosis and no bone enlargement or surrounding destruction. In the first decade of life the radiographic appearance of the lesion is usually the 'variant' type including cavities irregularly shaped, without sclerotic rim, extending into the epiphyses and intracortical, subperiosteal or multiple abscesses. An aggressive radiologic appearance may occasionally be evident (10%). It may include subperiosteal new bone formation and destruction of the cortex or surrounding matrix [10,14,18]. Lesions are typically localized to the metaphysis or diaphysis of tubular bones (86%) [34]. Magnetic resonance imaging (MRI) is a valuable examination and gadolinium-enhanced imaging is the most sensitive [35-38]. It is essential both for diagnosis and in the planning of surgical treatment [39].

Imaging clues to the diagnosis include the 'serpentine sign' on conventional radiographs and the 'penumbra sign' seen on MRI [40-42]. The 'serpentine sign' is usually evident when a lesion appears to be tethered to the growth plate, while the cavity progressively elongates, with growth extending from the epiphysis, through the metaphysis, into the diaphysis in a snakelike fashion [43]. The 'penumbra sign' is characteristically seen on T1-weighted MR images and is due to a thick layer of highly vascularized granulation tissue around a bone abscess cavity that has higher signal intensity than the cavity itself. This tissue is isointense to muscle on T1, enhances on contrast administration, and is hypointense on T2. It is the same as the inner ring described by Martí-Bonmatí., *et al*. [41]. It was also correlated with the 'double-line sign' described as a T2-weighted or short tau inversion recovery (STIR) feature of both the Brodie's abscess and avascular necrosis. The 'penumbra sign' can also be identified on unenhanced T1-weighted spin echo images due to its higher signal

intensity (muscle signal intensity) from the outer ring of the surrounding reactive new bone and the peripheral halo of bone marrow edema [41,44,45]. The 'penumbra sign' has a high specificity for musculoskeletal infection. This is also true for isolated soft tissue infection. The 'penumbra sign' is a characteristic, but not pathognomonic, MR finding supporting the diagnosis of bone infection and helping to exclude the presence of a tumor [44,46,47].

Primary subacute osteomyelitis in children may present as a unifocal lesion, in a much wider variety of bones than does the acute type, and as a multifocal type occurring at various sites or within a single affected bone that should be differentiated from chronic multifocal osteomyelitis [13,48,49]. The lower limb is affected much more often than the upper limb, and the tibia is affected relatively more often than the femur. It usually involves the long tubular bones. The most commonly affected site of tubular bones is the metaphysis but it may be localized to the epiphysis, which is contrary to the belief that primary bone infection does not occur in the epiphysis [50-53]. Communication of the lesion between the metaphysis and the epiphysis is also common. The diaphysis is occasionally affected though this occurs more often in adults than in children. Short tubular bones and non-tubular bones are rarely affected. Rare sites of involvement that have previously been reported include the pelvis, the femoral neck, the spine, the tarsal bones, the clavicle and the wrist [54-66]. Spinal lesions occur more often in adults than in children. The metacarpals/metatarsals, the phalanges and the patella are rarely involved with only scarce previously reported cases (Figures 1, 2) [67-69].

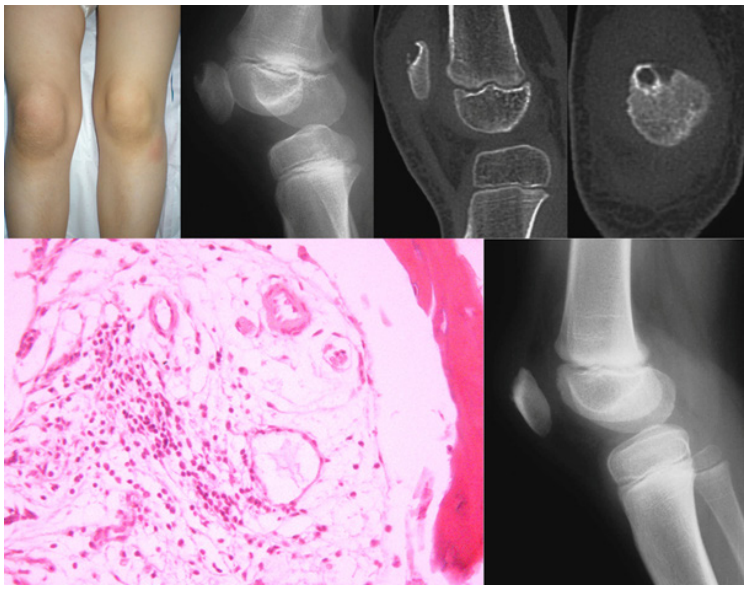

Figure 1: *Clinical and imaging appearance of a 6-year-old girl who presented with a painful right prepatellar swelling and walked with a limp. Symptoms and signs appeared 6 weeks ago but deteriorated significantly the last week. Radiographs and CT indicated a lytic lesion of the proximal pole of the patella. The lesion was curetted and histology of the content showed lymphocytes, plasma cells and granulation tissue with osteogenesis. Tissue culture was negative. Complete healing of the lesion was radiographically evident 6 months post-operatively.*

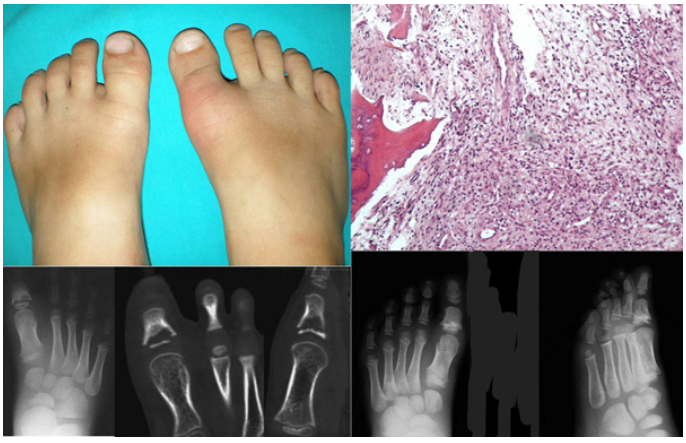

Figure 2: *Clinical and imaging appearance of a 7-year-old boy who presented with painful swelling and erythema of the base of the right great toe. Symptoms and signs appeared 2 months ago but deteriorated significantly the last week. Radiographs and CT indicated a lytic lesion of the proximal phalanx with no evidence of physeal plate destruction. The lesion was curetted and histology of the content showed lymphocytes, plasma cells and granulation tissue with bone destruction. Tissue culture isolated a methicillin-sensitive staphylococcus aureus. Complete healing of the lesion was radiographically evident 6 months post-operatively.*

Subacute osteomyelitis, whether it is primary or secondary, has been initially classified in four radiological types found only in the long bones [16]. This classification was modified and expanded into six types to include metaphyseal, diaphyseal, epiphyseal and vertebral lesions [70]. Several modified classification schemes have been proposed to describe all types of subacute osteomyelitis in children involving tubular and non-tubular bones and showing benign or aggressive radiological characteristics [20,22].

Therefore, based on imaging alone, two types of subacute osteomyelitis may be described:

A) Lesions involving long or short tubular bones, and

B) Lesions involving non-tubular bones (Table 1).

A) Tubular bones (long and short)
Metaphysis
I. Benign
Ia. Lucency without sclerotic margin
Ib. Lucency with sclerotic margin
II. Aggressive
IIa. Discreet erosive lesion involving cortex
IIb. Diffuse erosive lesion with reactive periosteal response
Diaphysis
III. Benign. Cortical abscess
IV. Aggressive. Medullary abscess with a reactive periosteal response
Epiphysis
Va. Lytic lesion of the epiphysis
Vb. Lytic lesion crossing the physeal plate
B) Non-tubular bones: spine, flat or small bones

Table 1: *Radiological classification of subacute osteomyelitis in children.*

A) Lesions involving the long or short tubular bones may be divided in five types.

Types I and II lesions occur in the metaphysis. Type I lesions show benign radiological characteristics, while type II lesions show aggressive findings. Type Ia lesion is a punched-out localized zone of lucency that can mimic forms of histiocytosis especially an eosinophilic granuloma. Type Ib resembles a typical Brodie's abscess with a sclerotic margin that may be mistaken for an osteoid osteoma (Figure 3). Type-IIa is a discreet erosive lesion involving the cortex with minimal reactive change. Type IIb is a diffuse erosive lesion with reactive periosteal response, resembling an osteogenic sarcoma, which may cross the growth plate. However, no cases with disturbance of growth have previously been reported [71]. Lesions similar to type II have been reported in cystic tuberculosis and also in fungal infection [72,73].

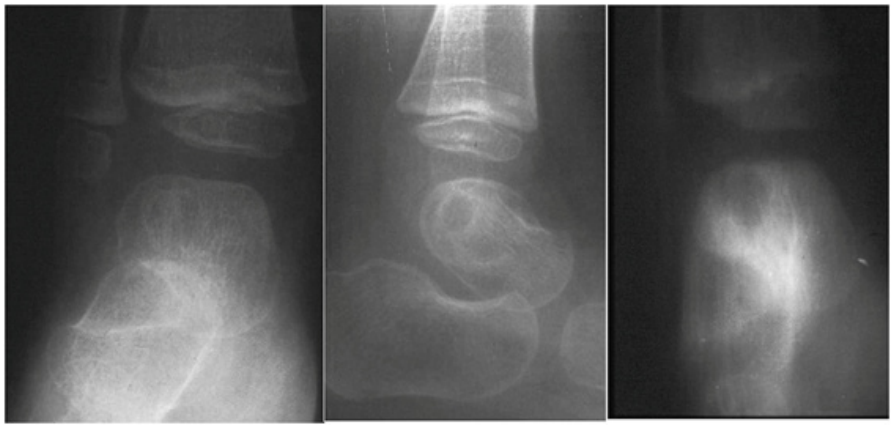

Figure 3: *A 4-year-old boy with a 2-month history of ankle pain and limping. Imaging including radiographs and conventional tomography indicated a lytic lesion of the talus with a sclerotic rim.*

Type III and IV lesions occur in the diaphysis. The cortical form (type III) has a benign radiological appearance presenting as a localised cortical lytic lesion with periosteal reaction simulating an osteoid osteoma. The periosteal form (type IV) has an aggressive radiological appearance with an onion-skin periosteal reaction. Type IV lesions are aggressive and destructive and are usually associated with the formation of 'onion-skin' or 'sunburst' subperiosteal new bone [74]. They may also be associated with a considerable amount of layered periosteal reaction [1]. The radiological picture in type IV lesions is indistinguishable from that of round-cell tumors of bone especially Ewing's sarcoma and also from leukemia [13,75,76].

Type V lesions occur in the epiphysis. Type Va lesion may appear as a punched out or irregular lucency usually eccendrically placed, with a faint sclerotic margin that may resemble a chondroblastoma. They usually occur in children less than six years old and do not cross the physeal plate (Figure 4). Type Vb lesions cross the physeal plate and involve both the epiphysis and the metaphysis (Figure 5). Similar lesions have been reported in tuberculosis [72].

B) Lesions involving non-tubular bones may be localized to the spine, flat bones and small bones, such as the short bones of the foot and wrist, and the sesamoid or accessory bones (Figures 1, 3). Involvement of the vertebral body may be a severely erosive or destructive process.

Primary subacute osteomyelitis mimics various benign and malignant tumors both clinically and radiologically. The differential diagnosis includes osteoid osteoma or osteoblastoma, nonossifying fibroma, giant cell tumor, eosinophilic granuloma, chondroblastoma, tuberculosis, fungal infection, fibrous dysplasia, osteosarcoma, small-round-cell tumors and leukemia [34,39,57,77-81].

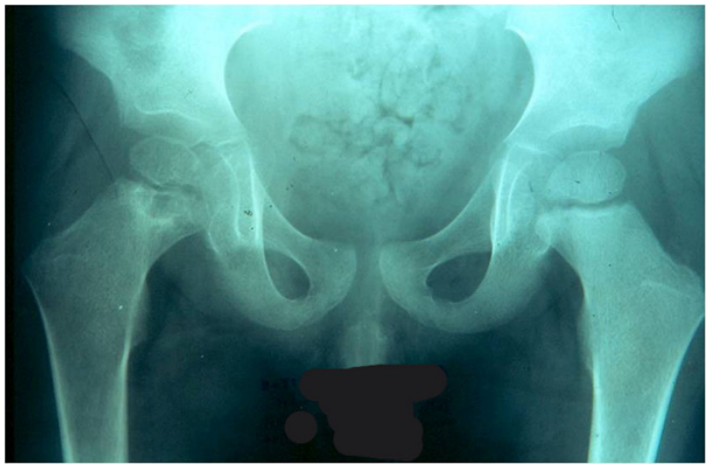

Figure 4: *A 5-year-old boy with a 6-week history of painful hip motion and limping. Anteroposterior radiograph indicated a cavity with sclerotic border of the proximal femoral metaphysis. There was no evidence that the lesion extended across the growth plate.*

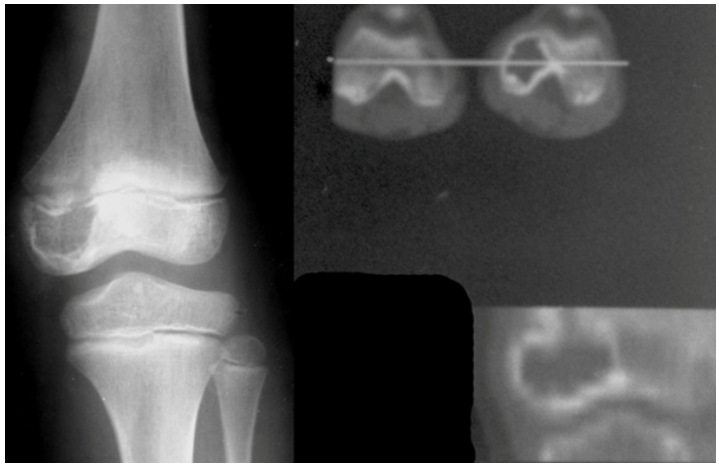

Figure 5: *An 8-year-old boy with a 2-month history of knee pain and limping. Imaging including radiographs and CT indicated a lytic lesion of the medial femoral condyle with a sclerotic rim extending to both epiphysis and metaphysis across the growth plate. The lesion was curetted and histology of the content showed lymphocytes, plasma cells and granulation tissue with bone destruction. Tissue culture was negative. No growth abnormality was detected at follow-up.*

Primary subacute osteomyelitis in children usually follows a benign course and the routine management is early antibiotic treatment and immobilization [6,51]. A sterile abscess can be treated conservatively, provided that the patient's symptoms are improving and the lesion is regressing radiographically. A conservative treatment policy in the management of both epiphyseal and epiphyseal-metaphyseal primary subacute osteomyelitis is also the treatment of choice. Surgery should be reserved for persistent infection that does not respond to appropriate antibiotic therapy or when bone lesions cannot be distinguished from bone tumors by use of all available imaging modalities. Radiologically 'aggressive' lesions usually require biopsy and surgical treatment followed by antibiotics and immobilization.

Treatment of a culture positive infection includes surgical debridement and targeted antibiotic therapy [10, 82-85]. In cases that no organisms are found the empirical treatment is based on antibiotics active against methicillin-sensitive staphylococcus aureus and drugs inhibiting prostaglandins in children older than 4 years, while in children younger than 4 years antibiotherapy should be directed against

Kingella kingae [27,86,87]. The need for antibiotics after the lesion has been cleared surgically is controversial [88] and recovery has been reported in 25% without antibiotics [16]. Cloxacillin is the antibiotic of choice in the treatment of subacute osteomyelitis. It is not effective for methicillin-resistant Staphylococcus aureus. An initial intravenous course of antibiotics for 5 to 7 days followed by oral use for 6 weeks to 4 months is usually suggested [13,79]. Subacute osteomyelitis and bone tumors can be similar in presentation, and the key to proper diagnosis is histopathological and microbiological confirmation in biopsy specimens [81].

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