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Unusual Presentation of Osteoid Osteoma with Exacerbating Pain during Menses

A case report

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Abstract

Osteoid osteomas (OO) are benign neoplasms commonly present during the second and third decade of life, showing a male predominance with classical nocturnal bone pain dramatically responding to nonsteroidal anti-inflammatory drugs. We report a rare OO in a young female who presented with right leg bone pain that was exacerbated during menstruation, a presentation that had never been reported before. The pain intensity increased and interfered with her daily activity, which urged for a careful evaluation by a computerized tomography scan showing OO signs. Surgical excision and histopathology confirmed OO. The patient's pain drops down to zero on the visual analog scale. Two years after the surgery, she is well with no recurrence signs. A novel OO presentation may increase physician awareness of atypical presentation. A careful

evaluation of a challenging presentation added to an imaging study may reveal the underlying cause and rule out other diagnostic dilemmas.

Keywords: Pain; Menstruation; Osteoid Osteoma; Prostaglandins; Female; Computerized Tomography Scan.

Introduction

Osteoid osteoma (OO) is an osteoblastic benign bone tumor with an incidence of 10 percent of all benign bone tumors. It usually has a preference for males in their second and third decades. It usually affects long bones, such as the femur, tibia, and spine (in 10%). The lower limbs are more frequently afflicted .[1,2] Based on its locality in the affected bone, OO can be subclassified into cortical, cancellous, and sub-periosteum. They rarely exceed the size of 2 cm; if they do, a differential diagnosis of osteoblastoma should be considered .[3]

The risk factors that cause this tumour to grow are unknown, but 30% of cases have a history of trauma.[4] We also observed a genetic predisposition, reporting FOS gene rearrangement in 90% of cases. Immunohistochemical studies indicate that the affected bone shows higher vascular blood flow and inflammatory reactions at the nerve endings. The prostaglandins (PG) levels at the nerve-supplying affected bone showed 100 to 1000 higher levels. OO is characterized by PG secretion, increasing blood flow to the region, and stimulating nerve fibers, which underscore the high pain felt. [6] The clinical presentation, primarily nocturnal pain responsive to nonsteroidal anti-inflammatory drugs (NSAID), confirms the diagnosis through imaging studies. Less commonly, those tumors present with joint pain, deformities, and walking difficulties. [7]Atypical presentation of OO has been documented, including atypical sites and symptoms.[8,9] However, there have never been any reports of menstrual pain exacerbation.

Case Report

A 22-year-old female presents with right (RT) lower leg pain during the last eight months. The pain was focal, affecting the distal tibia. It was sharp pricking, occurred only during her menses, and did not follow a nocturnal pattern; she was pain-free the rest of the month. She was sexually inactive; her periods were regular. She had an unremarkable past medical or surgical history; there was no history of prior trauma, and she did not report any drug allergies. She had taken

multiple prescriptions for NSAIDs, which provided only partial relief. During the last 4 months, the pain was aggravated to a level that made her awake from sleep, and thus, she sought medical advice. After a local examination revealed no abnormalities, the doctor sent her for a plain leg X-ray. The plain leg X-ray revealed a focal solid cortical thickening involving the anterior aspect of the distal tibial metaphysis, along with mild expansion, as shown in **Figure 1 (A and B)**. We diagnosed a stress fracture, administered treatment, and recommended a follow-up. She was referred to magnetic resonance imaging (MRI). It demonstrates extensive marrow edema involving the distal leg encircles, a small rounded lesion of abnormally low signal on T1, T2, and STIR images (short tau inversion recovery); **Figure 1 (C and D).** There was an anterior cortical thickening and periosteal edema at the distal tibial metaphysis; the differential diagnosis for the case at this point was either chronic osteomyelitis, stress fracture, or OO.

A computed tomography (CT) scan was done to evaluate this bony lesion better. It showed a well-defined small endosteal/peripheral medullary lytic lesion, nidus measuring (12 x 6 mm) with a sclerotic lucence margin and central calcific focus. An adjacent medullary sclerotic reaction, cortical hyperostosis, multiple vascular channels, and soft tissue thickening (vascular groove sign) were diagnostic of OO (**Figure 2).** One week after the diagnosis, the patient was advised to undergo surgical removal. During surgery, en bloc removal of the tumor was done (total removal of the tumor along with surrounding tissue to ensure complete excision of the nidus) with bone grafting, and the lesion was removed and sent for histopathology. The operation went smoothly, and the patient was discharged home . The histopathology report showed trabeculae of woven bone that were not organised and had prominent osteoblastic rimming. This histological picture is consistent with OO **(Figure 3**).The patient followed; postoperatively, she was pain-free, and there were no signs of local recurrence (she is at two years post-surgery now). Informed consent was obtained from the patient for publication of the case and its image.

Discussion

The relationship between pain and female hormonal changes is not a new concept; sex hormone fluctuation across the menstrual cycle was linked to many clinical illnesses—for instance, migraine, irritable bowel disease, and muscle myalgia.[10] A study tested female pain intensity and perception during different menstrual cycle phases and highlighted that the follicular phase was linked with the highest pain perception.[11] Researchers suggested that estrogen receptors exert

opioidergic activity (analgesic effect), and thus, the pain during estrogen abundance is less and gets worse when the estrogen is the lowest.[12]

During menses, the interplay of hormonal fluctuations, PG levels, and endometrial sloughing can all contribute to higher pain perception. The menstrual cycle has 2 phases: the follicular phase, where estrogen predominates under FSH control, and PG is the lowest. Then, in the luteal phase, progesterone predominates after the LH surge. The increase of PG occurs mainly during menstruation, causing an increased pain sensation during menses.[10,11] See **supplementary Figure 1.**

Many factors, including the patient's gender, ethnic group, and religion, influence the complexity of pain perception.[10-13] Pain can show inter and intra-personal variation. In the current case, we believe that the complex interplay of those factors may be responsible for higher pain perception [13,14] including:

Higher PG levels: They reach higher levels, especially PG E2 and PG F2α; both increase pain receptor sensitivity and thus cause worse pain. PGs are inflammatory promoters, causing higher inflammatory responses in affected bony tissue and its surroundings.[6]

Lower oestrogen hormone during menses: Oestrogen is known for its analgesic and anti-inflammatory properties; decreasing its level will exacerbate pain perception..[12] Furthermore, estrogen maintains the balance of bone remodeling in women; reduced levels can temporarily disturb that delicate equilibrium, favoring bone resorption over formation. This will trigger microscopic bony damage and exacerbate the bone inflammation reflected by higher pain.[15]

Endometrial shedding during menses: It is associated with increased levels of chemokine and cytokines that serve as inflammatory mediators. The latter reduces the pain threshold all over the body, including the bone, and manifests as worse pain; [6] see **supplementary Figure 2.** Estrogen receptors are distributed all over the body, including the genital tract, bones, and the nervous system (including both the central and the peripheral). Those receptors are integral in

precepting, signaling, and processing the pain stimulus. Estrogen hormones modify pain experience in more than one way.[16]

The binding of estrogen to its receptors distributed in the brain and the spinal cord allows modification of neurotransmitters and neuromodulators balance, such as calcitonin gene-related peptide and substance P. The former is involved in pain transmission, processing, and perception of the pain. Estrogen drops dysregulate that imbalance and reduce the pain threshold.[17] A drop of estrogen at menses lowers the pain threshold and worsens it .[18]

Estrogen's anti-inflammatory action enables the reduction of bone vasodilation and edema. Thus, low estrogen levels in menses can increase pain sensation reflected by throbbing, aching, or shooting pain, especially in the lower limbs. Furthermore, estrogen can suppress bone nociceptors activation (pain receptors). The heightened PG production at menses, superadded by low estrogen, renders scale for charging bone nociceptors and magnifies pain sensation.[10,12,18] In the bone, there is an equilibrium between bone-forming cells, the osteoblast and bone resorption cells; the osteoclast. Estrogens promote osteoblast growth; their deficiency increases bone fragility and bone pain.[19]

The atypical criteria for OOs include abnormal clinical presentation, abnormal imaging criteria, and abnormal response to therapy. The current case had typical CT imaging; a single nidus less than 1 cm responds well to treatment. What is unique regarding the clinical presentation is described in **Table 1.**

Cases with a long history of pain and delayed diagnosis may cause depression, mood changes, and suicide attempts.[19] OO is an excellent mimicker; many patients have endured long, complex investigations and medications. A CT scan confirmed the initial diagnosis of the current case as a stress fracture.[7,19]

Imaging added to the clinical presentation confirms the diagnosis; pain is the most frequent feature, swelling and tenderness may be encountered, and in advanced neglected cases, there

may be deformities, limitations of joint movement, and growth discrepancy. Pathologically speaking, an OO is composed of 3 concentric components:

A nidus (usually less than 2 cm) represents the neoplastic lesion secreting PG, triggering pain, having an oval shape with a mineralized center; a *fibrovascular halo*; and a *reactive sclerotic reaction.*

Plain X-ray, CT; the investigation of choice in confirming the site and the diagnosis of OO. MRI is inferior to CT, and it may exclude other diagnoses, such as stress fractures. As our patient is a young female,we prefer an MRI exam over a CT to reduce the radiation exposure risk. Furthermore more recent studies have shown that an MRI with contrast study is equal to or even better than a CT scan in detecting the OO nidus. The c 99 HDP bone scintigraphy is used to differentiate other causes, such as osteomyelitis.[21]

Medical treatment is helpful, but in the long run, it increases the risk of gastric ulceration and shows reduced efficacy.

S*urgical option*: Open en-bloc surgical resection with nidus removal, which is curative. Surgery carries high morbidity, prolonged recovery, and rehabilitation. *Minimally invasive options* such as percutaneous ablation treatment (as Cryoablation, Microwave ablation, MRI-guided focused ultrasonic waves, and Interstitial laser ablation) have gained much popularity recently owing to their safety, low cost, and lower technical failure rate *vs.* open surgery.[3,22]

The treatment success rate is high; the pain scale improvement felt drops to zero by 1 month in most followed cases. The prognosis is excellent; recurrence risk is low, and it is seen following incomplete surgical removal or ablation in a 1-2 years window, so follow-up is recommended. The risk of malignant transformation is extremely low, at less than 0.1[1]

Since this was the first OO of its kind, we were unable to compare it with previous studies. The link between OO pain and menses is not fully understood; and warrants further investigation. The current cases have unique aspects. First, it is presented in females, a less common gender (F:

M is 1:3).[3] Second, OO usually presents as cortical lesions, which are endosteal lesions.[2] Third, OO presenting symptom is nocturnal pain relieved by NSAID; here, the pain occurs during menses without a nocturnal rhythm.[19] Uncovering atypical presentation adds insight into the underlying pathophysiology and unveils a previously undiagnosed disease aspect, which may be of diagnostic or therapeutic value. Physicians, particularly gynecologists who frequently manage female patients, should experience a high level of suspicion when evaluating unusual pain patterns. Integrating pharmacological and complementary interventions for holistic pain management is advised.

This case's novelty encourages further investigation into the hormonal impact on OO pain, particularly in menstruating women. A multidisciplinary approach will likely shed more insight into the management (including gynecologists, orthopedics, and pain management specialists). To improve the diagnostic and therapeutic outcomes in managing OO, we need a guideline for atypical OO presentations.

Conclusions

The current case represents a unique presentation of OO, never previously documented in the literature. Comprehensive clinical examination, added to the proper imaging test, helped rule out other differential diagnoses and identify the cause. This case broadens our understanding of hidden factors that may trigger OO growth and suggests potential therapeutic approaches.

Authors' Contribution

WN, SKA and NNA were equally involved in conceptualization, collecting data and writing. RAM, QAH and ACP were responsible for the literature review and editing. All authors contributed equally to the supervision and final editing. All authors approved the final version of the manuscript.

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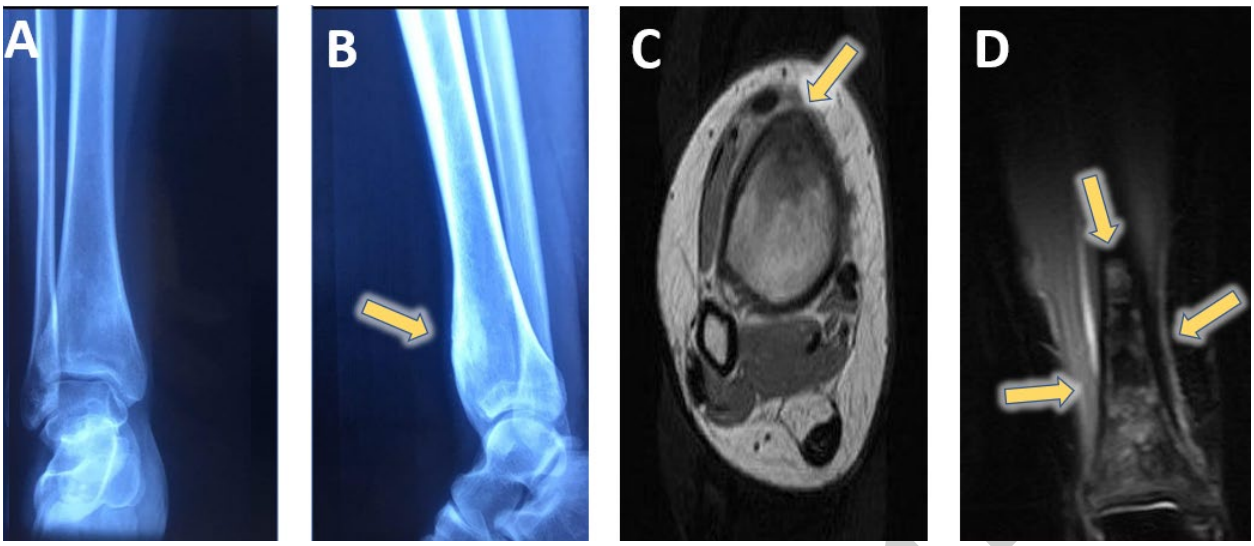

Figure 1. (A) Frontal and (B) lateral X-rays of the leg show focal solid cortical thickening with sclerosis involving the distal anterior medial tibial metaphysis (yellow arrows). **Figure 1.** (C) Magnetic resonance imaging axial T1, (D) STIR showing small subcortical rounded T1 and T2 hypointense lesion, posterior to hypointense cortical thickening, and surrounded by bone marrow edema (yellow arrows).

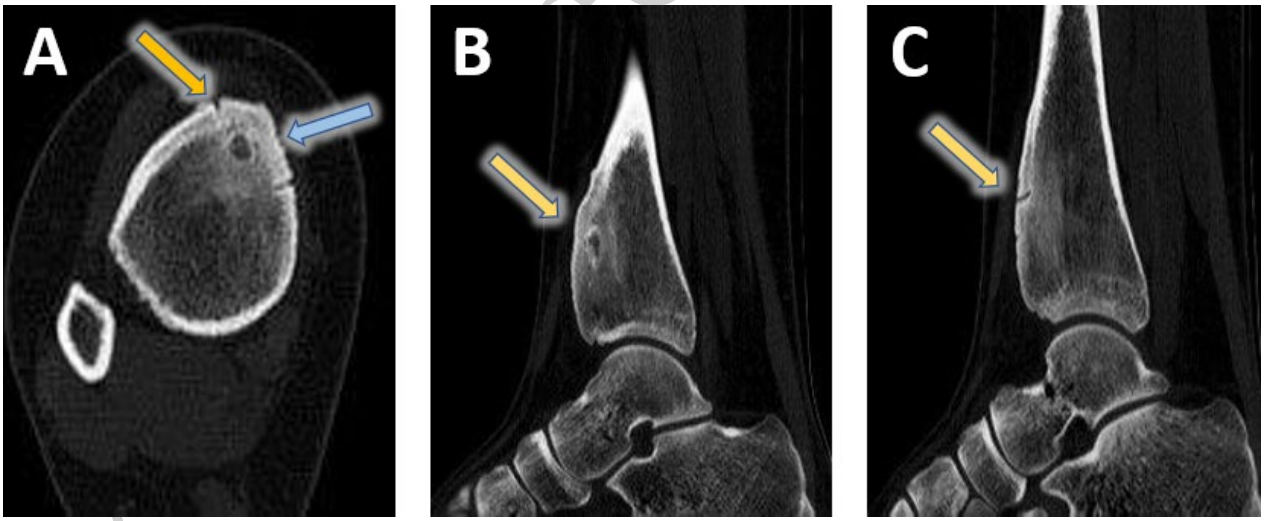

Figure 2. Computerized tomography scan of the lower leg (bone window): (A) axial (B) and (C) sagittal reformatted images show a small lytic lesion (yellow and blue arrows), with a central focus of calcification, surrounded by cortical thickening, with few thin linear radiolucent grooves tracking toward the nidus (yellow arrows).

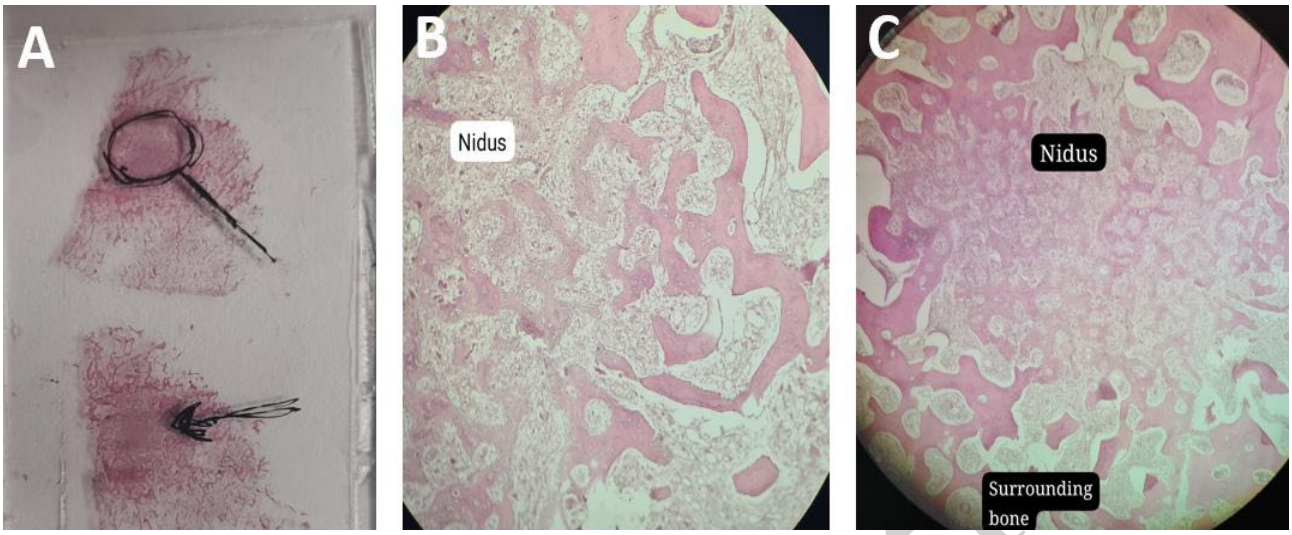

Figure 3. A histological slide of the specimen 40 X magnification using a high-power lens. **(**A) An osteoid osteoma (black arrow) nidus and normal surrounding bone as demonstrated in the histological slide and sections, (B) and (C) *the nidus*: looks like haphazard trabeculae of woven bone associated with prominent osteoblastic rim of different thickness and mineralized levels; surrounding bone: showing thick trabeculae of bone surrounded by adjacent loose fibrovascular stroma.

Table 1. Atypical clinical presentation of osteoid osteomas tumor

Parameters	**Typical OO presentation**	**Current case**	**Other atypical presentation**	**Supporting references**
Age and gender	typical age below 30 years, male predominate	female < 30.	There is a wide range of variance from 6 months to 87 years.	[9]
Pain	•Nocturnal •Typically respond to NSAID	•day and night pain are limited to menses likewise	•day-pain, or • pain reported after exercise. • Rarely, no pain is reported in OO from subungual	[20]
Affected bone	•long bone, mostly in the lower limbs (>85%), spin (10%) •The metaphysical or diaphyseal part of the bone	•Tibia: it is within the usual presentation •Tibial metaphysis	•Short and irregular bones like the wrist and ankle. •Impose diagnostic challenges with swelling, tenderness and joint restriction.	[2]

	•Arise from the cortical aspect of the bone	•It arises from endosteum, which is unusual.	•Imaging may not be as typical as in long bones.	

296 *OO: osteoid osteomas, NSAID: Nonsteroidal anti-inflammatory drug*