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Case Report

Parosteal osteosarcoma arising from the site of a prior excised osteoid osteoma: A rare progression, or an uncommon coincidence? Report of a case with brief review of the literature

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Abstract

Osteoid osteoma is a benign tumor of the bone widely regarded as devoid of malignant capacity or invasive potential. Osteosarcoma is a highly aggressive tumor with generally unfavorable prognosis. We present a case of a 65-year-old woman who presented with a large thigh mass proved to be a dedifferentiated high-grade parosteal osteosarcoma arising from the left femur with metastasis to the ribs, spine, and pelvic bones. The patient reported history of osteoid osteoma at the same site of the current osteosarcoma surgically removed 46 years prior to current presentation. In this report, we describe the difference between osteoid osteoma and osteosarcoma, and attempt to answer the question of possible progression of osteoma to osteosarcoma, or if it is just a coincidence.

Keywords: Osteoid osteoma; Osteosarcoma; tTumor; Malignant; Management

Abbreviations

OOs: Osteoid osteoma, **OS**: Osteosarcoma, **PO**: Parosteal osteosarcoma; **HIFU**: High intensity focused ultrasound

Introduction

Osteoid osteoma (OOs) is a benign, usually painful tumor characterized by a radiolucent nidus (lesion) of osteoid and vascular connective tissue with a dense sclerotic shell. This benign tumor often occurs in long bones of the lower extremities, such as the tibia or femur. The consensus is that OOs is idiopathic, but there is reported evidence that it can be a consequence of trauma eliciting microscopic change [1]. It is currently regarded as a pathology that evades transformation into a malignant entity. Surgical excision of the lesion is considered curative, and, in many cases, spontaneous remission has even been documented within 6-15 years of diagnosis. Therefore, the prognosis of OOs is generally excellent with no lasting health implications [2]. This case report, however, presents a parosteal osteosarcoma originating from the site of a prior osteoid osteoma that was excised 46 years prior, accompanied by metastatic lesions in the spine, ribs, and iliac bone.

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Primary osteosarcoma (OS) is the most common malignant bone tumor, characterized by osteoid matrix-depositing malignant mesenchymal cells [3]. In young adults, it is most associated with mutations in the tumor suppressor genes p53 or Rb [4]. In older populations, OS is often secondary to Paget's disease of the bone, a dysregulation of bone remodeling, which carries a less favorable prognosis compared to primary osteosarcoma [5]. Parosteal osteosarcoma (PO) is a variant of osteosarcoma characterized by a more insidious progression, but ultimately a better prognosis compared to conventional osteosarcoma [6]. Due to its insidious nature, this low-grade malignant variant has the capacity to become high-grade when left untreated and may result in metastasis [7]. Rarely, PO manifests in a dedifferentiated form, such as the one presented in this case report, which is associated with a more aggressive pathology and unfavorable outcome [3]. Therapeutic options pose a complex challenge, because, while recent studies demonstrate success at treating localized osteosarcoma with adjuvant radiotherapy, it presents more toxicity for patients with metastatic lesions [8]. As such, the therapy requires a thorough analysis of risks and benefits to the patient.

In this report, we provide a brief literature review to determine; does this case report represent a rare progression of osteoma to osteosarcoma, or is it just an uncommon coincidence? As, current available data is inconclusive where it pertains to this question.

Case Presentation

A 65-year-old woman presented with pain involving left thigh, spine, ribs, and left pelvic region, and a large left thigh

mass recently enlarging in size. Patient reported history of an osteoid osteoma of the left femur, which was excised and cured 46 years prior to current presentation. Abdominal and pelvic CT without contrast demonstrated lytic lesions in left iliac bone and L3 vertebral body one of which showed cortical interruption, suspicious for metastatic disease. Mildly enlarged left pelvic lymph nodes were also noted, largest measuring 1.5 cm as well as scattered multiple retroperitoneal small nodules but no ascites. No gross visceral abdominal or pelvic organ mass was identified.

Further investigation included 3 phase NB Bone imaging Radiopharmaceutical 25 mCi of Tc-99m MDP which demonstrated a calcified soft tissue mass in left mid-thigh, without encasing to left femur. In addition, foci of focal uptake in the ribs, L3, and left hemi pelvis were noted and most suspicious for osseous metastasis. The mass appeared to arise from the outer periosteum in the juxtacortical region, with extension to soft tissue forming a calcified mass.

A CT guided core biopsy of the left thigh mass, calcified tissue and soft tissue was performed (Figure 1A). Microscopic examination revealed a high-grade spindle cell sarcoma (**Figure 1B, 1C**) focally forming malignant osteoid, with haphazard lace-like appearance consistent with osteosarcoma (**Figure 1D, 1E**). The tumor cells were positive for S100 (focally), Actin, and Vimentin, while negative for Desmin, Cytokeratin AE1/AE3, and CD34. With the presence of high grade sarcomatous cells with malignant fibrous histiocytoma-like histomorphology producing malignant osteoid, the diagnosis of dedifferentiated parosteal osteosarcoma was made. The final diagnosis was reported as Dedifferentiated High Grade Parosteal Osteosarcoma most consistent with origin from site of prior excised Osteoma. Tissue sampling from the ribs and vertebrae yielded similar findings to the left thigh tumor and the diagnosis of widely metastatic dedifferentiated high grade Parosteal osteosarcoma was rendered.

Patient was not a surgical candidate due to extensive metastatic disease, and difficult to access sites of metastasis. Patient expired 6 months later after a course of chemotherapy and radiation due to generalized metastatic disease and multiple organ failure. The treatment included innovative therapeutic approaches because of poor prognosis, but details of the therapeutic regimen is not available for reporting.

Discussion

This study presents a case of dedifferentiated parosteal osteosarcoma likely arising from osteoid osteoma in the left femur of a 65-year-old female excised 46 years prior. It demonstrates a previously undocumented relationship between OOs and OS which holds significant clinical implications due to the stark difference between long-term survival rates [5]. The two pathologies are readily distinguished according to clinical presentation, characteristic radiographic appearance, and histomorphologic features.

Osteoid osteoma is a benign tumor that has been believed to lack potential for malignant transformation. It is most prevalent in

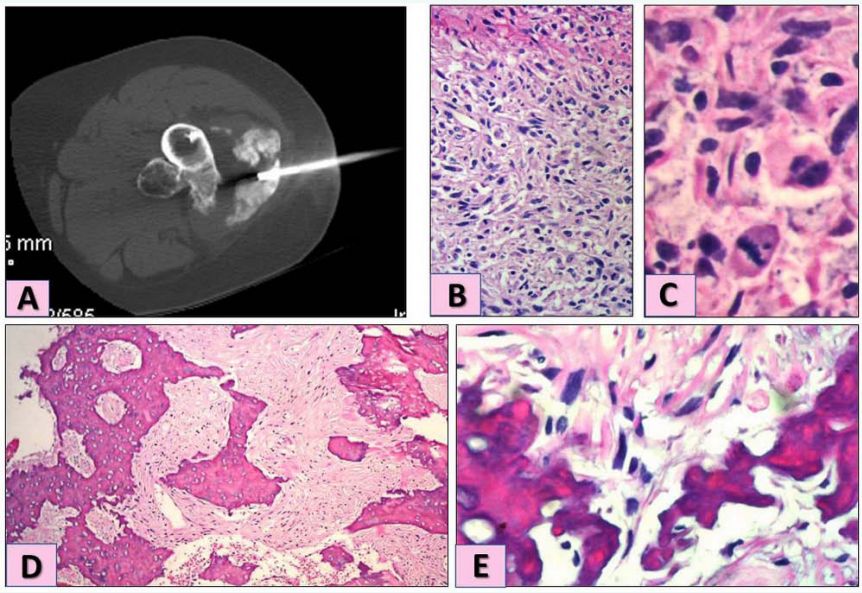

Figure 1 CT guided core biopsy and microscopic findings of the thigh mass
Figure 1A: CT guided core biopsy from both the calcified mass and the soft tissue mass
Figure 1B: Low power view of spindle cell sarcoma (H&E stain X20)
Figure 1C: High power view of spindle cell sarcoma showing nuclear pleomorphism and abnormal mitotic figure (H&E stain X100)
Figure 1D: Low power view of malignant osteoid produced by malignant spindle cells (H&E stain X20)
Figure 1E: High power view of malignant osteoid produced by malignant spindle cells showing haphazard lace-like characteristic appearance (H&E stain X100).

males between the ages of 5-25 and is typically a single unilateral lesion localized to the long bones of the lower extremities. The most frequently reported complaint is transient and recurring pain at night. The region to which the pain is localized may present with swelling [1]. OOs is believed to be idiopathic, but recent evidence suggests a correlation between previous trauma or infection-mediated inflammation. The mechanism associated with this is likely attributed to remodeling processes causing invagination of the periosteum, making the region susceptible to malformation and subsequent osteoid osteoma development [9]. Recent studies indicate elevated levels of prostaglandin E2 and overexpression of cyclooxygenase-2 (COX2), which is likely the mechanism mediating pain and inflammation localized to the lesion [2].

Osteoid osteoma results in the formation of a small, circular nidus comprised of haphazardly arranged woven bone. A dense sclerotic shell encompasses the nidus as a result of reactive bone transformation [2]. On radiology, a double density sign is seen in bone scintigraphy, with 100% sensitivity, indicating an elevation in technetium-99 uptake most intensely at the focal center with a lesser degree of uptake rimming the nidus. The nidus is radiolucent due to both osteoclast mediated bone resorption as well as the presence of osteoblasts and rich vascularity. The surrounding sclerotic shell is radiopaque indicating hyperdensity [10].

Histologically, osteoclasts are pervasive throughout the fibrovascular trabeculae, with thin spiracles indicative of active bone turnover and remodeling. The matrix consists of haphazardly arranged, newly deposited bone. The perimeter of the nidus is lined by immature osteoblasts. All cells are benign and cellular malignant features are not present [2].

Limited data is known about genetic changes in osteoma. M.R. Baruffi et. al reported cytogenetic analysis in two osteoid osteomas. In both, the modal chromosome number was 46. One of the cases presented a del(22)(q13.1) as the sole clonal chromosome alteration. The other had clonal monosomies of chromosomes 3, 6, 9, 17, 19, and 21, as well as a +del(22)(q13.1), which was detected as a non-clonal chromosome alteration. However, insufficient data is present to support definitive conclusion [11].

Conservative management is generally preferred with osteoid osteoma, as it has been widely believed to not pose a risk to health. Intense pain at night can be relieved by use of NSAIDs, which inhibit COX2-mediated synthesis of pro-inflammatory prostaglandins. Surgical resection is recommended for those experiencing severe pain that is unresponsive to NSAIDs and that affects quality of life. Similarly, surgical treatment should be considered for patients with NSAID contraindication - considering the risks of long-term usage such as gastrointestinal complications, renal complications, NSAID-induced asthma, as well as pharmacological interactions with existing prescriptions. Surgical resection is over 90% successful, generally without lasting health implications [2].

This case study presents osteoid osteoma possibly complicated by the development of parosteal osteosarcoma. Parosteal osteosarcoma is a low-grade and indolent variant of conventional osteosarcoma, the most common primary malignant bone tumor. It constitutes 4% of osteosarcoma cases, arising from the outer periosteum in the juxtacortical region. While parosteal osteosarcoma generally has a better prognosis and long-term survival rate compared to the conventional form, it can manifest in a dedifferentiated form which is associated with a poorer prognosis due to its potential to invade and metastasize to distant sites, as is the case in this patient [3]. Additionally, dedifferentiated lesions present with a much higher rate (43% in dedifferentiated compared to 18% in low-grade) of medullary cavity involvement, where bone marrow is stored.

In assessment of medullary involvement, dynamic-enhanced MRI is superior to CT in distinguishing angiogenesis, linked to tumor infiltration, from inflammatory edema in the medullary cavity. However, dual-energy CT may be preferred in early stages, when imaging of tumor infiltration and edema appear most similarly, because of its high specificity compared to MRI. Due to their similar radiological presentation, it is important to choose an appropriate imaging technique to distinguish pathological activity. This is to spare the patient aggressive surgery mandated by medullary infiltration, if the radiological findings are due, instead, to inflammation [6]. In this case study, CT was performed, demonstrating amorphous ossification lateral to the left femur. Typically, radiography of parosteal sarcoma demonstrates a sessile, lobulated mass with ossification originating at the metaphysis of the bone. This finding is often mistaken for benign conditions such as osteochondroma, which shares a similar age distribution [3].

Histologically, soft tissue samples of the left thigh returned hypercellularity of chondrocytes with mild atypia, indicating upregulation of cellular replication. Samples from the iliac lesion demonstrate pleomorphic spindle cells with osteoid-like matrix, consistent with metastatic dedifferentiated parosteal osteosarcoma. The presence of malignant mesenchymal cells, though low grade, associated with prominent malignant osteoid formation, together with absence of cells from non-mesenchymal origin is diagnostic of osteosarcoma [7].

Commonly observed antigens used to determine lineage include S100, actin, vimentin, cytokeratin, osteocalcin, and osteonectin. The patient's immunohistological findings support the diagnosis of sarcoma, with positive staining for actin, vimentin, and S100. The immunohistochemical profile of osteosarcoma lacks specificity because expression is highly variable. Therefore, immunohistochemistry studies alone are not sufficient for subclassification. The presence of malignant osteoid produced by malignant cells is diagnostic of osteosarcoma, skeletal or extraskeletal [12].

Osteosarcoma is currently treated with pre-and postoperative chemotherapy in association with surgical removal of the tumor. About 15–20% of patients have evidence of metastases at diagnosis, particularly to the lungs. Patients with metastatic disease have a very poor prognosis, with approximately 20–30% of long-term survivors, as compared with 65–70% of patients with localized disease. The optimum management

of these patients has not been standardized yet due to several patterns of metastatic disease harboring different prognoses. Complete surgical resection of all sites of disease is mandatory and predictive of survival [13]. In cases requiring a wide surgical margin, a bone defect may remain that is generally amenable to various reconstructive surgeries including endoprosthesis, prophylactic fixation with bone plate, and reimplantation following extracorporeal irradiation [3].

Patients with multiple sites of disease not amenable to complete surgical removal should be considered as candidates for innovative therapies. Because these tumors can be hard to treat, clinical trials of newer treatments may be a good option in many cases [13]. One such method is the use of artificially induced hyperthermia administered alongside other treatment modalities in order to increase tissue perfusion and oxygenate tumor cells, consequently enhancing the susceptibility to chemotherapy and radiotherapy-mediated apoptosis. Novel methods are being studied to improve the localization of hyperthermia treatment, including the use of nanoparticle agents, electromagnetic waves, ultrasound, and particle-beam therapy. Gold nanotherapy has thus far demonstrated promising results in localization with low toxicity. A recent randomized clinical trial noted regional hyperthermia therapy improved progression-free survival, but risks included pain and burns localized to the site of administration [8].

High intensity focused ultrasound (HIFU) works by a similar principle, inducing the conversion of mechanical energy to heat the target at the cellular level. This produces gas pockets that reduce the stability of cell membranes, leading to cell death [8].

Photodynamic therapy is another treatment being explored with considerable interest due to the relatively low risk of toxicity. It works by administering light localized to the tumor at a wavelength that excites photosensitive electrons. This induces apoptosis due to the generation of reactive oxygen species which causes damage to membranes and organelles [8].

Our case and literature review failed to prove that this osteosarcoma arose from osteoid osteoma, even at the molecular level. One definite positive supporting finding would have been the presence of a preexisting osteoma, within or adjacent to the osteosarcoma. This was not identified, and the only reason to raise the question is the presence of osteosarcoma at the site of prior excised osteoma. Review of the literature provides no support for such possibility; therefore, we conclude it is just a coincidence to have the osteosarcoma at the site of prior osteoma. However, it is our hope that this report raises awareness of what remains an unmet need in understanding this possible phenomenon, and that continued investigation drives further development of efficacious investigation, diagnosis and safe treatments for improving patient outcomes.

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